THEMED ISSUE

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H1N1 influenza and pandemic flu

A special themed issue of the *Health Technology Assessment* journal series

In this issue

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Health Technology Assessment

Volume 14: No. 46, October 2010

The National Institute for Health Research

The National Institute for Health Research (NIHR) has been established as a part of the Government's strategy, 'Best Research for Best Health'. It provides the framework through which the research staff and research infrastructure of the NHS in England is positioned, maintained and managed as a national research facility.

The NIHR provides the NHS with the support it needs to conduct first-class research funded by the Government and its partners alongside high-quality patient care, education and training. Its aim is to support outstanding individuals (both leaders and collaborators), working in world-class facilities (both NHS and university), conducting leading-edge research focused on the needs of patients.

This themed issue of the *Health Technology Assessment* journal series contains a collection of research commissioned by the NIHR as part of the Department of Health's (DH) response to the H1N1 swine flu pandemic. The NIHR through the NIHR Evaluation Trials and Studies Coordinating Centre (NETSCC) commissioned a number of research projects looking into the treatment and management of H1N1 influenza.

NETSCC managed the pandemic flu research over a very short timescale in two ways. Firstly, it responded to urgent national research priority areas identified by the Scientific Advisory Group in Emergencies (SAGE). Secondly, a call for research proposals to inform policy and patient care in the current influenza pandemic was issued in June 2009. All research proposals went through a process of academic peer review by clinicians and methodologists as well as being reviewed by a specially convened NIHR Flu Commissioning Board.

The final reports from these projects have been peer reviewed by a number of independent expert referees before publication in this journal series.

Criteria for inclusion in the HTA journal series

Reports are published in the HTA journal series if (1) they have resulted from work for the HTA programme or, in the case of this national priority, the NIHR, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reports in this themed issue were funded through the Cochrane Collaboration; the Health Services Research programme (HSR); the Health Technology Assessment programme (HTA); the Policy Research Programme (PRP); the Public Health Research programme (PHR); and the Service Delivery and Organisation Programme (SDO).

The Cochrane Collaboration is an international not-for-profit and independent organisation, dedicated to making up-to-date, accurate information about the effects of health care readily available worldwide. It produces and disseminates systematic reviews of health-care interventions and promotes the search for evidence in the form of clinical trials and other studies of interventions. Cochrane reviews and the Cochrane Central Register of Controlled Trials are published and updated in *The Cochrane Library* (www.cochranelibrary.com).

The HSR programme aims to lead to an increase in service quality and patient safety through better ways of planning and providing health services. It funds both primary research and evidence syntheses, depending on the availability of existing research and the most appropriate way of responding to important knowledge gaps.

The HTA programme produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The PRP provides the evidence base for policy development on public health and social care issues. It funds research in three main ways: 5-year programmes of research in 16 research units, a primary-care research centre, a public health research consortium, and a surveillance unit; programmes of interlinked studies on key policy initiatives; and single projects and literature reviews.

The PHR programme evaluates public health interventions, providing new knowledge on the benefits, costs, acceptability and wider impacts of non-NHS interventions intended to improve the health of the public and reduce inequalities in health. The scope of the programme is multi-disciplinary and broad, covering a range of interventions that improve public health.

The SDO programme commissions research evidence that improves practice in relation to the organisation and delivery of health care. It also builds research capability and capacity amongst those who manage, organise and deliver services – improving their understanding of the research literature and how to use research evidence.

The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report. The views expressed in this publication are those of the authors and not necessarily those of the NIHR or the Department of Health.

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Themed issue introduction

Welcome to the second of three special themed issues of the *Health Technology Assessment* journal series, relating to NIHR-funded projects into H1N1 influenza and pandemic flu. The influential journal series is now over 10 years old and has published more than 500 titles, covering a wide range of health technologies in a diverse set of applications. In general, the series publishes each technology assessment as a separate issue within each annual volume.

This themed issue departs from that format by containing a collection of reports on projects which have been commissioned by the NIHR through the NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC) as part of the H1N1 influenza research portfolio. The research within this themed issue has been carried out, not only by the Health Technology Assessment programme (HTA), but also by other NIHR research programmes: the Health Services Research programme (HSR); the Public Health Research programme (PHR); and the Service Delivery and Organisation programme (SDO). It also contains reports carried out under The Cochrane Collaboration and the Policy Research Programme (PRP).

To ensure rapid and timely publication of this vital research, it has been brought together in this series of themed issues to ensure that all NIHR-funded projects into H1N1 influenza and pandemic flu can publish the full results and outcomes from their research in a respected, peer-reviewed resource. The significant impact of *Health Technology Assessment* was again confirmed by its recently published impact factor (2009) of 6.91, ranking the series in the top 10 per cent of medical and health-related journals. It is also indexed on MEDLINE, CINAHL, EMBASE, UK PubMed Central and the Cochrane Library and the ISI Science Citation Index.

The papers in this themed issue report on the ongoing Department of Health response to the H1N1 swine flu pandemic, and we hope that the reports of the work carried out will be of interest and value to readers.

Further details of each of the projects are available on the NETSCC website (www.netscc.ac.uk) and we welcome comments on the themed issue via the HTA website (www.hta.ac.uk).

Professor Tom Walley
Director of NETS
Editor-In-Chief, *Health Technology Assessment*

Open-label, randomised, parallel-group, multicentre study to evaluate the safety, tolerability and immunogenicity of an $AS03_B$/oil-in-water emulsion-adjuvanted ($AS03_B$) split-virion versus non-adjuvanted whole-virion H1N1 influenza vaccine in UK children 6 months to 12 years of age

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Declared competing interests of authors: Vaccines were manufactured by GlaxoSmithKline vaccines and Baxter, both of whom donated the vaccine, but had no role in study planning or conduct. AJP, AF, PTH, SNF and ACC act as chief or principal investigators for clinical trials conducted on behalf of their respective NHS Trusts and/or universities, sponsored by vaccine manufacturers, but receive no personal payments from them. AJP, AF, PTH and SNF have participated in advisory boards for vaccine manufacturers, but receive no personal payments for this work. MDS, SL, PTH and AF

have received financial assistance from vaccine manufacturers to attend conferences. All grants and honoraria are paid into accounts within the respective NHS Trusts or universities, or to independent charities.

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Abstract

Open-label, randomised, parallel-group, multicentre study to evaluate the safety, tolerability and immunogenicity of an AS03$_B$/oil-in-water emulsion-adjuvanted (AS03$_B$) split-virion versus non-adjuvanted whole-virion H1N1 influenza vaccine in UK children 6 months to 12 years of age

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Objective: To evaluate the safety, tolerability and immunogenicity of an AS03$_B$/oil-in-water emulsion-adjuvanted (AS03$_B$) split-virion versus non-adjuvanted whole-virion H1N1 influenza vaccine in UK children aged 6 months to 12 years.
Design: Multicentre, randomised, head-to-head, open-label trial.
Setting: Five UK sites (Oxford, Bristol, Southampton, Exeter and London).
Participants: Children aged 6 months to < 13 years, for whom a parent or guardian had provided written informed consent and who were able to comply with study procedures, were eligible for inclusion.
Interventions: A tocopherol/oil-in-water emulsion-adjuvanted (AS03$_B$) egg culture-derived split-virion H1N1 vaccine and a non-adjuvanted cell culture-derived whole-virion vaccine, given as a two-dose schedule, 21 days apart, were compared. Participants were grouped into those aged 6 months to < 3 years (younger group) and 3 years to < 13 years of age (older group) and were randomised by study investigators (1 : 1 ratio) to receive one of the two vaccines. Vaccines were administered by intramuscular injection (deltoid or anterior-lateral thigh, depending on age and muscle bulk). Local reactions and systemic symptoms were collected for 1 week post immunisation, and serum was collected at baseline and after the second dose. To assess safety and tolerability, parents or guardians recorded the following information in diary cards from days 0–7 post vaccination: axillary temperature, injection site reactions, solicited and unsolicited systemic symptoms, and medications.
Main outcome measure: Comparison between vaccines of the percentage of participants demonstrating seroconversion by microneutralisation assay.
Results: Among 937 children receiving vaccine, per-protocol seroconversion rates were higher after the AS03$_B$-adjuvanted vaccine than after the whole-virion vaccine (98.2% vs 80.1% in children < 3 years, 99.1% vs 95.9% among those aged 3–12 years), as were severe local reactions (3.6% vs 0.0% in those under 5 years, 7.8% vs 1.1% in those aged 5–12 years), irritability in children < 5 years (46.7% vs 32.0%), and muscle pain in older children (28.9% vs 13.2%). The second dose of the adjuvanted vaccine was more reactogenic than

the first, especially for fever >38.0°C in those under 5 years of age (8.9% vs 22.4%).
Conclusion: The adjuvanted vaccine, although reactogenic, was more immunogenic, especially in younger children, indicating the potential for improved immunogenicity of influenza vaccines in this age group.
Trial registration number: ISRCTN89141709

Contents

List of abbreviations

CI	confidence interval
EMEA	European Medicines Agency
GSK	GlaxoSmithKline
UK-SAGE	UK Scientific Advisory Group for Emergencies
WHO	World Health Organization
WHO-SAGE	WHO Strategic Advisory Group of Experts on Immunisation

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Background

Children are a priority for vaccination in an influenza pandemic, but safety and immunogenicity data for new-generation adjuvanted and whole-virion vaccines are limited.

Objectives

Immunogenicity

- How does the percentage of children aged 6 months to 12 years of age with a fourfold rise in microneutralisation titres between the prevaccination sample and the sample taken 3 weeks after completion of a two-dose course of the non-adjuvanted, whole-virion vaccine and the $AS03_B$-adjuvanted split-virion vaccine compare?
- How does the percentage of children aged 6 months to 12 years of age with haemagglutination inhibition titres of ≥ 1 : 32 3 weeks after completion of a two-dose course of the non-adjuvanted, whole-virion vaccine and the $AS03_B$-adjuvanted split-virion vaccine compare?
- How does the percentage of children aged 6 months to 12 years of age with a fourfold rise in haemagglutination inhibition titres between the prevaccination sample and the sample taken 3 weeks after completion of a two-dose course of the non-adjuvanted, whole-virion vaccine and the $AS03_B$-adjuvanted split-virion vaccine compare?
- What is the geometric mean fold rise in haemagglutination inhibition titres from baseline to 3 weeks after two doses of the non-adjuvanted, whole-virion vaccine and the $AS03_B$-adjuvanted split-virion vaccine?
- What is the geometric mean haemagglutination inhibition titre 3 weeks after two doses of the non-adjuvanted, whole-virion vaccine and the $AS03_B$-adjuvanted split-virion vaccine?

Reactogenicity

- How does the percentage of children aged 6 months to 12 years of age experiencing fever and local reactions within the 7 days following each dose of the non-adjuvanted, whole-virion and the $AS03_B$-adjuvanted split-virion vaccines compare?
- What percentage of children aged 6 months to 12 years of age experience non-febrile systemic reactions within the 7 days following each dose of the non-adjuvanted, whole-virion and the $AS03_B$-adjuvanted split-virion vaccine?

Methods

The safety, reactogenicity and immunogenicity of a tocopherol/oil-in-water emulsion-adjuvanted ($AS03_B$) egg culture-derived split-virion H1N1 vaccine and a non-adjuvanted cell culture-derived whole-virion vaccine, given as a two-dose schedule, 21 days apart, were compared in a randomised, open-label trial of children aged 6 months to 12 years of age. Local reactions and systemic symptoms were collected for 1 week post immunisation, and serum was collected at baseline and after the second dose.

Results

Among 937 children receiving vaccine, per-protocol seroconversion rates were higher after the $AS03_B$-adjuvanted vaccine than after the whole-virion vaccine (98.2% vs 80.1% in children < 3 years, 99.1% vs 95.9% among those aged 3–12 years), as were severe local reactions (3.6% vs 0.0% in those under 5 years, and 7.8% vs 1.1% in those aged 5–12 years), irritability in children < 5 years (46.7% vs 32.0%), and muscle pain in older children (28.9% vs 13.2%). The second dose of the adjuvanted vaccine was more reactogenic than the first especially for fever > 38.0°C in those under 5 years of age (8.9% vs 22.4%).

Conclusion

In this first direct comparison of an $AS03_B$-adjuvanted split-virion vaccine versus whole-virion non-adjuvanted H1N1 vaccine, the adjuvanted vaccine – while reactogenic – was

more immunogenic, especially in younger children, indicating the potential for improved immunogenicity of influenza vaccines in this age group.

Trial registration

This trial was registered as ISRCTN89141709.

Chapter 1
Introduction

The first illness caused by a new influenza A virus was confirmed in the UK on 27 April 2009. Since then, the virus has become much more common in both the UK and across the world, and the World Health Organization (WHO) declared a pandemic on 11 June 2009. Children have experienced pandemic influenza A(H1N1) infections at four times the rate of adults and are hospitalised more frequently.[1,2] Although most childhood disease has been mild, severe disease and deaths have occurred, mainly in those with comorbidities.[3–5] As children are also very effective transmitters of the virus,[6–8] they are a high-priority group for vaccination against pandemic influenza in many countries.[8–10]

In response to this pandemic, the WHO's Strategic Advisory Group of Experts on Immunisation (WHO-SAGE), held an extraordinary meeting on 7 July 2009 to consider the role for immunisation in the prevention of this disease.[11] The key recommendations of this report were:

- All countries should immunise their health-care workers as a first priority to protect the essential health infrastructure. As vaccines that are available initially will not be sufficient, a step-wise approach to vaccinate particular groups may be considered. WHO-SAGE suggested the following groups for consideration, noting that countries need to determine their order of priority based on country-specific conditions: pregnant women; those aged above 6 months with one of several chronic medical conditions; healthy young adults of 15–49 years of age; healthy children; healthy adults of 50–64 years of age; and healthy adults of 65 years of age and above.
- Since new technologies are involved in the production of some pandemic vaccines, which have not yet been extensively evaluated for their safety in certain population groups, it is very important to implement postmarketing surveillance of the highest possible quality. In addition, rapid sharing of the results of immunogenicity and postmarketing safety and effectiveness studies among the international community will be essential for allowing countries to make necessary adjustments to their vaccination policies.
- In view of the anticipated limited vaccine availability at a global level, and the potential need to protect against 'drifted' strains of virus, WHO-SAGE recommended that promoting production and use of vaccines, such as those that are formulated with oil-in-water adjuvants and live attenuated influenza vaccines, was important.
- As most of the production of the seasonal vaccine for the 2009–10 influenza season in the northern hemisphere is almost complete and is therefore unlikely to affect production of pandemic vaccine, WHO-SAGE did not consider that there was a need to recommend a 'switch' from seasonal to pandemic vaccine production.

The UK Department of Health provided two H1N1 vaccines for the national immunisation programme: a split-virion, egg culture-derived $AS03_B$-adjuvanted vaccine, manufactured by GlaxoSmithKline (GSK) and a non-adjuvanted Vero cell culture-derived whole-virion vaccine manufactured by Baxter.[12] Both manufacturers initially gained marketing authorisation approval from the European Medicines Agency (EMEA) for a pandemic strain vaccine under the 'mock-up' dossier route, based on limited clinical trial data for a candidate H5N1 vaccine. These vaccines were modified to cover the novel influenza AH1N1 strain.

Novel adjuvants had not been routinely used in early childhood prior to this pandemic, but were believed to provide enhanced immunogenicity, particularly in infants in whom traditional influenza vaccines have limited efficacy,[9] and potentially allow antigenic sparing and induction of cross-clade immunity.[13–15]

Although whole-virion influenza vaccines have previously been associated with unacceptable reactogenicity rates,[16] H5N1 'mock-up' whole-virion vaccines were well tolerated,[17] and these vaccines avoid problems with egg-allergic individuals.[18] Use of cell culture for manufacture was expected

to shorten production times, by avoiding the bottleneck of supply of hens' eggs.[12,19]

Although substantial safety data regarding the use of trivalent seasonal split and subunit non-adjuvanted inactivated influenza vaccines in children existed, similar safety and efficacy data for novel H1N1 vaccines were lacking.[20–23] The need for comparative immunogenicity and reactogenicity data for these two products in children was identified by the UK Scientific Advisory Group for Emergencies (UK-SAGE) as a high priority to help guide national recommendations on which to use in a paediatric population.

This study was therefore conducted to compare the immunogenicity, reactogenicity and safety of the two H1N1 vaccines in children aged 6 months to 12 years in a multicentre, open-label, randomised head-to-head trial. Immunogenicity was assessed by both the haemagglutination inhibition assay and microneutralisation assay.

Chapter 2
Methods

Vaccines

Two novel H1N1 vaccines were compared: a split-virion, $AS03_B$-adjuvanted vaccine (GSK Vaccines, Rixensart, Belgium) and a non-adjuvanted whole-virion vaccine (Baxter Vaccines, Vienna, Austria).

The split-virion adjuvanted vaccine was constructed from the influenza A/California/07/2009 (H1N1) v-like strain antigen (New York Medical College x-179A), generated by classical reassortment in eggs, combining the *HA*, *NA* and *PB1* genes of influenza A/California/07/2009 (H1N1)v to the PR8 strain backbone.[23,24] Each dose (0.25 ml, one-half of the adult dose) contained 1.875 µg of haemagglutinin antigen and the oil-in-water emulsion-based adjuvant $AS03_B$ [containing squalene (5.345 mg), DL-α-tocopherol (5.93 mg) and polysorbate 80 (2.43 mg) and thiomersal], and was supplied as suspension and emulsion in multidose vials. Opened vials were used within 24 hours but not stored overnight.

The non-adjuvanted whole-virion vaccine derived from Vero cell culture was supplied in multidose vials. Opened vials were used within 3 hours; each dose (0.5 ml) contained 7.5 µg of haemagglutinin from influenza A/California/07/2009 (H1N1).

Study design

Between 26 September and 11 December 2009, we conducted an open-label, randomised, parallel-group, phase II study at five UK sites (Oxford, Bristol, Southampton, Exeter and London) in children aged 6 months to 12 years, comparing the safety, reactogenicity and immunogenicity of two novel H1N1 vaccines in a two-dose regimen.

The study was approved by the UK Medicines and Healthcare Products Regulatory Agency (EUDRACT 2009–014719–11), the Oxfordshire Ethics Committee (09/H0604/107) and the local NHS organisations by an expedited process.[25] The study was registered at ClinicalTrials.gov, and was conducted in accordance with the principles of the Declaration of Helsinki, the standards of Good Clinical Practice (as defined by the International Conference on Harmonisation) and UK regulatory requirements.

Recruitment was by media advertising and direct mailing. Children aged 6 months to < 13 years, for whom a parent or guardian had provided written informed consent and who were able to comply with study procedures, were eligible for inclusion. In addition, verbal assent was sought from participants aged 7 years and older. Those with laboratory-confirmed pandemic H1N1 influenza or with clinically diagnosed disease meriting antiviral treatment were excluded to target an immunologically naive population. For safety reasons, those with allergy to egg or any other vaccine components and coagulation defects were excluded. Other exclusions included those with significant immunocompromise, immunosuppressive therapy, recent receipt of blood products, intent to immunise with another H1N1 vaccine, or, participation in another clinical trial. Participants were grouped into those aged 6 months to < 3 years (younger group) and 3 years to < 13 years of age (older group). Participants were randomised by study investigators (1 : 1 ratio) to receive one of the two vaccines (randomisation group stratified for age group with block sizes of 10 and concealed until immunisation by opaque envelope generated by the Health Protection Agency). Vaccines were administered by intramuscular injection (deltoid or anterior-lateral thigh, depending on age and muscle bulk) at enrolment and at day 21 (± 7) days. Sera were collected at study days 0 and 21 (–7 to +14) after second vaccination.

Safety and tolerability assessments

From days 0–7 post vaccination, parents or guardians recorded axillary temperature, injection site reactions, solicited and unsolicited systemic symptoms, and medications (including antipyretics/analgesic use) in diary cards. Primary reactogenicity end points were frequency and severity of fever, tenderness, swelling and erythema post vaccination. Secondary end points were the frequency and severity of non-febrile

solicited systemic reactions or receipt of analgesic/antipyretic medication. Solicited systemic reactions were different in those under and over 5 years of age to reflect participants' ability to articulate symptoms. Erythema and swelling were graded by diameter as mild (1–24 mm), moderate (25–29 mm) or severe (≥ 50 mm). Other reactions were graded by effect on daily activity as none, mild (transient reaction, no limitation in activity), moderate (some limitation in activity) or severe (unable to perform normal activity) or by frequency/duration into none, mild, moderate and severe categories.

Medically significant adverse events (any ongoing solicited reaction or any event necessitating a doctor's visit or study withdrawal after day 7 post vaccination) were recorded on a diary card. Monitoring of adverse events of special interest, as recommended by the EMEA,[26] was undertaken (for full details, see Appendix 1, subappendix E).

All data from case report forms and participant diary cards were double-entered and verified on computer.

Assays

Antibody responses were measured by microneutralisation and haemagglutination inhibition assays on sera using standard methods[27,28] at the Centre for Infections, Health Protection Agency (UK). Assays were performed with the egg-grown NIBRG-121 reverse-genetics virus based on influenza A/California/07/2009 and A/Puerto Rico/8/34 (see Appendix 1).

The primary immunogenicity objective was a comparison between vaccines of the percentage of participants demonstrating seroconversion by the microneutralisation assay, with seroconversion defined as a fourfold rise to a titre of ≥ 1 : 40 from prevaccination to 3 weeks post second dose. A secondary objective based on the microneutralisation assay was a comparison between vaccines of the percentage with post-second-dose titres ≥ 1 : 40. Further secondary objectives based on the haemagglutination inhibition assay were comparisons between vaccines of the percentage with fourfold rises to titres ≥ 1 : 32 post second dose, the percentage with post-second-dose titres ≥ 1 : 32, geometric mean fold rises from baseline to post second dose, and geometric mean titres post second dose.

For microneutralisation assays, the initial dilution was 1 : 10 and the final dilution was 1 : 320, unless further dilutions were necessary to determine fourfold rises from baseline. For haemagglutination inhibition assays, the initial dilution was 1 : 8 and the final dilution was 1 : 16,384. For both assays, negative samples were assigned a value of one-half of the initial dilution. Sera were processed in 1 : 2 serial dilutions in duplicate and the geometric mean of each pair used.

Statistical analysis

With 200 participants in each age and vaccine group, the study had 80% power to detect differences of –14% to 12% around a 70% reactogenicity and seroconversion rate. Planned recruitment was up to 250 participants per group to allow for dropout and non-availability of sera.

Proportions with local or systemic reactions, and with seroconversion or titres above given thresholds, were calculated for each age and vaccine group. Comparisons between vaccines were made using a two-sided Fisher's exact test. For reactions, comparisons between doses were made using the sign test for paired data.

Geometric mean haemagglutination inhibition titres and fold rises were calculated for each age and vaccine group, along with 95% confidence intervals (CIs). Logged postvaccination haemagglutination inhibition titres were compared between vaccines using normal errors regression in a univariable model and then in a multivariable model adjusting for age, study site, sex, and interval from second vaccine dose to obtaining final serum sample. The interaction between age and vaccine was also investigated.

A planned interim analysis on the reactogenicity data from the first 500 participants was performed to provide rapid data to the UK Department of Health. The study site investigators remained blinded to the results of this analysis while visits were ongoing.

Data analysis was undertaken with STATA software, version 10. The level of statistical significance was 5%. The data were analysed per protocol. As planned, no intention-to-treat analyses were conducted, as < 10% of subjects would have been classified differently in such an analysis.

Summary of protocol changes

- Version 1.1 – increased sample size to 1000 participants, clarification of the role of the Data Monitoring Committee, procedures for vaccine labelling, specification of needle size for immunisation
- Version 1.2 – addition of an interim analysis of the safety data, change in indemnity information
- Version 2 – modification of serious adverse event reporting timelines and procedures, and addition of monitoring and reporting of adverse events of special interest
- Version 3 – addition of the possibility of using a half-adult dose of vaccine if that became the recommended dose; the suggested dose for the split-virion adjuvanted vaccine in children did become half of the adult dose before the trial commenced and therefore this was used; and the recommendation remained to use a full adult dose of the whole-virion vaccine.

Chapter 3
Results

Recruitment visits were attended by 949 participants, of whom 943 were enrolled and 937 included in the per-protocol analysis (*Figure 1* and *Table 1*). Overall, 913 participants received the second vaccine dose per protocol, at a mean interval of 20 days (range 14–28 days). Sera were obtained in 827 participants (88.2%) after the second vaccine dose as per protocol, at a mean interval of 20 days (range 14–35).

Safety and tolerability

Solicited reactions are shown in *Tables 2* and *3*.

The split-virion $AS03_B$-adjuvanted vaccine was associated with more frequent severe local reactions than the whole-virion vaccine after either dose in those aged over 5 years (dose 1, 7.2% vs 1.1%, $p = < 0.001$; dose 2, 8.5% vs 1.1%,

TABLE 1 *Baseline characteristics of study subjects, according to group*

	Age of participants			
	6 months to <3 years		**3–12 years**	
Characteristic	**Split-virion $AS03_B$-adjuvanted vaccine (*n* = 210)**	**Whole-virion (*n* = 229)**	**Split-virion $AS03_B$-adjuvanted vaccine (*n* = 254)**	**Whole-virion vaccine (*n* = 244)**
Race or ethnic group (no.)				
White	189	201	231	222
Indian	0	1	0	0
Pakistani	1	0	2	1
Asian other	1	2	1	0
Mixed ethnic group	14	19	9	10
Black African	1	3	3	3
Black Caribbean	2	0	3	1
Chinese	0	0	2	2
Other	2	3	3	5
Sex (no.)				
Male	116	123	131	121
Female	94	106	123	123
Previous seasonal influenza vaccine (no.)	5	5	22	28
Age (years/months)				
Median	23 months	23 months	82 months	84 months
Range	6–35 months	6–35 months	36–151 months	36–155 months
Site in the UK				
Bristol	44	46	41	42
Exeter	16	23	24	19
Oxford	70	79	66	59
Southampton	67	58	72	80
St George's	13	23	51	44

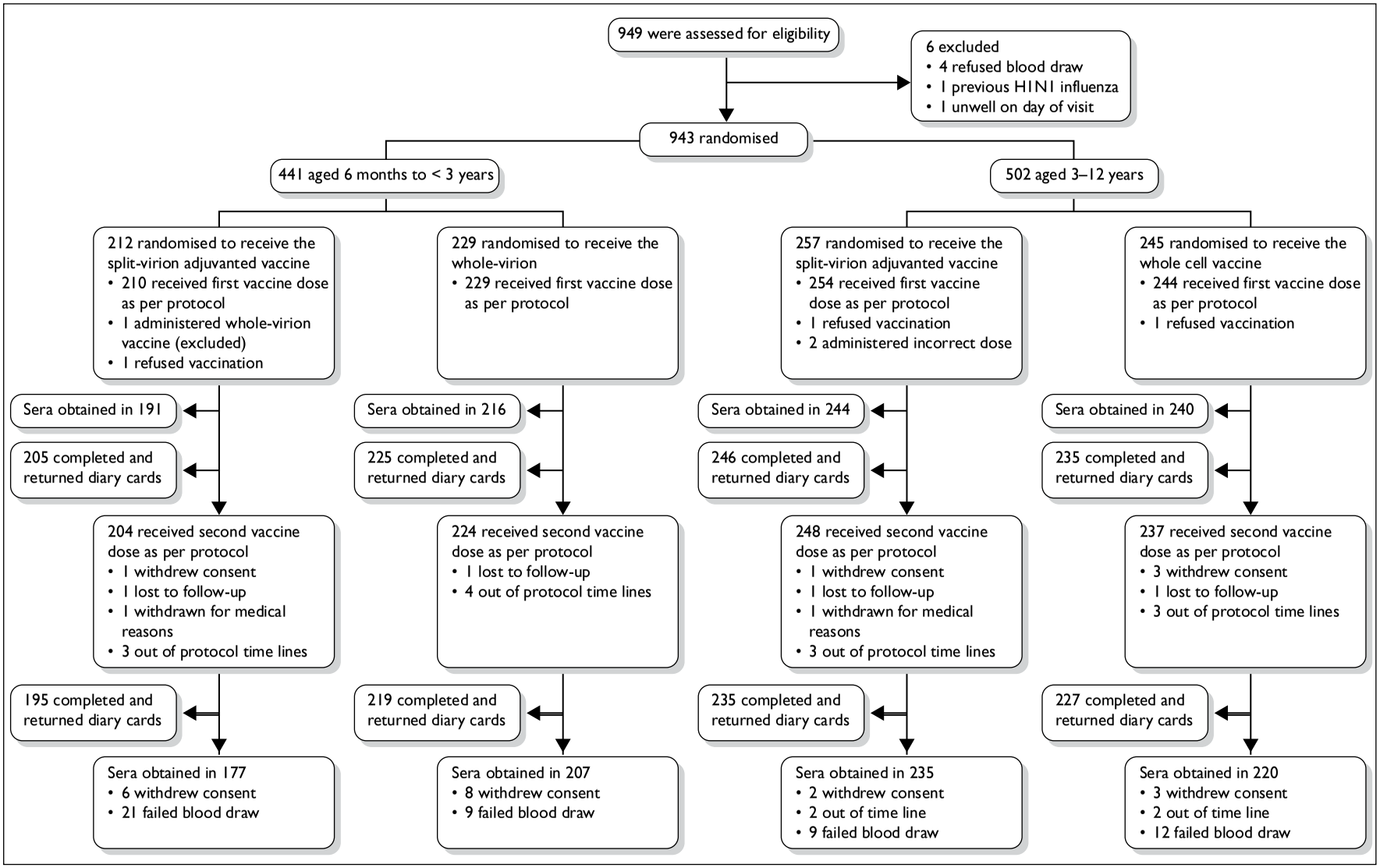

FIGURE 1 *Enrolment and follow-up of study participants.*

TABLE 2 *Local and systemic reactions in participants 6 months to < 5 years of age, by vaccine and dose*

		Vaccine			
		Split-virion AS03$_B$ adjuvanted		Whole-virion	
Measurement	**Level**	**Dose 1,[a] *n* (%)**	**Dose 2,[b] *n* (%)**	**Dose 1,[c] *n* (%)**	**Dose 2,[d] *n* (%)**
Pain	Mild	77 (28.5)	79 (31.1)	48 (17.2)	46 (17.0)
	Moderate	6 (2.2)	19 (7.5)	3 (1.1)	1 (0.4)
	Severe	2 (0.7)	2 (0.8)	0 (0)	0 (0)
	Any	85 (31.5)[e,f]	100 (39.4)[e,f]	51 (18.3)[e]	47 (17.3)[e]
Redness	1–24 mm	67 (24.8)	59 (23.2)	64 (22.9)	52 (19.2)
	25–49 mm	9 (3.3)	8 (3.1)	0 (0)	0 (0)
	≥ 50 mm	0 (0)	11 (4.3)	0 (0)	0 (0)
	Any	76 (28.1)	78 (30.7)[e]	64 (22.9)	52 (19.2)[e]
Swelling	1–24 mm	42 (15.6)	37 (14.6)	26 (9.3)	17 (6.3)
	25–49 mm	8 (3)	6 (2.4)	0 (0)	1 (0.4)
	≥ 50 mm	2 (0.7)	7 (2.8)	0 (0)	0 (0)
	Any	52 (19.3)[e]	50 (19.7)[e]	26 (9.3)[e]	18 (6.6)[e]
Any local reaction	Severe	4 (1.5)[f]	15 (5.9)[e,f]	0 (0)	0 (0)[e]
Decreased feeding	Mild	67 (24.8)	70 (27.6)	75 (26.9)	59 (21.8)
	Moderate	17 (6.3)	27 (10.6)	17 (6.1)	14 (5.2)
	Severe	5 (1.9)	6 (2.4)	2 (0.7)	8 (3)
	Any	89 (33)	103 (40.6)[e]	94 (33.7)	81 (29.9)[e]
Decreased activity	Mild	34 (12.6)	45 (17.7)	26 (9.3)	33 (12.2)
	Moderate	17 (6.3)	33 (13)	24 (8.6)	11 (4.1)
	Severe	4 (1.5)	3 (1.2)	2 (0.7)	3 (1.1)
	Any	55 (20.4)[f]	81 (31.9)[e,f]	52 (18.6)	47 (17.3)[e]
Increased irritability	Mild	89 (33)	84 (33.1)	64 (22.9)	45 (16.6)
	Moderate	28 (10.4)	34 (13.4)	28 (10)	26 (9.6)
	Severe	6 (2.2)	4 (1.6)	7 (2.5)	6 (2.2)
	Any	123 (45.6)[e]	122 (48)[e]	99(35.5)[e]	77 (28.4)[e]
Persistent crying	Mild	52 (19.3)	49 (19.3)	32 (11.5)	35 (12.9)
	Moderate	8 (3)	13 (5.1)	12 (4.3)	13 (4.8)
	Severe	1 (0.4)	1 (0.4)	2 (0.7)	1 (0.4)
	Any	61 (22.6)	63 (24.8)	46 (16.5)	49 (18.1)
Vomiting	Mild	28 (10.4)	28 (11)	29 (10.4)	26 (9.6)
	Moderate	6 (2.2)	5 (2)	3 (1.1)	3 (1.1)
	Severe	0 (0)	0 (0)	0 (0)	0 (0)
	Any	34 (12.6)	33 (13)	32 (11.5)	29 (10.7)
Diarrhoea	Mild	54 (20)	49 (19.3)	58 (20.8)	46 (17)
	Moderate	9 (3.3)	6 (2.4)	10 (3.6)	12 (4.4)
	Severe	3 (1.1)	3 (1.2)	3 (1.1)	4 (1.5)
	Any	66 (24.4)	58 (22.8)	71 (25.4)	62 (22.9)
Any symptoms	Severe	14 (5.2)	19 (7.5)	12 (4.3)	14 (5.2)
Fever	≥ 38°C	24 (8.9)[f]	57 (22.4)[e,f]	26 (9.3)	34 (12.5)[e]
GP visit for any reason	Any	14 (5.2)	14 (5.5)	11 (3.9)	16 (5.9)

continued

TABLE 2 *Local and systemic reactions in participants 6 months to < 5 years of age, by vaccine and dose (continued)*

Hospital visit for any reason	Any	1 (0.4)	0 (0)	0 (0)	1 (0.4)
Analgesic or antipyretic medication	Any	85 (31.5)[f]	111 (43.7)[e,f]	77 (27.6)	64 (23.6)[e]

a Total vaccinated, $n = 278$; diary cards available, per protocol, $n = 270$.
b Total vaccinated, $n = 275$; diary cards available, per protocol, $n = 254$.
c Total vaccinated, $n = 286$; diary cards available, per protocol, $n = 279$.
d Total vaccinated, $n = 285$; diary cards available, per protocol, $n = 271$.
e $p < 0.05$ for comparison between vaccines.
f $p < 0.05$ for comparison between doses.

TABLE 3 *Local and systemic reactions in participants 5–12 years of age by vaccine and dose*

		Split-virion AS03$_B$ adjuvanted		**Whole-virion**	
		Dose 1,[a] *n* (%)	**Dose 2,[b] *n* (%)**	**Dose 1,[c] *n* (%)**	**Dose 2,[d] *n* (%)**
Measurement	**Level**	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**
Pain	Mild	89 (49.2)	78 (44.3)	68 (37.6)	65 (37.1)
	Moderate	44 (24.3)	43 (24.4)	4 (2.2)	8 (4.6)
	Severe	3 (1.7)	4 (2.3)	0 (0)	1 (0.6)
	Any	136 (75.1)[e]	125 (71)[e]	72 (39.8)[e]	74 (42.3)[e]
Redness	1–24 mm	41 (22.7)	40 (22.7)	38 (21)	34 (19.4)
	25–49 mm	8 (4.4)	8 (4.5)	3 (1.7)	4 (2.3)
	≥ 50 mm	7 (3.9)	9 (5.1)	0 (0)	0 (0)
	Any	56 (30.9)	57 (32.4)[e]	41 (22.7)	38 (21.7)[e]
Swelling	1–24 mm	24 (13.3)	28 (15.9)	21 (11.6)	24 (13.7)
	25–49 mm	9 (5)	6 (3.4)	2 (1.1)	1 (0.6)
	≥ 50 mm	8 (4.4)	5 (2.8)	2 (1.1)	1 (0.6)
	Any	41 (22.7)[e]	39 (22.2)	25 (13.8)[e]	26 (14.9)
Any local reaction	Severe	13 (7.2)[e]	15 (8.5)[e]	2 (1.1)[e]	2 (1.1)[e]
Loss of appetite	Mild	33 (18.2)	26 (14.8)	17 (9.4)	16 (9.1)
	Moderate	5 (2.8)	5 (2.8)	2 (1.1)	3 (1.7)
	Severe	4 (2.2)	2 (1.1)	2 (1.1)	1 (0.6)
	Any	42 (23.2)[e]	33 (18.8)	21 (11.6)[e]	20 (11.4)
Generally unwell	Mild	39 (21.5)	31 (17.6)	27 (14.9)	14 (8)
	Moderate	20 (11)	13 (7.4)	16 (8.8)	12 (6.9)
	Severe	3 (1.7)	2 (1.1)	2 (1.1)	0 (0)
	Any	62 (34.3)	46 (26.1)[e]	45 (24.9)[f]	26 (14.9)[e,f]

$p = 0.002$) and after dose 2 in those under 5 years (5.9% vs 0.0%, $p < 0.001$). There were also more systemic reactions among participants 6 months to < 5 years of age with more irritability after either dose (dose 1, 45.6% vs 35.5%; dose 2, 48% vs 28.4) and, after dose 2, more decreased feeding (40.6% vs 29.9%) and decreased activity (31.9% vs 17.3%).

Participants aged over 5 years experienced more muscle pain after either dose (dose 1, 32.6% vs 13.8%; dose 2, 25% vs 12.6%) and were more often generally unwell after dose 2 (26.1% vs 14.9%).

In younger children, dose 2 of the split-virion AS03$_B$-adjuvanted vaccine was more reactogenic

		Split-virion $AS03_B$ adjuvanted		Whole-virion	
		Dose 1,[a] *n* (%)	Dose 2,[b] *n* (%)	Dose 1,[c] *n* (%)	Dose 2,[d] *n* (%)
Measurement	**Level**	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**
Headache	Mild	51 (28.2)	38 (21.6)	50 (27.6)	36 (20.6)
	Moderate	25 (13.8)	21 (11.9)	10 (5.5)	10 (5.7)
	Severe	1 (0.6)	1 (0.6)	1 (0.6)	0 (0)
	Any	77 (42.5)	60 (34.1)	61 (33.7)	46 (26.3)
Nausea/vomiting	Mild	30 (16.6)	25 (14.2)	20 (11)	15 (8.6)
	Moderate	4 (2.2)	1 (0.6)	1 (0.6)	0 (0)
	Severe	0 (0)	1 (0.6)	1 (0.6)	2 (1.1)
	Any	34 (18.8)	27 (15.3)	22 (12.2)	17 (9.7)
Diarrhoea	Mild	24 (13.3)	11 (6.3)	25 (13.8)	17 (9.7)
	Moderate	4 (2.2)	2 (1.1)	2 (1.1)	3 (1.7)
	Severe	0 (0)	1 (0.6)	0 (0)	1 (0.6)
	Any	28 (15.5)[f]	14 (8)[f]	27 (14.9)	21 (12)
Muscle pain	Mild	40 (22.1)	29 (16.5)	22 (12.2)	17 (9.7)
	Moderate	19 (10.5)	13 (7.4)	3 (1.7)	5 (2.9)
	Severe	0 (0)	2 (1.1)	0 (0)	0 (0)
	Any	59 (32.6)[e]	44 (25)[e]	25 (13.8)[e]	22 (12.6)[e]
Joint pain	Mild	17 (9.4)	15 (8.5)	19 (10.5)	13 (7.4)
	Moderate	3 (1.7)	3 (1.7)	4 (2.2)	2 (1.1)
	Severe	0 (0)	1 (0.6)	0 (0)	0 (0)
	Any	20 (11)	19 (10.8)	23 (12.7)	15 (8.6)
Any symptoms	Severe	5 (2.8)	5 (2.8)	3 (1.7)	2 (1.1)
Fever	≥ 38°C	14 (7.7)	11 (6.3)	6 (3.3)	5 (2.9)
GP visit for any reason		0 (0)	0 (0)	1 (0.6)	0 (0)
Hospital visit for any reason		66 (36.5)[e]	50 (28.4)[e]	40 (22.1)[e]	29 (16.6)[e]
Analgesic/ antipyretic medication	Any	66 (36.5)[e]	50 (28.4)[e]	40 (22.1)[e]	29 (16.6)[e]

a Total vaccinated, $n = 181$; number of diary cards available, per protocol, $n = 181$.
b Total vaccinated, $n = 188$; number of diary cards available, per protocol, $n = 176$.
c Total vaccinated, $n = 187$; number of diary cards available, per protocol, $n = 181$.
d Total vaccinated, $n = 185$; number of diary cards available, per protocol, $n = 175$.
e $p < 0.05$ for comparison between vaccines.
f $p < 0.05$ for comparison between doses.

than dose 1, with more fever ≥ 38°C (22.4% vs 8.9%, $p < 0.001$), local severe reactions (5.9% vs 1.5%, $p = 0.02$) and decreased activity (31.9% vs 20.4%, $p = < 0.001$). The second dose of the whole-virion vaccine was associated with decreased frequency of being generally unwell (14.9% vs 24.9%).

More recipients of the split-virion $AS03_B$-adjuvanted vaccine used antipyretic/analgesic medication after either dose of vaccine in the older participants (dose 1, 36.3% vs 22.1%; dose 2, 28.4% vs 16.6%) and after the second dose in younger participants (43.7% vs 23.6%, $p < 0.001$).

Adverse events

In participants receiving the split-virion adjuvanted vaccine, three adverse events of special interest occurred. One was an episode of reactive arthritis, in a participant aged 11 months, in the leg in which vaccine had been administered 2 days previously; this was considered possibly related. In brief, this participant became febrile to 39.1°C on the evening of vaccination. Two days later he was noted to be hesitant to weight bear on his right leg and was crawling unusually. Hospital review showed a well, afebrile child with a slightly erythematous and warm right knee with a reduced range of movement. There was no other obvious joint involvement and the vaccination site appeared normal. Blood tests were performed, including a C-reactive protein (1.00 mg/l) and white cell count (13.9×10^9), which were normal; throat swab and blood cultures were also taken, which showed no growth on either culture. Radiographs of both pelvis and right knee were normal. A diagnosis of reactive arthritis, possibly related to the vaccination, was made. The participant made a full recovery after 10 days. The second was a self-terminating generalised seizure 22 days post second vaccination in a participant aged 11 years 7 months with a previous history of possible seizure following head injury; this was considered unrelated to vaccination. The third was a possible seizure 20 days post second vaccination in a participant aged 12 years and 7 months, with a history of seizure following head injury; this was considered unrelated to vaccination.

In participants receiving the whole-virion vaccine, one adverse event of special interest occurred. This was a right focal seizure in a participant, aged 11 months, associated with fever, 9 days post second vaccination; this was considered unrelated to vaccination.

Five serious adverse events occurred, not in the category of adverse events of special interest and all considered unrelated to vaccination. In participants receiving the split-virion adjuvanted vaccine, these included an episode of exacerbation of asthma and an episode of tonsillitis with associated exacerbation of asthma; in participants receiving the whole-virion vaccine, these included an episode of exacerbation of asthma, a chest infection and vaccine failure with microbiologically confirmed influenza A(H1N1) 17 days post completion of vaccine course.

Immunogenicity

Prior to vaccination, 4.0% of participants (2.9% younger group, 5.0% older group) had microneutralisation titres ≥ 1 : 40, suggesting pre-existing immunity. Antibody responses are shown in *Tables 4–6* and *Figure 2*.

Seroconversion rates were higher with the split-virion $AS03_B$-adjuvanted vaccine than with the whole-virion unadjuvanted vaccine both by microneutralisation assay (younger group, 98.2% vs 80.1%, $p < 0.001$; older group, 99.1% vs 95.9%, $p = 0.03$) and haemagglutination inhibition assay (younger group, 99.4% vs 64.0%; older group, 98.7% vs 88.5%, $p = < 0.001$ for both groups). Compared with the whole-virion vaccine, the split-virion $AS03_B$-adjuvanted vaccine was associated with a higher percentage of participants with microneutralisation titres ≥ 1 : 40 (99.3% vs 88.5%, $p < 0.001$), a higher percentage with haemagglutination inhibition titre ≥ 1 : 32 (99.3% vs 78.2%, $p < 0.001$), higher geometric mean haemagglutination inhibition titres (411.0 vs 69.3) and greater geometric fold rise in haemagglutination inhibition titre from baseline (89.5 vs 15.0) ($p < 0.001$ for all comparisons). Although 95% CIs for the degree of pre-existing immunogenicity for the two groups overlapped, the 95% CIs did not overlap for post second dose immunogenicity results.

The multivariable analysis on logged haemagglutination inhibition titres showed a significant interaction between age and vaccine ($p < 0.001$), with 10.5-fold (95% CI 8.1 to 13.5) higher titres induced by the split-virion $AS03_B$-adjuvanted vaccine in the younger participants compared with 3.6-fold (95% CI 3.0 to 4.3) higher titres in older children. This difference in the age effect by vaccine was further evaluated by including age as a continuous variable in the multivariable model, which showed a 3% decrease in titre per year of age (95% CI 0.5 to 5, $p = 0.02$) for the split-virion adjuvanted vaccine and a 16% increase per year (95% CI 12 to 21, $p < 0.001$) for the whole-virion vaccine.

TABLE 4 *Seroconversion by microneutralisation titre*

		Pre-vaccine		Post second dose		Fold rise	
Vaccine	**Age**	***n/N***	**% MN ≥ 1 : 40 (95% CI)**	***n/N***	**% MN ≥ 1 : 40 (95% CI)**	***n/N***	**% ≥ fourfold to ≥ 1 : 40 (95% CI)**
Whole-virion	< 3 years	9/216	4.2 (1.9–7.8)	166/206	80.6 (74.5–85.8)	157/196	80.1 (73.8–85.5)
	3–12 years	11/240	4.6 (2.3–8.1)	211/220	95.9 (92.4–98.1)	208/217	95.9 (92.4–98.1)
	All	20/456	4.4 (2.7–6.7)	377/426	88.5 (85.1–91.3)	365/413	88.4 (84.9–91.3)
Split-virion, $AS03_B$-adjuvanted	< 3 years	3/191	1.6 (0.3–4.5)	175/177	98.9 (96.0–99.9)	163/166	98.2 (94.8–99.6)
	3–12 years	13/244	5.3 (2.9–8.9)	234/235	99.6 (97.7–99.9)	226/228	99.1 (96.9–99.9)
	All	16/435	3.7 (2.1–5.9)	409/412	99.3 (97.9–99.8)	389/394	98.7 (97.1–99.6)

MN, microneutralisation.

TABLE 5 *Seroconversion by haemagglutination inhibition titre*

		Pre-vaccine		Post second dose		Fold rise	
Vaccine	**Age**	***n/N***	**% HI ≥ 1 : 32 (95% CI)**	***n/N***	**% HI ≥ 1 : 32 (95% CI)**	***n/N***	**% ≥ fourfold to ≥ 1 : 32 (95% CI)**
Whole-virion	< 3 years	8/216	3.7 (1.6–7.2)	136/207	65.7 (58.8–72.1)	126/197	64.0 (56.8–70.7)
	3–12 years	7/240	2.9 (1.2–5.9)	198/220	90.0 (85.3–93.6)	192/217	88.5 (83.5–92.4)
	All	15/456	3.3 (1.9–5.4)	334/427	78.2 (74.0–82.0)	318/414	76.8 (72.4–80.8)
Split-virion, $AS03_B$-adjuvanted	< 3 years	3/191	1.6 (0.3–4.5)	174/175	99.4 (96.9–99.9)	163/164	99.4 (96.6–99.9)
	3–12 years	13/244	5.3 (2.9–8.9)	233/235	99.1 (97.0–99.9)	225/228	98.7 (96.2–99.7)
	All	16/435	3.7 (2.1–5.9)	407/410	99.3 (97.9–99.8)	388/392	99.0 (97.4–99.7)

HI, haemagglutination inhibition.

TABLE 6 *Haemagglutination inhibition geometric mean titres*

		Pre-vaccine		Post second dose		Fold rise	
Vaccine	**Age**	***n***	**GMT (95% CI)**	***n***	**GMT (95% CI)**	***n***	**GMT (95% CI)**
Whole-virion	< 3 years	216	4.6 (4.2–5.1)	207	44.0 (35.6–54.3)	197	9.5 (7.8–11.6)
	3–12 years	240	4.6 (4.2–4.9)	220	106.3 (90.2–125.3)	217	22.7 (19.3–26.8)
	All	456	4.6 (4.3–4.9)	427	69.3 (60.3–79.6)	414	15.0 (13.2–17.2)
Split-virion, $AS03_B$-adjuvanted	< 3 years	191	4.2 (4.0–4.5)	175	461.0 (409.0–519.6)	164	107.4 (93.9–122.9)
	3–12 years	244	4.8 (4.3–5.3)	235	377.3 (339.2–419.7)	228	78.5 (69.9–88.1)
	All	435	4.5 (4.3–4.8)	410	411.0 (379.4–445.2)	392	89.5 (81.9–97.8)

GMT, geometric mean titre.

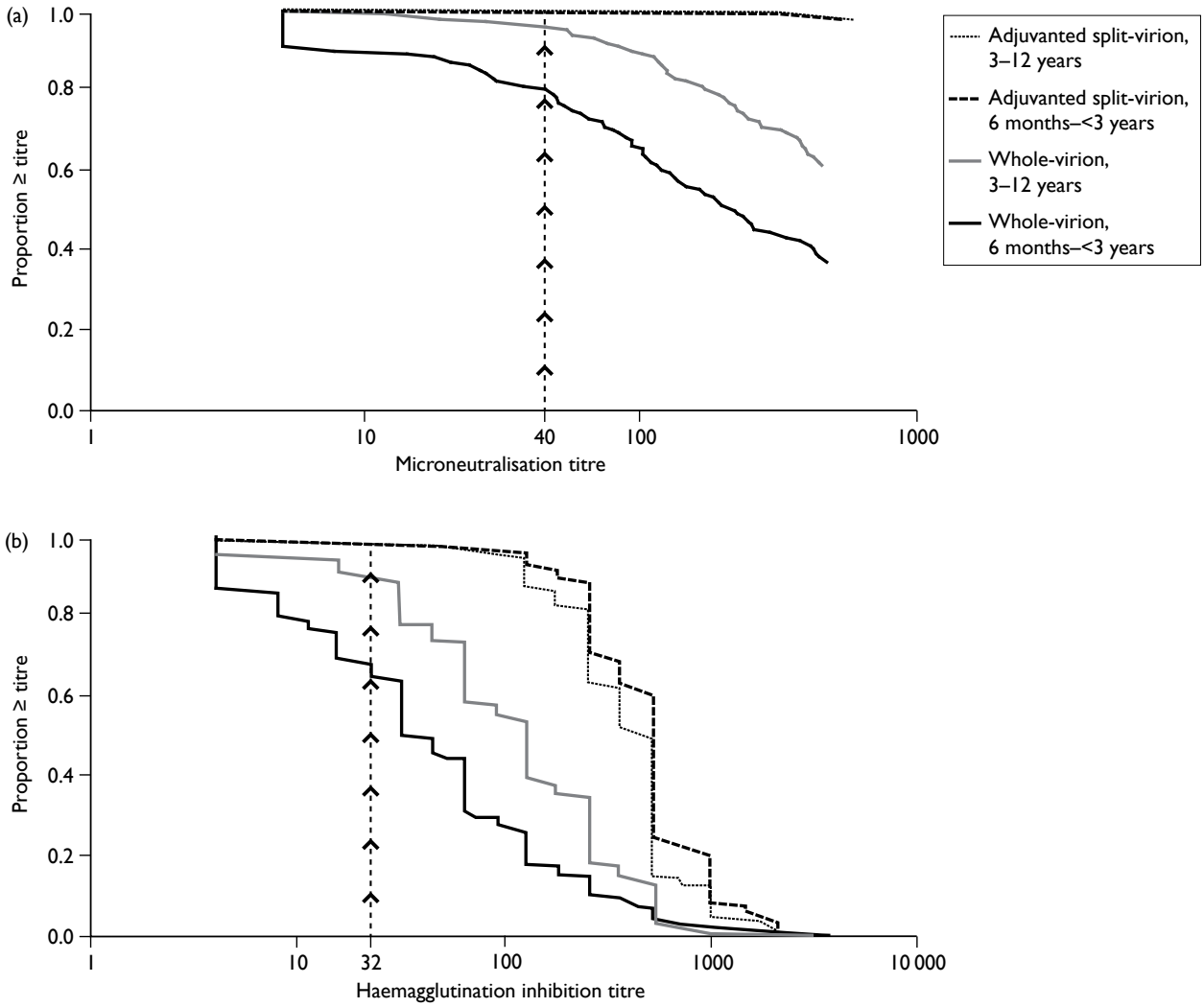

FIGURE 2 *Reverse cumulative distribution curves of antibody titres as measured by microneutralisation curves and haemagglutination inhibition assays by age group and vaccine. Arrows indicate seroprotection thresholds.*

Chapter 4
Discussion

This is the first paediatric head-to-head study of the GSK split-virion $AS03_B$-adjuvanted H1N1 pandemic vaccine and the Baxter whole-virion non-adjuvanted vaccine. The vaccine containing the novel adjuvant was more immunogenic than the whole-virion vaccine, especially in young children, but was also more reactogenic. Children with comorbidities are at increased risk of severe H1N1 disease, and for this reason we did not exclude children with pre-existing medical conditions (except immunodeficiency), making our findings relevant to the general paediatric population. A UK vaccination programme, principally using the adjuvanted split-virion vaccine[29] was announced in August 2009, initially targeting those with comorbidities,[30] but the programme was widened to all children aged 6 months to 5 years in December 2009 following a review of interim data from this study and other data.[29]

The haemagglutination inhibition assay is used extensively in the serological assessment of immunity to influenza viruses and as licensure criteria.[27,31–33] However, the haemagglutination inhibition assay measures only antibody directed to the receptor binding site, whereas the microneutralisation assay may be more sensitive, as it detects antibody directed at this and other antigenic sites in the virus,[31,34,35] and was therefore chosen as the primary immunogenicity end point.

Only 3.5% of participants had prevaccination antibody levels ≥ 1 : 32 by haemagglutination inhibition, suggestive of prior infection with the pandemic strain H1N1.[1] This was lower than that found in a recent serosurvey in England, which was conducted after the first wave, and may reflect geographical differences in exposure risk.[1] Moreover, we excluded children with a history of confirmed H1N1 disease or who had been treated for suspected infection. Follow-up took place during the second wave of the UK pandemic, but any boosting effect of natural infection would be expected to be similar between vaccine groups.

An important finding of this study was that the whole-virion vaccine showed a strong age-dependent response, with a 16% increase in immunogenicity per year with age. Similarly, the immunogenicity of both seasonal influenza vaccines[16] and other non-adjuvanted H1N1 vaccines[22] in young children is less than in older children and adults. New-generation adjuvants (such as MF59 and $AS03_B$) have been used to improve immunogenicity[13,14,35] and in *this study* the split-virion adjuvanted vaccine was highly immunogenic, even in young children, but was slightly less immunogenic in older children than in infants (3% per year with age), a pattern not previously described for inactivated vaccines.

Other H1N1 vaccines, including both adjuvanted and non-adjuvanted vaccines, are immunogenic in children but contain considerably more antigen than the split-virion adjuvanted vaccine used in this trial.[21,36,37] Antigen sparing is important in a pandemic setting where vaccine requirements exceed manufacturing capability.[38] Pre-pandemic H5N1 vaccine trials demonstrated the need for a two-dose regimen in immunologically naive individuals,[24] and two-dose regimens of several H1N1 vaccines are more immunogenic than single-dose regimens.[21,22,36] However, limited data have suggested that a single-dose regimen of the split-virion $AS03_B$-adjuvanted vaccine used in this trial may be sufficient to meet licensing criteria,[23,24] and the UK has recently recommended a single-dose regimen in healthy children.[29] When we were designing this study, a two-dose pandemic vaccine schedule was planned for children, and for this reason our pragmatic trial did not include a blood test after one dose to simplify the study in the face of the need for rapid recruitment. With the subsequent change to a single-dose regimen in the UK, our results would have been strengthened by addition of assessment of immunogenicity after a single dose. Furthermore, a comparison with a non-adjuvanted split-virion vaccine would be of interest but none was used in the UK during the 2009 H1N1 pandemic, and we limited the study to these two novel vaccines.

Even during interpandemic periods, children experience significant morbidity and mortality from influenza infection, and their role in virus transmission results in a much wider burden.[16] The favourable immunogenicity and reactogenicity

of the split-virion $AS03_B$-adjuvanted vaccine demonstrated in this study suggest that novel adjuvants may also have a role in seasonal influenza vaccines.

Whole-virion influenza vaccines have previously been associated with high reactogenicity rates.[16] This study provides the first data showing that a whole-virion H1N1 vaccine in children was well tolerated. Increased reactogenicity was seen with an MF59-adjuvanted H1N1 vaccine in children,[37] as well as in adult trials of oil-in-water adjuvanted vaccines.[13–15,23,35] The $AS03_B$-adjuvanted vaccine in this trial was similarly associated with more local reactions, and some increase in systemic reactions, compared with the whole-virion vaccine. The higher reactogenicity observed with the split-virion adjuvanted vaccine may influence parental uptake of the vaccine. No data on the parental feelings on the tolerability were collected, so the likely effective of this cannot be assessed. Our observed local and systemic reactogenicity rates were generally in keeping with data in the *Summary of Product Characteristics*.[23,24] However, although we found the rate of fever to be slightly higher in infants after the second dose compared to the first, these are one-half of the reported rate (43.1% of 51 infants).[24]

Chapter 5
Conclusions

This is the first direct comparison of two commercially available novel H1N1 vaccines. The split-virion AS03$_B$-adjuvanted vaccine was more immunogenic and induced high seroconversion rates in young children. These data provide important information to guide immunisation policy in an influenza pandemic and indicate the potential for improved immunogenicity of seasonal influenza vaccines in children.

Implications for health care, recommendations for research

Further studies evaluating the breadth and duration of the immune response to single- and two-dose regimens are needed, in particular the persistence of antibody and the degree of cross-clade protection. Our observation that the split-virion adjuvanted vaccine was slightly less immunogenic in older children than in infants (3% per year with age) is a pattern that is not previously described for inactivated vaccines. Further research is needed to see if this is a consistent finding with adjuvant use, and, if so, what the underlying mechanisms are. The role of adjuvants in seasonal influenza vaccines to provide enhanced immunogenicity in infants is also needed.

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Appendix 1

Protocol, version 3, dated 25 September 2009

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Study Title: Open Label, Randomized, Parallel-Group, Multi-Centre Study to Evaluate the Safety, Tolerability and Immunogenicity of Baxter H1N1 vaccine and GlaxoSmithKline H1N1 vaccine in children 6 months to 12 years of age.

Internal Reference No: 2009/08 H1N1

Ethics Ref: 09 H0604/107

EudraCT Number: 2009-014719-11

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1. SYNOPSIS

Study Title	**Open Label, Randomized, Parallel-Group, Multi-Centre Study to Evaluate the Safety, Tolerability and Immunogenicity of Baxter H1N1 vaccine and GlaxoSmithKline H1N1 vaccine in children 6 months to 12 years of age.**
Internal ref. no.	2009/08 H1N1
Clinical Phase	Phase II
Trial Design	Open Label, Randomised
Trial Participants	Children aged 6 months to 12 years
Planned Sample Size	1000 participants
Follow-up duration	6 to 8 weeks
Planned Trial Period	12 weeks (for study visits)
Primary Objective	Immunogenicity • To compare the percentage of children aged 6 months to 12 years of age with a four fold rise in microneutralisation (MN) titres between the pre-vaccination sample and the sample taken three weeks after completion of a two dose course of the Baxter H1N1 vaccine and the GSK H1N1 vaccine. Reactogenicity • To compare the percentage of children aged 6 months to 12 years of age experiencing fever and local reactions within the seven days following each dose of the Baxter and GSK H1N1 vaccine
Secondary Objectives	• To compare the percentage of children aged 6 months to 12 years of age with haemagglutination inhibition (HAI) titres of ≥ 1:32 three weeks after completion of a two dose course of the Baxter H1N1 vaccine and the GSK H1N1 vaccine. • To compare the percentage of children aged 6 months

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	to 12 years of age with a four fold rise in HAI titres between the pre-vaccination sample and the sample taken three weeks after completion of a two dose course of the Baxter H1N1 vaccine and the GSK H1N1 vaccine. • To determine the geometric mean fold rises in HAI titres from baseline to three weeks after 2 doses of the Baxter H1N1 vaccine and the GSK H1N1 vaccine. • To determine the geometric mean fold rises in MN titres from baseline to three weeks after 2 doses of the Baxter H1N1 vaccine and the GSK H1N1 vaccine. • To determine the geometric mean HAI and MN titres three weeks after 2 doses of the Baxter H1N1 vaccine and the GSK H1N1 vaccine. • To assess the percentage of children aged 6 months to 12 years of age experiencing non-febrile systemic reactions within the seven days following each dose of the Baxter and GSK H1N1 vaccine • To investigate the effect of genetic polymorphisms on the immunogenicity and reactogenicity of the H1N1 vaccines in a given individual.
Primary Endpoint	Primary end points for the immunogenicity analysis will be defined as: • The percentage of children aged 6 months to 12 years of age with a four fold rise in microneutralisation (MN) titres between the pre-vaccination sample and the sample taken three weeks after completion of a two dose course of the Baxter H1N1 vaccine and the GSK H1N1 vaccine. Primary endpoints for reactogenicity analysis

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	• Percentage of participants experiencing each of fever (≥ 38°C per axilla), local tenderness, local swelling or local erythema within the 7 days following each immunisation with the study vaccines
Secondary Endpoints	• Percentage of subjects with an HAI titre ≥ 1 in 32 • The percentage of children aged 6 months to 12 years of age with a four fold rise in HAI titres between the pre-vaccination sample and the sample taken three weeks after completion of a two dose course of the Baxter H1N1 vaccine and the GSK H1N1 vaccine. • The geometric mean fold rises in HAI titres from baseline to three weeks after 2 doses of the Baxter H1N1 vaccine and the GSK H1N1 vaccine. • The geometric mean fold rises in MN titres from baseline to after three weeks after 2 doses of the Baxter H1N1 vaccine and the GSK H1N1 vaccine. • The geometric mean HAI and MN titres three weeks after 2 doses of the Baxter H1N1 vaccine and the GSK H1N1 vaccine. • Percentage of participants experiencing each of: reduced feeding, reduced activity, irritability, persistent crying, vomiting or diarrhoea, receiving medication for pain or temperature (6 month to 5 year olds). • Percentage of participants experiencing each of: malaise, headache, nausea/ vomiting, diarrhoea, reduced appetite, muscle pain or joint pain, receiving analgesic/ antipyretic medication (5 to 12 year olds). • The effect of genetic polymorphisms on the immunogenicity and reactogenicity of the H1N1 vaccines.
Investigational	Baxter Novel Influenza A H1N1 Whole Virus Vaccine

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Medicinal Products	(Celvapan) GlaxoSmithKline Novel Influenza A H1N1 Split Virion Vaccine (Pandemrix)

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2. ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
CFI	Centre for Infections
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CT	Clinical Trials
CTA	Clinical Trials Authorisation
CTRG	Clinical Trials & Research Governance, University of Oxford
EMEA	European Medicines Agency
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
GP	General Practitioner
HAI	Haemaglutination Inhibition
HPA	Health Protection Agency
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
IMP	Investigational Medicinal Product
IRB	Independent Review Board
MHRA	Medicines and Healthcare products Regulatory Agency
MN	Microneutralisation
NRES	National Research Ethics Service
OVG	Oxford Vaccine Group

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PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
RVU	Respiratory Virus Unit
SAE	Serious Adverse Event
SAGE	Strategic Advisory Group of Experts on Immunisation
SAR	Serious Adverse Reaction
SMPC	Summary of Medicinal Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File
TSG	Oxford Radcliffe Hospitals Trust / University of Oxford Trials Safety Group
VRD	Virus Reference Department
WHO	World Health Organisation

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3. BACKGROUND AND RATIONALE

Two manufacturers, Baxter and GlaxoSmithKline, have gained marketing authorisation approval from the EMEA for a pandemic strain vaccine under the "mock-up" dossier route based on limited clinical trial data for a candidate H5N1 vaccine. These vaccines have now been modified to cover the novel influenza A H1N1 strain. The proposed study aims to assess the safety and immunogenicity of these two H1N1 vaccines when administered as two doses three weeks apart to children aged 6 months to 12 years of age.

The first illness caused by a new influenza A virus was confirmed in the United Kingdom on 27 April 2009. Since then the virus has become much more common in both the UK and across the world, and the World Health Organization (WHO) declared a pandemic on 11 June 2009. Internationally, human infections with the new virus have occurred in 120 countries including the UK (WHO). There have been more than 77,000 laboratory confirmed cases and 332 deaths globally. The actual number of cases of people infected with the new virus is likely to be much higher than these numbers suggest, as most cases are not tested. There have been 11,159 laboratory confirmed cases of new influenza A H1N1v in the United Kingdom, and 840 hospitalisations as of the 23rd July 2009[1].

In response to this pandemic the WHO's Strategic Advisory Group of Experts on Immunisation (SAGE), held an extraordinary meeting on 7th July 2009 to consider the role for immunisation in the prevention of this disease[2]. The full report is included as appendix A of this protocol, however the key recommendations were

- All countries should immunize their health-care workers as a first priority to protect the essential health infrastructure. As vaccines available initially will not be sufficient, a step-wise approach to vaccinate particular groups may be considered. SAGE suggested the following groups for consideration, noting that countries need to determine their order of priority based on country-specific conditions: pregnant women; those aged above 6 months with one of several chronic medical conditions; healthy young adults of 15 to 49 years of age; healthy children; healthy adults of 50 to 64 years of age; and healthy adults of 65 years of age and above.
- Since new technologies are involved in the production of some pandemic vaccines, which have not yet been extensively evaluated for their safety in certain population groups, it is very important to implement post-marketing surveillance of the highest possible quality. In addition, rapid sharing of the results of immunogenicity and

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post-marketing safety and effectiveness studies among the international community will be essential for allowing countries to make necessary adjustments to their vaccination policies.

- In view of the anticipated limited vaccine availability at global level and the potential need to protect against "drifted" strains of virus, SAGE recommended that promoting production and use of vaccines such as those that are formulated with oil-in-water adjuvants and live attenuated influenza vaccines was important.
- As most of the production of the seasonal vaccine for the 2009-2010 influenza season in the northern hemisphere is almost complete and is therefore unlikely to affect production of pandemic vaccine, SAGE did not consider that there was a need to recommend a "switch" from seasonal to pandemic vaccine production.

As children are recognised as being a high risk group for pandemic influenza, it is imperative to conduct a study comparing the immunogenicity and reactogenicity of the two vaccines likely to be available for use in the UK.

One vaccine, Celvapan, (manufactured by Baxter Vaccines) is a whole virus unadjuvanted vaccine, and the other, Pandemrix, (from GlaxoSmithKline vaccines (GSK)) is a split virion vaccine adjuvanted with an oil in water emulsion (ASO3) containing Squalene, Vitamin E- as immunostimulant and Tween 80 as surfactant. Both manufacturers have gained marketing authorisation approval from the EMEA for a pandemic strain vaccine under the “mock-up” dossier route based on limited clinical trial data for a candidate H5N1 vaccine. As the influenza strain on which these vaccines are based has changed from H5N1 to H1N1, vaccine manufacturers have had to apply for a ‘variation’ to the marketing authorisation for these vaccines. There are however limited data on safety and immunogenicity in children.

Previous studies have suggested that whole virus vaccine may be better at inducing a protective immune response in children following a single dose than a subunit or split virion vaccine. Reactogenicity may also vary between the two vaccines. There are, however, limited data on the immunogenicity and reactogenicity of these vaccines in a paediatric population, particularly in children under 3 years of age. The need for comparative immunogenicity and reactogenicity data for these two products in children has therefore been identified by the UK Scientific Advisory Group for Emergencies (SAGE) as a high priority to help guide national recommendations on which to use in a paediatric population.

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Information that is available on the immunogenicity and reactogenicity of the H5N1 version of the GSK pandemic influenza vaccine in children between the ages of 3 and 9 years suggests that initial seroconversion rates following immunisation with 2 doses of a half adult dose of vaccine (0.25 mL) are comparable to those observed after immunisation with 2 doses of the full 'adult' dose (0.5mL). As fever rates were higher in the full dose than half dose group (for 3 to 5 year olds 36% versus 16%, respectively, had temperatures above 37.5 °C), consideration has been given to using the half dose of GSK vaccine in this study. However it has been decided to use a full dose in all age groups. This decision has been made on the basis of:

- evidence that in the 3 to 5 year age group the full dose of the H5N1 vaccine resulted in better persistence of protective antibodies to 6 months post-immunisation than the half dose
- evidence that the full dose also provides better cross-protection against antigenically drifted versions of the H5N1 vaccine than the half dose
- the suggestion that the higher fever rates were predominantly seen in the 6 to 9 year old age groups rather than the 3 to 5 year old age groups, suggesting that this may be more of a feature with increasing, rather than decreasing, age
- advice from the Department of Health that, based on the above evidence, they would anticipate using a full dose of Pandemrix in all age groups in the event of mass immunisation of children against 'swine flu', as this would be more likely to protect against a 'second wave' of pandemic influenza with an antigenically drifted virus. Therefore evidence on the full dose of vaccine would be most relevant to immunisation policy.

If, however, it became apparent prior to the start of this study that a half dose of either vaccine were to be recommended for routine use in children, then we would use a half dose of the relevant vaccine in this study.

Cases of Guillian-Barré syndrome, characterised by symmetric paralysis, have previously been attributed to influenza vaccination. The possible association with the influenza vaccine was initially suggested following the 1976-1977 A/ New Jersey (Swine 'flu) season, when relative risks between 4.0 and 7.6 in the 6 or 8 week period post vaccination were seen. Variation in the number of cases of Guillian-Barré syndrome from year to year and season to season are well recognised. An extensive study of all cases of Guillian-Barré syndrome recorded on the General Practice Research Database (total cases 989) in the period 1990-

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2005 found no association of Guillian-Barré syndrome with influenza vaccination. In the 90 day period after vaccination the relative risk of Guillian-Barré syndrome was calculated as 0.76. This is in contrast to the relative risk following an influenza-like illness, calculated at 7.35. The occurrence of Guillian-Barré syndrome related to vaccination as part of this study is considered very unlikely and indeed the vaccine may well protect against Guillian-Barré syndrome by preventing influenza itself.

This study aims to compare the immunogenicity, reactogenicity and safety of the two H1N1 vaccines in children aged 6 months to 12 years in a multi centre, open label, randomised head to head trial. Immunogenicity will be assessed by both Haemagglutination inhibition and microneutralisation. Although EMEA guidelines for licensure of influenza vaccine are based on HAI assays, the primary objective for this study is to determine the percentage of subjects with seroconversions (i.e., fourfold or greater increases in antibody titre) by MN, while determination of the proportion of subjects which show seroconversion by HI will be a secondary objective. The decision for the preference of MN titres over HI titres was made based on recently published observations by CDC[3] and results from the Health Protection Agency's own analysis, which showed that the MN assay generally yields higher titres and detected more seroconversions (i.e., fourfold or greater increases in antibody titres) to A/California/04/2009 than the HI assay (although both generally show high correlation).

In addition to the collection of serum samples for analysis of vaccine immunogenicity, with specific consent the cellular 'plug' remaining after centrifugation from participants in Oxford, London, and Southampton will be stored and sent (as applicable) to the Oxford Vaccine Group for DNA extraction. The DNA samples obtained in this study can then contribute to a DNA bank pooling samples from multiple different Oxford Vaccine Group studies. These DNA samples can be used for genome wide analysis of the genetic factors influencing the host response (immunogenicity and reactogenicity) to the vaccines received in the relevant studies. This DNA extraction and storage will only occur with the specific consent of participants, and DNA will not be analysed for any other purpose than to assess factors influencing the response to vaccines. Funding for the DNA analysis is independent to funding for this influenza immunogenicity and reactogenicity study. Similarly, where appropriate consent is given by Bristol and Exeter participants, genetic samples will be stored in the Bristol Research in Infection & Immunity Collaboration Tissue Bank and aliquots made available for genetic analysis relating to this and potentially other future studies.

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With appropriate consent, serum samples remaining after the analyses required for this study will be stored for use in future infection and immunity related research studies at the relevant study sites.

4. OBJECTIVES

4.1 Primary Objective

Immunogenicity

- To compare the percentage of children aged 6 months to 12 years of age with a four fold rise in microneutralisation (MN) titres between the pre-vaccination sample and the sample taken three weeks after completion of a two dose course of the Baxter H1N1 vaccine and the GSK H1N1 vaccine.

Reactogenicity

- To compare the percentage of children aged 6 months to 12 years of age experiencing fever and local reactions within the seven days following each dose of the Baxter and GSK H1N1 vaccine

4.2 Secondary Objectives

- To compare the percentage of children aged 6 months to 12 years of age with Haemagglutination Inhibition (HAI) titres of ≥ 1:32 three weeks after completion of a two dose course of the Baxter H1N1 vaccine and the GSK H1N1 vaccine.
- To compare the percentage of children aged 6 months to 12 years of age with a four fold rise in HAI titres between the pre-vaccination sample and the sample taken three weeks after completion of a two dose course of the Baxter H1N1 vaccine and the GSK H1N1 vaccine.
- The geometric mean fold rise in HAI titres from baseline to three weeks after 2 doses of the Baxter H1N1 vaccine and the GSK H1N1 vaccine.
- The geometric mean fold rise in MN titres from baseline to three weeks after 2 doses of the Baxter H1N1 vaccine and the GSK H1N1 vaccine.

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- The geometric mean HAI and MN titres three weeks after 2 doses of the Baxter H1N1 vaccine and the GSK H1N1 vaccine.
- To assess the percentage of children aged 6 months to 12 years of age experiencing non-febrile systemic reactions within the seven days following each dose of the Baxter and GSK H1N1 vaccine
- To investigate the effect of genetic polymorphisms on the immunogenicity and reactogenicity of the H1N1 vaccines in a given individual.

5. TRIAL DESIGN

5.1 Summary of Trial Design

This is a multi centre, open-label, randomised, controlled study in 1000 children aged 6 months to 12 years.

A summary of the trial can be seen in table one:

Table One: Trial summary

	Day 0	Day 21 (3 weeks)	Day 42 (6 weeks)
Group A1 (N~250) 6mths - <3 yrs Baxter vaccine	Vaccination 1 Blood A	Vaccination 2	 Blood B
Group B1 (N~250) 6mths - <3 yrs GSK vaccine	Vaccination 1 Blood A	Vaccination 2	 Blood B
Group A2 (N~250) ≥3 yrs – 12 yrs Baxter vaccine	Vaccination 1 Blood A	Vaccination 2	 Blood B
Group B2 (N~250) ≥3 yrs – 12 yrs	Vaccination 1	Vaccination 2	

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GSK vaccine	Blood A		Blood B

5.2 Study Procedures

It is predicted that 1000 total participants will be recruited across the UK, 500 in each of 2 age categories (6 months to <3 years and ≥3 years to 12 years). 250 participants within each age group will be randomly allocated to receive two doses of either the Baxter vaccine or the GlaxoSmithKline vaccine. A baseline blood test will be taken at enrolment and a further blood test at 6 weeks (3 weeks after the second vaccine dose) to determine immunogenicity of the vaccine. A diary card detailing local and systemic effects of the vaccine and any AEs, medications used to treat these AEs and SAEs will be completed by parents/ guardians for the first week after each immunisation, as will a memory aid card used to record solicited adverse events persisting after the first week following immunisation and any medically significant adverse events occurring

5.3 Primary and Secondary Endpoints/Outcome Measures

Primary end points for the immunogenicity analysis will be defined as:

- Percentage of subjects with a 4 fold rise in MN titre between the pre-vaccination sample and sample taken 3 weeks after the second dose

Primary endpoints for reactogenicity analysis

- Percentage of participants experiencing each of fever (≥ 38°C per axilla), local tenderness, local swelling or local erythema within the 7 days following each immunisation with the study vaccines

Secondary endpoints:

- Percentage of subjects with an HAI titre ≥ 1 in 32
- Percentage of subjects with a 4 fold rise in HAI titre between the pre-vaccination sample and sample taken 3 weeks after the second dose
- The geometric mean fold rises in HAI titres from baseline to after three weeks after 2 doses of the Baxter H1N1 vaccine and the GSK H1N1 vaccine.
- The geometric mean fold rises in MN titres from baseline to three weeks after 2 doses of the Baxter H1N1 vaccine and the GSK H1N1 vaccine.

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- The geometric mean HAI and MN titres three weeks after 2 doses of the Baxter H1N1 vaccine and the GSK H1N1 vaccine.
- Percentage of participants experiencing each of: reduced feeding, reduced activity, irritability, persistent crying, vomiting or diarrhoea, receiving medication for pain or temperature (6 month to 5 year olds).
- Percentage of participants experiencing each of: malaise, headache, nausea/ vomiting, diarrhoea, reduced appetite, muscle pain or joint pain, receiving analgesic/ antipyretic medication (5 to 12 year olds).
- The effect of genetic polymorphisms on the immunogenicity and reactogenicity of the H1N1 vaccines.

5.4 Trial Participants

5.4.1 Overall Description of Trial Participants

We intend to recruit 1000 total participants from across the UK, 500 in each of 2 age categories, 6 months to <3 years (i.e. to day before 3rd birthday) and ≥ 3 years to 12 years. 250 participants within each age group will be randomly allocated to receive the Baxter vaccine and 250 the GSK vaccine.

5.4.2 Inclusion Criteria

The participant must satisfy all the following criteria to be eligible for the study:

- baby or child aged between 6 months to 12 years of age (i.e. to day before 13th birthday).
- for whom a parent/legal guardian has given written informed consent after the nature of the study has been explained;
- available for all the visits scheduled in the study
- willingness to complete all study procedures

5.4.3 Exclusion Criteria

The potential participants may not enter the study if ANY of the following apply:

- History of any vaccine against novel influenza A strain H1N1 (based on verbal confirmation from parent/guardian);

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- Previous laboratory confirmed case of novel influenza A strain H1N1 or treatment with oseltamivir or zanamivir for novel influenza A strain H1N1 (n.b. a child commenced on treatment with oseltamivir or zanamivir for novel influenza A strain H1N1 whose treatment was stopped following negative microbiological tests for H1N1 on nasals swabs would be allowed to enrol in the study].
- History of severe allergic reaction after previous vaccinations or hypersensitivity to any H1N1 vaccine component;
- Current egg allergy
- Known or suspected impairment/alteration of the immune system
- Disorders of coagulation
- Immunosuppressive therapy, use of systemic corticosteroids for more than 1 week within the 3 months prior to enrolment
- Receipt of blood, blood products and/or plasma derivatives or any immunoglobulin preparation within 3 months prior to enrolment;
- Intent to immunize with any other vaccine(s) against novel influenza A strain H1N1 throughout the study period;
- Participation in another clinical trial of an investigational medical product
- Any condition which, in the opinion of the investigator, might interfere with the evaluation of the study objectives. Children with chronic, stable medical illnesses that do not result in immunosuppression (e.g. cerebral palsy, epilepsy, cystic fibrosis, congenital heart disease) will be allowed to participate in the study, unless these conditions will in some way interfere with the completion of study procedures. Children with conditions that may alter the immune response to vaccines (e.g. Trisomy 21) or will affect the ability to accurately describe adverse events (e.g. children over 5 years of age but with severe learning difficulties) will be excluded.

5.4.4 Temporary Exclusion Criteria

- Participants who have experienced fever (>38.0°C) within the previous 24 hours.
- Participants receiving another immunisation within 3 days prior to enrolment (21 days for any live vaccine), or planning to receive another vaccine within 7 days of enrolment.

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5.5 Expenses and Benefits

All participants will be reimbursed £10 for each study visit to cover travel expenses. These payments will be provided to participants at the conclusion of the third and final study visit (or following the scheduled date for this visit if this were not to be completed).

5.6 Study Procedures

5.6.1 Recruitment and pre screening

In order to recruit the required cohort of 1000 participants, several strategies may be employed:

Direct mail-out: This will involve obtaining names and addresses of children via the Child Health Computer database or sending information home from schools with other school mailings.

Direct email and web newsletter advertising via local school parent email databases

Direct email and web newsletter advertising the study in Hospitals and Universities in participating regions

Radio and local newspaper advertisement campaign: adverts will be placed on local radio/newspapers with brief details of the study and contact details for further information.

Radio/television interviews: Regional radio and television stations will be contacted to arrange an interview opportunity with one of the study investigators.

Display of posters advertising the study in hospitals, at doctor's surgery, schools and other public places.

Presentation of relevant information at suitable locations, e.g. information sessions in schools and nurseries.

Description of study and copy of information booklet on study site websites.

Once an expression of interest has been received by the study centres an appointment would be made for them to attend at the designated recruitment centre where informed consent would be taken and the first study visit would be carried out. In schools, separate informed consent sessions may be arranged for parents where this is required. Due to the number of participants to be enrolled within a short time frame, some study centres may choose not to have a formal pre-screening process. Instead, the inclusion and exclusion criteria will be made clear in the information letter made available to all families interested in

participating in this study, and families will be encouraged to make an appointment only if their child has no exclusion criteria.

5.6.2 Informed consent

At Visit 1, written and verbal versions of the participant information and informed consent will be presented to the participants' parent or legal guardian detailing no less than:

the exact nature of the study;

the implications and constraints of the protocol;

the known side effects and any risks involved in taking part.

It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The participant's parent or legal guardian will be allowed as much time as required to consider the information, and the opportunity to question the researcher, their GP or other independent parties to decide whether they will participate in the study. Written Informed Consent will be obtained by means of a dated signature of the person legally responsible for the participant and signature of the person who presented informed consent. A copy of the signed Informed Consent will be given to the participant's parent or legal guardian. The original signed form will be retained at the study site. The informed consent discussion will be conducted by a nurse or doctor who has been trained in the consent process. The written informed consent form and any other written information will be revised whenever important new information becomes available that may be relevant to the consent. Any revised written informed consent form and written study information will be submitted to an ethics committee for approval before use.

The participant's parent or legal guardian will be informed in a timely manner if new information becomes available that may affect the decision to participate in the clinical trial. The communication of this information will be documented.

5.6.3 Screening and eligibility assessment

Following the attainment of informed consent, potential participants will be assessed by a study doctor to determine whether the candidate satisfies the inclusion/ exclusion criteria and to aid in the analysis of data. This assessment will include:

- Demographics: The date of birth, ethnicity and gender.
- Medical History: Details of any significant medical history based on parental recall

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(including previous seasonal influenza vaccination, atopy and a personal or family history of seizures).

- Gestational age at birth (for participants under 1 year of age only).
- Concomitant Medication: All immunosuppressive medication and non-steroidal anti-inflammatory medications.
- Physical Examination
- Axillary temperature.

The details of this assessment will be recorded in the CRF. If the inclusion/ exclusion criteria are satisfied (including willingness to have a blood sample taken) and the informed written consent has been obtained the participant will be randomised to receive either the Baxter or the GlaxoSmithKline vaccine

5.6.4 Randomisation

Envelope randomisation will be generated by Nick Andrews or another statistician at the Health Protection Agency. The randomisation envelope will only be opened once the participant has demonstrated their willingness to have a blood test; at the point of randomisation the child will be considered enrolled into the study. The study will be open label, however the group to which they have been randomised will be concealed until after the point of enrolment.

5.6.5 Baseline assessments

1. Perform blood draw collecting up to 6 ml in the 6 month to 3 year age groups and10ml in the 3 – 12 year age groups.
2. Randomise participant to receive either the Baxter or GSK vaccine
3. Administer vaccination, as per randomisation group.
4. Record vaccination details in participant's 'red book' and/or the study vaccination card.
5. Observe the participant for at least 20 minutes after vaccination for any immediate reactions.
6. Fill out an 'unscheduled vaccination' form for the participant's Primary Care Trust.
7. Fill out a notification to the participant's GP of the vaccine administered.
8. Provide participant with study centre contact details (including 24 hour telephone advice line contact details for study staff member).
9. Instruct participant on notifying study centre of any serious adverse events/reactions.
10. Instruct participants to use antipyretics only to treat fever or other adverse reactions, rather than prophylactically.

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11. Provide participant's parent or legal guardian with a Diary Card to detail local and systemic effects and AEs in first seven days after immunisation and Memory Card to record any ongoing solicited reactions or doctor's visit/visit to Emergency Department from day 8 to the next visit.
12. Schedule Visit 2, 21 days after Visit 1.

5.6.6 Subsequent assessments

Eligibility Check

The on-going eligibility of the participant will be reviewed at each visit. The participant's medical status will be assessed to detect:

1. any serious reaction related to the investigational vaccine
2. any further condition occurring which in the opinion of the investigator, might interfere with the evaluation of the study objectives.

Follow-up Phone Call

5-7 days after Visit 1

1. A follow-up phone call will be made to the participant's parent or legal guardian 7 days after the first administration of the study vaccine. This phone call will establish whether an SAE has occurred during the last 7 days.
2. Where an SAE has occurred that is deemed to need further review the information will be passed on to a nurse or medic from the study team who will phone the participant's parent or legal guardian to discuss further.
3. The phone call will also serve as a reminder to return the diary card and complete the memory card as appropriate.

Visit 2

21 days (+/-7 days) after visit 1 date.

1. Obtain interim history and check eligibility criteria, specifically assessing for:
    a. serious adverse events
    b. adverse events requiring a visit to a physician or emergency department or potentially leading to the withdrawal of the participant
    c. newly prescribed vaccines
    d. any solicited AEs continuing on after day 7 post-immunisation or any medically significant AEs (as recorded in the memory aid card).

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2. Measure axillary temperature immediately prior to vaccination and record on CRF.
3. If the participant is still suitable for inclusion in the study, administer vaccination with either Baxter or GSK vaccine as per randomisation group.
4. Record vaccination details in participant's 'red book' and/or study vaccination card.
5. Observe the participant for at least 20 minutes after vaccination for any immediate reactions.
6. Fill out an 'unscheduled vaccination' form for the participant's Primary Care Trust.
7. Fill out a notification to the participant's GP of the vaccine administered.
8. Ensure participant has study site contact details (including 24 hour emergency contact details for study staff member).
9. Instruct participant on notifying study site of any serious adverse events/reactions.
10. Provide participant's parent or legal guardian with a Diary Card to detail local and systemic effects and AEs in first seven days after immunisation and Memory Card to record ongoing solicited reactions or doctor's visit/visit to Emergency Department from day 8 to the next visit.
11. Schedule Visit 3, 21 days after Visit 2.

Follow-up Phone Call

5-7 days after Visit 2

1. A follow-up phone call will be made to the participant's parent or legal guardian 7 days after the second administration of the study vaccine. This phone call will establish whether an SAE has occurred during the last 7 days.
2. Where an SAE has occurred that is deemed to need further review the information will be passed on to a nurse or medic from the study team who will phone the participant's parent or legal guardian to discuss further.
3. The phone call will also serve as a reminder to return the diary card and complete the memory card as appropriate.

Visit 3

21 days (- 7 days to + 14 days) after Visit 2

1. Obtain interim history, specifically assessing for:
    a. serious adverse events
    b. adverse events requiring a visit to a physician or emergency department or potentially leading to the withdrawal of the participant

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c. newly prescribed vaccines
d. any solicited AEs continuing on after day 7 post-immunisation or any medically significant AEs (as recorded in the memory aid card).

2. Perform blood draw collecting up to 6 ms in the 6 month to 3 year age groups and 10 mls in the 3 – 12 year age groups.

Every endeavour should be made to respect the timelines indicated above, however if a participant is not able to undertake a study visit within these timelines (e.g. due to intercurrent illness) then as long as the visit is able to be done in a reasonably timely manner they will not be excluded from the study. In particular, every effort should be made to complete the immunisation course once this has been commenced.

5.6.7 Blood sampling

The volume of blood samples obtained from infants less than 3 years of age will be up to 6 mL, the volume after 3 years of age will be up to 10 mL. If the initial attempt at venepuncture is unsuccessful, (i.e. less than 4 ml obtained), then, depending on the judgment of the staff member, assent will be sought from the parents and child (as appropriate according to age) to have a further attempt. Following the initial attempt at venepuncture, a parent may decline any of these further attempts and their child will still be eligible to remain in the study. A local anaesthetic cream (Ametop or Emla according to local practice at each site) or cold spray (ethyl chloride) will be applied for an appropriate period of time prior to each venepuncture. The parent/guardian will be provided with the anaesthetic cream and instructions for use prior to Visit 3 so that they can apply it to the child's skin in the appropriate amount of time prior to the visit.

5.6.8 Diary card for recording local and systemic side effects

The participant's parent or guardian will be instructed to complete a diary card to record daily temperatures and describe local and systemic symptoms, all adverse events (AEs), and usage of analgesic/antipyretic medication for seven days following each vaccination starting on the day of administration.

Upon completion of the diary cards (i.e. 7 days after administration of the study vaccine) they will be mailed by the participant's parent or guardian directly to the Health Protection Agency. Data Clarification Forms or annotated photocopies of the diary card will be sent to the study site by the Health Protection Agency when queries arise from the participant's diary card.

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These data queries will be resolved with the participant's parent or guardian when the participant attends for the second (V2) visit and the third (V3) visit.

5.6.9 Memory Card for recording visits to doctors and emergency departments

The participant's parent or guardian will be instructed to complete a memory card to record any visits to a doctor or emergency department from the eighth day after vaccination until the next study visit and any adverse events recorded in the diary card that are ongoing after day 7.

The memory card will be returned to the study site at the following study visit at which point the study staff will review the recorded information with the participant's parent or guardian and record this in the CRF.

5.7 Laboratory methods

Blood samples taken from participants will be stored at room temperature for up to 60 minutes, and then stored at between 2 to 8°C. Samples collected at each study site will be centrifuged at 3000 rpm for 10 minutes within 24 hours at the study site and separated into at least 2 aliquots for storage at or below -30°C. Aliquots will be shipped separately to the Centre for Infections Virus Reference Department (VRD) for testing. All samples will be analysed by microneutralisation (MN) and haemagglutination inhibition (HAI) with the NIBRG121 virus (rg virus based on ACalifornia/7/2009 (vH1N1) and A/Puerto Rico/8/34). Pre and post vaccination sera will be tested in parallel.

Microneutralisation (MN)

The microneutralisation assay will be performed in 96- well format according to previously described protocols and SOPs developed at the Respiratory Virus Unit (RVU).

Serum Pre-treatment

Elimination of complement (e.g. from Foetal Calf Serum in culture medium) will be achieved by incubation of study sera and appropriate quality control sera (provided and chosen according to test virus by the RVU; usually serum of ferret, sheep or human, with/without neutralization activity) at +56°C / 30min. This step will be performed simultaneously for all study samples and control sera.

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MN Test

The MN analysis with the NIBRG121 virus will be performed as follows: a 6-step, two-fold dilution series (covering titres 20 to 640) will be set up for each of the samples and control sera. After addition of a pre-titred virus (usually around 100x$TCID_{50}$ per well or 0.1-1 virus particle per cell) neutralisation will be performed by incubation of the virus/serum mixture at room temperature for 1h.

After neutralization, a suspension of MDCK cells will be added and the plates will be incubated for 16h at 37°C in a CO2 incubator. The remaining infectivity of virus after neutralisation is determined in an EIA format using a mAb to detect expression of viral nucleoprotein. The amount of nucleoprotein expression is determined photometrically (OD450) using a plate reader.

Reading

An Optical Density reading for each dilution step for each sample will be used to calculate the titre. The titre will be reported as the reciprocal dilution at which 50% of the virus is neutralized (e.g. titre of 100). The microneutralisation analysis will be performed in duplicate (in separate runs on 2 days) for each sample.

The two titres for each sample must not differ by more than a two-fold serial dilution. In cases, where samples don't fall within this limit, a third analysis is performed and the two closest titres (which must be within a two-fold serial dilution) will be reported.

Haemagglutination Inhibition (HAI)

The principle of the HAI test is based on the ability of specific anti-influenza antibodies to inhibit haemagglutination of red blood cells (RBC) by influenza virus haemagglutinin antigen (HA). The sera to be tested have to be previously treated to eliminate the non-specific inhibitors and the anti-species HAs. The experiment will be performed in accordance to protocols and SOPs established by RVU.

Serum Pre-treatment

Elimination of non-specific inhibitors will be achieved by incubation of the unknown serum samples and quality control sera (serum of ferret or human immunized with influenza virus) with neuraminidase (RDE II; 18 h / +36°C followed by heat-inactivation 1h / +56°C).

All samples (sera pre- and post-vaccination and controls) will be prepared simultaneously.

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HAI Test

For the HI analysis with the NIBRG121 virus samples and controls will be titrated in an 8-step, two-fold dilution series (covering titres 8 to 1024) and incubated with the haemagglutinin antigen suspension (previously titrated to adjust the dilution at 4 haemagglutination units/25 µL; 50% endpoint). The haemagglutinin antigen is not added to the well dedicated to the RDE quality control.

The mixture is incubated for 1 hour at room temperature and 25 µL of the 0.5% RBC suspension (turkey blood) are added. The reaction is left for 1/2 hour at room temperature before reading.

Reading

The serum titre is equal to the highest reciprocal dilution, which induces a complete inhibition of haemagglutination. The titre of each quality control serum is close to the previously assigned value (within one serial two-fold dilution limits).

The RBC controls (red blood cell suspension without antigen) and the RDE controls do not produce any agglutination.

Each serum sample is titrated in duplicate and individual titres will be reported (two for each sample). These must not differ by more than a two-fold serial dilution. In cases, where samples don't fall within this limit, a third analysis is performed and the two closest titres (which must be within a two-fold serial dilution) will be reported.

5.8 Definition of End of Trial

The end of trial is the date at which the processing of samples for the purposes of this study has been completed.

5.9 Discontinuation/ Withdrawal of Participants from Study Treatment

Each participant has the right to withdraw study at any time. In addition, the investigator may discontinue a participant from the study at any time if the investigator considers it necessary for any reason including:

- Ineligibility (either arising during the study or retrospective having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with treatment regimen or study requirements
- An adverse event which requires discontinuation of the study medication or results in inability to continue to comply with study procedures
- Consent withdrawn
- Lost to follow up

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Withdrawn participants will not be replaced.
Data generated from participants that later withdraw will still be included in the analysis on an intention to treat basis.
The reason for withdrawal will be recorded in the end of study CRF if the participant offers an explanation.
If the participant is withdrawn due to an adverse event, the investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised.

5.10 Source Data

Source documents are original documents and records from which participants' data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, and correspondence.
CRF entries will be considered source data if the CRF is the site of the original recording (e.g., there is no other written or electronic record of data).
All documents will be stored safely in confidential conditions. With the exception of the study diary card (where the participant's first name only will be listed) and correspondence sent to the relevant child health computer department and general practitioner all documents leaving the study sites will refer to the participant by the study participant number/code, not by name.

6. TREATMENT OF TRIAL PARTICIPANTS

6.1 Description of Study Treatment

Baxter H1N1 vaccine
The novel Influenza A H1N1 Vaccine produced by Baxter Vaccines is a whole virus unadjuvanted vaccine with 7.5 µg of H1N1 virus per 0.5 ml dose. The H1N1 virus is grown in a vero cell culture. The vaccine is presented as a multidose vial (10 doses per vial).

GSK H1N1 vaccine
The novel Influenza A H1N1 Vaccine produced by GSK Vaccines is a split virion vaccine adjuvanted with an oil in water emulsion (ASO3) containing Squalene, Vitamin E- as immunostimulant and Tween 80 as surfactant. The vaccine also contains the preservative thiomersal. Each 0.5 ml dose contains 3.75 µg of H1N1 virus. The H1N1 virus is grown in an

egg cell culture and is presented in a multidose vial (10 doses per vial) to be reconstituted with the adjuvant (also in a multi-dose vial, 10 doses per vial) prior to administration.

If at the start of the trial there is clinical data or a recommendation from JCVI that supports the use of a half dose of either vaccine in children this will be used, however in the absence of any specific directive of this nature a full dose will be used (see section 3, background and rationale).

Both vaccines are to be administered intramuscularly via a 23 gauge, 25 mm needle into either the upper arm or thigh (if muscle bulk of the upper arm is insufficient). Vaccines should be administered into the non-dominant arm or thigh, ensuring consistency of limb administration between both doses of vaccine.

6.2 Storage of Study Vaccine

Prior to the commencement of the trial the Department of Health will supply the Baxter vaccine (Celvapan) to the Centre for Infections (CFI) which holds a GMP licence for re-labelling of IMPs. At CFI this vaccine will be relabelled for use in this clinical trial. They will then be shipped via cold chain to the trial sites using accredited couriers.
The GSK vaccine (Pandemrix) will be labelled for use in this clinical trial by GSK and shipped directly to the trial sites using accredited couriers.
The labels applied to these vaccines will include information on the study name/code, the CI and for 'clinical trial use only' and vial number.
The investigator (or delegate) will make an inventory and acknowledge receipt of all shipments of study medication/vaccine.
All vaccine supplies must be stored between +2 and +8°C. Vaccines that have been stored differently from the sponsor's recommendations must not be used unless the sponsor provides written authorization for use. In the event that the use cannot be authorized, vaccine supply must be replaced with fresh stock supplied by the sponsor.

6.3 Vaccine administration

The investigator will be responsible for the administration of the vaccine to subjects enrolled into the study according to the procedures stipulated in this study protocol. All vaccines will be administered only by personnel who are qualified to perform that function under applicable local laws and regulations for the specific study site.
The vaccine must be visually inspected before use.

Study vaccines should not be administered to individuals with known hypersensitivity to any component of the vaccines.

Any axillary temperature ≥ 38°C or serious active infection is reason for delaying vaccination. Standard immunization practices should be observed and care should be taken to administer the injection intramuscularly. A 23 gauge, 25 mm needle is to be used for administration. As with all injectable vaccines, appropriate medical treatment and supervision should be readily available in case of rare anaphylactic reactions following administration of the study vaccine. Epinephrine 1:1000 should be available in case of any anaphylactic reactions. Care must be taken to ensure the vaccine is not injected into a blood vessel.

6.4 Vaccine compliance

The investigator will be responsible for adequate and accurate accounting of vaccine usage. The investigator or designee will administer the study vaccines only to individuals included in this study following the procedures set out in this study protocol. The date, dosage, and time of the vaccinations will be recorded. The investigator will track vaccines received, used and wasted and will retain all unused or expired products until the sponsor is satisfied that the vaccine accountability records are correct. Thereafter, all unused vaccines are to be destroyed at the investigational site. An overall summary of vaccines supplied, received, wasted, used and returned will be prepared at the conclusion of the study.

6.5 Adherence to randomisation list

The investigator or his designate will administer the vaccine as indicated on the randomization list for the individual subject. Adherence to the randomization will be verified by the Study Monitor by checking the vaccination records maintained in the investigator's study file.

6.6 Accountability of the Study Treatment

All vaccine doses will be accounted for within an accountability log. Unused vaccine at the end of the trial will be disposed of with written documentation describing this process.

6.7 Concomitant medication

Any immunosuppressant or non-steroidal anti-inflammatory medication taken at the time of enrolment into the study is to be recorded on the CRF.

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7. SAFETY REPORTING

7.1 Definitions

7.1.1 Adverse Event (AE)

An AE or adverse experience is:

Any untoward medical occurrence in a patient or clinical investigation participants administered a medicinal product, which does not necessarily have to have a causal relationship with this treatment (the study medication).

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the study medication, whether or not considered related to the study medication.

7.1.2 Adverse Reaction (AR)

All untoward and unintended responses to a medicinal product related to any dose.

The phrase "responses to a medicinal product" means that a causal relationship between a study medication and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the study medication qualify as adverse reactions.

7.1.3 Severe Adverse Events

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonymous, the following note of clarification is provided:

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

7.1.4 Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence that at any dose:

- Results in death,

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- Is life-threatening, NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.
- Other important medical events. NOTE: Other events that may not result in death, are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

7.1.5 Serious Adverse Reaction (SAR)

An adverse event (expected or unexpected) that is both serious and, in the opinion of the reporting investigator, believed with reasonable probability to be due to one of the study treatments, based on the information provided.

7.1.6 Expected Serious Adverse Events/Reactions

No serious adverse events or reactions are expected. Extensive study of Guillian-Barré syndrome has demonstrated that there is no association between influenza vaccines and Guillian-Barré syndrome, and therefore Guillian-Barré syndrome is not expected to occur in this study.

7.1.7 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse reaction, the nature or severity of which is not consistent with the applicable product information.

7.1.8 Adverse event of special interest (AESI)

Adverse events of special interest are those AEs recommended by the CHMP for inclusion as part of Risk Management Plans to be submitted with the Marketing Authorisation Application for a Pandemic Influenza Vaccine (EMEA/359381/2009) and include: neuritis, convulsions, anaphylaxis, encephalitis, vasculitis, Guillain-Barré syndrome, Bell's palsy, demyelinating disorders, and vaccination failure.

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7.1.9 Potentially Immune Mediated Diseases or pIMDs

Adverse events that constitute pIMDs are those diseases and conditions listed in Appendix E.

7.2 Reporting Procedures for All Adverse Events

In the seven days following vaccine administration the following solicited symptoms will be recorded by the participants parents/guardian in their study diary:

- injection site reactions (local tenderness, swelling or erythema)
- Fever ((≥ 38°C per axilla)
- Non febrile systemic reactions, i.e:
- reduced feeding, reduced activity, irritability, persistent crying, vomiting or diarrhoea, receiving medication for pain or temperature (6 month to 5 year olds).
- malaise, headache, nausea/ vomiting, diarrhoea, reduced appetite, muscle pain or joint pain, receiving analgesic/ antipyretic medication (5 to 12 year olds).

In addition parents/ guardians will be requested to record any other general symptoms in the 7 days post vaccination in the diary card.

These study diaries will be sent directly to the HPA for review by medical staff prior to transciption of the data to the study database. If clarification of any adverse events is required then the study staff at the relevant study site will be contacted.

At visit 2 and 3 medically significant adverse events (as recorded on the memory aid card) that have occurred in the period between the seven days after vaccination and the subsequent study visit (visit 2 or 3) will be recorded on the CRF, whether or not these are attributed to the study medication. Medically significant AEs will be defined as AEs requiring a physician visit, Emergency Department visit, or leading to a subject's withdrawal (with the exclusion of pre-planned visits and GP or emergency department visits for routine medical care). Adverse events solicited in the diary card that are ongoing after day 7 (as recorded in the memory aid card) will similarly be recorded in the CRF.

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The following information will be recorded for medically significant AEs: description, date of onset and end date, severity, assessment of relatedness to study medication, other suspect drug or device and action taken. Follow-up information should be provided as necessary.

The relationship of medically significant AEs to the study medication will be assessed by a medically qualified investigator according to the following criteria:

- Related - If the causal relationship between the IMP and the SAE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.
- Not related - If there is no causal relationship between the IMP and the SAE i.e. the event is caused by something other that the IMP e.g. underlying disease, a concomitant medication.

Verbal consent will be sought from participants to follow up all AEs considered related to the study medication, AEs leading to the participant's withdrawal from the study, AESIs, pIMD and pregnancies until resolution or the event is considered stable. If obtained this verbal consent will be documented in participant's case report form (CRF).

It will be left to the investigator's clinical judgment whether or not an AE is of sufficient severity to require the participant's removal from treatment (see section 6.6). A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant must undergo an end of study assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.
The rates of adverse events experienced by participants will be reviewed by a data monitoring committee (see section 10 below).

7.3 Reporting Procedures for Serious Adverse Events

All SAEs must be reported to the chief investigator or delegate for review within one working day of discovery or notification of the event. The chief investigator or delegate will then forward these on to CTRG and to the relevant vaccine manufacturer within 24 hours of receipt. All SAE information must be recorded on a signed SAE form and relayed to the chief investigator by fax or email. Additional information received for a case (follow-up or

corrections to the original case) need to be detailed on a new SAE form and faxed to the chief investigator or delegate for review and forwarding to the CTRG.

All serious adverse reactions (SAR's), AESIs and pIMDs will be reported on CIOMS 1 forms to the relevant manufacturer within 24 hours of any study staff becoming aware of these events. These events should also be reported as SAE's using the appropriate forms.

The CI will report all SUSARs to the MHRA, the Research Ethics Committee concerned and Host NHS Trusts. Fatal or life-threatening SUSARs must be reported within 7 days and all other SUSARs within 15 days. The CI will also inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants.
In addition to the expedited reporting above, the CI shall submit once a year throughout the clinical trial or on request a safety report to the Competent Authority (MHRA in the UK), Ethics Committee, Host NHS Trust and sponsor.

The CTRG will ensure that all SAEs are reviewed by medical monitors on a weekly basis and at the next meeting of the Oxford Radcliffe Hospitals Trust / University of Oxford Trials Safety Group (TSG), who will meet at regular intervals and consider:

- Occurrence and nature of adverse events
- Whether additional information on adverse events is required
- Consider taking appropriate action where necessary to halt trials
- Act / advise on incidents occurring between meetings that require rapid assessment (e.g. SUSARs)

If deemed appropriate, the TSG will refer the SAEs experienced in the study to the data monitoring committee for review.

7.4 Reporting of Pregnancy

Although pregnancy tests will not be performed in this study due to the age range of the participants, if the investigators were to become aware of a study participant receiving a study vaccine within 30 days prior to pregnancy or during pregnancy, then they would inform the chief investigator or delegate, who will inform the sponsor, the ethics committee, the MHRA and the vaccine manufacturer of this occurrence.

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8. STATISTICS

8.1 Description of Statistical Methods

Immunogenicity

The following statistical parameters will be determined for each study group:

- Percentage of subjects with an HAI titre ≥ 1 in 32
- Percentage of subjects with a 4 fold rise in HAI titre between the pre-vaccination sample and sample taken 3 weeks after the second dose
- Percentage of subjects with a 4 fold rise in MN titre between the pre-vaccination sample and sample taken 3 weeks after the second dose
- Geometric mean of pre-vaccination serum HAI titres
- Geometric mean of post-vaccination serum HAI titres
- Geometric mean of pre-vaccination serum MN titres
- Geometric mean of post-vaccination serum MN titres
- Geometric mean of the rise in HAI titres from pre- to post-immunisation
- Geometric mean of the rise in MN titres from pre- to post-immunisation

The above analyses will be performed on all participants in the Per-protocol (PP) immunogenicity population (see section 8.8). In addition, a sub-analysis will be performed on the participants in the PP population who were seronegative by for the relevant assay (MN or HAI) at enrolment.

In the event of HAI titres being negative at the initial dilution (1:8) an arbitrary value of 4 will be assigned for calculation of fold rise and GMTs, while for the MN assay (initial dilution 1:20) this value will be 10.

Reactogenicity

- Percentage of participants experiencing each of fever (≥ 38°C per axilla), local tenderness, local swelling or local erythema within the 7 days following each immunisation with the study vaccines
- Percentage of participants experiencing each of: reduced feeding, reduced activity, irritability, persistent crying, vomiting or diarrhoea, receiving medication for pain or temperature (6 month to 5 year olds).

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- Percentage of participants experiencing each of: malaise, headache, nausea/ vomiting, diarrhoea, reduced appetite, muscle pain or joint pain, receiving analgesic/ antipyretic medication (5 to 12 year olds).

In children aged under 5 years the severity of solicited systemic reactions will be graded according to the following criteria:

Reduced Feeding:

0 None	
1 Mild	Eating less than normal for 1-2 feeds
2 Moderate	Missed 1-2 feeds completely
3 Severe	Refused most or all feeds

Reduced Activity

0 None	
1 Mild	Less interested in surroundings, toys etc
2 Moderate	No interest in above and sleeping through feeds
3 Severe	Sleeping most of the time

Increased Irritability

0 None	
1 Mild	Continuously irritable for less than 1 hour
2 Moderate	Continuously irritable for 1 to less than 3 hours
3 Severe	Continuously irritable for 3 or more hours

Persistent Crying

0 None	
1 Mild	Cried continuously for less than 1 hour
2 Moderate	Cried continuously for 1 to less than 3 hours
3 Severe	Cried continuously for 3 or more hours

Vomiting

0 None	
1 Mild	1-2 episodes without interfering with routine

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2 Moderate Several episodes & cannot keep any food down
3 Severe: Frequent episodes & taking nothing by mouth

Diarrhoea
0 None
1 Mild More loose stools than usual
2 Moderate Frequent runny stools without much solid material
3 Severe Multiple liquid stools without much solid material

In children aged 5 years or above the severity of solicited systemic events will be assessed on the following scale:

Generally unwell (malaise)
0 = No
1 = Mild (transient with no limitation on normal activity)
2 = Moderate (some limitation in daily activity)
3 = Severe (unable to perform normal daily activity).

Headache
0 = None
1 = Mild (transient with no limitation on normal activity)
2 = Moderate (some limitation in daily activity)
3 = Severe (unable to perform normal daily activity).

Vomiting
0 None
1 Mild 1-2 episodes without interfering with routine
2 Moderate Several episodes & cannot keep any food down
3 Severe: Frequent episodes & taking nothing by mouth

Diarrhoea
0 None
1 Mild More loose stools than usual
2 Moderate Frequent runny stools without much solid material

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3 Severe Multiple liquid stools without much solid material

Reduced feeding
0 None
1 Mild Eating less than normal for 1-2 meals
2 Moderate Missed 1-2 meals completely
3 Severe Refused most or all meals

Myalgia
0 = None
1 = Mild (transient with no limitation on normal activity)
2 = Moderate (some limitation in daily activity)
3 = Severe (unable to perform normal daily activity).

Arthralgia

0 = None
1 = Mild (transient with no limitation on normal activity)
2 = Moderate (some limitation in daily activity)
3 = Severe (unable to perform normal daily activity).

In both age groups, local erythema and swelling will be classified as absent, less than 2.5 cm and greater than or equal to 2.5 cm, while local tenderness will be assessed on the following scale:

0 = None
1 = Mild (transient with no limitation on normal activity)
2 = Moderate (some limitation in daily activity)
3 = Severe (unable to perform normal daily activity).

Reactogenicity will be assessed by calculating the percentage of participants with solicited local reactions and fever in each group (i.e. the percentage of participants within each age group receiving each vaccine experiencing these reactions).The percentage of participants in

each group experiencing each of these reactions after each vaccine will be calculated, as will the percentage of participants in each group experiencing each reaction during the immunisation course. The percentage of participants experiencing any solicited local reaction or fever may also be calculated, both after each immunisation and during the whole vaccine course. As well as being calculated for each group, these percentages may also be calculated for all recipients of each vaccine (regardless of age group).

The percentage of participants experiencing non-febrile solicited adverse events (e.g. irritability or vomiting) will be calculated for recipients of each vaccine aged less than 5 years and for those aged 5 years and over. This will be calculated for participants experiencing each non-febrile solicited adverse event after each vaccine dose and during the whole immunisation course, and the percentage of participants experiencing any solicited local reaction or fever may also be calculated, both after each immunisation and during the whole vaccine course.

The number of subjects with reported serious adverse events up to 7 days after each vaccination and during the whole study will also be calculated, as will the number of participants with any adverse event in the first week after immunisation and any medically significant adverse event during the study.

In the event of one of the vaccines not being available at the start of this study, an alternative enrolment strategy will be conducted, in which participants are initially recruited to receive the available vaccine alone. This could be done at all sites or a selection of sites as appropriate, and enrolment for this phase would continue until one half of the participants due to receive that vaccine had been recruited (i.e. 125 in each age group). Recruitment to the study will then cease until both vaccines are available, at which time a revised randomisation (2:1) scheme will be employed, so that equal numbers of participants will have received each vaccine by the study's end.

8.2 The Number of Participants

With a sample size of 100-200 in each of two age groups for each vaccine the precision (95% CI) of estimates of percentages with adverse reactions or responding to vaccination is shown in the table below.

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	N=100	N=150	N=200
Observed %	95% CI*	95% CI	95%CI
0	0 to 4	0 to 2	0 to 2
10	5 to 18	6 to 16	6 to 15
20	13 to 29	14 to 27	15 to 26
30	21 to 40	23 to 38	24 to 37
40	30 to 50	32 to 48	33 to 47
50	40 to 60	42 to 58	43 to 57
60	50 to 70	52 to 68	53 to 67
70	60 to 79	62 to 77	63 to 76
80	71 to 87	73 to 86	74 to 85
90	82 to 95	84 to 94	85 to 94

*exact 95% CIs are shown

So precision is within +/- 10% for N=100, +/- 8% for N=150 and +/- 7% for N=200

Detectable differences in percentages between vaccines or age groups will be as follows (80% power, 5% significance level, N=100-200 per group compared)

	N=100		N=150		N=200	
True % in first group	% in second group detectable (below)	% in second group detectable (above)	% in second group detectable (below)	% in second group detectable (above)	% in second group detectable (below)	% in second group detectable (above)

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0	-	9	-	6	-	5
10	0	26	2	22	3	21
20	6	39	8	35	10	33
30	13	50	16	46	18	44
40	21	61	24	57	26	54
50	30	70	33	67	36	64
60	39	79	43	76	46	74
70	50	87	54	84	56	82
80	61	94	65	92	67	90
90	74	100	77	98	79	97

So, for example, if one vaccine has a true local reaction rate of 10% in a given age group then a rate of 26% is detectable as different for the other vaccine with N=100 down to 21% for N=200. Similarly if one vaccine had a seroconversion rate of 70%, then it would be possible to detect a difference in seroconversion rates to the other vaccine if this value was below 56% or greater than 82%.

For comparison of geometric mean HI fold rises between vaccines or ages, the sample size of 200 will allow 1.34 fold differences to be detectable with 80% power at 5% significance. This uses an estimate of 0.45 for the log10 scale SD of post vaccination fold rises as seen with other influenza vaccines. For N=100 1.51 fold differences are detectable and for N=150 1.40 fold differences.

Based on these calculations a sample size of 200 per group has been chosen to optimise the power to detect a difference in the immunogenicity and reactogenicity of the two vaccines in the two age groups. Specifically, it was felt that a difference in seroconversion or local reaction/ fever rates of -14% and +12% around a (hypothetical) rate of 70% would be of

clinical importance, and that it would not be possible to this degree of variance with a smaller sample size.

In order to account for about 25% of participants not completing the study or not having blood samples obtained, the overall number of participants is therefore 1000. Due to the rapid nature of recruitment across multiple sites that is required for this study, it may not be possible to precisely match the number of participants to 1000; the actual figure enrolled may therefore be slightly higher or lower than this target figure. Recruitment is provisionally expected to be approximately 250 participants at 3 sites (Oxford, Southampton, and St. George's) and approximately 250 participants at 2 sites combined (Bristol and Exeter), however should it be required to optimise recruitment then it will be possible for any site to recruit more than the provisional number of participants.

If recruitment were to be lower than expected then the above calculations suggest that the immunogenicity and reactogenicity of the individual vaccines could still be assessed with reasonably narrow confidence intervals (e.g. +/- 10% for 100 participants in each group), however the ability to detect differences between the two groups would be reduced.

Withdrawn participants will not be replaced.

It is anticipated that some potential participants who will be allocated a participant number after completion of informed consent will not subsequently be enrolled or randomised (e.g. if an exclusion criterion is identified at medical assessment or the child is unwilling to have a blood sample taken). An excess of participant numbers will therefore be allocated for each study site to allow for this.

8.3 Interim analysis

An interim analysis may be performed when results of laboratory assays or adverse event rates are available on about 250 participants for each vaccine (i.e. half-way through). This analysis will consist of a descriptive analysis (proportions and 95% CI's) of the primary immunogenicity end point and a subset of safety end points (fever ≥ 38°C, local redness and swelling ≥ 2.5 cm). Continuation of recruitment will not be dependent on the results of this analysis, which is being performed due to the need for rapid data on these vaccines in children. An additional interim analysis, in which adverse event rates after the first dose of

vaccine are evaluated by study statistician's and/or the data monitoring committee, may be performed.

8.4 The Level of Statistical Significance

The level of statistical significance will be taken as 5%.

8.5 Criteria for the Termination of the Trial.

The study uses two vaccines produced by Baxter and GlaxoSmithKline. Both manufacturers have gained marketing authorisation approval from the EMEA for a pandemic strain vaccine under the "mock-up" dossier route based on limited clinical trial data for a candidate H5N1 vaccine. Trials of the mock up vaccines have been conducted in adults and there is some safety data of the use of the GSK H5N1 vaccine in children over 3 years of age. These trials have not reported significant safety concerns. The vaccines are similar to other influenza vaccines that have been licensed and used in children. It is unlikely that any safety issues should lead to termination of the trial, however the data monitoring committee will have the authority to recommend termination of the trial or for immunisation with either of the vaccines to be discontinued. In addition, the investigator has the right to discontinue this study at any time. If the clinical study is prematurely terminated, the investigator is to promptly inform the participants and should assure appropriate therapy and follow-up for the participants.

8.6 Procedure for Accounting for Missing, Unused, and Spurious Data.

The reason for missing data (consent withdrawn, lost to follow-up, removed from study due to serious side effects, death, or unable to obtain any laboratory results) will be indicated but missing data will not be imputed. Amount of missing data between the 2 groups and other demographic characteristics will be compared.

8.7 Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Any additional analysis or deviation(s) from the analysis plan will be documented and updated according to the statistical standard operating procedure.

8.8 Inclusion in Analysis

The primary immunogenicity analyses will be conducted on a per-protocol (PP) population, consisting of all participants who completed the study and did not experience any significant protocol deviations. All participants in the PP population providing a blood sample following immunisation will be included in the PP immunogenicity analyses, with the exception of

analyses related to the fold rises from baselines, in which all participants in the PP population providing blood samples both before and after baseline will be included in the PP immunogenicity analyses.

An intention to treat (ITT) immunogenicity population will also be defined, consisting of all participants receiving an immunisation and providing a blood sample after immunisation. If the ITT immunogenicity population differs from the PP population by more than 10% then the measures of immunogenicity will also be calculated for the ITT immunogenicity population.

All data will be included up until the time that a participant is withdrawn from the study.

The population for safety analysis will include all those that received a study vaccine and provided any safety/reactogenicity data.

9. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Direct access will be granted to authorised representatives from the sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

10. QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

The study will be conducted in accordance with the current approved protocol, ICH GCP, relevant regulations and the study sites standard operating procedures.

Regular monitoring will be performed according to ICH GCP. Monitoring of this study will be conducted by freelance monitors in collaboration with the quality assurance manager of the Oxford Vaccine Group and local staff at each study centre. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures and an approved monitoring plan, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

A trial steering committee will be formed that will include, but not be limited to, the chief investigator, a statistician, a quality assurance manager and project manager.

A Data Monitoring Committee (DMC) will be convened that will primarily have responsibility for reviewing the adverse event rates and serious adverse events experienced by participants in this study. Due to the rapid nature of recruitment intended for this study, it is not anticipated that the DMC will be able to review immunogenicity data during the study itself. The DMC will be independent of the study team and will report to the trial steering

committee. The DMC will include, but not be limited to, a paediatric infectious disease specialist, a statistician and a consultant with expertise in public health.
This committee will be in addition to the trial safety group (TSG), who will provide review of serious adverse events as part of routine procedures for the CTRG.

11. ETHICS

11.1 Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

11.2 ICH Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996.

11.3 Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), regulatory authorities (MHRA in the UK), and host institution(s) for written approval.
The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

11.4 Participant Confidentiality

The trial staff will ensure that the participants' anonymity is maintained. With the exception of the study diary card (where the participant's first name only will be listed) and correspondence sent to the relevant child health computer department and general practitioner all documents leaving the study sites will refer to the participant by the study participant number/code, not by name. All documents will be stored securely and only accessible by trial staff and authorised personnel. The study will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so.

11.5 Compensation for harm

As study sponsor the University of Oxford will provide indemnity for harm arising as a result of the study protocol.

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The Government has already provided an indemnity to Baxter and GSK in relation to any claims arising out of the use of the vaccines purchased under the Advance Purchase Agreements (APA) with those companies, other than where the harm is due to a defect in manufacture. That indemnity covers the use of the vaccine in research projects, as the contractual indemnity provisions are not limited by reference to the circumstances in which the vaccines are used.

In relation to the liability of the sponsors and investigators taking part in the research projects, the usual insurance or indemnity arrangements will apply (for example, in relation to NHS bodies and staff, the NHS Indemnity and Clinical Negligence Scheme arrangements apply).

Exceptionally, given the nature of this study, as part of a wider government response to a major public health emergency, the Department will also offer a “no fault” compensation scheme to trial participants, in relation to serious injury of an enduring and disabling character caused by the vaccines which are the subject of the trials

12. DATA HANDLING AND RECORD KEEPING

Information on study participants will be recorded on hard copy case report forms (CRFs) held locally. CRFs will be supplied by CFI in packs and will include the following:

i. Subject contact details (to be retained locally)
ii. Inclusion and exclusion criteria
iii. Medical history
iv. Immunosuppressive or non-steroidal medication at study start
v. Each vaccination and each blood
vi. Post vaccination follow up at 3 weeks
vii. Study termination record for subjects completing per protocol and for earlier withdrawals
viii. Age specific diary cards for completion by parents
ix. Memory aid card for completion by parents

Each study site will be responsible for generating and retaining their own source documents if required.

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Each study participant will have a unique study number which will be allocated following the taking of informed consent. For each participant, sufficient labels with the same study number will be generated at CFI to label all CRFs, diary cards, vaccine vials and blood sample tubes.

In order to identify study staff who have completed each CRF, each site will have a signature sheet, including full name and initials a copy of which will be provided to CFI.

12.1 Data entry at CFI

The CRFs from each trial site will be photocopied locally and the copy sent to CFI with the original retained at the local site. The diary cards will be sent directly to CFI by the participant's parent or legal guardian. The diary cards will be photocopied at CFI and a copy will be sent to the local site to retain in the participant's study file. The only patient identifying information on the CRFs sent to CFI will be study number and participant initials. The only patient identifying information on the diary cards sent to CFI will be the participant's first name on the front page to aid parents who may have more than one child enrolled in the study, and the study number and participant initials. A study database will be constructed at CFI to record the information collected in the CRFs and diary cards. As the data is being entered, the CRFs and diary cards will be monitored. Study diaries will be reviewed by medical staff at the HPA prior to transciption of the data to the study database. If clarification of any adverse events is required or completion errors or omissions are noted then the study staff at the relevant study site will be contacted.

When completion errors or omissions are noted the study site will be notified of the entries requiring correction or clarification. The local investigator will make the correction on the CRFs, crossing out any incorrect information with a single line, and will sign and date the change on the original CRF which will be photocopied again and sent to CFI. On return of the photocopy to CFI the database will be updated accordingly and the photocopy filed with the initial photocopy. Corrections to the diary cards will be made via data clarification forms that will be sent to the study sites to resolve with the participant's parent or guardian on the subsequent study visit.

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If diaries have not been returned to CFI at the specified time, the local site will contact the parent and advise CFI of any outstanding diaries weekly by a spreadsheet return. This return will also list by subject number and initials any subject who has withdrawn from the study and complete the "end of study" CRF as appropriate.

Information from the CRFs will be double entered onto the data base at CFI by two independent data-entry staff. Verification routine will be done weekly and data inputting errors corrected.

12.2 Data locking

At the end of the study, the database will be locked and a data extract provided to the study statistician for analysis according to a pre-defined statistical analysis plan. Should an interim analysis be conducted then a dated copy of the database will be made and locked and the analysis conducted on a data extract of that locked database.

13. FINANCE AND INSURANCE

The involved parties will be insured, in accordance with the Clinical Trials regulations, against financial loss resulting from personal injury and/or other damages, which may arise as a consequence of this study. For details see contract agreements.

14. PUBLICATION POLICY

The Investigator will co-ordinate dissemination of data from this study. All publications (e.g., manuscripts, abstracts, oral/slide presentations, book chapters) based on this study will be reviewed by each sub-investigator prior to submission.

15. REFERENCES

1. Health Protection Agency Weekly National Influenza Report 23rd July 2009.
2. World Health Organisation Pandemic (H1N1) 2009 briefing note 2: WHO recommendations on pandemic (H1N1) 2009 vaccines, 2009.
3. Katz J, Hancock K, Veguilla V, Zhong W, Lu X, Sun H, et al. Serum Cross-Reactive Antibody Response to a Novel Influenza A (H1N1) Virus After Vaccination with Seasonal Influenza Vaccine. *Morbidity and Mortality Weekly Review* 2009;58(19):521 - 524.

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APPENDIX A: PANDEMIC (H1N1) 2009 BRIEFING NOTE 2. WHO RECOMMENDATIONS ON PANDEMIC (H1N1) 2009 VACCINES

13 JULY 2009 | GENEVA -- On 7 July 2009, the Strategic Advisory Group of Experts (SAGE) on Immunization held an extraordinary meeting in Geneva to discuss issues and make recommendations related to vaccine for the pandemic (H1N1) 2009.

SAGE reviewed the current pandemic situation, the current status of seasonal vaccine production and potential A (H1N1) vaccine production capacity, and considered potential options for vaccine use.

The experts identified three different objectives that countries could adopt as part of their pandemic vaccination strategy:

- protect the integrity of the health-care system and the country's critical infrastructure;
- reduce morbidity and mortality; and
- reduce transmission of the pandemic virus within communities.

Countries could use a variety of vaccine deployment strategies to reach these objectives but any strategy should reflect the country's epidemiological situation, resources and ability to access vaccine, to implement vaccination campaigns in the targeted groups, and to use other non-vaccine mitigation measures.

Although the severity of the pandemic is currently considered to be moderate with most patients experiencing uncomplicated, self-limited illness, some groups such as pregnant women and persons with asthma and other chronic conditions such as morbid obesity appear to be at increased risk for severe disease and death from infection.

Since the spread of the pandemic virus is considered unstoppable, vaccine will be needed in all countries. SAGE emphasized the importance of striving to achieve equity among countries to access vaccines developed in response to the pandemic (H1N1) 2009.

The following recommendations were provided to the WHO Director-General:

- All countries should immunize their health-care workers as a first priority to protect the essential health infrastructure. As vaccines available initially will not be

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sufficient, a step-wise approach to vaccinate particular groups may be considered. SAGE suggested the following groups for consideration, noting that countries need to determine their order of priority based on country-specific conditions: pregnant women; those aged above 6 months with one of several chronic medical conditions; healthy young adults of 15 to 49 years of age; healthy children; healthy adults of 50 to 64 years of age; and healthy adults of 65 years of age and above.

- Since new technologies are involved in the production of some pandemic vaccines, which have not yet been extensively evaluated for their safety in certain population groups, it is very important to implement post-marketing surveillance of the highest possible quality. In addition, rapid sharing of the results of immunogenicity and post-marketing safety and effectiveness studies among the international community will be essential for allowing countries to make necessary adjustments to their vaccination policies.
- In view of the anticipated limited vaccine availability at a global level and the potential need to protect against "drifted" strains of virus, SAGE recommended that promoting production and use of vaccines such as those that are formulated with oil-in-water adjuvants and live attenuated influenza vaccines was important.
- As most of the production of the seasonal vaccine for the 2009-2010 influenza season in the northern hemisphere is almost complete and is therefore unlikely to affect production of pandemic vaccine, SAGE did not consider that there was a need to recommend a "switch" from seasonal to pandemic vaccine production.

WHO Director-General Dr Margaret Chan endorsed the above recommendations on 11 July 2009, recognizing that they were well adapted to the current pandemic situation. She also noted that the recommendations will need to be changed if and when new evidence becomes available.

SAGE was established by the WHO Director-General in 1999 as the principal advisory group to WHO for vaccines and immunization. It comprises 15 members who serve in their personal capacity and represent a broad range of disciplines from around the world in the fields such as epidemiology, public health, vaccinology, paediatrics, internal medicine, infectious diseases, immunology, drug regulation, programme management, immunisation delivery, and health-care administration.

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Additional participants in the SAGE meeting included members of the ad hoc policy advisory working group on influenza A (H1N1) vaccine, chairs of the regional technical advisory groups and external experts. Observers included industry representatives and regulators who did not take part in the recommendation process in order to avoid conflicts of interest.

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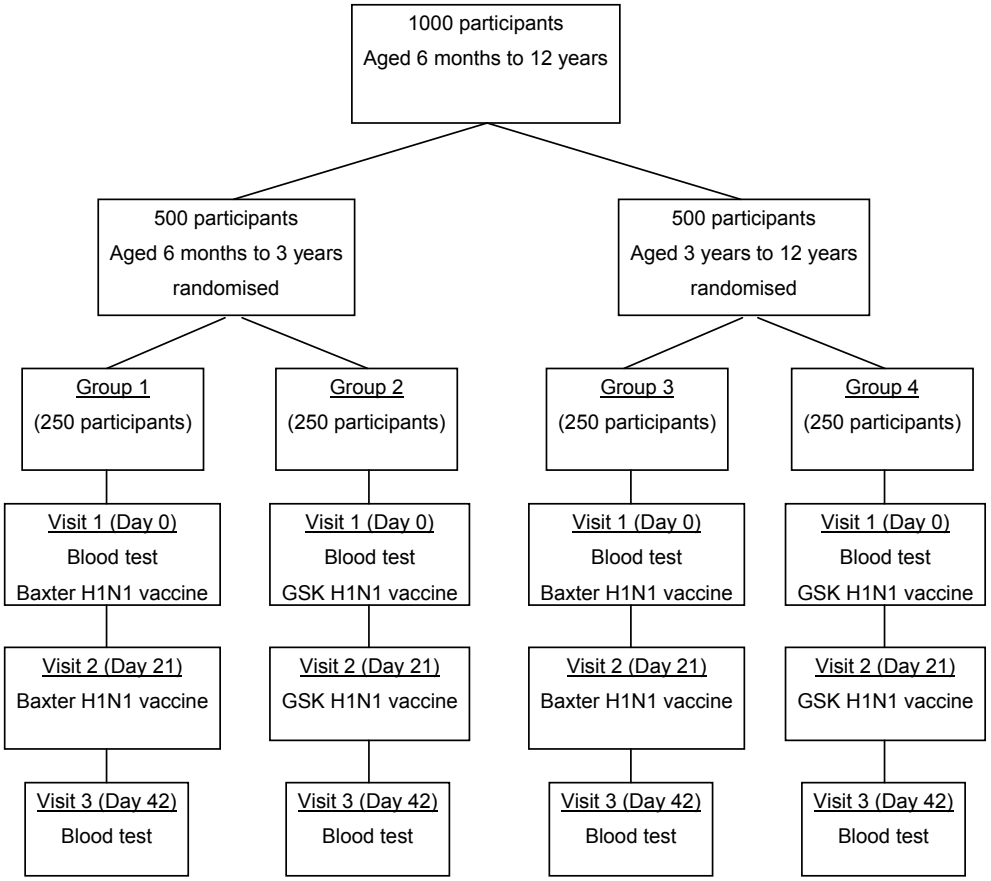
APPENDIX B: STUDY FLOW CHART



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APPENDIX C: STUDY TIMELINES

Stage	Timing (Planned start date 8th September, depending on vaccine availability and regulatory approval)
Visit 1	Week 1 to 3
Visit 2	Weeks 4 to 7
Visit 3	Weeks 7 to 12
Laboratory testing	Weeks 12 to 14
Analysis and initial report	Week 15
Completion of study for initial reporting	Week 15 (Week beginning 17th December if commence 8th September)

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APPENDIX D: STAFF PERSONNEL

CFI

Professor Elizabeth Miller:	Principal investigator for CFI site and overall trial co-ordinator
Nick Andrews:	Trial statistician
Liz Sheasby:	Quality Assurance at the CFI site
Pauline Kaye:	Trial data manager
Dr. Katja Hoschler:	Responsible for overseeing serological testing for the trial
Teresa Gibbs:	Senior administrator responsible for overseeing data entry and verification

OVG

Professor Andrew Pollard:	Chief investigator of study
Dr Matthew Snape:	Principal investigator for OVG site
Tessa John:	Clinical Team Leader at OVG site
Simon Kerridge:	Quality Assurance at the OVG site
Amanda Reiner:	Project Manager at OVG site

St George's Vaccine Institute

Dr Paul Heath:	Principal investigator at St George's site.
Dr Clarissa Oeser.	Research fellow
Dr Shamez Ladhani.	Consultant Paediatrician
Dr Ifeanyichukwu Okike:	Research Fellow

Bristol Children's Vaccine Centre

Professor Adam Finn:	Principal investigator at Bristol site
Dr Jolanta Bernatoniene:	Consultant paediatrician
Dr Edward Clarke:	Clinical Lecturer in Paediatric Infectious Diseases
Dr Ruth Allen:	Manager, Medicines for Children South West
Natalie Fineman:	MCRN Research Nurse team leader

Royal Devon and Exeter Hospital

Dr Andrew Collinson:	Principal Investigator at Royal Devon and Exeter

University of Southampton Wellcome Trust Clinical Research Facility

Dr Saul Faust:	Principal investigator at Southampton site

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APPENDIX E:

Immune Mediated Disorders (IMD)

Event Category	Immune-Mediated Disorder	MedDRA PT
Neuroinflammatory disorders	Cranial nerve disorders	Optic neuritis
		III nerve paralysis
		III nerve paresis
		IV nerve paralysis
		IV nerve paresis
		VI nerve paralysis
		Facial palsy
		Facial paresis
		VII nerve paralysis
		XI nerve paralysis
		Vagus nerve paralysis
		Acoustic nerve neuritis
		Glossopharyngeal nerve paralysis
		Trigeminal palsy
		Trigeminal nerve paresis
		Tongue paralysis
		Hypoglossal nerve paresis
		Anosmia
		Neuritis cranial
		Cranial neuropathy
		Paresis cranial nerve
		Cranial nerve paralysis
		Cranial nerve palsies multiple
	Multiple sclerosis	Multiple sclerosis
		Primary progressive multiple sclerosis
		Progressive multiple sclerosis
		Marburg's variant multiple sclerosis
		Secondary progressive multiple sclerosis
		Multiple sclerosis relapse
		Progressive relapsing multiple sclerosis
		Relapsing-remitting multiple sclerosis
	Demyelinating disease	Demyelination
		Leukoencephalomyelitis
		Acute disseminated encephalomyelitis
		Concentric sclerosis
		Neuromyelitis optica
		Chronic inflammatory demyelinating polyradiculoneuropathy
		Demyelinating polyneuropathy
	Transverse myelitis	Myelitis transverse
		Myelitis
	Guillain-Barré syndrome	Guillain-Barré syndrome
		Miller Fisher syndrome
	Myasthenia gravis	Myasthenia gravis
		Ocular myasthenia
	Encephalitis	Encephalitis
		Encephalomyelitis
		Encephalitis post immunisation

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Event Category	Immune-Mediated Disorder	MedDRA PT
		Encephalitis toxic
	Neuritis	Neuritis
		Cervical neuritis
		Mononeuritis
		Mononeuropathy multiplex
		Brachial plexopathy
		Radiculopathy
		Radiculitis
		Radiculitis brachial
		Radiculitis cervical
Musculoskeletal disorders	Systemic lupus erythematosus	Systemic lupus erythematosus
	Cutaneous lupus	Cutaneous lupus
	Sjogren's syndrome	Sjogren's syndrome
	Scleroderma	Scleroderma
		Systemic sclerosis
		CREST syndrome
		Morphoea
	Dermatomyositis	Dermatomyositis
	Polymyositis	Polymyositis
	Rheumatoid arthritis	Rheumatoid arthritis
		Juvenile arthritis
	Polymyalgia rheumatica	Polymyalgia rheumatica
	Reactive arthritis	Arthritis reactive
		Reiter's syndrome
	Psoriatic arthritis	Psoriatic arthropathy
	Ankylosing spondylitis	Ankylosing spondylitis
	Undifferentiated spondyloarthropathy	Spondyloarthropathy
	Mixed connective tissue disease	Mixed connective tissue disease
Gastrointestinal disorders	Crohn's disease	Crohn's disease
	Ulcerative colitis	Colitis ulcerative
	Ulcerative proctitis	Proctitis ulcerative
	Celiac disease	Coeliac disease
Metabolic disorders	Autoimmune thyroiditis	Autoimmune thyroiditis
	Hashimoto's thyroiditis	
	Grave's or Basedow's disease	Basedow's disease
	Insulin-dependent diabetes mellitus	Type 1 diabetes mellitus
	Addison's disease	Addison's disease
Skin disorders	Psoriasis	Psoriasis
	Vitiligo	Vitiligo
	Raynaud's phenomenon	Raynaud's phenomenon
	Erythema nodosum	Erythema nodosum
	Autoimmune bullous skin diseases	Pemphigus
		Pemphigoid
		Dermatitis herpetiformis
Other	Stevens-Johnson syndrome	Stevens-Johnson syndrome
		Erythema multiforme
		Toxic epidermal necrolysis

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Event Category	Immune-Mediated Disorder	MedDRA PT
	Autoimmune hemolytic anemia	Anemia heamolytic autoimmune
	Thrombocytopenias	Thrombocytopenia
		Autoimmune thrombocytopenia
		Idiopathic thrombocytopenic purpura
		Thrombocytopenic purpura
		Thrombotic thrombocytopenic purpura
	Antiphospholipid syndrome	Antiphospholipid syndrome
	Vasculitis	Vasculitis
		Diffuse vasculitis
		Leukocytoclastic vasculitis
		Behcet's syndrome
		Temporal arteritis
		Takayasu's arteritis
		Microscopic polyangiitis
		Polysrteritis nodosa
		Wegener's granulomatosis
		Allergic granulomatous angiitis
		Henoch-Schonlein purpura
		Kawasaki's disease
	Pernicious anemia	Pernicious anaemia
	Autoimmune hepatitis	Autoimmune hepatitis
	Primary biliary cirrhosis	Biliary cirrhosis primary
	Primary slerosisng cholangitis	Cholangitis sclerosing
	Autoimmune glomerulonephritis	Glomerulonephritis
	Autoimmune uveitis	Uveitis
	Autoimmune myocarditis	Autoimmune myocarditis
	Sarcoidosis	Sarcoidosis

Appendix 2

Information booklet

OXFORD VACCINE GROUP

Swine Flu (Novel Influenza A H1N1) Vaccine Study

Information Booklet

You and your child are being invited to take part in a study of a vaccine against Influenza A H1N1 (swine flu). The study is being run by the Oxford Vaccine Group, part of the University of Oxford.

Before you decide whether to take part, it is important for you to understand what the study is about and what participation would involve. Please take time to read the information carefully, and discuss with others if you wish.

If anything is unclear or you would like further information please contact the study team – details below.

Thank you for taking the time to consider taking part in this study.

Contact Details

Oxford Vaccine Group
Centre for Clinical Vaccinology and Tropical Medicine
Churchill Hospital
Oxford
OX3 7LJ
Tel/Fax: 01865 857080
Email: ovg@paediatrics.ox.ac.uk

Dear Parent/Legal Guardian,

The Oxford Vaccine Group would like to invite your child to be in a study that will look at how well children respond to two new vaccines against H1N1 influenza (swine flu). This booklet outlines the study and what it would involve if your child were to take part. This study is being sponsored by the University of Oxford and is being conducted by a network of vaccine study centres in collaboration with the Health Protection Agency (HPA). Approval for this study has been gained from the Oxfordshire Research Ethics Committee and the Medicines and Healthcare products Regulatory Agency (MHRA).

What is this study about?

In the first half of this year a new strain of Influenza A H1N1 virus (known as 'swine flu' or 'Mexican flu') began to cause infections in humans. As this virus is very different from previously circulating influenza strains, few people have immunity to it and a global influenza pandemic has occurred. Fortunately most people who catch swine flu have a relatively mild illness, but a few people become very unwell and may even die. Many of these people have other underlying health conditions, such as heart or lung disease that put them at increased risk of severe disease.

Two new vaccines have been made against swine flu in response to the pandemic. These vaccines have been tested in adults, but there is less information on how well they work in children. This study will assess these two new vaccines in children aged between six months and twelve years. Participating children would receive two doses of swine flu vaccine and blood tests would be taken before and after vaccination to see how well the immune system responds. We will also look at any side effects of the two vaccines.

Taking part in this study is voluntary and if you do not want your child to participate he/she would still be eligible to receive a swine flu vaccine if it were to become available as part of a government immunisation program.

What does the study involve?

This study would consist of 3 visits each occurring 3 weeks apart over a 6 week period and would involve 2 vaccinations and 2 blood tests. These visits would be conducted at the Children's Hospital (John Radcliffe Hospital) in Oxford.

At the first visit, the study would be explained and you would be given the chance to ask any questions you may have. Before enrolment into the study, a doctor would examine your child and ask you some questions to ensure s/he was able to be included. Reasons that children would not be able to take part in the study include:

- Previous swine flu vaccination
- Previous swine flu infection (only if confirmed by laboratory testing or treated with oseltamivir ('Tamiflu') or zanamivir ('Relenza'))
- History of egg allergy or allergic reaction after previous vaccinations
- Problems with the immune system
- Coagulation disorders
- Receiving steroid tablets or syrup (e.g. for asthma) for more than 1 week within the previous 3 months (steroid inhalers or creams are allowed)
- Recent transfusion of blood or blood products (within the previous 3 months)
- Concurrent participation in another clinical trial
- Not being available for all the study visits

If your child was able to be enrolled, s/he would be allocated to one of two groups to decide which vaccine s/he would receive. The group allocation would be determined by a computer programme so that this would be decided by chance (similar to tossing a coin). Neither you nor the study team would be able to influence which group your child was allocated to.The vaccines would be given at the 1st and 2nd visit.

In order to assess the response to the vaccine each child would have 2 blood tests, one before the first vaccination and the second 3 weeks after the 2nd dose of vaccine. For each blood test we would take 6 to 10 mls of blood (one to two teaspoonfuls, depending on the age of your child). Local anaesthetic cream or cold spray would be used to minimise the discomfort of the blood test.

A diary card would be given to you after each vaccine visit. In this diary we would ask you to record daily temperatures and any reactions, such as injection site redness or swelling for 7 days after each immunisation. After this, we would ask that you to send the completed diary card to the Health Protection Agency using a pre-paid envelope. A

member of the study team will phone you after 7 days to ensure that your child is well and to remind you to post the diary card. A memory card would also be given to you after each vaccine visit. In this card we would ask you to record any reactions recorded in the diary card that are ongoing after day 7 and any visits to a doctor or emergency department until your next study visit.

In order to conduct this study as quickly as possible we plan to see many children over a short space of time. We would therefore ask you to come prepared to wait at various points during the visits. We will try to see you and your child as quickly as possible.

How many participants are there in the study?

A total of 1000 children will take part in this study; 500 aged 6 months to 3 years and 500 aged 3 to 12 years. Children will be recruited in Oxford, Bristol, Exeter, Southampton and South London.

What vaccines are going to be used in this study?

The two vaccines being assessed in this study are those that the UK government has arranged to be supplied for use if routine immunisation is recommended. One of these vaccines is made from an inactivated form of the whole swine flu virus, and is produced by the pharmaceutical company Baxter Vaccines. The other vaccine is known as a 'split virion' vaccine, meaning that it is made from a few key components of the virus, and is produced by the pharmaceutical company GlaxoSmithKline. This vaccine also contains an adjuvant called AS03 (an adjuvant is a substance designed to stimulate the immune system) and the preservative thiomersal.

The table below summarises the study design:

	Day 0	Day 21 (3 weeks)	Day 42 (6 weeks)
Group A	Baxter swine flu vaccine Blood test	Baxter swine flu vaccine	Blood test
Group B	GSK swine flu vaccine Blood test	GSK swine flu vaccine	Blood test

(Each group will have 250 children aged 6 months to 3 years and 250 children aged 3 to 12 years)

What happens if my child receives the vaccine that is not used by the government in the future?

As a result of this research the government may choose to use the vaccine that your child DID NOT receive. There may be several reasons why one of the vaccines is chosen over the other including vaccine cost, side effect frequency, response of the immune system and vaccine availability. We are expecting both vaccines to give sufficient protection and therefore don't anticipate your child requiring a further vaccine in the future. However, if your child would be better protected by receiving the other vaccine at a later date then there is no medical reason why s/he could not receive it.

Why does my child need two doses of the vaccine?

The information that we have from previous research shows that children's immune systems do not respond sufficiently after just one vaccine dose. It is expected that giving 2 doses 3 weeks apart will give the best immune response in children. Having a good immune response will be especially important if the virus changes in the future.

What are the advantages of taking part in the study?

The study provides the opportunity for your child to receive a swine flu vaccine whilst helping us to assess the response to the vaccine.

What are the risks and side effects of taking part in the study?

Both of the vaccines to be used in this study have been adapted from vaccines originally designed to protect against 'bird flu' (influenza A H5N1), and most of the information that we have about the vaccines to be used in the study comes from trials of the 'bird flu' versions of the vaccines. Over 600 adults have received the 'bird flu' form of the Baxter vaccine in clinical trials, but this vaccine has not been tested in children or adolescents under 18 years of age. Over 5,000 adults and 300 children aged 3 to 9 years have received various doses of the 'bird flu' version of the GSK vaccine in clinical trials. Both companies have started, or are about to start, studies of their 'swine flu' vaccines in children.

From the studies of the GSK 'bird flu' vaccine in children it is possible that approximately one third of children receiving the GSK 'swine flu' vaccine will have a fever over 37.5 °C, and that this fever may be above 39°C in approximately 1 in 10

children. In the 'bird flu' vaccine studies these fevers are short lived and were not associated with any complications such as febrile convulsions (a seizure associated with fever that does not have long term effects), but it is possible that complications such as these could rarely be seen following the 'swine flu' vaccine. As no studies of the Baxter 'bird flu' vaccine have been completed in children we do not know what the fever rates following this vaccine will be, but it is to be expected that some children receiving this vaccine will also develop a fever. We would therefore suggest that you have a supply of medicine against fever (such as paracetamol or ibuprofen) available for the first few days after immunisation.

Other reactions that may be observed are tenderness, redness, bruising, swelling, hardness or warmth at the injection site. Uncommon reactions are a change in eating habits, sleepiness, persistent crying, irritability, swelling of lymph nodes ('glands'), muscle pain or joint pain. Very rare (less than 1 in 1000) reactions seen in adults receiving the H5N1 vaccines include vomiting, diarrhoea, rash, cough and a congested nose. We expect these events to be generally mild and to resolve within a few days. Other very rare events that have been seen with routine flu vaccines include seizures and temporary bleeding disorders. In the past Guillian-Barré syndrome (a rare disorder of nerves) has been associated with flu vaccines but the relationship remains uncertain, with some studies suggesting a possible link but others not finding it. One large study in the UK found that influenza-like illness itself was associated with an increased risk of the Guillian-Barré syndrome but there was no link with the seasonal influenza vaccines, suggesting that vaccination might actually protect against the disorder by preventing flu.

Following the blood tests your child may experience temporary soreness and bruising. This discomfort will be minimised by the use of a local anaesthetic cream or cold spray.
In addition to the reactions listed above, there is a chance that an unexpected reaction may occur as these are new vaccines that are still being evaluated in children. We would therefore ask that you tell the study team about any changes in your child's health.

As with all vaccines there is the very small possibility of an allergic reaction. Your child would be observed for at least 20 minutes following the vaccine to monitor for any such reaction; all staff are trained and specifically equipped to respond to this unlikely event.

What happens to the blood samples?

Blood samples obtained in the study would be labelled with your child's study code and study number, but not their name. The blood sample would be stored in a freezer until the tests looking at your child's immune response had been performed. Blood samples would be tested for markers of immunity to the swine flu virus. With your specific permission we would use a small amount of blood to look at your child's DNA as part of a project looking at the influence of genetic factors on the response to vaccines. This would help us understand the body's response to immunisation. We would also ask your permission to store your child's blood samples, including DNA, for future research into infection and the immune system. The blood samples would only be used for research and would not be sold or used directly for commercial purposes. The use of blood for the genetic study and the storing of blood for future research are voluntary; you could choose not to take part in these aspects of the study and still take part in the swine flu vaccine study.

Is there someone I can contact during the study?

If your child were to take part in this study we would provide you with a 24-hour telephone number to enable you to contact one of our study team should you have any concerns.

Who else would be told about my child's involvement in the study?

Your child's participation would remain confidential and if the results of the study were published your child would not be identified. With your permission we would inform your GP and child health department that your child was enrolled in this study and that we had administered the swine flu vaccine. Any study records with your child's name and address would be held by the Oxford Vaccine Group. Your child's first name will also be on the front of the diary card and memory card that will be sent to the Health Protection Agency.

In order to ensure that the study is being conducted correctly, the following groups may inspect the study records and your child's medical records, without violating your child's confidentiality:

- Monitors hired to check that the study is being conducted to a high standard
- The Ethics Committee (EC) - A group that oversees the conduct of human research and assures the protection of patient rights and welfare.
- The Clinical Trials and Research Governance Office, University of Oxford, who are responsible for ensuring the appropriate conduct of the research on behalf of the research sponsor (the University of Oxford)
- The Medicines and Healthcare products Regulatory Agency (MHRA), who regulate all medicines and vaccines in the United Kingdom.

By signing the consent form for this study, you would be giving permission for these groups to look at your child's medical records; however they would not be able to remove any information that identified your child from the premises of the Oxford Vaccine Group.

Your child's study information, removed of any identifying information, may also be used for additional unanticipated medical and/or scientific research projects in the future. If you do not want this information used in this way, or have any questions about the use of your child's information in the study, please inform the study team.

What happens if I say 'no'?

Taking part in research is voluntary. If you decided not to participate, this would not affect your child's routine care in any way. You are also free to change your mind at any time without giving any reason. If you decide not to take part in this study you should follow any advice from your GP or the government regarding swine flu or swine flu vaccines.

What if I wish to complain?

If you have any cause to complain about any aspect of the way in which you have been approached or treated during the course of this study we suggest that you contact us or, alternatively, the University of Oxford Clinical Trials and Research Governance Office on 01865 743005.

What else do I need to know?

In the highly improbable event that your child would suffer any harm during the study, compensation for harm arising from the vaccines would be provided by the vaccine manufacturers. The University has arrangements in place to provide for harm arising from participation in the study that is not due to the vaccines themselves. Should any information become available during the course of the study that may affect your child's participation, you would be informed as soon as possible.

At the end of the study we would pay you a fee of £10 per visit to compensate you for any travel costs incurred as a result of taking part in the study. The study has been funded by a grant from the NIHR Health Technology Assessment programme.

So, in summary, what would happen if I decide to take part in the study?

- We would administer 2 doses of the influenza A H1N1 (swine flu) vaccine and take two 6 to 10 ml blood samples from your child over 3 visits each occurring 3 weeks apart.
- You would have 24-hour telephone access to our study team should you have any concerns following vaccination.

What do I do now?

Participation in this study is voluntary. If you are interested in taking part, please phone our appointment line on 01865 857080 to arrange a time to come to the Oxford Children's Hospital. If you agree for your child to take part in the study it will still be possible to change your mind at any point and withdraw. If you wish to discuss any element of the study further, then please contact us by telephone (01865 857420) or e-mail (*ovg@paediatrics.ox.ac.uk*). If you do decide to take part we would be grateful if you could bring along your child's health record (the 'red book') to your first visit.

Yours sincerely,

Professor Andrew Pollard
Professor of Paediatric Infection and Immunity
Honorary Consultant Paediatrician

Dr Matthew Snape
Consultant Vaccinologist
Honorary Consultant Paediatrician

Dr Claire Waddington
Clinical Research Fellow

Mrs Tessa John
Clinical Team Leader

Appendix 3
Consent form

Centre for Clinical Vaccinology and Tropical Medicine
Churchill Hospital - Oxford OX3 7LJ
ovg@paediatrics.ox.ac.uk
Tel/Fax: 01865 857420

OXFORD VACCINE GROUP

Swine Flu (Novel Influenza A H1N1) Vaccine Study

Consent Form

Child's full name:..... Participant code: |___| |___| |___|

If you agree with each statement please initial in each box below;

I confirm that I have read the *Information booklet Swine Flu (Novel Influenza A H1N1) Vaccine Study Version 3 dated 18th September 2009.* I have had the opportunity to consider the information, discuss the study, to ask questions and have had these answered satisfactorily. ☐

I understand that data collected during the study may be looked at by authorised individuals from the University of Oxford, MHRA, Health Protection Agency and study monitors where it is relevant to my taking part in this research. I permit these individuals access to my research records. ☐

I understand that I am free to withdraw my child from the study at any time, without having to give a reason for leaving and without affecting his/her medical care. ☐

I agree to you informing my GP and Child Health Department of my child's participation in this study. ☐

I agree to my child being examined by a study doctor as required for this study. ☐

I agree to my chid receiving two immunisations with a swine flu (novel influenza A H1N1) vaccine. ☐

I agree to you taking and storing blood samples from my child as required for this study. ☐

I agree that my child's medical records may be read by study investigators. ☐

I agree that some identifiable data such as my child's first name on the diary and memory cards, will be sent to the HPA. ☐

For children over 7 years of age:

The study has been discussed with my child and they are happy to participate. ☐

If all of the above are initialled, meaning "yes", then please continue:

I voluntarily agree to my child taking part in this study ☐

Please note that your child can still participate in this study whether or not you agree to the next statement:

I agree that blood from my child may be used for analysis of genetic factor related to vaccine reactions. ☐

I agree that any remaining blood from my child may be stored and used in future research related to vaccines and infectious diseases (with the exception of the Human Immunodeficiency Virus [HIV]). ☐

Name:.....

Relationship to Child: .....

Signature:..... Date: |___ ___| |___ ___| |___ ___|

Investigator/Study nurse's name (*please delete as appropriate*): .....

Signature: ..... Date: |___ ___| |___ ___| |___ ___|

Appendix 4

Child information sheet

Swine Flu (Novel Influenza A H1N1) Vaccine Study

•Swine Flu is a new disease that can make some people very sick. You might have seen it on the television or heard people talking about it

•Vaccines are special medicines that we give as an injection. They stop you becoming unwell. You will have had some injections when you were a baby and before you went to school but you might not remember this.

•A new vaccine has been made to stop people becoming unwell with Swine Flu.

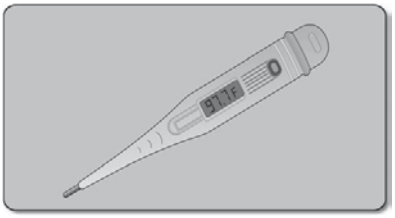
•We need to work out how well this new vaccine works and if it makes you feel unwell in any way. We would like you to help us do this.

•We would like to take a small amount of blood (about a teaspoonful) today.

•We will use a special (cream/spray) on your hand or elbow so that you won't feel the blood test, but you might have a little bruise afterwards. If you get upset when we are taking the blood you can ask us to stop and you won't be in trouble.

•We would then like to give you an injection to try and stop you getting Swine Flu.

•At home an adult will measure your temperature everyday for a week and write down if you feel unwell.



•To protect you from Swine Flu as much as possible we'd like you to come and see us again in 3 weeks time for another injection.

•To check that the injections have worked we'd like to see you one last time 3 weeks after the 2nd injection to do another blood test. We'd use special cream again so that it won't hurt.

•We have discussed this study with your mother/father/guardian. They are happy for us to do this, but we also want you to understand what we are doing and why we are doing it.

•You don't have to have this done as you are not poorly but it may stop you becoming unwell from Swine Flu and it will help us understand how the injections work.

•We will tell your doctor that you have taken part in the study, as well as the people who check on what vaccines children have been given

•We will not be telling anyone else about the study and you do not have to tell your friends and teachers at school unless you want to.

Thank you!

NHS National Institute for Health Research

Oxford Radcliffe Hospitals NHS Trust

Paediatric Infectious Diseases, Clinical Vaccine Research, Immunisation Education

Appendix 5
Diary cards

Swine Flu (Novel Influenza A H1N1) Vaccine Study

CHILDREN OVER 5 YEARS OF AGE DIARY

DIARY 1 / DIARY 2

7 DAY HEALTH DIARY

Study No:

First name: _____

Date of Vaccination: ____/_____/_____ Time of vaccination: _____

RIGHT / **LEFT** ARM

INSTRUCTIONS

Please note that Day 0 is the day of vaccination, Day 1 is the next day and so on. At about the same time each evening, please fill in the chart overleaf

HOW AND WHEN TO MEASURE YOUR CHILDS TEMPERATURE

Take the temperature under the arm (axillary)

Day 0 -6 hours after the injection / later that evening (6 - 8 pm)
Day 1 - 7 -Evening (6 - 8 pm)

Look at the vaccination site and measure the maximum width of any redness or swelling using the ruler and fill in the chart accordingly

GENERAL SYMPTOMS

*Please **circle** the appropriate number. If you child has symptoms then please evaluate the severity (mild, moderate or severe) of the symptom(s). Please complete each day.*

	Day 0 (Day of vaccine)		Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7		Please send in diary card now
Has your child been generally unwell? 0 None 1 Mild – transient with no limitation on normal activity 2 Moderate – some limitation in daily activity 3 Severe – unable to perform normal daily activity	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1	*If symptom was ongoing at day 7, document on memory aid card*
	2	3	2	3	2	3	2	3	2	3	2	3	2	3	2	3	
Has your child had a headache? 0 None 1 Mild – transient with no limitation on normal activity 2 Moderate – some limitation in daily activity 3 Severe – unable to perform normal daily activity	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1	
	2	3	2	3	2	3	2	3	2	3	2	3	2	3	2	3	
Has your child felt nauseous or vomited? 0 None 1 Mild - 1-2 episodes without interfering with routine 2 Moderate Several episodes and cannot keep any food down 3 Severe: Frequent episodes and taking nothing by mouth	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1	
	2	3	2	3	2	3	2	3	2	3	2	3	2	3	2	3	
Has your child had <u>diarrhoea</u>? **0 None** **1 Mild –** More loose stools than usual **2 Moderate** – Frequent runny stools without much solid material **3 Severe** – Multiple liquid stools without much solid material	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1	
	2	3	2	3	2	3	2	3	2	3	2	3	2	3	2	3	
Has your child been eating less than usual/had a loss of appetite? **0 None** **1 Mild –** Eating less than normal for 1-2 meals **2 Moderate** Missed 1-2 meals completely **3 Severe** Refused most or all meals	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1	
	2	3	2	3	2	3	2	3	2	3	2	3	2	3	2	3	
Has your child had muscle pain? 0 None 1 Mild – transient with no limitation on normal activity 2 Moderate – some limitation in daily activity 3 Severe – unable to perform normal daily activity	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1	
	2	3	2	3	2	3	2	3	2	3	2	3	2	3	2	3	
Has your child had joint pain? 0 None 1 Mild – transient with no limitation on normal activity 2 Moderate – some limitation in daily activity 3 Severe – unable to perform normal daily activity	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1	
	2	3	2	3	2	3	2	3	2	3	2	3	2	3	2	3	

VACCINE SITE SYMPTOMS: Please score any pain or tenderness at the injection site and measure any swelling or redness at the injection site.

	Day 0 (Day of vaccine)		***Day 1***		***Day 2***		***Day 3***		***Day 4***		***Day 5***		***Day 6***		***Day 7***		
Has there been pain at the injection site? 0 None 1 Mild – transient with no limitation on normal activity 2 Moderate – some limitation in daily activity 3 Severe – unable to perform normal daily activity	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1	If symptom was ongoing at day 7, document on memory aid card
	2	3	2	3	2	3	2	3	2	3	2	3	2	3	2	3	
RIGHT / LEFT arm maximum swelling (mm)																	
RIGHT / LEFT arm maximum redness (mm)																	

TEMPERATURE

Day	Day 0 Evening	Day 1 Evening	Day 2 Evening	Day 3 Evening	Day 4 Evening	Day 5 Evening	Day 6 Evening	Day 7 Evening
Axillary (under arm) temperature**	°C	°C	°C	°C	°C	°C	°C	°C
Any medication for pain or temperature used?	**YES / NO**	**YES / NO**	**YES / NO**	**YES / NO**	**YES / NO**	**YES / NO**	**YES / NO**	**YES / NO**
If medication used please specify name								

****TEMPERATURE (UNDER ARM):*** For an accurate temperature place the tip of the thermometer against the skin under the armpit and hold your child with his or her arm by their side closed for approximately 1 minute until the rapid beeps confirming that the temperature measurement is complete (see instruction leaflet enclosed with the thermometer for further information). On days 1 to 7, please measure your child's temperature at approximately the same time on each day.

If your child feels warm at any other time of day please record the date and time below:

_____°C ____/____/____ _____:_____ _____°C ____/____/____ _____:_____

_____°C ____/____/____ _____:_____ _____°C ____/____/____ _____:_____

_____°C ____/____/____ _____:_____ _____°C ____/____/____ _____:_____

If you need to see a doctor during the 7 day period following immunisation, please take this diary with you and tell the doctor about the study.

If your child is unwell at all, if you need to call a doctor or your child is seen by a doctor or is given any medicine then please write the details below:

Date	***Problem***	***Action taken*** (please circle answer)			***Medicine given***		
						(1st medicine)	(2nd medicine)
Start date: ____/____/____ Stop date: ____/____/____		Did you telephone a GP? Was your child seen by a GP? Seen by GP at Taken to hospital? **Admitted to hospital**	**Yes** **Yes** **Home/Surgery** **Yes** **Yes**	**No** **No** **No** **No**	Name: Start date: End date: Dosage:	______ ______ ______ ______	______ ______ ______ ______
						(1st medicine)	(2nd medicine)
Start date: ____/____/____ Stop date: ____/____/____		Did you telephone a GP? Was your child seen by a GP? Seen by GP at Taken to hospital? **Admitted to hospital**	**Yes** **Yes** **Home/Surgery** **Yes** **Yes**	**No** **No** **No** **No**	Name: Start date: End date: Dosage:	______ ______ ______ ______	______ ______ ______ ______
						(1st medicine)	(2nd medicine)
Start date: ____/____/____ Stop date: ____/____/____		Did you telephone a GP? Was your child seen by a GP? Seen by GP at Taken to hospital? **Admitted to hospital**	**Yes** **Yes** **Home/Surgery** **Yes** **Yes**	**No** **No** **No** **No**	Name: Start date: End date: Dosage:	______ ______ ______ ______	______ ______ ______ ______
						(1st medicine)	(2nd medicine)
Start date: ____/____/____ Stop date: ____/____/____		Did you telephone a GP? Was your child seen by a GP? Seen by GP at Taken to hospital? **Admitted to hospital**	**Yes** **Yes** **Home/Surgery** **Yes** **Yes**	**No** **No** **No** **No**	Name: Start date: End date: Dosage:	______ ______ ______ ______	______ ______ ______ ______
						(1st medicine)	(2nd medicine)
Start date: ____/____/____ Stop date: ____/____/____		Did you telephone a GP? Was your child seen by a GP? Seen by GP at Taken to hospital? **Admitted to hospital**	**Yes** **Yes** **Home/Surgery** **Yes** **Yes**	**No** **No** **No** **No**	Name: Start date: End date: Dosage:	______ ______ ______ ______	______ ______ ______ ______

If you, your doctor or anyone else needs advice regarding the study, he/she should contact:

H1N1 Study Team
Oxford Vaccine Group
Centre for Clinical Vaccinology and Tropical Medicine
Churchill Hospital
Old Road, Headington
Oxford
OX3 7LJ

Tel: 01865 857080
Email: ovg@paediatrics.ox.ac.uk

24 hour emergency telephone number: 07699 785400

Thank you for taking the time to fill in this diary. We would be grateful if you would return it to us using the prepaid envelope provided.

If you have lost the envelope, we would be obliged if you would post it to:

The Clinical Trials Admin Team
Immunisation Department
Health Protection Agency
61 Colindale Avenue
London
NW9 5EQ

Swine Flu (Novel Influenza A H1N1) Vaccine Study

INFANTS AND CHILDREN UNDER 5 YEARS OF AGE DIARY

DIARY 1 / DIARY 2

7 DAY HEALTH DIARY

Study No:

First name: _____

Date of Vaccination: ____/_____/_____ Time of vaccination: _____

RIGHT / **LEFT** **ARM / LEG**

INSTRUCTIONS

Please note that Day 0 is the day of vaccination, Day 1 is the next day and so on. At about the same time each evening, please fill in the chart overleaf

HOW AND WHEN TO TAKE YOUR CHILDS TEMPERATURE

Take the temperature under the arm (axillary)

Day 0	-6 hours after the injection / later that evening (6 - 8 pm)
Day 1 - 7	-Evening (6 - 8 pm)

Look at the vaccination site and measure the maximum width of any redness or swelling using the ruler and fill in the chart accordingly

Health Technology Assessment 2010; Vol. 14: No. 46, 1–130

GENERAL SYMPTOMS

*Please **circle** the appropriate number. If you child has symptoms then please evaluate the severity (mild, moderate or severe) of the symptom(s).*

	Day 0 (Day of vaccine)		***Day 1***		***Day 2***		***Day 3***		***Day 4***		***Day 5***		***Day 6***		***Day 7***		***Please send in diary card now***
Has your child been feeding less than usual? 0 None 1 Mild – Eating less than normal for 1-2 feeds/meals 2 Moderate – Missed 1-2 feeds/meals completely 3 Severe – Refused most or all feeds/meals	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	***If symptom was ongoing at day 7, document on memory aid card***
Has your child been less active than usual? 0 None 1 Mild – transient with no limitation on normal activity 2 Moderate – some limitation in daily activity 3 Severe – unable to perform normal daily activity	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	
Has your child been more irritable than usual? 0 None 1 Mild – Continuously irritable for less than 1 hour 2 Moderate – Continuously irritable for 1 to less than 3 hours 3 Severe – Continuously irritable for 3 or more hours	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	
Has your child cried persistently? 0 None 1 Mild – Cried continuously for less than 1 hour 2 Moderate – Cried continuously for 1 to less than 3 hours 3 Severe – Cried continuously for 3 or more hours	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	
Has your child vomited? 0 None 1 Mild – 1-2 episodes without interfering with routine 2 Moderate – Several episodes & cannot keep any food down 3 Severe – Frequent episodes & taking nothing by mouth	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	
Has your child had diarrhoea? 0 None 1 Mild – More loose stools than usual 2 Moderate – Frequent runny stools without much solid material 3 Severe Multiple liquid stools without much solid material	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	

VACCINE SITE SYMPTOMS: Please score any pain or tenderness at the injection site and measure any swelling or redness at the injection site.

	Day 0 (Day of vaccine)		***Day 1***		***Day 2***		***Day 3***		***Day 4***		***Day 5***		***Day 6***		***Day 7***		
Has there been pain at the injection site? 0 None 1 Mild – transient with no limitation on normal activity 2 Moderate – some limitation in daily activity 3 Severe – unable to perform normal daily activity	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1	If symptom was ongoing at day 7, document on memory aid card
	2	3	2	3	2	3	2	3	2	3	2	3	2	3	2	3	
RIGHT / LEFT arm maximum swelling (mm)																	
RIGHT / LEFT arm maximum redness (mm)																	

TEMPERATURE

Day	Day 0 Evening	Day 1 Evening	Day 2 Evening	Day 3 Evening	Day 4 Evening	Day 5 Evening	Day 6 Evening	Day 7 Evening
Axillary (under arm) temperature**	°C	°C	°C	°C	°C	°C	°C	°C
Any medication for pain or temperature used?	**YES / NO**	**YES / NO**	**YES / NO**	**YES / NO**	**YES / NO**	**YES / NO**	**YES / NO**	**YES / NO**
If medication used please specify name								

*****TEMPERATURE (UNDER ARM):*** For an accurate temperature place the tip of the thermometer against the skin under the armpit and hold your child with his or her arm by their side closed for approximately 1 minute until the rapid beeps confirming that the temperature measurement is complete (see instruction leaflet enclosed with the thermometer for further information). On days 1 to 7, please measure your child's temperature at approximately the same time on each day.

If your child feels warm at any other time of day please record the date and time below:

_____°C ____/____/____ _____:_____ _____°C ____/____/____ _____:_____

_____°C ____/____/____ _____:_____ _____°C ____/____/____ _____:_____

_____°C ____/____/____ _____:_____ _____°C ____/____/____ _____:_____

If you need to see a doctor during the 7 day period following immunisation, please take this diary with you and tell the doctor about the study.

If your child is unwell at all, if you need to call a doctor or your child is seen by a doctor or is given any medicine then please write the details below and overleaf:

Date	***Problem***	***Action taken*** (please circle answer)			***Medicine given***		
Start date:		Did you telephone a GP?	**Yes**	**No**		(1[st] medicine)	(2[nd] medicine)
___/___/___		Was your child seen by a GP?	**Yes**	**No**	Name:	___	___
Stop date:		Seen by GP at	**Home/Surgery**		Start date:	___	___
___/___/___		Taken to hospital?	**Yes**	**No**	End date:	___	___
		Admitted to hospital	**Yes**	**No**	Dosage:	___	___
Start date:		Did you telephone a GP?	**Yes**	**No**		(1[st] medicine)	(2[nd] medicine)
___/___/___		Was your child seen by a GP?	**Yes**	**No**	Name:	___	___
Stop date:		Seen by GP at	**Home/Surgery**		Start date:	___	___
___/___/___		Taken to hospital?	**Yes**	**No**	End date:	___	___
		Admitted to hospital	**Yes**	**No**	Dosage:	___	___
Start date:		Did you telephone a GP?	**Yes**	**No**		(1[st] medicine)	(2[nd] medicine)
___/___/___		Was your child seen by a GP?	**Yes**	**No**	Name:	___	___
Stop date:		Seen by GP at	**Home/Surgery**		Start date:	___	___
___/___/___		Taken to hospital?	**Yes**	**No**	End date:	___	___
		Admitted to hospital	**Yes**	**No**	Dosage:	___	___
Start date:		Did you telephone a GP?	**Yes**	**No**		(1[st] medicine)	(2[nd] medicine)
___/___/___		Was your child seen by a GP?	**Yes**	**No**	Name:	___	___
Stop date:		Seen by GP at	**Home/Surgery**		Start date:	___	___
___/___/___		Taken to hospital?	**Yes**	**No**	End date:	___	___
		Admitted to hospital	**Yes**	**No**	Dosage:	___	___
Start date:		Did you telephone a GP?	**Yes**	**No**		(1[st] medicine)	(2[nd] medicine)
___/___/___		Was your child seen by a GP?	**Yes**	**No**	Name:	___	___
Stop date:		Seen by GP at	**Home/Surgery**		Start date:	___	___
___/___/___		Taken to hospital?	**Yes**	**No**	End date:	___	___
		Admitted to hospital	**Yes**	**No**	Dosage:	___	___

If you, your doctor or anyone else needs advice regarding the study, he/she should contact:

H1N1 Study Team
Oxford Vaccine Group
Centre for Clinical Vaccinology and Tropical Medicine
Churchill Hospital
Old Road, Headington
Oxford
OX3 7LJ

Tel: 01865 857080
Email: ovg@paediatrics.ox.ac.uk

24 hour emergency telephone number: 07699 785400

Thank you for taking the time to fill in this diary. We would be grateful if you would return it to us using the prepaid envelope provided.

If you have lost the envelope, we would be grateful if you would post it to:

The Clinical Trials Admin Team
Immunisation Department
Health Protection Agency
61 Colindale Avenue
London
NW9 5EQ

Appendix 6

Memory aid card

Swine Flu (Novel Influenza A H1N1) Vaccine Study

Memory Aid Card

Your child's next visit is scheduled for:
__ __ /__ __ /__ __ __ __ at __ __:__ __ hours

Child's first name:_____ **Child's Number:** _____

WHY DO I NEED TO COMPLETE THIS MEMORY CARD?

Dear Parent/Legal Guardian

Thank you very much for completing the diary card for the 7 days after your child was vaccinated. Please remember to return the diary card in the pre-paid envelope.

We would be grateful if you could fill in this memory card from 8 days after the vaccine until we see you at the next visit. We would like to know if any of the **symptoms that your child may have had after vaccination continued beyond day 7.** We would also like you to record any change in your child's health **that has led to your child being seen by a doctor or going to the Emergency Department (A&E).**

If your child needs hospitalisation for any reason or if you are concerned about your child's health, please contact the study team immediately

Our contact details are:
01865 857080 (Office hours)

24 hours advice number:
07703134238

Vaccine reactions continuing after day 7

Injection site reactions •tenderness •swelling •Redness	Start date(s) of reaction dd/mm	Stop date(s) of reaction dd/mm	Date(s) of doctor / Emergency Department visit (A&E)?	Medication(s) to treat the reaction
				□No □Yes, specify:

General reactions •fever (≥ 38°C) •changing in feeding/ eating •reduced activity/ irritability/ generally unwell •vomiting or diarrhoea •For children <5 years: persistant crying •For children >5 years: muscle pain or joint pain	Start date(s) of reaction dd/mm	Stop date(s) of reaction dd/mm	Date(s) of doctor / Emergency Department visit (A&E)?	Medication(s) to treat the reaction
				□No □Yes, specify:

SYMPTOMS/ILLNESSES requiring a visit to a doctor or emergency department (A&E)

Symptom / Illness	Start date (s) of reaction dd/mm	Stop date(S) of reaction dd/mm	Date(s) of doctor / Emergency Department visit (A&E)?	Medication(s) to treat the illness/ symptom
				□No □Yes, specify:

Reminder: Please bring this card with you to the next visit

Appendix 7

Recruitment poster

Children's Swine Flu Vaccine Study

The Oxford Vaccine Group is part of a network of 5 centres in the UK conducting a study of 2 new vaccines aimed at providing protection against Swine Flu.

We would like to invite you and your child to take part in this study.

If you are the parent of a child aged between 6 months and 12 years inclusive and want to find out more information please access the website via the web address below to view the information for parents:

www.swineflutrial.org

For further information or to talk to one of our team please contact the Oxford Vaccine Group on 01865 857080 or email ovg@paediatrics.ox.ac.uk

Evaluation of droplet dispersion during non-invasive ventilation, oxygen therapy, nebuliser treatment and chest physiotherapy in clinical practice: implications for management of pandemic influenza and other airborne infections

AK Simonds,[1]* A Hanak,[1] M Chatwin,[1] MJ Morrell,[1] A Hall,[2] KH Parker,[3] JH Siggers[3] and RJ Dickinson[3]

[1]Clinical and Academic Unit of Sleep & Breathing, Royal Brompton & Harefield NHS Foundation Trust, London, UK
[2]Department of Microbiology, Royal Brompton & Harefield NHS Foundation Trust, London, UK
[3]Department of Bioengineering, Imperial College, London, UK

*Corresponding author

Declared competing interests of authors: AKS has an unrestricted research grant from ResMed Ltd for the investigation of an autotitrating ventilator, which is not related to the present study.

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Abstract

Evaluation of droplet dispersion during non-invasive ventilation, oxygen therapy, nebuliser treatment and chest physiotherapy in clinical practice: implications for management of pandemic influenza and other airborne infections

AK Simonds,[1*] A Hanak,[1] M Chatwin,[1] MJ Morrell,[1] A Hall,[2] KH Parker,[3] JH Siggers[3] and RJ Dickinson[3]

[1]Clinical and Academic Unit of Sleep & Breathing, Royal Brompton & Harefield NHS Foundation Trust, London, UK
[2]Department of Microbiology, Royal Brompton & Harefield NHS Foundation Trust, London, UK
[3]Department of Bioengineering, Imperial College, London, UK

*Corresponding author

Background: Influenza viruses are thought to be spread by droplets, but the role of aerosol dissemination is unclear and has not been assessed by previous studies. Oxygen therapy, nebulised medication and ventilatory support are treatments used in clinical practice to treat influenzal infection are thought to generate droplets or aerosols.
Objectives: Evaluation of the characteristics of droplet/aerosol dispersion around delivery systems during non-invasive ventilation (NIV), oxygen therapy, nebuliser treatment and chest physiotherapy by measuring droplet size, geographical distribution of droplets, decay in droplets over time after the interventions were discontinued.
Methods: Three groups were studied: (1) normal controls, (2) subjects with coryzal symptoms and (3) adult patients with chronic lung disease who were admitted to hospital with an infective exacerbation. Each group received oxygen therapy, NIV using a vented mask system and a modified circuit with non-vented mask and exhalation filter, and nebulised saline. The patient group had a period of standardised chest physiotherapy treatment. Droplet counts in mean diameter size ranges from 0.3 to > 10 μm were measured with an counter placed adjacent to the face and at a 1-m distance from the subject/patient, at the height of the nose/mouth of an average health-care worker.
Results: NIV using a vented mask produced droplets in the large size range (> 10 μm) in patients ($p = 0.042$) and coryzal subjects ($p = 0.044$) compared with baseline values, but not in normal controls ($p = 0.379$), but this increase in large droplets was not seen using the NIV circuit modification. Chest physiotherapy produced droplets predominantly of > 10 μm ($p = 0.003$), which, as with NIV droplet count in the patients, had fallen significantly by 1 m. Oxygen therapy did not increase droplet count in any size range. Nebulised saline delivered droplets in the small- and medium-size aerosol/droplet range, but did not increase large-size droplet count.
Conclusions: NIV and chest physiotherapy are droplet (not aerosol)-generating procedures, producing droplets of > 10 μm in size. Due to their large mass, most fall out on to local surfaces within 1 m. The only device producing an aerosol was the nebuliser and the output profile is consistent with nebuliser characteristics rather than dissemination of large droplets from patients. These findings suggest that health-care workers providing NIV and chest physiotherapy, working within 1 m of an infected patient should have a higher level of respiratory protection, but that infection control measures designed to limit aerosol spread may have less relevance for these procedures. These results may have infection control implications for other airborne infections, such as severe acute respiratory syndrome and tuberculosis, as well as for pandemic influenza infection.

Contents

List of abbreviations

AGP	aerosol-generating procedure
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
DH	Department of Health
EPAP	expiratory positive airway pressure
IPAP	inspiratory positive airway pressure
mod NIV	modified NIV circuit with exhalation filter
NIV	non-invasive ventilation
O2	oxygen therapy
$PaCO_2$	partial pressure of arterial carbon dioxide
PaO_2	partial pressure of arterial oxygen
PPE	protective personal equipment
RR	relative risk
SaO_2	arterial oxygen saturation
SARS	severe acute respiratory syndrome
SD	standard deviation
$TcCO_2$	transcutaneous partial pressure of carbon dioxide
WHO	World Health Organization

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Background

Influenza viruses are thought to be spread by droplets, but the role of aerosol dissemination (defined as droplet size range < 5 μm) is unclear. A subgroup of patients, often with underlying chronic disorders or risk factors, such as pregnancy or immunosuppression, can develop pneumonia/respiratory insufficiency with H1N1 swine flu or other influenzal infection requiring treatment by oxygen therapy (O2), nebulised medication and ventilatory support. These therapies are thought to generate droplets or aerosols, and in the severe acute respiratory syndrome (SARS) outbreak were associated with an increased incidence of SARS in health-care workers and higher risk of superspreading events in hospital wards. Non-invasive ventilation (NIV) is unlikely to be effective in rapidly progressive acute lung injury, but may have a role in chronic patients in whom influenza has caused an infective exacerbation, and its use may reduce pressure on intensive care beds. Previous studies have not assessed droplet or aerosol generation during respiratory support interventions in clinical practice.

Objectives

We evaluated the characteristics of droplet/aerosol dispersion around delivery systems during NIV, O2, nebuliser treatment and chest physiotherapy by measuring droplet size, geographical distribution of droplets, decay in droplets over time after the interventions were discontinued, and the impact of modification of the NIV circuit in clinical practice.

Methods

Three groups were studied: (1) normal control subjects, (2) subjects with coryzal symptoms and (3) adult patients with chronic lung disease who were admitted to hospital with an infective exacerbation.

Each group received O2, NIV using a vented mask system and a modified circuit with non-vented mask and exhalation filter, and nebulised saline. The patient group had a period of standardised chest physiotherapy treatment. Droplet counts in mean diameter size ranges from 0.3 to > 10 μm were measured with a counter placed adjacent to the face (D1) and at 1-m distance (D2) from subject/patient at the height of the nose/mouth of an average health-care worker.

Results

Non-invasive ventilation using a vented mask produced droplets in the large size range (> 10 μm) in patients ($p = 0.042$) and coryzal subjects ($p = 0.044$) compared with baseline values, but not in normal controls ($p = 0.379$). This increase in large droplets was not seen using the NIV circuit modification. Chest physiotherapy produced droplets predominantly of > 10 μm ($p = 0.003$), which, as with NIV droplet count in the patients, had fallen significantly by 1 m. O2 did not increase droplet count in any size range. Nebulised saline delivered droplets in the small- and medium-size aerosol/droplet range in keeping with the specified performance characteristics of the device but did not increase large-size droplet count. Preliminary analysis suggests that droplet counts fall to within a baseline range within 20–40 minutes of discontinuing the NIV and chest physiotherapy.

Conclusions

Non-invasive ventilation and chest physiotherapy are droplet (not aerosol)-generating procedures, producing droplets of > 10 μm in size. Due to their large mass, most fall out on to local surfaces within 1 m. The only device producing an aerosol was the nebuliser and the output profile is consistent with nebuliser characteristics rather than dissemination of large droplets from patients. These findings suggest that health-care workers providing NIV and chest physiotherapy working within 1 m of an infected patient should have a higher level of respiratory protection, but that infection control measures designed to limit aerosol spread, for example negative-pressure rooms, may have less relevance. The results may have infection control implications for other airborne infections, such as SARS and tuberculosis, as well as for pandemic influenza infection.

Chapter 1
Introduction

Respiratory viral infections, such as influenza, are spread by droplets, an aerosol of infected material or by direct or indirect contact with contaminated surfaces. The mode of transmission and the factors influencing this are important, as they have key implications for infection control in patients and staff, and therefore pandemic planning. Droplets in the respirable range (around 5 μm) may play a significant part in transmission,[1] but the role of aerosols has been questioned[2] and there are few studies quantifying viral load in droplets or aerosols. An observational study[3] of influenza A and influenza B in exhaled breath showed viral RNA in one-third of infected patients, and 99% of particles had a diameter of < 5 μm when sampled during tidal breathing.

While some individuals recover from seasonal or H1N1 influenza, having experienced minimal symptoms, a subgroup of high-risk patients may develop complications, including respiratory failure,[4,5] and, in new more pathogenic strains, such as H5N1, respiratory insufficiency may occur in more than 50% of those affected. These patients are managed with antiviral therapy and antibiotics for secondary bacterial pneumonia, but the mainstay of management is supportive respiratory care, which includes high-flow oxygen therapy (O2) for hypoxaemic patients, and ventilatory support for those with ventilatory insufficiency.[6,7] Adjunctive therapy can include nebulised bronchodilator for patients with underlying asthma or chronic obstructive pulmonary disease (COPD), and physiotherapy is used to facilitate secretion clearance for those in whom influenza has precipitated an infective exacerbation of chronic lung disease, such as COPD, bronchiectasis or cystic fibrosis.

Coughing and sneezing patients can shed relatively large particles (> 10 μm) that travel short distances and may contaminate the bedside environment. Smaller droplets or aerosols will remain airborne for longer periods and disseminate over greater distances.[1] The definition of an aerosol varies but most authorities characterise this as consisting of droplets of < 5 μm. Some medical procedures have been termed 'aerosol generating', as the common feature is that they are associated with high or augmented inspiratory and expiratory tidal flows, which may increase viral dissemination but this classification is based on assumptions rather than systematic evidence. The list of aerosol-generating procedures (AGPs) differs a little from country to country but in Department of Health (DH) guidance[7,8] these include bronchoscopy, intubation of the airway and invasive ventilation manoeuvres, such as open suctioning, cardiopulmonary resuscitation, non-invasive ventilation (NIV) and continuous positive airway pressure (CPAP) therapy, high-frequency oscillation ventilation, and induction of sputum. Certain other procedures, such as delivery of nebulised medication therapy and high-flow O2 are considered to be possible aerosol generators, but a lesser infective risk.[8] There is an association between some of these AGPs and an increased incidence of severe acute respiratory syndrome (SARS) in health-care workers[9–11] and the risk of superspreading events on wards.[12] This has implications for the safe care of patients and risk management for nurses, doctors, physiotherapists and other health-care workers, and has provoked an ethical debate on the duty of care of health-care staff in pandemics.[13,14]

Much of the evidence for the link between AGPs and increased transmission of respiratory viral infection was generated during the SARS epidemic. In Toronto and Singapore, health-care workers constituted approximately 20% of critically ill cases. Infection rates were higher in doctors and nurses carrying out endotracheal intubation [relative risk (RR) 13.29, 95% confidence interval (CI) 2.99 to 59.04, $p = 0.03$], while nurses caring for SARS patients receiving NIV may have been at increased risk (RR 2.23), but this finding did not reach significance (95% CI 0.25 to 21.76, $p = 0.5$).[9] In a case–control study of dissemination of SARS from an index case to other patients on the same ward, Yu *et al.*[12] showed an increased risk associated with the index patient requiring O2 or bilevel NIV. Case reports[15,16] have also linked transmission of infection to nebuliser use in the index patient. However, patient variables are also likely to be important, as sicker patients who may have a higher viral load are more likely to require O2 and ventilatory support, and those with underlying asthma who require nebuliser therapy

may cough more due to airway hyper-reactivity. For these reasons specific infection control precautions have been introduced for unavoidable AGPs and these include use of high-efficiency FFP3 (or N95) masks, eye protection, gowns, aprons and gloves.[8] Guidelines also suggest that AGPs should only be used if necessary, and controversy has arisen over the role of NIV.[17,18] Its use is recommended with appropriate precautions in some national guidelines,[7] but not in other guidelines, and NIV use is cautioned against by some authorities.[19–21]

Non-invasive ventilation (NIV) and CPAP are unlikely to have a role in acute lung injury caused by influenza or in secondary bacterial pneumonia, or in patients with multisystem failure.[17] However, NIV was used successfully in some SARS cases,[22,23] and as indicated in DH guidelines,[24] there is potential for NIV to reduce the need for intubation in influenza pneumonia in those with chronic respiratory disease,[25] to facilitate extubation, and to widen the provision of ventilatory support outside the intensive care unit. It may also be used as a ceiling of ventilatory care in patients with COPD, congestive cardiac failure and other serious comorbidities, and to palliate symptoms in those with end-stage disease in whom ICU admission is not indicated. These indications should be set against the risks of droplet dissemination during the delivery of NIV – yet at present those risks have not been quantified.

It is also important to note that there are problems in interpreting the evidence of transmission of infection during SARS. This is because transmissibility could have been increased by an inadequate use of protective personal equipment (PPE) in early cases;[11,26] NIV equipment has evolved since 2003–4, and there have been subsequent experimental studies that have investigated air flows around oxygen masks and during NIV.[27–30] These studies used human simulator models or normal subjects mimicking respiratory distress. Hui *et al.*[28,31] have carried out a series of experimental studies analysing particle spread from NIV and oxygen masks,[32] using smoke particles as a proxy of droplets in expired air. However, human simulators may not closely reflect the behaviour of sick patients, and smoke particles are considerably smaller (< 1 μm) than droplets generated by coughing and sneezing (range 5 to > 10 μm). Therefore, the behaviour of smoke particles may not accurately represent droplet dispersion. Other workers have used a Schlieren optical visualisation technique[33] to demonstrate exhaled air flows in normal subjects when coughing with and without masks. These provide useful information on expiratory flow profiles but none of the investigations has been carried out using the range of common clinical interventions defined as AGPs, analysed droplet size or studied patients with respiratory infections.

This background therefore provided the rationale of this study, the aim of which was to investigate droplet dispersion during O2, NIV and nebuliser treatment in patients with coryzal symptoms, patients with an infective exacerbation of chronic lung disease and a control group of normal subjects, to inform safe use. We reasoned that patients with a chronic exacerbation of lung disease or a coryzal infection would generate droplets regardless of the aetiology of the infection, therefore we did not specify that the infection had to be due to H1N1 or any other subtype of influenza A or influenza B. We sought to:

1. determine droplet size and concentration
2. determine geographical distribution of droplets
3. compare and contrast droplets generated during different interventions
4. examine whether modifications of treatment delivery affect droplet dissemination
5. estimate droplet decay after the intervention had ceased.

Although not classified as an AGP, we added an analysis of droplet counts and dispersion during a standardised session of chest physiotherapy in the chronic respiratory patients. This was because there was a high level of concern by physiotherapists that droplet dissemination would be considerable, thus putting these health-care workers at risk. In addition, in 40 patients admitted to the respiratory wards at the Royal Brompton Hospital NHS Foundation Trust with suspected swine flu in the first and second wave of H1N1 in 2009, all had underlying respiratory disease (predominantly cystic fibrosis and asthma) or neuromuscular disease, and required chest physiotherapy as part of their clinical management.

Chapter 2
Methods

Trial design

This was an observational trial carried out in a standard single-bedside room on a respiratory ward at the Royal Brompton & Harefield NHS Foundation Trust. The study was approved by Brompton, Harefield and NHLI Research Ethics Committee (ref. no. 09/H0708/58).

Normal subjects

Normal subjects were recruited from a departmental database of normal people aged 18 years and above. Individuals with a current illness or underlying condition were excluded.

Coryzal patients

To fulfil entry criteria these patients were individuals, aged 18 years and above, who were previously well with no underlying health condition but, within the previous 24–48 hours, had developed a pyrexia or history of pyrexia and any two of the following flu-like symptoms: sore throat, muscle aches and pains, cough and/or headache.

Patients

We recruited patients with an acute infective exacerbation of chronic respiratory disease requiring admission to a respiratory ward. Inclusion criteria: aged 18 years and above, clinically confirmed infective exacerbation and with an underlying diagnosis of asthma, cystic fibrosis, COPD, bronchiectasis or chest wall disease for which O2 and/or NIV was clinically indicated. Exclusion criteria: haemodynamic instability, partial pressure of arterial oxygen (PaO_2) < 7.4 kPa, partial pressure of arterial carbon dioxide ($PaCO_2$) > 7.5 kPa, pH < 7.34 on oxygen/NIV therapy, cognitive inability such that patient was unable to understand information sheet or that the patient was unable to breathe spontaneously for more than 4 hours.

Droplet visualisation

Droplets were detected using an optical particle sizer (Aerotrak 8220, TSI Instruments Ltd, High Wycombe, UK), which counts particles in the range 0.3 to > 10 μm within ranges of 0.3–0.5, 0.5–1.0, 1.0–3.0, 3.0–5.0, 5.0–10.0 and > 10.0 μm, with a counting efficiency of 50% ± 10% at 0.3 μm and 100% ± 10% at 0.45 μm and greater. Particles or droplets are measured in size and concentration per cubic metre by detecting the light scattered from individual droplets as they are drawn through a focused laser beam. The intensity of scattered light is a composite function of the diameter, shape and refractive index of the droplet, as well as the light wavelength and the geometry of the optical detector. A photodetector within the Aerotrak measures the amount of light each droplet scatters and records a count for each size range, for example 0.3–0.5 μm, 5–10 μm, etc. The two Aerotrak devices were calibrated before and after the series of normal subject, coryzal and patient study runs, using polystyrene latex spheres made to particle standards in each size band from 0.3–10 μm. The count efficiency of the device for droplets of 0.45 μm and larger was 100% ± 10%, and at 0.3 μm it was 50% ± 10%. The baseline zero count assurance test using a HEPA filter was passed at a count of < 1 particle per 5 minutes at a 95% confidence level in accordance with ISO (International Organisation for Standardisation) 21501–4. Sampling flow rates of both Aerotrak devices were within 5% of tolerance when calibrated before and after the study runs.

Droplet sampling was carried out over 30 seconds, at 5-minute intervals during baseline periods, and treatment interventions with an Aerotrak detector placed at two sampling points: D1, adjacent (within 20 cm) to patient/subject mouth or treatment mask/interface, and D2, 1.0 m from subject/patient at 45 degrees in the lateral plane. The position D2 was chosen to represent a typical location of a health-care worker providing assistance to the patient. Each Aerotrak counter was zeroed using a HEPA filter before each study run. To maintain

accuracy and reproducibility of measurements, the Aerotrak at D1 was placed in a fixed position on a bed table and the Aerotrak at 1.0 m was mounted on a tripod, adjusted to a height of approximately 1.52 m (5 ft) from the floor, which is equivalent to the height of the nose/mouth of an average-sized health-care worker.

Equipment

Non-invasive ventilation (NIV) was provided using a VPAP ST III (ResMed UK Ltd, Abingdon, UK) bilevel positive pressure ventilator set in spontaneous timed mode. NIV was delivered (1) using a vented full-face mask that was sized to subject (ResMed vented hospital-use face mask) or (2) using a modified circuit. The modified circuit consisted of non-vented full-face mask (ResMed non-vented hospital face mask) and a viral/bacterial filter (Intersurgical filter 1944) placed between the mask and an expiratory leak so that exhalate was filtered [modified NIV (mod NIV)]. The ventilator was started once the mask was secured on the face. In the normal subjects and the coryzal group the ventilator settings were: inspiratory positive airway pressure (IPAP) 20 cmH_2O, expiratory positive airway pressure (EPAP) 5 cmH_2O, with back-up rate of 15 per minute. In patients the IPAP, EPAP and back-up rate were set at clinically required levels, with oxygen entrained into the NIV circuit as clinically indicated to maintain arterial oxygen saturation of > 90%. We used a standard jet nebuliser with compressor (Actineb, Clement Clark International Ltd, Harlow, UK), which was designed to generate a droplet profile of mass mean diameter 3.3 μm, with 72% droplets < 5 μm, at average flow rate of 7 l/minute. In each nebuliser intervention this delivered 4 ml of normal saline to the normal subjects, coryzal subjects and the patients.

Interventions

Normal controls and coryzal patients

On arrival in the side room, subjects were seated in a semirecumbent position on the bed. The Aerotrak counters were aligned to the subject as described, and baseline readings of droplet counts at the two sampling positions D1 and D2 were obtained over 40 minutes, sampling at 5-minute intervals. Subjects were then asked to do a series of spontaneous coughs both without and with a surgical mask. They then received O2 via a 60% Ventimask for 20 minutes, then NIV delivered through the non-vented hospital full-face mask (ResMed) using the modified filtered circuit for 20 minutes, then NIV via standard circuit with a vented mask for 20 minutes, and, finally, 4 ml of nebulised normal saline via the mouthpiece. Between interventions there were periods of 40 minutes to allow background droplet counts to fall to baseline levels (*Figure 1*).

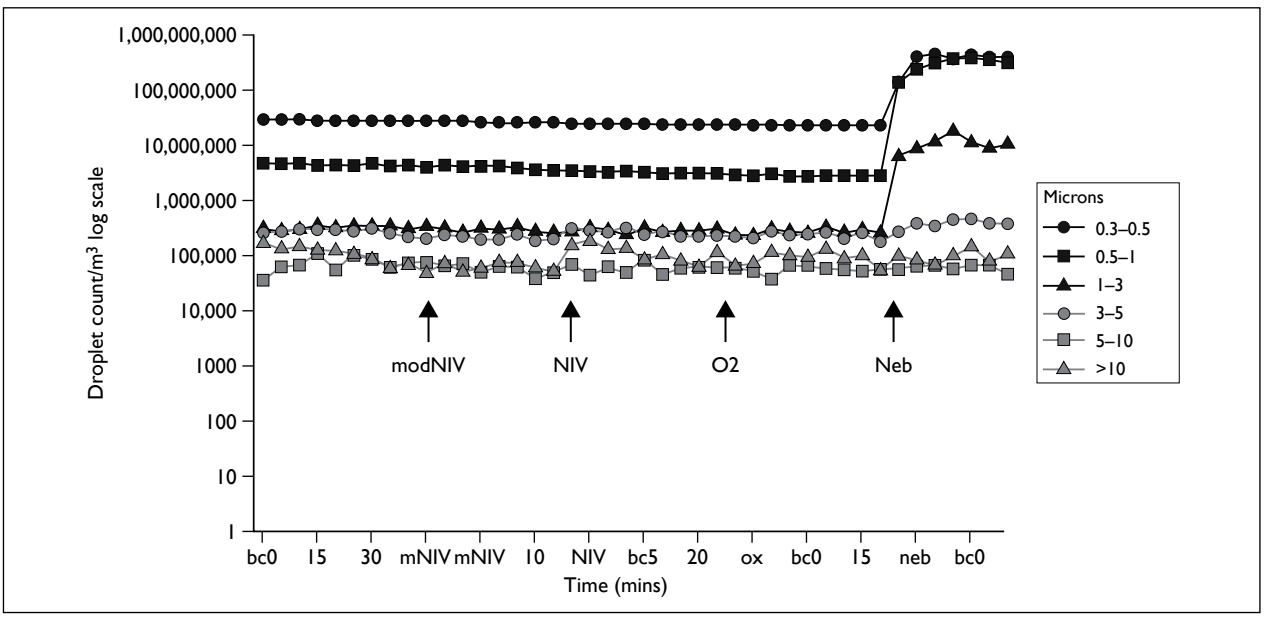

FIGURE 1 *Example of coryzal subject experimental run. bc, baseline count; mNIV, modified NIV; neb, nebuliser; ox, oxygen therapy.*

Patients

Measurements were carried out as above but with the following differences. All patients had arterial oxygen saturation (SaO_2), heart rate and transcutaneous PCO_2 monitored throughout the experimental interventions. After baseline measurements patients received 24% oxygen via Venturi mask for 20 minutes. Those who were using NIV received 20 minutes of ventilatory support at their current clinically indicated IPAP and EPAP settings, with oxygen entrained to maintain saturation to > 90%, first with the modified circuit and non-vented mask (2) and secondly with the vented face mask (1). The patients also underwent a standardised session of chest physiotherapy over 10 minutes. This consisted of cycles of deep breathing with percussion or shaking to loosen any secretions, followed by an assisted cough initiated manually, augmented by the physiotherapist performing inward and upwards pressure on the lower thorax to aid expectoration, after which the patient rested and cycles were repeated for 10 minutes. Throughout the study only two physiotherapists performed the physiotherapy in order to standardise the techniques as far as possible. Intervals of 40 minutes between interventions were added as in normal subjects and coryzal patients to re-establish baseline droplet levels (*Figure 2*).

Study area/baseline readings

A standard ward side room, of width and length 3.37 × 3.37 m and height 2.84 m, was used for all experiments. There was no external window or external ventilation system. Disturbances in the room were minimised by keeping the door shut throughout and allowing one investigator to be present. The investigator wore a surgical mask throughout, and provided the physiotherapy. The experiments were usually undertaken in two runs, in the morning and afternoon of the same day, each lasting approximately 2.5 hours. This length of time was needed in order to allow 20–40 minutes between consecutive interventions so that baseline droplet counts could be restored. Patients and subjects rested in a position of comfort in the bed throughout the interventions, and the position was not changed between the interventions in order to maintain D1 and D2 distances.

Analysis

There are few previous data on droplets generated by respiratory interventions on which to base the sample size. We reasoned that if infection is predominantly transmitted by coughing and sneezing then an increase in droplet count caused

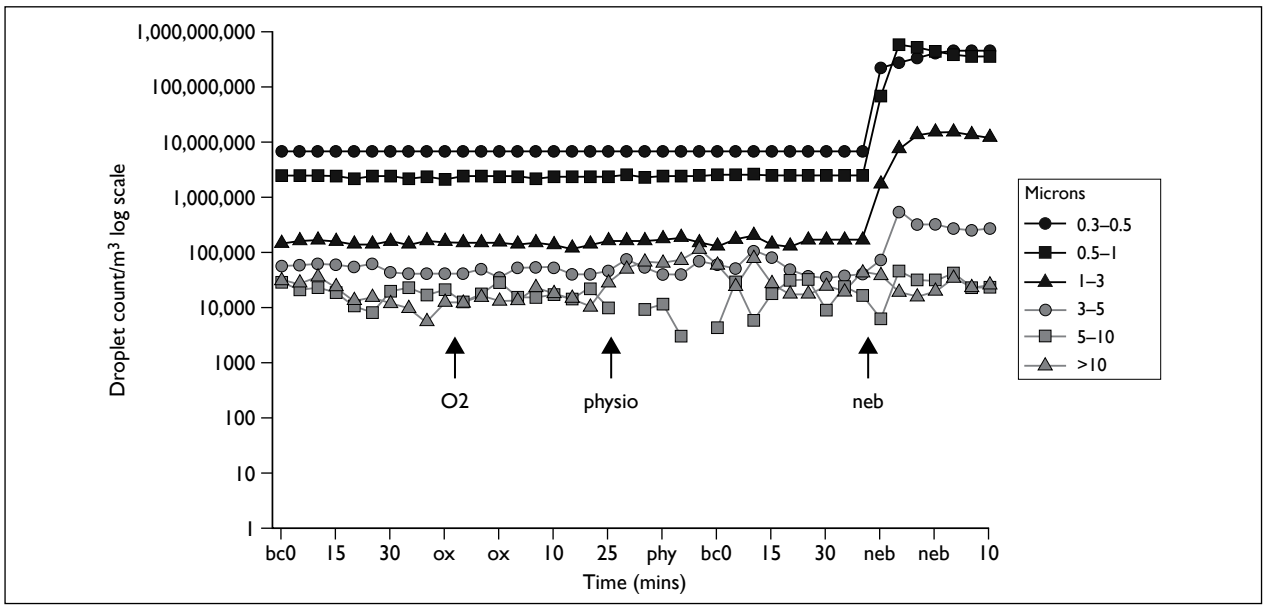

FIGURE 2 *Example of patient experimental run. bc, baseline count; neb, nebuliser; ox, oxygen therapy.*

by interventions, equivalent to the increase seen from tidal breathing to spontaneous cough, would be clinically meaningful. Pilot studies suggested that a doubling in droplet size would occur in the ranges of 5–10 µm and > 10 µm, with possibly a greater increase in the aerosol range. A doubling in count of 5–10 µm or > 10 µm from a mean of 900 in 5–10 or > 10 µm range to 1800 [standard deviation (SD) 100], with a false-positive rate of 0.05 and 80% power, suggested that very small groups would be needed. We increased the patient group size to account for the possibility that counts and variability might be higher in patients and therefore aimed to study a minimum of 10 normal subjects, 10 with coryzal symptoms and 20 patients.

For each of the five interventions, droplet sampling was carried out on four occasions at 5-minute intervals before treatment, and on four occasions during the intervention, and these values were averaged to give N_{pre} and N_{post}. As we were interested in the relative change due to the intervention rather than absolute values in each subject, this difference was normalised by the average of the four control samples taken before the intervention to give the normalised difference Δ or D $(N_{post}–N_{pre})/N_{pre}$ was calculated. The significance of this normalised difference was calculated using the two-sided Student's *t*-test.

Chapter 3
Results

In total, 44 subjects and patients were studied: 12 normal controls, 11 with coryzal symptoms and 21 patients. Subject and patient characteristics are given in *Tables 1–3*. The patients had a range of chronic lung conditions and all had been admitted because of an acute infective exacerbation. None of the patients or coryzal individuals had an H1N1 infection. All normal subjects and 10 of the coryzal subjects completed the 60% O2, NIV, mod NIV and nebuliser therapy. One coryzal patient completed all interventions except NIV modes, as these provoked claustrophobia. All patients received physiotherapy, but normal subjects or coryzal patients did not; all patients received 24% O2 via Ventimask and nebuliser therapy. Eight patients received NIV and mod NIV, as this was indicated to manage hypercapnic respiratory failure. A total of 19 coryzal subjects and patients therefore underwent the NIV and mod NIV interventions.

Physiotherapy

In the patients there was an increase in > 10-μm droplets at D1, but this has fallen at 1 m (D2) ($p < 0.003$) (*Figure 3*). There was no increase in the other droplet ranges.

NIV using vented mask

The mean difference increased in the coryzal and patient group in the > 10-μm range at D1, but not in the normal controls, and this count was elevated at D2 in 3–5 μm, 5–10 μm and > 10-μm ranges at D2 in the coryzal subjects.

Modified NIV

Using the circuit modification the mean difference was not significantly different from baseline values

TABLE 1 *Normal subjects: age and trial interventions*

Normal subject no.	Age (years)	Trial interventions
1	38	O2, NIV, mod NIV, Neb
2	35	O2, NIV, mod NIV, Neb
3	52	O2, NIV, mod NIV, Neb
4	24	O2, NIV, mod NIV, Neb
5	32	O2, NIV, mod NIV, Neb
6	52	O2, NIV, mod NIV, Neb
7	32	O2, NIV, mod NIV, Neb
8	28	O2, NIV, mod NIV, Neb
9	25	O2, NIV, mod NIV, Neb
10	24	O2, NIV, mod NIV, Neb
11	28	O2, NIV, mod NIV, Neb
12	34	O2, NIV, mod NIV, Neb
Mean (SD)	33.7 (9.6)	

mod NIV, modified non-invasive ventilation circuit; Neb, nebulised saline; NIV, non-invasive ventilation; O2, oxygen therapy 60%; SD, standard deviation.

TABLE 2 *Coryzal group: age and interventions*

Coryzal patient no.	Age (years)	Trial interventions
1	30	O2, Neb[a]
2	24	O2, NIV, mod NIV, Neb
3	32	O2, NIV, mod NIV, Neb
4	45	O2, NIV, mod NIV, Neb
5	28	O2, NIV, mod NIV, Neb
6	37	O2, NIV, mod NIV, Neb
7	25	O2, NIV, mod NIV, Neb
8	38	O2, NIV, mod NIV, Neb
9	24	O2, NIV, mod NIV, Neb
10	28	O2, NIV, mod NIV, Neb
11	30	O2, NIV, mod NIV, Neb
Mean (SD)	31 (6.6)	

mod NIV, modified NIV circuit; Neb, nebulised saline; NIV, non-invasive ventilation; O2, oxygen therapy 60%; SD, standard deviation.
a Coryzal patient no. 1 did not complete NIV and mod NIV interventions due to claustrophobia.

TABLE 3 *Patient age, diagnosis and interventions*

Patient	Age (years)	Diagnosis	Indication for admission	Study interventions
1	74	Bronchiectasis	Infective exacerbation	O2, NIV, mod NIV, Neb, Physio
2	55	COPD	Infective exacerbation	O2, NIV, mod NIV, Neb, Physio
3	37	Cystic fibrosis	Infective exacerbation	O2, Physio, Neb
4	34	Cystic fibrosis	Infective exacerbation	O2, Physio, Neb
5	18	Bronchiectasis	Infective exacerbation	O2, Physio, Neb
6	27	Cystic fibrosis	Infective exacerbation	O2, Physio, Neb
7	29	Cystic fibrosis	Infective exacerbation	O2, Physio, Neb
8	58	Bronchiectasis	Infective exacerbation	O2, Physio, Neb
9	62	Bronchiectasis	Infective exacerbation	O2, Physio, Neb
10	20	Cystic fibrosis	Infective exacerbation	O2, Physio, Neb
11	25	Cystic fibrosis	Infective exacerbation	O2, Physio, Neb
12	64	Obesity hypoventilation syndrome	Chest infection	O2, NIV, mod NIV, Neb, Physio
13	48	Bronchopulmonary aspergillosis	Infective exacerbation	O2, NIV, mod NIV, Neb, Physio
14	39	Scoliosis	Chest infection	O2, NIV, mod NIV, Neb, Physio
15	80	COPD	Infective exacerbation	O2, NIV, mod NIV, Neb, Physio
16	59	Asthma	Infective exacerbation	O2, NIV, mod NIV, Neb, Physio
17	58	Bronchiectasis	Infective exacerbation	O2, NIV, mod NIV, Neb, Physio
18	24	Cystic fibrosis	Infective exacerbation	O2, NIV, mod NIV, Neb, Physio
19	44	Cystic fibrosis	Infective exacerbation	O2, Physio, Neb
20	27	Cystic fibrosis	Infective exacerbation	O2, Physio, Neb
21	18	Cystic fibrosis	Infective exacerbation	O2, Physio, Neb
Mean (SD)	42.8 (19.1)			

COPD, chronic obstructive pulmonary disease; mod NIV, modified NIV circuit; Neb, nebulised saline; NIV, non-invasive ventilation; O2, oxygen therapy 24%; Physio, chest physiotherapy; SD, standard deviation.

on NIV in any group at D1 or D2, indicating that droplet count was significantly reduced compared with standard NIV with vented mask (*Figure 4*).

Oxygen therapy

In normal controls, the coryzal group and in patients no significant increase in droplets in aerosol or large droplet range was seen either at D1 or D2 (*Figure 5*).

Nebuliser therapy

In all groups there was a significant increase across all droplet size ranges on therapy at D1 and D2 in normal subjects. In coryzal subjects and patients there were increases in the 0.3–0.5, 0.5–1, 1–3 and 3.5-μm aerosol ranges both at D1 and D2, but no significant mean difference in the larger droplet ranges of 5–10 and > 10 μm (*Figure 6*).

Mean differences and *p*-values for all interventions in each group are given in *Table 4*.

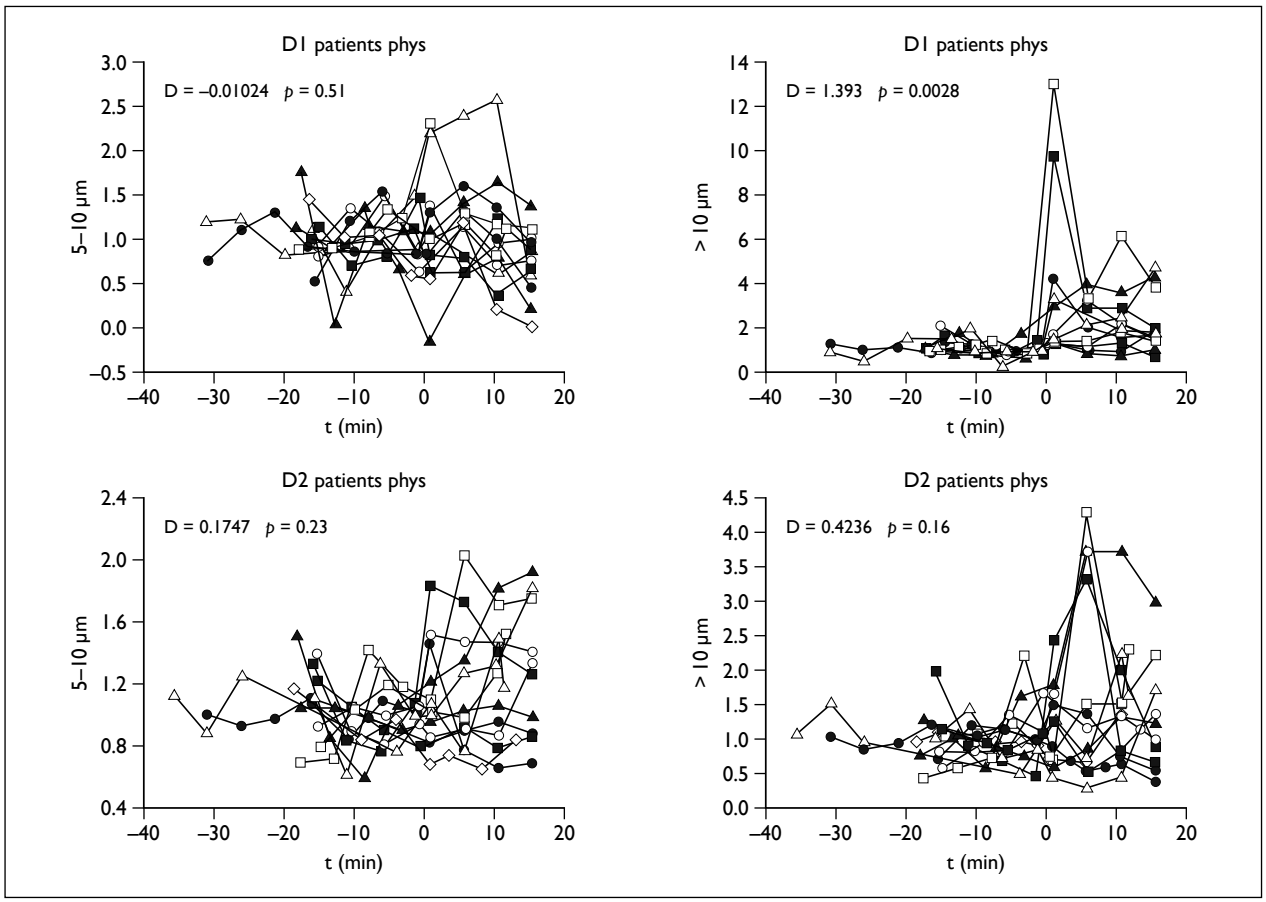

FIGURE 3 *Physiotherapy results: droplet size > 10 µm at D1 and D2 in patients.*

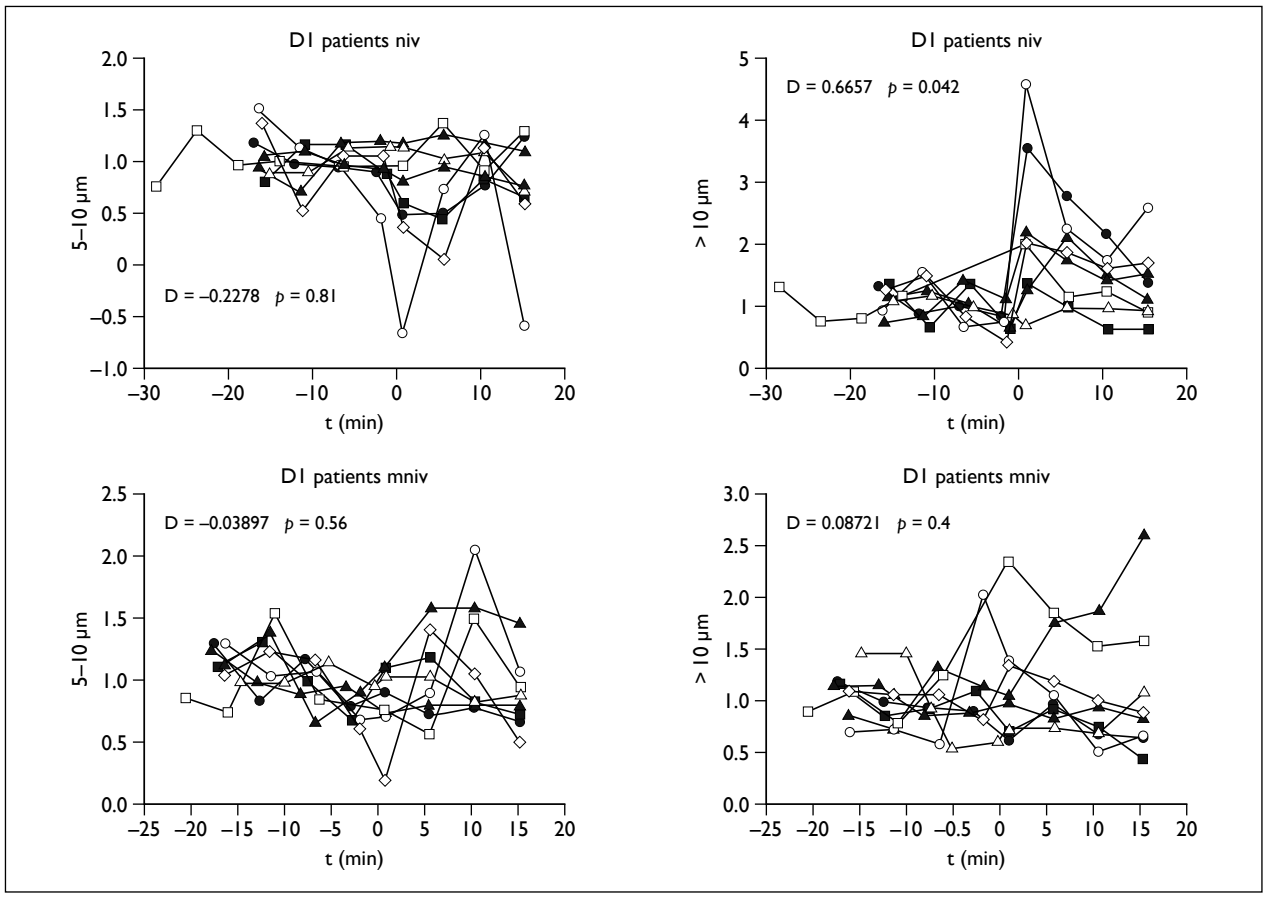

FIGURE 4 *Non-invasive ventilation circuit (NIV) (top row) and modified NIV results (bottom row) in patients at D1 in ranges 5–10 µm and > 10 µm.*

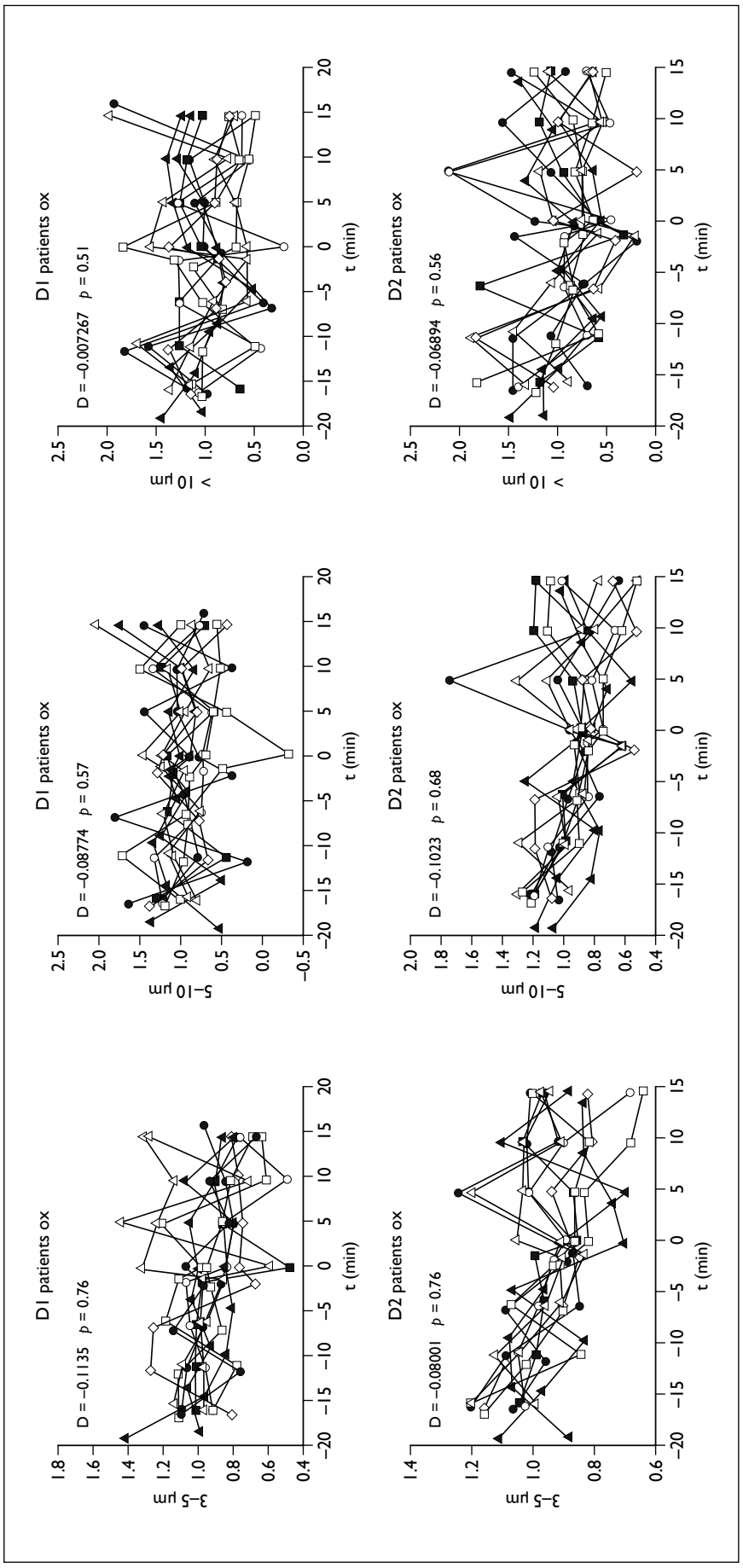

FIGURE 5 *Oxygen results in patients at D1 and D2 in droplet ranges 3–5, 5–10 and > 10 µm.*

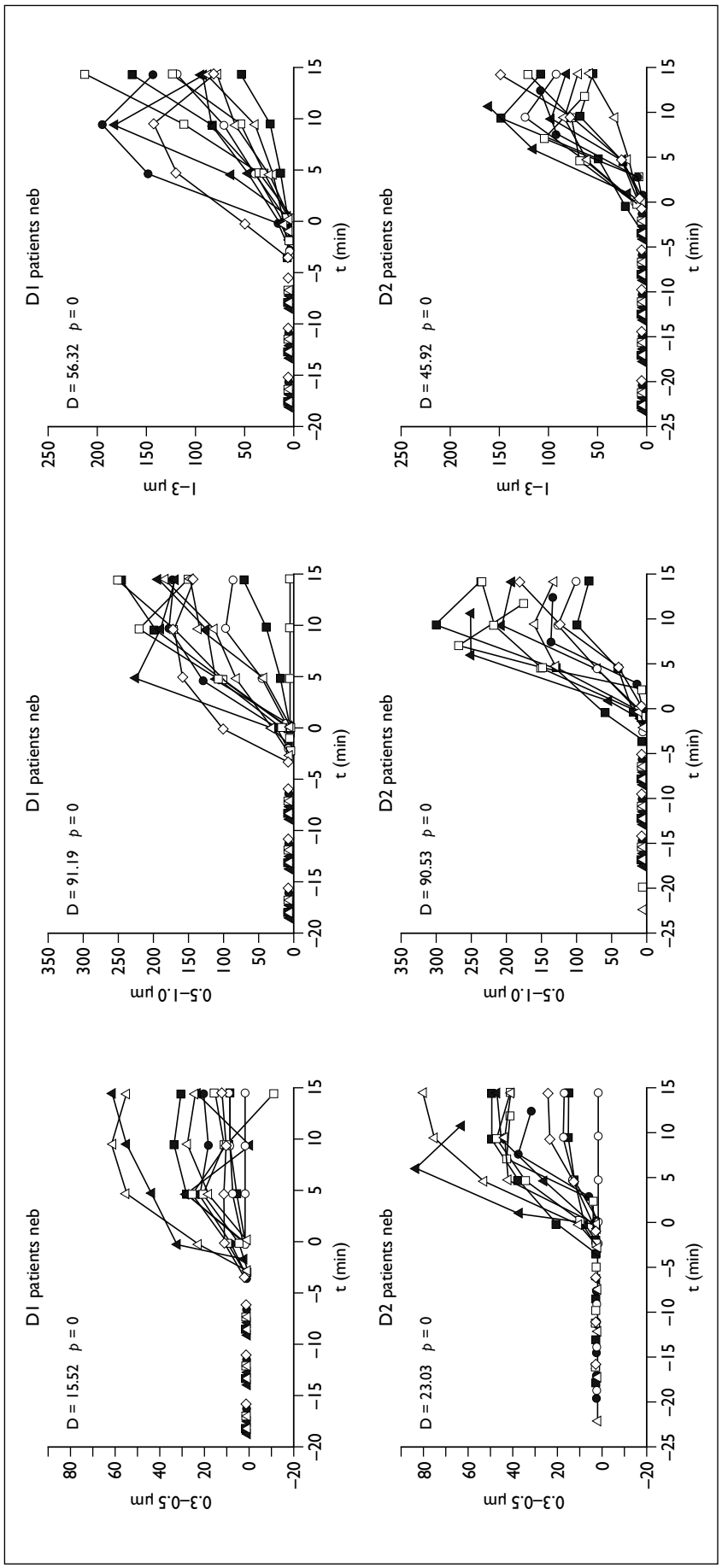

FIGURE 6 *Nebuliser results in patients at D1 and D2 in droplet ranges 0.3–0.5 to 1–3 µm.*

TABLE 4 *Effect of intervention in droplet ranges D – difference between mean value pre and during intervention*

Microns	D1	0.3–0.5	0.5–1	1–3	3–5	5–10	> 10	D2	0.3–0.5	0.5–1	1–3	3–5	5–10	> 10
NIV														
Normal	D	–0.097	–0.103	0.096	–0.073	–0.108	0.148		–0.062	–0.065	–0.057	–0.013	0.028	0.100
	p	0.0991	0.992	0.863	0.653	0.636	0.379		0.968	0.938	0.873	0.544	0.449	0.407
Patient	D	–0.003	0.004	0.021	0.143	–0.228	**0.666**		–0.002	–0.002	0.027	0.067	0.165	0.184
	p	0.565	0.412	0.400	0.231	0.806	**0.042**		0.470	0.298	0.298	0.308	0.243	0.339
Coryzal	D	–0.038	–0.068	–0.043	0.175	–0.060	**0.807**		–0.045	–0.055	0.036	**0.233**	**0.422**	**0.574**
	p	0.894	0.912	0.639	0.143	0.552	**0.044**		0.908	0.909	0.238	**0.047**	**0.018**	**0.052**
Mod NIV														
Normal	D	–0.071	–0.073	–0.054	–0.078	–0.084	–0.086		–0.073	–0.081	–0.089	–0.114	–0.125	0.057
	p	0.971	0.963	0.703	0.703	0.690	0.588		0.975	0.970	0.963	0.836	0.734	0.431
Patient	D	–0.020	0.005	0.027	0.013	–0.039	0.087		–0.018	–0.017	–0.003	–0.014	–0.005	0.236
	p	0.829	0.437	0.393	0.463	0.558	0.402		0.776	0.687	0.521	0.545	0.513	0.244
Coryzal	D	–0.024	–0.026	–0.011	–0.147	–0.208	0.151		–0.016	–0.037	–0.092	–0.125	–0.153	0.011
	p	0.776	0.774	0.539	0.861	0.770	0.240		0.671	0.815	0.857	0.813	0.745	0.486
Oxygen														
Normal	D	–0.063	–0.083	–0.041	–0.003	–0.234	–0.013		–0.050	–0.057	–0.062	–0.049	–0.077	0.081
	p	0.961	0.942	0.572	0.502	0.576	0.519		0.947	0.902	0.847	0.709	0.713	0.400
Patient	D	–0.003	–0.009	–0.023	–0.114	–0.068	–0.007		–0.011	–0.027	–0.051	–0.090	–0.102	–0.069
	p	0.578	0.636	0.577	0.748	0.565	0.507		0.728	0.789	0.736	0.764	0.685	0.554
Coryzal	D	–0.047	–0.067	–0.075	–0.108	–0.171	–0.012		–0.037	–0.045	–0.032	–0.001	0.004	0.058
	p	0.955	0.913	0.773	0.750	0.732	0.511		0.905	0.846	0.699	0.503	0.489	0.429

continued

TABLE 4 *Effect of intervention in droplet ranges D – difference between mean value pre and during intervention (continued)*

Microns	D1	0.3–0.5	0.5–1	1–3	3–5	5–10	>10	D2	0.3–0.5	0.5–1	1–3	3–5	5–10	>10
Physio														
Patient	D	–0.005	0.057	0.123	0.128	–0.010	**1.393**		–0.011	0.024	0.070	0.169	0.175	0.424
	p	0.610	0.118	0.164	0.260	0.511	**0.003**		0.702	0.206	0.151	0.134	0.228	0.158
Nebuliser														
Normal	D	**15.660**	**109.480**	**71.681**	**27.054**	**404.932**	**2.270**		**25.878**	**87.932**	**46.887**	**1.549**	0.232	0.207
	p	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**		**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	0.120	0.270
Patient	D	**15.516**	**91.193**	**56.320**	**3.967**	0.426	0.253		**23.080**	**90.576**	**45.920**	**1.642**	0.149	0.309
	p	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	0.111	0.261		**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	0.241	0.281
Coryzal	D	**11.204**	**64.822**	**38.341**	**1.871**	0.197	0.349		**17.994**	**49.458**	**30.454**	**1.144**	0.234	0.384
	p	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	0.229	0.192		**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	0.097	0.133

D1, distance 1; D2, distance 2; *p*, *p*-value.
p-values <0.05 are highlighted in bold text.

Chapter 4
Discussion

The results suggest that NIV using a vented mask in patients with an acute exacerbation of chronic lung disease disseminates large droplets locally. However, at a distance of 1 m the count has fallen significantly. There was no evidence of the generation of small droplets, i.e. an aerosol. Coryzal subjects also produced large droplets that spread for at least 1 m, which indicates that those with rhinorrhoea/upper airway inflammation also generate droplets. This group might be more representative of patients with an early progressive viral infection who are unlikely to produce large volumes of infected sputum when compared with those with cystic fibrosis or bronchiectasis. However, we did not see a difference in counts in those with markedly productive coughs compared with those with minimal sputum production (asthma, obesity hypoventilation) on the day of study. The large droplet count proximal to the mask was significantly reduced in both the patients and coryzal group in the NIV circuit with exhalation port filter, indicating that this modification minimises large droplet dissemination. These filters do not appear to increase the work of breathing if changed regularly. The finding that bilevel NIV with a vented mask disseminates large droplets is in keeping with the superspreading episodes seen in the SARS outbreak, where NIV use was found to be a risk factor on multiple logistic regression analysis.[12]

Physiotherapy has not previously been included in the list of interventions in which PPE and FFP3 masks are indicated. Indeed the results show that it is not an AGP but, perhaps not surprisingly, given that the point of chest physiotherapy is to clear secretions, there was a significant increase in large droplets. As expected, these levels have dropped by D2 but the findings indicate that use of full PPE may be prudent for physiotherapists and respiratory therapists carrying out these procedures in patients with chronic respiratory disease in whom the H1N1 virus has generated an infective exacerbation or secondary bacterial pneumonia.

Oxygen therapy was not associated with an increase in droplets in any group, in any aerosol or droplet range. While it may be possible that 24% O2 might be an insufficient flow rate to shear droplets from the upper airway or disseminate those generated by spontaneous coughing or sneezing, we did not see an increase in droplet count in coryzal subjects who used 60% O2 – a flow rate more typical of that required by patients with acute lung injury due to viral pneumonia. These results should be contrasted with those from Yu *et al.*,[12] who showed O2 was a significant risk factor for superspreading events. However, their results were based on correlation rather than direct measurement of droplet densities and may be affected by the fact that sicker patients with higher viral loads are more likely to require O2 than those with milder disease who do not.

The association of spread of SARS with nebuliser use is controversial. Although there are case reports,[15,16] in this study it is not possible to separate out droplets generated by the nebuliser itself from those generated by the patient. In addition, in clinical practice, patients being treated with nebulised bronchodilator are likely to have air flow obstruction due to asthma or COPD and are therefore more likely to be coughing and wheezing spontaneously. It is plausible that the flow from the nebuliser (either powered by a compressor or oxygen) would disseminate spontaneously generated droplets further. It is notable that the nebuliser was the only intervention that produced in droplets in the aerosol range (< 5 μm). This is entirely in line with the droplet range designed to be generated by this device, and means that this intervention also acts as a quality control confirming that the Aerotrak counters were fully able to detect particles in this range in clinical circumstances. However, in both the coryzal group and the patients we did not detect droplets in the 5- to 10-μm and > 10-μm ranges as occurred during NIV and physiotherapy. This indicates that the vast majority of droplets are likely to be nebulised saline as opposed to patient droplet secretions.

Limitations

We have used droplets as a proxy for viral dissemination, so we do not know whether an increase in droplet count confers an increased risk

of infection for an exposed individual, although we believe this to be biologically plausible. This inference can be confirmed only in viral sampling studies in individuals with influenza, SARS, tuberculosis or other airborne pathogens. This further work would be valuable.

Furthermore, the patients had infective exacerbations of chronic lung disease and the pathology of this is completely different to the acute lung injury that is seen in young patients with normal lungs that are infected with H1N1 or H5N1 influenza. NIV is not indicated in patients with rapidly progressive acute lung injury, although in those with milder disease, and if used earlier in the course of the illness, it might have a role. Emerging evidence suggests that selected cases of H1N1 pneumonia worldwide were treated with NIV with variable results.[34,35] We believe, however, that the group with chronic lung disease and infectious exacerbations is the most likely to benefit from NIV, and the coryzal group used in this study may reflect airway secretion levels in viral pneumonia patients more closely. However, coryzal patients are clearly less unwell, less dyspnoeic and their lung compliance is likely to be near normal. This is relevant as decreased lung compliance enhanced the dispersion of smoke particles in the human simulator model.[36]

We sampled droplets at two points – proximal to the subject's nose/mouth/mask and at a 1-m distance. As Hui *et al.*[31] have shown in smoke particle experiments, flow from mask vents and leaks creates a high to low density vortex, and it is possible that we missed important sampling areas. In order to minimise this risk we used the information gained from those studies to site D1, the point of maximum density demonstrated by Hui *et al.*,[31] and placed D2 counter at 1 m, as DH guidelines suggest that health-care workers beyond this distance may use surgical masks as risk of transmission lower. Additionally, we placed D2 at a height of approx 1.52 m (5 ft) equivalent to the nose level of average health-care worker standing 1 m from the patient.

The experiments were carried out in a single room and we minimised disturbances, such as door opening and ventilation, to control the number of variables. Ventilation and air currents are likely to have a significant effect on small size droplets and aerosols, and, indeed, we saw a continued small fall in background count through interventions, which contributes to the mean differences seen in *Table 4*. However, the main impact of treatments (apart from nebuliser) was on large droplets, which, due to greater mass and terminal velocity, will be less affected by air currents.

We have carried out a series of comparisons and have expressed results as mean difference and *p*-values. In the discussion we have used *p*-values of < 0.05 to express significance. It could be argued that adjustments should be made for multiple comparisons. However, we believe the interventions to be independent, and, if comparisons are reduced by either considering one intervention at a time or pooling large versus small droplets, similar conclusions will be reached. We believe, on balance, that it is important to interpret the data erring on the side of caution with respect to risk of dissemination,[37] and that these inferences are clinically plausible.

Chapter 5
Conclusions

Despite the limitations, this study indicates that NIV, O2 and physiotherapy are not AGPs. Physiotherapy and NIV generate large droplets adjacent to the patient, but these fall significantly at 1 m from the patient. A mod NIV circuit using a non-vented mask and filtered exhalate reduces the number of large droplets produced. Nebulised saline delivered by a mouthpiece produces an aerosol of droplets, but most are in the expected droplet range for the device and large droplets were not seen in patients and coryzal subjects. O2 at 60% and 24% did not appear to be an aerosol or droplet-generating procedure.

What are the implications for clinical practice and infection control? These results imply that during NIV and physiotherapy use of full PPE should be considered for health-care team members working within 1 m of the patient, as droplet count is increased. As the droplets are large and many drop out within 1 m over bedside surfaces, the crucial importance of handwashing and decontamination of near surfaces is evident, as transmission in these circumstances is likely to be direct via droplet spread or from fomites and direct contact with the patient's local environment. As small and aerosolised particles were not demonstrated, the role other protective measures, such as negative pressure rooms, which have been advocated in some pandemic flu guidelines, may be less important.

Recommendations for further research:

1. Droplet sampling should be carried out in patients with pandemic influenza to confirm that droplets generated in this situation are comparable to those produced by patients in this study.
2. Droplet sampling sizing could be carried out in human simulator models with laser droplet imaging to corroborate results.
3. Viral carriage in different size droplets should be assessed to test whether using droplets as a proxy of infectivity risk is a realistic clinical substitute.

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Contribution of authors

AK Simonds, Consultant and Reader in Respiratory Medicine, Royal Brompton & Harefield NHS Foundation Trust, designed the study, wrote the grant application, analysed results with KP, JS and RD, and wrote the report.

A Hanak, Senior Respiratory Support Technician and Physiotherapist, Royal Brompton & Harefield NHS Foundation Trust, carried out the experiments, including performing physiotherapy, and created and maintained the database.

M Chatwin, Consultant Physiotherapist, Royal Brompton & Harefield NHS Foundation Trust, carried out the experiments, including performing physiotherapy, performed pilot studies and recruited patients.

MJ Morrell, Reader in Sleep Physiology, National Heart & Lung Institute, Imperial College, contributed to study design and critical analysis of results.

A Hall, Consultant in Microbiology & Infection Control Lead, Royal Brompton & Harefield NHS Foundation Trust, contributed to study design, provided infection control and microbiology advice, and critical analysis of results.

KH Parker, Professor Physiological Fluid Mechanics (Emeritus) Department of Bioengineering, Imperial College, provided guidance on droplet characterisation and mathematical analysis, analysed results, provided statistical advice and critical review, and contributed to writing the report and figures.

JH Siggers, Lecturer, Department Bioengineering, Imperial College, advised on study design, mathematics of droplet analysis, critical review of results and contributed to writing the report.

RJ Dickinson, Senior Lecturer, Department of Bioengineering, Imperial College, advised on study design, droplet analysis, critical review of results and contributed to writing the report.

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Appendix 1
Protocol

Evaluation of droplet dispersion during NIV, O2 and nebulised drug delivery in clinical practice

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- Funder: NIHR HTA
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Introduction

Background

Influenza viruses are spread by droplets, but aerosols may be implicated. While many patients recover without serious illness, some with H1N1 swine flu will develop pneumonia/respiratory insufficiency requiring treatment by oxygen therapy (O2), ventilatory support or nebulised drugs, and this is more likely in those with underlying respiratory or cardiac disorders, for example chronic obstructive pulmonary disease (COPD), asthma, cystic fibrosis, genetic susceptibility, pregnancy or if the virus mutates. These therapies may generate droplets or aerosol during delivery, which, in the severe acute respiratory syndrome (SARS) outbreak, were associated with an increased incidence of infection in health-care workers (Fowler *et al.* 2004)[9] and superspreading events on hospital wards (Yu *et al.* 2007).[24] Non-invasive ventilation (NIV) is unlikely to be effective in patients with overwhelming acute lung injury, but in early pneumonia and in those in whom influenza has caused an exacerbation of COPD or heart failure NIV may be effective in reducing the need for intensive care unit (ICU) admission. Currently, use of NIV in pandemic flu is controversial. Department of Health Pandemic Influenza guidance recommends that NIV should be used with full infection control (aerosol-generating) precautions by experienced units employing practice guidelines that have been developed by our team (Simonds 2007),[25] but there is no substantive evidence base and NIV use is not advocated in other national guidelines. Hui *et al.* (2006) carried out studies of NIV droplet distribution using a patient simulator and smoke particles, but there have been no systematic studies in humans or during oxygen and nebuliser therapy, or physiotherapy.

Rationale for current study

This research should provide the first analysis of droplet distribution around respiratory therapies in clinical circumstances that are relevant to H1N1 infection. Although the patients with chronic respiratory disease will not specifically have an exacerbation triggered by H1N1 influenza in this study, the results should be representative of any acute exacerbation and we will also study those with coryzal symptoms, some of whom may have H1N1 infection. The findings should enable health-care professionals to understand patterns of geographical distribution of respirable droplets when caring for patients, inform selection of circuitry and interfaces to reduce dissemination, and by modelling the profile of decay of particles after therapy we hope to guide health-care workers' entry into rooms of unstable patients.

Impact on practice

As this is the first analysis of distribution of droplets during NIV, O2 and nebuliser therapy in representative clinical circumstances, the results obtained should influence clinical practice and policy immediately by:

1. informing the choice of interface/delivery systems
2. guiding health-care workers to safer application in pandemic flu and enable them to understand relative risks
3. reducing the risk of dissemination to other patients and staff in superspreading events

4. wider, safe use of NIV may reduce ICU bed pressures, as NIV may be performed in respiratory ward areas/high-dependency single rooms.

Study objectives

The key objective is to understand the characteristics of droplet and aerosol dispersion around delivery systems during NIV, O2 therapy, nebuliser therapy and physiotherapy procedures.

We will examine:

1. droplet size and count
2. geographical distribution of droplets
3. rise and decay of droplets over time after the therapies are initiated and discontinued
4. the impact of modifications to the delivery system to reduce droplet/aerosol dissemination in:
   i. normal subjects
   ii. individuals with coryzal symptoms
   iii. patients with an acute exacerbation of chronic lung disease.

Primary objective

- To evaluate the characteristics of droplets and aerosol generated using NIV, O2 therapy, nebuliser therapy and physiotherapy in clinical practice.

Secondary objectives

- To determine whether particular delivery methods/interfaces generate more droplets.
- To establish how can droplet characteristic information be applied to inform safe use of these therapies in patients with H1N1 swine flu, and other droplet/aerosol-borne diseases.

Study methodology

Overall design

This is an observational study with subjects and patients acting as their own control.

Setting and timescale

The study will be carried out in a single centre (Royal Brompton Hospital) over 4 months (September to December 2009).

Study outcome measures

Number of droplets in size range 0.3–10 μm, measured during conditions listed below.

Specific methods

Droplet count and sizing

We will count droplets in size range 0.3–10.0 μm within distributions of 0.3–0.5, 0.5–1.0, 1.0–3.0, 3.0–5.0, 5.0–10.0 and > 10 μm using Aerotrak Model 8220 optical particle counter with counting efficiency 50% ± 10% at 0.3 μm and 100% ± 10% at 0.45 μm and greater. We will examine dissemination of smaller droplet (aerosol) size using a P-Trak Ultrafine Condensation particle counter (particle size range 0.02–1.0 μm) at sample flow rate 100 cm^3/minute. Each sampling will be carried out twice over 10 seconds, on three occasions, at sampling points: (1) adjacent (within 2 cm) to mouth or mask; (2) 0.5 m from mouth or mask; (3) 1 m from mouth or mask; and (4) 3 m from mouth or mask with sampling points (2)–(4) being carried out in radial positions – two laterally to subject/patient, one directly in front of subject/patient and one above subject. The Aerotrak and P-Trak counter devices will be mounted on tripods to maintain accuracy and reproducibility of measurements.

Mathematical modelling

We will use mathematical modelling of droplet motion and dispersion to derive the expected droplet distribution at different distances. Fitting the model with observations at a number of positions will allow interpolation and extrapolation of the measured droplet distribution as a function of size of the droplet and distance from the patient–mask interface, for a range of room conditions. In turn, this will enable us to predict the safe times and distances beyond which exposure can be considered comparable to spontaneous breathing or negligible.

Participants

Groups

We will study three groups: normal subjects, subjects with coryzal (common cold or flu-like) symptoms and adult patients with chronic lung disorders.

Inclusion criteria

Normal subjects Age 18 years and above. Able to speak English and understand protocol.

Coryzal subjects Age 18 years and above. Have two of any of following: raised temperature or history of raised temperature, sore throat, headache, muscle aches and pains, cough in previous

24–48 hours. Arterial oxygen saturation 95% or above on air.

Patients A clinical diagnosis confirmed by medical consultant of COPD, asthma, cystic fibrosis, bronchiectasis, chest wall disorder or neuromuscular disease, for example Duchenne muscular dystrophy. Admitted with infective exacerbation defined by increased breathlessness, raised white cell count or temperature or CRP (C-reactive protein – raised values indicate infection or inflammation). Requiring treatment with O2 and NIV as clinically indicated.

Exclusion criteria
Normal subjects Current illness or underlying chronic condition. Pneumothorax in previous 3 months. Unable to understand English or trial information.

Coryzal subjects Underlying chronic condition. Arterial oxygen saturation < 95% on air. Pneumothorax in previous 3 months. Unable to understand English or trial information.

Patients Haemodynamically unstable (systolic blood pressure < 90 mmHg, uncontrolled arrhythmia), medically unstable, arterial oxygen tension (PaO_2) < 7.5 kPa on O2 or NIV, arterial carbon dioxide tension ($PaCO_2$) > 7.5 kPa on NIV or O2, unable to breathe spontaneously for < 4 hours. Unable to understand English or trial information.

Sampling method
Normal subjects Will be recruited from departmental database of normal subjects who have participated in previous studies.

Coryzal subjects Will be recruited from occupational health department, and staff who develop symptoms while on duty.

Patients Will be recruited from those already inpatients on respiratory ward, with an acute infective exacerbation of chronic lung disease. At any one time we have around 15–20 patients on the ward receiving O2/NIV. The research team are either members of the clinical team or they interact with the team on a daily basis.

Sample size
Background:

- It should be stressed that this work is almost exclusively exploratory in nature. This is because there are very many unknowns.
- It is not known whether the material generated by infected individuals breathing, coughing or undergoing interventions is in the form of a fine aerosol or larger droplets.[1] NIV and nebulisation have been termed 'potential aerosol-generating procedures' but this is based on presumption, not evidence. In the Department of Health Pandemic Flu guidelines[3] it is stipulated that high-efficiency masks should be used when working within 1 m of the patient, and that beds of patients being cohort nursed should be more than 1 m apart. There is little primary evidence for either of these stipulations but in the SARS outbreak superspreading events (i.e. at least three cases arising from one index case) were associated with a distance between beds of < 1 m and index cases with the use of O2 or non-invasive ventilation.[24]
- Further, the 'dose' needed to infect is not clear as droplets are a proxy measure of virus presence/infectivity, and sicker patients with higher viral loads are likely to need more therapeutic interventions.
- Moreover we do not know the rate of decay of droplets over time after interventions have been discontinued. Again, this will be partly related to size as larger droplets with greater mass will more quickly fall to the floor or onto bedding.

Droplet size and number – pilot data, variability and clinically meaningful difference:

- We have pilot data from five normal subjects sampled at the mouth or mask and in one droplet size range (5–10 μm). This size range is known as the 'respirable range', representing droplets likely to be deposited in lungs; larger droplets are not inspired and very small aerosol particles do not have sufficient mass to drop out in lung and are expired as easily as they are inspired. Droplets generated by interventions (O2, NIV, etc.) should be compared with those generated by the subject/patients breathing spontaneously, as a baseline of zero droplets is not clinically realistic. We are therefore carrying out comparisons with spontaneous breathing with each subject/patient acting as their own control.
- Our pilot data above estimated a droplet count of 900 (standard deviation = 100) with spontaneous breathing.
- In the absence of any other published information and the uncertainties outlined above, we have chosen a doubling in this

droplet count to represent a significant increase in risk of spread to health-care staff or other patients. This estimate is informed by the observation that coughing and sneezing in pilot work resulted in a count of around 1800, and that coughing and sneezing increase the risk of infection.

We used Statistical Analysis Systems (SAS), version 9.1, to estimate the required study group sizes:

- Using our pilot estimates and a false-positive rate (α) of 0.05, calculations for a single two-group comparison with 80% power indicate that very small groups would be required.
- We have, however, increased our group sizes to account for the possibility that variability may be higher in patients (currently unknown) and the four comparisons that are to be undertaken. Sample sizes are therefore normal subjects = 10, coryzal subjects = 10, patients = 20.
- This model is based on droplet counts in one size range at the mouth and is suitable for our primary purpose. Again, with the lack of any information from elsewhere, we do not know whether our sample size will be sufficient for our other questions: for example, number of droplets at different distances from patient or the decay over time. Initial findings will provide further information. If variability estimates are greater or differences smaller compared to spontaneous breathing, further recruitment will be possible.

Statistical advice was provided by Mr Winston Banya, Senior Statistician, R&D Department, Royal Brompton Hospital.

Preregistration evaluations

We will check that arterial oxygen saturation level is 95% or above in normal subjects and subjects with coryzal symptoms using an oximeter ear probe. In coryzal subjects nasopharyngeal aspiration will be carried out along with throat and nasal swabs. Virology results will not be known until after study tests are done, so they will inform the analysis but are not needed for study entry as symptoms alone determine eligibility.

Patients will have an arterial oxygen saturation value of more than 88% and $TcCO_2$ value of less than 7.5 kPa on O2 and or NIV.

Withdrawal criteria

The trial will be discontinued if the chief investigator feels it is unsafe to continue. As the therapies used are in routine clinical practice in patients, and researchers are members of the clinical team and routinely apply these therapies in patients, including those in first wave of swine flu, this risk is relatively low.

Recruitment and methodological process

Recruitment

Recruitment will take part at the Royal Brompton Hospital. Normal subjects will be recruited from departmental database and volunteers working in the hospital. Coryzal subjects will be recruited from the occupational health department and from individuals working in the hospital who develop symptoms while on duty.

Written informed consent will be obtained by the research fellow, Dr Michelle Chatwin or CI at the Royal Brompton Hospital, who have all had training in obtaining consent. Subjects and patients will be provided with information sheets. Normal subjects and patients will have 24 hours to decide whether to participate and coryzal subjects will have 1 hour to decide.

Methodological process

- This is an observational trial that will be carried out in a single hospital side room on respiratory ward at the Royal Brompton Hospital. The aim is to measure the size and number of droplets and smaller (aerosol) particles generated during treatment with NIV, O2, nebuliser therapy and during physiotherapy.

Three groups will take part:

- (A) normal subjects
- (B) subjects with coryzal (common cold or flu-like) symptoms
- (C) patients with respiratory insufficiency due to COPD, cystic fibrosis, chronic asthma, bronchiectasis, neuromuscular disease receiving NIV/O2/nebuliser therapy as indicated for an infective exacerbation. Each subject or patient will take part on one occasion, the study taking approximately 3 hours to complete.

Subjects and patients:

- (A) Normal subjects will be recruited from our database of normals (aged 18 years and above) and above. *Exclusion criteria*: no current illness or underlying chronic condition.
- (B) Individuals with common cold or flu-like (coryzal) symptoms defined by pyrexia, and two of sore throat, muscle aches and pains, headache, cough within previous 24–48 hours (age 18 years and above) will be recruited from contacts from normal patient database, occupational health department of the Royal Brompton Hospital and from staff developing symptoms while on duty. They will be studied after having nasopharyngeal swabs for viral screening, to confirm diagnosis. *Exclusion criteria*: no underlying chronic health conditions, medically stable.
- (C) Patients with chronic respiratory failure will be recruited from those admitted to the ward with an infective exacerbation of chronic respiratory disease. Inclusion criteria: those with COPD, cystic fibrosis, bronchiectasis, chest wall disorder and neuromuscular disease. These groups are selected as will contain older patients with COPD and younger patients with cystic fibrosis and, for example, Duchenne muscular dystrophy, in whom NIV and O2 therapy is clinically indicated. *Exclusion criteria*: haemodynamically or medically unstable, $PaO_2 < 7.5$ kPa, $PaCO_2 > 7.5$ kPa pH < 7.34 on therapy, cognitive inability to able to understand study information sheet, able to breathe spontaneously for < 4 hours.

Technologies being assessed:

- Non-invasive ventilation using standard bilevel pressure support device with a range of interfaces and settings, nasal continuous positive airway pressure (CPAP) therapy, O2 therapy via 60%, 35% and 24% masks

Measurements:

- Droplets will be visualised using a Model 8220 Aerotrak Optical particle counter (TSI Inc.) with particle size detection of 0.3–10 μm, and a Model 8525 P-Trak Ultrafine Condensation particle counter (TSI Inc.) adjacent to subject/delivery system, 1 m from delivery system and 3 m from patient/subject, at six fixed radial points.

Investigation plan:

- On arrival in the side room, subjects and patients will be assessed breathing spontaneously at rest, during simulated coughing, and then, when receiving NIV and O2, physiotherapy and nebulised saline therapy in random order.
- Droplet distribution will be measured in the following test conditions (selected as clinically representative).

1. For (A) normal subjects and (B) subjects with coryzal symptoms:
   - *i. Control* Spontaneous breathing and simulated cough with and without surgical mask, which will take approximately 10 minutes.
   - *ii. Non-invasive ventilation* A bilevel ventilator will be used: in random order delivery with non-vented full-face mask, total face mask and helmet with and without filter modification and vented full-face mask. Ventilator settings: inspiratory positive airway pressure (IPAP), expiratory airway pressure (EPAP), IPAP/EPAP 20/5 15/5 10/5 cmH_2O. CPAP 5 and 10 cmH_2O. This will take approximately 1 hour.
   - *iii. O2 therapy* Will be delivered using 60%, 35%, 24% masks. This will take approximately 30 minutes. This will take about 20 minutes.
   - *iv. Nebulised 0.9% saline* Delivered from standard nebuliser. This will take 10 minutes.
   - *v. Standardised physiotherapy* This will take 10 minutes.

Subjects will be able to have rest periods between the runs, as we will be sampling the room to ensure control conditions obtain and get background counts.

2. For (C) patients with respiratory insufficiency:
   - *i. Spontaneous breathing and during simulated cough* This will take approximately 10 minutes.
   - *ii. Non-invasive ventilation* Using current clinically indicated NIV settings deovered in random order through non-vented full-face mask, total face mask, helmet with and without filter modification and vented mask. This will take approximately 45 minutes.

iii. O2 therapy 24% Ventimask spontaneously breathing. This will take approximately 5–10 minutes.

iv. Nebulised 0.9% saline Delivered by standard nebuliser. This will take approximately 10 minutes.

v. During physiotherapy using 24% O_2 mask This will take about 10 minutes.

Patients will be monitored with arterial oxygen saturation (SaO_2), transcutaneous carbon dioxide tension ($TcCO_2$) and heart rate measurement using a non-invasive ear probe (Tosca) throughout stages (i)–(iv).

They will be able to have rest periods between the runs as we will be sampling the room to ensure control condition obtain and get background counts.

Droplet and aerosol characterisation:

- We will count droplets in size range 0.3–10.0 μm within distributions 0.3–0.5, 0.5–1.0, 1.0–3.0, 3.0–5.0, 5.0–10.0 and > 10 μm using Aerotrak Model 8220 optical particle counter with counting efficiency 50% ± 10% at 0.3 μm and 100% ± 10% at 0.45 μm and greater. We will examine dissemination of smaller droplet (aerosol) size using a P-Trak Ultrafine Condensation particle counter (particle size range 0.02–1.0 μm) at sample flow rate 100 cm^3/minute. Each sampling will be carried out twice over 10 seconds, on three occasions, at sampling points: (1) adjacent (within 2 cm) to mouth or mask; (2) 0.5 m from mouth or mask; (3) 1 m from mouth or mask; and (4) 3 m from mouth or mask, with sampling points (2)–(4) being carried out in radial positions – two laterally to subject/patient, one directly in front of subject/patient and one above subject. The Aerotrak and P-Trak counter devices will be mounted on tripods to maintain accuracy and reproducibility of measurements.

Mathematical modelling:

- We will use mathematical modelling of droplet motion and dispersion to derive the expected droplet distribution at different distances. Fitting the model with observations at a number of positions will allow interpolation and extrapolation of the measured droplet distribution as a function of size of the droplet and distance from the patient–mask interface, for a range of room conditions. In turn, this will enable us to predict the safe times and distances beyond which exposure can be considered comparable to spontaneous breathing or negligible.

Equipment:

- Non-invasive ventilation: we will use a Saime Elisee bilevel ventilator, which can deliver a variety of IPAP and EPAP and fixed-level CPAP through a single- limb circuit and a double-limb circuit. The pressures of IPAP/EPAP 20/5, 15/5 and 10/5 cmH_2O (spontaneous triggered mode) and CPAP 5 and 10 cmH_2O have been selected as clinically representative. These pressures will be used in normal subjects and those with coryzal symptoms. In the patient group we will use the IPAP/EPAP settings and back-up respiratory rate as clinically indicated.

Interfaces:

- We will use a full-face masks (ResMed), non-vented with filtered (intersurgical) exhalation port, and vented masks (ResMed), and total masks (Respironics/Philips) in all subjects and patients, and, in five subjects, a helmet (Rusch).

Oxygen therapy:

- Oxygen therapy 60% and 35% via high-flow reservoir mask, 24% via Venturi mask in normal subjects and those with coryzal symptoms, 24% via Venturi mask in patients.

Physiotherapy:

- Will be standardised as cycles of deep breathing, with percussion or shaking to loosen any secretions, followed by an assisted cough initiated manually, augmented by a physiotherapist performing inwards and upwards pressure on the lower thorax to aid expectoration, after which the patient rests and the cycle repeated as required. It will be performed by one physiotherapist (MC) who has performed standardised physiotherapy manoeuvres in other randomised crossover trials.

Nebuliser:

- Actineb nebuliser (Clement Clark) generating droplets of 3–10 μm of 0.9% saline.

There will be an interim analysis and mathematical modelling after 10 subjects and 10 patients have been studied.

Non-invasive ventilation, O2, nebuliser therapy and standardised physiotherapy will be delivered by research fellow and Dr Michelle Chatwin.

Ethical considerations

The main risk is to research staff in the dissemination of H1N1 and other coryzal viruses. Full personal protective equipment will be used – the research team members are fully familiar with this and have experience in managing H1N1 patients. Some team members have already had swine flu themselves so will be immune.

There is a very small risk of a subject or patient using NIV developing a pneumothorax. The patients already will be using NIV as part of their clinical management.

Adverse events

Potential adverse events:

- Research team member becoming infected with swine flu. The individual would be with drawn from doing the project and treated with oseltamivir in the normal way. In practice it will be difficult to establish if the individual was infected during the study, by contact with other infected patients or from contact from within or outside the hospital

All adverse events will be reported. Depending on the nature of the event the reporting procedures below will be followed. Any questions concerning adverse event reporting will be directed to the chief investigator in the first instance.

Non-serious adverse events

All such events, whether expected or not, will be recorded.

Serious adverse events

An SAE form should be completed and faxed to the chief investigator within 24 hours. However, hospitalisations for elective treatment of a pre-existing condition will not be reported as SAEs.

All SAEs will be reported to the REC overseeing the research and the research sponsor, where, in the opinion of the chief investigator, the event was:

- '*related*' i.e. resulted from the administration of any of the research procedures, or
- '*unexpected*' i.e. an event that is not listed in the protocol as an expected occurrence.

Reports of related and unexpected SAEs will be submitted within 15 days of the chief investigator becoming aware of the event, using the COREC SAE form for non-IMP studies.

Investigators will report any SAEs as required by their local research ethics committee and/or research and development office.

Assessment and follow-up

We do not plan to follow up patients after the study. Virology results will be fed back to coryzal subjects and appropriate action advised.

Statistics and data analysis

Data will by analysed using ANOVA with correction for repeated measure. Statistical advice will be provided by Mr Winston Banya, R&D Department, Royal Brompton & Harefield NHS Foundation Trust.

Data and all appropriate documentation will be stored for a minimum of 5 years after the completion of the study, including the follow-up period.

Regulatory issues

Ethics approval

The chief investigator will obtain ethical approval from a research ethics committee via the IRAS system. The study will not commence until ethical approval is obtained, and will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964, and later revisions.

Consent

Consent to enter the study will be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent will be obtained. The right of the participant to refuse to participate without giving reasons will be respected. All participants are free to withdraw at any time from the research without giving reasons and without prejudicing further treatment. Consent will be obtained by the patient's existing clinical consultant.

Confidentiality

The chief investigator will preserve the confidentiality of participants taking part in the study in line with the Data Protection Act 1998.

Indemnity

NHS indemnity cover.

Sponsor

Royal Brompton & Harefield NHS Foundation Trust.

Funding and costs

NIHR HTA will fund this study. Travel costs to £20 are available to normal and coryzal subjects.

Audits and inspections

Sponsor and other regulatory bodies will ensure adherence to Good Clinical Practice and the NHS *Research Governance Framework for Health and Social Care* (2nd edn).

Study management

The day-to-day management of the study will be co-ordinated through by Dr Michelle Chatwin (M.Chatwin@rbht.nhs.uk).

Publication policy

Results from this research will be reported and disseminated via peer-reviewed journals and via conference presentations. No personal or identifiable data will be present in any public reports of this research.

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Evaluation of triage methods used to select patients with suspected pandemic influenza for hospital admission: cohort study

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Declared competing interests of authors: KC was one of the developers of the PMEWS score, evaluated in this report.

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Abstract

Evaluation of triage methods used to select patients with suspected pandemic influenza for hospital admission: cohort study

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Background: Triage methods are necessary in emergency departments to provide clinicians with a reliable method for determining each patient's risk of adverse outcome. Prior to the 2009 H1N1 influenza pandemic the CURB-65 (a risk prediction score for pneumonia, based on confusion, urea level, respiratory rate, blood pressure and age over 65 years) pneumonia score and the Pandemic Modified Early Warning Score (PMEWS) were used to assess adults. In response to the emergence of the pandemic, national guidance produced a new swine flu hospital pathway for use adults and children. However, none of these methods had been widely validated or tested in the setting of pandemic influenza.

Objectives: To use the initial waves of the 2009 H1N1 pandemic to evaluate existing triage methods in patients presenting with suspected pandemic influenza, and to determine whether an improved triage method could be developed.

Methods: A prospective cohort study was undertaken of patients with suspected swine flu presenting to four hospitals during the second wave of the 2009 H1N1 pandemic. Staff completed a standardised assessment form that included the CURB-65 score, PMEWS and the swine flu hospital pathway. Patients who died or required respiratory, cardiovascular or renal support during the 30-day follow-up were defined as having a poor outcome. Patients who survived to 30 days without requiring respiratory, cardiovascular or renal support were defined as having a good outcome.

Results: Data were collected and analysed from 481 cases across three hospitals. Most of the cases were children, with 347 out of 481 (72%) aged 16 years or less. There were five poor outcomes: two deaths and three survivors who required respiratory support. The five patients with poor outcomes had CURB-65 scores of zero, one (three cases) and two, and PMEWS scores of one, five, six, seven and eight. The swine flu hospital pathway was positive in three out of five cases. The *C*-statistic for each method was CURB-65 0.78 [95% confidence interval (CI) 0.58 to 0.99], PMEWS 0.77 (95% CI 0.55 to 0.99) and the swine flu hospital pathway 0.70 (95% CI 0.45 to 0.96). Patients with a higher CURB-65 score were more likely to be admitted ($p < 0.001$): 25 out of 101 (25%) with a score of zero, 11 out of 24 (46%) with a score of one, 7 out of 8 (88%) with a score of two, and the patient with a score of three were admitted. Admitted patients had a higher mean PMEWS score (4.6 vs 2.0, $p < 0.001$). The *C*-statistics for CURB-65, PMEWS and the swine flu hospital pathway in adults in terms of discriminating between those admitted and discharged were 0.65 (95% CI 0.54 to 0.76), 0.76 (95% CI 0.66 to 0.86) and 0.62 (95% CI 0.51 to 0.72) respectively.

Limitations: The 2009 H1N1 pandemic was much smaller and less severe than predicted and resulted in a lack of sufficient data.

Conclusions: Potential concerns were raised about the use of existing triage methods for patients with suspected pandemic influenza, as these methods may fail to discriminate between patients who will have an adverse outcome and those with a benign course. Clinicians in the study did not generally appear to admit or discharge on the basis of these methods, despite their recommended use. Further research is required to evaluate existing triage methods and develop new triage tools for suspected pandemic influenza.

Contents

List of abbreviations

AUROC	area under the receiver–operator characteristic curve (*C*-statistic): a measure of the discriminant value of a risk prediction score
CAF	Clinical Assessment Form
CAT	Community Assessment Tool: a decision pathway for determining which patients with suspected pandemic influenza require hospital assessment and admission; it forms the basis of the swine flu hospital pathway
CLRN	Comprehensive Local Research Network
CURB-65	A risk prediction score for pneumonia, based on confusion, urea level, respiratory rate, blood pressure and age over 65 years
ECC	Ethics and Confidentiality Committee: a subcommittee of the NIGB
ECG	electrocardiogram
GCS	Glasgow Coma Score
HPA	Health Protection Agency
ICNARC	Intensive Care National Audit and Research Network
IRAS	Integrated Research Application System
NIGB	National Information Governance Board
PMEWS	Pandemic Modified Early Warning Score: a risk score for pandemic influenza based on physiological variables, age, social factors, chronic disease and performance status
PMG	Project Management Group
REC	Research Ethics Committee
ROC	receiver-operator characteristic
SD	standard deviation
SLSP	System Level Security Policy
SSI	Site Specific Information

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Background

The UK influenza pandemic contingency plan published in 2007 predicted around 750,000 excess emergency department attendances and 82,500 excess hospitalisations during a pandemic. Clinicians working in the emergency department need a rapid and reliable method for determining each patient's risk of adverse outcome. Prior to the emergence of the 2009 H1N1 pandemic, Health Protection Agency (HPA) guidance, supported by the British Thoracic Society and British Infection Society, recommended the use of the CURB-65 (a risk prediction score for pneumonia, based on confusion, urea level, respiratory rate, blood pressure and age over 65 years) pneumonia score for adults. Department of Health guidelines on surge capacity in a pandemic also considered use of a physiological–social score [Pandemic Modified Early Warning Score (PMEWS)] for adults. National guidance produced in response to the emergence of H1N1 influenza included a new swine flu hospital pathway for emergency department management with seven criteria based upon a Community Assessment Tool (CAT) for adults and children. These potential triage methods have not been widely validated and, in particular, have not been tested in the setting of pandemic influenza.

Objectives

We aimed to use the initial waves of the 2009 H1N1 pandemic to evaluate existing emergency department triage methods for predicting severe illness or death in patients presenting with suspected pandemic influenza, and to determine whether an improved triage method could be developed. Our specific objectives were to determine:

1. the discriminant value of the CURB-65 score, PMEWS and the swine flu hospital pathway for predicting severe illness or death in adults presenting with suspected pandemic influenza and the discriminant value of the swine flu hospital pathway for predicting severe illness or death in children
2. the independent predictive value of presenting clinical characteristics and routine tests for severe illness or death in patients presenting with suspected pandemic influenza
3. whether the discriminant value of emergency department triage can be improved by developing two new triage methods based upon (1) presenting clinical characteristics alone and (2) presenting clinical characteristics, electrocardiogram, chest radiograph and routine blood test results.

Methods

We undertook a prospective cohort study of patients presenting to the emergency department of four hospitals with suspected pandemic influenza during the second wave of the 2009 H1N1 pandemic. Emergency department staff identified patients with suspected pandemic influenza and then completed a standardised assessment form that included the elements of the CURB-65 score, PMEWS, the swine flu hospital pathway and any other measures that could be routinely recorded in the emergency department.

Outcome assessment was based on researcher review of hospital computer records and case notes. Patients who died or required respiratory, cardiovascular or renal support during the 30-day follow-up were defined as having a poor outcome. Patients who survived to 30 days without requiring respiratory, cardiovascular or renal support were defined as having a good outcome. We also recorded whether they were treated with antiviral agents or antibiotics, and the length and location of any hospital stay.

We planned to assess CURB-65, PMEWS and the swine flu clinical pathway by calculating the area under the receiver–operator characteristic curve (*C*-statistic) for discriminating between cases with and without a poor outcome. We also planned to use multivariable logistic regression to determine the independent predictive value of presenting clinical characteristics and routine tests and to develop two new triage scores: one based on initial assessment only and the other based on all emergency department data.

Results

The 2009 H1N1 pandemic was much smaller and less severe than predicted. Data were collected and analysed from 481 cases across three hospitals in the second wave of the pandemic. Most of the cases were children, with 347 out of 481 (72%) aged 16 years or less. There were only five poor outcomes according to our definition: two deaths and three survivors who required respiratory support. We therefore lacked sufficient data to determine the independent predictive value of presenting clinical characteristics and routine tests or develop any new triage methods.

The five patients with poor outcomes had CURB-65 scores of zero, one (three cases) and two, and PMEWS scores of one, five, six, seven and eight. The swine flu hospital pathway was positive in three out of five cases. The *C*-statistic for each method was CURB-65 0.78 [95% confidence interval (CI) 0.58 to 0.99], PMEWS 0.77 (0.55 to 0.99) and the swine flu hospital pathway 0.70 (0.45 to 0.96).

Patients with a higher CURB-65 score were more likely to be admitted ($p < 0.001$): 25 out of 101 (25%) with a score of zero, 11 out of 24 (46%) with a score of one, 7 out of 8 (88%) with a score of two, and the patient with a score of three were admitted. Admitted patients had a higher mean PMEWS score (4.6 vs 2.0, $p < 0.001$). The *C*-statistics for CURB-65, PMEWS and the swine flu hospital pathway in adults in terms of discriminating between those admitted and discharged were 0.65 (95% CI 0.54 to 0.76), 0.76 (95% CI 0.66 to 0.86) and 0.62 (95% CI 0.51 to 0.72) respectively.

Conclusions

We can draw no reliable conclusions from the data available other than raise potential concerns about the use of existing triage methods for patients with suspected pandemic influenza. Our very limited data suggest these methods may fail to discriminate between patients who will have an adverse outcome and those with a benign course. Furthermore, clinicians in our study did not generally appear to admit or discharge on the basis of these tools, despite being recommended for use in the pandemic.

Implications for practice

In the absence of evidence for the use of these triage tools, emergency department clinicians should continue to base triage decisions for patients with suspected pandemic influenza upon their clinical judgement.

Recommendations for research

Further research is required to evaluate existing triage tools and develop new triage methods for suspected pandemic influenza. This may require evaluation in surrogate conditions, such as pneumonia or seasonal influenza. Research is also required to determine the feasibility and acceptability to patients of undertaking research during a pandemic using confidential patient information without consent.

Chapter 1
Introduction

Influenza pandemics have occurred at least three times in the last century. Their severity ranges from similar to seasonal influenza to a major international threat to health, with millions becoming ill and a proportion dying. A pandemic thus has the potential to place a huge strain upon health services, particularly the emergency care services, which may be exacerbated by staff sickness absence due to influenza.

The timing, course and severity of a pandemic are difficult to predict, but estimates of the number of cases and the burden upon health services are necessary to assist planning. The UK influenza pandemic contingency plan published in 2007 predicted around 750,000 excess emergency department attendances and 82,500 excess hospitalisations during a pandemic.[1] Under these circumstances it would be impractical for all patients fully to be assessed by a senior clinician. We therefore need methods of triage and resource allocation that are fair, robust and reproducible.[2]

The term *triage* is often used to describe a brief initial assessment in the emergency department to determine patient order of priority in the queue to be seen. However, it can be used more broadly to include the full process of emergency assessment, including investigations such as blood tests and radiography, and can be applied to decision-making regarding whether the patient should be admitted to hospital and whether he/she should be referred for high-dependency or intensive care.

Emergency department triage methods need to accurately predict the individual patient's risk of death or severe illness. The predicted risk can then guide decision-making. Patients with a low risk may be discharged home, those with a high risk admitted to hospital, and those with a very high risk referred for high-dependency or intensive care. The level of risk used to trigger these decisions need not necessarily be fixed or determined in advance. Indeed, decision-making thresholds could change during the course of a pandemic as the balance between resource availability and demand changes. Triage methods that use a risk prediction score to determine the need for hospital care may therefore be more useful than a triage rule that classifies patients into admission and discharge categories.

In April 2009, a new strain of the A/H1N1 influenza virus (known as swine flu) was detected in Mexico and started to spread globally. In June, the World Health Organization declared the outbreak to be a pandemic. The virus spread to the UK, leading to a first wave of cases in July 2009 and a second wave in October and November 2009. The initial waves of the pandemic provided an opportunity to undertake research that could then guide patient management in subsequent waves or future pandemics.

Prior to the emergence of the 2009 H1N1 pandemic, Health Protection Agency (HPA) guidance, supported by the British Thoracic Society and British Infection Society, recommended the use of the CURB-65 pneumonia score[3] in adults, shown in Appendix 1. This score uses five variables (confusion, urea level, respiratory rate, blood pressure and age) to generate a score between zero and five. Department of Health guidelines on surge capacity in a pandemic also considered use of a physiological–social score [Pandemic Modified Early Warning Score (PMEWS)][4] for adults, shown in Appendix 2. This score uses physiological variables, age, social factors, chronic disease and performance status to generate a score between zero and 20. National guidance produced in response to the emergence of H1N1 influenza included a new swine flu hospital pathway for emergency department management with seven criteria. This was based upon a Community Assessment Tool (CAT) consisting of seven criteria, any one of which predicts increased risk and the need for hospital assessment[5] in adults and children. This is shown in Appendices 3 (adults) and 4 (children).

Existing literature shows CURB-65 to perform reasonably well as a mortality predictor in an emergency department population with community-acquired pneumonia {AUROC [area under the receiver–operator characteristic curve (*C*-statistic): a measure of the discriminant value of a risk prediction score] 0.76},[6] but less well in predicting the need for high-level care (AUROC

0.69[7] and 0.64[8]). The physiological–social score considered by the Department of Health (PMEWS) is not a particularly good predictor of death in community-acquired pneumonia (used as a proxy for pandemic influenza), with an AUROC score of 0.66, but performed much better when predicting a requirement for higher-level care (AUROC 0.83)[8] and has shown promise when used in the prehospital setting to determine need for emergency department attendance (AUROC 0.71[9] and 0.8[10]). The national guidelines produced for the H1N1 pandemic appear to have been developed by expert consensus without validation in the appropriate patient populations.

To our knowledge there have been no studies evaluating any of these triage methods in patients with suspected pandemic influenza, and no studies to develop a risk-prediction score in the emergency department population with suspected pandemic influenza. We therefore aimed to use the initial waves of the H1N1 pandemic to evaluate existing emergency department triage methods for predicting severe illness or death in patients presenting with suspected pandemic influenza, and determine whether an improved triage method could be developed.

Our specific objectives were to determine:

1. the discriminant value of the CURB-65 score, PMEWS and the swine flu hospital pathway for predicting severe illness or death in adults presenting with suspected pandemic influenza, and of the swine flu hospital pathway for predicting severe illness or death in children
2. the independent predictive value of presenting clinical characteristics and routine tests for severe illness or death in patients presenting with suspected pandemic influenza
3. whether the discriminant value of emergency department triage can be improved by developing two new triage methods based upon (1) presenting clinical characteristics alone and (2) presenting clinical characteristics, electrocardiogram (ECG), chest radiograph and routine blood test results.

The first new triage method would use only variables available at initial patient assessment, i.e. history and examination, including simple technologies such as automated blood pressure measurement and pulse oximetry. This triage method could be used to assess patients for the need for hospital investigation and identify patients that could be discharged without further assessment.

The second new triage method would be based upon all available emergency department data, including routine blood tests, ECG and chest radiograph findings. This triage method could be used for two potential purposes: (1) identification of patients with a low risk of adverse outcome, who can be discharged home after emergency department assessment, and (2) identification of high-risk patients who are likely to need high-dependency or intensive care.

Chapter 2
Methods

We undertook a prospective cohort study of patients presenting to the emergency department of the participating hospitals with suspected pandemic influenza during the second wave of the 2009 H1N1 pandemic. Patients were eligible for inclusion if they met the clinical diagnostic criteria of (1) fever (pyrexia ≥ 38°C) or a history of fever and (2) influenza-like illness (two or more of cough, sore throat, rhinorrhoea, limb or joint pain, headache, vomiting or diarrhoea) or severe and/or life-threatening illness suggestive of an infectious process.

Emergency department staff identified eligible patients and then completed a standardised assessment form that doubled as a clinical notes and study data collection form [referred to hereinafter as the clinical assessment form (CAF) and prepared in adult and paediatric variants – see Appendix 5]. It included the elements of the CURB-65 score, PMEWS, the swine flu hospital pathway and any other measures that could be routinely recorded in the emergency department (comorbidities, physiological observations, routine blood tests, ECG and chest radiograph). Details of any prepresentation antiviral medication, antibiotics and immunisation status were also recorded. The study did not involve any change to patient management, so patients were treated and then discharged home or admitted to hospital according to normal emergency department practices.

Patients were informed of the study by means of posters displayed in the emergency department, and leaflets distributed from reception and the pandemic influenza assessment area. They were informed that they could withdraw their data from the study but were not asked to consent to participate in the study. We did not seek patient consent to participate on the basis that the study was limited to collection of routinely available data and any delays in patient assessment could have risked compromising patient care.

Research staff followed patients up until 30 days after attendance by hospital record review and, if appropriate, general practitioner contact to identify patient outcomes. Data were abstracted from the CAF and hospital notes by researchers working with an honorary contract from the hospital Trust or researcher passport recognised by the Trust. The researcher kept a record of any patients who withdrew from the project. He/she entered anonymised data on to a secure online database provided by the Clinical Trials Unit at the University of Sheffield, Sheffield, UK. Other members of the research team had access only to anonymised data on the secure database.

The CAF constituted the clinical notes and was kept in each hospital according to normal practice. A copy of the CAF was retained by the researcher in a secure location in each hospital, to be destroyed 6 months after the end of the project. The Clinical Trials Unit will maintain an anonymised database until 10 years after the end of the project.

Outcome measures

Patients who died or required respiratory, cardiovascular or renal support during the 30-day follow-up were defined as having a poor outcome. Patients who survived to 30 days without requiring respiratory, cardiovascular or renal support were defined as having a good outcome. We also recorded whether they were treated with antiviral agents or antibiotics and the length and location of any hospital stay.

Respiratory support was defined as any intervention to protect the patient's airway or assist their ventilation, including non-invasive ventilation or acute administration of continuous positive airway pressure. It did not include supplemental oxygen alone or nebulised bronchodilators. Cardiovascular support was defined as any intervention to maintain organ perfusion (such as inotropic drugs) or invasively monitor cardiovascular status (such as central venous pressure, pulmonary artery pressure monitoring or arterial blood pressure monitoring). It did not include peripheral intravenous cannulation and/or fluid administration. Renal support was defined as any intervention to assist renal function, such as haemoperfusion, haemodialysis or peritoneal

dialysis. It did not include intravenous fluid administration.

Outcome assessment was based primarily on researcher review of hospital computer records and case notes. If there was no evidence of a poor outcome in these the patient was recorded as having a good outcome. If the outcome was uncertain (for example, if the patient was transferred to another hospital or left hospital against medical advice) the researcher contacted the patient's general practitioner for clarification.

Proposed sample size

The sample size depended upon the size and severity of the pandemic. We planned to collect data during the pandemic at four hospitals in Sheffield and Manchester covering a population of > 1 million. Prior to the pandemic, the Department of Health estimated that a 25% clinical attack rate with illustrative case hospitalisation and case fatality rates of 0.55% and 0.37%, respectively, suggested that a pandemic could lead to 12,500 emergency department attendances, 1400 hospitalisations and 900 excess deaths in our population.[1] If one-half of these occurred while we were collecting data then around 6000 cases with 600 poor outcomes would be available for analysis.

We planned to split the database for analysis into two data sets of equal size, one for developing new scores and testing existing scores, and one for comparing the new and existing scores. To develop a new triage method we estimated needing around 10 events per parameter tested in the model, so 200 cases with a poor outcome would allow us to test 20 parameters. A sample size of 283 cases with a poor outcome would ensure a power of 80% to compare an area under the ROC curve of 0.85 versus 0.90 at 5% significance, assuming a correlation of 0.6 between scores.[11]

Statistical analysis

Existing triage methods

We planned to assess CURB-65, PMEWS and the swine flu clinical pathway in adults and in children by calculating the AUROC (*C*-statistic) for discriminating between cases with and without a poor outcome (defined as death or need for support of respiratory, cardiovascular or renal function) and sensitivity and specificity at key decision-making thresholds. For each score we assumed a score of zero or a negative categorisation for any variable or criterion that was missing.

New triage methods

As outlined above, we planned to develop two new triage scores: one based on initial assessment only and the other based on all emergency department data. We planned to test the association of each potential clinical predictor variable with outcome and then undertake logistic regression to identify independent predictors of outcome. The strongest independent predictors of outcome would then be combined to form a new triage score. Continuous predictor variables would be divided into categories on the basis of the relationship of the variable with outcome. Integer weights would be assigned to each category of predictor variable according to the coefficient derived from a multivariate model using categorised independent predictors. This would generate a composite clinical score in which risk of poor outcome increases with the total score.

Chapter 3

Ethical and governance arrangements

The North West Research Ethics Committee (REC) and the National Information Governance Board (NIGB) reviewed and approved the study protocol. The University of Sheffield was the study sponsor. The Project Management Group (PMG), consisting of the coapplicants and the appointed research staff, managed the study. A steering group was appointed, consisting of the chief investigator, project manager, an independent clinician (Chairperson), statistician and layperson to provide independent oversight.

Study progress and changes to the protocol

The study commenced on 1 September 2009, after the first wave of the pandemic in July 2009 but before the second wave in October and November 2009. The Integrated Research Application System (IRAS) application form was completed and lodged in the system on 10 August 2009. On 11 August 2009 the REC debated the proposal and the project team received their written feedback on 18 August. Following the submission of the IRAS form, the South Yorkshire Comprehensive Local Research Network (CLRN) contacted the NIGB on 14 August 2009 to initiate discussions on 'fast tracking' the application, which they agreed to do. The chief investigator contacted the NIGB on the 17 August 2009 and the application form was delivered shortly after. First comments from the NIGB were issued on 24 August 2009. Responses by the chief investigator to the issues raised were returned to the NIGB on 4 September 2009 [together with the first draft of the System Level Security Policy (SLSP)]. Responses to issues raised by the REC were despatched on 7 September 2009. The NIGB referred the SLSP to their in-house security adviser, who, in turn, sent on further queries to the project team on 14 September 2009. A revised draft of the SLSP was prepared and sent back to the NIGB on 17 September 2009, which was accepted by the security adviser on 18 September 2009. Full NIGB approval was issued on the 22 September 2009 resulting in final approval from the REC being issued on 24 September 2009.

Running in tandem with the processing of ethics documentation was a parallel process of securing local governance approval from the four participating sites. The 'R&D' part of the IRAS form was received by the national CLRN responsible for England on 4 September 2009. Arrival of this form triggered notifications to the Greater Manchester CLRN and the South Yorkshire CLRN, who, in turn, liaised with the Trusts within their jurisdiction concerning the local approvals. The lead investigators at each site concurrently submitted Site Specific Information (SSI) forms, (generated through IRAS) to their own research departments.

The dates of initiation for the local approvals process were:

- 4 September 2009 CLRN received the IRAS R&D form
- 15 September 2009 Sheffield Teaching Hospitals SSI form submitted
- 25 September 2009 Sheffield Children's Hospital SSI form submitted
- 15 October 2009 Pennine Acute Hospitals SSI form submitted
- 25 November 2009 University Hospitals of South Manchester SSI form submitted.

Research governance approval was secured at each site on the following dates:

- 10 November 2009 Sheffield Teaching Hospitals
- 11 November 2009 Pennine Acute Hospitals
- 26 November 2009 University Hospitals of South Manchester
- 22 December 2009 Sheffield Children's Hospital.

There were delays in securing the individual Trust approvals. These delays resulted from the requirements of each Trust's research governance procedures (involving forms for project registration, finance and data protection each requiring 'wet ink' signatures) and the problems of a process developed for interventional studies, such as clinical trials (with associated Good Clinical

Practice training, Standard Operating Procedures, delegation logs and enhanced Criminal Records Bureau checks for research field staff) being inappropriately applied to data-based research.

In the period between main REC and NIGB approval being granted and the local approvals coming through, the chief investigator and the local investigators at three sites took the decision to use the REC-approved CAF for routine clinical assessment of cases of suspected pandemic influenza. The forms were distributed around the participating emergency departments, together with the patient information leaflets and information posters, and staff were advised to use the forms for clinical assessment, as outlined in the study protocol. Examining doctors followed the procedures agreed with the REC and the NIGB on informing patients about the study and pointing out the individual's right to withdraw should they wish to do so. We felt that it was appropriate to take this initiative because had we waited for granting of research governance approval we might have missed the second wave of the pandemic and the opportunity to collect valuable data. We were unable to start data collection at the fourth hospital until after the second wave had passed, so this hospital did not contribute to the study.

In summary, the process of REC review was efficient, reflecting the activation of an emergency policy by the National Research Ethics Service. NIGB review was also efficient, although the requirements of submission (such as the need for a SLSP) would have prevented researchers with no previous experience of using confidential data without consent from undertaking rapid submission. The process of securing local UK NHS approvals was slow and inefficient. This contrasts with experience reported by other pandemic studies,[12] where, for example, one multicentre study apparently obtained local approvals within 5 days in over 100 hospitals.

The pandemic was much less severe than predicted. As of 5 January 2010 there had been 28,456 laboratory-confirmed cases of H1N1 influenza, with 4930 reported as being hospitalised and 355 deaths.[13] However, serological testing in children has shown that clinical surveillance may identify only one in 10 cases of H1N1 infection, and around one child in every three was infected with 2009 pandemic H1N1 in the first wave of infection in regions with a high incidence.[14] The low numbers of hospitalisations and deaths therefore reflect lack of disease severity rather than lack of disease in the community. This meant that instead of the predicted 1400 hospitalisations and 900 excess deaths in our population it was likely that the pandemic would only have resulted in around 80–90 hospitalisations and 5–6 deaths if our population were typical of the UK (estimated by multiplying total UK hospitalisations and deaths by the approximate proportion of the UK population covered by the participating hospitals).

It became apparent during the study that the sample size would be markedly less than our original prediction and the study would be underpowered. In an attempt to address this we proposed a change to the study methods and amended the protocol accordingly. We proposed using routine hospital data collection systems to retrospectively identify all patients who presented to all four hospitals with symptoms consistent with suspected pandemic influenza during both waves of the pandemic and suffered a poor outcome (as defined above). This would allow us to use a case–control approach, with a maximised number of cases and thus optimise the statistical power of the study within the available resources and caseload. However, this approach would involve a substantial change to methodology and the need to use data without informing patients. We therefore submitted the amended protocol for review by the REC and the NIGB. The notice of substantial amendment is shown in Appendix 6.

In response, the NIGB requested that a new application for section 251 support be submitted to their next Ethics and Confidentiality Committee (ECC) meeting and stated that the ECC position on retrospective studies of relatively small numbers of patients was that consent should be sought via the members of the direct clinical care team involved in the care and treatment of the individual cohort. There was also an expectation that consent should be sought from the family of patients who were deceased. If consent were not feasible (and this would only be accepted if strong justification were provided), data extraction from the clinical record would need to be carried out by the direct clinical care team and only fully anonymised data returned to the researchers. The REC rejected the proposed amendment pending the decision of the NIGB, and also suggested that informed consent to the use of data should be requested from those who had not died. Responses from the NIGB and REC are in Appendices 7 and 8, respectively.

We decided that, based on these responses, we would not be able to undertake a meaningful

study with section 251 support using the proposed case–control methodology. We had some ethical concerns about contacting recently bereaved family members, as suggested by the NIGB, but accepted that there were no insurmountable barriers to seeking consent, so we could not claim this was not feasible. However, we anticipated that a substantial proportion of patients or relatives would not respond to our request for consent and subsequent responder bias would render the findings of the study worthless, or at least of such limited value as to not justify the expense of the project or intrusion into patients' and relatives' lives. Furthermore, clinical staff in the participating hospitals indicated that they were neither willing nor able to commit time to extract data from the clinical records. We therefore proceeded with the initial investigation plan. Our reply is in Appendix 9.

Chapter 4
Results

As insufficient cases presented to the participating hospitals to complete our initial analysis plan, we have restricted our analysis to the ability of the various existing triage tools to predict hospital admission and poor outcome.

Cases were identified and data collected at the Northern General Hospital between 29 September 2009 and 10 January 2010, Sheffield Children's Hospital between 10 October 2009 and 31 December 2009 and South Manchester between 24 September 2009 and 7 February 2010. We identified and collected data from a total of 492 cases, 11 of whom asked for their data to be withdrawn, leaving 481 for analysis. There were 77 cases at the Northern General Hospital, 226 at the Sheffield Children's Hospital and 178 at South Manchester. Ages ranged from infant to 96 years. Most of the cases were children, with 347 out of 481 (72%) aged 16 years or less. The modal age group was 1–2 years, accounting for 69 out of 481 (14%). There were 237 females (49%) and 244 males (51%). Most patients self-referred (399/481, 83%), while only 41 (8%) were referred via their GP and 15 (3%) were referred via NHS Direct.

Symptom duration was recorded for 379 patients. Mean duration was 3.1 days, median was 2 days and most patients (213 out of 379, 56%) had 1–2 days of symptoms. Prior to their index hospital attendance, 30 (6%) had attended hospital with the same complaint, eight patients (2%) had received vaccination against H1N1, 39 (8%) had been given oseltamivir, and 46 (10%) had been given antibiotics, although not always specifically for their presenting complaint.

Social isolation (defined as living alone or having no fixed abode) was reported by 12 (2%). *Table 1* shows the proportion reporting different levels of performance status. This was not recorded for one-third of patients but most cases that did report it had unrestricted normal activity. *Table 2* shows the proportion reporting chronic disease or medication use. The only chronic problem recorded with any frequency was asthma, in 13% of cases.

Influenza was thought by the physician to be the most likely diagnosis in 214 out of 368 cases (58%). The most common alternatives were upper respiratory tract infection (79 cases) and tonsillitis (23 cases).

TABLE 1 *Proportion reporting different levels of performance status (self or parental report)*

Performance level	*n* (%)
Unrestricted, normal activity	223 (46)
Limited strenuous activity, can do light	46 (10)
Limited activity, can self-care	34 (7)
Limited self-care	11 (2)
No self-care	4 (1)
Not recorded	163 (34)
Total	481 (100)

TABLE 2 *Proportion reporting chronic disease or medication use (n = 481)*

Chronic problem	*n* (%)
Heart disease	4 (1)
Lung disease	6 (1)
Renal impairment	1 (< 1)
Steroid therapy	9 (2)
Asthma	61 (13)
Diabetes	7 (1)
Malignancy	4 (1)
Immunosuppression	4 (1)

Presenting physiological features were not recorded in all cases. Temperature ($n = 425$) ranged from 35.0°C to 40.7°C [mean 37.8, standard deviation (SD) 1.1] and peripheral oxygen saturation ($n = 369$) ranged from 79% to 100% (mean 97%, SD 6%). Some 19 out of 369 (5%) cases had peripheral oxygen saturation below 94%. Results for pulse rate, respiratory rate and blood pressure (*Table 3*) are categorised by age group to allow for age-related variation in normal values for these parameters. Tachycardia and tachypnoea were relatively common, whereas blood pressure was generally normal.

Variables that were relevant only to younger children were present as follows: 6 out of 207 (3%) had been managed on a special care baby unit, 8 out of 234 (3%) had not had their routine vaccinations, 51 out of 227 (22%) were not taking feeds and 47 out of 205 (23%) of clinicians reported parental anxiety as being a concern.

Blood tests were only ordered for 55 out of 481 cases (11%). The results are summarised in *Table 4*. Chest radiographs were ordered and were abnormal in 12 cases, normal in 19, not done in 284 and not recorded in 166. An ECG was ordered and abnormal in 10 cases, normal in 24, not done in 67 and not recorded in 380.

The clinical plan included oseltamivir for 58 cases and antibiotics for 56 (22 amoxicillin, nine augmentin, one cefotaxime, two ceftriaxone, three clarithromycin, one gentamycin and 18 penicillin). The attendance resulted in admission for 83 out of 481 cases (17%): 12 aged 0–1 years, 14 aged 2–5 years, 13 aged 6–16 years and 44 adults.

Tables 5 and *6* show the CURB-65 scores and PMEWS scores (adults only). The recommended threshold for admission[4] for CURB-65 is a score of two or more. *Table 5* suggests that 9 out of 134 (7%) of patients should have been admitted. Applying a similar threshold for PMEWS would have resulted in 81 out of 134 (60%) being admitted.

Patients with a higher CURB-65 score were more likely to be admitted ($p = 0.001$, chi-squared test for trend): 25 out of 101 (25%) with a score of zero, 11 out of 24 (46%) with a score of one, 7 out of 8 (88%) with a score of two and the patient with a score of three were admitted. Admitted patients had a higher mean PMEWS scores (4.6 vs 2.0, $p < 0.001$, *t*-test). The *C*-statistics for CURB-65, PMEWS and the swine flu hospital pathway in adults in terms of discriminating between those admitted and discharged were 0.65 (95% CI 0.54 to 0.76), 0.76 (95% CI 0.66 to 0.86) and 0.62 (95% CI 0.51 to 0.72), respectively.

TABLE 3 *Presenting physiological features*

		Age			
		0–1 years (*n* = 87)	**2–5 years (*n* = 135)**	**6–16 years (*n* = 125)**	**> 16 (*n* = 134)**
Pulse rate (*n* = 424)	Mean (SD)	147 (24)	130 (24)	113 (22)	100 (18)
	Range	108–204	80–196	72–182	62–152
Respiratory rate (*n* = 390)	Mean (SD)	35 (10)	28 (8)	23 (6)	20 (6)
	Range	20–62	16–60	12–52	12–40
Systolic BP (*n* = 141)	Mean (SD)	–	–	118 (14)	128 (19)
	Range	–	–	92–140	80–188
Diastolic BP (*n* = 140)	Mean (SD)	–	–	63 (12)	73 (12)
	Range	–	–	40–78	38–111

BP, blood pressure. This was recorded in only one child aged 0–1 years and four children aged 2–5 years.

TABLE 4 *Summary of blood results*

Blood test	Mean (SD)	Range	Extreme values
Haemoglobin (g/dl)	13.6 (2.1)	6.5–17.0	4 < 11.0
White cell count ($\times 10^9$/l)	10.3 (7.2)	1–50	4 < 4.0, 21 > 10.0
Platelet count ($\times 10^9$/l)	228 (84)	38–452	7 < 150, 2 > 400
Sodium (mmol/l)	136 (4)	119–142	12 < 135
Potassium (mmol/l)	4.1 (0.5)	3.2–5.7	7 < 3.5, 1 > 5.5
Urea (mmol/l)	11.4 (41.2)	1.4–305.0	11 > 6.5
Creatinine (μmol/l)	89 (71)	44–569	6 > 120

TABLE 5 *CURB-65 scores for adults*

CURB-65 score	*n* (%)
0	101 (75)
1	24 (18)
2	8 (6)
3	1 (1)
Total	134 (100)

TABLE 6 *PMEWS scores for adults*

PMEWS score	*n* (%)
0	24 (18)
1	29 (22)
2	21 (16)
3	15 (11)
4	9 (7)
5	15 (11)
6	6 (4)
7	3 (2)
8	9 (7)
9	2 (1)
10	1 (1)
Total	134 (100)

Tables 7 and *8* show the results for adults and children (aged 16 or less), respectively, on the swine flu hospital pathway, along with the number and proportion with each criterion admitted. Among the adults, 16 out of 28 (57%) with a positive criterion were admitted, compared with 28 out of 106 (26%) with no positive criteria. Among the children, 14 out of 39 (36%) with a positive criterion were admitted, compared with 25 out of 308 (8%) with no positive criteria.

Only 5 out of 481 (1%) patients had a poor outcome according to our definition. Their details are as follows:

1. Female, aged 60, no chronic illnesses, presented with respiratory rate 30, heart rate 90, temperature 38.0, blood pressure 160/62, peripheral oxygen saturation 90%, Glasgow Coma Score (GCS) 15, haemoglobin 13.4, platelets 198.0, white cell count 12.7, sodium 119.0, potassium 4.4, urea 12.9, creatinine 102.0, chest radiograph abnormal, CURB-65 score 2, PMEWS score 6, positive for swine flu hospital pathway criterion C, died 5 days after admission.

TABLE 7 *Swine flu hospital pathway criteria for adults*

Criterion	*n* (%) meeting criterion	*n* admitted (% admitted of those meeting criterion)
A	2 (1)	2 (100)
B	7 (5)	5 (71)
C	11 (8)	9 (82)
D	2 (1)	1 (50)
E	12 (9)	4 (33)
F	3 (2)	3 (100)
G	3 (2)	2 (66)
Any category positive	28 (21)	16 (57)

TABLE 8 *Swine flu hospital pathway criteria for children*

Criterion	*n* (%) meeting criterion	*n* admitted (% of those meeting criterion)
A	0	–
B	23 (7)	9 (39)
C	4 (1)	2 (50)
D	0	–
E	10 (3)	2 (20)
F	0	–
G	6 (2)	3 (50)
Any category positive	39 (11)	14 (36)

2. Female, aged 43, known asthma, presented with respiratory rate 22, heart rate 95, temperature 39.2, blood pressure 188/111, peripheral oxygen saturation 95%, GCS 15, haemoglobin 15.3, platelets 275.0, white cell count 14.0, sodium 138.0, potassium 4.2, urea 3.4, creatinine 100.0, chest radiography performed but findings not recorded, CURB-65 score 0, PMEWS score 5, negative for all swine flu hospital pathway criteria, required non-invasive ventilation.
3. Male, aged 39, known renal failure, presented with respiratory rate 16, temperature 38.7, haemoglobin 11.7. platelets 38, white cell count 1.0, sodium 132.0, potassium 4.3, urea 14.8, creatinine 569.0, chest radiography performed but findings not recorded, CURB-65 score 1, PMEWS score 1, negative for all swine flu hospital pathway criteria, required non-invasive ventilation. Also required haemodialysis for pre-existing renal failure.

TABLE 9 *Sensitivity and specificity of existing triage methods*

		Sensitivity (95% CI)	Specificity (95% CI)
CURB-65	Score > 1	20% (4 to 62)	94% (88 to 97)
PMEWS	Score > 1	80% (38 to 96)	40% (32 to 49)
Swine flu hospital pathway	Any criterion positive	60% (23 to 88)	81% (73 to 87)

4. Female, aged 25, known epilepsy, presented with respiratory rate 22, heart rate 90, blood pressure 80/40, temperature 37.5, peripheral oxygen saturation 79%, GCS 15, haemoglobin 11.8. platelets 75, white cell count 1.7, sodium 136.0, potassium 3.2, urea 4.7, creatinine 53.0, chest radiography not recorded, ECG not recorded, CURB-65 score 1, PMEWS score 7, positive for swine flu hospital pathway criteria C and E, required positive pressure ventilation and then died after 54 days.
5. Female, aged 51, known chronic lung disease, presented with respiratory rate 36, heart rate 135, temperature 37.8, blood pressure 116/80, peripheral oxygen saturation 95%, GCS 15, haemoglobin 15.3. platelets 247, white cell count 10.0, sodium 136.0, potassium 3.8, urea 4.4, creatinine 85.0, chest radiography not recorded, ECG abnormal, CURB-65 score 1, PMEWS score 8, positive for swine flu hospital pathway criterion B, required non-invasive ventilation and positive pressure ventilation.

All five patients were admitted to hospital at the initial attendance. CURB-65 scores were zero, one (three cases) and two. PMEWS scores were one, five, six, seven and eight. The swine flu hospital pathway was positive for three cases and negative for two. The *C*-statistic for each method was CURB-65 0.78 (95% CI 0.58 to 0.99), PMEWS 0.77 (95% CI 0.55 to 0.99) and the swine flu hospital pathway 0.70 (95% CI 0.45 to 0.96). *Table 9* shows sensitivity and specificity for CURB-65 and PMEWS, with a threshold of > 1 and the swine flu hospital pathway with any criterion positive.

A further four adults and one child were admitted to critical care environments, but did not have interventions qualifying for our definition of a poor outcome. One other adult was admitted to the intensive therapy unit, but no specific interventions were recorded.

There were insufficient data for multivariate analysis to determine which clinical features and tests were independent predictors of outcome or develop new triage methods.

Chapter 5
Discussion

The number of cases of suspected pandemic influenza was much lower than predicted and the number of cases with a poor outcome was lower still. We identified two deaths and three patients who survived after requiring respiratory support among those who presented to the emergency departments of three hospitals during the second wave of the pandemic. All five cases were adults. The CURB-65 score and swine flu hospital pathway did not reliably detect these cases. A CURB-65 score of two or more has been recommended to trigger admission.[4] In our study the CURB-65 score was two or more in 7% of the adult patients and one of the five cases with a poor outcome. The swine flu hospital pathway was positive for 21% of the adult patients and three out of five cases with a poor outcome. The PMEWS score does not have a recommended threshold but a threshold of two or more has been suggested (K Challen, University Hospitals of South Manchester, May 2010, personal communication). According to this threshold PMEWS would be positive in 60% of the adult patients and four out of five cases with a poor outcome.

The findings are substantially limited by the small sample and, in particular, only including five cases with a poor outcome. These five cases may have been atypical, so we can draw no firm conclusions regarding the value of these three triage tools, other than raise some concerns about the discriminant value of existing triage methods. Furthermore, we did not test the application of the methods in practice, but calculated or inferred their performance from clinical data. Some criteria, such as the swine flu hospital pathway criterion G (other clinical concern), may have identified some of the cases with a poor outcome when used in practice.

We did not require virological testing or confirmation as both national and local guidance recommended that patients with influenza-like illness fulfilling the HPA criteria (which we used as our inclusion criteria) should be assumed to be suffering from H1N1 influenza and treated accordingly. Our aim was to complete pragmatic 'real world' research, reflecting as closely as possible standard working conditions. We did not use hospital admission as an outcome because we thought that this would be heavily influenced by the triage method in use. However, it is interesting to note that CURB-65 and the swine flu hospital pathway appeared to discriminate poorly between those admitted and those discharged, despite being recommended for use in triage to hospital admission. It appears that clinicians in the participating hospitals were basing their decisions on other criteria.

The study was unable to deliver on its main objectives because the caseload arising from the pandemic was much smaller than predicted. The Department of Health prepandemic planning assumptions used a base scenario of a cumulative attack rate of 25% of the population over one or more waves of 15 weeks each, with a 0.37% case fatality rate.[1] This was based on the occurrence in previous UK pandemics of an attack rate of 25–35%, and case fatality of 0.2–2%.[1] Based on data from Mexico in early 2009, the critical care bed requirement was calculated to be 140% of capacity in North West England and 160% of capacity in Yorkshire.[15] The first clinical data from Mexico in March–April 2009 demonstrated a 10- to 11-fold increase in severe pneumonia mortality in the 20- to 30-year-old age group.[16] Similarly, intensive care admissions in Australia and New Zealand were 28.7 cases per million population (15 times the normal admission rate for viral pneumonitis) in winter (June–August) 2009.[17] First-wave hospitalisations in Ontario, Canada, resulted in a 25% intensive care admission rate,[18] as did the first 272 hospitalisations in the USA, with the USA also reporting a 7% mortality rate.[19] However, the second pandemic wave in Mexico in June–July 2009 demonstrated much lower severity and mortality rates, possibly due to earlier antiviral treatment coincident with a nationwide publicity campaign.[20] Similarly, there were no fatalities in the first 426 hospitalised cases in China, and only a 3.9% attack rate in screened close contacts.[21] Worldwide case severity, hospitalisation and mortality rates were all low, and in fact lower than seasonal influenza in some countries.[22]

It is unclear why the experience in the UK was not similar to that in Australasia. Retrospective

immunological examination of samples taken pre-pandemic (2008 and early 2009) showed protective levels of antibody to the pandemic H1N1 influenza strain in 23% of patients aged over 65 years.[23] This presumably represents crossreactivity from previous H1N1 exposure. However, there were significant pockets of H1N1 activity, notably in Birmingham and London. As of 18 March 2010, 342 deaths due to H1N1 influenza had been reported in England. Birmingham Heartlands Hospital reported that 7 out of 78 inpatients had required intensive care admission (including two patients requiring extracorporeal membrane oxygenation),[24] and serological testing demonstrated an odds ratio of 5.23 for exposure to the H1N1 virus in the West Midlands (using East Midlands as a referent group).[23]

There are a number of potential explanations for the lack of similar findings in the North West and Yorkshire. It may be that our inclusion criteria (derived from the HPA case definition) excluded a significant number of patients who were, in fact, infected with the H1N1 virus. It is notable that 29 out of 71 children admitted to hospital in Birmingham did not fulfil the HPA criteria.[25] As Birmingham and London were early hotspots it may be that the populations of Manchester and Sheffield were more aware of the availability of antiviral agents and therefore sought treatment earlier and mitigated the severity of their infection. There may also be confounding factors in terms of local viral evolution and pre-existing local population health that will be explored by other national projects, such as Flu-CIN (Influenza Clinical Information Network).

Although the lack of available cases was the main reason for the failure to address the main research questions, the study was also hampered by delays in acquiring research governance approval and our inability to find a case–control method that was both acceptable to the NIGB and REC and likely to yield worthwhile results. Our experience contrasts with other studies undertaken during the pandemic. At the start of the H1N1 swine influenza pandemic, participating case mix programme units were asked to submit data for confirmed H1N1 cases for rapid analysis and feedback. In addition, the Intensive Care National Audit and Research Network (ICNARC) gained ethics and research regulatory approval within 6 weeks for approximately 250 acute hospitals to collect data on critical care admissions with confirmed or suspected H1N1 influenza.[26] This process was presumably facilitated by existing ICNARC data management processes that support routine critical care audit and allow collection of anonymised data. This highlights the importance of having routine collection of audit and research data and the need to develop similar systems in emergency care. It also highlights the need to have research centres with established expertise in data processing and management. We would not have been able to meet the requirements of the NIGB within a practical timeframe were it not for our previous experience of applying for approval for a similar project.

This study also highlights the value of having reliable estimates of pandemic size and severity to assist sample size estimates. Predictions of pandemic size and severity are inevitably subject to substantial uncertainty. We could be justifiably criticised for not taking this uncertainty into account in planning this project. Future proposals for pandemic research should base sample size estimates on the full range of potential scenarios, including the possibility of no significant pandemic. Simulation methods could be useful to explore the potential value of different research methods in a range of different scenarios. These could be used to refine the research question and focus data collection upon the most useful variables, and guide adaptation of the study design as the pandemic emerges. However, it is important that simulation and analysis of different scenarios takes place well in advance of any emerging pandemic. Our proposal was developed over a few weeks in response to the emerging 2009 H1N1 pandemic, leaving no time for sophisticated protocol development. Future pandemic research should be planned and any preparatory work undertaken before the next pandemic emerges. In a similar vein, pilot data would have been helpful for protocol development and sample size estimates. However, the unpredictable nature of a pandemic means that the only opportunity to collect pilot data may also represent the only opportunity to undertake the full project. Some piloting could be undertaken prior to a pandemic, such as developing systems for data collection and protection and addressing information governance requirements. Undertaking this pilot work prior to the emergence of a pandemic could allow research to commence in a quick and efficient manner when a pandemic occurs.

As the 2009–10 H1N1 pandemic in the UK has not produced adequate numbers of severely ill patients from which to draw robust conclusions, health service planners must revert to the pre-existing evidence base. This includes information from

multiple sources: non-flu risk stratification tools, SARS and H5N1, and international experience of H1N1.

Pre-pandemic advice advocated the use of pneumonia severity scores to risk stratify influenza patients.[3] Some evidence exists to support their use in identifying patients who are likely to require critical care facilities; the Pneumonia Severity Index predicts critical care admission with AUROC scores of 0.6[27]–0.75[28] and CURB-65 similarly achieves AUROC scores of 0.61[29]–0.77.[30] Other tools designed specifically to predict requirement for critical care exist,[31–32] but have yet to be fully validated. However, in extrapolating from pneumonia-specific severity scores, it should be remembered that atypical presentation was well recognised in H5N1 patients.[33] A significant minority of both paediatric and adult patients eventually diagnosed with H1N1 did not fulfil HPA screening criteria, notably for pyrexia.[25,34] Little literature exists on risk assessment of undifferentiated emergency patients, and what there is concentrates on mortality risk.[35–37]

It appears from the international experience that obesity,[17] pre-existing comorbidity[19] and pregnancy[17,38] convey a worse prognosis during pandemic influenza infection. A single study of bacterial pneumonic superinfection in influenza from Taiwan identified shock, respiratory rate of over 24 breaths/minute, acidosis, raised creatinine and a pneumonia severity index of class IV or V as indicators of poor prognosis.[39]

The SARS outbreaks in South-East Asia and Toronto, Canada, highlighted the importance of developing surge capacity in the hospital and critical care spheres, and of being able to alter institutional priorities.[40] Changes in working pattern were particularly driven by high risks of nosocomial viral transmission.[41] The surge capacity and resilience of the NHS was not severely tested by the 2009–10 A/H1N1 influenza virus outbreak, except in isolated pockets. However, there were significant problems identified with misdiagnosis and missed diagnoses during the outbreak.[42]

Emergency departments should remain prepared to deal with patients with diffuse non-specific symptomatology from influenza, and retain the capability to cohort these potentially infectious patients in the emergency department and the hospital. Risk assessment will still take place in an absence of evidence but should be guided by information from the international experience.

Chapter 6
Conclusions

We can draw no reliable conclusions from the data available, other than raise potential concerns about existing triage methods for patients with suspected pandemic influenza. Our very limited data suggest that these methods may fail to discriminate between patients who will have an adverse outcome and those with a benign course. Furthermore, clinicians in our study did not generally appear to admit or discharge on the basis of these tools, despite being recommended for use in the pandemic.

Implications for practice

Currently available triage methods for patients with suspected pandemic influenza are not supported by sufficient data to allow them to be recommended for routine use. In the absence of evidence for the use of these triage tools, emergency department clinicians should continue to base triage decisions for patients with suspected pandemic influenza upon their clinical judgement.

Recommendations for research

Further research is clearly required to evaluate existing triage tools and develop new methods. This should remain a priority in future waves of the 2009 H1N1 pandemic and any future pandemics. However, the barriers to progress encountered by this study raise concerns about the ability of the NHS to undertake this research. Delays in acquiring research governance approval slowed progress generally and prevented data collection at one hospital. If the pandemic had developed as anticipated, these delays could have been critical to the success of the project. Despite the experience gained in this project we are not confident that it could be successfully undertaken in a full-scale pandemic. Alternative ways of evaluating triage methods should therefore be explored. These could include evaluation in surrogate conditions, such as seasonal flu or pneumonia, and the development of simulation techniques to explore the application of triage methods to theoretical scenarios.

The need to limit access to patient data is important to ensure that public trust in research is maintained. However, the requirements of information governance may limit our ability to undertake potentially valuable research. The public need to be informed of the potential trade-off between data protection and NHS research, and involved in determining when patient data can be used for research purposes without consent. Research could be helpful in exploring public attitudes to the use of patient data for research purposes, developing information systems that allow researchers to access anonymised data, and piloting data collection and protection processes.

It is essential that this research is planned, and, where possible, undertaken prior to the emergence of the next pandemic. Our study has highlighted the difficulties of planning and undertaking research in an emerging pandemic. If future pandemic research is not planned or undertaken until the next pandemic emerges we can expect that similar difficulties will be encountered.

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Contributions of authors

SG and KC conceived the study; SG, KC, MC and the management group designed the study; RW managed the project; RW and KC oversaw data collection; SG and MC analysed the data; SG drafted the report, and all authors contributed to writing the report and approved the final draft.

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Appendix 1

CURB-65 score

One point each for:

- **C**onfusion
- **U**rea > 7 mmol/l
- **R**espiratory rate ≥ 30/minute
- **B**lood pressure: low systolic (< 90 mmHg) or diastolic (≤ 60 mmHg)
- age ≥ **65** years.

Appendix 2

Pandemic Modified Early Warning Score (PMEWS)

PLUS

Physiological Data (MEWS)
Ring 1 value for each factor

SCORE	3	2	1	0	1	2	3
Resp Rate	≤ 8			9-18	19-25	26-29	≥ 30
O2 Sats	<89	90-93	94-96	>96			
Heart Rate	≤ 40	41-50		51-100	101-110	111-129	≥ 130
Systolic BP	≤ 70	71 - 90	91 - 100	>100			
Temp		≤35.0	35.1-36	36.1-37.9	38-38.9	≥ 39	
Neuro				Alert	Confused Agitated	Voice	Pain Uncon

Total P-MeWS =

Patient Data

Score 1 for each factor

Age >65 ... ... ☐

Social Isolation ... OR ... ...
Lives alone/No fixed abode

Chronic Disease ... OR ... .. ☐
Respiratory, cardiac, renal, immunosuppressed, DM

Performance Status >2 ...

Normal activity without restriction	1
Strenuous activity limited, can do light	2
Limited activity but capable of self care	3
Limited activity, limited self care	4
Confined to bed/chair, no self care	5

Appendix 3

Community Assessment Tool for Adults

Criteria label	ADULTS WILL BE CONSIDERED FOR ADMISSION AT THE NEAREST GENERAL HOSPITAL IF THEY PRESENT WITH ANY OF THE FOLLOWING:
A	**Severe respiratory distress** Severe breathlessness, e.g. unable to complete sentences in one breath. Use of accessory muscles, supra-clavicular recession, tracheal tug or feeling of suffocation.
B	**Increased respiratory rate** measured over at least 30 seconds. Over 30 breaths per minute.
C	**Oxygen saturation ≤92% on pulse oximetry, breathing air *or* on oxygen** Absence of cyanosis is a poor discriminator for severe illness.
D	**Respiratory exhaustion** New abnormal breathing pattern, e.g. alternating fast and slow rate or long pauses between breaths.
E	**Evidence of severe clinical dehydration or clinical shock** Systolic blood pressure <90mmHg and/or diastolic blood pressure <60mmHg. Sternal capillary refill time >2 seconds, reduced skin turgor.
F	**Altered conscious level** New confusion, striking agitation or seizures.
G	**Causing other clinical concern to the clinical team or specialist doctor** e.g. a rapidly progressive or an unusually prolonged illness.

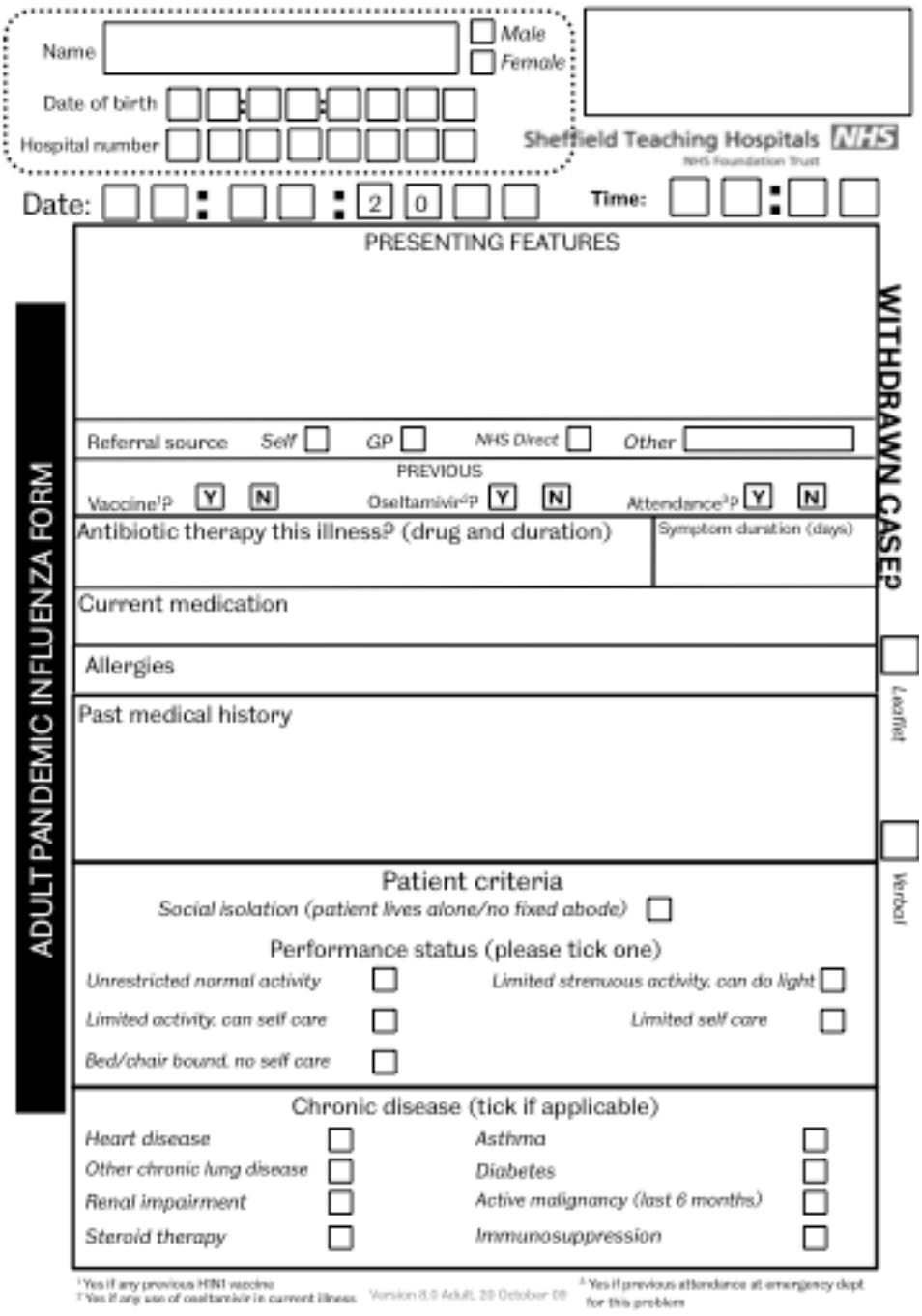
Appendix 4

Community Assessment Tool for Children

Criteria label	CHILDREN UNDER 16 YEARS OLD WILL BE CONSIDERED FOR ADMISSION AT THE NEAREST GENERAL HOSPITAL IF THEY PRESENT WITH ANY OF THE FOLLOWING:
A	**Severe respiratory distress** Lower chest wall indrawing, sternal recession, grunting, or noisy breathing when calm.
B	**Increased respiratory rate** measured over at least 30 seconds. ≥50 breaths per minute if under 1 year, or ≥40 breaths per minute if ≥1 year.
C	**Oxygen saturation ≤92% on pulse oximetry, breathing air or on oxygen** Absence of cyanosis is a poor discriminator for severe illness.
D	**Respiratory exhaustion or apnoeic episode** Apnoea defined as a ≥20 second pause in breathing.
E	**Evidence of severe clinical dehydration or clinical shock** Sternal capillary refill time >2 seconds, reduced skin turgor, sunken eyes or fontanelle.
F	**Altered conscious level** Strikingly agitated or irritable, seizures, or floppy infant.
G	**Causing other clinical concern to the clinical team or specialist doctor** e.g. a rapidly progressive or an unusually prolonged illness.

Appendix 5

Clinical Assessment Form (CAF)



Name ☐ Male ☐ Female

Date of birth ☐☐:☐☐:☐☐☐☐

Hospital number ☐☐☐☐☐☐☐☐

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

Date: ☐☐:☐☐:20☐☐ Time: ☐☐:☐☐

ADULT PANDEMIC INFLUENZA FORM

PRESENTING FEATURES

WITHDRAWN CASE? ☐ Leaflet ☐ Verbal

Referral source Self ☐ GP ☐ NHS Direct ☐ Other ☐

PREVIOUS

Vaccine[1]? Y ☐ N ☐ Oseltamivir[2]? Y ☐ N ☐ Attendance[3]? Y ☐ N ☐

Antibiotic therapy this illness? (drug and duration) | Symptom duration (days)

Current medication

Allergies

Past medical history

Patient criteria

Social isolation (patient lives alone/no fixed abode) ☐

Performance status (please tick one)

Unrestricted normal activity ☐ *Limited strenuous activity, can do light* ☐

Limited activity, can self care ☐ *Limited self care* ☐

Bed/chair bound, no self care ☐

Chronic disease (tick if applicable)

Heart disease ☐ *Asthma* ☐

Other chronic lung disease ☐ *Diabetes* ☐

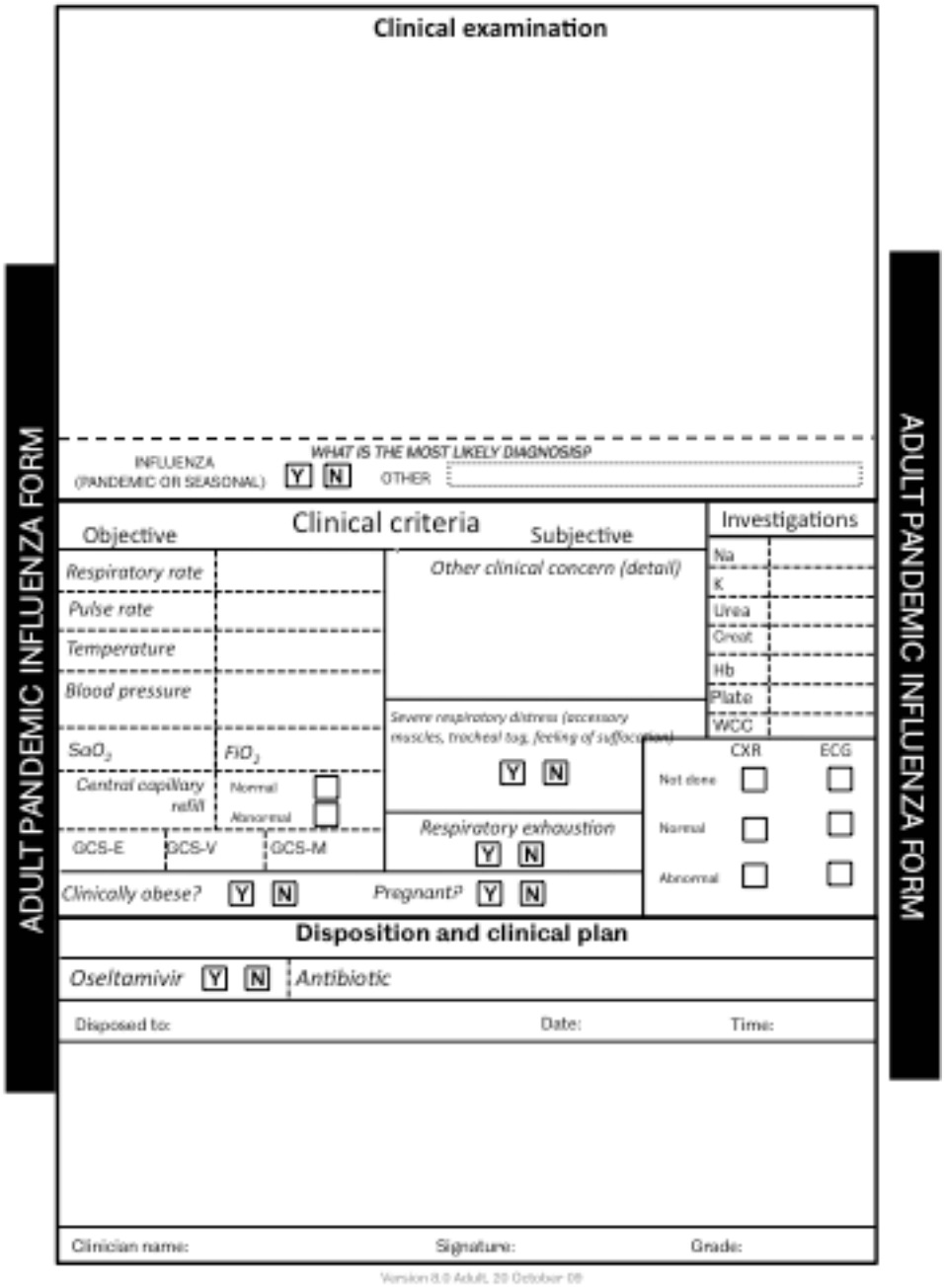
Renal impairment ☐ *Active malignancy (last 6 months)* ☐

Steroid therapy ☐ *Immunosuppression* ☐

[1] Yes if any previous H1N1 vaccine
[2] Yes if any use of oseltamivir in current illness

Version 8.0 Adult, 20 October 09

[3] Yes if previous attendance at emergency dept for this problem



Appendix 6

Notice of substantial amendment submitted to NIGB and REC

Details of Chief Investigator:	
Name:	Prof. Steve Goodacre
Address:	Health Services Research, ScHARR, University of Sheffield, Regent Court, Sheffield S1 4DA, UK
Telephone:	0114 2220842
Email:	s.goodacre@sheffield.ac.uk
Fax:	
Full title of study:	Pandemic Influenza Triage in the Emergency Department
Name of main REC:	North West 5 Main Research Ethics Committee
REC reference number:	09/H1010/60
Date study commenced:	19 October 2009
Protocol reference *(if applicable)*, current version and date:	version 0.003, 20 August 2009
Amendment number and date:	2; 29 January 2010

Summary of changes

Briefly summarise the main changes proposed in this amendment using language comprehensible to a layperson. Explain the purpose of the changes and their significance for the study. In the case of a modified amendment, highlight the modifications that have been made.

If the amendment significantly alters the research design or methodology, or could otherwise affect the scientific value of the study, supporting scientific information should be given (or enclosed separately). Indicate whether or not additional scientific critique has been obtained.

The swine flu pandemic has failed to manifest itself on the scale that had been expected. Predicted numbers of swine flu cases were used to inform the design and methodology of the Painted project. To compensate for the greatly reduced number of cases presenting at hospital emergency departments (a reduction which compromises the study's ability to adequately test the predictive value of the various triage components) we propose extending the duration of the study by three months and to use that time to undertake a retrospective examination of emergency departments' attendances. The intention is to reconfigure the study along the lines of a case–control model. We will retrospectively identify additional positive cases, as defined in the protocol, and then add the new positive cases to those accrued prospectively. Negative cases in the data set then act as the 'controls'. Statistical commentary on the reconfiguration is presented in the revised version of the protocol (on pages five and six).

The project funder (the National Institute for Health Research) has approved the extension of the project.

Any other relevant information

Applicants may indicate any specific ethical issues relating to the amendment, on which the opinion of the REC is sought.

We do not propose to inform the retrospectively identified positive cases that we are using their routinely available data. Our reasoning is as follows. By definition these patients will have been critically ill (or they would not be positive cases) and of these some will have died. But it is not possible for us to reliably identify those who have fully recovered or those who have not. Further, this process of retrospectively identifying an individual as a potential positive case for Painted is occurring some months after the original infection event. Thus there is uncertainty over the final outcome for the patients concerned and a considerable time delay in identifying them. Given this uncertainty and delay we feel that attempts to inform these individuals will run the risk of causing such confusion and distress as to outweigh any potential ethical benefit that might otherwise have been gained.

List of enclosed documents

Document	*Version*	*Date*
Protocol	5	January 2010

Declaration

I confirm that the information in this form is accurate to the best of my knowledge and I take full responsibility for it.

I consider that it would be reasonable for the proposed amendment to be implemented.

Signature of Chief Investigator: ……

Print name: Professor Steve Goodacre

Date of submission: 29 January 2010

Appendix 7
Response from NIGB

12 February 2010

Re: Application to Ethics and Confidentiality Committee for section 251 support – Emergency department triage methods for suspected pandemic influenza

Thank you for the revised study protocol for section 251 support to access patient identifiable data without consent.

Members have considered the revised protocol and due to the issues raised, requested that a new application be submitted to the next Ethics and Confidentiality Committee (ECC) meeting taking place in March. Members agreed that this application would not be suitable to be considered under the fast track procedure for the following reasons:

1. The previous application was given fast track approval at a time when there was a real urgency to have the application considered due to the level of risk which the pandemic influenza A/H1N1 2009 may have presented.
2. The pandemic influenza did not turn out to be as widespread as expected and this has implications on considerations within this new request for section 251 approval.
3. The proposed changes to the study appear to be a complete change of study methodology with a new retrospective arm.

Please explicitly consider and address the following in your submitted application:

1. The ECC position on retrospective studies of relatively small numbers of patients is that consent should be sought via the members of the direct clinical care team involved in the care and treatment of the individual cohort. If consent is not feasible, data extraction from the clinical record should be carried out by the direct clinical care team and only fully anonymised data returned to the researchers.
2. If consent is to be sought from the living cohort as described above then section 251 approval would not be required. If consent is considered to be impracticable then the section 251 application must provide strong justification as to why consent cannot be sought.
3. Similarly, justification should be provided in relation to those patients who are deceased and consent from the family cannot be obtained. Please note a clear differentiation is needed in the application between patients who are still alive and those that are deceased.
4. Please note that the deadline for submitting a fully completed application is **26 February 2010.** Please ensure all required documents are submitted along with the application. A list of the documents can be found here.

If you have any queries please do not hesitate to contact me on 020 7633 7021.

Appendix 8
Response from REC

NHS

National Research Ethics Service

North West 5 Research Ethics Committee - Haydock Park

North West Centre for Research Ethics Committees
3rd Floor - Barlow House
4 Minshull Street
Manchester
M1 3DZ

Tel: 0161 625 7819
Fax: 0161 237 9427

26 February 2010

Professor Steve Goodacre
Health Services Research
ScHARR
University of Sheffield
Regent Court
30 Regent Street
Sheffield S1 4DA

Dear Professor Goodacre

Study title:	**Evaluation and development of triage methods used to select patients with suspected pandemic influenza for hospital admission**
REC reference:	**09/H1010/60**
Amendment number:	**2, 29th January 2010**
Amendment date:	**29 January 2010**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review decided that they could not give a favourable ethical opinion of the amendment, for the following reasons:

The swine flu pandemic has failed to manifest itself on the scale that had been expected. The predicted numbers of swine flu cases were used to inform the design and methodology of the study. To compensate for the greatly reduced number of cases presenting at hospital emergency departments' the amendment (Amendment 2; 29th January 2010) sought approval for a three month extension to the study and to undertake a retrospective examination of emergency departments' attendances in order to reconfigure the study along the lines of a case-control model. It is intended to retrospectively identify additional positive cases and add new positive cases to those accrued prospectively. Negative cases in the dataset will then act as the 'controls'. It is not proposed to inform patients who have been retrospectively identified as positive cases that the research team intends to use their data.

A revised protocol (version 5 dated 29 January 2010) had been submitted in support of the amendment.

The Sub-Committee expressed the following concern with the proposed amendment as follows:-

A. It was noted that the study had received approval from the National Information Governance Board for Health and Social Care (NIGB) to process identifiable patient data without consent (under section 251 of the NHS Act 2006). It was further noted that the proposed amendment had also been submitted to the NIGB for approval. Thus the REC sought written confirmation that the NIGB approval to process identifiable patient data without consent had been extended to include patients who have been retrospectively identified as positive cases. Ethical approval for the amendment will not be issued until such time as notification of NIGB approval is received.

B. Leading on from the above, the Sub-Committee questioned the rationale underpinning the proposal not to inform patients that their data would be used in research without consent, i.e. because it was not possible to reliably identify those who had fully recovered or those who had died. Specifically, if in the first instance it was possible to identify (presumably via NHS numbers?) retrospective cases from the examination of emergency department attendances, why was it not also possible to use NHS numbers to identify patients who had died? This would presumably enable reliable identification of patients who had subsequently recovered in order to seek informed consent to use their data.

In conclusion should Amendment 2 dated 29th January 2010 fail to obtain NIGB approval then the REC would expect the research team to fully address the issues which have been raised in point B above.

In light of the request for NIGB approval as outlined above, the REC had no option but to reject the proposed amendment.

We regret to inform you that the amendment is therefore not approved. The study should continue in accordance with the documentation previously approved by the Committee.

Modifying the amendment

You may modify or adapt the amendment, taking into account the Committee's concerns. Modified amendments should be submitted on the standard Notice of Amendment form. The form should indicate that it is a modification of the above amendment. Please ensure that you submit all of the documents again that need to be reviewed, that is any of those listed below which are still relevant, as well as any revised or new documents.

A revised Notice of Amendment form must be submitted at least 14 days before you plan to implement the amendment. The Committee will then have 14 days from the date of receiving the notice in which to notify you that the amendment is rejected, otherwise the amendment may be implemented.

Documents reviewed

The documents reviewed at the meeting were:

Document	Version	Date
Covering Letter: From Richard Wilson, Project Manager		02 February 2010
Notice of Substantial Amendment (non-CTIMPs): 2, 29th January 2010		29 January 2010
Protocol	5	29 January 2010

Membership of the Committee

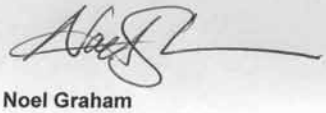
The members of the Committee who took part in the review at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

09/H1010/60:	**Please quote this number on all correspondence**

Yours sincerely



Noel Graham
Committee Co-ordinator

E-mail: noel.graham@northwest.nhs.uk

Enclosures: List of names and professions of members who took part in the review

Copies to:

Mr R Hudson
Research Office
The University of Sheffield
SHEFFIELD
S10 2TN

Mr R Wilson
Project Manager
The PaInTED Study
Health Services Research Section
ScHARR University of Sheffield
Regent Court
Regent Street
SHEFFIELD S1 4DA

R&D office for NHS care organisation at lead site: -

Ms G McVey
Sheffield Teaching Hospitals NHS Foundation Trust
Research Department
1st Floor
11 Broomfield Road
SHEFFIELD
S10 2SE

North West 5 Research Ethics Committee - Haydock Park

List of names and professions of members who took part in the review

Name	*Profession*	*Capacity*
Dr Donal Manning (Chair)	Consultant Paediatrician	Expert
Dr Tim Sprosen (Vice-Chair)	Chief Scientific Officer – UK Biobank and Medical Researcher/Epidemiologist	Expert
Professor Elizabeth Perkins	Director of The Health and Community Care Research Unit – The University of Liverpool	Lay

Appendix 9

Chief investigator reply to NIGB

Re: Application to Ethics and Confidentiality Committee for section 251 support Emergency department triage methods for suspected pandemic influenza

Thank you for your letter of 12 February 2010 and for considering the revised protocol for this study. We will not be submitting a new application to the next Ethics and Confidentiality Committee (ECC) meeting but will instead complete the project according to the original protocol. Unfortunately, based on the information outlined in your letter, it is apparent that we will not be able to undertake a meaningful study with section 251 support using the proposed case–control methodology.

The ECC position, as outlined in your letter, is that consent should be sought via the members of the direct clinical care team involved in the care and treatment of the individual cohort, and apparently that consent should be sought from the family of those who are deceased. We have some ethical concerns about contacting recently bereaved family members but there are no insurmountable barriers to seeking consent, so we cannot claim this is not feasible. However, we would anticipate that a substantial proportion of patients or relatives would not respond to our request for consent and subsequent responder bias would render the findings of the study worthless, or at least of such limited value as to not justify the expense of the project or intrusion into patients and relatives lives.

Even if the ECC could be persuaded to alter its position on this issue we would not be able to complete the project in the timeframe required. We do not have funding available to extend staff contracts while considerations continue and would therefore have no staff available to complete the project work by the time section 251 support for the revised protocol were in place. Furthermore, clinical staff in the participating hospitals have informed us that they are neither willing nor able to commit time to extract data from the clinical records as they already have a heavy burden of clinical commitments.

We would be grateful if our comments could be fed back to the ECC.

Appendix 10
Study protocol

Research objectives

1. To determine the discriminant value of currently available emergency department triage methods for predicting severe illness or death in patients presenting with suspected pandemic influenza.
2. To determine the independent predictive value of presenting clinical characteristics and routine tests for severe illness or death in patients presenting with suspected pandemic influenza.
3. To determine whether the discriminant value of emergency department triage can be improved by developing two new triage methods based upon (1) presenting clinical characteristics alone and (2) presenting clinical characteristics, electrocardiogram (ECG), chest X-ray and routine blood test results.

Existing research

The United Kingdom (UK) influenza pandemic contingency plan predicts around 750,000 excess emergency department attendances and 82,500 excess hospitalisations during a pandemic.[1] Given that there is likely to be significant staff absence it will be impractical for all patients fully to be assessed by a senior clinician. If, as is likely, interpandemic levels of care cannot be offered during a pandemic, methods of triage and resource allocation will have to be fair, robust and reproducible.[2]

The term triage is often used to describe a brief initial assessment in the emergency department to determine patient order of priority in the queue to be seen. In this proposal we use the term triage more broadly to include the full process of emergency department assessment, potentially including investigations such as blood tests and X-rays, and apply it to decision-making regarding whether the patient should be admitted and whether they should be referred for high dependency or intensive care.

Emergency department triage methods need to accurately predict the individual patient's risk of death or severe illness. The predicted risk can then guide decision-making. Patients with a low risk may be discharged home, those with a high risk admitted to hospital, and those with a very high risk referred for high dependency or intensive care. The level of risk used to trigger these decisions need not necessarily be fixed or determined in advance. Indeed, it is likely that decision-making thresholds could change during the course of a pandemic as the balance between resource availability and demand changes. Triage methods that use a risk prediction score to determine the need for hospital care may therefore be more useful than a triage rule that classifies patients into admission and discharge categories.

Current Health Protection Agency (HPA) guidance, supported by the British Thoracic Society and British Infection Society, recommends the use of the CURB-65 pneumonia score.[3] This score uses five variables (confusion, urea level, respiratory rate, blood pressure and age) to generate a score between zero and five. More recent Department of Health guidelines on surge capacity in a pandemic also considered use of a physiological–social score [Pandemic Modified Early Warning Score (PMEWS)].[4] This score uses physiological variables, age, social factors, chronic disease and performance status to generate a score between zero and seven. The most recent national guidance, specific to H1N1 (swine), includes a new swine flu hospital pathway for emergency department management with seven criteria, any one of which predicts increased risk and the need for hospital assessment.[5]

Existing literature shows CURB-65 to perform reasonably well as a mortality predictor in an emergency department population with community-acquired pneumonia [area under the receiver–operator Curve (AUROC) 0.76],[6] but less well in predicting the need for high-level care (AUROC 0.69[7] and 0.64[8]). The physiological–social score considered by the Department of Health (PMEWS) is not a particularly good mortality predictor in community-acquired pneumonia (used as a proxy for pandemic influenza), with an AUROC score of 0.66, but performed much better predicting requirement for higher-level care (AUROC 0.83)[8] and has shown promise when used in the prehospital setting to determine need

for emergency department attendance [AUROC 0.71[9] and 0.8 (J Grey, February 2009, personal communication)]. The most recently issued national guidelines appear to have been developed by expert consensus and have as yet undergone no validation in the appropriate patient populations.

To our knowledge there have been no studies evaluating any of these triage methods in patients with suspected pandemic influenza and no studies to develop a risk prediction score in the emergency department population with suspected pandemic influenza.

We are not aware of any studies currently planned or under way to test or develop emergency department triage methods in the current pandemic. The Intensive Care National Audit and Research Centre (ICNARC) have been commissioned to undertake a swine flu triage project (SwiFT) for admitted patients referred to critical care. SwiFT involves modelling to identify which of those patients who would usually be admitted to critical care may be refused admission at the height of the pandemic (once all surge capacity measures have been instituted) – i.e. both those with a very high likelihood of death despite critical care and those that may be expected to survive without critical care.

Our project and SwiFT will be examining different triage decisions and different patient groups and are clearly separate projects. We will be collaborating with INCARC to ensure that our research is synergistic and does not involve any unnecessary duplication of work.

Research methods

We will undertake a prospective cohort study of patients presenting to the emergency department with suspected pandemic influenza. Emergency department staff will be provided with a standardised form for assessing such cases that will double as clinical notes and study data collection form. It will include the elements of the CURB-65 score, the physiological–social score, the swine flu hospital pathway and any other measures that could be routinely recorded in the emergency department (comorbidities, physiological observations, routine blood tests, ECG and chest X-ray). We will also record details of any prepresentation antiviral medication, antibiotics and immunisation status (once available). Research staff will then follow patients up until 30 days after attendance by hospital record review and, if appropriate, general practitioner contact to identify patient outcomes.

Planned intervention

We will evaluate triage methods used to determine whether a patient with suspected pandemic influenza should be admitted to hospital or not, and whether they should be admitted to intensive or high dependency care. These will include the CURB-65 score, the physiological–social score and the swine flu hospital pathway. We will also develop two new triage methods based upon (1) presenting clinical characteristics alone and (2) presenting clinical characteristics, ECG, chest X-ray and routine blood test results.

The first score will only use variables available at initial patient assessment, i.e. history and examination, including simple technologies such as automated blood pressure measurement and pulse oximetry. This triage method can be used to assess patients for the need for hospital investigation and identify patients that can be discharged without further assessment. It could potentially be used, with appropriate validation, to assess patients in the community.

The second triage method will be based upon all available emergency department data, including routine blood tests, ECG and chest X-ray findings. This triage method can be used for two potential purposes: (1) identification of patients with a low risk of adverse outcome who can be discharged home after emergency department assessment, and (2) identification of high-risk patients who are likely to need high dependency or intensive care.

We will evaluate the ability of each method to predict whether patients die or require respiratory, cardiac or renal support. We will not evaluate the impact of triage methods upon patient care. Intervention in the study will therefore only consist of data collection and follow-up. Patient management will continue according to current Department of Health guidance.

Planned inclusion/exclusion criteria

We will include all adults and children presenting the emergency department of the participating hospitals with suspected pandemic influenza during the peak of the pandemic. Patients will be eligible for inclusion if they meet the current clinical diagnostic criteria of (1) fever (pyrexia ≥ 38°C) or

a history of fever and (2) influenza-like illness (two or more of cough, sore throat, rhinorrhoea, limb or joint pain, headache, vomiting or diarrhoea) or severe and/or life-threatening illness suggestive of an infectious process, or if they meet any future clinical diagnostic criteria recommended by the Department of Health. The assessing clinician will determine eligibility and complete the data collection form if the patient is considered to have suspected pandemic influenza. We will not attempt to retrospectively apply the clinical diagnostic criteria and exclude patients who appear to have been inappropriately included. Patients will only be excluded if they request exclusion from the study.

Ethical arrangements

We are seeking fast track Research Ethics Committee (REC) and National Information Governance Board (NIGB) approval. Application forms for both are completed and ready to send as soon as a funding decision is made.

Risks and anticipated benefits for trial participants and society

The study will not alter patient management and will simply collect routinely available data at presentation and follow-up. No additional diagnostic tests will be performed. The risks to patients involved in the study are therefore very low and principally relate to data protection and confidentiality.

Data will be abstracted from the collection form and hospital notes by researchers working with an honorary contract from the hospital Trust or researcher passport recognised by the Trust. This researcher will keep a record of all patients who withdraw from the project but will not communicate details to other staff. He/she will enter anonymised data onto a secure online database provided by the Clinical Trials Unit at the University of Sheffield. The research team in general will only have access to anonymised data on the secure database.

Patients involved in the study will potentially benefit from the use of the standardised patient assessment form. This will ensure that important variables are recorded and communicated between staff providing care. The standardised form can also be used to remind staff of current guidance for management.

Future patients with suspected pandemic influenza and society in general will benefit from evaluation and development of accurate triage methods that have the potential to improve clinical decision-making and ensure that patients receive the right care and health service resources are optimally used.

Informing potential trial participants of possible benefits and known risks

Posters in all participating departments will be prominently displayed advising patients of the project and providing contact details for further information. Information leaflets will be available that briefly describe the nature and purpose of the study and provides contact details for further information.

Obtaining informed consent from participants

We will not be seeking patient consent to participate on the basis that the study is limited to collection of routinely available data and any delays in patient assessment would risk compromising patient care. The information leaflet outlined above will provide a tear-off slip with contact details that patients can use to inform the hospital or research team if they wish to withdraw from the study. Patients who wish to withdraw from the study will have their study records deleted. Their decision to withdraw will not be communicated to clinical staff providing further care and will not influence their subsequent management.

Proposed time period for retention of relevant study documentation

The original data collection form will constitute the clinical notes and be kept in each hospital according to normal practice. A copy of the data collection form will be retained by the researcher in a secure location in each hospital. These will be destroyed 6 months after the end of the project. The anonymised database will be maintained by the Clinical Trials Unit until 10 years after the end of the project.

Proposed sample size

The sample size will ultimately depend upon the size and severity of the pandemic, but combining

our data collection method with clinical case documentation will ensure that data are collected for most cases. We plan to collect data during the pandemic at four hospitals in Sheffield and Manchester, covering a population of over 1 million. We are piloting data collection now so that it can start as soon as funding is approved and ethical and regulatory requirements are satisfied.

Department of Health estimates of a 25% clinical attack rate and illustrative case hospitalisation and case fatality rates of 0.55% and 0.37%, respectively, suggest that a pandemic may lead to 12,500 emergency department attendances, 1400 hospitalisations and 900 excess deaths in our population.[1] If half of these occur while we are collecting data then around 6000 cases with 600 positive outcomes will be available for analysis.

We will split the database for analysis into two data sets of equal size, one for developing new scores and testing existing scores, and one for comparing the new and existing scores. To develop a new triage method we need around 10 events per parameter tested in the model, so 200 positive cases would allow us to test 20 parameters. A sample size of 283 positive cases ensures a power of 80% to compare an AUROC curve of 0.85 versus 0.90 at 5% significance, assuming a correlation of 0.6 between scores.[10]

Statistical analysis

Existing triage methods

CURB-65, the physiological-social score and the swine flu clinical pathway will be assessed by calculating the AUROC (*C*-statistic) for discriminating between cases with and without a positive outcome (defined as death or need for support of respiratory, cardiovascular or renal function) and sensitivity and specificity at key decision-making thresholds.

New triage methods

As outlined above, we will develop two new triage scores: one based on initial assessment only and the other based on all emergency department data. We will test the association of each potential clinical predictor variable with outcome and then undertake logistic regression to identify independent predictors of outcome. The strongest independent predictors of outcome will then be combined to form a new triage score. Continuous predictor variables will be divided into categories on the basis of the relationship of the variable with outcome. Integer weights will be assigned to each category of predictor variable according to the coefficient derived from a multivariate model using categorised independent predictors. This will generate a composite clinical score in which risk of positive outcome increases with the total score.

The data set will be split randomly into two equal sets. The first set will be used to compare the *C*-statistic of existing scores and derive the two new scores. The second set will be used to compare the *C*-statistic of the two new scores to that of the best existing score.

Proposed outcome measures

Patients will be followed up by researcher review of case note and hospital computer record review up to 30 days after emergency department presentation. If they die or require respiratory, cardiovascular or renal support they will be defined as having a positive outcome. If they survive to 30 days without requiring respiratory, cardiovascular or renal support they will be defined as having a negative outcome. If a severe pandemic leads to hospital resources being overwhelmed we will categorise patients as having a positive outcome if they were deemed to have needed respiratory, cardiovascular or renal support but were denied this due to lack of resources. We will also record whether they are treated with antiviral agents or antibiotics, and the length and location of any hospital stay.

Respiratory support is defined as any intervention to protect the patient's airway or assist their ventilation, including non-invasive ventilation or acute administration of continuous positive airway pressure. It does not include supplemental oxygen alone or nebulised bronchodilators. Cardiovascular support is defined as any intervention to maintain organ perfusion, such as inotropic drugs, or invasively monitor cardiovascular status, such as central venous pressure or pulmonary artery pressure monitoring, or arterial blood pressure monitoring. It does not include peripheral intravenous cannulation and/or fluid administration. Renal support is defined as any intervention to assist renal function, such as haemoperfusion, haemodialysis or peritoneal dialysis. It does not include intravenous fluid administration.

Outcome assessment will be based primarily on researcher review of hospital computer records and case notes. If there is no evidence in these of a positive outcome the patient will be recorded as

having a negative outcome. If outcome is uncertain (for example, if the patient is transferred to another hospital or leaves hospital against medical advice) the researcher will contact the patient's general practitioner for clarification. This means that there will be a small risk of misclassification if the patient dies or attends another hospital after discharge home, but we believe the resource implications of attempting to identify such cases does not justify the small potential risk of bias.

We have selected an outcome measure that has a relatively clear definition and unequivocally indicates a case in which hospital admission and high-dependency care would be desirable. The disadvantage of this definition is that it excludes patients who might benefit from other aspects of hospitalisation, such as oxygen supplementation or intravenous fluids. However, oxygen and intravenous fluids are often administered to patients with little clinical need for these treatments, administration is often poorly recorded and administration may be based on the clinical variables being tested in this project rather than objective clinical need. Including these treatments in our definitions of respiratory or cardiovascular support would thus carry a substantial risk of overestimating the prevalence of serious outcome and of overestimating the association between predictor variables and outcome.

We will also not attempt to determine whether deaths were likely to be amenable to treatment and will thus not explore the issue of whether treatment would be futile. It is possible that a severe pandemic could result in a need to identify cases where treatment would be futile, but this is beyond the scope, and possibly incompatible with the aims, of this proposal.

Research governance

The University of Sheffield will be the study sponsor. The project management group (PMG), consisting of the coapplicants and the appointed research staff, will manage the study. The PMG will meet monthly by teleconference or in person to oversee study progress.

Time constraints mean that we will not be able to convene a formal steering committee to review the protocol, meet regularly and fulfil all the normal functions. However, we will ask an independent statistician, clinician and layperson to form a steering committee that will provide independent advice and monitor progress by email or telephone.

Project timetable and milestones

We have already prepared ethics and NIGB applications, and are currently piloting the data collection forms. We will be able to start the project as soon as a funding decision is made. Research staff have been identified and can start work on the project at short notice.

	Aug	Sep	Oct	Nov	Dec	Jan
Processes						
Ethics, NIGB and governance	×					
Data collection		×	×	×		
Follow-up			×	×	×	
Data analysis					×	×
Reporting and dissemination						×
Staffing						
Project manager	×	×	×	×	×	×
Clerical assistant	×	×	×	×	×	×
Database manager	×	×	×	×	×	
Researchers		×	×	×	×	

Expertise

The research team combines the leading experts on emergency management of suspected pandemic influenza (KC, DW and AB) with the statistical expertise and research infrastructure of the Medical Care Research Unit (SG, JN, MC and RW). We also have public health input from MS who is currently on secondment with the HPA.

The proposal builds on an existing collaboration developed as part of the Medical Research Council (MRC)-funded DAVROS Study (Development and validation of risk-adjusted outcomes for systems of emergency care). For the DAVROS Study we have collected presenting data from over 10,000 patients admitted to hospital with a medical emergency and then followed them up to determine their 30-day outcomes. This has involved establishing processes for using routine data without patient consent, including data management and data protection, which have been approved by the REC and NIGB, and used effectively without significant problems. DAVROS was undertaken to develop a

risk-adjustment method but is now also being used by KC, SG and JN to develop a clinical triage tool for emergency medical admissions. Our proposal will apply the data collection and analysis methods used in DAVROS to the specific problem of suspected pandemic influenza.

David Harrison, from ICNARC, has agreed to be a collaborator on the project. He is currently working with us on the DAVROS study. We will draw upon his expertise in risk prediction and ensure that our project works synergistically alongside pandemic influenza research currently being undertaken by ICNARC.

Specific details of the collaborating units

Medical Care Research Unit, Sheffield

Steve Goodacre and Jon Nicholl have undertaken many major national evaluations in emergency care, including development of clinical prediction methods. Current projects provide the necessary infrastructure to rapidly undertake the proposed research. Richard Wilson is currently managing the DAVROS study and has developed extensive expertise in data collection, management and protection in observation studies using routine data sources without patient consent.

University Hospital of South Manchester NHS Trust

Kirsty Challen and Darren Walter are emergency physicians and Andrew Bentley is an accredited critical care and respiratory physician. They have previously evaluated triage methods for pandemic influenza and are leading experts in this field.

Department of Public Health, Sheffield

Mark Strong is a public health specialist who is currently on secondment with the HPA.

Sheffield Clinical Trials Unit

Mike Campbell is an experienced medical statistician with expertise in development and validation of clinical prediction rules.

Service users

Enid Hirst has agreed to be the patient/public representative for the project and has reviewed the proposal. She has acted as a user representative for many previous health service research projects undertaken by our group, including being a lay member of the Steering Committee of the DAVROS study.

Enid previously spent 8 years with Sheffield Community Health Council, was a lay member of the Steering Committee for NHS Direct Yorkshire and Humber, was a member of Unscheduled Care Network Board in Sheffield, spent 3 years with Sheffield Children's Hospital Patient Forum, and has attended Trust Board meetings at Sheffield Children's Hospital for many years as an observer for the Community Health Council and then the Patient Forum. She is now a member of Sheffield LINk (Local Involvement Network), a lay member of the Out of Hours Accreditation Group, is on the Dental Services Joint Planning Group for Sheffield, is a patient representative for the Group looking into Dentally Anxious Patients, and is a patient representative on the new Critical Care/Emergency Medicine Priority Group.

Her role will include the following:

1. reviewing the protocol and specifically advising on ethical issues and arrangements for data protection and confidentiality
2. reviewing the poster and information leaflet
3. patient/public representation on the steering committee
4. lay input into reporting and dissemination of findings.

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Virus shedding and environmental deposition of novel A (H1N1) pandemic influenza virus: interim findings

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Abstract

Virus shedding and environmental deposition of novel A (H1N1) pandemic influenza virus: interim findings

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Background: The relative importance of different routes of influenza transmission, including the role of bioaerosols, and ability of masks and/or hand hygiene to prevent transmission, remains poorly understood. Current evidence suggests that infectious virus is not typically released from adults after 5 days of illness, however, little is known about the extent to which virus is deposited by infected individuals into the environment and whether deposited virus has the ability to infect new hosts. Further information about the deposition of viable influenza virus in the immediate vicinity of patients with pandemic influenza is fundamental to our understanding of the routes and mechanisms of transmission.

Objectives: To collect data on patients infected with pandemic H1N1 2009 (swine flu). Primary objectives were to correlate the amount of virus detected in a patient's nose with that recovered from his/her immediate environment, and with symptom duration and severity. Secondary objectives were to describe virus shedding and duration according to major patient characteristics: adults versus children, and those with mild illness (community patients) versus those with more severe disease (hospitalised patients).

Methods: Adults and children, both in hospital and from the community, who had symptoms of pandemic H1N1 infection, were enrolled and visited every day during follow-up for a maximum of 12 days. Symptom data was collected and samples were taken, including nose swabs and swabs from surfaces and objects around patients. Samples of air were obtained using validated sampling equipment. The samples were tested for the presence of pandemic H1N1 virus, using polymerase chain reaction (PCR) to detect virus genome and an immunofluorescence technique to detect viable virus.

Results: Forty-three subjects were followed up, and 19 of them were subsequently proven to be infected with pandemic H1N1 virus. The median duration of virus shedding from the 19 infected cases was 6 days when detection was performed by PCR, and 3 days when detection was performed by a culture technique. Over 30% of cases remained potentially infectious for at least 5 days. Only 0.5% of all community and none of the hospital swabs taken revealed virus on surfaces. Five subjects had samples of the air around them collected and virus was detected by PCR from four; some of the air particles in which virus was detected were small enough to be inhaled and deposited deep in the lungs.

Limitation: Small number of subjects recruited.

Conclusions: The finding that over 30% of infected individuals have infectious virus in their noses for 5 days or more has infection control implications. The data suggest that contact transmission of pandemic influenza via fomites may be less important than previously thought, but transmission via bioaerosols at short range may be possible, meaning that high-level

personal protective equipment may be needed by health-care workers when attending patients with pandemic influenza. Further work is being undertaken to consolidate these findings, as they have important potential implications for the protection of health-care workers and the formulation of advice to households, nationally and internationally.

Contents

List of abbreviations

AC	adult in the community
AH	adult in hospital
ARI	acute respiratory infection
CC	child in the community
CH	child in hospital
CI	confidence interval
HA	haemaglutinin
HPA	Health Protection Agency
ILI	influenza-like illness
LRT	lower respiratory tract
MDCK	Madin–Darby Canine Kidney
NIHR	National Institute for Health Research
NIOSH	National Institute of Occupational Safety and Health
NPA	nasopharyngeal aspirate
PCR	polymerase chain reaction
PCT	Primary Care Trust
PPE	personal protective equipment
RSV	respiratory syncitial virus
SFM	serum-free medium
TCID	tissue culture infectious dose
URT	upper respiratory tract
VTM	viral transport medium

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Background

The threat posed by pandemic influenza is high on the agenda of health-care organisations and governments around the world. As pandemic mitigation strategies have been developed over recent years it has become very clear that influenza transmission is an area that is poorly understood and hotly debated. The biggest controversy relates to whether influenza is mainly transmitted by touching virus deposited on surfaces, or by droplets or bioaerosols in the air. If touch is important then hand washing offers a major defence. If droplets are important, simple barriers, such as a surgical mask, will stop transmission. But if bioaerosols are important, specialised respirators are needed. Thus, infection control guidance is difficult to formulate and mainly based on weak evidence. Current evidence suggests that infectious virus is not typically released from adults after 5 days of illness (slightly longer in children). However, little is known about the extent to which virus is deposited by infected individuals into the environment and whether deposited virus has the ability to infect new hosts, i.e. whether it remains viable. The generation of information about the deposition of viable influenza virus in the immediate vicinity of patients with pandemic influenza is fundamental to our understanding of the routes and mechanisms of transmission.

Objectives

This study was conducted to collect data on patients who had pandemic H1N1 2009 infection (swine flu). The primary objectives were to correlate the amount of virus detected in a patient's nose with that recovered from his/her immediate environment (on fomites and in the air), and with symptom duration and severity. Secondary objectives were to describe virus shedding and duration according to major patient characteristics: adults versus children, and those with mild illness (community patients) versus those with more severe disease (hospitalised patients).

Methods

Adults and children, both in hospital and from the community, who had symptoms of pandemic H1N1 infection, were enrolled and visited every day during follow-up for a maximum of 12 days. Information about symptoms was collected and samples were taken, including nose swabs and swabs from surfaces and objects (fomites) around patients (e.g. door handles, remote controls). Samples of air were obtained using validated sampling equipment. These samples were tested for the presence of pandemic H1N1 virus, using polymerase chain reaction (PCR) to detect virus genome and an immunofluorescence technique to detect viable (live) virus.

Results

Forty-three subjects were followed up, and 19 of them were subsequently proven to be infected with pandemic H1N1 virus. The median duration of virus shedding from the 19 infected cases was 6 days when detection was performed by PCR, and 3 days when detection was performed by a culture technique. Over 30% of cases remained potentially infectious for at least 5 days. However, contrary to conventional understanding, virus shedding was not always greatest when an individual was most symptomatic. Few fomites were found to be contaminated with virus – in fact only 0.5% of all community and none of the hospital swabs taken revealed virus. Five subjects had samples of the air around them collected and virus was detected by PCR from four. Some of the air particles in which virus was detected were small enough to be inhaled and deposited deep in the lungs.

Conclusions

Despite some limitations caused by the small number of subjects recruited, important observations have been made. The finding that over 30% of infected individuals have infectious virus in their noses for 5 days or more has infection

control implications. The evidence for the significance of both contact and bioaerosol routes of transmission, depends upon demonstrating that viable virus is deposited from an infected patient. This has been shown for touched fomites. Virus has been demonstrated by PCR in air samples, but the results of live virus testing are inconclusive. The data generated suggest that contact transmission of pandemic influenza via fomites may be less important than hitherto emphasised, whereas transmission via bioaerosols at short range may be possible, meaning that high-level personal protective equipment (PPE) might be needed by health-care workers when attending patients with pandemic influenza. Further work is being undertaken to consolidate these findings as they have important potential implications for the protection of health-care workers and the formulation of advice to households, nationally and internationally.

Chapter 1
Introduction

As pandemic mitigation strategies have been developed over recent years it has become very clear that influenza transmission is one area that is poorly understood and hotly debated. Distinguishing the relative importance of the various modes of transmission (*Box 1*) is critical for the development of infection control precautions in health-care settings and in the home.

If contact transmission is dominant then hand hygiene becomes the most critical intervention. However, if respiratory droplet transmission is significant, surgical face masks that provide a barrier against droplets may be important, and the safe distance away from an infected person without a mask might be as close as 4 feet (ft), because droplets fall out of the air quickly and do not travel far. At present, opinions are sharply divided on the importance of bioaerosol transmission.[1,2] Tellier[1] in particular, argues that the potential of short-range bioaerosol transmission has largely been ignored. At present, the UK recommends droplet precautions as opposed to bioaerosol precautions (surgical masks rather than respirators) for most forms of contact with patients with pandemic influenza,[3] based on the current balance of limited evidence; however, this is contested by some frontline health-care workers who believe that these safeguards are inadequate, and there is little evidence with which to reassure them.

In parallel, the dynamics of viral shedding in relation to symptom onset and severity are important factors, highly relevant to estimates of the period of infectivity and to therapeutic management. In all previous research on influenza virus excretion, shedding has been determined by measurement of the quantity of virus recoverable from the patient's nasopharynx, i.e. virus has been recovered by a deliberately performed invasive technique. These so called 'viral shedding' studies measure virus shed from infected cells; they do not actually measure virus that is deposited into the touched or respired environment; i.e. they do not define environmental contamination and the hazard posed to others. While such data are useful, if they could be linked to near-patient environmental sampling, estimates of the extent to which infectious virus is deposited on to surfaces and into the air in the patient's immediate vicinity could be made.

Background data

It is well established that viral titres in nasopharyngeal samples taken from adults are proportional to symptom severity and decline steadily from symptom onset.[4–7] Studies in the community of patients who are infected with influenza A show that the mean duration of viral shedding [as measured by polymerase chain reaction (PCR)] for seasonal influenza A viruses is 5–6 days from symptom onset[6,7] compared with culture methods that are normally negative by day 6.[4,5] It is also well documented that children, patients with chronic illnesses and the immunocompromised can shed live virus for longer periods.[8–11] Published data are now available that describe viral shedding from patients with pandemic H1N1 virus infection. Shedding (as determined by nasal sampling) detectable by PCR lasts for approximately 6 days,[12–15] but culture-positive specimens, i.e. detecting viable virus, appear rare after 5 days of illness.[15,16]

While PCR is almost certainly more sensitive because it detects both viable and non-viable virus, its interpretation is far more problematic because it is not possible to determine the presence of viable (transmissible) virus from this technique; it can be used only to illustrate the potential for viable virus to be present. However, there have also been difficulties in deciphering studies looking at live virus because of the range of techniques used for detection (cell lines, animal models and human subjects) and variation in sensitivities between, and even within, such methods, for example a human infectious dose is likely to differ from a tissue culture infectious dose (TCID).

Fomites

A role for fomites, including surfaces, in the transmission of influenza A appears widely accepted but limited data are available to directly support the possibility of contact transmission

of influenza. In contrast, studies of rhinovirus[17] and respiratory syncitial virus (RSV)[18] have shown contact transmission to be significant. Furthermore, there is a paucity of scientific data on virus survival on fomites. An experimental study of influenza virus survival on a range of porous and non-porous surfaces is often cited, but was conducted over 25 years ago.[19] In this study both influenza A (H1N1) and B viruses could be cultured from experimentally contaminated, non-porous surfaces, such as steel and plastic, for between 24 and 48 hours. However, they survived for < 12 hours on porous materials such as cloth, paper and tissues. Viable virus could be transferred from non-porous surfaces to hands for 24 hours, and from tissues to hands for 15 minutes, but live viruses could be recovered from hands only within 5 minutes of their transfer. Banknotes have been experimentally contaminated with influenza A viruses, and live virus has been shown to be present for up to 3 days, although this period of time was dependent on the concentration of inocula. Interestingly, the presence of respiratory mucus significantly increased survival times.[20] Other studies have looked at fomite contamination in the environment of individuals with acute respiratory infections (ARIs), but they have either not looked for or not found viable influenza virus.[21,22]

Air

If influenza virus can transmit via bioaerosols then we would expect to be able to detect virus in such aerosols, and we might expect to find evidence of long-range transmission of infection. Studies performed over 40 years ago showed that artificially aerosolised influenza could be recovered (by using infection in animals as a detection method) for up to 24 hours after release,[23,24] and that aerosolised virus is able to infect humans.[25] More recently, influenza virus was detected by PCR in aerosol samples taken from medical facilities.[26,27] Despite the above, the detection of live virus in aerosols, generated by humans has not been demonstrated before. In addition, there is a striking absence of robust epidemiological proof for the long-range transmission of influenza. Studies that have reported such an occurrence[28,29] are confounded by the fact that droplet and contact transmission cannot be excluded. However, it must also be said that literature claiming that bioaerosols are unlikely to play a significant role have often ignored the potential for short-range bioaerosol transmission.[2,30]

Assimilating the available evidence leads us to conclude that infectious virus is not typically

BOX 1 *Definitions*

Airborne transmission has generally been used to refer to infections that spread over long distances through particles in the air, for example tuberculosis. Only bioaerosols (aerosols that contain living organisms) suspended in the air can travel over long distances but some confusion can arise because:

- droplets could also be considered to be airborne, although only for a short period of time and over short distances
- bioaerosols can transmit infection over short distances as well as long; in fact, because bioaerosols are more concentrated nearer their source, they are more likely to transmit over short distances than long

Because of this confusion, we prefer the terms *respiratory* and *contact transmission* to 'airborne transmission' when discussing influenza.

Respiratory transmission can include:

- *Bioaerosol transmission* Bioaerosols are particles typically < 5 μm in diameter, which carry microorganisms and are capable of both remaining suspended for long periods and travelling distances greater than 6 ft. They can be generated by coughing, talking and even breathing and may transmit infection on being inhaled into the respiratory tract (reviewed by Tellier[1])
- *Droplet transmission* Respiratory droplets are larger particles (≥ 20 μm) that fall out of circulation typically within 3–4 ft. They are generated by coughing and sneezing, and transmit infection on coming into contact with the respiratory tract, often the mucous membranes of the nose and mouth (reviewed by Nicas *et al.*[31])

It should be recognised that there is no absolute cut-off between aerosols and droplets; particles lie on a continuum, with larger particles tending towards droplet behaviour

Contact transmission concerns physical contact with respiratory secretions, for example hands coming into contact with contaminated fomites or person-to-person contact, such as a handshake. We recognise that traditionally this type of contact has been referred to as 'indirect contact' and that droplets have been regarded as a form of direct contact transmission, but we find the term 'contact transmission' more intuitive

released from adults after 5 days of illness (slightly longer in children), and that little is known about deposition patterns and persistence of virus released into the environment or its ability to infect new hosts. The generation of information about the presence of viable influenza virus in the environment is fundamental to our understanding of the routes and mechanisms of transmission. This study was therefore conducted to collect data on conventional virus shedding and environmental contamination (fomites and air), and to investigate the relationships between them.

Chapter 2
Methods

This multicentre, prospective, observational descriptive cohort study recruited subjects between 14 September 2009 and 25 January 2010, in accordance with the principles of the Declaration of Helsinki and UK regulatory requirements. It was approved by Leicestershire, Northamptonshire & Rutland Research Ethics Committee 1 (09/H0406/94).

Research objectives

The primary objectives were to correlate the amount of virus detected in a patient's nose with:

1. that recovered from the environment around them
2. symptom duration, and
3. symptom severity.

Secondary objectives were to describe virus shedding and duration according to important patient subgroups: adults versus children, and those with mild illness (community patients) versus those with more severe disease (hospitalised patients). An additional secondary objective concerned the environmental deposition of virus in association with aerosol-generating procedures.

A number of 'policy' objectives were also stated, which included: (1) 'safety distances' around patients with pandemic and seasonal influenza; (2) appropriate use of respiratory personal protective equipment (PPE) and infection control practices for pandemic and seasonal influenza, according to patient type, illness severity and time since symptom onset; and (3) antiviral treatment duration for patients with pandemic influenza. Due to a lack of data, these points cannot be adequately addressed and are therefore not discussed further in this report.

Participants

Subjects were recruited from the following groups:

- adults in hospital (AH)
- children in hospital (CH): age range 1 month–16 years
- adults in the community (AC)
- children in the community (CC): age range 1 month–16 years.

Recruiting centres were Nottingham University Hospitals NHS Trust (AH + CH), Nottingham City Primary Care Trust (PCT) (AC + CC), Nottingham County PCT (AC + CC), Leicester University Hospitals NHS Trust (AH) and Sheffield Teaching Hospitals NHS Trust (AH). [Note: the designation AH and CH denote that the patient (adult or child, respectively) was enrolled during hospital admission. However, subjects discharged from hospital before the end of follow-up were then seen in the community; so, while initial environmental specimens will have been taken in hospital, later ones will be from the subject's home. No subjects initially enrolled in the community were subsequently admitted to hospital.]

Sampling frames

- *Hospital* All cases of suspected pandemic H1N1 influenza identified to researchers by clinical care teams who had agreed to be approached by a researcher. Hospitals involved in recruitment were: Queens Medical Centre and City Hospital, Nottingham; Leicester Royal Infirmary; and Royal Hallamshire Hospital, Sheffield.
- *Community* Individuals living in the Nottingham area, who had symptoms of pandemic H1N1 virus infection, received an invitation to take part in the research and had use of a telephone. Invitations were given by the following methods: local newspapers, posters sited in community areas, 3000 leaflets posted in the NG2 area, 15,000 letters given to parents via schools, and 3000 invitations given out at antiviral collection points in areas covered by Nottingham City and Nottinghamshire County PCTs.

A formal sampling fraction was not used to identify cases.

Eligibility criteria

Subjects were eligible to take part if they fulfilled our definition of influenza-like illness (ILI):

- fever (or recent history of fever) plus any one of cough, sore throat, runny nose, fatigue or headache

or

- any two of cough, sore throat, runny nose, fatigue or headache.

Exclusions

Subjects were excluded if they: had experienced illness for > 48 hours (community cases) or > 96 hours (hospital cases); were PCR-negative for pandemic H1N1 (as part of NHS care); had taken part in influenza research involving an investigational medicinal product within the last 3 months (including vaccination). See Appendix 4, Eligibility checklist.

Enrolment

Informed consent was obtained and an influenza rapid antigen test (Quidel QuickVue® Influenza A+B test) was performed on a nasal swab. A positive rapid antigen test was initially an inclusion criterion, but it was abandoned as an entry requirement after 2 weeks because of perceived low sensitivity (see Discussion, below).

A subject was defined as a case if:

- he/she met our criteria for ILI, and
- tested PCR-positive on a nasal swab for pandemic H1N1.

It had not been our intention to recruit and follow up patients who were pandemic H1N1-negative, but this did occur. Data on these subjects are presented below (see Results).

Study procedures

Adult subjects were followed for up to 10 days from the start of symptoms and children < 13 years of age were followed for up to 12 days. In addition to collecting initial symptom data to confirm a subject's eligibility, daily records of were taken of symptoms, temperature readings, medications, bioaerosol-generating procedures (if hospitalised), room temperature and humidity. A symptom diary was completed by each subject on a daily basis; symptoms were given a severity score on a scale of 0–3 (see Appendix 1, Symptom diary card). The following samples were collected:

- *Daily nasal swabs* A dry cotton swab with a polystyrene shaft (FB57835, Fisherbrand) was passed around one nostril in a circular motion three times and then immersed in viral transport medium (VTM).
- *Surface swabs* Samples were taken approximately every other day during the period of follow-up. Three surfaces were swabbed in hospital rooms: patient table; Patientline® console or nurse call button and window sill. In the home, samples were taken from the dining table, kettle handle, TV remote control, bedside table, bathroom tap and bathroom door handle. Cotton swabs with polystyrene shafts (FB57835) were moistened with VTM and then rubbed across a maximum area of $4 \times 5\,cm^2$ in three different directions, applying even pressure. The same part of any fomite was swabbed each day. This sampling method was validated during a previous study (B Killingley, University of Nottingham, May 2010, personal communication). In addition to using swabs, the use of sponges was trialled to sample the patient or bedside tables. The sponges (TS/15-B:PBS, Technical Service Consultants) were $50\,cm^2$ in size, sterile, and dosed with 10 ml of a neutralising buffer. They were wiped over a $4 \times 5\text{-}cm^2$ area (a different area to that sampled by swab) and then sealed in a sterile medical grade plastic bag. No specific cleaning instructions were given to households, and hospital cleaning continued as normal during follow-up of any subjects. If other household members became ill during the period of follow-up, sampling of the original participant continued, and the age and symptoms of any potential secondary cases were recorded.

Swabs (in VTM) and sponges were kept on 'wet' ice for no longer than 3 hours before being frozen at –80°C.

Air particles were collected using a National Institute for Occupational Safety and Health (NIOSH) two-stage cyclone bioaerosol sampler, which has been validated for use with influenza.[26] The first stage of the sampler has a 3-mm inlet, a 6-mm outlet and a disposable 15-ml collection tube (35–2096, Falcon). The second stage has a 1.3-mm inlet, a 2.5-mm outlet and a disposable 1.5-ml tube

(02 681–339, Fisher Scientific). The samples then pass through a 37-mm polytetrafluoroethylene (PTFE) filter with 2-mm pores (225–27–07, SKC). At 3.5 l/min, the first stage will collect particles with a diameter > 4 μm, the second stage collects particles with a diameter of 1–4 μm, and the filter collects particles with a diameter of < 1 μm. The sampler conforms to the American Conference of Governmental Industrial Hygienists/International Organization for Standardization criteria for respirable particle sampling. The flow rate through each sampler was set with a flow calibrator (Model 4143, TSI) before use. Samplers were mounted on tripods at a height of 150 cm, were placed at distances of either 3 ft or 7 ft from the subject, and ran for either 1, 2 or 3 hours. Not all subjects were stationary during the sampling period (though they were asked to remain in the same position if they could), so the distance from the subject to the sampler may have varied a little over time. Sampling was performed on just one follow-up day. After sampling, intact samplers were taken straight to a laboratory, where 750 μl of VTM was added to both stage-one and stage-two tubes, and the filter paper was immersed in a 15-ml tube, also containing 750 μl of VTM. These procedures were carried out in sterile conditions, under a microbiological safety hood. Samples were then stored at –80°C.

Laboratory methods

The following sample-processing 'rules' were instituted:

- Nasal swabs from day 4 onwards were not tested if days 1–3 were all PCR-negative.
- Culture was only performed on PCR-positive samples.
- Environmental swabs were not processed if nasal swabs, taken on the three previous days from a case, were PCR-negative.
- Sponges were tested on day 1 only.

Laboratory work was carried out at Health Protection Agency (HPA) and University of Cambridge virology laboratories at Addenbrooke's Hospital, Cambridge, UK. Each sample was defrosted and split into six aliquots – three for PCR and three for culture – and then refrozen at –70°C. On the day of testing, the sponges were defrosted and the liquid removed by squeezing the sponge within its bag. The liquid was separated into aliquots for testing. PCR was performed once the RNA was extracted and samples for potential culture were refrozen at –80°C.

Polymerase chain reaction

Nucleic acid was extracted from the samples using the Qiagen Symphony SP extractor mini kits, including onboard lysis and a bacteriophage (MS2) as internal control. A novel influenza A H1N1 pentaplex assay was devised to detect virus genome in the samples. The assay was designed to detect novel H1N1 influenza A, seasonal H1 influenza A, seasonal H3 influenza A, influenza B, and the internal control, MS2. Details of the primers, probes and protocol used can be found in Appendix 6 (see PCR protocol). Reactions were carried out on a Rotorgen™ 6000 (Corbett Research) real-time DNA detection system. Viral load data were generated using the PCR assay and plasmids containing the gene target to create a standard curve, such that the concentration of genome present in each sample could be calculated.

Culture

Cultures were performed from the last day of nasal swab PCR positivity, for example if a swab was PCR positive on day 5, cultures were performed in the following order: day 5, 4, 3, 2 and 1. If a culture was positive on any given day then an assumption was made that previous days would also have been culture-positive and no further testing was done. Pandemic H1N1 did not form plaques readily and gave only a weak cytopathic effect, the latter meant that the TCID of 50 was difficult to calculate. Consequently, immunofluorescence to detect the influenza A nucleoprotein was used to demonstrate the presence of live replicating virus in the nuclei of cultured nasopharyngeal cells. See Appendix 6 (Culture protocol) for further details.

Genomic sequencing was performed by Geneservice™.

Outcome measures

1. *Virus shedding (nose swab) and environmental deposition (fomites and air) as measured by PCR and virus culture techniques* Laboratory confirmation was defined as a positive result of any specimen tested for pandemic H1N1 virus. The duration of viral shedding was defined as the time between symptom onset and the last day that a

positive specimen was taken. Because patients were seldom recruited on the day symptoms began, an assumption has been made that they were shedding virus from the first day of symptoms to the last positive specimen.

2. *Daily symptom scores* Each symptom score within a category is summed to give an overall category score, for example cough – 2, shortness of breath – 1 = lower respiratory tract (LRT) score of 3.
    - upper respiratory tract (URT) score – stuffy nose, runny nose, sneezing, sore throat, sinus tenderness, earache
    - LRT score – cough, shortness of breath
    - systemic score – fatigue, myalgia, headache
    - total symptom score is the sum of URT, LRT and systemic symptom scores, plus a score for diarrhoea and a score for vomiting.
3. *Medication logs* If the day symptoms began is assigned as day 1, then we have assumed that patients received oseltamivir within 48 hours if they received it on or before day 3.

Statistical methods

The recruitment target was 100 subjects in total, comprising approximately 25 patients in each of the four groups. Statistical analysis was planned to examine correlations between virus shedding and virus deposition in the environment. Subgroup sizes of 25 [which allow pooling of data by adults or children (50 per group) or the whole population] gives high statistical power (> 80%) to detect correlations of > 0.55 in groups of size $n = 25$, 0.4 in groups of size $n = 50$, and 0.3 in groups of size $n = 100$. Viral shedding data is primarily descriptive, but it was important to be able to make formal statistical comparisons of the duration of shedding between adults and children. By pooling data into adults versus children ($n = 50$ per group), a difference of one day (two tailed-test) could be detected with power > 80%, provided that the coefficient of variation in shedding was ≤ 0.3. For larger differences, for example 2 or 3 days, the study was well powered to coefficients of variation up to 0.6.

A detailed descriptive analysis of the data is presented. The Student's *t*-test was used to compare mean values. The Pearson's product–moment correlation test was used to test associations between variables. Fisher's exact test was used to test the significance of risk ratios.

Changes to protocol

Minor amendments to protocol 1.0:

- application of corrected document version numbers to adult and parent/guardian consent forms
- creation of a new study document: 'letter to ward managers'
- abandonment of a positive influenza rapid antigen test as an inclusion criterion.

Substantial amendment resulting in protocol version 1.1:

- addition of stool sample collection for a substudy involving The Centre for Ecology & Hydrology. (Note, this substudy did not ultimately take place.)
- clarification of the role of clinical teams in recruiting patients.

Minor amendment to protocol 1.1:

- creation of new study documents: 'letter to parent/guardians', 'study poster' and 'study leaflet'
- extended study duration to 31 August 2010
- extended virology testing on samples already collected.

Chapter 3
Results

One hundred and fifty subjects were screened between 14 September 2009 and 25 January 2010; 107 were ineligible, and 43 were enrolled and followed up. Reasons for exclusion at screening included: symptoms being present for too long (48%), influenza PCR test (as part of medical care)-negative (15%), declined to take part (9%). Pandemic H1N1 virus was detected in 19 subjects. The group of 24 pandemic-negative cases consisted of: RSV = 5 (all children); rhinovirus = 5; corona virus = 2; rhinovirus + corona virus = 1; NHS-pandemic H1N1 test-positive, study laboratory pandemic H1N1 test-negative = 2; unknown = 9. In the final analyses, one subject was excluded on the basis of having received pandemic H1N1 vaccine prior to enrolment, and three subjects were removed (all of whom tested negative for pandemic H1N1 according to the study laboratory); two because clinical (as part of medical care) and study pandemic H1N1 2009 PCR tests did not agree; and one because study documents were lost. Recruitment by group of the 39 remaining subjects was as follows: 9 AC, 12 AH, 15 CC and 3 CH (*Figure 1*).

Of the remaining 39 subjects, 19 (49%) tested positive for pandemic H1N1 virus and 20 (51%) were negative. Follow-up of at least 8 days occurred in 16/19 positives and 12/20 negatives. The numbers enrolled, along with a demographic description of pandemic H1N1 cases, is shown in *Table 1*.

Pandemic H1N1 cases

Of the 19 cases recruited, 10 (53%) were female, 11 (58%) were children and 11 (58%) were community cases. Seven subjects reported comorbidities and in six cases these were respiratory conditions. *Table 2*

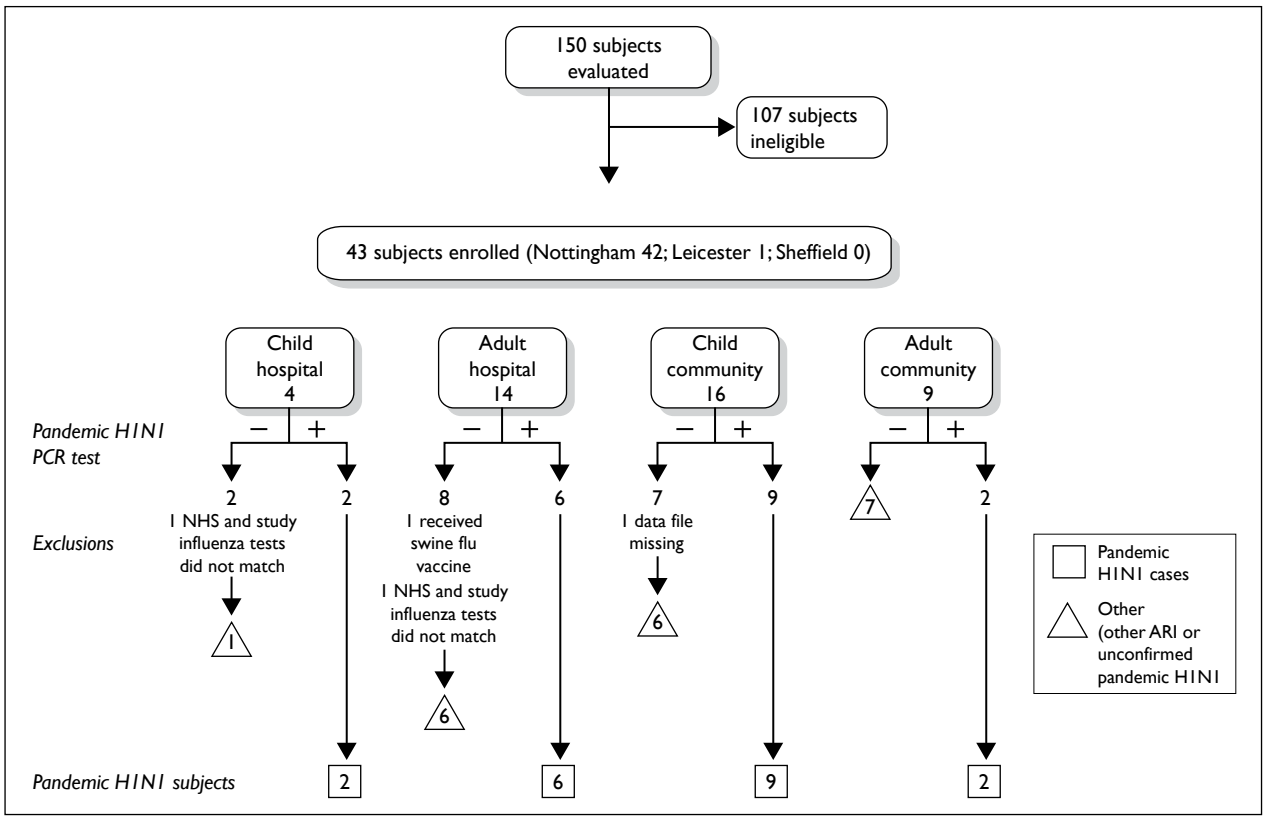

FIGURE 1 *Participant flow diagram.*

TABLE 1 *Numbers enrolled and overall demographic description of subjects with pandemic H1N1 influenza*

	AC	AH	CC	CH	Total (%)
Enrolled	9	14	16	4	43
Excluded/removed from analyses	0	2	1	1	4
Pandemic H1N1-positive subjects	2	6	9	2	19 (49)
Pandemic H1N1 subjects only					
Male sex (%)	0	2	7	0	9 (47)
Median age (years), range	24.5, 21–28	28.5, 19–34	6, 2–12	7.5, 0–15	12, 0–34
Ethnic group					
White	0	1	6	2	9 (47)
Black	1	1	0	0	2(11)
Asian	1	4	2	0	7 (37)
Mixed	0	0	1	0	1 (5)
Mean time from symptom start to enrolment (days)	1.5	2.2	1.3	2.5	1.7

lists the 19 cases of pandemic H1N1 recruited into the study and shows some of the key outcome measures for each. No recruited cases needed high-dependency care or died during follow-up.

Symptoms

The most frequently reported symptoms in our subjects with pandemic H1N1 were: stuffy nose (100%), runny nose (100%), cough (100%), fatigue (95%) and sneezing (89%) (*Table 3*). Fever was reported on the day illness began in 13/19 (68%) cases, and was measured as high (≥38°C) during follow-up in 7/19 (37%) of cases.

In general, symptom scores declined over time. URT and systemic symptoms peaked on day 2 of illness and LRT symptoms peaked on day 3. However, it should be noted that most subjects were recruited > 36 hours after illness onset, which may give misleading information on maximal symptom scores; there was only one patient with information available on day 1, and only five for day 2 (*Figure 2a*). *Figure 2b* shows mean symptom scores of subjects with pandemic H1N1 influenza as a function of the number of days since illness onset.

In a comparison of subjects who were positive for pandemic H1N1 infection with others recruited, no significant difference was seen in the average time from symptom onset to recruitment: positive cases (1.7 days), others (1.7 days) ($p = 0.90$). Visual inspection of plots showing mean symptom scores (broken down into categories) over time suggests that subjects who were negative for pandemic H1N1 infection had higher URT symptom scores and LRT symptoms that peaked 3 days after pandemic H1N1-positive subjects (*Figure 3*). However, no significant differences between these two groups were detected when comparing symptoms scores on the day of recruitment (URT $p = 0.11$, LRT $p = 0.18$ or systemic symptoms $p = 0.20$) or in the total mean symptom score over time (46.5 for subjects with pandemic H1N1 vs 52.3 for others, $p = 0.54$).

Antiviral drugs

Overall, 21/39 (54%) of enrolled subjects took an antiviral drug [either oseltamivir (20/21) or zanamivir (1/21)] and this occurred within 2 days of illness onset in 12/17 cases (71%) for which data are available. Of the pandemic H1N1-positive cases, 11/19 (58%) received an antiviral drug (all oseltamivir); hospital cases 7/8 (88%) and community cases 4/11 (36%). A total of 44% of pandemic H1N1 cases took oseltamivir within 48 hours, and the average time from symptom onset to treatment initiation in these subjects was 1.7 days (data on when treatment was begun for one patient is not available). The mean total symptom score on the first day of enrolment in

TABLE 2 *Pandemic H1N1-positive cases*

Subject	Age (years)	Sex (M/F)	Ethnicity	Comorbidity	Time from symptom onset to enrolment (days)	Peak total symptom score (day of follow-up)	Peak viral load (day of follow-up)	Duration of viral shedding by PCR (days[a])	Last day culture-positive by IF[a]	Day oseltamivir begun[b]
AC01	21	F	Asian	Nil	2	6 (1)	4.2×10^5 (1)	6	5	–
AC04	28	F	Black	Asthma	1	13 (1)	1.3×10^5 (1[c])	3	3	–
AH01	19	F	White	Cystic fibrosis	2	13 (1)	1.8×10^5 (6)	9	–	2
AH03	27	F	Asian	Nil	2	28 (1)	1.0×10^6 (1)	9	4	3
AH04	30	F	Asian	Nil	2	17 (1)	1.6×10^7 (6)	10	8	3
AH05	24	F	Asian	Nil	3	12 (1)	N/A	5	–	–
AH07	34	M	Asian	Nil	2	20 (6)	N/A	5	4	N/A
AH08	33	M	Black	Asthma	2	25 (1)	3.9×10^4 (1[c])	3	–	2
CC01	12	M	Mixed	Asthma	2	18 (1)	1.8×10^5 (1)	5	–	2
CC02	11	M	Asian	Nil	2	18 (1)	3.4×10^6 (1)	8	–	–
CC03	6	M	Asian	Nil	2	5 (2)	4.7×10^5 (1)	6	4	4
CC04	2	M	White	Nil	1	10 (1)	3.5×10^5 (3[c])	4	–	–
CC05	9	M	White	Asthma	1	23 (1)	2.1×10^7 (1)	7	3	2
CC06	4	M	White	Eczema	0	8 (2)	1.0×10^5 (1)	6	5	–
CC07	3	F	White	Nil	1	8 (1)	1.2×10^3 (2)	3	3	2
CC14	6	M	White	Nil	1	12 (1)	5.3×10^9 (1)	7	6	–
CC15	2	F	White	Nil	2	10 (4)	2.3×10^{11} (3)	8	–	–
CH01	15	F	White	Nil	2	10 (1)	3.3×10^6 (1)	6	6	3
CH03	0	F	White	Cystic fibrosis	3	4 (1)	3.1×10^7 (1)	7	5	4

IF, immunofluorescence; N/A; not available.
a Time from symptom onset to last day swab positive.
b First day of symptoms = day 1, therefore treatment at day 3 is within 48 hours.
c Only data on one viral load available.

TABLE 3 *Symptoms reported over the course of study follow-up in both patients with pandemic H1N1 influenza and others*

	No. of patients, *n* (%)	
	Pandemic H1N1 subjects (*n* = 19)	**Others (*n* = 20)**
Fever (on day of onset)[a]	13 (68)	12 (57)
Runny nose	19 (100)	20 (95)
Sore throat	12 (63)	17 (81)
Cough	19 (100)	21 (100)
Shortness of breath	14 (74)	20 (95)
Stuffy nose	19 (100)	18 (86)
Sneezing	17 (89)	17 (81)
Earache	3 (16)	8 (38)
Sinus tenderness	12 (63)	15 (71)
Diarrhoea	6 (32)	8 (38)
Vomiting	10 (53)	10 (48)
Fatigue	18 (95)	20 (95)
Headache	15 (79)	12 (57)
Myalgia	14 (74)	15 (71)

a The symptom of fever was not recorded on a daily basis, although an oral measurement of body temperature was.

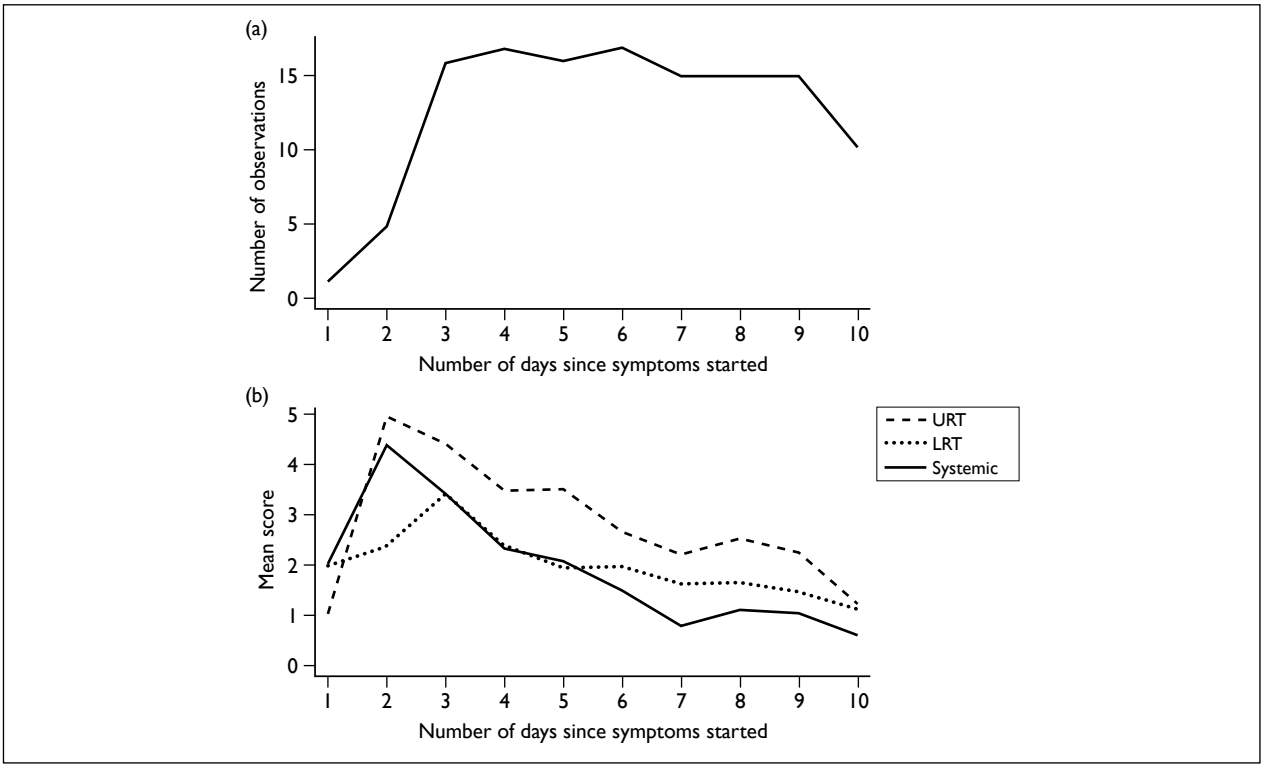

FIGURE 2 *Mean symptom scores of pandemic H1N1 cases over time. (a) Number of observations (subject data) available for each day. Day 1 is the day of symptom onset. (b) Mean symptom scores of subjects with pandemic H1N1 as a function of the number of days since symptoms started.*

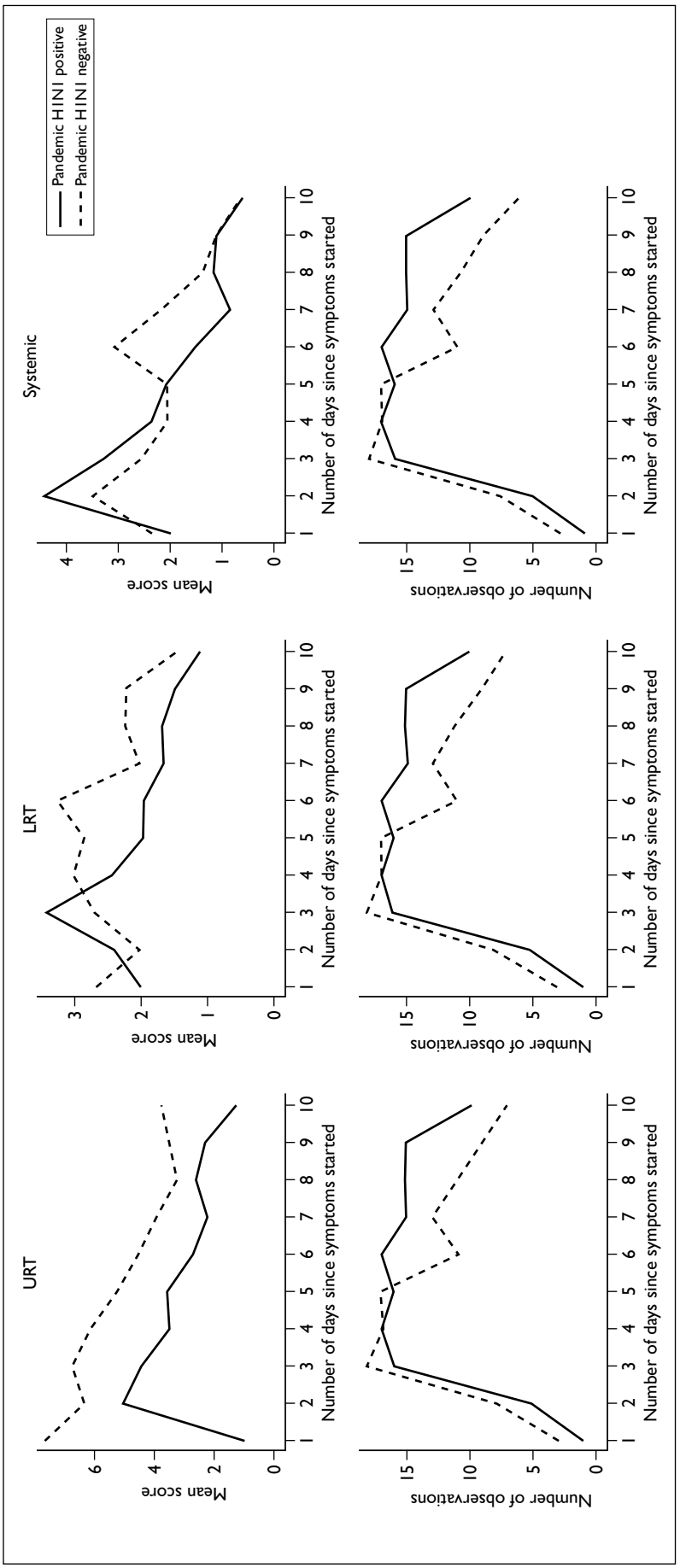

FIGURE 3 *Upper respiratory tract, lower respiratory tract and systemic symptom scores over time. First row: mean symptom scores for positive pandemic H1N1 cases (solid line) and negative cases (dashed line) as a function of the number of days since symptoms started. Second row: number of observations available for each day; pandemic H1N1 cases (solid line) and negative cases (dashed line). Day 1 is the day of symptom onset.*

the study was significantly higher for subjects with pandemic H1N1 who received antiviral drugs within 48 hours of symptom onset (mean score 16.6) than subjects with pandemic H1N1 who either did not take oseltamivir or did so after 48 hours of illness onset (8.6) ($p = 0.018$) (*Figure 4a*).

Viral load

Subject viral loads were examined over time and in relation to symptom scores. Nasal swab viral loads, measured by PCR, varied widely across our pandemic H1N1-positive subjects, ranging from 0.9×10^1 to 1.7×10^{11} copies/ml. Viral loads plotted over time are shown for four subjects from whom the most complete data were obtained (*Figure 5a*). All subject viral loads over time are shown in *Figure 5b*, which illustrates the heterogeneity of the data; for each individual trajectory, viral loads tend to decrease with time, but there is an apparent increase in the mean value, because individuals with high viral loads tend to shed for longer.

The mean peak viral loads of the four recruitment groups were 5.9×10^5 for AH, 2.4×10^5 for AC, 1.0×10^7 for CH and 1.6×10^6 for CC. No significant differences were detected between any of the groups, although there was a trend towards higher peak loads in children (*Figure 6*). The mean peak viral load of adults was 4.4×10^5, and that of children was 2.2×10^6, with no significant difference detected between them ($p = 0.28$).

Neither total, URT or systemic symptom scores correlated with viral loads at different points in time. However, the LRT symptoms score on day 5 was significantly correlated ($p = 0.049$) (*Figure 7*).

Rapid antigen tests

Overall, 10/19 (53%) of subjects with pandemic H1N1 influenza were antigen test-positive: 2/8 (25%) adults and 8/11 (73%) children. No pandemic H1N1-negative patients were antigen test-positive. There were no significant differences in symptom scores on the first day of the study between subjects who had a positive rapid antigen test and those who had a negative one. For URT, LRT and systemic symptoms, the mean symptom score on the first days of study were 5, 3.2 and 4.2, respectively, for those with a positive test, and 6, 3.0 and 3.7 for those with a negative test (p-values 0.53,

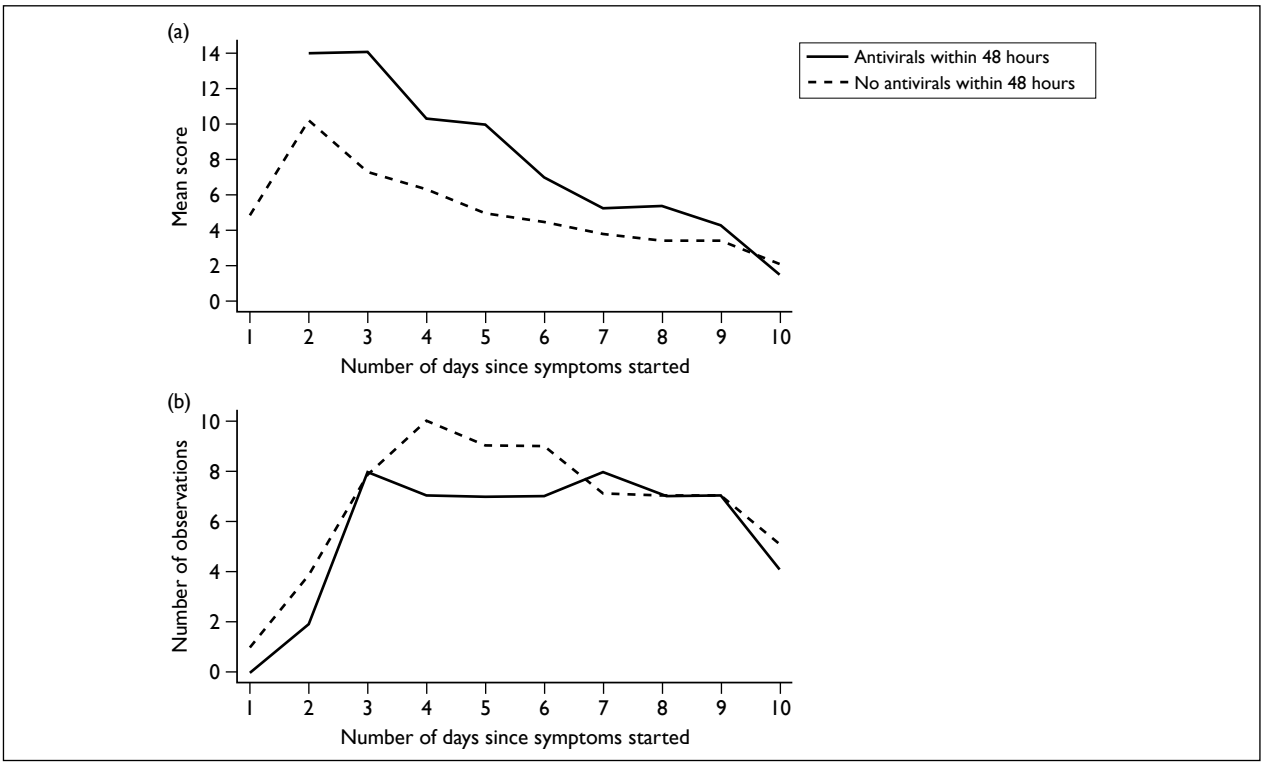

FIGURE 4 *Symptom scores over time for pandemic H1N1 cases who took antiviral drugs within 48 hours and those who did not. (a) Mean total symptom score as a function of the number of days since symptom onset for pandemic H1N1 subjects who received antivirals within 48 hours of symptoms onset (solid line) and those with pandemic H1N1 who did not (dashed line). (b) Number of observations available for each day.*

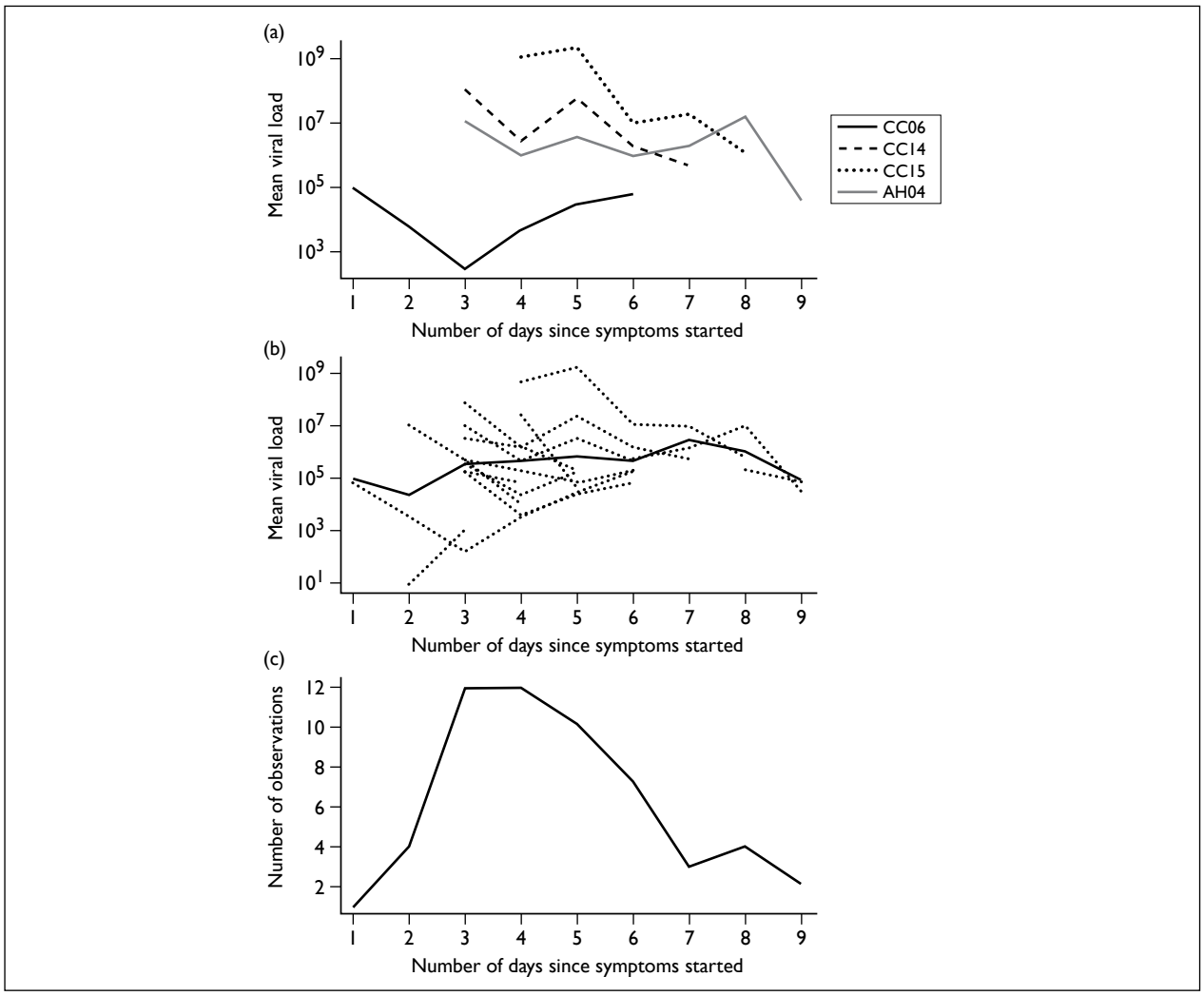

FIGURE 5 *Viral loads plotted over time. (a) Viral loads from selected subjects are shown. (b) All viral load data are shown. Subject trajectories are shown as dashed lines and the mean of these is shown as a solid line. (c) Number of observations available for each day. Day 1 is the day of symptom onset.*

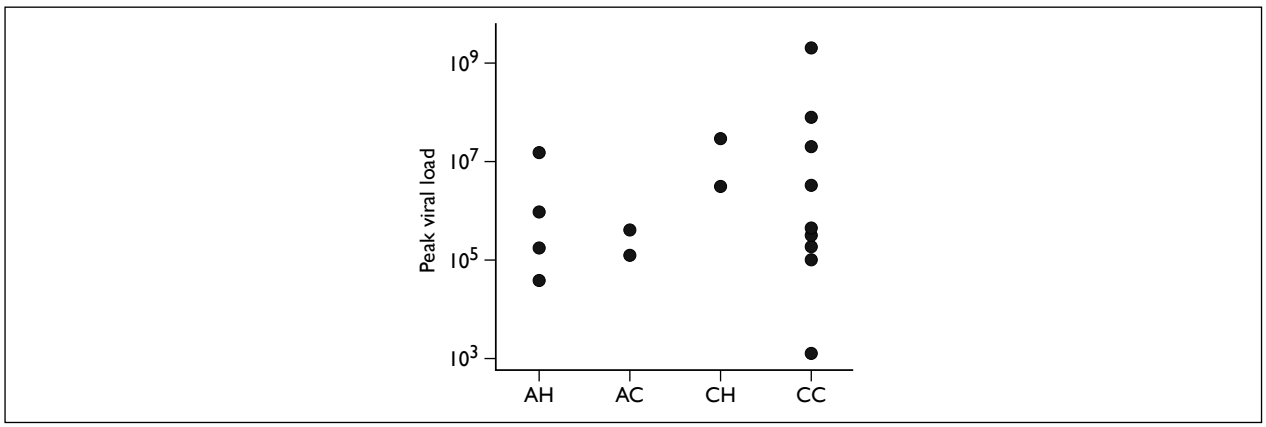

FIGURE 6 *Peak viral loads of subjects categorised into their recruitment groups.*

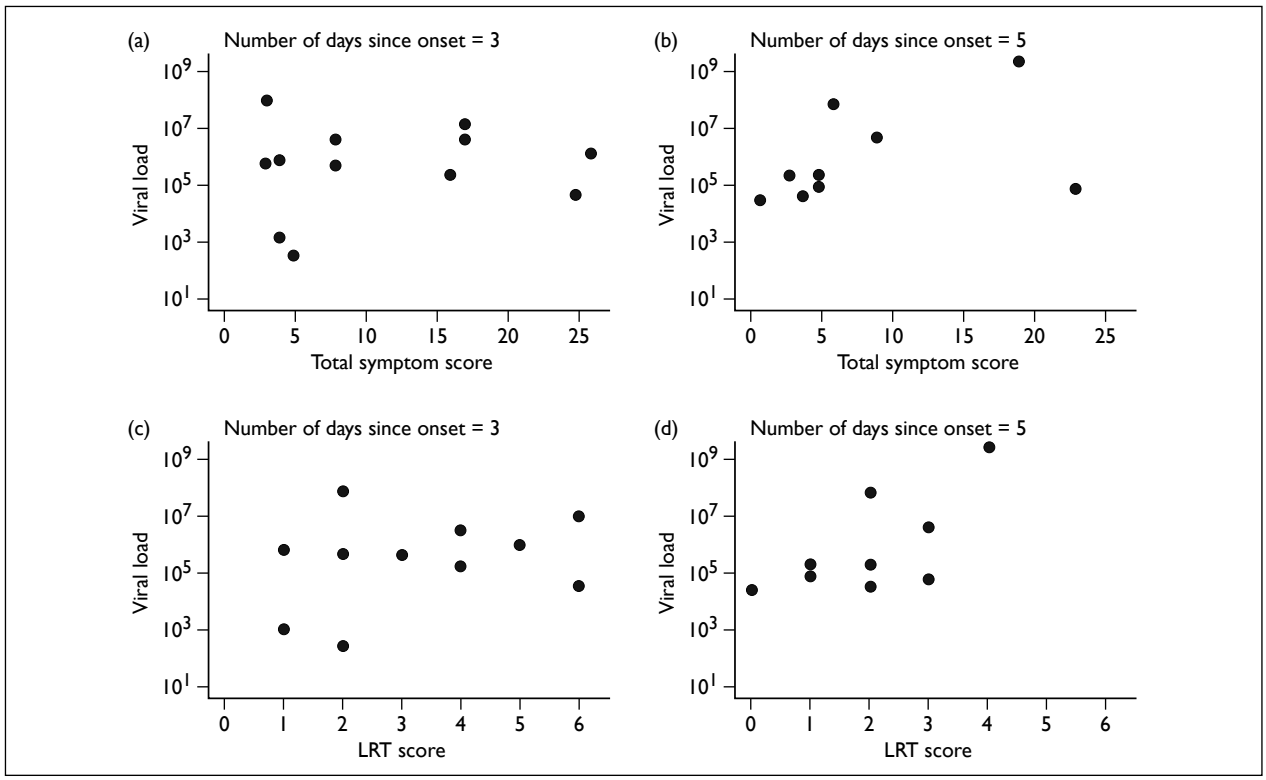

FIGURE 7 *Scatter plots showing symptom scores and viral loads over time. (a) and (b) Total symptom score versus viral load as a function of the number of days since illness onset. (c) and (d) LRT score versus viral load as a function of the number of days since symptom onset.*

0.72 and 0.67, respectively). Among the 13 subjects who had a viral load measurement performed on the first day of the study, eight (62%) had a positive rapid test. The mean viral load on the first day of study was larger for the eight patients with a positive rapid test (198×10^4 copies/ml) than for the five patients with a negative rapid test (4×10^4 copies/ml), although the difference was not statistically significant ($p = 0.15$).

Virus shedding

The duration of virus shedding measured by PCR had mean of 6.2 days and a range of 3–10 days. There was no difference between children (mean 6.1 days) and adults (mean 6.3 days) ($p = 0.89$). Based on the numbers involved, the power to detect a difference was 19% if adult shedding was 6 days and child shedding was 7 days. The duration of shedding of hospital cases (mean 6.8 days) was slightly longer than that of community cases (mean 5.7 days), although the difference was not significant ($p = 0.33$) (*Figure 8*).

No substantial correlation between the duration of shedding and symptom score on the day of recruitment was detected, with coefficients of correlation with URT symptoms of 6% ($p = 0.8$), with LRT symptoms 19% ($p = 0.43$) and with systemic symptoms 8% ($p = 0.75$).

A total of 12/19 cases (63%) were culture positive for pandemic H1N1. The mean duration of live virus shedding from these 12 cases was 4.7 days (range 3–8 days). However, because cases with no positive culture were excluded (durations too short to be observed or false-negative testing), this represents an upper bound for the duration of shedding. To obtain a lower bound for the duration, the calculation was repeated with the assumption that 'negative' patients do not shed live virus (duration of shedding = 0). This gives a mean duration of 2.9 days (range 0–8). The median value when all 19 subjects were included was 3 days, and 6/19 (31%) subjects shed live virus for at least 5 days from the onset of illness.

Figure 9 shows the distribution of live virus shedding for the 12 positive cases, and highlights the recruitment group to which each subject belongs. There was no significant correlation between the duration of the live virus shedding and total symptom score of these 12 cases on the day

of recruitment [correlation coefficient –0.09, 95% confidence interval (CI) –0.63 to 0.51, $p = 0.78$] or the sum of total symptom scores during the whole follow-up (correlation coefficient –0.22, 95% CI –0.71 to 0.40, $p = 0.48$).

The mean duration of shedding determined by both PCR and culture was not significantly different for subjects who received antivirals within 48 hours and those who received them after 48 hours or not at all [PCR: 6.4 days vs 5.9 days, $p = 0.61$; culture-positives: 4.6 days vs 4.8 days, $p = 0.88$). All culture results (assuming six have 0 days): 3.4 days vs 2.4 days, $p = 0.43$].

Box 2 summarises symptom and virus shedding findings.

Environmental deposition

Surfaces

In total, 414 community swabs (+ 52 sponges) and 45 hospital swabs (+ seven sponges) were taken, of which 397 swabs and 12 sponges were tested (not all swabs were tested because of sample processing rules, see Chapter 2, Laboratory methods). Pandemic H1N1 virus was detected by PCR on two occasions on surfaces from around one patient in the community (following discharge from hospital), giving a swab positivity rate of 0.5%. Quantitative PCR could only be performed on one sample because the amount of sample available in the other was insufficient. Live virus was recovered from one of these surfaces. The subject from around whom the swabs were taken was found to

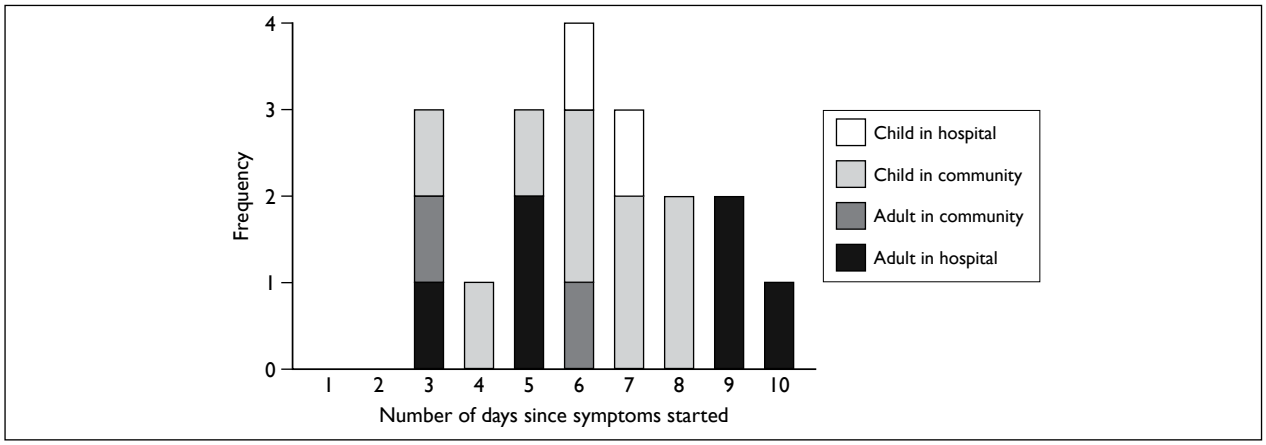

FIGURE 8 *Distribution of the duration of virus shedding by PCR. The duration of viral shedding is defined as the time between symptom onset and the last day that a positive specimen was taken. Because patients were seldom recruited on the day symptoms began, an assumption has been made that they were shedding virus from the first day of symptoms to the last positive specimen.*

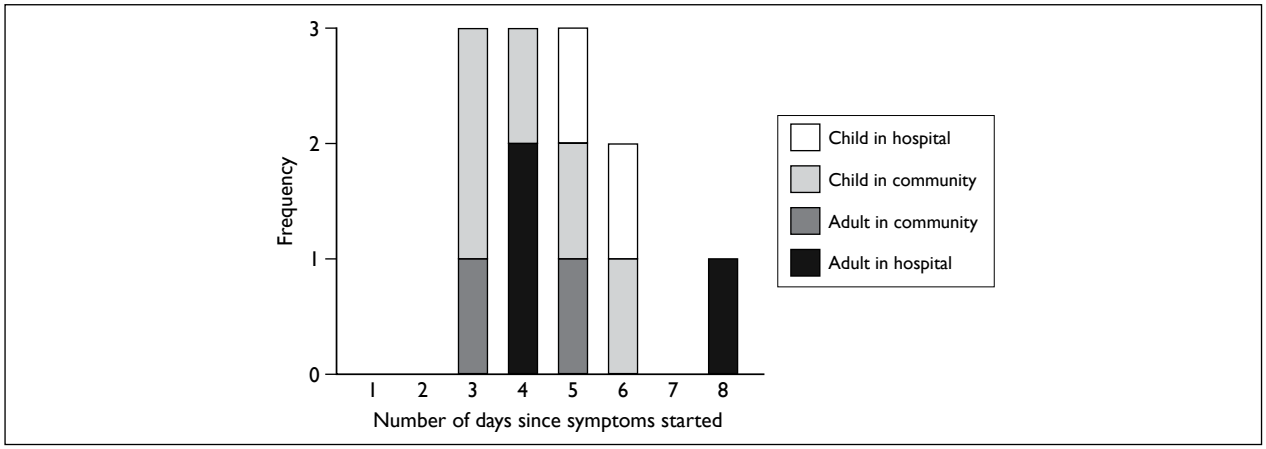

FIGURE 9 *Distribution of the duration of virus shedding by culture positivity (n = 12). The duration of viral shedding is defined as the time between symptom onset and the last day that a positive culture was obtained. Cultures were performed from the last day of nasal swab PCR positivity. If a culture was positive on any given day then it was assumed that previous days' would also have been culture-positive.*

BOX 2 *Symptom and virus shedding data summary*

- Symptoms decline over time
- Initial symptom scores were similar in subjects positive or negative for pandemic H1N1 influenza
- Subjects with pandemic H1N1 had fewer URT symptoms and an earlier peak in LRT symptoms than other subjects
- Viral load was highly variable between subjects; children had higher peak viral loads than adults but this difference was not statistically significant
- No clear relationship was evident between symptom scores and viral load
- No clear distinction was shown in the duration of virus shedding between adults and children
- Mean duration of PCR-detectable virus shedding was 6.2 days (maximum was 10 days)
- Median duration of viable virus shedding was 3 days (maximum was 8 days)
- Total duration of virus shedding detectable by PCR or culture was unrelated to initial symptom severity
- No obvious relationship between shedding of viable virus and any particular symptom(s) was identified

be shedding virus from the nose on the same day, although other household members were also unwell on these days; a 5-year-old was unwell with cough and fever on day 4, and a 2-year-old was unwell with cough and fever on day 10 (*Table 4*).

TABLE 4 *Details of surface swabs that were positive for pandemic H1N1 virus*

	Specimen no.	
	1	2
Subject ID	AH04	AH04
Surface (setting)	Kettle handle (home)	Bathroom tap (home)
Surface material	Plastic	Metal
Swab method	Cotton swab	Cotton swab
Number of days after symptoms began that swab was taken	4	10
Viral load from surface swab (copies/ml)	91,205	N/A
Viral load from nose on day swab collected (copies/ml)	902,703	N/A
Culture	Positive	Negative

N/A, not available.
Note, at the time swabs were taken other household members in this subject's family were also unwell with symptoms of ILI.

Air

Air samples were collected from the immediate environment of five subjects (all of whom were rapid antigen test positive): three while in hospital and two in the community. Seventeen separate collections were undertaken, generating 51 samples (although one could not be processed because of insufficient sample volume). Air samples were positive from four out of five subjects. Eight out of 17 (47%) collections and 22/50 (44%) samples were positive for PCR. No samples were confirmed to contain live virus (*Table 5*).

Quantitative PCR demonstrated a range of values between 238 and 24,231 copies/ml; higher values were recorded in instances when more than one infected person was present in the sampling room. Samples collected over a 1-hour period generated 8/24 PCR-positives (33%), those over a 2-hour period zero out of three positives, and those over a 3-hour period 14/23 positives (61%). The risk ratio for a sample to be positive over a 3-hour period relative to a 1-hour period was 1.83 (95% CI 0.95 to 3.51, $p = 0.082$). Samples collected at a distance close to the subject (approximately 3 ft) generated 13/23 PCR-positives (57%), whereas those collected further away (at least 7 ft) generated 9/27 PCR-positives (33%). The risk ratio for a sample to be PCR positive at a distance of 3 ft versus ≥ 7 ft was 1.70 (95% CI 0.89 to 3.22, $p = 0.15$). Virus was detected in all particle sizes collected: particles < 1 μm gave 7/16 positives (44%); particles 1–4 μm gave 8/17 positives (47%) and particles > 4 μm gave 7/17 positives (41%). Among particles of size 1–4 μm and > 4 μm, the relative risk of obtaining a positive sample relative to particles of size < 1 μm was 1.08 (95% CI 0.51 to 2.28, $p > 0.99$) and 0.94 (95% CI 0.43 to 2.08, $p > 0.99$), respectively (*Table 5*).

Initially it appeared that 3 samples were culture positive for virus. To verify that the cultured virus in the air samples was the same as that from subject's nose, PCR was carried out on

TABLE 5 *Description of air particle samples collected*

	Subject																	
	AH03				**AH04**			**CC05**				**CC15**				**CH03**		
Subject setting (+ infected others)	Hospital bed in side room				Hospital bed in side room			Playing in bedroom				Playing in living room (6-year-old infected child also present)				Cot on neonatal unit (two infected neonates also present)		
Room temperature (°C)	21.6				23.3			20.0				18.0				24.0		
Room humidity (relative %)	50				50			64				60				40		
No. of days after symptoms began that sample was taken	4				3			3				3				5		
Viral load from nose on day sample collected (copies/ml)	238,091				10,625,714			699,723				178,923,317,453				24,208		
Virus cultured in the nose on sampling day?	Yes				Yes			Yes				No				Yes		
Duration of sampling (hours)	1	1	3	3	1	1	2	1	1	3	3	1	1	3	3	3	3	
Approximate distance from subject (ft)	3	7	3	7	3	7	7	3	7	3	7	3	7	3	7	3	7	
Pandemic H1N1 virus detected by PCR	+	–	+	–	+	–	–	–	–	–	–	+	+	+	+	+	+	
Particle size virus detected in μm	< 1	–	< 1	–	–	–	–	–	–	–	–	< 1	< 1	N/A	< 1	< 1	< 1	
	–	–	1–4	–	1–4	–	–	–	–	–	–	1–4	1–4	1–4	1–4	1–4	1–4	
	–	–	>4	–	–	–	–	–	–	–	–	>4	>4	>4	>4	>4	>4	

N/A, not available.

the harvested virus to confirm the presence of pandemic H1N1. However, as well as the clear presence of pandemic H1N1 there was a signal that indicated the presence of another virus. Work was then undertaken to try and identify this virus though it is important to note the following: (1) there were no original samples left to reanalyse; (2) the signal was detected only in harvested, amplified virus; and (3) this signal was not seen in the air sample on which the initial PCR was done.

- PCR assays were performed (see Appendix 6, PCR protocol), which confirmed the contaminating virus to be influenza A, H1. Plaque assay on the harvested air sample virus was strongly positive (titre $30 \times 10^7 \times 2.5/\text{ml} = 7.5 \times 10^8$ plaque-forming units (pfu)/ml). (Note: pandemic H1N1 does not plaque in these cells.)

- Contamination with another influenza virus did not preclude there being live pandemic H1N1 virus in the cells as well. Therefore, an experiment was performed whereby diluted virus was cultured and an attempt made to quantify the amount of virus by PCR. If live pandemic H1N1 was present in the original sample, we postulated that extracted nucleic acid should be at higher concentration in the re-amplified aliquots. Harvested virus was diluted in 10-fold steps from neat to 10^{-7}. Each dilution was split into two aliquots: one frozen and the other inoculated into fresh MDCK (Madin–Darby Canine Kidney) cells. The MDCK cells were incubated for 48 hours before the virus was again harvested. Results indicate that there was no live pandemic H1N1 virus in these samples (at least by these methods). Three out of 11 dilutions were positive for pandemic H1N1 influenza prior to reamplification, but none of the dilutions was positive post re-amplification.

- Finally, in an attempt to determine conclusively the identity of the contaminating virus, samples of the matrix gene amplicons were sequenced. Results show that influenza A PR8 was the contaminating isolate (undoubtedly from the laboratory).

Findings from the environmental sampling are summarised in *Box 3*.

Composite charts

In order to best demonstrate the information we have generated for each subject, charts integrating data from nasal swabs and environmental samples are shown below for selected patients (*Figure 10*). All patient charts are shown in Appendix 7.

BOX 3 *Environmental sampling data summary*

- Almost no fomite contamination was found (0.5% of all specimens taken)
- Five subjects had samples of the air around them taken and virus was detected by PCR from four of them; PCR positive specimens were equally well represented across all of the particle size ranges measured
- Although viable virus was recovered from three samples, we were unable to prove that this virus was pandemic H1N1, as opposed to a contaminant

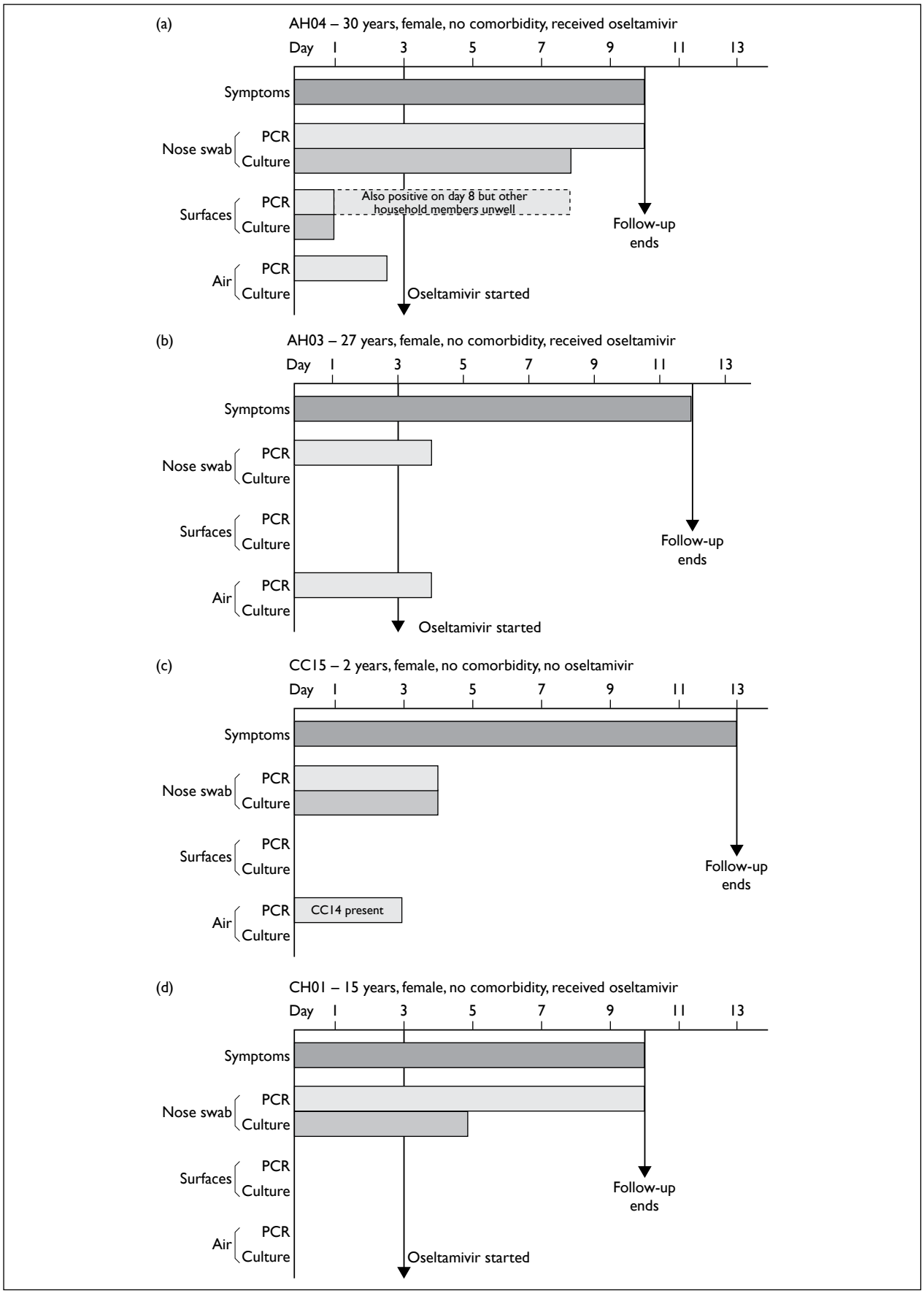

FIGURE 10 *Composite charts for subjects. (a) AH04; (b) AH03; (c) CC15; (d) CH01. The 'symptom' bar shows the number of days for which symptoms were present. The 'nasal swab' bar shows the last day that a swab was either PCR-positive or culture-positive. The 'surface' and 'air' bars show days up to the time that a positive sample was obtained. Arrows show the days when oseltamivir was started and when follow-up ended. 'Day 1' is the day of illness onset.*

Chapter 4
Discussion

This is the first study that has attempted to assess actual viral shedding from patients with influenza, by examining the near-patient environment for virus as opposed to simply taking respiratory specimens. Sampling virus, particularly live virus, in the environment is challenging; getting to the subject in time, executing optimal sampling while preserving virus viability and performing sensitive detection tests in the laboratory are all key factors that necessitate very extensive and complex logistic arrangements. An attempt to overcome this first problem was carried out by targeting recruitment in the community, as well as in hospital (when presentation is often delayed), enabling an approach to subjects early in their illness when virus shedding is usually at its highest. In addition, the use of a bioaerosol sampler, designed and validated by collaborators at NIOSH enabled us to sample air around infected subjects.

Subjects' with pandemic H1N1 experienced a range of symptoms, but a mild illness was evident in the majority of cases, as has been reported elsewhere.[32] There were no significant differences with respect to symptom type or duration between those positive for pandemic H1N1 virus and those who were non-confirmed (negative). Although the non-confirmed cases included some individuals who were infected with other respiratory viruses, undoubtedly some were falsely negative on pandemic H1N1 virus testing.

Viral loads, in general, declined over time, although a lack of data hinders further interpretation. Only 5/19 subjects had data available at four or more time points. The wide range of results seen may in part be reflected by differences in sample quality. The peak viral load was found to be higher in children than adults, in line with other studies,[12,15] although this was not significant. There was a significant association, however, found between viral load and LRT symptoms on day 5 of a subject's illness, suggesting that persistent LRT symptoms might be a clinical marker for prolonged shedding. However, cautious interpretation of this result is necessary, given the lack of data.

Our findings on virus shedding, as conventionally described, are broadly in agreement with other published findings relating to pandemic H1N1 virus (*Table 5*). The median duration of virus shedding from the 19 infected cases was 6 days when detection was performed by PCR, and 3 days when detection was performed by a culture technique. Forty-four per cent of these subjects received oseltamivir within 2 days of illness onset. Fifty-eight per cent of subjects were recruited directly from the community, and these cases shed virus for a shorter period of time than the hospital cases (5.7 vs 6.8 days). Although this finding was not significant it accords, nevertheless, with data suggesting that hospitalised influenza cases shed virus for longer,[9,10] with potential infection control implications for health-care institutions.

When comparing studies (*Table 6*), it should be borne in mind that differences in study populations may exist (children vs adults, hospital vs community cases), a variety of sampling methods are used and that the proportions of cases receiving antiviral drugs (particularly whether they received them within 48 hours) may differ. In a Vietnamese hospitalised cohort of 292 pandemic H1N1 cases, PCR detected virus in combined nose and throat swabs in the following proportion of patients: after 1 day of treatment 86% (165/192); day 2 59% (45/76); day 3 38% (27/72); day 4 25% (34/138); and day 5 14% (11/76). After 5 days of treatment, 7% (12/179) were still positive, although no positive cultures were obtained after day 5.[17] Laboratory findings from a study of 70 cases in Singapore gave a mean duration of viral shedding of 6 days, with shedding > 7 days in 37% of patients. The mean duration of positive culture results on six patients was 4 days.[13] Finally, in a Canadian study, 43 community patients with pandemic H1N1 had a nasopharyngeal specimen collected on day 8 of their illness: 74% were PCR-positive and 19% were culture-positive.[33]

One subject from our study who demonstrated the shedding of live virus up to day 8 will be considered further. She was a 34-year-old woman, of South-Asian origin, who had no comorbidities, and did not take regular medicine. She spent one

TABLE 6 *Published studies describing shedding patterns from cases of pandemic H1N1*

	UK (this study)	China[13]	Hong Kong[16]	Singapore[14]	Germany[15]
Setting	Hospital and community	Hospital	Hospital	Hospital	Community
No. of cases	19	421	22	70	15
Adults and children	Yes	Yes	Yes	Yes	Yes
Percentage who received oseltamivir within 48 hours	44	72.4	95	51	40 (three were given prophylactically)
Duration of viral shedding by PCR	6.2 (mean)	6 (median)	4 (median)	6 (mean)	6.6 (mean)
Duration of viral shedding by culture	3 (median) Range 0–8	–	– Range 1–5	4 (mean, $n=6$)	–
Risk factors for prolonged shedding	–	Age < 14 years, male sex, delayed oseltamivir	Younger age	–	–

night in hospital on the first day of her illness and began taking oseltamivir on day 2 (the subject reported taking oseltamivir each day and, while there is no reason to suspect non-compliance, this cannot be excluded). Prominent symptoms early in her illness were fever, cough, sore throat and fatigue. The virus was sequenced across the HA gene during the period of time that it was shed, and no changes were detected. In addition, no common oseltamivir resistance mutations were detected. All of the other household family members subsequently developed symptoms of cough and fever; a 5-year-old daughter became unwell on day 4 of the mother's illness, followed by a 2-year-old son on day 5 and her 30-year-old husband on day 6. Thus, a high secondary attack rate in this family was associated with high levels and prolonged shedding of virus, despite the index case being treated with oseltamivir.

It is interesting to note that no difference was found in the duration of viral shedding (PCR or culture) between those who took oseltamivir within 48 hours and those who did not, although our numbers are small (10 vs 8), and it is impossible to draw conclusions because a sample size of at least several hundred subjects would have been needed. Other studies have demonstrated a shortened duration or suppressed levels of shedding in association with oseltamivir when it is given early.[13,34,35] Subjects with pandemic H1N1 who did receive antiviral drugs had significantly higher initial symptom scores than those who did not, perhaps indicating that patients with more severe symptoms were more likely to access to early treatment. This difference might mask any effect of antiviral drugs on duration of shedding. In addition, it may explain why symptom scores were consistently lower among those who received no or late treatment than among those who received early treatment.

Our findings relating to the duration of live virus shedding have infection control implications. They suggest that over 30% of cases remain potentially infectious for at least 5 days and, given that live virus may persist in the environment for up to 48 hours,[19] viable virus may be present for 7 days after an index case first develops symptoms. These data are consistent with other recent studies that suggest that pandemic H1N1 may be contagious for a longer period of time than seasonal flu.[13,33] This has clear implications for pandemic infection control and self-isolation guidelines.

However, despite finding that live virus shedding continued for over 4 days in most subjects, fomites contaminated with virus were found in only two instances, involving only one subject. Therefore, only 0.5% of all community fomites, and none of the hospital fomites, swabbed revealed virus, although on one occasion live virus was found. This instance occurred in a household where, at the time of taking the surface swab, a 5-year-old child was also experiencing her first day of symptoms, but the surface contamination was from a kettle handle and so is unlikely to have been directly handled by the secondary case. These findings are in contrast with those of Boone and Gerba,[21] who detected influenza virus (by PCR) on over 50% of all swabs taken from a number of fomites in the home and in child-care centres. They also differ from the findings of a study that involved subjects who were experimentally infected with influenza virus. Swabs taken from fomites in subjects' rooms (two subjects shared a room) revealed influenza (detected by PCR) in 9/48 swabs (19%), although no live virus was found (B Killingley, University of Nottingham, May 2010, personal communication). It is also likely that more than one individual contributed to virus deposition in Boone and Gerba's study.[21] This contrasts with the circumstances of the current study, where only one individual was ill when the vast majority of swabs were taken. In addition, the homes used in Boone and Gerba's study[21] contained a symptomatic child 100% of the time compared with 79% of homes in the current study. It is also worth noting that no specific cleaning instructions were given during the follow-up of our subjects, so, for example, daily cleaning of hospital rooms would have continued, which may have contributed to the low positive swab rate. A more speculative suggestion would be that pandemic H1N1 is less stable in the environment than other influenza strains, and indeed there is some evidence to suggest that some influenza viruses may be more robust than others. In experimental conditions an avian virus survived for up to 6 days on some surfaces[36] and unpublished observations (J Greatorex, HPA, May 2010, personal communication) suggest a laboratory-adapted PR8 (H1N1) virus is more hardy than seasonal wild-type strains. The finding of influenza RNA on fomites on its own does not prove that disease can be spread via the contact route – demonstration of live virus transmitted in an infectious dose would be required for this. Despite an isolated discovery of live virus, our findings overall suggest that the contact route of transmission for pandemic H1N1 may well play a more minor role in the transmission of influenza than hitherto suggested by experts, and by the current emphasis placed on hand hygiene as a means of interrupting transmission.

A noteworthy finding of this study is the demonstration of virus in particles collected from the air around subjects who have influenza; this has not previously been attempted in a community setting. Five subjects had samples of the air around them taken, and virus was detected by PCR from four of them. In two instances there were additional patients with pandemic H1N1 (children) present in the room as well as the study subject during air sampling, and it was these samples that revealed the most virus. All particle sizes collected contained virus detectable by PCR, including the < 1-μm and 1–4-μm fraction sizes, which are bioaerosols of a respirable size, i.e. they can reach the distal airways of the respiratory tract.[37] Sampling for a longer time period, and nearer to the subject, led to the detection of more virus as one might expect, although analyses did not reveal any statistical significance because numbers were small.

Unfortunately, we have been unable to conclusively demonstrate the presence of live pandemic H1N1 in any samples. Initial culture results indicated the presence of live virus in three samples from one subject (AH03) and PCR detected only pandemic H1N1 in the original samples. However, following amplification of the virus to permit further analysis, it appears that the sample became contaminated with a laboratory influenza strain. It was not possible to go back to the original sample (as none remained) or subsequently prove that the live virus detected was pandemic H1N1 as opposed to the contaminant.

There were no unusual room temperature or humidity readings recorded during sampling, but there are insufficient data to study the effects of these variables further.

It is unclear why it was not possible to culture live virus from specimens when most subjects had live virus detected on nasal swabs, although detecting live virus in samples is challenging and the techniques are still relatively new. Difficulties include the fragility of the virus particle (especially its susceptibility to desiccation) and the fact that sufficient virus needs to be collected to enable culture. Because the amount and concentration of virus being sampled in air is much lower than that from nasal swabs, detection is more difficult. The use of VTM during sample collection (as opposed to its addition afterwards) to help preserve

virus has been cited as a necessity by some,[38] and with sound reason. But, as has demonstrated in other unpublished laboratory work (B Killingley, University of Nottingham, May 2010, personal communication), this does not appear to be an absolute requirement with the samplers used.

Evidence backing up at least the potential for bioaerosol transmission of influenza infection has recently been reviewed;[39] supporting evidence comes from the detection of influenza virus (by PCR) in the air around patients,[26,27] the demonstration of bioaerosol transmission in animal models,[40,41] and increasingly sophisticated mathematical modelling techniques, which suggest a role for bioaerosol spread.[42] Detecting the presence of influenza in the air is the first step in a chain of evidence needed to confirm that influenza viruses – emitted from an infected individual and existing as bioaerosols – can initiate infection in a person exposed to them. The other steps in this sequence are (1) confirming that live, i.e. infectious, virus is present and (2) confirming that sufficient live virus exists that can be inhaled by an individual to initiate infection. Couch *et al.*[43] conducted a series of experiments in 1966, culminating in a human-to-human transmission study attempting to follow this line of evidence for coxsackie virus, and came to the conclusion that bioaerosol transmission 'unquestionably occurred'. Similar data on influenza are lacking and it remains that the human infectious dose of influenza in natural conditions is not known for any route. Alford *et al.*[25] showed that three times the TCID50 was needed to infect volunteers via bioaerosols; this compares to other studies showing that 127–320 TCID50 are needed to initiate infection by the intranasal route.[44] Using these data, attempts have been made to estimate the risk of infection attributable to the different routes of infection,[45] but the outputs of such models are only ever as good as the input assumptions. However, if Alford *et al.*'s[25] supposition is true then even small quantities of viable virus expressed via bioaerosols might have significant infectious potential.

Detection of virus by PCR was seen from air samples collected at close range (3 ft) to subjects, well within the contact distance of an attending health-care worker suggesting that the theory of short range bioaerosol transmission advanced by Tellier[39] cannot be dismissed. Although clearly based on extremely limited data, these finding are of sufficient importance to justify further efforts to reproduce them including further attempts to detect of live virus.

There are several limitations to this study. First, the numbers of subjects recruited was well below target. The study began recruiting just prior to the beginning of the second wave of the pandemic in England, but the overall number of people infected during the second wave was well below what had been predicted[46] and seroconversions during the first wave were far higher than expected.[47] In addition a mild illness, including a high asymptomatic infection rate[47] contributed to our difficulty. It is also evident that enrolling people early in the course of their illness is challenging. Over one-half of the volunteers we saw were ineligible because symptoms had been present for too long. A further problem was difficulty in identifying subjects as having influenza as opposed to other ARIs. It has been shown that the standard definition of ILI cannot be relied upon to distinguish pandemic H1N1 from other ARIs,[48,49] and the low numbers of people with illness in the local population made the positive predictive value of even our modified definition of ILI low (48%). A near-patient rapid antigen test was used to help reveal influenza cases, but our original inclusion criteria that required a positive antigen test were modified because the sensitivity of the test in our hands (with a nasal swab) was low. Overall, 10/19 (53%) of our cases were antigen test-positive; the sensitivity in adults was 25% and in children 73%. These findings concur with a number of other reports about the low sensitivity of these tests to detect pandemic H1N1.[50–52] This resulted in a difficulty in reliably recruiting only subjects with pandemic H1N1, such that we followed up subjects who had other ARI. For technical and logistic reasons, the capacity to generate PCR results on samples quickly enough to limit this follow-up in most cases did not exist. The modest recruitment of pandemic H1N1 cases limits the study in several ways, including the generalisability of our findings and because of a lack of data the ability to address our primary aim – to correlate virus shedding on nose swabs with environmental samples.

Second, the sampling methods used require further consideration, as care is needed during interpretation of the results:

- *Nasal swab* Although a nasopharyngeal aspirate (NPA) is considered to be the best specimen for detecting influenza A viruses,[53–55] this procedure causes more discomfort and is more difficult to perform, particularly in children. Indeed, studies attempting to collect daily NPA samples from subjects have reported problems with subjects' tolerance and compliance with

the procedure.[15] A nasal swab, however, has been shown to be an acceptable alternative that is not statistically less sensitive than a NPA,[54–56] although suboptimal sampling (caused by interoperator variation in technique) can still occur.

- *Fomite swabbing* Despite adopting a similar swabbing technique to other comparable studies,[22,23] and validating this in advance using experimentally deposited virus (B Killingley, University of Nottingham, May 2010, personal communication), virus was rarely isolated from fomites. Furthermore, the fomites sampled were similar, except that four of our nine chosen surfaces (bedside table, dining table, patient table and window sill) are not items that are actually picked up or grasped by the hand. Virus may well be transferred to, or settle on, such surfaces, but sampling was performed from only a small proportion of the surface area. Furthermore, many of these surfaces were made of wood, a material that does not support virus survival (J Greatorex, HPA, May 2010, personal communication). In future, consideration will be given to alternative sampling methods, for example using a sponge (wiping a surface may collect more material and can cover a larger surface area) and increasing our focus on 'grasped' items. We used and tested the sponge too infrequently during this study to draw any firm conclusions about its performance compared with a cotton swab.

Finally, all subjects from whom air samples were obtained tested positively on rapid antigen testing. This may have biased the group somewhat, as a positive rapid antigen test has been associated with higher viral loads in nasal samples.[50] On the other hand, our intention was to prove whether viable virus deposition on surfaces or in the air was possible in practice; so selection of these individuals was important. Also no measurements or estimates of room air flow patterns or ventilation were made when collecting samples. Such parameters are likely to have an influence on the ability to detect virus in the air.

Chapter 5
Conclusion

Despite limitations resulting in an inability to fully address the primary aims of the study, important observations have been made. Our findings show that live pandemic H1N1 virus can be found in the noses of over 30% of infected individuals for at least 5 days after symptoms begin. The evidence for the significance of both contact and bioaerosol routes of transmission, depends upon demonstrating that viable virus is deposited from an infected patient. This has been shown for touched surfaces, although the data suggest that contact transmission via fomites may be less important than hitherto emphasised. Transmission via bioaerosols at short range is not ruled out; virus was detected by PCR in aerosols, but we were unable to conclusively demonstrate the presence of live virus.

Implications for health care/recommendations for research

As the current data are inconclusive further work is being undertaken to consolidate these findings, as they have important potential implications for PPE requirements in health-care workers, nationally and internationally. In order to address recruitment difficulties, involvement of specific groups (for example university students) and targeting contacts of index cases who present to a general practitioner or hospital will be attempted during the influenza season 2010–11.

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Contributions of authors

Professor Jonathan Nguyen-Van-Tam (Professor of Health Protection) contributed to study design, data interpretation and was chief investigator.

Dr Ben Killingley (MRC Clinical Research Fellow) contributed to study design, data collection, patient enrolment and data interpretation, as well as being responsible for project management, including co-ordination across sites, study logistics, data management and preparation of regulatory submissions. He drafted the study protocol and this report, which were both reviewed by all authors.

Dr Jane Greatorex (Senior Research Scientist) contributed to study design and data interpretation, and was responsible for laboratory analysis.

Dr Simon Cauchemez (Research Councils UK Research Fellow) contributed to data interpretation and was responsible for statistical analysis.

Ms Joanne Enstone (Research Co-ordinator) contributed to study design and data interpretation.

Dr Martin Curran (Head of Molecular Diagnostic Microbiology) contributed to study design, data interpretation and laboratory analysis.

Professor Robert Read (Professor, Infectious Diseases) contributed to study design and data interpretation and was the principal investigator at the Sheffield site.

Dr Wei Shen Lim (Consultant, Respiratory Medicine) contributed to study design and data interpretation, and was the principal investigator at the Nottingham site.

Dr Andrew Hayward (Senior Lecturer, Infection and Population Health) contributed to study design and data interpretation.

Professor Karl Nicholson (Professor, Infectious Diseases) contributed to study design and data interpretation, and was the principal investigator at the Leicester site.

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Appendix 1

Protocol, version 1.1, 8 October 2009

The University of Nottingham

CONFIDENTIAL PROTOCOL

Virus shedding and environmental deposition of novel A(H1N1) pandemic influenza virus

Sponsor:	University of Nottingham
Funding Source:	National Institute of Health Research
REC Reference:	Leicester 1 – 09/H0406/94

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2. CONTENTS

3. SYNOPSIS

Title	Virus shedding and environmental deposition of novel A(H1N1) pandemic influenza virus
Short title	Virus shedding in novel influenza A(H1N1)
Chief Investigator	Professor Jonathan Van-Tam
Objectives	The objectives of the proposed study are: ***Primary:*** • To determine the quantity of infectious virus present in the nose, on surfaces, in the air and in stool, according to time from symptom onset, symptom constellation (e.g. presence of cough or sneeze), distance from source and particle size (in air); • To correlate serial virus shedding in pandemic influenza patients against data on near-patient environmental contamination (surfaces and air). *Secondary:* • To describe virus shedding (quantity of infectious virus) and duration according to important patient sub-groups, notably adults and children, those with mild illness (community patients) and those with more severe disease (hospitalised patients). • To determine if aerosol generating procedures (most likely to be performed on ITU) are associated with changes in the quantity of environmental contamination with live virus, either in relation to quantity or particle size, or distance from source. • To investigate the possibility of estimating the number of influenza-infected individuals in an area by the quantity o influenza virus recovered in sewage influent. *Policy related (to provide scientific data suitable for policy refinement on):* • 'Safety distances' around patients with pandemic and seasonal influenza. • Appropriate use of respiratory personal protective equipment (RPPE) and infection control practices for pandemic and seasonal influenza, according to patient type, illness severity and time since symptom onset. • Antiviral treatment duration for patients with pandemic influenza. • To develop an alternative surveillance strategy for quantifying influenza infections in a community.

Study Configuration	Multi-centre, observational + interventional
Setting	Community and Hospital
Sample size estimate	We will aim to recruit groups of about 25 patients with recent onset H1N1 influenza in each of the four main sub-groups identified under 'research methods'. Most statistical analysis will involve examining correlations between virus shedding and virus deposition in the environment. The figure below illustrates that sub-group sizes of 25, which also allow pooling of data by adults or children (50 per group) or the whole population gives high statistical power (>80%) to detect correlations of >0.55 in groups of size n=25, 0.4 in groups of size n=50, and 0.3 in groups of size n=100. As regards the duration of virus shedding, these data will be primarily descriptive but it will be important to be able to make formal statistical comparisons of the duration of shedding between adults and children. However by pooling data into adults vs. children (n=50 per group) differences of 5 days (adults) vs. 6 days (children) (two tailed-test) could be detected with >80% provided that the coefficient of variation in shedding was 0.3 or less. For larger differences e.g. 5 days vs.7 days or 5 days vs. 8 days, the study is well powered to coefficients of variation up to 0.6. We aim to recruit about 20 patients within the Nottingham patient group to participate in the viral shedding in stool sub-study. The patients will include roughly an equal mix of adults and children.
Number of participants	100
Eligibility criteria	Our clinical case definition of pandemic influenza (swine flu) is; • Fever (or recent history of) + any 1 of cough, sore throat, runny nose, fatigue or headache • Any 2 of cough, sore throat, runny nose, fatigue or headache **Planned Inclusion / Exclusion Criteria** <u>Inclusion criteria:</u> • Subject fulfils case definition • Informed consent obtained (from Parent/Guardian where appropriate) • Age >1 month • Near-patient test positive for influenza A or other substantive test positive for influenza A (including 'swine flu') • Willing to participate and agrees to allow both nasal and environmental samples to be taken

	Exclusion criteria: • Illness for >48h (community cases) • Illness for >96h (hospital cases) • Existing case of ILI in the household • A negative for swine flu (as part of NHS care) • Has taken part in influenza research involving an investigational medicinal product within the last 3 months
Description of interventions	Symptom assessment – At the first visit participants will be asked to complete a number of assessment forms that cover their medical history and current symptoms. Subsequently they will ask you to complete a diary of your symptoms. They will complete a simple chart which asks whether they are feeling certain symptoms and how severe they are. In addition to this we will take an oral temperature reading. These things will happen once a day. Nose swab – A large cotton bud will be used to take a swab from the inside of the nose. This will be collected every day. Surface sampling – A number of common household and hospital room surfaces will be swabbed. We will take swabs every other day when we visit. Air sampling – For a few patients we would like to conduct some air sampling in the room in which they spend most time. This involves running 2 small machines that suck in air and collect air particles. The machines will stand in a room and run for a maximum of 3 hours. This will be done every other day during the study. Stool sampling – We will ask patients to submit a stool sample each day
Duration of study	Total duration = 6 months Maximum for a participant; Adult = 10, Child = 12 Planned start date = 25th August 2009
Outcome measures	• Virus shedding and deposition as measured by virus culture and quantitative PCR. • (Quantitative PCR and plaque assay of respiratory virus specimens (nasal swabs) from patients and surfaces and air around them).Virus shedding and deposition as measured by virus culture and quantitative PCR. • Daily symptom scores and patient temperature readings • Medication logs • Household/ward daily temperature and humidity logs
Statistical methods	We will perform a detailed descriptive analysis of the data. The symptom constellation of patients in the different groups will be presented. The mean (standard deviation, range) of the quantity of infectious virus in the patient, on surfaces and in the air will be plotted for each patient group and as a function of time since onset, symptom constellation and

	distance from source (when relevant). The mean (standard deviation, range) duration of shedding will also be plotted for each patient group and as a function of symptom constellation. For a better representation of inter-individual variation (which is expected to be important), we will also plot individual trajectories. In a second stage, formal tests will be used to determine which outcomes are significantly associated / correlated. Statistical tests will also be implemented to compare the mean duration of shedding among children and adults as well as among mild and severe cases. In a third stage, a Generalized Linear Model with random effects will be used to determine the key predictors for the quantity of infectious virus in surfaces and in the air. A survival analysis will also be implemented to assess the key predictors for the duration of viral shedding.

4. ABBREVIATIONS

AGP	Aerosol Generating Procedures
CI	Chief Investigator
CRF	Case Report Form
GCP	Good Clinical Practice
ICF	Informed Consent Form
ILI	Influenza Like Illness
PIS	Participant Information Sheet
REC	Research Ethics Committee

5. Background Information and Rationale

As pandemic preparedness activities in the UK and worldwide have gathered pace over the last 5 years, it has become very clear that influenza transmission is one area that is very poorly understood. In particular it has not been conclusively established to what extent influenza transmission occurs via direct and indirect contact (contact with contaminated surfaces), by large droplets (typically >5 microns in size that settle at short range (with 3-4 feet) or by smaller particles (aerosols) that can remain suspended for longer periods of time and travel longer distances. Distinguishing the relative importance of these modes of transmission is critical for the development of infection control precautions in healthcare settings and in the home. For example, if contact transmission is dominant then hand hygiene is the most critical intervention. However, if droplet transmission is important, surgical face masks may be important and the safe distance away from an infected patient might be as great as 4 feet. Such issues are highly relevant to seasonal influenza, but have been brought into sharper focus by the emerging novel A/H1N1 pandemic virus, which is expected to produce widespread UK activity in autumn 2009. At present opinions are sharply divided on the importance of aerosol versus droplet transmission [1, 2]. Currently the UK recommends droplet as opposed to aerosol precautions (surgical masks rather than respirators) for most forms of contact with pandemic flu patients; however, this is contested by some frontline healthcare workers who believe these safeguards are inadequate and there is little evidence with which to reassure them.

In parallel, the kinetics of nasopharyngeal and faecal virus shedding (duration) in relation to symptom onset and severity are both unknown for the novel A/H1N1 virus, but highly relevant in relation to estimation of the likely period of infectivity and in relation to virus replication and therapeutic management (in particular, optimal duration of antiviral drug therapy). In all previous research on influenza virus excretion, shedding has been determined by measurement of the quantity of virus recoverable from the patient's nasopharynx by the deliberate insertion of a cotton swab, nasopharyngeal aspiration or the performance of a nasal wash; i.e. virus has been recovered by a deliberately performed invasive technique. Whilst this data is useful, we propose that these data should be linked to near-patient environmental sampling which would determine the extent to which infectious virus has been deposited onto surfaces and into the air in the patient's immediate vicinity (thus allowing an estimation of the potential for contact transmission) and the measurement of infectious virus in air according to particle size and distance from the patient. We believe that the correlation of virus shedding data against environmental contamination via linked data is critical translational research that will assist policy development far more effectively than virus shedding data obtained in isolation.

Our consortium already has experience in performing virus shedding studies in experimentally infected patients with influenza and virus sampling and virus survival work in relation to contaminated surfaces. It also has air sampling equipment provided on loan from the US Centers for Disease Control (CDC) and the National Institute for Occupational Safety and Health (NIOSH) which has been validated for use with patients with confirmed influenza infection. Although the findings of this research will clearly have long-term relevance to influenza infection control practices, given the strong likelihood of significant pandemic activity by mid-late autumn 2009, the emphasis will be on gaining early data from pandemic influenza patients in August and September 2009, with the intention of providing an early 'policy steer' as well as a longer-term answer.

The Centre for Ecology & Hydrology will be dedicated to using the viral shedding data from stools to inform a model which is being generated to predict the number of influenza-infected people within a geographic area based on the quantity of influenza virus recovered in sewage

influent. This generic approach is already in use by the WHO to assess polio infections/immunizations in an area. It is our aim to test whether sewage influent can serve as a medium for estimating (pandemic) influenza-infected individuals within a region. We believe that if this study can demonstrate that there is a predictable amount of viral shedding in the stool of influenza-infected patients, the sewage-based epidemiology screening approach could be used as an early detection tool for the spread of pandemic influenza within an area.

Existing Research:

Virus Shedding:
To our knowledge no data are yet available publicly on the kinetics of virus shedding in patients with novel influenza A (H1N1). However, confidential data obtained from diagnostic specimens by the Health Protection Agency suggest that the duration of shedding may be slightly longer than with seasonal influenza and up to 8 days in some patients. However these data derive from semi-quantitative PCR readings and so relate to the detection of swine virus specific nucleic acid but not to the presence of infectious virus. In addition, the data are cross-sectional, i.e. pooled from single samples taken from individuals at different time points in their illnesses as opposed to serial measurements from the same individuals (*M.Zambon: personal communication; confidential unpublished data*). Most data are from schoolchildren in whom the duration of shedding tends to be longer than in adults in any case. Until data become available from studies such as the one we propose, the estimated duration of influenza virus shedding is based upon previous experience with seasonal influenza virus infection.
The period of viral shedding can be inferred from the length of time that virus can be recovered from respiratory secretions and is influenced by age of the person infected, level of immune competence and treatment with antiviral agents. It may also be influenced by symptom severity and fever (both proxies for virus replication and viral load) or other unknown factors.

Adults;
Older data suggest that virus shedding is proportional to symptom severity and that virus shedding in adults declines markedly on the third day after symptom onset. Contemporary data on virus shedding in healthy adults derives from studies performed for the licensure of antiviral drugs [3, 4]. It is normally quoted that the shedding of infectious virus (as opposed to PCR detectable virus) is 5 days in adults and CDC infection control guidance reflects this. PCR can detect virus after this time but culture is usually negative. A recent study found that adult patients could shed virus (detected by polymerase chain reaction (PCR) and culture) beyond this traditional period, though patients were elderly and nearly all had underlying medical conditions [5]. Indeed, it is well documented that older patients, those with chronic illnesses and those with immunocompromise can shed live virus for longer periods because virus replication is less inhibited [6]. In the current pandemic however, this may not apply to the elderly because there is already (unpublished) evidence that the level of cross-protective immunity in elderly subjects to the novel A/H1N1 virus is higher than in younger adults and children.

It should be remembered that approximately 50% of all influenza infections are asymptomatic [7] and that infected people (typically adults) can shed influenza virus without any evidence of respiratory symptoms [8]. However, the importance of transmission from infected people during the incubation period or from those with asymptomatic infection is uncertain and is probably substantially less than from symptomatic people.

Children:
CDC guidelines state that children shed virus for up to 10 days (http://www.cdc.gov/flu/professionals/infectioncontrol/healthcarefacilities.htm). Studies of naturally occurring influenza B infection in children have shown that 93% shed detectable virus during the first three days of symptomatic illness, 74% on day four and roughly 25% on day six and that viral shedding is proportional to severity of illness and temperature elevation [9]. In general, children cease shedding influenza virus seven to eight days after onset of symptoms, but they can shed infectious virus several days before onset of illness [10,11]

Other virus shedding work:
The applicants are already involved in work which is similar to the current proposal, studying A/H3N2 experimental virus infection in health volunteers (ITSDG-01 Proof of Concept study; funder - Department of Health England; sponsor - University of Nottingham). The primary aim of this study is to establish that an experimental influenza infection induced by means of viral challenge is transmissible to other individuals. Healthy young adult subjects (Donors) were inoculated with Influenza A/H3N2/Wisconsin/67/2005. At the onset of symptoms consistent with an influenza-like illness (ILI), a second group of healthy young adult volunteers (Recipients) were exposed to Donors by occupying the same living space and performing certain tasks, consistent with close social mixing, as in a household setting. After 48 hours the two groups were separated into different quarantine areas. Use of symptom diaries and diagnostic tests for influenza allowed the presence of subsequent illness to be identified. Additionally, during the study serial nasal washes were obtained from donors and recipients to study virus shedding and environmental sampling (fomites and air) was performed using validated equipment from CDC/NIOSH, with the aim of detecting environmentally shed influenza virus by PCR and infectious virus by plaque assay. The laboratory assays are currently awaited but there are several uncertainties about extrapolating data from a seasonal influenza challenge model in healthy volunteers to wild type infection with a novel virus in a wider range of patient groups including children.

Influenza in the near-patient environment:

Fomites:
The role of fomites and surfaces in the transmission of influenza A is unclear and studies assessing the presence of virus on fomites are lacking. Similarly there is a paucity of scientific data on virus survival on surfaces and no studies looking at viable virus in the vicinity or homes of infected individuals. Limited data are available to support the possibility of indirect contact transmission of influenza; Morens et al concluded that influenza transmission may have been mediated by staff via either contaminated hands or fomites during an outbreak of influenza in a nursing home [12] while Bean et al. indicated that spread of infection by contact with contaminated fomites is possible. They showed that human influenza viruses could survive on a variety of surfaces at 35%–49% humidity and a temperature of 28^0C. Both influenza A and B viruses were cultured from experimentally contaminated, nonporous surfaces, such as steel and plastic, up to 24–48 h after inoculation, and from cloth, paper, and tissues up to 8–12 h after inoculation. However, viruses could be recovered from hands for only 5 min and only if the hands were contaminated with a high viral titer. Viable virus could be transferred from nonporous surfaces to hands for 24 h and from tissues to hands for 15 min [13].

Air:
If influenza virus can transmit via aerosols then we would expect to be able to detect virus in such aerosols and such evidence is now emerging. Studies performed over 30 years ago showed that artificially aerosolised influenza could be detected for up to 24 hours after release and that aerosolized virus is able to infect some animals [14, 15]. More recently influenza virus was detected in aerosol samples taken from medical facilities. Air sampled in an emergency department during an influenza season showed virus to be present [16] and during the 2009 influenza season, air sampling for aerosol particles containing influenza and RSV viruses was conducted at an urgent care walk-in medical clinic. During each of 11 sessions, healthcare workers wore personal aerosol samplers and tripods holding two stationary samplers were placed in six examination rooms, two procedure rooms, and next to the patient scale in the connecting corridor. Three tripods were also placed in the patient waiting room. Preliminary results indicate that 46 of the stationary samplers (17%) and 4 of the personal samplers (19%) captured influenza A RNA and 84 stationary samplers (32%) and 8 personal samplers (38%) contained RSV RNA. During the peak session with 4 confirmed influenza patients, 79% of the stationary samplers collected influenza A viral RNA (*D. Beezhold & W. Lindsley: personal communication;* ***confidential unpublished data***).

Despite the above, the detection of *viable* virus in aerosols generated by humans has not been shown before (as far as we know). The generation of information about the presence of viable influenza virus in the environment will be fundamental to our understanding of the routes of transmission. With this in mind, we have recently attempted to demonstrate that viable influenza virus can be found in aerosols as part of the Proof of Concept study (ITSDG-01) mentioned earlier. In preparation for this, the University of Nottingham received sampling equipment from CDC/NIOSH (identical to that used by Beezhold et al above). Prior to its use we approached the Health and Safety Laboratory in England to pilot setting-up of the sampling equipment, calibration and evaluating the utility of the sampler for capturing live influenza. Following experiments that involved aerosolizing influenza virus in a laboratory, live virus could be detected by an air sampler using the virus plaque assay technique (and PCR results were concordant). Following on from this, air sampling recently took place during the proof of concept study – results are awaited. Thus the technique of air sampling using the CDC/NIOSH equipment has been validated in the UK at the Health and Safety Laboratory and (pending results) during a quarantine based challenge study.

Research at CEH has already demonstrated in preliminary research the capacity of the influenza virus to persist in sewage influent for over 2 hours with only a 60% loss in total counts (quantitative PCR). Given that our ability to detect the virus spans >8 orders of magnitude using quantitative PCR, a 60% decline is negligible (e.g., lowering virus counts from 5.0×10^6 to 2.0×10^6). Hence, there is every reason to expect that if the virus is being shed by influenza-infected patients, the virus should be recoverable in the sewage influent.

6. Research Objectives

The objectives of the proposed study are:

Primary:

i) To determine the quantity of infectious virus present in the nose, on surfaces, in air and in stools, according to time from symptom onset, symptom constellation (e.g. presence of cough or sneeze), distance from source and particle size (in air);
ii) To correlate serial virus shedding in pandemic influenza patients against data on near-patient environmental contamination (surfaces and air).

Secondary:

iii) To describe virus shedding (quantity of infectious virus) and duration according to important patient sub-groups, notably adults and children, those with mild illness (community patients) and those with more severe disease (hospitalised patients)
iv) To determine if aerosol generating procedures (most likely to be performed on ITU) are associated with changes in the quantity of environmental contamination with live virus, either in relation to quantity or particle size, or distance from source.
v) To investigate the possibility of estimating the number of influenza-infected individuals in an area by the quantity o influenza virus recovered in sewage influent.

Policy related (to provide scientific data suitable for policy refinement on):

vi) 'Safety distances' around patients with pandemic and seasonal influenza
vii) Appropriate use of respiratory personal protective equipment (RPPE) and infection control practices for pandemic and seasonal influenza, according to patient type, illness severity and time since symptom onset
viii) Antiviral treatment duration for patients with pandemic influenza
ix) To develop an alternative surveillance strategy for quantifying influenza infections in a community.

The primary objective of this study is to correlate the amount of virus detected in a patient's nose with that found in the environment around them and with the time since illness onset and symptom severity. The point being that so called 'virus shedding' studies that measure virus recovered from the nose do not actually define environmental contamination and hazard to others. To the best of our knowledge such work has not been done before. The study has the potential to address the issues of how, when and where in relation to virus transmission, all of which we believe could inform policy. By collecting stools, we can also correlate influenza shedding in the nose with the stool and thereby provide a mechanism for generating estimates of influenza in the stool to populate the sewage-based epidemiology model.

How – Are touched surfaces important in virus transmission and does respired air present a significant transmission route?

A virus can get on to a surface in a number of ways (e.g. indirectly via touch and droplets of any size settling out), but which surfaces (both in terms of proximity to the patient and physical nature) are commonly contaminated and how long virus remains viable for are uncertain. A virus can also become airborne and transmit through this route (inhalation and direct impaction of droplet nuclei on mucous membranes). The proposed research will evaluate the relative hazard of the touched environment versus the respired environment. In doing this it will provide a policy steer towards interventions that are likely to be important in reducing transmission. For example; if the touched environment is associated with much higher quantities of viable virus than the respired environment then hand hygiene and surface cleaning advice needs greater emphasis; but conversely if the respired environment is more important, strengthening PPE guidance (particularly around face masks and respirators) or applying 'distance or proximity rules' would be of greater importance.

Where - 'Safety distances' around patients with pandemic and seasonal influenza;

The devices we propose to use for air sampling are not only portable but are also validated and capable of separating out particles into three size ranges. Sampling air within 3 feet and >7 feet away from a patient will inform safety distances. For example;

Healthcare settings;

- If air sampling detects virus only within 3 feet of a patient then we can be confident about need for PPE within 3 feet. If viable virus is detected in the air at greater distances then the standard 3 feet safety distance should be revised; but the need for respirators would depend on the size of particles from which we detect viable virus.
- This may have a significant impact on the care of patients in NHS facilities and the advice given to HCWs regarding the implementation of infection control procedures.

Community;

- When a person with a high risk condition (for complications of influenza) resides in a household with an index case, then safety distances around an infected case could be important, potentially helping co-habitees to protect themselves. At the height of the pandemic, it is almost certain that families will have to care for each other as hospital capacity will be saturated. Families need to know the safest procedures to adopt and the government needs to issue this advice.

When - Appropriate use of respiratory personal protective equipment (RPPE) and infection control practices for pandemic and seasonal influenza

Several variables may impact on 'viral shedding' from patients; adult v child, illness severity, time since symptom onset and the effect of antivirals. Knowledge about how long PPE is needed for when caring for patients is important, especially when considering the need to preserve stockpiles of PPE. For example;

Healthcare settings;

- If viable virus can only be recovered from patients for example, up to 3 days after symptom onset, isolation precautions, including use of PPE would not be needed for longer than this, especially if there were shortages.

Community:

- Information about how long patients are infectious for could inform guidance around how long patients need to isolate themselves e.g. avoid caring for children, staying off work / school.

7. Research Team

Expertise
The consortium making this application has several key strengths:

1. Prof Van-Tam, Drs Hayward, Killingley, Greatorex and Cauchemez and Mrs Enstone have worked closely together on the recent influenza virus challenge study, ITSDG-01.
2. Profs Van-Tam and Nicholson are recognised global experts on influenza; both are members of the UK Scientific Pandemic Influenza Advisory Committee (SPI) and the UK Scientific Advisory Group for Emergencies (SAGE). They have worked together for almost 20 years.
3. Dr. Lim was responsible for the creation of the UK national pandemic influenza clinical management guidance.
4. Profs Van-Tam, Nicholson and Read, and Dr Lim are FLU-CIN co-participants.
5. The group has recent experience of conducting virus shedding studies and has validated techniques for this purpose (DH funded study: ITSDG-01).
6. The group has recent experience of conducting virus survival studies using commonly touched household materials and has extensively validated protocols for virus recovery, RT-PCR and plaque assay (HPA funded study).
7. The group has access to BSL Level 3 facilities in Cambridge for its virology work.
8. Dr Hayward is the leader of MRC FluWatch and its subsequent proposed extension. Prof Van-Tam is a FluWatch co-applicant.
9. Dr Singer is a leader in the effort to understand the environmental implications of pharmaceutical use during an influenza pandemic and is a member of the UK Scientific Pandemic Influenza Advisory Committee (SPI).
10. Dr Singer and Dr. Hussey are experienced in molecular virology techniques and have access to the BSL Level 3 facilities at the Centre for Ecology & Hydrology, Oxford.
11. Dr. Andrew Johnson is a world leader in the field of modelling of pollutants in the environment and has significant experience working within sewage works—a necessary component of the epidemiology model.

We have asked members of a team at the Health and Safety Laboratory in Buxton to collaborate with us on this study. HSL is the UK's premier health and safety facility with over thirty years experience in understanding the causes of ill-health and major incidents in UK workplaces. It has specialists from a diverse range of disciplines all under one roof, working to help control hazards and assist in the management of occupational health.
HSL also has a strong track record in healthcare related research and consultancy, in the public, private and charity sectors with a range of clients including the Department of Health, NHS Estates, Hospital Infection Society, Care Quality Commission and BUPA. Therefore, HSL is well placed to offer specialist technical support and has expert scientists specialising in the

areas of virology, aerobiology, environmental microbiology and ventilation in-house;

- Dr Brian Crook: Microbiology Team Leader; expertise in environmental microbiology and aerobiology
- Dr John Saunders: Ventilation and Aerosols team leader; expertise in ventilation systems, air movement
  measurement and control of aerosol hazards
- Dr Jonathan Gawn: Virology Team Leader; expertise in virology, including the extraction of live viruses from the air
- Steve Stagg: General microbiology field scientist; expertise in all aspects of microbiological workplace sampling

HSL is active in Pandemic Flu research and they have recently completed a large study for the Department of Health to evaluate the efficacy of fumigation devices for hospital acquired infections (including influenza) and are developing proposals to assess the efficacy of surgical facemasks and respirators in relation to the transmission of influenza.
We propose to conduct 3 face to face meetings with this team over the course of the study to discuss the design, methods and ultimately outcomes of the environmental sampling work. One meeting should happen as soon as possible to inform our final protocol, the second should take place prior to study start and a third after the study ends.

Collaborators:
Dr David Thomas – Consultant Paediatrician, Nottingham University Hospitals NHS trust.
Dr Paul Digard – Senior University Lecturer, Virology Department, University of Cambridge.
Dr William Lindsley – National Institute for Occupational Safety and Health, USA
Dr Donald Beezhold - National Institute for Occupational Safety and Health, USA

Clinical Team:
A team of nurses will be covering the 3 different sites (Nottingham, Leicester and Sheffield). These nurses will work under the clinical direction of Dr Killingley and the administrative control of the Support Worker who will coordinate daily patient tracking and maintain deployment logs. In each location the nurses will be supported by a consultant physician / paediatrician. Regarding laboratory work, Dr Greatorex (Post Doc Scientist at the HPA laboratory in Cambridge) will be responsible with assistance from a laboratory scientist.

8. Research Methods

Study Design – Multi Centre, Observational + Interventional

When performing studies of virus shedding, certain principles are important:

1. Because serial virus shedding is labour intensive to measure and costly to analyse in the laboratory, there must be a strong likelihood that subjects who are recruited have the disease in question, i.e. the predictive value of screening procedures applied to potential participants must be high. This can be achieved by careful selection criteria and application of a near-patient test.
2. Virus shedding needs to be monitored by taking daily measurements over at least one week during which shedding would be expected to decline; thus it is desirable to recruit 'fresh' patients as soon as practically possible after symptom onset. Nevertheless it is

important to recognise that patients will be recruited to any such study at different intervals after symptom onset; and that patients admitted to and recruited in hospital, may well have been ill for several days when sampling starts. An 'ideal study' would choose hospitalised patients by choosing only those which were followed from community onset into hospital; however achieving this in practice would require following hundreds of patients to identify that subset of 5% who are admitted, and would be wholly impractical. Nevertheless, selection criteria can be used to avoid patients who have already been ill for an excessively large number of days.

3. Single index cases in households or patients housed in single rooms on wards should be recruited whenever possible because these offer the best chance of providing data that are easy to interpret in the context of environmental sampling. For example, if two brothers shared a bedroom and both had symptoms, it would be easy to perform the virus shedding work on both, but impossible to deduce which of the two cases had contaminated the environment.

It is anticipated that this particular study will be performed mainly in August and September 2009 in order that sufficient preliminary data are available to give a policy steer to the Department of Health, England by early October 2009 in advance of a large second wave. Since the daily number of pandemic influenza cases is growing at the present time, but the trajectory of the epidemic curve still contains a high degree of uncertainty, it is impossible to predict precisely how many cases of pandemic influenza will be occurring by study start.

Our study design will therefore be based around the following principles:

1. Based on confidential unpublished HPA data from the FF100 database of confirmed swine flu patients, we already know that the most commonly experienced symptoms are: fever (91%), fatigue (79%), cough (76%) and sore throat (75%). We will select a clinical case definition based on the most common symptoms. We would alter the case definition if new epidemiological data suggested this was warranted.
2. In addition, patients who fit the clinical case definition will be tested with a Quidel QuickVue ® near patient test before proceeding to the next stage of the protocol and only those with a positive test would proceed to sampling. We recognise that patients who pass a near patient test clearly have measurable virus and this might bias the sample towards patients with a higher viral load. However the alternative of over-sampling and later discarding 'non-flu' patients would be too labour intensive and wasteful of resources. However, if we found in practice that most patients recruited on symptoms alone were also positive on near-patient testing, this stage could be amended (omitted) via a protocol modification.
3. We have a limited number of air sampler units available (n=6). Thus we will only sample the environment where it will be possible to interpret the results clearly (patients in side rooms or single (index) cases in households).
4. In order to ensure that patients with relatively recent onset of symptoms are recruited we will set exclusion criteria of >48h after symptom onset for community cases (but aim for recruitment of cases who are within 24h of symptom onset); and > 96h after symptom onset for hospitalised cases (but aim for recruitment within 48h).

Study Management

The study will be managed from a central coordinating site (Nottingham University) by a project manager and administrator. Data will be collected on to source documents and CRFs by the clinical team. Data will subsequently be entered onto a database. All data will be stored at the

University of Nottingham and they will act as custodian of it. Data generated from CEH will be shared with the project team and stored along with the rest of the virus shedding data.

Duration of the study and participant involvement
Each participant's involvement with the study will last for up to 2 weeks. No follow up of participants is planned. Enrolment will begin in August 2009 and will cease in October 2009. Processing of samples collected and data extraction will continue until February 2010

End of the Study
The end of the trial will follow the completion of the laboratory analysis of samples and subsequent data analysis and presentation.

9. Selection and withdrawal of participants

See Appendix 1 for study outline

Cases
We propose the study of small numbers of symptomatic pandemic influenza patients from four groups:

i) Hospitalised adults
ii) Hospitalised children (up to the age of 16 years)
iii) Adults in their own homes
iv) Children in their own homes (up to the age of 16 years)

We regard these four groups as the minimum desirable based on known differences in virus shedding and respiratory etiquette between adults and children and likely differences in symptom severity between patients managed in the community and those who require hospital admission.

Hospital cases once discharged will be followed up and further sampling will take place in the patient's own home with consent. Similarly if a community patient is admitted to hospital mid-way through sampling we would attempt to follow them up in hospital.

Recruitment

HOSPITAL CASES:

Hospital cases will be identified through the clinical teams (including Flu-CIN nurses – see below) looking after patients in the 3 participating centres; Nottingham, Leicester and Sheffield. We will not receive personal information about patients or approach them until their consent for us to do so has been granted.

FLU-CIN is an acronym for the newly formed Influenza (flu) Clinical Information Network funded by the Department of Health, England. When the swine influenza crisis began, the Department of Health and the Scientific Advisory Group for Emergencies considered it essential that a system was put in place rapidly to gain as full an understanding as possible of the most serious

effects of the virus, and the effectiveness of different methods of treatment for those effects. This means collecting information rapidly on the clinical condition and treatment of any patients hospitalised as a result of pandemic influenza. Cases are likely to appear in four main areas – adult medicine including infectious diseases and respiratory medicine; children's services; maternity services; and intensive care. Provisional guidelines for the clinical management of patients with an influenza-like illness during an influenza pandemic have been drawn up by the British Infection society, the British Thoracic Society and the Health Protection Agency in collaboration with the Department of Health. FLU-CIN will provide data which will allow revision of those guidelines in the light of emerging information specific to swine influenza.

Hospital cases will be identified from participating FLU-CIN centres in the East Midlands (Nottingham and Leicester) and South Yorkshire (Sheffield). These hospitals form three of five pilot centres for the network. They have the advantage of being close to the co-ordinating centre for this proposal, and will be staffed by DH funded Support Nurses whose job it will be to identify early, patients admitted with pandemic influenza.

Recruitment targets at these sites;
Nottingham - 9 adults and 25 children
Sheffield – 8 adults
Leicester – 8 adults

We recognise that some patients are likely to have been ill for a period of time before being admitted to hospital and therefore may have passed their peak of viral shedding. Nevertheless some patients may well have deteriorated relatively quickly and patients requiring hospital admission usually have more severe disease. In all probability this may lead to a higher viral load and slower decline in virus shedding than in community patients and healthcare workers will be heavily and closely exposed to such patients. Thus we are firmly of the opinion that viral shedding data in this group of patients will still be of significant value.

<u>COMMUNITY CASES:</u>
We plan to recruit via 2 sources;

1. Local Media

We will advertise in the local press for volunteers with flu like symptoms to take part in the study. The advert will invite people who have or who develop a flu-like illness to participate in a research study that aims to improve our understanding of how swine flu is transmitted between people. We will ask people who are interested in helping to call our research office. Preliminary details will be obtained to establish their potential eligibility and an appointment will then be made for a member of the research team to visit the patient at home. Advertising in this way should enable us to pick up patients early in their illness. Adverts will run once a week for 4 weeks depending on recruitments rates.

2. Antiviral Collection Points

A back up to our planned recruitment via the local media will be to recruit patients who have been diagnosed with swine flu and who have been issued with a 'prescription' for oseltamivir. When a patient's family member or 'flu friend' collects the medicine from a designated collection point, a leaflet will be given out that describes our study and invites people to take part. Interested patients will be asked to ring our research office for further information and we can then establish their eligibility.

This method of recruitment gives us access to a significant number of people already clinically confirmed to have swine flu. A drawback is that we would only be able to recruit patients taking oseltamivir, i.e. we would not be study the natural course of infection in this group. Furthermore, by using this approach it may be that some cases have had symptoms for some time before we make contact with them.

We have the support of the director of Public Health for Nottingham PCT (Dr Chris Packham) for this recruitment mechanism.

Case definitions:
There are a number of options available to us in defining the patients we wish to recruit;

1. Formal virological diagnosis of novel influenza A or novel A(H1N1) swine flu
2. Symptomatic and influenza antigen rapid test positive i.e. confirmed Influenza A/B
3. Symptomatic and a close contact of a case of confirmed swine flu
4. Symptomatic and fulfils a clinical case definition

It is likely that our case definition may change as the epidemic in the UK progresses. For example, before case numbers escalate the positive predictive value (PPV) of symptoms of ILI being swine flu may not be high and in this instance we will want to conduct a rapid test. However, as the PPV of symptoms being caused by swine flu rises, a rapid test may not be needed. So, our initial method of case selection will be number 2 above (symptomatic definition + rapid test), possibly followed by number 4 (symptoms alone). Some patients may already have a confirmed diagnosis by PCR at the point of recruitment (1). However, we recognise that at the present time there is a significant delay between symptom onset and formal diagnosis in the majority of patients. We therefore do not feel confident that relying on formal PCR diagnosis alone will ensure that a large enough number of patients will be detected with 'fresh' symptoms. In addition, as the pandemic progresses it is likely that diagnostic testing will not be performed routinely. Option 3 is also unsuitable for our purposes because we cannot perform environmental sampling if there are two possible patient sources as the data would not be easily interpretable at individual level.

Clinical case definition:
Symptom data are beginning to emerge from swine flu patients in the UK via the unpublished HPA FF100 dataset (**confidential**) and from US patients via online sources;

Symptom	Symptom Frequency	
	UK	US
Fever	91%	94% (371 / 394)
Cough	76%	92% (365 / 397)
Sore Throat	75%	66% (242 / 367)
Fatigue	79%	-
Headache	74%	-
Runny Nose	69%	-
Sneezing	60%	-

US data;
http://www.cidrap.umn.edu/cidrap/content/influenza/swineflu/biofacts/swinefluoverview.html

Our clinical case definition of pandemic influenza (swine flu) is;

- Fever (or recent history of) + any 1 of cough, sore throat, runny nose, fatigue or headache
- Any 2 of cough, sore throat, runny nose, fatigue or headache

Planned Inclusion / Exclusion Criteria

Inclusion criteria:

- Subject fulfils case definition
- Informed consent obtained (from Parent/Guardian where appropriate)
- Age >1 month
- Near-patient test positive for influenza A or other substantive test positive for influenza A (including 'swine flu')
- Willing to participate and agrees to allow both nasal and environmental samples to be taken

Exclusion criteria:

- Illness for >48h (community cases)
- Illness for >96h (hospital cases)
- Existing case of ILI in the household
- A negative for swine flu (as part of NHS care)
- Has taken part in influenza research involving an investigational medicinal product within the last 3 months

Randomization

Randomisation to the days of surface swabbing will occur. 50% of participants will have surface swabbing done on alternate days from the first visit whilst the other 50% will have swabbing done on alternate days from the second visit. Envelopes will contain instructions to 'swab from Day 1' or 'swab from Day 2' in a 1:1 ratio. The envelopes will be identical and number of them will be given to each study nurse who will open an envelope following enrolment of a participant.

Participant Withdrawal

Participation in this study may be discontinued for any of the following reasons:

1. The wish of the subject. A subject can withdraw from the study at any time, for any reason, without prejudice to their future medical care. Participants will be made aware (via the information sheet and consent form) that should they withdraw the data collected to date cannot be erased and may still be used in the final analysis.
2. Non compliance with study procedures.
3. If a patient has a virological test that is negative for swine flu as part of NHS care.
4. Investigator's decision that withdrawal from further participation would be in the subject's best interest.
5. Termination of the study by the Investigator or Sponsor.

Data will be collected on participants who are withdrawn with outlining the reason(s) for discontinuation.

Criteria for terminating the study

Termination of the study as a whole may result from new information regarding H1N1 or issues with study conduct (e.g. poor recruitment, loss of resources).

Informed consent
All participants will provide written informed consent or in the case of a child a parent / guardian will be asked to provide consent. The Consent Form will be signed and dated by the participant before they enter the study. The Investigator will explain the details of the study and provide a Participant Information Sheet, ensuring that the participant has sufficient time to consider participating or not. The Investigator will answer any questions that the participant has concerning study participation.

Informed consent will be collected from each participant before they undergo any interventions (including physical examination and history taking) related to the study. One copy of this will be kept by the participant, one will be kept by the Investigator, and a third will be retained in the patient's hospital records (where appropriate).

In the event that a patient loses the capacity to consent during the study e.g. sedated ventilated patients, we would wish to retain them in the study. Within the consent form there will be a section seeking agreement to continue to sample patients if they do become incapacitated. In this instance we will also seek consent to continue from a relative (to whom an information sheet will be provided). We will not recruit patients who lack capacity to consent at the outset.

Should there be any subsequent amendment to the final protocol, which might affect a participant's participation in the study, continuing consent will be obtained using an amended Consent Form which will be signed by the participant.
Study Sites

Nottingham – Nottingham University Hospitals. Contact Dr Wei Shen Lim
City Hospital Campus, Hucknall Road, Nottingham, NG5 1PB
Queens Medical Centre Campus, Derby Road, Nottingham, NG7 2UH

Sheffield – Sheffield Teaching Hospitals. Contact Prof Robert Reid
The Royal Hallamshire Hospital, Glossop Road, Sheffield, South Yorkshire, S10 2JF

Leicester – Leicester University Hospitals. Contact Prof Karl Nicholson
Leicester Royal Infirmary, Infirmary Square, Leicester LE1 5WW

10. Study Procedures

See Appendix 2 for a sample patient schedule

Collection of data (Hospital and Home):
In addition to collecting initial symptom data to confirm a patient's eligibility, ongoing data collection will be needed to achieve our primary and secondary objectives. These will include;

- Daily symptom diary cards – This will allow a correlation of illness and viral shedding to be made. It will be completed by the patient on each researcher visit. A sample is attached as appendix 3; this scale has been previously validated in numerous live challenge studies.
- Daily temperature readings. Patients at home will be supplied with a digital thermometer and asked to take twice daily readings and additional readings whenever feeling feverish.
- A record of all medication taken during the follow up period will be kept. This would include paracetamol, aspirin, antivirals and antibiotics.

- Whilst in hospital a log documenting the performance of any aerosol generating procedures will be kept (e.g. aspiration of respiratory tract, intubation, resuscitation, bronchoscopy)
- A log will also be kept of the use of nebulisers as it is possible that the use of these generates aerosols [17] .
- Room temperature and humidity records will be kept by the visiting researcher. Recordings will be taken at the beginning of any sample collection.

Sample Collection
We will be collecting the following samples;

1. Upper respiratory tract specimens from patients.
2. Surface swabs to detect virus on commonly touched surfaces near the patient.
3. Air particles to detect virus in room air around a patient.
4. Stool samples from patients.

1. Upper respiratory tract specimens:
Consideration has been given to what specimens should be collected for influenza tests from persons with suspected influenza. A number of papers compare the utility of nasal swabs (NS) versus nasopharyngeal aspirates (NPA) in the diagnosis of respiratory viral infections, mostly in children. Whilst the sensitivity of viral detection is slightly higher with NPA (with both PCR and culture diagnostic techniques) NS are regarded as adequate by many, especially for collection done at home where less equipment is needed [18,19,20,21,22]. In addition NS will be easier to manage in terms of staff training and consistency of specimen collection. It is for these reasons that NS will be preferred method of specimen collection. However, we recognise that children may also have NPAs done for therapeutic reasons as part of their normal medical care. In this instance we would still perform a nasal swab.

Patients will undergo daily nasal swabbing (dry cotton swab passed around the anterior nares and then immersed in viral transport medium (VTM). As discussed earlier, seasonal influenza virus is generally shed by adults for up to 5 days and young children for up to 10 days. There is some early evidence to suggest that viral shedding with H1N1 swine flu is occurring over a slightly extended time. In light of this we will attempt to undertake sampling daily for up to 10 days from the start of symptoms in adults and children ≥13 years of age and up to 12 days in children <13 years. In practice this will likely mean performing swabs daily on average 8 days in adults and 10 days in children <13 years.

We expect to collect 950 samples in total:
- Hospitalised adults: 25 patients, 1 sample a day for (on average) 8 days = 200
- Hospitalised children: 25 patients, 1 sample a day for (on average) 11 days = 275
- Adults in their own homes: 25 patients, 1 sample a day for(on average) 8 days = 200
- Children in their own homes: 25 patients, 1 sample a day for (on average) 11 days = 275

2. Surface Swabbing
The purpose of this is to establish the relationship between viral shedding and contamination of the environment with viable virus. The consortium is already heavily involved in HPA funded work concerned with virus survival, which is specifically looking at virus survival on fomites and the efficacy of household cleaning agents. The consortium therefore has particular expertise in this area and has already validated methods of environmental sampling.

To analyse such a relationship between viral shedding and environmental contamination, it will be necessary to ensure that only one person (the index case) is contributing to environmental shedding. Therefore it will be necessary to limit our sampling to those hospital patients who are in side rooms and those patients at home who are the only symptomatic members of that household. However, we recognise that over a period of sampling time (up to 10 days in adults, 12 in children) other members of a household may well develop symptoms. In this instance we would continue sampling (index case and surfaces) but would record the symptoms of all symptomatic individuals.
It will be necessary to clean down surfaces following swabbing each day to remove viral genomic material, so that the following days swabs reflect the deposition of new material. This will preferably be done with a chlorine based agent but will depend on the surface. It may then be necessary to was the wash the cleaned surface with distilled water to remove any residue of cleaning agent that may affect virus that is subsequently shed upon it.

Samples will be taken every other day during the period of follow up, i.e. nasal swab one day, nasal swab + surface swabs on the next day. We will randomly allocate patients to have surface swabbing done on either days 1, 3, 5, 7, 9 and 11 or 2, 4, 6, 8, 10 and 12.
Samples will be taken by swabbing 2 cm^2 areas on selected surfaces from within the rooms housing patients. For consistency we have chosen the following surfaces;

Hospital;
- Patient table (mid-point or nearest to midpoint)
- Patient line console (e.g. on/off button) / Nurse call button – depending on circumstances
- Window sill

Home;
- Kitchen – Dining table + kettle handle
- Lounge – TV remote control (mid point on the back of the device)
- Bedroom – Bedside table
- Bathroom – Tap + door handle

We expect to obtain 1875 samples in total:
- Hospitalised adults: 12.5 patients (we estimate that 50% of hospital patients will be in side rooms), 12 samples (3 samples every other day for 8 days) = 150
- Hospitalised children: 12.5 patients (we estimate that 50% of hospital patients will be in side rooms), 18 samples (3 samples every other day for 12 days) = 225
- Adults in their own homes: 25 patients, 24 samples (6 samples every other day for 8 days) = 600
- Children in their own homes: 25 patients, 36 samples (6 samples every other day for 12 days) = 900

Method of sampling:
Cotton swabs to be dipped in tube containing 1.5 ml viral transport medium and then rubbed across 2 cm^2 area of surface in 6 different directions, applying even pressure. Swab to be broken off into tube containing SFM.

3. Air Particle Collection

A two-stage bio aerosol cyclone sampler will be used to i) measure the quantity of influenza virus and ii) look for live virus in aerosol particles around patients. The sampling devices and accessory equipment have been loaned by NiOSH as previously mentioned and have been validated both in the UK and the US (see picture at appendix 2). The sampler draws in air at 3.5 litres/min and separates particles into three size fractions (>4, 1-4 and <1 micrometers). The particles are collected in falcon conical tubes containing VTM or on filter paper These fraction sizes are important because particles of less than 4 micrometers in diameter (aerosols) are capable of being inhaled and reaching the lower respiratory tract, where as particles >4 micrometers behave as droplets. It would therefore be interesting to know whether influenza, particularly viable influenza can be found in such particles as this would weight to premise that influenza can be transmitted by aerosols. In addition, by placing samplers at specified or consistent distances away from patients we can assess whether larger particles (droplets) can travel more than commonly accepted 4ft distance.

The samplers will run for 3 hours for each collection. They are powered by an air pump which does generate some noise but this is not excessively intrusive. They will be positioned in the following places;

- Hospital setting: One sampler will be placed within 4ft of the patient's bed, at chest height and within a 180 degree angle of the patients face. A further sampler will be placed at a distance of >7ft from the patients bed ideally against the wall opposite the patient, 150cm off the ground. Samplers will be mounted on drip stands.
  If a patient moves out of a side room we will continue nasal swabbing but will stop environmental sampling.

- Household setting: We will only collect samples if we know that a patient will be relatively stationary for the duration of sampling, e.g. in bed. Samplers will be placed as above.

Samples will be taken every other day during a patients follow up from the first day. We expect to have the use of 6 sampling devices but because of equipment and time constraints we will not be able to perform air sampling around every patient. Over the course of the study we will aim to follow 16 patients.

Based on this we expect to obtain 480 samples in total:

- Hospitalised adults: 4 patients, 4 sampling days (sampling every other day for 8 days), 6 samples each time (3 from each sampler) = 96
- Hospitalised children: 4 patients, 6 sampling days (sampling every other day for 12 days), 6 samples each time (3 from each sampler) = 144
- Adults in their own homes: 4 patients, 4 sampling days (sampling every other day for 8 days), 6 samples each time (3 from each sampler) = 96
- Children in their own homes: 4 patients, 6 sampling days (sampling every other day for 12 days), 6 samples each time (3 from each sampler) = 144

A sample patient schedule can be seen at appendix 2.

4. Stool Sample Collection

Detailed instructions will be provided explaining how to obtain a sample. We will ask the patient to empty their bladder first if possible. They will then place a collecting plate in the toilet bowl which will catch the stool. A sample can then be taken and put in the container. The remaining stool is then tipped into the toilet and flushed away. The plate is disposed of in a rubbish bag.

Once the sample container has been securely capped, it should be placed in a specimen bag and kept in a small cooler box (which will be provided). Hand washing / hygiene measures will be stressed. Stool samples will be collected daily along with the other samples.

Sample Processing (stool samples dealt with separately – see below)
The generation of ≈ 3,300 samples for both PCR and PA is a considerable amount of work requiring not just expertise but also significant laboratory resources, including time. Thus, it is not possible to generate results on all samples collected in a short period. We therefore propose to define a sample processing protocol based on results from the first few cases. It could include the following;

- If a patient tests negative for swine flu (as part of NHS care) we will exclude them from further study.
- Environmental swabs will not be processed if nasal swabs from a case are PCR negative.
- Environmental swabs will only be processed if nasal swabs from a case show a high viral load.
- Environmental swabs will not be processed for PA if nasal swabs from a case are PA negative.

Note; samples that are not processed rapidly will be retained for analysis in the future should this be of interest.

Transport and storage of participant samples

Transport
Collected samples will be placed into viral transport medium and kept on 'wet' ice until being frozen at -80^{0}C. For hospital samples freezing would likely happen within 4 hours and community samples within 9 hours. Samples will be carried / transported locally by researchers in dedicated equipment. Samples will be sent to the Cambridge laboratory once each week from each of the 3 centres and will be transported by a professional delivery company.

Storage
Samples will be kept frozen until analysis at the HPA microbiology laboratories, Addenbrookes Hospital, Cambridge. They will be identifiable through participant study codes, participant initials and date of birth. Following analysis all samples will be destroyed. Analysis is expected to be complete by February 2010

Laboratory analyses

Sample Processing
The generation of ≈ 3,300 samples for both PCR and PA is a considerable amount of work requiring not just expertise but also significant laboratory resources, including time. Thus, it is not possible to generate results on all samples collected in a short period. We therefore propose to define a sample processing protocol based on results from the first few cases. It could include the following;

- If a patient tests negative for swine flu (as part of NHS care) we will exclude them from further study.

- Environmental swabs will not be processed if nasal swabs from a case are PCR negative.
- Environmental swabs will only be processed if nasal swabs from a case show a high viral load.
- Environmental swabs will not be processed for PA if nasal swabs from a case are PA negative.

Note; samples that are not processed rapidly will be retained for analysis in the future should this be of interest (note this will happen within the study timecourse).

Laboratory Testing

- HPA Laboratory, Addenbrookes Hospital, Cambridge will be process samples by PCR methods. The contact person is Dr Jane Greatorex.
- University of Cambridge department of pathology, virology laboratory, Addenbrookes Hospital, Cambridge will process samples for virus culture. The contact person is Dr Jane Greatorex.

Samples will be analysed using real-time quantitative PCR and/or plaque assay (PA - quantification of infectious virus present in the sample). Upon defrosting prior to testing, samples will be split for PCR (refrozen) to detect genome and culture to detect viable virus. The PCR assay is a modification of the real-time quadriplex PCR assay for the detection of influenza (VSOP 25) issued by the Standards Unit, Health Protection Agency, Centre for Infections, Colindale, London. The assay will be performed following good laboratory practice, by trained individuals. Appropriate controls, both negative and positive will be included in each run. All machinery and laboratory equipment is maintained to clinical standards by the East of England Regional Health Protection Laboratory.

The plaque assays are performed in the Division of Virology, Department of Pathology, University of Cambridge, following a risk assessed procedure. The laboratories are maintained by the University and are regularly inspected. Both PCR and plaque assays will be performed by trained biomedical scientists.

Stool sample processing

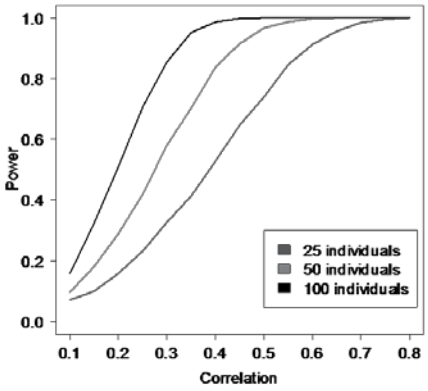
Centre for Ecology & Hydrology will process samples using the same PCR methods as determined by Dr. Jane Greatorex. Stool samples will be stored in a -80C freezer located at the Centre for Ecology & Hydrology, Oxford, Mansfield Rd., Oxford, OX1 3SR. Samples will be identifiable through participant study codes and date of birth, as per the nasal swab samples. Following analysis, all samples will be destroyed. Analysis is expected to be complete by February 2010.

11. STATISTICS

Proposed Sample Size

We will aim to recruit groups of about 25 patients with recent onset H1N1 influenza in each of the four main sub-groups identified under ‘research methods’. Most statistical analysis will involve examining correlations between virus shedding and virus deposition in the environment. The figure below illustrates that sub-group sizes of 25, which also allow pooling of data by adults or children (50 per group) or the whole population gives high statistical power (>80%) to

detect correlations of >0.55 in groups of size n=25, 0.4 in groups of size n=50, and 0.3 in groups of size n=100.



As regards the duration of virus shedding, these data will be primarily descriptive but it will be important to be able to make formal statistical comparisons of the duration of shedding between adults and children. However by pooling data into adults vs. children (n=50 per group) differences of 5 days (adults) vs. 6 days (children) (two tailed-test) could be detected with >80% provided that the coefficient of variation in shedding was 0.3 or less. For larger differences e.g. 5 days vs.7 days or 5 days vs. 8 days, the study is well powered to coefficients of variation up to 0.6.

Statistical Analysis

We will perform a detailed descriptive analysis of the data. The symptom constellation of patients in the different groups will be presented. The mean (standard deviation, range) of the quantity of infectious virus in the patient, on surfaces and in the air will be plotted for each patient group and as a function of time since onset, symptom constellation and distance from source (when relevant). The mean (standard deviation, range) duration of shedding will also be plotted for each patient group and as a function of symptom constellation. For a better representation of inter-individual variation (which is expected to be important), we will also plot individual trajectories.

In a second stage, formal tests will be used to determine which outcomes are significantly associated / correlated. Statistical tests will also be implemented to compare the mean duration of shedding among children and adults as well as among mild and severe cases.

In a third stage, a Generalized Linear Model with random effects will be used to determine the key predictors for the quantity of infectious virus in surfaces and in the air. A survival analysis will also be implemented to assess the key predictors for the duration of viral shedding.

Outcome Measures

1. Virus shedding and deposition as measured by virus culture and quantitative PCR. (Quantitative PCR and plaque assay of respiratory virus specimens (nasal swabs) from patients and surfaces and air around them).Virus shedding and deposition as measured by virus culture and quantitative PCR.
2. Daily symptom scores and patient temperature readings
3. Medication logs
4. Household/ward daily temperature and humidity logs

12. ADVERSE EVENTS

The occurrence of adverse as a result of participation within this study is not expected and no adverse event data will be collected routinely.

13. ETHICAL AND REGULATORY ASPECTS

The study does not raise particular ethical issues as it will not impinge upon normal care provided by the NHS. No personal or sensitive information will be disclosed.

Risks / Benefits

There is no specific treatment benefit as we will not influence participants normal care. The work as a whole is seeking to provide information on swine flu infection that could improve the way we deal with it, particularly from an infection control point of view and the public will benefit from this. Participants may gain some reassurance from the fact that a member of the research team will be visiting each day. However, as stated above they would not interfere directly with normal medical care. Of course, should there be any concerns they will raise them with the participant or their family so they can contact a GP or other responsible medical professional.

The study will not be initiated before the protocol, consent forms and participant and GP information sheets have received approval / favourable opinion from the Research Ethics Committee (REC), and the respective National Health Service (NHS) Research & Development (R&D) department. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant and GP information sheets (if appropriate) have been reviewed and received approval / favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, and the Department of Health Research Governance Framework for Health and Social care, 2005.

Informed consent and participant information

The process for obtaining participant informed consent or assent and parent / guardian informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The investigator or their nominee and the participant or other legally authorised representative shall both sign and date the Consent Form before the person can participate in the study.

The participant will receive a copy of the signed and dated forms and the original will be retained in the Study records. A second copy will be filed in the participant's medical notes (when available) and a signed and dated note made in the notes that informed consent was obtained for the study.

The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasize to them that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss

of benefits to which the participant is otherwise entitled. No study-specific interventions will be done before informed consent has been obtained.

The investigator will inform the participant of any relevant information that becomes available during the course of the study, and will discuss with them, whether they wish to continue with the study. If applicable they will be asked to sign revised consent forms.

If the Consent Form is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Consent Form by the REC and use of the amended form (including for ongoing participants).

Records
Case Report Forms;
Each participant will be assigned a study identity code number, for use on CRFs, other study documents and the electronic database. The documents and database will also use their initials (of first and last names separated by a hyphen or a middle name initial when available) and date of birth (dd/mm/yy). CRFs will be treated as confidential documents and held securely in accordance with regulations. The investigator will make a separate confidential record of the participant's name, date of birth, local hospital number or NHS number and participant study number, to permit identification of all participants enrolled in the study. CRFs shall be restricted to those personnel approved by the Chief or local Investigator and recorded as such in the study records.' All paper forms shall be filled in using black ballpoint pen. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initialled and dated.
The Chief or local Investigator shall sign a declaration ensuring accuracy of data recorded in the CRF.
Source documents;
Source documents shall be filed at the investigator's site and may include but are not limited to, consent forms, study records, field notes, interview transcriptions and audio records. A CRF may also completely serve as its own source data. Only study staff shall have access to study documentation other than the regulatory requirements listed below.

Direct access to source data / documents;
The CRF and all source documents shall made be available at all times for review by the Chief Investigator, Sponsor's designee and inspection by relevant regulatory authorities.

Data protection
All study staff and investigators will endeavour to protect the rights of the study's participants to privacy and informed consent, and will adhere to the Data Protection Act, 1998. The CRF will only collect the minimum required information for the purposes of the trial. CRFs will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the trial staff and investigators and any relevant regulatory authorities (see above). Computer held data including the study database will be held securely and password protected. Access will be restricted by user identifiers and passwords. Information about the study in the participant's medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information. Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

14. QUALITY ASSURANCE & AUDIT

Insurance and indemnity
Insurance and indemnity for clinical study participants and study staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but study participants may have recourse through the NHS complaints procedures.

The University of Nottingham has taken out an insurance policy to provide indemnity in the event of a successful litigious claim for proven non-negligent harm.

Study conduct
Study conduct will be subject to systems audit of the Trial Master File for inclusion of essential documents; permissions to conduct the trial; Study Delegation Log; CVs of study staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, correct randomisation, timeliness of visits); accountability of study materials and equipment calibration logs.

Study data
Monitoring of study data shall include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The Study Coordinator, or where required, a nominated designee of the Sponsor, shall carry out monitoring of study data as an ongoing activity.

Entries on CRFs will be verified by inspection against the source data. A sample of CRFs (10%) will be checked on a regular basis for verification of all entries made. In addition the subsequent capture of the data on the study database will be checked. Where corrections are required these will carry a full audit trail and justification.
Study data and evidence of monitoring and systems audits will be made available for inspection by the REC as required.

Record retention and archiving
In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Research Code of Conduct, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.
The study documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the University of Nottingham. This archive shall include all study databases and associated meta-data encryption codes.

Discontinuation of the trial by the sponsor
The Sponsor reserves the right to discontinue this study at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice as appropriate in making this decision.

Statement of confidentiality
Individual participant medical or personal information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted

above. Participant confidentiality will be further ensured by utilising identification code numbers to correspond to data in the computer files. Such medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare. Data generated as a result of this study will be available for inspection on request by the participating physicians, the University of Nottingham representatives, the REC, local R&D Departments and the regulatory authorities.

15. PUBLICATION AND DISSEMINATION POLICY

The Department of Health as funder would be involved in the dissemination of any key findings. They have responsibility for public health issues and are tasked with communicating health related messages to the public. It is envisaged that they may find the results of this study critical in underpinning guidance given to the public about minimising influenza transmission. If there was a desire to publicise such information to the media or other organisations in a timely fashion, perhaps in advance of the Department of Health's own comprehensive campaign, the UoN communications office would be in a position to liaise with the Department of Health (or other appropriate agencies) to facilitate this. The UoN has a communications office with extensive experience of disseminating research findings. In addition to liaising with the national and international media and publications industry they are used to working closely with funding bodies and government departments. Prof Van-Tam retains strong links with the Health Protection Agency and its Press Office who have considerable experience in relation to public communication on avian and pandemic influenza. Confidentiality of participants in the study will be maintained and they will not be identified in any publications.

16. USER AND PUBLIC INVOLVEMENT

N/A

17. STUDY FINANCES

This study is funded by HTA programme within the NIHR
Participants will not be paid to participate in the study

18. CHIEF INVESTIGATOR'S SIGNATURE

The Investigators and the Sponsor have discussed and agreed upon the content of this protocol. The Investigators agree to perform this investigation according to protocol and in conformance with GCP, and to abide by this protocol except in the case of medical emergencies or where departures from the protocol are necessary in the interest of subject safety. They agree to give access to all relevant data and records to the monitors, auditors, Clinical Quality Assurance representatives, and regulatory authorities as required.

Chief Investigator, Professor Jonathan Van-Tam
MBE, BMedSci, BMBS, DM, FFPH, FRIPH
GMC No. 3241998

Date: 08 Oct 2009

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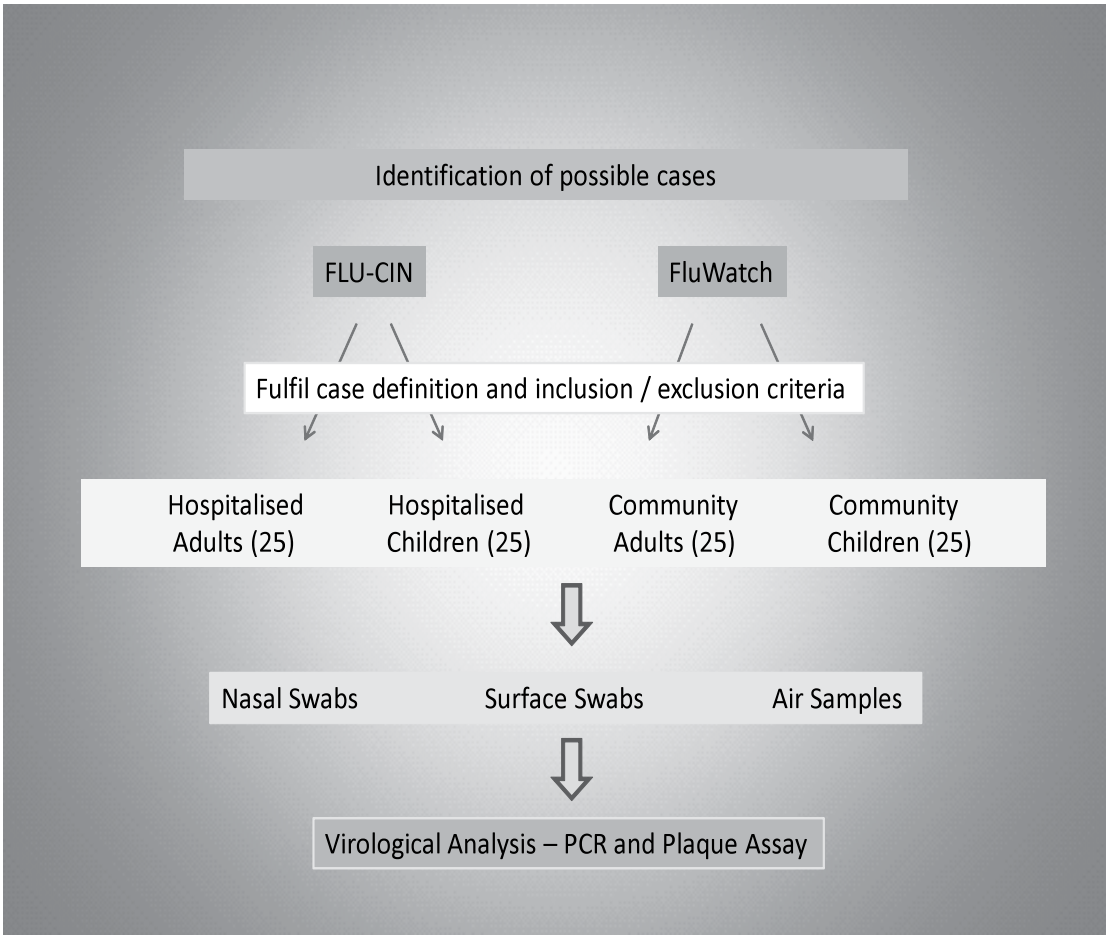
Appendix 1 – Study outline



Appendix 2 – Sample patient schedule

Procedures		Day1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12
Meets case definition		x											
Fulfils entry criteria		x											
Consent		x											
Symptom diary card		x	x	x	x	x	x	x	x	x	x	x	x
Oral temperature		x	x	x	x	x	x	x	x	x	x	x	x
Room temperature and humidity		x		x		x		x		x		x	
Concomitant meds?		x	x	x	x	x	x	x	x	x	x	x	x
Adverse event?		x	x	x	x	x	x	x	x	x	x	x	x
Nasal swab		x	x	x	x	x	x	x	x	x	x	x	x
Surface swabs		x		x		x		x		x		x	
Air sampling		x		x		x		x		x		x	
Stool sample (optional)		x	x	x	x	x	x	x	x	x	x	x	x

Appendix 3 - Symptom Diary

Subject Number	Subject Initials	Date
	F M L	D D M M Y Y Y Y

Time (24 hour) _____ Study Day: ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 ☐11 ☐12

Place an "X" in the box in each symptom row that best describes how you have felt since completing your last diary card. Grade your symptoms based on the descriptions provided. Use the space to the right to note down any other symptoms you have.

Level	0	1	2	3	Other Symptoms:
Symptoms:	I have NO symptoms	Just noticeable	It's clearly bothersome from time to time, but it doesn't stop me from participating in activities	It's quite bothersome most or all of the time, and it stops me from participating in activities	
Runny Nose					
Stuffy Nose					
Sneezing					
Sore Throat					
Earache					
Sinus Tenderness					
Malaise (tiredness)					
Cough					
Shortness of breath					
Wheezing					
Headache					
Muscles and/or joint ache					

Appendix 2
Consent forms

Adult

The University of Nottingham

CONSENT FORM (adults)

Virus Shedding Study

Virus shedding and environmental deposition of novel A(H1N1) pandemic influenza virus

Patient Identification Number for this trial: _____

Please Initial Boxes

1. I confirm that I have read and understood the information sheet for the above study dated 06 August 2009 (version 1.1). I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily ☐
2. I understand that my taking part is voluntary and that I am free to pull out at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by members of the research team, responsible individuals from the University of Nottingham (inspectors) or regulatory authorities where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
4. I agree that should I lose the capacity to consent during the study, my full participation in it can continue. ☐
5. I agree to my GP/hospital clinician being informed of my taking part in the study. ☐
6. I agree to take part in the study. ☐

_____	_____	_____
Name of person	Date	Signature
_____	_____	_____
Name of person taking consent	Date	Signature

Parent/guardian

The University of Nottingham

CONSENT FORM (Parent / Guardian)

Virus Shedding Study

Virus shedding and environmental deposition of novel A(H1N1) pandemic influenza virus

Patient Identification Number for this trial: _____

Please initial boxes

1. I confirm that I have read and understood the information sheet for the above study, dated 06 August 2009 (version 1.1). I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily ☐
2. I understand that my child's participation is voluntary and that they are free to withdraw at any time, without giving any reason, without their medical care or legal rights being affected ☐
3. I understand that relevant sections of my child's medical notes and data collected during the study may be looked at by members of the research team, responsible individuals from the University of Nottingham (inspectors) or regulatory authorities where it is relevant to his / her taking part in this research. I give permission for these individuals to have access to their records ☐
4. I agree to my child's GP/hospital clinician being informed of their taking part in the study. ☐
5. I agree to my child taking part in the study. ☐

_____	_____	_____
Name of person	Date	Signature

_____	_____	_____
Name of person taking consent	Date	Signature

Appendix 3
Information sheets

Adult

Adult Information Sheet

Study title **Virus shedding and environmental deposition of novel A(H1N1) pandemic influenza virus**

You are being invited to take part in this University of Nottingham sponsored medical research. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully.

Ask us if there is anything that is not clear or if you or your child would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the research project?
An influenza pandemic has recently been declared, involving the novel A(H1N1) 'swine flu' virus. This has spread to almost 100 countries worldwide in less than two months, causing widespread disease so far in Mexico, USA and Canada. It is highly likely that over the next 12 months, many countries including the UK will be affected by widespread illness. In the UK this wave of intense flu activity is most likely to occur in late autumn 2009.

Very little is known about the new H1N1 pandemic virus. For example we do not know how long the virus is excreted by infected humans and how much virus is spread to surfaces and carried in the air. This is very important to know as soon as possible because it affects the advice that will be given to healthcare workers about controlling the spread of infection to themselves and other patients. Similarly we need this information so we can give good quality advice to families who will have to look after each other in their own homes.

The best way to obtain this information is to ask patients who get pandemic flu soon (in August, September and October) to help us by agreeing to give a daily nose swab sample for just over one week so we can see how much virus is in the nose day by day and how quickly this disappears. At the same time we will take samples from hard surfaces in a patient's room or home and sample the air using a special filter device. We can then work out how much virus is being excreted, how long the 'danger period' is, whether surfaces are more or less important than the air that we breathe (in terms of catching the virus) and if we can advise on a 'safe distance' from the patient, beyond which there is relatively little chance of catching the illness. We need to do these studies in children as well as adults.

The study involves a simple daily nasal swab and subjects who agree to take part will be inconvenienced to some extent. However, the technique of sampling from the nose is quick and not painful and should not present any problems. Normal medical care will not be affected in any way.

The team has been performing this kind of work for some time and is well qualified and experienced to carry out the study. Several members of the study team are leading international experts on influenza.

Why have I been chosen?
You have been chosen as you have had a diagnosis of swine flu made.
This trial will include about 100 adults and children from Nottingham, Leicester and Sheffield. We are recruiting patients both from the community and in hospital.

Do I have to take part?
No. If you do, you will be given this information sheet to keep and be asked to sign a consent form. You are still free to withdraw at any time, without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

If you do withdraw, we will ask why, as it might be important for other people, but you don't have to give a reason if you don't want to.

What will happen to me if we agree to take part?
If you choose to take part, the care you receive will not be different from that should you choose not to take part. You will be asked to sign a consent form. You will be given a copy of the information sheet and signed consent form to keep for your records.

We will confirm your entry into the study following a few questions. We will ask about your symptoms and their duration and if anyone else in your household has been ill. If your answers fit our criteria we might also then do a test for influenza by taking a nose swab. The test will be done whilst we are with you. If the test is positive you are eligible, if the test is negative you won't be able to take any further part. This test is only being done for our research purposes, the result will not change the way you are being managed by your GP or anyone else.

If eligible, you will be involved in the trial for a maximum of 10 days and a minimum of 7. The number of days will depend on how long you have had symptoms before we meet you. If we meet on the day your symptoms begin we would like to visit every day for 10 days. If we meet 2 days after symptoms begin we will visit every day for 8 days. A member of the research team will carry out the visit, the person will usually be a nurse but maybe another healthcare professional. All staff will have undergone the necessary checks and training needed to conduct such work. We will arrange appointment times with you.

We would like to visit you every day during the study and perform the following procedures (in addition to what has been mentioned above already);

- Symptom assessment – At the first visit you will be asked to complete a number of assessment forms that cover your medical history and current symptoms. Subsequently we will ask you to complete a diary of your symptoms. You will complete a simple chart which asks whether you are feeling certain symptoms and how severe they are. In addition to this we will take an oral temperature reading.

- Nose swab – A large cotton bud will be used to take a swab from the inside of the nose, it does not need to go very far back! This will be collected once every day (except on the first day when it might be done twice).

- Surface sampling – We have already chosen a number of common household and hospital room surfaces that we would like to swab, e.g. dining table, taps, door handles, remote control. We want to see if we can find influenza virus on these surfaces. After swabbing we will clean these surfaces. We will take swabs every other day when we visit. You will be randomly split into 2 groups for this; Group 1 will have swabs done on Days 1, 3, 5, 7 and 9. Group 2 will be done on Days 2, 4, 6, 8 and 10.

- Air sampling – For a few patients we would like to conduct some air sampling in the room in which they spend most time. This involves running 2 small machines that suck in air and collect air particles. We want to see if we can find influenza virus in these particles. The machines will stand in a room and run for a maximum of 3 hours. They do make a small amount of noise. This will be done every other day during the study. A member of the research team will be present to set the machine up and collect it afterwards.

Each of the visits will last for up to one hour except when air sampling is performed (see above) which will take longer. The researcher may set up the air sampling equipment, leave it running and then return before if finishes.

If you have been recruited in hospital and are later sent home, we would wish to follow you up at home for the remainder of the study period. Similarly, if you have been recruited in the community and need to be admitted to hospital we would follow you up in hospital.

This study will not interfere with the normal medical care you may receive. This includes the use of any medicines, e.g. antivirals

If for any reason you lose the capacity to consent during the study (e.g. the remote possibility that they are admitted to hospital and need to be sedated to help with breathing) we have included a box in the consent form to tick if you are happy for us to continue with our sampling during this period.

Initially your diagnosis of swine flu is likely to have been made on clinical grounds, i.e. the symptoms that you have. Some people may have a test to confirm this diagnosis (this will be different from the test we might have done initially on the nose

swab). If swine flu is confirmed you will remain in the study but should this test come back as negative, we will not perform any further sampling on or around you and you will be excluded from the study.

What are the possible benefits of taking part?
There is no specific treatment benefit as we will not influence your normal care. The work as a whole is seeking to provide information on swine flu infection that could improve the way we deal with it, particularly from an infection control point of view and the public will benefit from this.

You may gain some reassurance from the fact that a member of the research team will be visiting each day. However, as stated above they would not interfere directly with normal medical care. Of course, should there be any concerns they will raise them with you or your family so that you can contact your GP or other responsible medical professional.

Contact details
If you have any problems, concerns or other questions about this trial, you should contact the research member of staff who visits each day. If you have any complaints about the way the research staff are carrying out the study you can make a complaint to the study Chief Investigator, Professor Jonathan Van-Tam, Clinical Sciences Building, City Hopstial, Hucknall Road, Nottingham, NG5 1PB. Tel 0115 823 0276.

What will happen if I don't want to carry on with the trial?
You can withdraw from the study at any time but it would be best to stay in contact with us and keep to the study assessments if possible. We will ask for your reasons for withdrawing, as they might be important for other people. You don't have to give any reasons if you don't want to.

What if there is a problem?
In the event that something goes wrong and you are harmed during the trial the University of Nottingham carries insurance to make sure that if any participant incurs any unexpected adverse event that leads to their being harmed and that the event occurred as a consequence of the protocol (i.e. non-negligent harm), then the participant will be compensated. In addition, all research staff have their own professional indemnity insurance which will cover any unexpected adverse event that leads to participant harm caused by negligence.

This study will be conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines (directive CPMP/ICH/135/95), local regulatory requirements and the declaration of Helsinki, and all relevant local laws and regulations.

Will my participation in this trial be kept confidential?
When you enter the trial the researcher will record information about your illness, medical history and the subsequent course of the illness. Some of this information may be taken from your medical notes (if you are in hospital). Collection and analysis of this information is an important part of the research. Your contact details will also be recorded but will be kept separate from the study data on a secure database.

The results of the trial will be published in medical journals and sent to regulatory authorities. However, all identifying personal details will be kept strictly confidential and no information will be published or given out through which you could be identified.

What will happen to the results of the trial?
Any results will be presented to the Department of Health in the first instance. Subsequently, results may be presented at scientific medical meetings and published in a leading medical journal and possibly in national and local media too. You will not be individually identified in any report or publication.

Who is organising and funding the research?
The University of Nottingham is organising this study. The NHS Health Technology Assessment (HTA) Programme has provided the research grant and no member of the research team are being directly paid for including you in this study.

Who has reviewed the study?
The trial was peer reviewed before funding by the HTA. This study was given a favourable ethical opinion for conduct in the public-health sector by the Leicester 1Research Ethics Committee, and was approved by the local NHS Trust Research & Development departments.

You will be given a copy of this Adult Information Sheet and a copy of the signed Consent Form to keep.

THANK YOU FOR TAKING THE TIME TO READ THIS INFORMATION SHEET

Parent/guardian

Parent / Guardian Information Sheet

Study title **Virus shedding and environmental deposition of novel A(H1N1) pandemic influenza virus**

You and your child, or teenager, are being invited to take part in this University of Nottingham sponsored medical research. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully.

Ask us if there is anything that is not clear or if you or your child would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the research project?
An influenza pandemic has recently been declared, involving the novel A(H1N1) 'swine flu' virus. This has spread to almost 100 countries worldwide in less than two months, causing widespread disease so far in Mexico, USA and Canada. It is highly likely that over the next 12 months, many countries including the UK will be affected by widespread illness. In the UK this wave of intense flu activity is most likely to occur in late autumn 2009.

Very little is known about the new H1N1 pandemic virus. For example we do not know how long the virus is excreted by infected humans and how much virus is spread to surfaces and carried in the air. This is very important to know as soon as possible because it affects the advice that will be given to healthcare workers about controlling the spread of infection to themselves and other patients. Similarly we need this information so we can give good quality advice to families who will have to look after each other in their own homes.

The best way to obtain this information is to ask patients who get pandemic flu soon (in August, September and October) to help us by agreeing to give a daily nose swab sample for just over one week so we can see how much virus is in the nose day by day and how quickly this disappears. At the same time we will take samples from hard surfaces in a patient's room or home and sample the air using a special filter device. We can then work out how much virus is being excreted, how long the 'danger period' is, whether surfaces are more or less important than the air that we breathe (in terms of catching the virus) and if we can advise on a 'safe distance' from the patient, beyond which there is relatively little chance of catching the illness. We need to do these studies in children as well as adults because we already know that

children seem to hold on to the flu virus for longer and are not very good at respiratory hygiene!

The study involves a simple daily nasal swab and subjects who agree to take part will be inconvenienced to some extent. However, the technique of sampling from the nose is quick and not painful and should not present any problems, even in children. Normal medical care will not be affected in any way.

The team has been performing this kind of work for some time and is well qualified and experienced to carry out the study. Several members of the study team are leading international experts on influenza.

Why has my child been chosen?
Your child has been chosen as they have had a diagnosis of swine flu made. This trial will include about 50 children, aged 0 to 16 years primarily from Nottingham. We are recruiting patients both from the community and in hospital.

Does my child have to take part?
No. You and your child decide whether or not to take part. If you do, you will be given this information sheet to keep and be asked to sign a consent form. You are still free to withdraw at any time, without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care your child receives.

If you do withdraw, we will ask why, as it might be important for other children, but you don't have to give a reason if you don't want to.

What will happen to my child if we agree to take part?
If you and your child choose to take part, the care your child receives will not be different from that should you choose not to take part. You will be asked to sign a consent form. You will be given a copy of the information sheet and signed consent / assent forms to keep for your records.

We will confirm your child's entry into the study following a few questions. We will ask about their symptoms and their duration and if anyone else in the household has been ill. If the answers fit our criteria we might also then do a test for influenza by taking a nose swab. The test will be done whilst we are with you. If the test is positive your child will be eligible, if the test is negative they won't be able to take any further part. This test is only being done for our research purposes, the result will not change the way your child is being managed by your GP or anyone else.

If eligible your child will be involved in the trial for a maximum of 12 days and a minimum of 9. The number of days will depend on how long your child has had symptoms before we meet you. If we meet on the day your child's symptoms begin we would like to visit every day for 12 days. If we meet 2 days after symptoms begin we will visit every day for 10 days. A member of the research team will carry out the visit (the person will usually be a nurse but maybe another healthcare professional).

All staff will have undergone the necessary checks and training needed to conduct such work. We will arrange appointment times with you.

We would like to visit your child every day during the study and perform the following procedures (in addition to what has been mentioned above already);

- Symptom assessment – At the first visit you and your child will be asked to complete a number of assessment forms that cover your child's medical history and their current symptoms. Subsequently we will ask your child (with your help if necessary) to complete a diary of their symptoms. They will complete a simple chart which asks whether they are feeling certain symptoms and how severe they are. In addition to this we will take an oral temperature reading.

- Nose swab – A large cotton bud will be used to take a swab from the inside of the nose, it does not need to go very far back! This will be collected once every day (except the first day when it might be done twice).

- Surface sampling – We have already chosen a number of common household and hospital room surfaces that we would like to swab, e.g. dining table, taps, door handles, remote control. We want to see if we can find influenza virus on these surfaces. After swabbing we will clean these surfaces. We will take swabs every other day when we visit. You will be randomly split into 2 groups for this; Group 1 will have swabs done on Days 1, 3, 5, 7, 9, 11. Group 2 will be done on Days 2, 4, 6, 8, 10 and 12.

- Air sampling – For a few patients we would like to conduct some air sampling in the room in which they spend most time. This involves running 2 small machines that suck in air and collect air particles. We want to see if we can find influenza virus in these particles. The machines will stand in a room and run for a maximum of 3 hours. They do produce a little bit of noise. This will be done every other day during the study. A member of the research team will be present to set the machine up and collect it afterwards.

Each of the visits will last for up to one hour except when air sampling is performed (see above) which will take longer. The researcher may set up the air sampling equipment, leave it running and then return before if finishes.

If your child has been recruited in hospital and is later sent home, we would wish to follow them up at home for the remainder of their study period. Similarly, if your child has been recruited in the community and needs to be admitted to hospital we would follow them up in hospital.

This study will not interfere with the normal medical care your child may receive. This includes the use of any medicines, e.g. antivirals

If for any reason your child loses the capacity to consent / assent during the study (e.g. the remote possibility that they are admitted to hospital and need to be sedated to help with breathing) we have included a box in the consent form to tick if you and your child are happy for us to continue with our sampling during this period.

Initially your child's diagnosis of swine flu is likely to have been made on clinical grounds, i.e. the symptoms that they have. Some people may have a test to confirm this diagnosis (this will be different from the test we might have done initially on the nose swab). If swine flu is confirmed your child will remain in the study but should this test come back as negative we will not perform any further sampling on or around your child and they will be excluded from the study.

What are the possible benefits of taking part?
There is no specific treatment benefit as we will not influence your child's normal care. The work as a whole is seeking to provide information on swine flu infection that could improve the way we deal with it, particularly from an infection control point of view and the public will benefit from this.

You may gain some reassurance from the fact that a member of the research team will be visiting each day. However, as stated above they would not interfere directly with normal medical care. Of course, should there be any concerns they will raise them with you or your family so that you can contact your GP or other responsible medical professional.

Contact details
If you have any problems, concerns or other questions about this trial, you should contact the research member of staff who visits each day. If you have any complaints about the way the research staff are carrying out the study you can make a complaint to the study Chief Investigator, Professor Jonathan Van-Tam, Clinical Sciences Building, City Hopstial, Hucknall Road, Nottingham, NG5 1PB. Tel 0115 823 0276.

What will happen if I don't want to carry on with the trial?
You and your child can withdraw from the study at any time but it would be best to stay in contact with us and keep to the study assessments if possible. We will ask for your reasons for withdrawing, as they might be important for other families. You don't have to give any reasons if you don't want to.

What if there is a problem?
In the event that something goes wrong and your child is harmed during the trial The University of Nottingham carries insurance to make sure that if any participant incurs any unexpected adverse event that leads to their being harmed and that the event occurred as a consequence of the protocol (i.e. non-negligent harm), then the participant will be compensated. In addition, all research staff have their own professional indemnity insurance which will cover any unexpected adverse event that leads to participant harm caused by negligence.

This study will be conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines (directive CPMP/ICH/135/95), local regulatory requirements and the declaration of Helsinki, and all relevant local laws and regulations.

Will my child's taking part in this trial be kept confidential?
When your child enters the trial the researcher will record information about your child's illness, medical history and the subsequent course of the illness. Some of this information may be taken from their medical notes (if they are in hospital). Collection and analysis of this information is an important part of the research. Your contact details will also be recorded but will be kept separate from the study data on a secure database.

The results of the trial will be published in medical journals and sent to regulatory authorities. However, all identifying personal details will be kept strictly confidential and no information will be published or given out through which you or your child could be identified.

What will happen to the results of the trial?
Any results will be presented to the Department of Health in the first instance. Subsequently, results may be presented at scientific medical meetings and published in leading medical journals and possibly in national and local media too. You or your child will not be individually identified in any report or publication.

Who is organising and funding the research?
The University of Nottingham is organising this study. The NHS Health Technology Assessment (HTA) Programme has provided the research grant and no member of the research team are being directly paid for including you in this study.

Who has reviewed the study?
The trial was peer reviewed before funding by the HTA. This study was given a favourable ethical opinion for conduct in the public-health sector by the Leicester 1Research Ethics Committee, and was approved by the local NHS Trust Research & Development departments.

You will be given a copy of this Parent / Guardian Information Sheet and a copy of the signed Consent Form to keep.

THANK YOU FOR TAKING THE TIME TO READ THIS INFORMATION SHEET

Children 0–8 years

Child Information Sheet (0-8 year olds)

A Study To Find Out How Much Flu Is Around You

Your invitation:
Can you help us do this study?

Talk about it with your family, friends, doctor or nurse.

And ask us lots of questions!

Why have I been asked to help?
Because you are unwell with flu. 50 children aged 0 to 16 years will be helping.

Do I have to take part?
No! It's up to you. If you do help, you can change your mind later. This won't upset anyone.

What will happen to me?
We would like to take a sample from your nose using a cotton bud and we will take some samples from objects and even the air around you. When we take samples from your nose it won't hurt.

We will visit you every day, for about 10 days. You may be in hospital or at home, we will follow you wherever you go!

You will be visited by a member of our team, usually a nurse. They will make appointments to see you and your parents.

Will joining in help me?
It won't help to make you better faster but the information we get might help us prevent other people from catching flu.

What if something goes wrong?
Any trouble you or your parents have will be looked into. Details about this are in the Parent / Guardian Information Sheet.

Will my medical details be kept private? Will anyone else know?
Yes. Some people (called research inspectors) may see your medical notes to make sure the study is done properly.

What if I don't want to do the trial any more?
You and your parents can pull out of the trial treatment at any time.

You will have a copy of this Information Sheet to keep.

THANKS FOR READING THIS – please ask us anything you want.

Contact details:
If you have any worries or questions, please tell your parents. You can also contact;

Study Doctor: Prof Jonathan Van-Tam - 0115 823 0276

Children 9–15 years

Young Person Information Sheet (9-15 year olds)

A Study To Find Out How Much Flu Is Around You

What is research?
Research helps us to improve how much we know about things. This study is research to find out how much flu people carry around with them when they are ill.

Your invitation:
Would you like to be in this trial?

Before you decide, read this leaflet carefully. Talk about it with your family, friends, doctor or nurse.

Ask us if there is anything that's not clear or if you want to know more.

Why have I been asked to help?
Because you are unwell with flu. 50 children aged 0 to 16 years will be helping.

Do I have to take part?
No! It's up to you. If you do help, you can still pull out at any time. If you do decide to stop this won't upset anyone.

If you do pull out, we will ask you why, as it might be important for other young people. You don't have to give a reason if you don't want to.

What will happen to me?
We would like to take a sample from your nose using a cotton bud and we will take some samples from objects and even the air around you. When we take samples from your nose it won't hurt.

We will also ask you to answer some questions about how you are feeling each day and we will take your temperature.

We will visit you every day, for about 10 days. You may be in hospital or at home, we will follow you wherever you go!

You will be visited by a member of our team, usually a nurse. They will make appointments to see you and your parents.

Might anything else about the research upset me?
We don't think so!

Will joining in help me?
It won't help to make you better faster but the information we get might help us prevent other people from catching flu.

What happens when the trial stops?
Nothing! You should be feeling better and we have the samples we need.

What if something goes wrong?
Any trouble you or your parents have will be looked into. Details about this are in the Parent / Guardian Information Sheet.

Will my medical details be kept private? Will anyone else know?
Yes. Some people (called research inspectors) may see your medical notes to make sure the study is done properly.

What if I don't want to do the trial any more?
You and your parents can pull out of the trial treatment at any time.

You will have a copy of this Information Sheet to keep.

THANKS FOR READING THIS – please ask us anything you want.

Contact details:
If you have any worries or questions, please tell your parents.

You can also contact;
Study Doctor:
Prof Jonathan Van-Tam
0115 823 0276

Appendix 4
Eligibility checklist

Eligibility checklist

VIRUS SHEDDING STUDY

ELIGIBILITY CRITERIA

DATE: ____ /____ / 2009 Participant Code = ☐☐☐☐

	Yes / Positive	No / Negative
Consent		
Symptoms;		
Fever		
Cough		
Sore throat		
Headache		
Fatigue		
Runny nose		
• Fever + 1 other or • 2 of the above		
Symptoms for <48 hrs (Community)		
Symptoms for < 96 hrs (Hospital)		
Near Patient Test for influenza done?		
• If Yes, positive or negative?		
Specific test for swine flu		
• If Yes, positive or negative?		
Any other household member with symptoms?		
Taken part in other influenza research testing medicinal products in last 3 months?		

If only Green Boxes ticked = Eligible

Any Red boxes ticked = Not Eligible

Appendix 5

Recruitment leaflet

Swine Flu Research:

The University of Nottingham

If you or any of your family have flu we need your help!

Should you or other members of your family / household become unwell with symptoms such as cough, fever, sore throat, tiredness and runny nose over the next few weeks, we would like to invite you to take part in some medical research being run by the University of Nottingham.

The Department of Health has provided funding for this vital research. The study involves a nurse or doctor visiting daily to collect a nose swab and swabs from some surfaces in your home. Your help is really important to us. We hope to improve our understanding of how swine flu is spread which may lead to fewer people becoming infected.

So, if you or any family or household member develops flu-like symptoms and you/they feel able to take part in our study, please ring us and speak to one of our team. We are looking for people who have had symptoms for no more than 2 days so please call as soon as you think you are unwell. It does not matter whether medication is being taken or not.

Keep this card and call **0115 823 1813** anytime

Appendix 6

PCR protocol and culture protocol

PCR protocol

PCR

Nucleic acid was extracted from the samples using the Qiagen Symphony SP extractor mini kits, including onboard lysis and a bacteriophage (MS2) as internal control. A novel influenza A H1N1 pentaplex assay was devised to detect virus genome in the samples. The assay was designed to detect novel H1N1 influenza A, seasonal H1 influenza A, seasonal H3 influenza A, influenza B and the internal control, MS2. Reactions were carried out on a Rotorgene™ 6000 (Corbett Research) real-time DNA detection system. Viral load data were generated using the PCR assay and plasmids containing the gene target to create a standard curve, such that the concentration of genome present in each sample could be calculated.

The primers and probes used were as shown below.

Primers

Novel H1N1 influenza A (Metabion):

- H1FORSW: 5′–TCA ACA GAC ACT GTA GAC ACA GTA CT–3′
- H1REVSW: 5′–GTT TCC CGT TAT GCT TGT CTT CTA G–3′

Seasonal H1 influenza A (MWG Biotech):

- AH1 Forward: 5′–GGA ATA GCC CCC CTA CAA TTG–3′
- AH1 Reverse: 5′–AAT TCG CAT TCT GGG TTT CCT A–3′

Seasonal H3 influenza A (MWG Biotech):

- AH3 Forward: 5′–CCT TTT TGT TGA ACG CAG CAA–3′
- AH3 Reverse: 5′–CGG ATG AGG CAA CTA GTG ACC TA–3′

Influenza B (Metabion):

- BNP-F: 5′–GCA GCT CTG ATG TCC ATC AAG CT–3′
- BNP-R: 5′–CAG CTT GCT TGC TTA RAG CAA TAG GTC T–3′

MS2 control (MWG Biotech):

- MS2 Forward: 5′–TGG CAC TAC CCC TCT CCG TAT TCA CG –3′
- MS2 Reverse: 5′–GTA CGG GCG ACC CCA CGA TGT=A C–3′

Probes

Novel H1N1 influenza A (Metabion):

- H1SWp3: 5′–Cy5-AAT GTA ACA GTA ACA CAC T CTG TTA ACC BHQ-3

Seasonal H1 influenza A (ABI):

- AH1 Probe: 5′–6FAM CGT TGC CGG ATG GA-MGBNFQ–3′

Seasonal H3 influenza A (ABI):

- AH3 Probe: 5′–VIC-CCT ACA GCA ACT GTT ACC-MGBNFQ–3′

Influenza B (Biosearch Technologies):

- Flu-B Probe: 5′–Quasar 705-CCA GAT CTG GTC ATT GGR GCC CAR AAC TG-BHQ-2–3′

MS2 control (Metabion):

- MS2 Probe: 5′–ROX-CAC ATC GAT AGA TCA AGG TGC CTA CAA GC-BHQ-2–3′

Culture protocol

Cultures were performed from the last day of nasal swab PCR positivity. If a culture was positive on any given day then an assumption was made that previous days would also have been culture positive.

Technique

Pandemic H1N1 did not form plaques readily and gave only a weak cytopathic effect, the latter meaning that the tissue culture infectious dose (TCID) 50 was difficult to calculate. Consequently, immunofluorescence to detect the influenza A nucleoprotein was used to demonstrate the

RT-PCR protocol

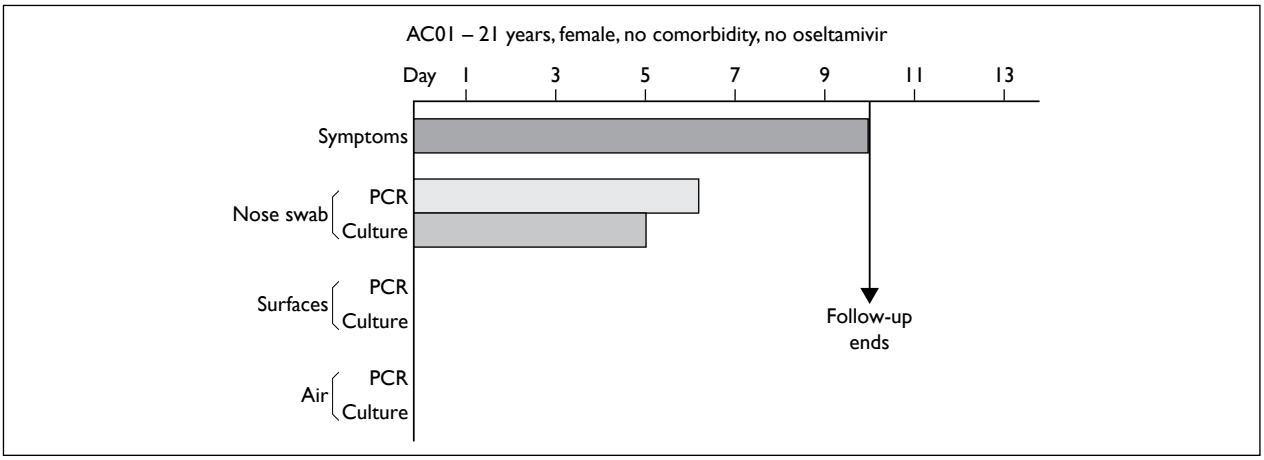
Stock concentration (pmol/µl)	Volume of stock/ reaction (µl)	For 80 reactions (µl)
HIFORSW (20)	0.5	40
HIREVSW (20)	0.5	40
AH1 Forward (50)	0.45	36
AH1 Reverse (50)	0.45	36
AH3 Forward (50)	0.45	36
AH3 Reverse (50)	0.45	36
BNP-F (20)	0.25	20
BNP-R (20)	0.25	20
MS2 Forward (20)	0.1	8
MS2 Reverse (20)	0.1	8
H1SWp3 (10)	0.2	16
AH1 Probe (10)	0.1	8
AH3 Probe (10)	0.1	8
Flu-B Probe (10)	0.2	16
MS2 Probe (10)	0.2	16
2 RT platinum buffer (Invitrogen)	12.5	1000
Superscript III platinum enzyme	0.5	40
Water	2.7	216
Total volume	*20*	*1600*

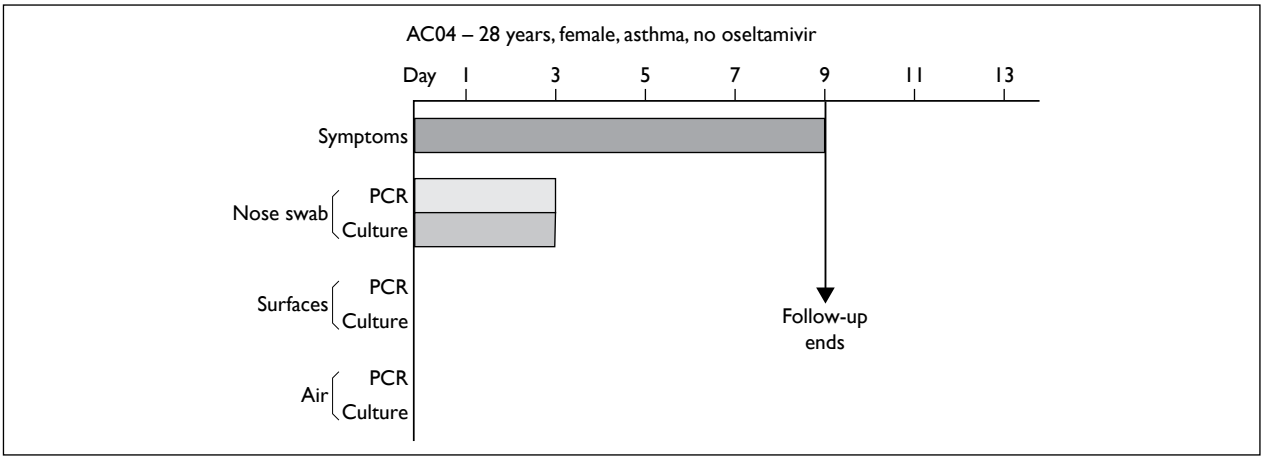
presence of live replicating virus in the nuclei of infected cells.

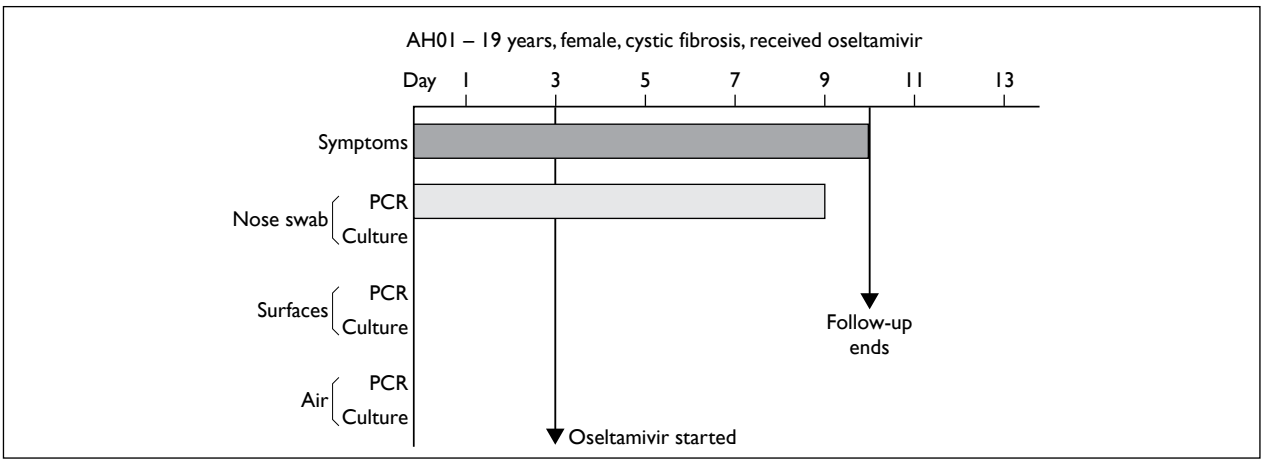
Madin–Darby Canine Kidney (MDCK) cells were used to propagate the virus. Initially, cells were plated on to six-well tissue culture dishes (Corning), at a concentration of 7.5×10^5/well. Following 24 hours' incubation, the samples were defrosted. The cells were washed ×2 in serum-free medium [SFM – Dulbecco's Modified Eagle's Medium (DMEM)] and 400 µl of each sample was applied to the respective well. After 30 minutes the cells were overlaid with 2 ml of SFM containing 0.14% fetal calf serum (FCS) and 0.1% Worthington's trypsin. Dilutions (1 : 10) of influenza A (H1N1 human influenza virus A/PuertoRico/8/34) and a novel H1N1 influenza A isolate (A H1N1 Cambridge AHO4/2009) were also inoculated on to cells as positive controls. The cells were then incubated for 48 hours at 37°C. The following day, 24-well tissue culture dishes were seeded with 1×10^5 MDCK cells per well. Then, 48 hours after infection the virus was harvested. Two dilutions were made in SFM: 1 : 2 and 1 : 10. After washing the cells in the 24-well dishes ×2 in SFM, 250 µl of each dilution was added to the appropriate well. Following 30 minutes' incubation at 37°C, 1 ml of overlay (as before) was added to each well and the cells were incubated overnight. After overnight incubation, the virus dilutions were aspirated off the cells. The cells were washed ×2 with phosphate-buffered saline (PBS) and then fixed with 250 µl of 4% formaldehyde at room temperature for 20 minutes. The fix was aspirated off and the cells were washed ×3 with blocking solution (1% FCS in PBS). The cells were permeabilised in detergent (0.2% Triton 100 in PBS) and then washed ×2 in block. Then 250 µl of a mouse monoclonal antibody (anti-NP, Abcam, ab43821) was added to each well and the plates were incubated for 60 minutes before washing ×3 with block. The secondary antibody (goat anti-mouse 488 IgG2a, Molecular Probes) was diluted 1 : 1000 in block, and 4′,6 diamino-2-phenylindole (DAPI) diluted 1 : 2000. Then 250 µl of this mix was added to the cells. Incubation was in the dark for 30–45 minutes. Cells were washed thoroughly with block, left in PBS and examined on the fluorescence microscope.

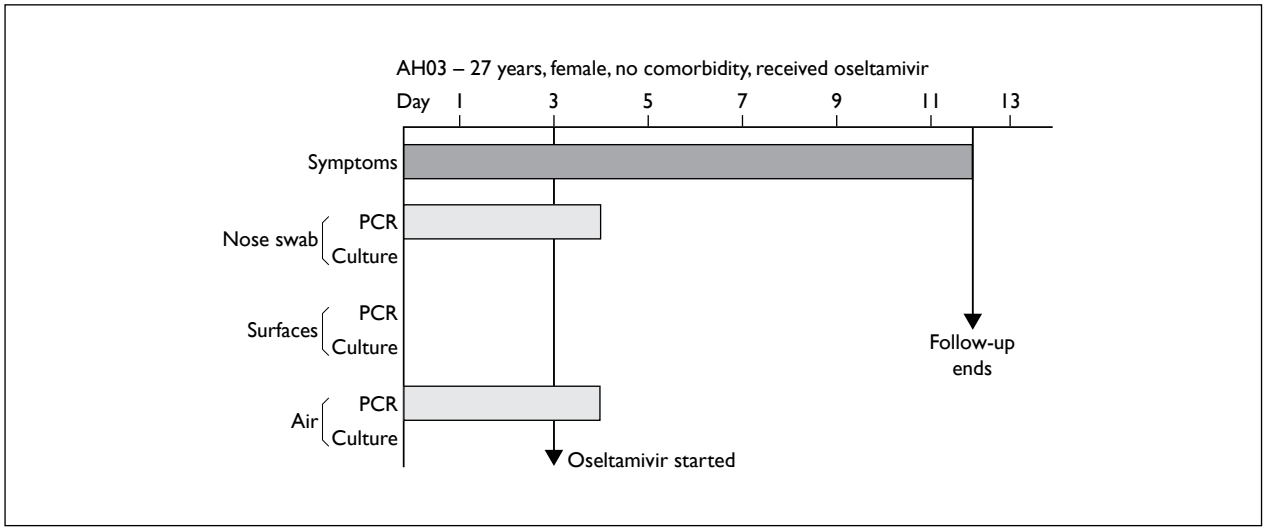
Appendix 7

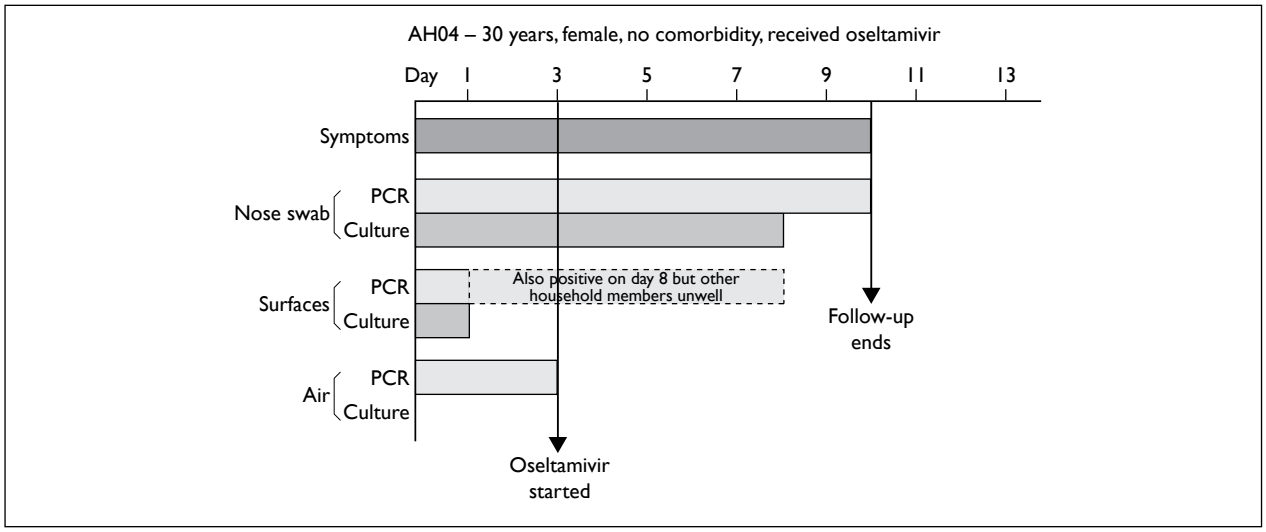
Composite subject charts

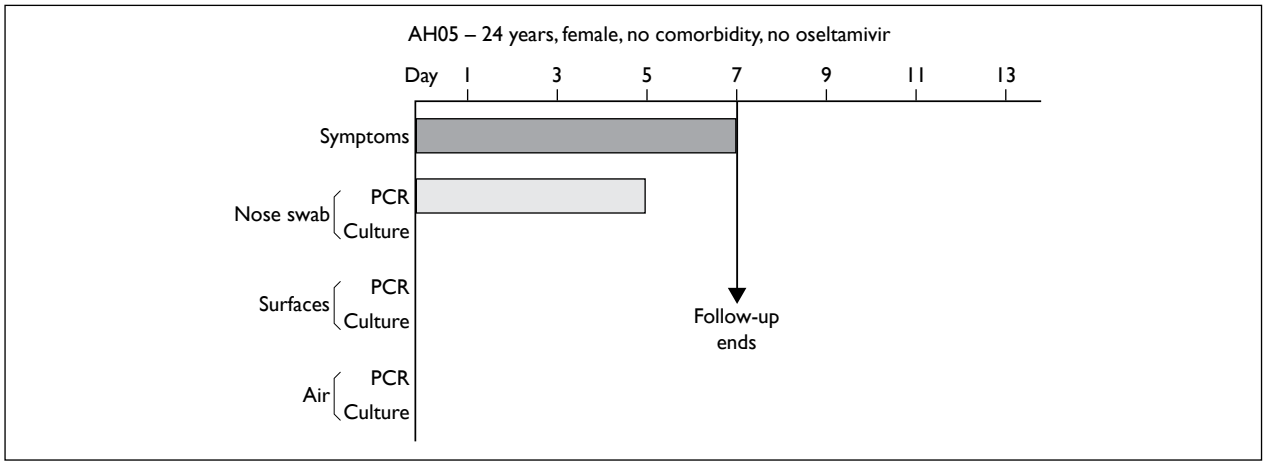

AC01 – 21 years, female, no comorbidity, no oseltamivir
Day 1 3 5 7 9 11 13
Symptoms
Nose swab PCR Culture
Surfaces PCR Culture
Air PCR Culture
Follow-up ends

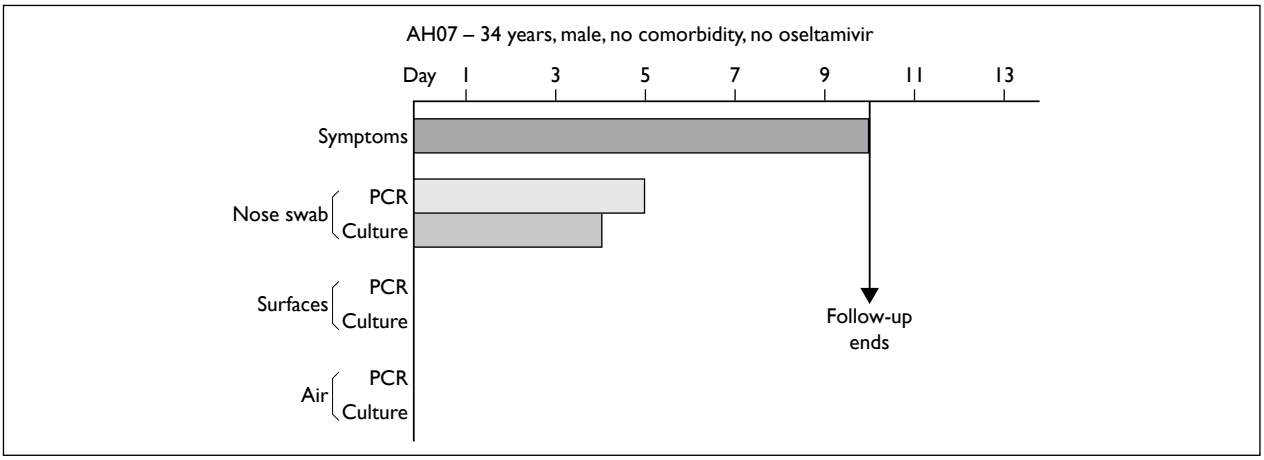

AC04 – 28 years, female, asthma, no oseltamivir
Day 1 3 5 7 9 11 13
Symptoms
Nose swab PCR Culture
Surfaces PCR Culture
Air PCR Culture
Follow-up ends

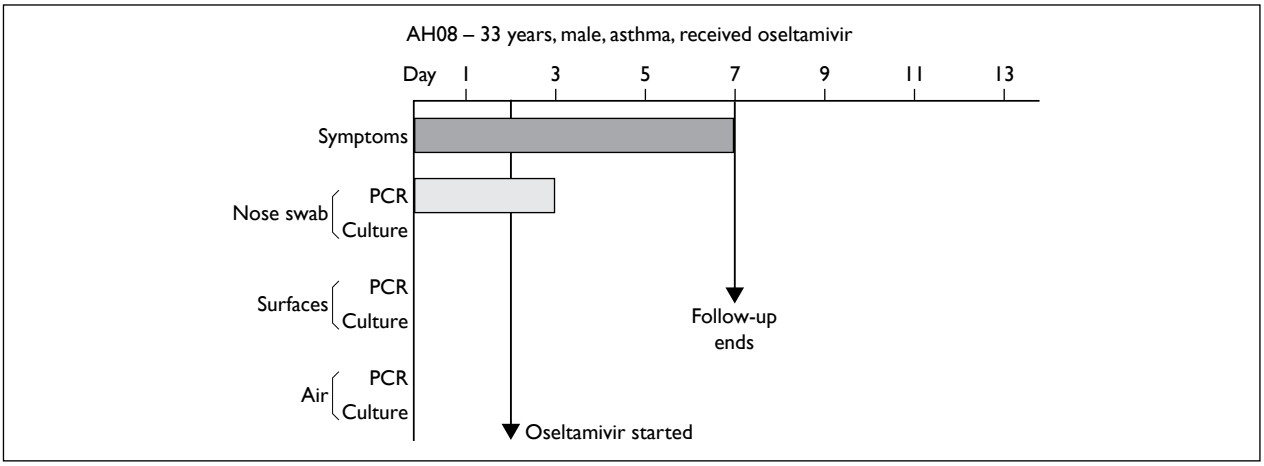

AH01 – 19 years, female, cystic fibrosis, received oseltamivir
Day 1 3 5 7 9 11 13
Symptoms
Nose swab PCR Culture
Surfaces PCR Culture
Air PCR Culture
Follow-up ends
Oseltamivir started

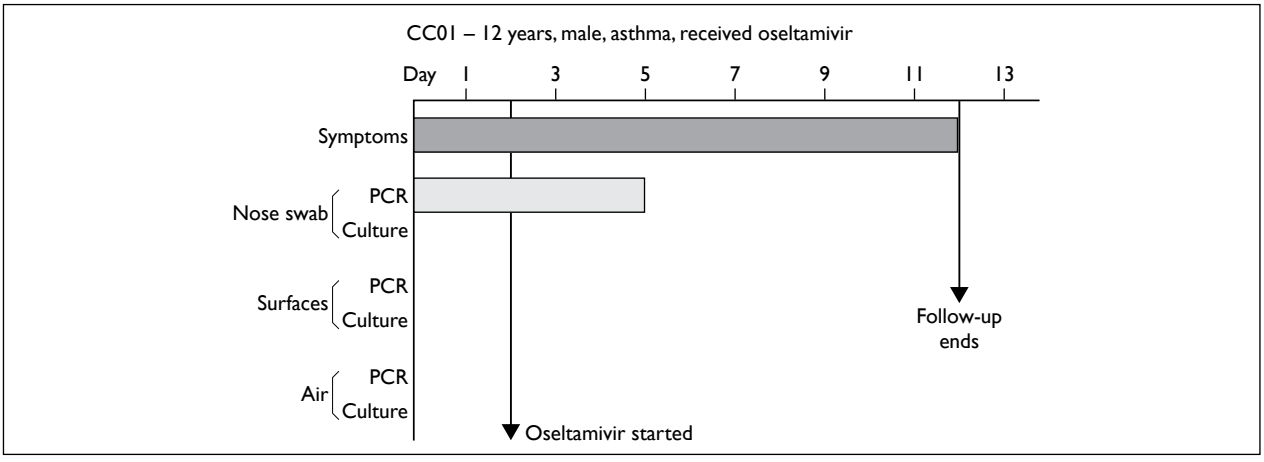


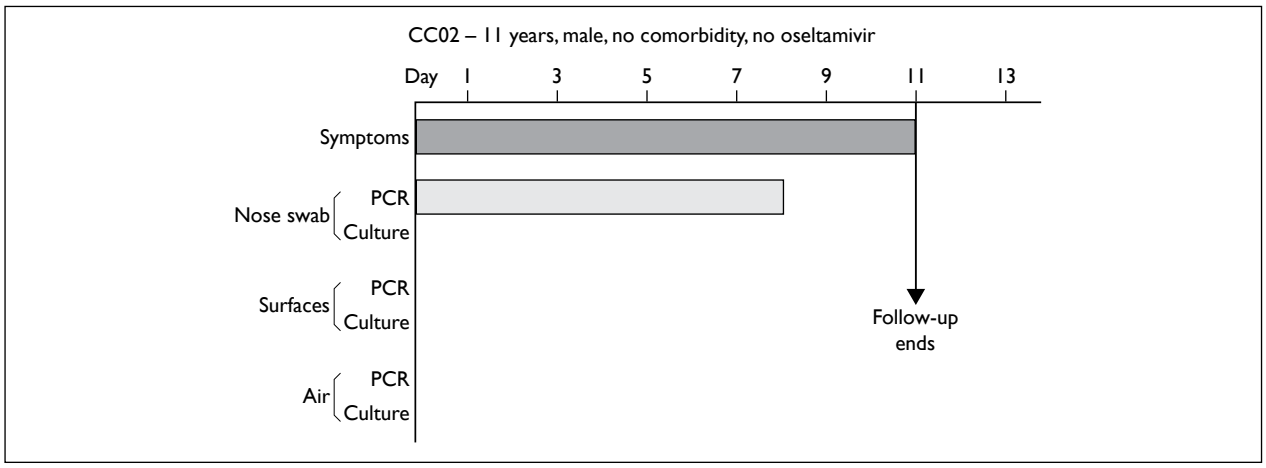


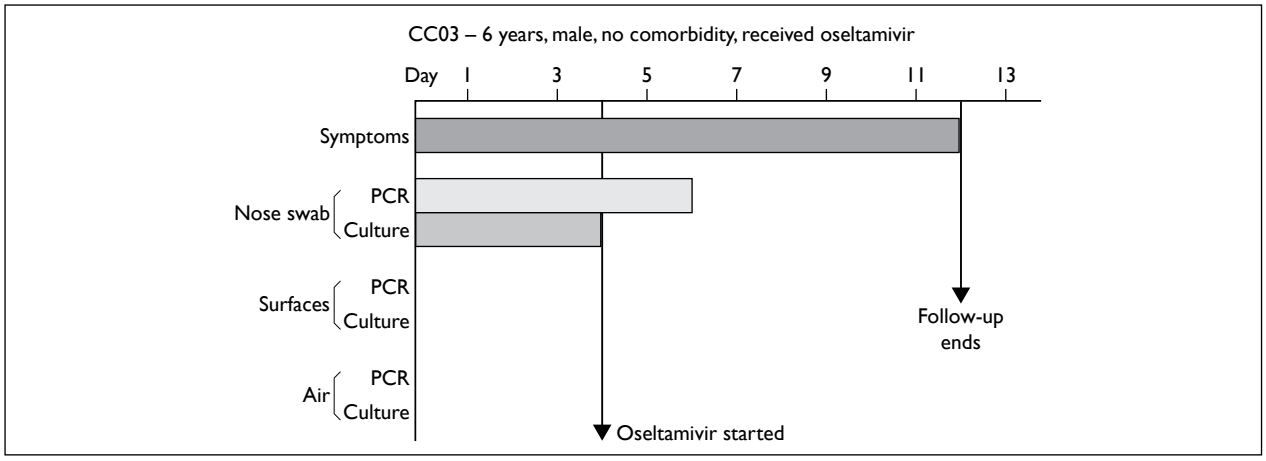


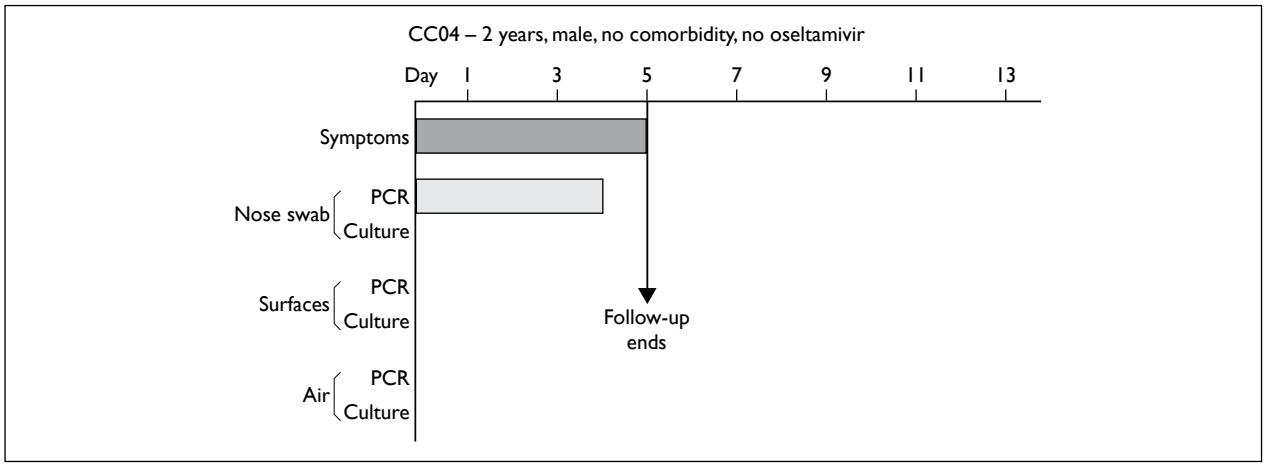

AH07 – 34 years, male, no comorbidity, no oseltamivir
Day 1 3 5 7 9 11 13
Symptoms
Nose swab
PCR
Culture
Surfaces
PCR
Culture
Air
PCR
Culture
Follow-up ends

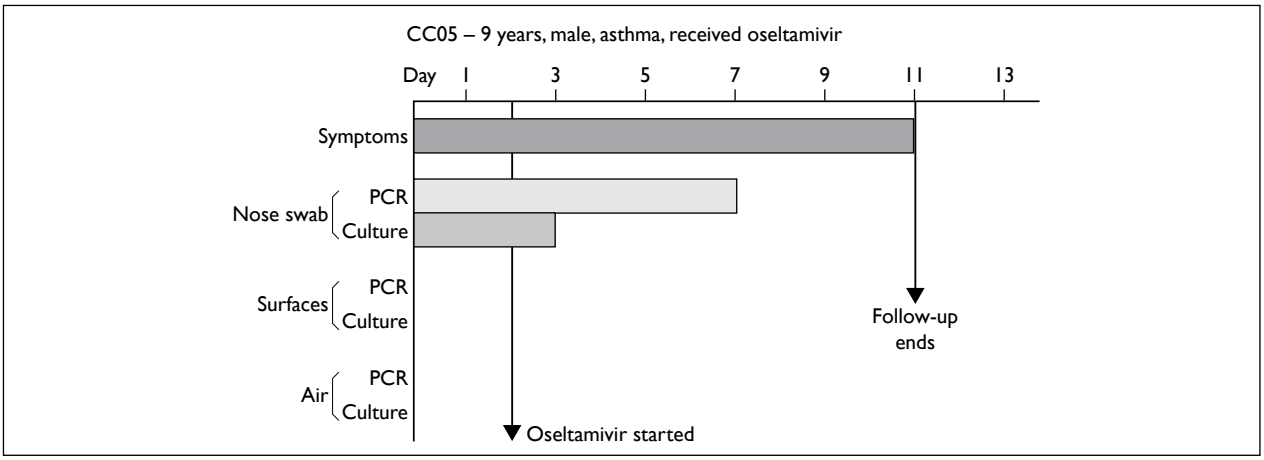

AH08 – 33 years, male, asthma, received oseltamivir
Day 1 3 5 7 9 11 13
Symptoms
Nose swab
PCR
Culture
Surfaces
PCR
Culture
Air
PCR
Culture
Follow-up ends
Oseltamivir started

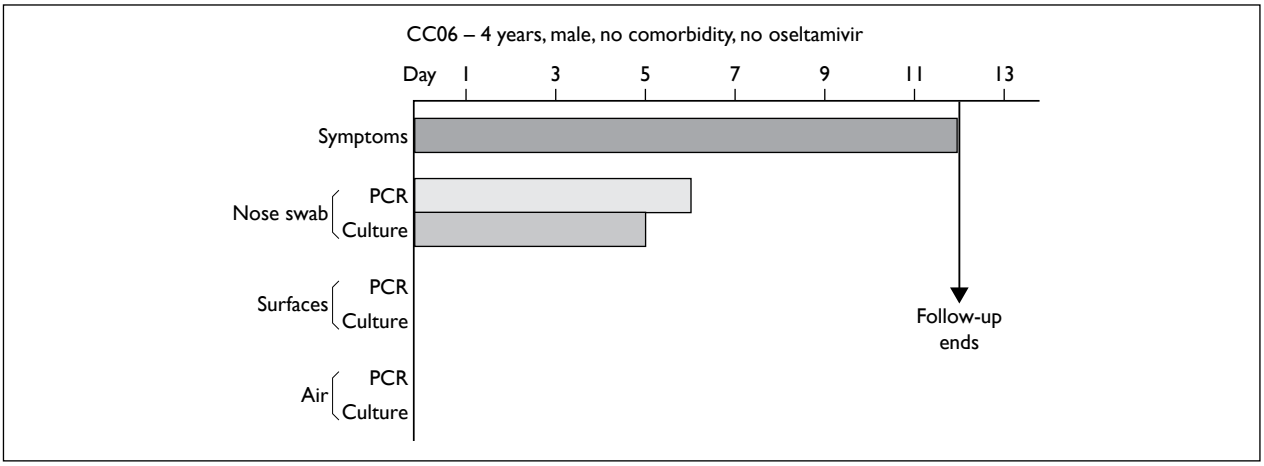

CC01 – 12 years, male, asthma, received oseltamivir
Day 1 3 5 7 9 11 13
Symptoms
Nose swab
PCR
Culture
Surfaces
PCR
Culture
Air
PCR
Culture
Follow-up ends
Oseltamivir started

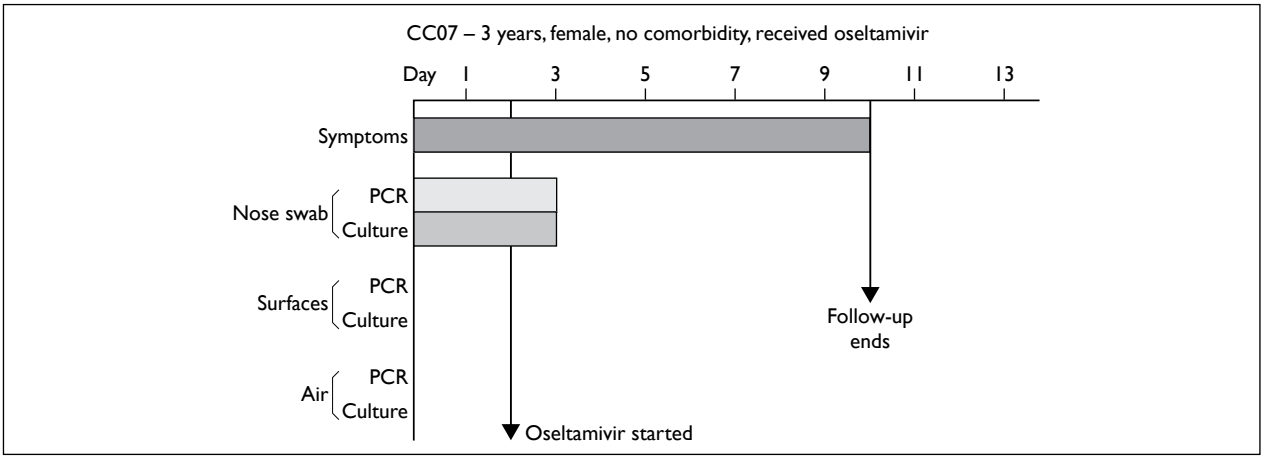


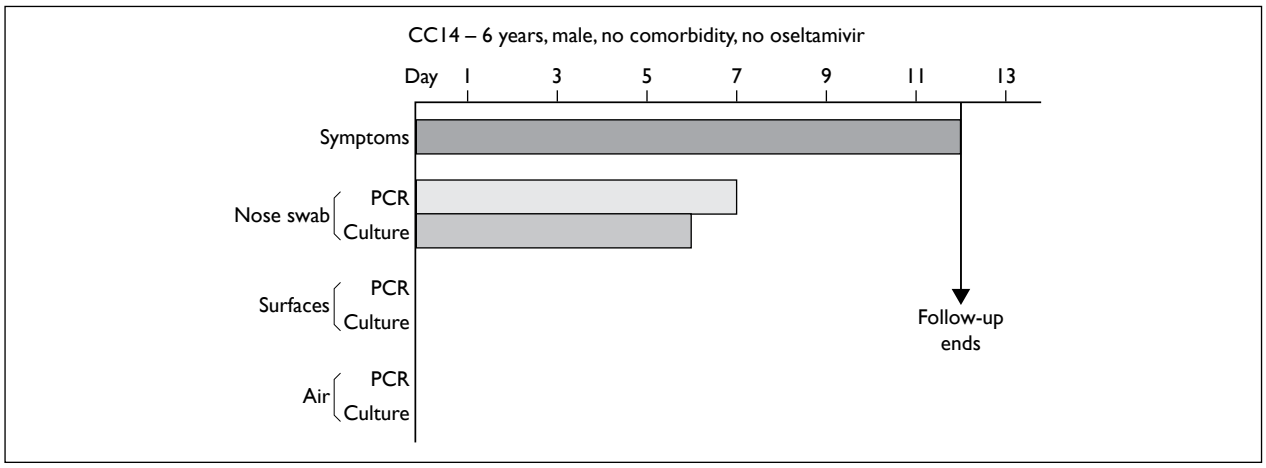


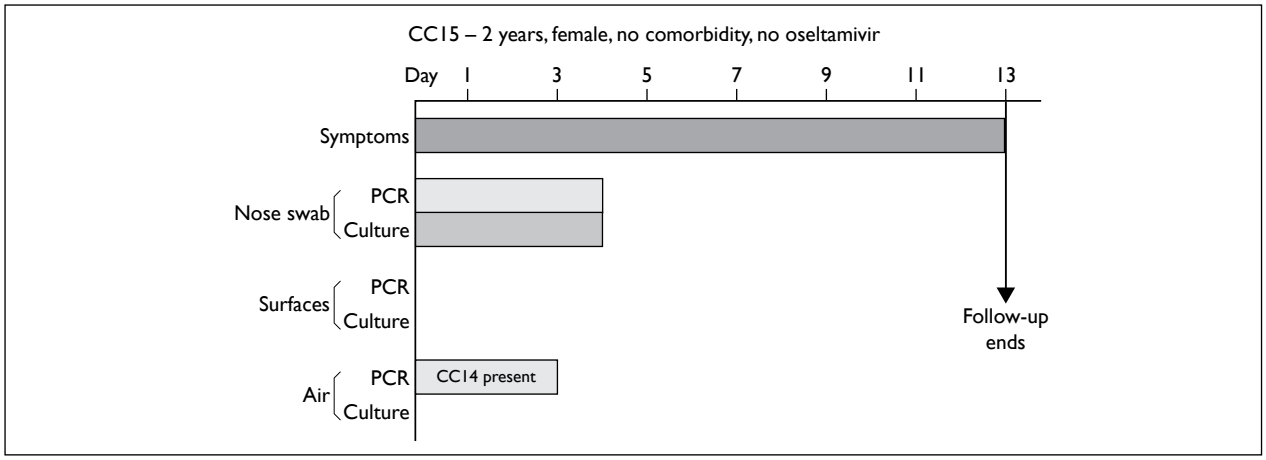


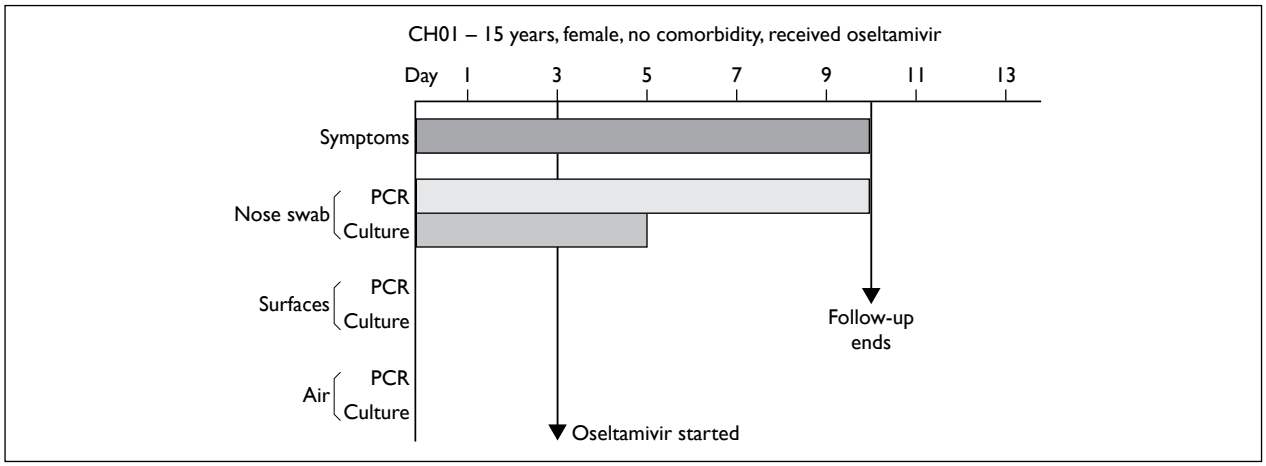

CC05 – 9 years, male, asthma, received oseltamivir
Day 1 3 5 7 9 11 13
Symptoms
Nose swab PCR
Culture
Surfaces PCR
Culture
Air PCR
Culture
Follow-up ends
Oseltamivir started

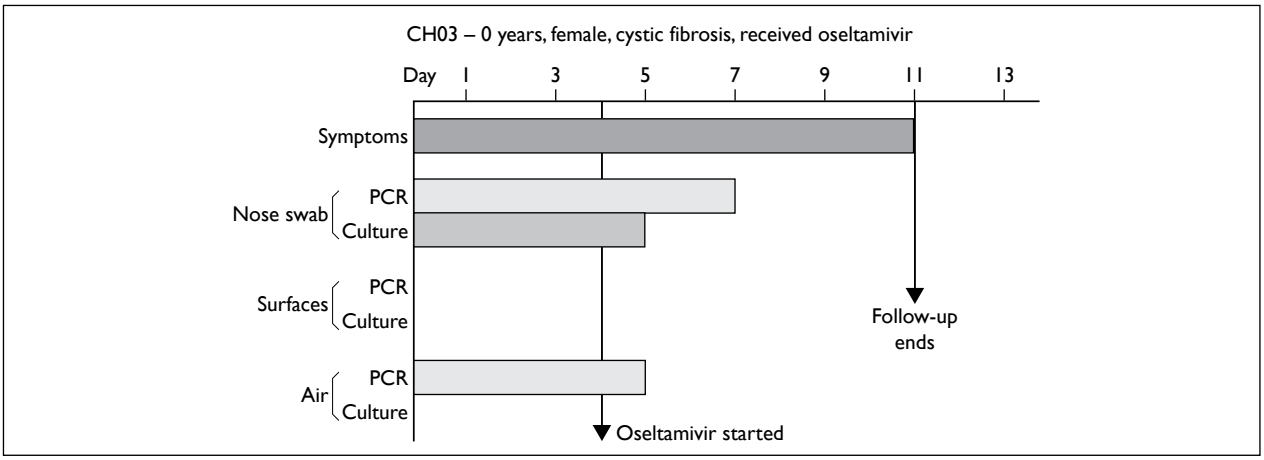

CC06 – 4 years, male, no comorbidity, no oseltamivir
Day 1 3 5 7 9 11 13
Symptoms
Nose swab PCR
Culture
Surfaces PCR
Culture
Air PCR
Culture
Follow-up ends


CC07 – 3 years, female, no comorbidity, received oseltamivir
Day 1 3 5 7 9 11 13
Symptoms
Nose swab PCR
Culture
Surfaces PCR
Culture
Air PCR
Culture
Follow-up ends
Oseltamivir started








CH03 – 0 years, female, cystic fibrosis, received oseltamivir
Day 1 3 5 7 9 11 13
Symptoms
Nose swab
PCR
Culture
Surfaces
PCR
Culture
Air
PCR
Culture
Follow-up ends
Oseltamivir started

Neuraminidase inhibitors for preventing and treating influenza in healthy adults: a Cochrane review

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Abstract

Neuraminidase inhibitors for preventing and treating influenza in healthy adults: a Cochrane review

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Background: Neuraminidase inhibitors (NI) are recommended for use against influenza and its complications in inter-pandemic years and during pandemics.
Objectives: To assess the effects of NIs in preventing and treating influenza, its transmission, and its complications in otherwise healthy adults, and to estimate the frequency of adverse effects.
Search strategy: We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2009, issue 3) which contains the Acute Respiratory Infections Group's Specialised Register, MEDLINE (1950 to August 2009) and EMBASE (1980 to August 2009).
Selection criteria: Randomised controlled trials (RCTs) or quasi-randomised placebo-controlled trials of NIs in healthy adults exposed to naturally occurring influenza.
Data collection and analysis: Two review authors independently applied inclusion criteria, assessed trial quality, and extracted data. We structured the comparisons into prophylaxis, treatment, and adverse events, with further subdivision by outcome and dose.
Main results: We identified four prophylaxis, 12 treatment and four post-exposure prophylaxis trials. In prophylaxis compared to placebo, NIs had no effect against influenza-like illnesses (ILI) (risk ratio (RR) ranging from 1.28 for oral oseltamivir 75 mg daily to 0.76 for inhaled zanamivir 10 mg daily). The efficacy of oral oseltamivir against symptomatic influenza was 76% (at 75 mg daily), and 73% (at 150 mg daily). Inhaled zanamivir 10 mg daily performed similarly. Neither NI had a significant effect on asymptomatic influenza. Oseltamivir induced nausea (odds ratio (OR) 1.79, 95% CI 1.10 to 2.93). Oseltamivir for post-exposure prophylaxis had an efficacy of 58% and 84% in two trials for households. Zanamivir performed similarly. The hazard ratios for time to alleviation of symptoms were in favour of the treated group 1.20 (1.06 to 1.35) for oseltamivir and 1.24 (1.13 to 1.36) for zanamivir. Because of the exclusion of a review of mainly unpublished trials of oseltamivir, insufficient evidence remained to reach a conclusion on the prevention of complications requiring antibiotics in influenza cases (RR 0.57, 95% CI 0.23 to 1.37). Analysis of the US FDA and Japan's PMDA regulators' pharmacovigilance dataset, revealed incomplete reporting and description of harms preventing us from reaching firm conclusions on the central nervous system toxicity of neuraminidase inhibitors.
Authors' conclusions: Numerous inconsistencies detected in the available evidence, followed by an inability to adequately access the data, has undermined confidence in our previous conclusions for oseltamivir. Independent RCTs to resolve these uncertainties are needed.

Contents

Plain language summary

Influenza is an acute infection of the airways and the whole body, caused by a virus

Influenza symptoms include fever, headache and cough. Serious complications such as pneumonia can also occur. This review of trials found that neuraminidase inhibitors (Nls) such as zanamivir (*Relenza*) and oseltamivir (*Tamiflu*) are effective in preventing ('prophylaxis') and treating the symptoms of influenza. They do not prevent infection or stop influenza viruses leaving the nose. Because the review authors could not verify the content of a Roche-sponsored review of 10 randomised trials (eight of which were unpublished), it was excluded. This changes the conclusions as there now is insufficient evidence to say whether NIs prevent complications such as pneumonia. Oseltamivir causes nausea, vomiting and retching while zanamivir causes diarrhoea but the full picture on the drugs' toxicity cannot be reconstructed as the regulators' data are incomplete and too generic. There is no randomised controlled trial evidence to tell us whether NIs are or are not effective against pandemic influenza. Trials are urgently needed to test whether NIs are more effective than symptomatic treatment and hygiene and barrier measures to interrupt influenza transmission in healthy adults.

Background

Description of the condition

Influenza is an acute, usually benign and self-limiting infection of the upper airways and at times affects the whole body.

Description of the intervention

In recent years a new generation of antiviral compounds has been developed. These compounds, known collectively as neuraminidase inhibitors (NIs) are nebulised zanamivir (*Relenza,* (formerly known as GG167) developed by GlaxoWellcome PLC (UK) and oral oseltamivir (*Tamiflu,* formerly known as RO 64-0796 or GS 4104) co-developed by Gilead Sciences Inc (Foster City, CA,USA) and Hoffman La Roche Ltd (Basel, Switzerland). Other NIs are still under development for parenteral or long acting use (Hayden 2009).

How the intervention might work

NIs act by inhibiting the release of virions from the infected cell, neuraminidase being essential for both viral entry and exit from the target cell. The World Health Organization (WHO) encouraged member countries to use antivirals in influenza "inter-pandemic periods". The rationale given is as follows: "wide scale use of antivirals and vaccines during a pandemic will depend on familiarity with their effective application during the inter-pandemic period. The increasing use of these modalities will expand capacity and mitigate the morbidity and mortality of annual influenza epidemics. Studies conducted during the inter-pandemic period can refine the strategies for use during a pandemic" (WHO 2005). The European Medicines Agency (EMEA) took a different line, identifying NIs (especially oseltamivir) as compounds with a complementary effect to vaccines to be used in an influenza pandemic (EMEA 2005) for treatment of index cases and influenza prophylaxis in key personnel (police, fire brigade, healthcare workers).

Why it is important to do this review

The use of NIs has increased dramatically with the spread of the A/H1N1 pandemic beginning in April 2009, a novel and potentially serious infection. Partly because of the rise in amantadine/rimantadine resistance coupled with the lack of an effective vaccine, NIs became a widespread public health intervention. Their use for early containment and interruption was also recommended in many pandemic plans, and the WHO had previously encouraged member countries to gain experience with them.

Although several systematic reviews of the effects of NIs are available, none are up-to-date or evaluate the potential role of NIs in an influenza pandemic, where high viral load and high transmission appear to be the norm; nor do they systematically investigate the potential harms of NIs (Burch 2009; Burls 2002; Cooper 2003; Jefferson 2000; Tappenden 2009; Turner 2003). In this context, trade-off between dosage and adverse event profile in prophylaxis, activity against influenza infection regardless of symptoms (symptomatic and asymptomatic influenza) and viral excretion through body fluids become important (Ward 2005).

In addition, our previous Cochrane review updates (Jefferson 2006; Jefferson 2009c) summary of the evidence on the effects of oseltamivir on lower respiratory tract complications was challenged by Hayashi through the public Cochrane reviews feedback mechanism (Feedback 1). In updating our review, we addressed these additional issues.

Objectives

1. To assess the efficacy and effectiveness of NIs in preventing cases and complications of influenza (prophylaxis) in healthy adults.
2. To assess the efficacy and effectiveness of NIs in shortening or reducing the impact and complications of influenza (treatment) in healthy adults.
3. To assess the effectiveness of NIs in interrupting the spread of influenza virus.
4. To estimate the frequency of adverse effects associated with NI administration in healthy adults.

Methods

Criteria for considering studies for this review

Types of studies

Any RCT or quasi-RCT comparing oral oseltamivir and/or zanamivir in humans with placebo, control antivirals or no intervention or comparing doses or schedules of oseltamivir and/or zanamivir. Studies assessing prophylaxis or treatment from exposure to naturally occurring influenza only were considered.

Types of participants

Individuals with no known pre-existing chronic pathology known to aggravate the course of influenza. In keeping with our objective of reviewing evidence on healthy adults, we only considered studies in which no less than 75% of the subjects were aged 14 to 60 to exclude older subjects who are at higher risk of complications.

Types of interventions

Oseltamivir and/or zanamivir as prophylaxis and/or treatment for influenza (efficacy) or for influenza-like illness (ILI/effectiveness).

Types of outcome measures

Primary outcomes

1. Mortality.
2. Hospitalisation and complications.
3. Harms.
4. Drug resistance.

Secondary outcomes

1. Symptom relief.
2. Viral excretion.
3. Interruption of transmission.

Search methods for identification of studies

Electronic searches

For this 2009 update we ran update searches for effectiveness studies and conducted a separate search for adverse effects studies. In previous versions of this review no specific searches for adverse effects were undertaken. We relied instead on information gathered from the RCTs and quasi-RCTs identified in the effectiveness searches. Growing concerns about harms caused us to broaden our approach for this update. We conducted separate, specific adverse effects searches based on the work of Cochrane Adverse Effects Methods Group. As these searches had not been carried out previously they were run over all years.

To identify **effectiveness studies** we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2009, issue 3) which contains the Acute Respiratory Infections Group's Specialised Register; MEDLINE (2008 to July2009); and EMBASE (2008 to July 2009). See Appendix 3 for dates of previous effectiveness searches. We also searched for postmarketing pharmacovigilance data and comparative safety cohorts. The following search strategy was used in MEDLINE in conjunction with the Cochrane highly sensitive search strategy for identifying RCTs (Lefebvre 2008). The same strategy was used to search CENTRAL and the terms were adapted to search EMBASE. See Appendix 1 for the EMBASE search strategy.

MEDLINE (OVID)

1 exp INFLUENZA/

2 influenza$.mp.

3 or/1-2

4 neuraminidase inhibitor$.mp.

5 oseltamivir.mp.

6 zanamivir.mp.

7 GS4071.mp.

8 or/4-7

9 3 and 8

To identify **adverse effects** studies we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2009, issue 3), MEDLINE (Ovid) (1950 to July Week 5 2009) and EMBASE (Ovid) (1980 to 2009 Week 31).

The following search strategy (based on the work of Golder 2006) was used in MEDLINE. The search strategy was adapted for CENTRAL and EMBASE (Appendix 4).

MEDLINE (Ovid)

1 exp Oseltamivir/

2 exp Zanamivir/

3 (oseltamivir or zanamivir or GS4071 or tamiflu or relenza).tw.

4 neuraminidase inhibitor*.tw.

5 1 or 2 or 3 or 4

6 (ae or to or po or co).fs.

7 (safe or safety).tw.

8 side effect*.tw.

9 ((adverse or undesirable or harms* or serious or toxic) adj3 (effect*or reaction* or event* or outcome*)).tw.

10 exp Product Surveillance, Postmarketing/

11 exp Adverse Drug Reaction Reporting Systems/

12 exp Clinical Trials, Phase IV as Topic/

13 exp Poisoning/

14 exp Substance-Related Disorders/

15 exp Drug Toxicity/

16 exp Abnormalities, Drug-Induced/

17 exp Drug Monitoring/

18 exp Drug Hypersensitivity/

19 (toxicity or complication* or noxious or tolerability).tw.

20 exp Case-Control Studies/

21 exp Cohort Studies/

22 or/6-21

23 5 and 22

Searching other resources

We also checked the bibliographies of other systematic reviews of the topic (Burch 2009; Burls 2002; Cooper 2003; Tappenden 2009; Turner 2003). No language or publication restrictions were applied. Please refer to Appendix 2 for a glossary of terms.

Data collection and analysis

Selection of studies

For this 2009 update, two review authors (ED, TOJ) independently read all titles and studies retrieved in the search and applied inclusion criteria. Disagreements were resolved by discussion with a third review author (CDM).

Data extraction and management

The following data were extracted onto standard forms, checked and recorded:

Characteristics of participants

1. Number of participants.
2. Age, gender, ethnic group, risk category.

Characteristics of interventions

1. Type of NI, type of placebo, dose, treatment or prophylaxis schedule, length of follow up (in days).

Characteristics of outcome measures

1. Number and severity of influenza cases in NI and placebo groups.
2. Concentration of influenza viruses excreted by nasal mucous.
3. Adverse effects: presence and type.
4. Date of trial.
5. Location of trial.
6. Funder of trial (specified, known or unknown).
7. Publication status.

No new data were extracted for this 2009 update. Twenty-eight studies were retrieved and 29 studied were excluded.

Assessment of risk of bias in included studies

In the previous publication of this review (Jefferson 2009c) assessment of methodological quality for RCTs was carried out using the risk of bias tool, as recommended in the *Cochrane Handbook of Reviews of Interventions* (Higgins 2008a). We assessed studies according to adequacy of methods of generation of the allocation sequence, allocation concealment and blinding and dealing with losses to follow up. When there was disagreement among the review authors (TOJ, DR) on the quality of a trial, a third review author (VD) arbitrated. No new studies were included in this updated review.

In this update, there were no new trials to assess. One study (Kaiser 2003), a review of 10 other trials, was re-assessed, and found to be ineligible. A full discussion can be found in Appendix 5 (Doshi 2009).

Measures of treatment effect

We used random-effects methods to compare dichotomous outcomes (RR for efficacy and OR for safety), therefore estimates meta-analysed over multiple trials are average treatment effects. Where hazard ratios were not provided, we converted the ratio of medians of treatment groups into (log) hazard ratios (estimating the variance of these) (Parmar 1998) to enable meta-analysis of time to event outcomes.

Assessment of heterogeneity

We assessed heterogeneity used the I^2 statistic and Chi^2 test. Due to the low power of the Chi^2 test we assumed $p<0.1$ to indicate evidence of heterogeneity.

Assessment of reporting biases

See Appendix 5.

Data synthesis

We structured the comparisons into prophylaxis, treatment and adverse events and further subdivided them by outcome and dose. The RRs of events comparing prophylaxis and placebo groups from the individual trials were combined using random-effects models to include between-trial variability.

Subgroup analysis and investigation of heterogeneity

We planned to investigate possible reasons for heterogeneity using variables such as trial quality and trial sponsorship (industry versus other).

Sensitivity analysis

We carried out a sensitivity analysis of methods used comparing our results obtained using the fixed-effect and random-effects models. In the prophylaxis trials efficacy was derived as 1-RR (risk ratio) x 100 or the RR when not significant. Odds ratios (OR) were used to estimate association of adverse effects with exposure to antivirals. In the treatment trials, analysis of "time to alleviation of symptoms" and "time to return to normal activity" outcomes provided some difficulty due to inconsistent and non-standard reporting in the majority of the trial reports. Most reports described these outcomes in terms of medians for each treatment group. However, standard reporting in a meta-analysis requires these outcomes to be expressed as (log) hazard ratios. If it is assumed that the treatment effect is constant over time (as seems reasonable) then the ratio of the medians can be used to estimate the hazard ratio. To estimate the variance of the log hazard ratio, the method given by Parmar et al was used (Parmar 1998). The number of events was estimated from survival curves when these were available or, when they were not available, assumed to be all patients completing the trial providing follow up was sufficiently long enough for this to be a reasonable assumption.

In one study (Boivin 2000) follow up was possibly not long enough for this to be a reasonable assumption, however this was a small trial (27 participants in total) and follow up was sufficiently long enough for more than 90% of the patients to be expected to reach the endpoint. The impact of including this trial in the overall analysis is likely to be negligible. As a check to see if the estimation methods used are accurate, one study (Makela 2000) provided both hazard ratios and medians. The two methods provided identical results for the intention-to-treat (ITT) population and similar results for the influenza-positive population. The random effects inverse variance method was used for the meta-analysis of the log hazard ratio. Two studies presented nasal viral titre data as medians and ranges (Nicholson 2000; Treanor 2000). The data were converted into means and standard

deviations (SDs) to be consistent with other studies and allow meta-analysis. Means were converted directly from the medians as both are measures of central tendency and should be similar for approximately symmetrical data. The range was converted to a SD using the method described by Hurlburt 1994. The inter-quartile range (IQR) was converted to SD by multiplying by 68/50 (as 50% of the data is contained within the IQR while +/- 1 SD contains 68% of the data providing it is approximately normally distributed) then dividing by 2 (to estimate 1 SD).

We also searched for evidence of harms more widely, including submitting a Freedom of Information Act request to the US Food and Drug Administration (FDA) for all data on the harms of oseltamivir and zanamivir, and pursuing authors of some papers and manufacturers to obtain raw data (FDA 2009b).

We were unable to meta-analyse the same outcomes reported by Kaiser et al (Kaiser 2003) because the data for those outcomes were not available to us for individual trials. We carried out a sensitivity analysis of complications by excluding the unpublished trials included in the Kaiser review, criticised by Hayashi (Feedback1).

Results

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

In this updated search we retrieved a total of 399 records in the search for effectiveness studies, and a total of 1793 records in the search for adverse effects studies. We excluded 18 safety and 10 effectiveness studies (six were identified through both search strategies as they assessed both dimensions). We identified four prophylaxis, 12 treatment and four post-exposure prophylaxis (PEP) trials. Twenty-eight studies were retrieved and 29 studied were excluded, Figure 1 and Figure 2. However, two studies provided information on harms of oseltamivir (Blumentals 2007; Toovey 2008). This left 20 included trials in 19 publications (Aoki 2000; Boivin 2000; Hayden 1997; Hayden 1999a; Hayden 2000a; Hayden 2004; Kaiser 2000; Kashiwagi 2000a; Kashiwagi 2000b; Li 2003; Makela 2000; Matsumoto 1999; MIST 1998; Monto 1999a; Monto 1999b; Monto 2002; Nicholson 2000; Puhakka 2003; Treanor 2000; Welliver 2001).

Included studies

Prophylaxis trials

We identified four prophylaxis trials, two comparing a total of 697 treated with inhaled zanamivir 10 mg daily versus 602 with placebo (followed for 22 days) (Kaiser 2000; Monto 1999a), and two trials comparing a total of 675 treated with

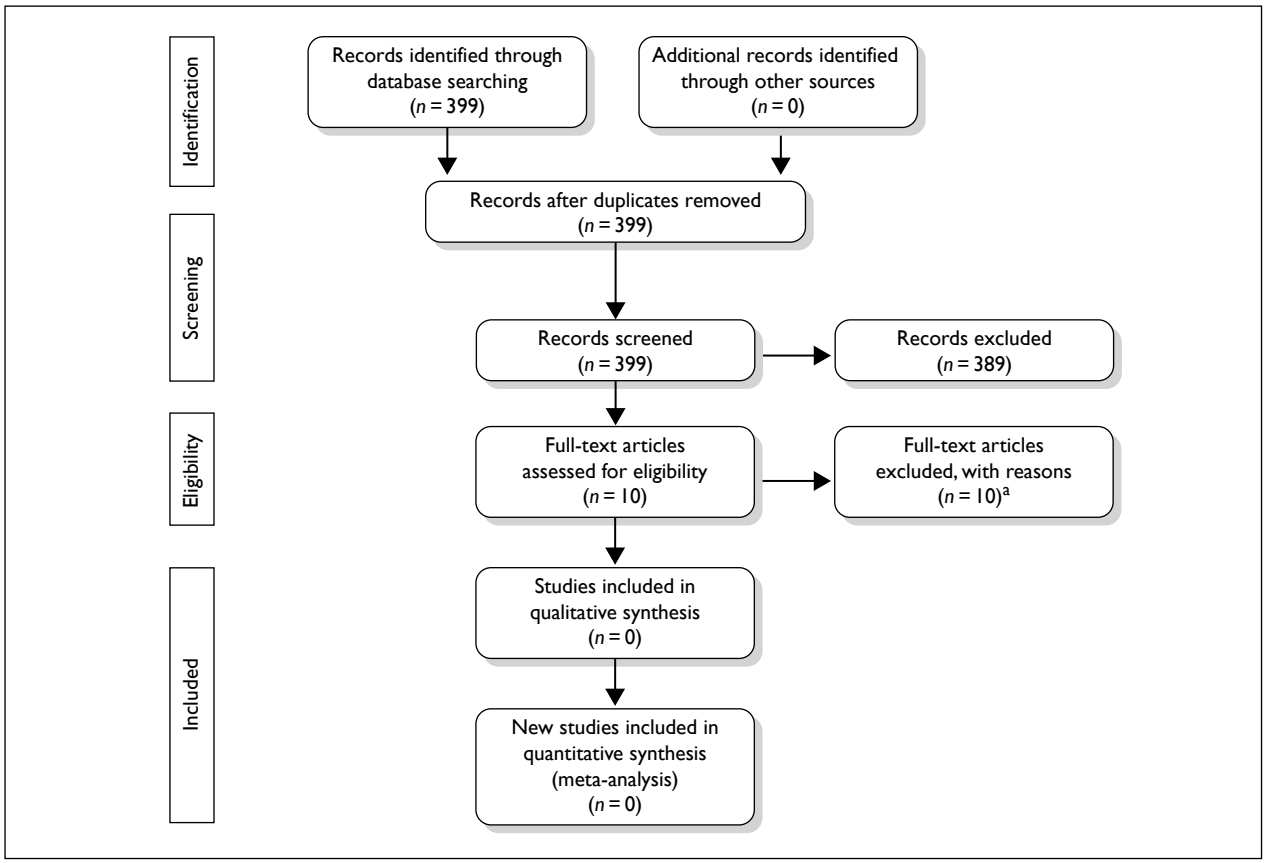

Figure 1 *Flow of studies identified from randomised controlled trials. [a]data from one meta-analysis 1, included in the previous versions of this Cochrane review, was excluded in this review, as described in the text.*

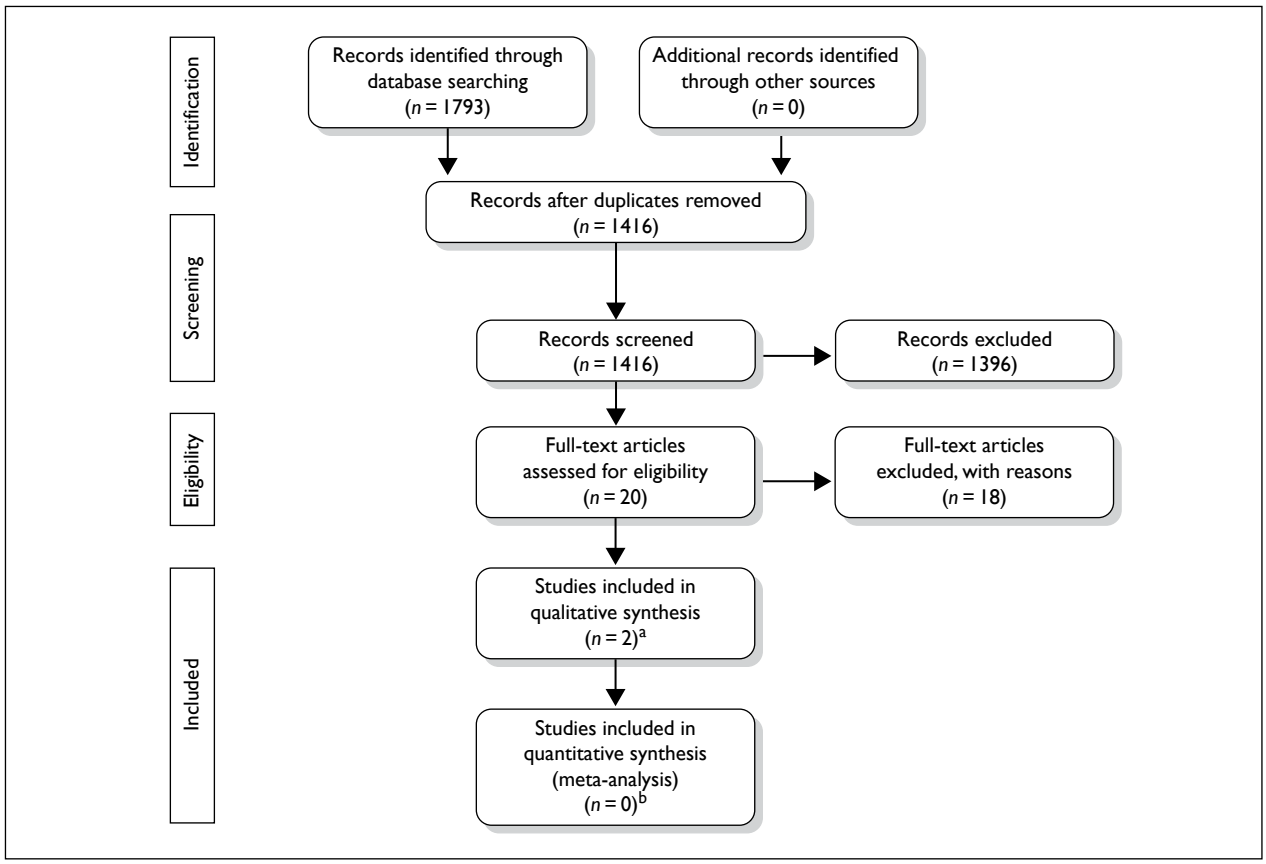

Figure 2 *Flow of studies identified from the search for evidence from post-marketing studies (excluding AERS) [a]studies providing background data on adverse events, but excluded from the effectiveness part of the review: (1) Blumenals WA, Song X. The Study of oseltamivir in patients with influenza: analysis of healthcare claims data from six influenza seasons. MedGenMed 2007;9.23. (2) Toovey S, Rayner C, Prinssen E, Chu T, Donner B, Thakrar B, et al. Assessment of neuropsychiatric adverse events in influenz patients treated with oseltamivir: a comprehensive review. Drug Saf 2008:31; 1097–114. bIn addition, data from the following US and Japanese websites were evaluated: (1 Japan Pharmaceuticals and Medical Devices Agency. New drug approval related information http://www.info.pmda.go.jp/shinyaku_hanbaimei_index.html (accessed 16 Nov 2009). (2)US Food and Drug Administration. The Adverse event Reporting System (AERS): Older Quarterly Data Files. www.fda.gov/Drugs/GuidanceCompllianceRegulatoryinformation/Surveillance/AdverseDrugEffects/ucm083765.htm (accessed 13 October 2009). (3) US Food and drug Administration. The Adverse Event Reporting System (AERS): Latest Quarterly Data files. www.fda.gov/Drugs/GuidanceCompllianceRegulatoryinformation/Surveillance/AdverseDrugEffects/ucm082193htm.*

oral oseltamivir 75 mg daily versus 413 placebos (followed for 49 days) (Hayden 1999a; Kashiwagi 2000a). Compared to placebo, NIs had no effect against ILI (RR 1.28, 95% CI 0.45 to 3.66 for oseltamivir 75 mg daily, RR 0.76, 95% CI 0.49 to 1.19 for zanamivir 10 mg daily) (Figure 3). Higher dosages made no difference, although this is based on a single study with only nine events (Hayden 1999a; Hayden 2000a; Kaiser 2000.) Oseltamivir 75 mg daily reduced the chance of symptomatic laboratory-confirmed influenza (RR 0.24, 95% CI 0.12 to 0.48). Zanamivir 10 mg daily was similarly efficacious (RR 0.33, 95% CI 0.18 to 0.59) (Figure 4). Neither protected against asymptomatic influenza (Hayden 1999a; Kashiwagi 2000a; Monto 1999a).

Treatment trials

We identified eight treatment trials of zanamivir (Aoki 2000; Boivin 2000; Hayden 1997; Makela 2000; Matsumoto 1999; MIST 1998; Monto 1999b; Puhakka 2003), of which two (Aoki 2000; Boivin 2000) were linked to others (MIST 1998; Monto 1999b) (a total of 1878 in the treatment arm and 1310 controls, with a mean length of follow up of 26 days). Four of oseltamivir (Kashiwagi 2000b; Li 2001; Nicholson 2000; Treanor 2000), and another trial (Li 2003) was linked to a redundant publication (Li 2001), (totaling 1118 treatment; 679 controls, 21 days follow up).

There was evidence of benefit in shortening duration of influenza like-illness for zanamivir (hazard ratio, (HR) 1.24, 95% CI 1.13 to 1.36), and

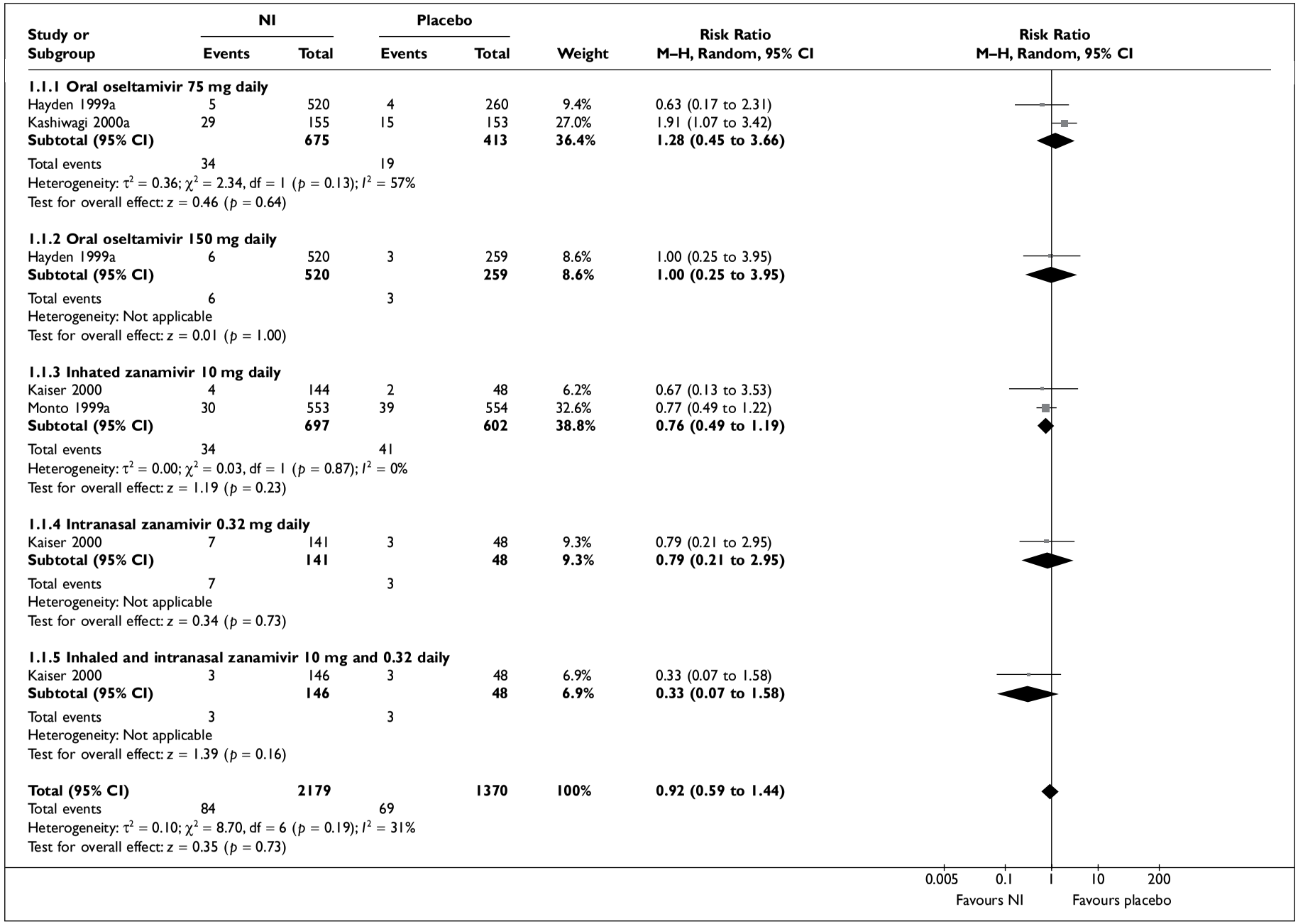

Figure 3 *Forest plot of comparison: 1 NI versus placebo for prophylaxis, outcome: 1.1 Influenza-like illness.*

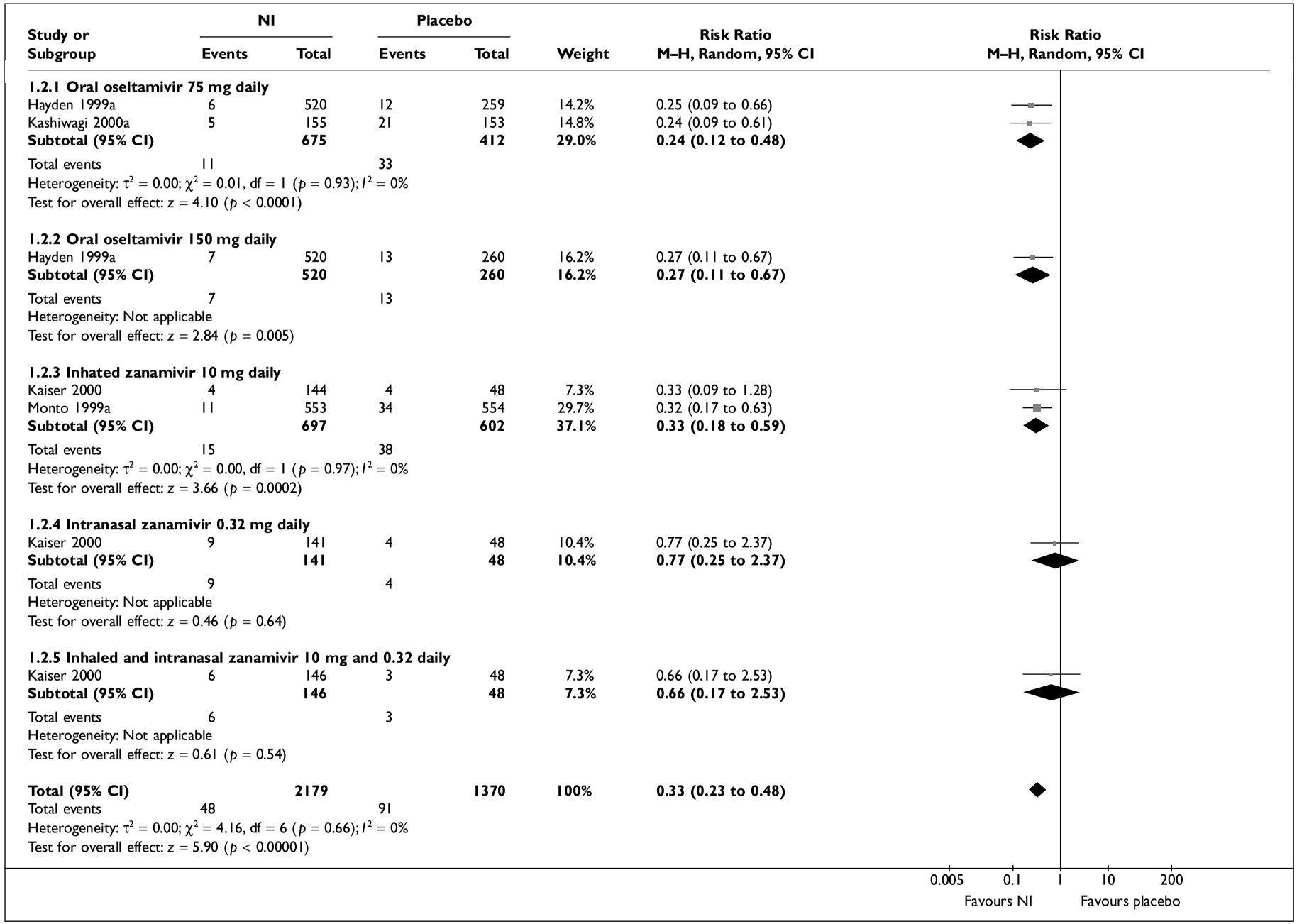

Figure 4 *Forest plot of comparison: 1 NI versus placebo for prophylaxis, outcome: 1.2 Influenza (symptomatic).*

for oseltamivir (HR 1.20, 95% CI 1.06 to 1.35), (Figure 5). This finding is likely to be due to the high percentage of influenza-like illness caused by influenza in some of the included trials (for example, 66%) (Nicholson 2000).

Post-exposure prophylaxis (PEP) trials

We identified two PEP trials of different design assessing the effects of oseltamivir. Hayden 2004 is a C-RCT comparing the effects on household contacts of expectant treatment with oseltamivir with commencing immediate PEP. Welliver 2001 investigated the effects of oseltamivir on the spread of influenza by randomizing household contacts of index cases with influenza to the active principle or placebo. The mean and median oseltamivir arm size was 447 (25th percentile 422 and the 75th percentile 470).

Two further PEP trials assessed zanamivir (Hayden 2000a; Monto 1999a). In both trials, household contacts of an index case with ILI were randomised to either placebo of zanamivir. The oseltamivir trials reported significant protection for household (RR 0.16 and 0.42) and the zanamivir trials reported similar results (RR 0.19 and 0.21).

See the 'Characteristics of included studies' table for a full description of all included studies.

Excluded studies

For this 2009 update overall, 29 studies made up of 10 effectiveness and 10 safety studies (six were identified by both searches) were excluded. After additional deliberations, another three effectiveness studies were excluded (Blumentals 2007; Kaiser 2003; Toovey 2008). This left 20 included trials in 19 publications. Two studies that were excluded from the effectiveness screen were included in the safety data sources (Blumentals 2007; Toovey 2008), Figure 1 and Figure 2.

Risk of bias in included studies

One prophylaxis trial had adequate methodological quality (Monto 1999a), one had an unclear measures to protect double blinding (Hayden 1999a) and two (Kaiser 2000; Kashiwagi 2000a) had unclearly described methods. Kaiser 2000 reported no dropouts from the trial. Four treatment studies (Makela 2000; MIST 1998; Nicholson 2000; Treanor 2000) had adequate methodological quality, three trials (Aoki 2000; Boivin 2000; Kashiwagi 2000b) has unclearly described processes, although two (Aoki 2000; Boivin 2000) were linked to larger studies. The remainder had at least one unclearly described item. One trial (Li 2003) did not include withdrawals in the analysis.

Withdrawals were included in all PEP trials but all other items were poorly described. Hayden 2004 was an open-label C-RCT. Allocation concealment was not described in the zanamivir trials.

Allocation

On the basis of the published text only five trials were judged adequate by usual Cochrane Collaboration methods (Higgins 2008b). One trial on prophylaxis (Monto 1999a) and four on treatment (Makela 2000; MIST 1998; Nicholson 2000; Treanor 2000).

Incomplete outcome data

Most of the trials were at risk of bias, arising from poor descriptions of the methods (Aoki 2000; Boivin 2000; Kaiser 2000; Kashiwagi 2000a; Kashiwagi 2000b; Hayden 1999a) such as no description of losses to follow up and blinding (Kaiser 2000). Attempts to deal with these shortcomings were unsuccessful. To address the Hayshi comment (Feedback 1) we wrote to all first or corresponding trial authors of studies on oseltamivir treatment. Although five responded to our contact, none had original data and referred us to the manufacturer (Roche), which was not able to unconditionally provide the information as quickly as we needed it to update this review (Doshi 2009). The Kaiser et al 2003 meta-analysis (Kaiser 2003) was made up of data from 10 studies. We were obliged to exclude the meta-analysis because we were unable to determine the number of healthy adults experiencing complications in each study (some studies contained mixed populations of healthy and comorbid participants), nor the number of patients experiencing one of more of "bronchitis, lower respiratory tract infection, or pneumonia" presenting to each study.

Other potential sources of bias

We are unable to assess the size and direction of the obvious bias in the treatment data set due to the non-publication or partial publication of eight trials, as the data provided to us by Roche are insufficient to fill the gaps in our understanding of the population, methods and results of the studies.

Study or Subgroup	log [Hazard ratio]	NI SE	NI Total	Placebo Total	Placebo Weight	Hazard ratio IV, Random, 95% CI
2.1.1 Zanamivir						
Hayden 1997	0.105	0.1183	273	144	8.9%	1.11 (0.88 to 1.40)
Makela 2000	0.405	0.1183	174	182	8.9%	1.50 (1.19 to 1.89)
Matsumoto 1999	0.288	0.2449	77	39	2.1%	1.33 (0.83 to 2.16)
MIST 1998	0.262	0.1048	227	228	11.4%	1.30 (1.06 to 1.60)
Monto 1999b	0.154	0.0744	834	422	22.5%	1.17 (1.01 to 1.35)
Puhakka 2003	0.207	0.8366	293	295	0.2%	1.23 (0.24 to 6.34)
Subtotal (95% CI)			**1878**	**1310**	**54.0%**	**1.24 (1.13 to 1.36)**
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 4.41$, df = 5 ($p = 0.49$); $I^2 = 0\%$						
Test for overall effect: $z = 4.48$ ($p < 0.00001$)						
2.1.2 Oseltamivir						
Li 2003	0.049	0.0969	216	235	13.3%	1.05 (0.87 to 1.27)
Nicholson 2000	0.216	0.0854	484	235	17.1%	1.24 (1.05 to 1.47)
Treanor 2000	0.253	0.0894	418	209	15.6%	1.29 (1.08 to 1.53)
Subtotal (95% CI)			**1118**	**679**	**46.0%**	**1.20 (1.06 to 1.35)**
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 2.67$, df = 2 ($p = 0.26$); $I^2 = 25\%$						
Test for overall effect: $z = 2.96$ ($p = 0.003$)						
Total (95% CI)			**2996**	**1989**	**100.0%**	**1.22 (1.14 to 1.31)**
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 7.32$, df = 8 ($p = 0.50$); $I^2 = 0\%$						
Test for overall effect: $z = 5.64$ ($p < 0.00001$)						

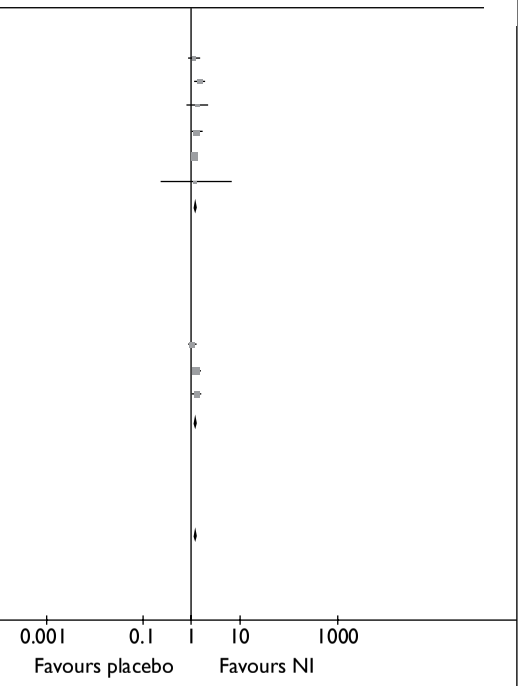

Figure 5 *Forest plot of comparison: 2 NI versus placebo for treatment, outcome: 2.1 Time to alleviation of symptoms (ITT).*

Effects of interventions

We carried out three main comparisons with placebo: NIs in a pre-exposure, post-exposure prophylaxis (PEP) and treatment roles. We further subdivided each comparison according to outcome case definition. We did not meta-analyse data from the PEP trials, as they had different study designs.

Prophylaxis trials

Compared to placebo, NIs have no effect against ILI (RR 1.28, 95% CI 0.45 to 3.66 for oral oseltamivir 75 mg daily (Figure 3); and RR 0.76, 95% CI 0.49 to 1.19 for inhaled zanamivir 10 mg daily).Higher dosages appear to make no difference, although this observation is based on single studieswith very low viral circulation (Hayden 1999a; Kaiser 2000).

The efficacy of oral oseltamivir 75 mg daily against symptomatic influenza is 76% (RR 0.24, 95% CI 0.12 to 0.48), or 73% (RR 0.27, 95% CI 0.11 to 0.67) at 150 mg daily, although this last observation is based on a single study. Inhaled zanamivir 10 mg daily is 67% efficacious (RR 0.33, 95% CI 0.18 to 0.59) (Figure 4). The addition of an intranasal dose does not seem to enhance its prophylactic activity (RR 0.66, 95% CI 0.17 to 2.53), although again this last observation is based on a single study.

Oseltamivir confers 64% protection against symptomatic and asymptomatic influenza (RR 0.46, 95% CI 0.31 to 0.68) at a lower dose of 75 mg daily. An increase to 150 mg daily does not appear to enhance its activity (RR 0.48, 95% CI 0.29 to 0.80) although this observation is based on a single study. Similarly zanamivir has a 43% protective effect (RR 0.67, 95% CI 0.50 to 0.91) and based on a single study the addition of intranasal dose does not appear to enhance its activity (RR 0.77, 95% CI 0.38 to 1.56).

However, when the outcome is asymptomatic influenza no NI has significant effects (oseltamivir 75 mg daily RR 0.73, 95% CI 0.43 to 1.26; oseltamivir 150 mg daily RR 0.67, 95% CI 0.35 to 1.28; zanamivir 10 mg daily 0.98, 95% CI 0.65 to 1.47). These observations are based on three studies (Hayden 1999a; Kashiwagi 2000a; Monto 1999a) with a combined denominator of 2974 in the presence of relatively high viral circulation (5% in the combined placebo arms).

Oseltamivir induces nausea (OR 1.79, 95% CI 1.10 to 2.93), especially at the higher prophylactic dose of 150 mg daily (OR 2.29, 95% CI 1.34 to 3.92).

Post-exposure prophylaxis (PEP) trials

Hayden 2004 reports that PEP provided an efficacy of 58.5% (15.6% to 79.6%) for households and of 68% (34.9% to 84.2%) for individual contacts. Given the high circulation of virus (184 out of 298 index cases had influenza, 66% of which had influenza AH1N1 and remainder influenza B virus) effectiveness was high 62.7% (26% to 81%).

Welliver 2001 reports 89% (67% to 97%) protective efficacy in contacts of index cases with influenza and 84% (45% to 95%) for index cases. Neither trial reported the onset of viral resistance after five (Hayden 2004) and seven days (Welliver 2001) of prophylaxis at a dose of 75 mg twice daily (Hayden 2004) and once daily (Welliver 2001). Neither the background rate of infection in the community nor the viral strains are reported, although influenza A and B were co-circulating at the time.

Monto 2002 reports a 79% effectiveness and 81% efficacy (64% to 90%) for households and 82% for individuals against symptomatic influenza, 55% to 59% against all asymptomatic and symptomatic influenza. Zanamivir shortened duration of illness by 1.5 days and was well tolerated and no viral resistance was reported.

Hayden 2000a concludes that zanamivir was 79% (57% to 89%) effective and 72% (42% to 87%) effective in preventing contacts from developing symptomatic influenza and 53% (27% to 70%) effective and 48% (15% to 68%) efficacious in preventing symptomatic and asymptomatic influenza. Zanamivir also shortened duration of symptoms by 2.5 days. There was no evidence of the onset of resistance.

Treatment trials

Time to alleviation of symptoms (considering ITT population) was assessed in nine trials (Hayden 1997; Li 2003; Makela 2000; Matsumoto 1999; MIST 1998; Monto 1999b; Nicholson 2000; Puhakka 2003; Treanor 2000). The estimated hazard ratios for zanamivir were greater than one, hence in favour of the treated group and there was

no evidence of heterogeneity (I^2 statistic = 0%). The pooled hazard ratio is 1.24 (95% CI 1.13 to 1.36) indicating that the treated group are 24% more likely to have their symptoms alleviated than the placebo group by a given time-point. We obtained a similar result for oseltamivir (hazard ratio 1.20, 95% CI 1.06 to 1.35) (Figure 5). For time to alleviation of symptoms in influenza-positive participants, the hazard ratios were significantly in favour of the treated group 1.33 (95% CI 1.29 to 1.37) forzanamivir and 1.30 (95% CI 1.13 to 1.50) for oseltamivir. There was no evidence of heterogeneity for the zanamivir data metaanalysis, but I^2 statistic was 37.5% for oseltamivir. Application of the fixed-effect model did not materially alter the hazard ratio (Boivin 2000; Hayden 1997; Kashiwagi 2000b; Li 2003; Makela 2000; Matsumoto 1999; MIST 1998; Monto 1999b; Nicholson 2000; Puhakka 2003; Treanor 2000).

Time to return to normal activities (considering ITT population) was assessed by four studies (Matsumoto 1999; MIST 1998; Monto 1999b; Treanor 2000). The pooled estimated hazard ratios for zanamivir was 1.28 (95% CI 1.13 to 1.45), while the single study assessing oseltamivir (Treanor 2000) had a non-significant hazard ratio (1.23, 95% CI 1.02 to 1.48). There was no heterogeneity (I^2 statistic = 0). In influenza-positive participants the pooled hazard ratio was just below significance 1.17 (95% CI 1.00 to 1.37, P value 0.06) for zanamivir (Makela 2000; MIST 1998; Hayden 1997) and significant for oseltamivir 1.34 (95% CI 1.07 to 1.67) although this observation is based on a single study (Treanor 2000). There was no evidence of heterogeneity (I^2 statistic = 0%).

Five studies reported assessing the effect of NI administration on viral load (as estimated by mean nasal titres of excreted viruses at 24 and 48 hours since randomisation) (Boivin 2000; Kashiwagi 2000b; Nicholson 2000; Puhakka 2003; Treanor 2000). Titres were significantly diminished by both zanamivir and oseltamivir (WMD -0.62, 95% CI -0.82 to -0.41). The effect is more marked the longer the time since randomisation (and commencement of treatment). Exclusion of data from the Treanor 2000 and Nicholson 2000 studies does not affect our conclusions. There was evidence of heterogeneity (I^2 statistic = 34.6%) but analysis using a fixed-effect model did not materially affect our findings, except for the comparison zanamivir against placebo where the effect on mean nasal titres at 48 hours since randomisation is not significant when analysed using a fixed-effect model. However, treatment did not suppress viral excretion, apparently regardless of the dose. We found insufficient data to comment on the effects on nasal excretion of viruses of higher doses of medication.

There is insufficient evidence for oseltamivir 75 mg daily in preventing complications (pneumonia, bronchitis, otitis media, sinusitis) requiring antibiotics in influenza cases (RR 0.57, 95% CI 0.23 to 1.37) (Figure 6). There is also insufficient evidence for zanamivir in preventing complications of all types in influenza cases (RR 0.73, 95% CI 0.50 to 1.06). However, zanamivir is effective in preventing complications of all types in the ITT population (RR 0.69, 95% CI 0.49 to 0.96), although these observations are based on a single study (Makela 2000).

Oseltamivir is associated with nausea (OR 2.50, 95% CI 1.49 to 4.20). Finally, use of relief medications and antibiotics is unaffected by consumption of NIs (OR 0.82, 95% CI 0.60 to 1.11).

Evidence of harms

The trials identified only one serious adverse event (Nicholson 2000) (so labeled in the Japanese data, a patient with neutropenia), and, in particular, no neuropsychiatric events. Oseltamivir induced nausea (OR 1.79, 95% CI 1.10 to 2.93), especially at the higher dose of 150 mg daily (OR 2.29, 95% CI 1.34 to 3.92) (Figure 7). No statistically significant adverse event was found for zanamivirfrom the trials (Matsumoto 1999; MIST 1998; Monto 1999b; Puhakka 2003).

Two published studies reported additional retrospective comparative safety data on oseltamivir (Blumentals 2007; Toovey 2008). Their data suggest an incidence of neuropsychiatric adverse events per 1000 adults aged between 18 to 49 at 14 days and 30 to 40 at 30 days (Blumentals 2007) and for neuropsychiatric adverse events in prospective clinical trials, an incidence of 0.5% (Toovey 2008).

AERS-1 includes 2275 adverse event reports for oseltamivir and 453 for zanamivir (excluding follow up reports on the same individual event) generated worldwide between December 1999 and July 2009 (the month our request was answered). Unfortunately it indicates neither reporting country nor how long the event occurred before receipt of the report by the FDA. The period from 2004 onwards overlaps with AERS-2, which

Study or Subgroup	NI Events	NI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M–H, Random, 95% CI
2.6.1 Zanamivir						
Makela 2000	33	136	47	141	67.8%	0.73 (0.50 to 1.06)
Subtotal (95% CI)		**136**		**141**	**67.8%**	**0.73 (0.50 to 1.06)**
Total events	33		47			
Heterogeneity: Not applicable						
Test for overall effect: $z = 1.65$ ($p = 0.10$)						
2.6.2 Oseltamivir						
Nicholson 2000	1	158	8	161	3.4%	0.13 (0.02 to 1.01)
Treanor 2000	8	124	14	129	19.3%	0.59 (0.26 to 1.37)
Li 2003	5	134	5	139	9.5%	1.04 (0.31 to 3.50)
Subtotal (95% CI)		**416**		**429**	**32.2%**	**0.57 (0.23 to 1.37)**
Total events	14		27			
Heterogeneity: $\tau^2 = 0.22$; $\chi^2 = 3.04$, df = 2 ($p = 0.22$); $I^2 = 34\%$						
Test for overall effect: $z = 1.26$ ($p = 0.21$)						
Total (95% CI)		**552**		**570**	**100.0%**	**0.68 (0.46 to 1.00)**
Total events	47		74			
Heterogeneity: $\tau^2 = 0.02$; $\chi^2 = 3.29$, df = 3 ($p = 0.35$); $I^2 = 9\%$						
Test for overall effect: $z = 1.94$ ($p = 0.05$)						

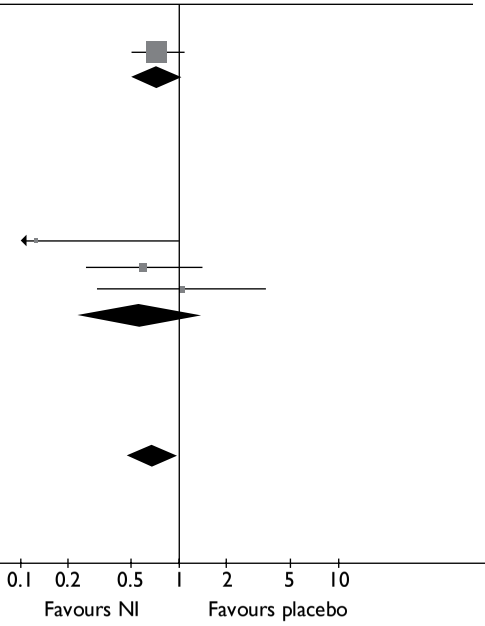

Figure 6 *Forest plot of comparison: 2 NI versus placebo for treatment, outcome: 2.6 Complications – all types (influenza cases only).*

Study or Subgroup	NI Events	NI Total	Placebo Events	Placebo Total	Weight	Odds Ratio M–H, Random, 95% CI
1.5.1 Oral oseltamivir 75 mg daily						
Hayden 1999a	63	520	19	260	83.8%	1.75 (1.02 to 2.99)
Kashiwagi 2000a	8	155	4	153	16.2%	2.03 (0.60 to 6.88)
Subtotal (95% CI)		**675**		**413**	**100.0%**	**1.79 (1.10 to 2.93)**
Total events	71		23			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.05$, df = 1 ($p = 0.83$); $I^2 = 0\%$						
Test for overall effect: $z = 2.33$ ($p = 0.02$)						
1.5.2 Oral oseltamivir 150 mg daily						
Hayden 1999a	76	520	18	259	100.0%	2.29 (1.34 to 3.92)
Subtotal (95% CI)		**520**		**259**	**100.0%**	**2.29 (1.34 to 3.92)**
Total events	76		18			
Heterogeneity: No applicable						
Test for overall effect: $z = 3.03$ ($p = 0.002$)						

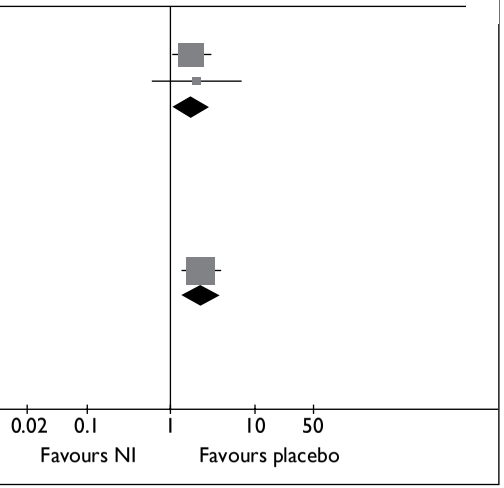

Figure 7 *Forest plot of comparison: 1 NI versus placebo for prophylaxis, outcome: 1.5 Adverse events - nausea.*

has reports from January 2004 to March 2009, indicating both initial and follow up reports, and reporting the date of the adverse event (FDA 2009b; FDA 2009c). From July 2005 it indicates the reporting country. From July 2005 to March 2009, 1205 initial adverse events occurred. Most (681, 56.5%) were reported from Japan, followed by the United States (390, 32.4%). Most (1109, 92.0%) were for oseltamivir (perhaps reflecting its higher use). A disproportionate amount of reports are for people aged less than 20 (with data on age missing for many).

Discussion

Summary of main results

Role of NIs in seasonal influenza

We have assembled a good-quality up to date evidence base of the prophylactic and treatment effects of NIs. These compounds have low effectiveness, high efficacy and appear to be well tolerated, with the possible exception of oseltamivir-induced nausea and vomiting and zanamivir-induced diarrhoea. Existing trials on NIs were clearly designed and undertaken within a registration and regulation perspective. This is reflected in the cryptic reporting of continuous outcome data which forced us to resort to summary measures such as hazard ratio (HR), which although methodologically virtuous, may not be relevant to workers in the field. Onset of resistance is a possibility.

Although none of the studies included in the review reported it, Kiso and colleagues found an 18% isolation rate of NI-resistant A/H3N2 viruses in 50 very young children at day 4 of treatment, and a high prolonged viral excretion even after five days of treatment (Kiso 2004). Resistance to oseltamivir is reported to be the around 0.5% from other trials in the Roche database (Ward 2005). Recently resistance of H1N1 viruses to oseltamivir has been reported from 59/437 (14%) isolates from nine European countries (Lackenby 2008). Given the highly selective nature of the isolatesit is not possible to generalise the data. However the onset of resistance is a further reason against the routine use of neuraminidase inhibitors.

NIs affect influenza symptoms, either preventing their appearance or curtailing their duration and, although we found clear evidence of their capacity to interrupt transmission of seasonal influenza in households, NIs do not prevent infection and decrease - but do not interrupt - nasal shedding of seasonal influenza viruses. We cannot explain how NIs can affect respiratory complications of seasonal influenza such as bronchitis and pneumonia while not preventing infection and this effect should be further studied. An explanation for what we have observed is a possible effect in preventing a proportion of NI recipients to seroconvert into symptomatic influenza cases. This would explain the observed effects of NIs on serious complications and interruption of transmission in households during seasonal influenza. Whichever explanation is chosen, prophylactic use of NIs in a serious epidemic or a pandemic may enhance vulnerability to infection by preventing seroconversion and facilitating the selection of NI-resistant mutant viruses. Because of their low effectiveness and the possibility of the onset of resistance we conclude that NIs should not be routinely used in seasonal influenza. In the case of a serious localised confirmed epidemic, NIs could be used to prevent serious complications. Our inability to provide a satisfactory response to the observations made in the Hayashi challenge, compounded by the inability of corresponding authors or the manufacturers to provide their original data, (for the latter, because it was contingent on our signing a secret confidentiality agreement), has undermined our confidence in our previous findings Cooper 2003. The treatment effects of oseltamivir now seem less credible.

NIs had low effectiveness, high efficacy against symptoms (shortening the illness by half to one day, and preventing symptoms from appearing), and initially appeared to be well tolerated (with the possible exception of oseltamivir-induced nausea and vomiting and zanamivir-induced diarrhoea).

Commercial interests may explain the cryptic reporting of continuous outcome data which forced us to resort to summary measures such as hazard ratio (HR). A surprising finding is the very high percentage (from 57% to 78%) of influenza in the ITT populations of the neuraminidase treatment trials. We remain at a loss to explain this (Jefferson 2009a) and questions to authors and pharmaceutical company remain unanswered or unsatisfactory, (WebExtra).

Viral resistance is monitored by several organisations. One recently reported resistance of seasonal A/H1N1 to oseltamivir at 98% of 259 tested specimens, but no resistance for the 26 novel A/H1N1 tested, or for any of 285 specimens to zanamivir (ECDPC 2009). Yet resistance was reported as 0.5% from other trials in the Roche database (Ward 2005). The risk of resistance

is one reason to advise against routine use of neuraminidase inhibitors except in life-threatening situations.

Role of NIs in avian influenza

We identified no comparative evidence of the role of NIs in avian A/H5N1 influenza or for the current novel A/H1N1 pandemic. Oseltamivir was used against three subtypes of avian influenza viruses with proven bird-to-human and human-to-human transmission: A/H5N1, A/H7N7 and H7N3. The virological and transmission profile of avian H5N1 influenza is not clear. One review reports that experience from the cases of avian influenza transmitted to man in South East Asia suggests that viral shedding commences before symptoms appear and ceases after 48 hours from onset of symptoms (Yuen 2005). The WHO-led review of H5N1 influenza cases suggests that viral shedding and infectivity of index cases could be protracted (WHOWC 2005). What appears clear, however, is that viral load can be up to 10 times greater than in seasonal influenza (WHOWC 2005). In the South East Asia outbreaks, use of oseltamivir was not associated with any obvious effect on mortality, although this could be due to late commencement of therapy and high initial viral load. Resistance to oseltamivir was detected in up 16% of children given the drug (WHOWC 2005), accordingly with evidence from Japan (Kiso 2004), a country with very high NI prescription rates, and in two out of eight Vietnamese people aged eight to 35 years (de Jong 2005).

The apparently common feature favouring the selection of resistant viruses is immunological naivety to the infecting viral subtype. A large outbreak of avian A/H7N7 influenza with bird-to-human and human-to-human transmission took place in chicken farms in the Netherlands between February and June 2003. Eighty-five of the 453 people who reported symptoms (mainly ILI and/or conjunctivitis) had A/H7N7 isolation from lacrimal fluid and/or upper airway swabs. Among other measures, PEP with oseltamivir 75 mg was started. Ninety people in the case registry probably had prophylactic treatment. Avian influenza virus infection was detected in one of 38 (2.6%) people who used oseltamivir, compared with five of 52 (9.6 %) who reported that they had not taken prophylactic medication. The difference was not significant (P value 0.38), probably because of small numbers and of the late nature of the commencement of PEP (Koopmans 2004). A similar outbreak of A/H7N3 took place in British Columbia, Canada in 2004. Twelve possible cases (22% of total) reported taking prophylactic oseltamivir at symptom onset, and 11 (20%) received oseltamivir for treatment. Maximum duration of oseltamivir assumption is thought to have been 12 weeks (Ward 2005). The remaining 22 patients with suspected cases were identified more than 48 hours after onset or refused treatment. All recovered fully (Tweed 2004). Evaluation of the effects of oseltamivir was outside a formal study and in all three cases data on the effectiveness of oseltamivir are insufficient to reach a conclusion. The use of NIs in avian influenza or in a possible pandemic is not supported by any credible data at present and we have doubts as to the generalisability of the evidence from seasonal influenza to avian influenza. Given the circumstances (ad hoc studies carried out during actual localised epidemics of avian influenza and the future characteristics of any pandemic) this is not surprising.

It should be remembered that at times the manufacturer makes no claims for oseltamivir to influence symptoms and complications: "Tamiflu has not been proven to have a positive impact on the potential consequences (such as hospitalisations, mortality, or economic impact) of seasonal, avian, or pandemic influenza" (Doerler 2009). Since NIs do not prevent infection or stop nasal viral excretion, they may be a sub-optimal means of interrupting viral spread in a pandemic. If used to contain a severe pandemic outbreak, NIs should be part of a package of measures to interrupt spread, including physical measures (Jefferson 2009d), rather than used alone. Finally, the inability of NIs to prevent infection and to suppress viral nasal excretion raises doubts as to their effectiveness in interrupting viral spread in a pandemic, although NIs may have a role in addressing symptoms and complications. We conclude that in a pandemic, NIs should be used within a package of measures to interrupt spread, that is to say, together with barrier, distance and personal hygiene measures.

Possible rare harms associated with NIs

A key limitation of the post-marketing pharmacovigilance data we obtained from FDA is the likely under-representation of non- USA-generated reports. Manufacturers are not required to inform FDA of non-USA events that are not "both serious and unexpected" (FDA 2009a). This has important implications for evaluating the complete

safety profile of oseltamivir, as 79% of global consumption has occurred outside of the USA (76% in Japan) (Toovey 2008). Of particular concern are neuropsychiatric adverse events (NPAEs) known to the manufacturer but not in the AERS database. The Roche Global Safety Database contains reports of 2466 NPAE patients between 1999 and 15 September 2007 of which they classified 562 (23%) as "serious" (Toovey 2008). However, the total AERS database (all types of adverse events) during this time period contains only 1805 reports.

Another important limitation of the AERS database is the FDA's practice of not registering into AERS non-electronically submitted reports of non-serious adverse events three years after a drug's initial approval (personal correspondence with FDA 14 October 2009). There is a possible association with NIs and the onset of rare harms. According to a review of phase IV evidence from eight cases (adolescents and adults) by Hama (Hama 2008), oseltamivir may induce sudden behavioural changes in recipients including hallucination and suicidal tendencies and sudden death while sleeping. This evidence comes hard on the heels of the review ordered by the Japanese government which is in part triggered by the 567 serious neuropathic cases received since the 2001 launch of the drug and May 2007 (Hama 2008). However it is estimated that >36 million doses have been prescribed since 2001 (Toovey 2008), making such harms (even if confirmed) rare. These findings are similar to our review of the US AERS data (Jefferson 2009b). We therefore found under-reported evidence of varied quality which could not answer concerns about the toxicity of NIs, especially oseltamivir. Governments should set up studies to monitor the safety of oseltamivir (Jefferson 2009b).

In the course of conducting this review it was discovered that Chugai Pharmaceuticals Co., Ltd. a Japanese subsidiary drug manufacturer controlled by Hoffmann La Roche Ltd. had published adverse event data from randomised trials of oseltamivir on its website. Data from prophylaxis trials comes from Hayden 1999a as well as two trials in the elderly (one unpublished). Notable adverse events are presented in Table 1 where there is strong evidence of increased incidence of nausea and vomiting due to oseltamivir as well as some evidence of an increased incidence of headache, pain in extremities, earache, major psychotic events, hyperglycaemia, and renal/urinary tract adverse events. Data from treatment trials comes from Nicholson 2000 and Treanor 2000, as well as from an unpublished study of otherwise healthy adults. These data, shown in Table 2, show strong evidence of increased incidence of nausea and vomiting due to oseltamivir.

Overall completeness and applicability of evidence

We have concerns about the difference between efficacy (treatment response to influenza virus infection) and effectiveness (the real life response to influenza-like illness, when real cases of influenza are indistinguishable from other causative agents not responsive to neuraminidase inhibitors) (Smith 2006). Understanding the proportion of influenza-like illness caused by both seasonal and epidemic influenza is critical to generalising the results of this review to clinical practice. The finding of treatment effectiveness for the neuraminidase inhibitors may be enhanced by the high percentage of influenza-like illness caused by influenza in some of the included trials for example, up to 80% (Kashiwagi 2000b).

Quality of the evidence

Only five trials were judged adequate by usual Cochrane Collaboration methods (Higgins 2008b): one prophylaxis (Monto 1999a), and four treatment trials (Makela 2000; MIST 1998; Nicholson 2000; Treanor 2000). There was risk of bias in most trials, arising from poor descriptions of the methods (Aoki 2000; Boivin 2000; Kaiser 2000; Kaiser 2003; Hayden 1999a; Kashiwagi 2000a; Kashiwagi 2000b), such as no description of loss of follow up and blinding (Kaiser 2000). Attempts to address shortcomings were unsuccessful: although four out of five first authors of oseltamivir trials responded to our contact, none had original data and referred us to the manufacturer (Roche).

Data about the effectiveness against influenza complications confused us. After studying available FDA and EMEA regulatory product information documents, we asked the EMEA for the basis behind its decision to approve statements that oseltamivir reduces lower respiratory tract complications (EMEA 2009). Answers did not resolve this satisfactorily. We contacted the manufacturer (Roche), asking for the complete complications data, in particular the unpublished data used by Kaiser et al (Kaiser 2003) as indicated in the Hayashi Feedback comment. In response, the lead review author was sent a confidentiality

Table 1 *Adverse events in randomised controlled trials of oseltamivir for prophylaxis (75 mg o.d. group of WV15673/697, WV15708 and WV15825#)*

Type of event (during on-treatment unless indicated as "+off ")[a]	Placebo (*n* = 973) *n* (%)	Oseltamivir 75mg o.d. (*n* = 986) *n* (%)	*p*-value (Fishers exact)
All AEs	1780	1933	
Patients with any AE	673 (69.2)	717 (72.7)	0.091
Nausea	50 (5.1)	92 (9.3)	< 0.001
Vomiting	9 (0.9)	27 (2.7)	0.004
Diarrhoea	38 (3.9)	49 (5.0)	0.27
All GI tract	155 (15.9)	214 (21.7)	0.001
Headache	243 (25.0)	286 (29.0)	0.047
All neurological	270 (27.7)	314 (31.8)	0.048
Pain in extremities	5 (0.5)	16 (1.6)	0.026
Eearache	2 (0.2)	11 (1.1)	0.022
All ear and vestibular	8 (0.8)	22 (2.2)	0.015
Major psychotic[b]	0 (0.0)	5 (0.5)	0.062
Major psychotic + off[c]	1 (0.1)	8 (0.8)	0.039
+Major psychiatric[d]	7 (0.7)	17 (1.7)	0.062
All psychiatric	13 (1.3)	24 (2.4)	0.096
All psychiatric + off	18 (1.8)	31 (3.1)	0.082
Mild psychiatric[e]	6 (0.6)	9 (0.9)	0.61
Hyperglycaemia + off[f]	0 (0.0)	8 (0.8)	0.008
Renal/urinary tract[g]	3 (0.3)	15 (1.5)	0.007
Upper respiratory infection	51 (5.2)	57 (5.8)	0.62
Influenza	41 (4.2)	46 (4.7)	0.66
Influenza like illness	23 (2.4)	19 (1.9)	0.54
Fever (general system)	33 (3.4)	28 (2.8)	0.52
Viral infection	5 (0.5)	4 (0.4)	0.75
All infections	227 (23.3)	234 (23.7)	0.87

a "+ off " Including events during off-treatment period.
b Major psychotic disorders? hallucination, Korsakov psychosis, schizophrenia, psychosis NOS, attempted suicide? One psychosis NOS in placebo group and hostility, hallucination aggravated and delusion in Tamiflu group were added.
d a + b + major psychiatric events (depression, depression worsened, intrinsic depression, confusion, bipolar mood disorders).
e Mild psychiatric events: all others that are not included in a, b, c and d? Anxiety, alcoholism, sleep disorder, stress symptoms, restlessness are included.
f Four hyperglycaemia and three diabetes aggravated during on-treatment, and one diabetes aggravated during off-treatment period.
g One nephrotic syndrome and one acute renal failure in Tamiflu group.
Sources: Chugai Pharm Co 2004. New drug approval package (NAP) of oseltamivir (in Japanese); oseltamivir capsule for prevention (2004) (in Japanese): available at: http://www.info.pmda.go.jp/shinyaku/g040703/index.html?submit3=%C9%BD%BC%A8. Hama R. Re: Oseltamivir: psychotic and neurological adverse reactions in the randomized controlled trials Rapid response: http://www.bmj.com/cgi/eletters/339/dec07˙2/b5106#227187.

agreement which included a clause forbidding ever mentioning the confidentiality agreement's very existence (WebExtra). We felt signing might compromise our aims. We persisted with Roche, who provided excerpts from company study reports apparently authored by people who did not appear in the published trials, and with insufficient detail to understand some data (for example, complication data from several trials were combined). This precluded us from addressing the Hayashi Feedback comment. It also meant we were obliged to now disregard a Roche-funded review

Table 2 *Comparison of adverse events in healthy adults (< 65 years) in oseltamivir treatment trials (WV15670,WV15671,WV15730)**

Type of event	Placebo (*n* = 466) *n* (%)	75mg b.i.d. (*n* = 479) *n* (%)	*p*-value (Fishers exact)
Vomiting	15 (3.2)	57 (11.9)	<0.001
Nausea	29 (6.2)	70 (14.6)	<0.001
Insomnia	3 (0.6)	7 (1.5)	0.34
Constipation	1 (0.2)	4 (0.8)	0.37
Back pain	2 (0.4)	4 (0.8)	0.69
Type of dizziness	2 (0.4)	4 (0.8)	0.69
Headache	11 (2.4)	13 (2.7)	0.84
Pharyngitis	5 (1.1)	6 (1.3)	1.0
Stomach ache	11 (2.4)	12 (2.5)	1.0
Fatigue	7 (1.5)	6 (1.3)	0.79
Herpes simplex	5 (1.1)	4 (0.8)	0.75
Fever	4 (0.9)	2 (0.4)	0.45
Cough	10 (2.1)	7 (1.5)	0.47
Dizziness	16 (3.4)	11 (2.3)	0.33
Nasal congestion	10 (2.1)	5 (1.0)	0.20
Diarrhoea	40 (8.6)	35 (7.3)	0.47

* Source: PMDA website document, Tamiflu 75 mg, Chugai document, p.294.

of 10 trials containing a mixture of published and unpublished data (Kaiser 2003) that is being promoted by the manufacturer (Burns 2009) and cited in US influenza treatment recommendations (Burns 2009).

Potential biases in the review process

In our 2005 review (Jefferson 2006) we failed to resolve the questions posed by Hayashi, the numerous inconsistencies found during the review process (Doshi 2009) and to assess the harms profile of oseltamivir in a satisfactory manner. This, in our view, may present an uncertain but perhaps optimistic view of the performance of oseltamivir.

Agreements and disagreements with other studies or reviews

Our review is now in disagreement with the conclusions of the Burch 2009, Tappenden 2009, and Turner 2003 reviews as our investigations could not answer the Hayashi comment and we were forced to exclude the Kaiser et al 2003 (Kaiser 2003) data on the effects of oseltamivir on complications.

Authors' conclusions

Implications for practice

We do not recommend NIs for routine use in seasonal influenza except for life-threatening illness, and in circumstances where they used as an adjunct to other public health measures. We urge caution in the administration of NIs until some of the problems such as psychotropic effects and resistance have been clarified. Updating this Cochrane review has increased uncertainty about the safety of NIs, their capacity to interrupt viral transmission, or to affect complications rates.

Implications for research

To provide that, adequate trials should be carried out to test NIs against a viable alternative for symptoms and duration of illness (such as a non-steroidal anti-inflammatory drug, or a statin) (Frost 2007), and compare its performance against hand washing and masks to interrupt influenza transmission (Jefferson 2009d), and powered to detect potentially rare adverse events.

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**Indicates the major publication for the study*

Characteristics of studies

Characteristics of included studies [ordered by study ID]

Aoki 2000

Methods	Multicentre, randomised, double-blind parallel group study, performed in 14 countries in Europe and North America during the 1995–1996 winter
Participants	One thousand two hundred and fifty six patients were included in study, of which 722 had laboratory confirmed influenza. The report only includes data for the 722 influenza cases. Participants were healthy individuals over 13 years old with acute influenza like illness (ILI) lasting less than 48 hours. The patients had to be able to use the inhaler and nasal devices. Patients with unstable chronic illness (for example, hospitalised) or were pregnant or breast feeding were excluded. Randomisation was carried out with an allocation schedule of 2:2:1:1 respectively
Interventions	Treatment lasted for five days
Outcomes	Serological: Serum samples were collected on days 1 and 21, and assayed for the presence of anti-influenza antibodies by haemagglutination inhibition Effectiveness: ILI (feverishness and at least two of the following symptoms: headache, myalgia, cough, or sore throat) Productivity Health status Sleep quality Healthcare utilisation Treatment satisfaction Social functioning Physical functioning Role functioning Body pain Current health perception Psychological distress The clinical efficacy of zanamivir and was reported is the Monto 1999c trial Safety outcomes are not reported
Notes	The authors conclude that zanamivir treatment reduced absenteeism, improved patient productivity and well being, and reduced the additional use of healthcare resources in patients with influenza. It is very difficult to understand the basis for this conclusion when Table II shows equal proportion of influenza cases throughout the arms. The use of aggregate measures such as lest-squares mean scores for health status indicators and presentation in histogram form makes interpretation very difficult

Risk of bias

Item	Authors' judgment	Description
Allocation concealment?	Unclear	B - Unclear

Boivin 2000

Methods	Double-blind, randomised, placebo controlled, multi centre sub-study, part of the MIST study, assessing the relationship between alleviation of all clinical important symptoms (as defined by no fever and other flu symptoms recorded as absent or mild for at least 24 hours) and reduction of viral load. The study was conducted during the 1997–1998 season in Québec and Winnipeg, Canada
Participants	Thirty-five patients were enrolled. 27 (77%) had an influenza virus infection laboratory-confirmed on day 1. All subjects had influenza A virus H3 infections. 10 received a placebo, 17 received zanamivir. Three influenza virus positive high-risk subjects were enrolled (2 in the placebo, 1 in zanamivir group). Healthy adolescents and adults, older than 12 years, and high risk subjects (defined as those with chronic respiratory, cardiovascular, or renal disease) with naturally occurring influenza A virus infections
Interventions	Inhaled zanamivir 10 mg 2 x daily for 5 days
Outcomes	Laboratory: serial swabs viral resistance insurgence analysis viral load Effectiveness: fever time to alleviation of symptoms Safety: no safety outcomes are mentioned
Notes	The authors conclude that: 1) zanamivir produced a rapid antiviral effect following inhalation, and this was noted as early as 12 hours after beginning treatment, 2) the decrease in virus load induced by zanamivir correlated with a significant reduction in the median time to alleviation of symptoms. 3) neither phenotypic nor genotypic assays detected any evidence of emergence of zanamivir-resistant strains during therapy. This is a sub-study of the pivotal treatment trial MIST. The claim of the relation between decreased viral load and alleviation of symptoms does not appear to be substantiated in the text of the report. All outcomes reported are non-clinical

Risk of bias

Item	Authors' judgement	Description
Allocation concealment	Unclear	B - Unclear

Hayden 1997

Methods	Two multi centre trials in North America (38 centres, 220 individuals) and Europe (32 centres, 197 individuals) conducted during the 1994–1995 influenza season. Both trials assessed the treatment effects of zanamivir using a randomised, double-blind, placebo controlled design
Participants	Otherwise healthy individuals with symptoms suggestive of influenza persisting longer than 48 hours. Mean ages of subjects in the three arms were 31 to 33 years
Interventions	Participants were randomised to receive either 10 mg of inhaled zanamivir by mouth plus 6.4 mg by intranasal spray or 10 mg of inhaled zanamivir and intranasal placebo spray or aqueous placebo by both routes twice daily for five days. During convalescence HAI titres were assessed and 262 individuals had laboratory confirmed influenza. Of these, 56% were due to A/H3N2 and 44% to B virus
Outcomes	Overall nine placebo patients and ten from each of the other arms withdrew or were lost to follow up (explained in the text as failure to at tend for the follow up visits). The major outcome assessed in the trial was "time to alleviation of major symptoms" (defined as absence of fever and headache, muscle ache, sore throat and cough). Additionally, time to resumption of usual activities are also reported
Notes	Individuals who commenced treatment 30 hours or less from the onset of illness fared significantly better than those who commenced later. Both interventions significantly shortened duration of illness compared to placebo (5.3 and 5.4 days compared to 6.3 days). Inhaled and intranasal zanamivir significantly shortened non-effective time compared to placebo. Importantly, no effect was seen on non-influenza infected patients (although the data are not presented in the text). Adverse effects are presented in the text as overall and broken down by generalised (respiratory tract and gastrointestinal) and local (perinasal). The authors conclude that zanamivir is safe and effective treatment against influenza A and B if given early in the illness Although clearly randomised, no details of allocation or double blinding are given. The intention to treat analysis has clearly taken place

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Hayden 1999a

Methods	Multicentre randomised double-blind placebo-controlled preventive phase III trials of oseltamivir. Follow up was 8 weeks. Medication continued for 6 weeks after recognition of the outbreak in the study area. Randomisation and allocation were carried by using a computer-generated sequence. Due to the low incidence of influenza (2.4% or 38/1559) the data from the two studies were combined. The study was conducted during the winter of 1997–1998 in Virginia, Texas and Kansas with circulating A/Sydney/5/97 H3N2 strain
Participants	One-thousand five-hundred and fifty-nine healthy unvaccinated adults aged 18 to 65. There were 33 withdrawals from the treatment arms and 21 from the placebo arm
Interventions	Oral oseltamivir 75 mg daily (n = 520), or twice daily (n = 520) or placebo (n = 519) for six weeks. Acetaminophen could also be taken by protocol agreement
Outcomes	Serological/Laboratory: viral isolation and paired sera for antibody titres were taken Effectiveness: influenza (presence of ILI symptoms and culture within two days of symptom onset and/or antibody rise) asymptomatic influenza (antibody rise in the absence of symptoms) ILI: oral temp of 37.2 degrees C or more with at least one respiratory (cough, sore throat, coryza) or one constitutional symptom (aches, fatigue, headache, chills, sweats) Safety: study withdrawals: withdrawals due to Aminotransferase concentration increase withdrawals due to gastrointestinal events headache nausea vomiting
Notes	The authors conclude that protection of 76 per cent is satisfactory given the low level of influenza activity. The study is reasonably reported but procedures for double blinding are not described and effectiveness outcomes are very confusingly named and described

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Hayden 2000a

Methods	Multicentre, double-blind, randomised, placebo-controlled PEP trial that took place during the 1998 to 1999 winter in the USA
Participants	Two hundred and twenty one index cases aged 18 to 20 and 837 family contacts aged around 25 to 26 years in 337 families (168 assigned to placebo and 169 to zanamivir)
Interventions	Index cases received either inhaled zanamivir 10 mgs daily or placebo for five days. Family contacts received either zanamivir 10 mgs daily or placebo for ten days
Outcomes	Serological: serum assays, PCR and culture (with resistance assay) Effectiveness: ILI Efficacy: Influenza and duration of symptoms Safety: not better defined but authors report a profile similar to placebo
Notes	The authors conclude that zanamivir was 79% (57% to 89%) effective and 72% (42% to 87%) effective in preventing contacts from developing symptomatic influenza and 53% (27%to 70%) effective and 48% (15% to 68%) efficacious in symptomatic and asymptomatic influenza. Zanamivir shortened duration of symptoms by 2.5 days. There was no evidence of the onset of resistance. Allocation concealment is not described

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D – Not used

Hayden 2004

Methods	(WV 16163) Multicentre, open-cluster randomised trial conducted in Europe and North America during the 2000–2001 influenza season. The aims of the study were to assess the effects of post-exposure prophylaxis (PEP) with oseltamivir compared with standard treatment (oseltamivir if symptoms occurred in contacts) and the possible onset of resistance Eligible households had a maximum of 3 and a minimum of 8 members, including at least 1 index case and at least 2 eligible contacts aged 1 year or more. Children aged younger than 1 year were excluded. Randomization was stratified by the presence or absence of an infant (aged younger than 1 year) in the household and by the presence or absence of a second index case (IC) in the household. ICs and contacts recorded symptoms twice daily on diary cards for 30 days
Participants	Eight-hundred and twelve healthy and non-pregnant household contacts of 298 index cases presenting with an influenza-like illness (temperature 37.8C or more plus cough and/or coryza) during a documented community influenza outbreakwere randomised by household (n = 277). There were 20 contact exclusions, 11 because of lack of information and 9 due to lack of laboratory infected status data
Interventions	PEP with oseltamivir for 10 days or treatment at the time of developing illness (expectant treatment) during the post exposure period beginning within 48 h of the reported onset of symptoms in the index case. All index cases received oseltamivir treatment twice daily for 5 days. Contacts in the expectant treatment arm were also given a standard 5-day treatment course if illness developed (adults and adolescents older than 12 years received 75 mg oseltamivir capsules twice daily, whereas children aged 1 to 2, 3 to 5, and 6 to 12 years received 30, 45, and 60 mg oseltamivir suspension, respectively, twice daily). A second course of treatment could be provided in the event that the subject developed an ILI after the completion of the first course of oseltamivir
Outcomes	Serological: throat and nose swabs and paired serum samples for determining influenza strain-specific hemagglutination-inhibition (HAI) antibody titers Effectiveness: percentage of households with at least 1 secondary case of influenza during the 10-day period after the start of treatment in the ICs (primary efficacy outcome) Percentage of households with at least 1 secondary case of ILI during the 10-day period after the start of treatment in the ICs Both outcomes were also calculated for individual contacts and for children aged 1 to 12 years Duration of illness (time to alleviation of symptoms for treated ICs and for ill contacts: the first 24 h period in which the severity of all influenza symptoms were remained as mild or none) Efficacy analyses were carried out for: intention-to-treat index-infected (ITTII) population defined as those households and contacts of laboratory-confirmed, influenza-infected ICs Subpopulation of contacts who were virus-negative at baseline (ITTIINAB) Overall intention-to-treat (ITT) population (all randomised households and contacts, regardless of infection status in the IC) Safety: withdrawals nausea vomiting The data for children aged 1 to 12 were not extracted
Notes	The authors conclude that oseltamivir is safe and effective in interrupting household transmission. A very confusing report with unclear alternative interventions and outcomes which had to be pieced together from fragments of text. Randomisation details are lacking together with cluster co-efficient data

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D – Not used

Kaiser 2000

Methods	Multicentre, double-blind, placebo-controlled randomised controlled trial. The trial assessed the prophylactic activity of zanamivir after presumed exposure to influenza in the community. The study was conducted from November 1995 to March 1996 in Europe and North America when A/H3N2 was the predominant strain
Participants	Five hundred and seventy five asymptomatic subjects aged 13 to 65 years (mean age 34 to 35 years) who had been in close contact with index cases of influenza like illness of no longer than 4 days duration (ILI was defined as temp of 37.8C or more or feverishness with at least two of the following: headache, myalgia, cough and/or sore throat). No withdrawals are mentioned
Interventions	Participants were randomised to four treatment groups: 1) 2 intranasal sprays of zanamivir (16 mg/mL) per nostril (0.1 mL per spray) plus 2 placebo inhalations 2) 2 zanamivir inhalations (5mg per inhalation) plus 2 placebo sprays per nostril 3) inhaled and intranasal zanamivir 4) 2 placebo inhalations and 2 placebo sprays per nostril All were self administered for 5 days
Outcomes	Outcomes Serological/laboratory: serum samples (days 1 and 21) and viral upper airways samples were taken Effectiveness: six point scale of influenza like symptoms ILI, including: - headache sore throat feverishness, muscle aches, cough, nasal congestion, weakness loss of appetite Observations were recorded twice daily for 10 days Safety: no detailed outcome data are reported
Notes	The authors conclude that short term treatment with intranasal zanamivir was ineffective. However, inhaled zanamivir treatment reduced the rate of influenza, which was 2% to 3%among zanamivir recipients versus 6% among placebo recipients The results in the text are reported in a very confusing fashion. It is likely that "influenza at 21 days" and "Symptomatic or asymptomatic influenza 21 days after initiation" are the same outcome reported twice differently in the text and table 2. Because of the possibility of error, data on asymptomatic influenza have not been extracted

Risk of bias		
Item	**Author's judgement**	**Description**
Allocation concealment	Unclear	B- Unclear

Kashiwagi 2000a

Methods	Double-blind placebo-controlled randomised controlled trial of the preventive effects of oseltamivir against influenza A and B. The study was carried out in 33 centres in Japan. Both H3N2 and H1N1 were co-circulating at a low level the time with H3N2 accounting for 10 of the 13 cases in the placebo arm of the trial. Follow up and administration of the drug was for 42 days, with a further post-administration of 57 days' duration
Participants	Three hundred and eight healthy subjects aged 16 to 89 (mean 34 years), predominantly non-smokers. There were three withdrawals in the intervention arm (one each for adverse events, protocol violation and voluntary withdrawal)
Interventions	Oral oseltamivir (Roche) 75 mg or placebo daily for six weeks

Outcomes	Serological: viral antibody titres Effectiveness: Group 1: participants with fever of 37.5 degrees C or more and at least two other influenza symptoms with laboratory confirmed influenza Group 2: participants without fever of 37.5 degrees C or more or at least two other influenza symptoms with laboratory confirmed influenza Group 3: participants with no symptoms or signs with laboratory confirmed influenza Group 4: participants with symptoms without laboratory confirmed influenza Safety: diarrhoea, abdominal pain upper, nausea, abdominal pain, vomiting, abdo, distension, stomatitis, loose stools, retching, sore throat, faecal abnormality, gingivitis, constipation, oral discomfort, tooth loss, toothache, gingival oedema, dyspepsia, food poisoning, oesophagitis, glossitis, enterocolitis, headache, sneezing, dizziness, somnolence, insomnia, paraesthesia, cough, rhinorrhea, epistaxis, allergic rhinitis, nasal passage irritation, nasal congestion, tonsillitis. Other adverse events are grouped by infectious, local, musculoskeletal, reproductive, metabolic, cutaneous, injury and poisoning, eye, vascular, ENT, renal An extensive list of laboratory and diagnostic tests is reported
Notes	The authors conclude that oseltamivir is safe and effective in the prevention of influenza. Despite not being able to consult the text, the tables and abstract report sufficient information. The study appears welldesigned and well reported

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Kashiwagi 2000b

Methods	Double-blind placebo-controlled randomised trial of the treatment effects of oseltamivir against influenza A and B. The study was carried out in 79 centres in Japan. Both H3N2 and H1N1 were co-circulating at the time with H3N2 accounting for nearly 60% of infections in both arms of the trial. Follow up and administration of the drug was for 5 days, with a further post-administration of 21 days' duration
Participants	Three hundred and sixteen subjects were enrolled, 162 in the placebo arm and 154 in the active arm (including one in the placebo arm was given the study drug by mistake). There were 3 withdrawals from the active arm (one each for overdosing not turning up for follow up and voluntary withdrawal) and 11 from the placebo arm (4 for adverse events, 4 for voluntary withdrawal, 1 was given the study drug by mistake, 1 "other" and 1 for not turning up for follow up) so 151 in each arm completed the trial. Participants were aged 16 to 89 (mean age 35.5 in the active arm and 33.6 in the placebo arm). Five were inpatients. One hundred and twenty two participants were infected with influenza and 130 in the placebo arm. These represented the ITT1 population
Interventions	Oral oseltamivir (Roche) 75 mg or placebo twice daily for five days. In the ITT1 population, administration took place within 36 hours of onset of symptoms for all but 8 in the active arm and 5 in the placebo arm
Outcomes	Serological: viral antibody titres Effectiveness: time to resolution of illness (ITT1) time to resolution of symptoms (ITT1) cases of influenza (ITT1) influenza viral titre severity (symptom scores) Safety: diarrhoea, abdominal pain upper, nausea, abdominal pain, vomiting, abdo, distension, stomatitis, loose stools, retching, sore throat, faecal abnormality, gingivitis, constipation, dry mouth, oral pain, tooth ache, gingival oedema, dyspepsia, tongue coated, oesophagitis, glossitis, enterocolitis, headache, sneezing, dizziness, somnolence, insomnia, paraesthesia, cough, rhinorrhea, dizziness, grand mal convulsion, epistaxis, allergic rhinitis, nasal passage irritation, nasal congestion, tonsillitis. Other adv events are grouped by infectious, local, musculoskeletal, reproductive, metabolic, cutaneous, injury and poisoning, eye, cardiac, ENT, renal An extensive list of laboratory and diagnostic tests is reported

Notes	The authors concluded that oseltamivir is safe and effective in reducing length of illness. Lack of translation of parts of the text make assessment of quality difficult. The imbalance in denominators is not explained

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Li 2003

Methods	Double-blind randomised placebo-controlled trial to assess the efficacy of oseltamivir in the treatment of naturally occurring influenza. Background rates of infections are not described, nor strains isolated from participants are described
Participants	Four hundred and seventy eight healthy adults aged 18 to 65 with symptoms consistent with influenza (fever of 37. 8 degrees C or more, plus at least two others: coryza/nasal congestion, sore throat, cough, myalgia/muscles aches and pain, fatigue, headache or chills/sweats). People with influenza vaccination less than 12 months before the study were excluded. Sixteen participants were lost to follow up or refused to continue the trial, 3 were excluded prior to taking medication because they did not meet the entry criteria, and 8 were excluded because of protocol violation. Four hundred and fifty one individuals were analyzed for efficacy as the ITT population (216 oseltamivir and 235 placebo) with 273 individuals were identified as influenza infected through laboratory test and were regarded as the ITTI population (134 oseltamivir and 139 placebo). For the safety analysis, 459 individuals were included (137 oseltamivir group with influenza, 84 oseltamivir group without influenza, 141 placebo group with influenza, and 97 placebo group without influenza)
Interventions	Oral oseltamivir phosphate or placebo (Roche) 75 mg bid for 5 days
Outcomes	Serological: culture or serological tests were used to confirm influenza cases (symptoms and a positive culture on day 1 and/or = 4 fold increase in HAI antibody between baseline and day 21 of the study). Viral cultures were performed on all participants: 224 positive and 254 negative. Of 224 individuals with positive culture, serum HAI antibodies on days 1 and 21 were completed in 160 individuals (133 positive, 27 negative). Of 254 with negative cultures, HAI antibodies were completed in 146 individuals (58 positive, 88 negative) Effectiveness: the primary outcome was time to resolution of symptoms (from the onset of symptoms to the time that all symptoms were resolved). A symptom severity scale was used (0 = no problem, 1 = minor, 2 = moderate, 3 = severe). Symptoms scores are reported as median areas under the curve of decreased total score and cumulative alleviation proportion by arm as survival curve Logrank test Safety: nausea, upset upper abdomen, vomiting, vertigo, insomnia, and rash were reported with an increased frequency in the active arm but the difference was not significant. Numerators are not reported. Follow up took place at days 3, 6, 8 and 21 (vital signs and laboratory examinations included blood routine, urine routine, liver and renal function)
Notes	The authors conclude that oseltamivir is well tolerated and efficacious in relieving symptoms within 36 of onset of influenza and could be used routinely on all symptomatic subjects during an outbreak. A very badly reported trial, with impenetrable outcome reporting

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Makela 2000

Methods	Randomised double-blind, placebo-controlled trial to assess the effectiveness of zanamivir in the treatment of subjects presenting with influenza symptoms during a period of influenza activity. The trial took place in 11 European countries during the winter of 1997–1998. The predominant strain was A/H3N2. Follow up was up to 28 days
Participants	Three hundred and fifty six patients aged 12 or more. Patients presenting with acute febrile influenza-like illness. Patients were required to have a fever 37.8C or more for patients aged less than 65, 37.2C or more for patients aged 65 or more, with at least two of the following symptoms: headache, myalgia, cough and sore throat. They had to start therapy within 2 days of symptom onset. Women who were pregnant or at risk of pregnancy were excluded

Interventions	Within two days of onset of typical influenza symptoms and received orally inhaled zanamivir 10 mg via diskhaler twice daily for five days or matching placebo
Outcomes	Serological: influenza was confirmed by diagnosis of virus culture, virus isolation, seroconversion, or by virus detection PCR. Influenza A subtyping was performed by serology and PCR Effectiveness: time until alleviation of clinically significant symptoms of influenza time to alleviation and no use of relief medication, time to return to normal activities influenza high risk influenza positive Safety: bronchitis sinusitis diarrhoea pharyngitis nausea and vomiting pneumonia
Notes	The authors conclude that zanamivir is effective in reducing the duration and severity of influenza illness and is well tolerated. No age breakdown is given and the whole text gives the idea of careful editing to enhance effect of zanamivir. Reporting of clinical outcomes is in the format of Area Under the Curve (AUC)

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Matsumoto 1999

Methods	Double-blind, randomised, placebo-controlled trial of the treatment efficacy of inhaled and intranasal zanamivir for five days. Follow up was up to 28 days. ITT analysis was carried out. The study was carried out in 28 centres in Japan during January to March 1995. The dominant strain was A/H3N2
Participants	One hundred and sixteen healthy subjects aged 16 to 65 recruited in 28 centres randomised to three arms. Participants with a set list of symptoms who presented themselves to their family doctor within 36 hours of onset were enrolled. Two participants dropped out from arm 1 and 2 from arm 3 because of lack of improvement
Interventions	Zanamivir (Nippon Glaxo) dry powder (5 mg/inhalation) or matching placebo or aqueous intranasal spray (1.6 mg/spray) or matching placebo were administered. Participants received either two inhalations (10 mgs) plus intranasal placebo, or 10 mg inhaled zanamivir plus two spray per nostril (6.4 mg) or double placebo for five days. As initial analysis failed to detect any difference between arm 1 and arm 2, the data from the two arms was compared with placebo
Outcomes	Serological: serology and virological samples were taken and influenza viruses identified with PCR Effectiveness: participants were instructed in the use of diaries to record symptoms - Time to alleviation of: fever, headache and myalgia, cough and sore throat (used in the text as corporate indicator of lower fever, headache and myalgia) - Time to resumption of normal activities Safety: possible adverse events hoarse voice, headache, diarrhoea

Notes	The authors conclude that participants in the active arms recovered faster by one day compared to placebo recipients (3 days instead of four). Continuous outcomes are summarised in the text either median and interquartile ranges (time to alleviation) or as Kaplan-Meyer plots (time to resumption of normal activities). Average reporting quality but randomisation and double blinding are not described

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

MIST 1998

Methods	Multi-centre randomised placebo-controlled trial of the treatment and safety effects of zanamivir in healthy adults with ILI and influenza. Randomisation and allocation were centralised. Concealment was by means of sealed envelopes on site. Follow up was 28 days and symptoms were self-recorded with diaries. The study was conducted in 1997 in Australia, New Zealand and South Africa, with A/H3N2 being the dominant viral strain
Participants	Four hundred and fifty five healthy and non-pregnant persons aged 12 or more (mean 37 years) with influenza symptoms of no more than 36 h (temp of higher than 37.8 degrees C or feverishness or both and at least two of the following myalgia, sore throat, cough, headache). There were 76 participants (57 with respiratory diseases,15 aged 65 or more, 11 with a metabolic disease, 8 hypertensives and 2 immunocompromised). There were 58 withdrawals: 31 for adverse events (27 in the zanamivir arm and 4 on placebo), withdrawn consent (5 and 3), loss to follow up (7 and 10) and 2 because of protocols violation (1 and 1)
Interventions	Inhaled zanamivir 10 mg bd or placebo for five days. An antipyretic and antitussive were also dispensed with a request not be used routinely
Outcomes	Serological/Laboratory: viral cultures and paired antibody titre estimations Effectiveness: symptoms (duration and severity): feverishness, cough, headache, sore throat, myalgia, nasal congestion, weakness and anorexia were rated on a 4-point scale (0 = no symptoms; 1 = mild; 2 = moderate; 3 = severe) temp sleep disturbance ability to perform normal activity complications antibiotic use Safety: adverse events bronchitis cough sinusitis LRTC diarrhoea nausea and vomiting
Notes	The authors conclude that zanamivir was effective and well-tolerated. A well reported study although safety outcome definitions are not given and it is difficult to see how adv events such as bronchitis could be distinguished from influenza disease. The format of reporting of outcomes ay lead to considerable loss of data

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Monto 1999a

Methods	Double-blind randomised, placebo-controlled trial assessing the effects of zanamivir, administered once daily, in the prevention of influenza infection and disease. Follow up was for 35 days. Randomisation was stratified in blocks of 10 for each site and participant were assigned sequentially to pre-randomised packaged drug or placebo. The study was conducted during the 1997–1998 influenza season in two Midwest university communities, United States (Universities of Michigan and Missouri). A/Sydney/5/97 H3N2 was the dominant strain
Participants	One thousand one hundred and seven healthy adults, mean age 29, range 18 to 69 years, mainly students or community volunteers. 1107 included in the ITT analysis. Eleven discontinued the trial for adverse events, 16 for consent withdrawal or loss to follow up. Follow up was for up to 28 days with a final visit at day 35
Interventions	Zanamivir 10 mg or placebo for six days or more up to 28 days, administered by self-activating inhalation once daily using a Diskhaler device
Outcomes	Serological/Laboratory: serum samples and paired sera for antibody titres Effectiveness: influenza if had 2 of the following recorded successively in at least 3 diary entries: cough, headache, sore throat, myalgia, feverishness or temp of at least 37.8 C with a rise in antibody titres and/or viral isolation febrile influenza if temp of at least 37.8 degrees C with a rise in antibody titres and/or viral isolation febrile illness if only temp of at least 37.8 degrees C Safety is not mentioned in detail, only as any adverse event
Notes	The authors conclude that zanamivir administered once daily is efficacious and well tolerated in the prevention of influenza for a 4-week period in healthy adults. A reasonably reported study

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequae

Monto 1999b

Methods	Double-blind randomised placebo-controlled multi-centre parallel group study. Follow up was for 21 days. The study was conducted in November to March 1996 in North America and Europe. The dominant strains were A/H3N2 and A/H1N1
Participants	One thousand two hundred and fifty six healthy patients, aged 13 years or more (mean around 35 to 36 years) who had symptoms of influenza up to 48 h duration were enrolled. See below for definition of symptoms. There were seventy four withdrawals, these were for adverse events, lost to follow up and other reasons. Seven hundred and twenty two (57%) participants were found to have influenza. There were 158 participants described as high risk (*n* = 69 with asthma; *n* = 31 with cardiovascular disease; *n* = 18 had metabolic conditions; *n* = 39 were aged 65 or more
Interventions	Zanamivir 10 mg 2 x daily by oral inhalation plus 6.4 mg 2 x daily nasal spray versus zanamivir 10 mg 4 x daily by oral inhalation plus 6.4 mg 4 x daily by nasal spray versus placebo by both routes 2 x daily versus placebo by both routes 4 x daily. Placebo groups were combined for analysis. Medication was self administered and patients were instructed to take the inhaled medication before the intranasal medication. All patients were provided with acetaminophen tablets and dextromethorphan cough suppressant but were instructed to avoid using these medications unless their symptoms became sufficient to warrant them

Outcomes	Serological: serum assays at days 1 and 21 and viral isolation from airways Effectiveness: oral temp severity of symptoms: rated on six point scale in which '0' corresponded to no symptoms and '5' corresponded to severe symptoms sleep disturbances level of ability to perform normal activities health questionnaire time to alleviation of clinically significant symptoms, defines as the absence of feverishness, a temperature less than 37.8C and a score of 0 (none) or 1 (mild) for other major symptoms (i.e., headache, myalgia, sore throat and cough) for at least 24 hrs or more time to return to normal activities use of acetaminophen and cough mixture to relieve symptoms Safety Diarrhoea Nausea and vomiting Nasal signs and symptoms Headaches Bronchitis Withdrawal due to possible adverse events
Notes	The authors conclude that zanamivir can significantly reduce the duration and overall symptomatic effect of influenza. A summarily reported trial with selective and heterogeneous reporting of outcomes

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Monto 2002

Methods	Double-blind randomised placebo controlled PEP trial
Participants	Four hundred and eighty seven households with 1291 contacts aged 5 or more (mean age around 19 years)
Interventions	Inhaled zanamivir 10 mgs once daily for ten days. Index patients with ILI received symptomatic medication only
Outcomes	Serological: serum assays, PCR and culture (with resistance assay) Effectiveness: ILI Efficacy: Influenza Safety: not better defined but authors report a profile similar to placebo (no cases of bronchospasm are reported in the intervention arm, but two are reported in the placebo arm)
Notes	The authors conclude that zanamivir is effective in prophylaxis and interrupting transmission (79% effectiveness and 81% efficacy - 64% to 90% - for households and 82% for individuals and was well tolerated. Zanamivir shortened duration of illness by 1.5 days. No viral resistance was reported. A reasonably reported trial

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B – Unclear

Nicholson 2000

Methods	(WV 15670) Randomised double-blind placebo-controlled preventive phase IIIa trials of Ro 64-0796. WV 15670 was conducted in Europe, Canada and China during the 1997–1998 winter. 473 otherwise healthy individuals who presented with at least on respiratory and one constitutional symptom were randomised within 36 hours of onset. AH3N2 was the dominant strain
Participants	Seven hundred and twenty six healthy (apart from ILI symptoms) participants aged 18 to 65 were enrolled. Four hundred and seventy five participants had influenza (161, 158, 156 respectively) There were seven withdrawals for lack of compliance and 15 because of adverse events and 23 protocol violations
Interventions	Either oseltamivir 75 mg daily orally (n = 155), or twice daily (*n* = 157), or "matching" placebo (*n* = 161) for five days
Outcomes	Serological: culture and serological specimens were used to diagnose influenza infection Effectiveness: the main outcome was the time to alleviation of symptoms expressed in days and type and incidence of adverse events. Additionally severity of illness was also assessed bymeans of a symptomscore and antibiotic use was recorded in each arm influenza was defined as viral isolation and/or antibody titre (at 3/52 interval) increase. The laboratory assessment was done in a blinded fashion Safety: nausea vomiting (reported as mean frequencies by arm) all outcomes were assessed twice daily for 21 days
Notes	The authors conclude that the time to alleviation of symptoms was significantly reduced in the active arms. Equally there was a 30% reduction in the symptoms scores of the active arms of both trials. As in the prophylaxis/prevention trials of oseltamivir, nausea was the most reported systemic adverse event, especially at the higher dose. The methodological quality of the study is reasonable. Randomisation by centralised computer and robust allocation concealment procedures are explicitly mentioned in the text

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Puhakka 2003

Methods	Multi-centre double-blind randomised placebo-controlled trial of treatment effects of zanamivir in Finnish armed forces conscripts. Randomisation was computerised in blocks of 6. Only investigator-prescribed paracetamol was allowed. The study was conducted (2000–2001) over two influenza seasons with A/H3N2 and A/H1N1 respectively as dominant strains
Participants	Five hundred and eighty eight conscripts aged around 19 and mainly males, presenting with symptoms of ILI of less than 48 h duration with a temp of 38C or more and at least 2 of the following: headache, muscle/ joint aches sore throat or cough during periods of influenza viral circulation. Surveillance was carried out throughout the influenza season. Diary cards were kept by participants for 28 days
Interventions	Inhaled zanamivir 5 mg per inhalation or placebo (lactose powder) bid for 5 days

Outcomes	Laboratory: real-time PCR, nasal and throat swabs (at 0, 8, 24 and 48h) and antibody titres (days 1 and 28) were collected Effectiveness: time to alleviation of symptoms (temp less than 37.8C and feverishness score as "none" and other symptoms recorded as 0 or 1 for 24 h) time to alleviation of symptoms with no use of relief medication (temp less than 37.8C and feverishness score as "none" and other symptoms recorded as 0 or 1 for 24 h in patients who have not taken relief medication) viral load use of relief medication severity of symptoms (overall symptoms, headache, cough, feverishness, sore throat, anorexia, muscle/joint aches and pains, weakness; on a scale: 0 = no symptoms; 1 = mild; 2 = moderate; 3 = severe) Complications: use of antibiotics for complications use of diagnostic procedures general well being was assessed using the - measure yourself medical outcomes - MYMOP questionnaire Safety: ILI symptoms that got worse bronchitis COPD or asthma that got worse Acceptability: ease of use of diskhaler device (data not extracted)
Notes	The authors conclude that zanamivir significantly reduces viral load, however startling improvements in symptoms could not be observed because of the characteristics of this very healthy population. In the discussion the authors observe the short and benign duration of the illness (median 2.33 d in the placebo arm). A reasonably reported study with no mention of blinding procedures. Data are not reported for a number of outcomes (for example, general well-being, use of relief medication, etc) for which data were apparently collected
Risk of bias	
Item	**Authors' judgement** **Description**
Allocation concealment?	Unclear B - Unclear

Treanor 2000

Methods	(WV 15671) Multicentre double-blind placebo-controlled randomised trial of the efficacy of oseltamivir in cases of influenza of 36 hours' duration or more. Randomisation and allocation were centralised through an automated phone programme. Although the aim of the study is to test the efficacy of the drug, data for both efficacy influenza) and effectiveness (ILI) are reported. The study was conducted between January and March 1998 in the USA. A/H3N2 was the dominant viral strain
Participants	Six hundred and twenty nine unvaccinated previously healthy adults aged 18 to 65 presenting within 36 h of symptom onset (oral temp 38 degrees C or more and at least one of the following: cough, sore throat, nasal symptoms and headache, malaise, myalgia, sweats/chills, fatigue). There were 46 withdrawals (16, 19 and 11 respectively) Follow up was 21 days, with twice daily observations recorded on diaries
Interventions	Interventions Oral oseltamivir 75 mg or 150 bd or placebo for 5 days

Outcomes	Serological/laboratory: viral culture for airway swabs and antibody titres at days 1 and 21 Effectiveness: symptom severity (graded on a 4 point scale) ability to perform usual activities and health status (11-point visual analogue scales) oral temp number and type of complications Safety: nausea vomiting withdrawals due to adverse effects
Notes	The authors conclude that oseltamivir reduces duration of illness and may reduce complications. Convoluted reporting and extensive use of medians may lead to loss of important data

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Welliver 2001

Methods	Multicentre double-blind placebo-controlled cluster randomised controlled trial (C-RCT) of the effects of oseltamivir in the interruption of transmission of influenza in families. The study was conducted in the winter of 1989–1999 in North America and Europe (76 centres)
Participants	Three hundred and seventy four households (962 healthy contacts with a mean age of 33, minimum 2 members and maximum 8 members per household) of 377 index cases (ICs) presenting within 48 h of onset of cough and coryza. Children aged up to 12 were enrolled only if other contacts in the household met the enrolment criteria A household represented a cluster (all members were randomised to the same treatment) There were 4 withdrawals due to contact not taking study medication and 7 withdrawals due to adverse events (5 in the active and 2 in the placebo arm)
Interventions	Oseltamivir 75 mg die or placebo within 48 h of symptom onset for 7 days and 500 mg of acetaminophen if needed. ICs were not treated
Outcomes	Serological: nasal swabs and paired antibody titres Effectiveness: proportion of contacts of IC with influenza within days 1 to 7 of the intervention ILI (oral temp of 37.2 degrees C or more and at least cough, nasal congestion or sore throat and headache, fatigue, chills or myalgia within 24 h) influenza (ILI plus laboratory confirmation) Safety: GI adverse events nausea withdrawals due to adverse events
Notes	The authors conclude that oseltamivir was well tolerated and prevented spread of influenza. Poor reporting of randomisation, cluster correlation calculations and allocation procedures

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclelar

bd, twice daily; bid, twice daily; d, day; ENT, ear, nose and throat; h, hour; IC, index cases; ILI, influenza-like illness; ITTI, intention-to-treat index; ITTII, intention-to-treat index-infected; ITTIINAB, intention-to-treat index-infected virus-negative at baseline.

Characteristics of excluded studies [ordered by study ID]

Ambrozaitis 2005	Prevention of transmission placebo-controlled RCT in elderly in long term care facilities
Aoki 2003	No control arm (Roche study code WV 76006)
Barroso 2005	Viral challenge study on new NI peramivir
Bettis 2006	Data from 1997-1999 registration studies already in review
Bijl 2007	No data presented
Blumentals 2007	Contains retrospective, observational data
Calfee 1999	Experimental influenza only
Cass 1999	No denominator breakdown by arm
Fuyuno 2007	News piece
Hama 2008	Review of Phase IV data
Hayden 1999b	Experimental influenza only
Hayden 2000b	Experimental influenza only
Ison 2003	Population of persons with underlying medical conditions
Kaiser 2003	Unable to determine the number of healthy adults experiencing complications in each study nor the number of patients experiencing one of more of "bronchitis, lower respiratory tract infection, or pneumonia" presenting to each study
Kawai 2005	Prospectve cohort study non comparative with all oseltamivir exposure
Kawai 2006	Non comparative cohort study
Kawai 2007a	Porospective cohort study all treated with zanamivir
Kawai 2007b	Retrospective cohort
Kawai 2007c	Non comparative study with sole exposure to oseltamivir
Kawai 2008	Prospective cohort study with oseltamivir versus nothing
LaForce 2007	Placebo controlled RCT in elderly
Li 2001	Same data set as Li 2003
Li 2004	Redundants publication of Li 2003
Lin 2006	Very small RCT high risk oseltamivir versus do-nothing
Macfarlane 2005	Editorial
Massarella 2000	Phase 2a study with no safety outcomes reported
Monto 1999c	Meta-analysis. No original data presented
Murphy 2000	At risk participants
Peng 2000	Dose-ranging study
Sato 2005	Children admitted to hospital with A/B diagnosis subsequently randomised to oseltamivir, zanamivir, or do-nothing
Sato 2008	Prospective cohort study in children
Toovey 2008	Review. Contains retrospective, observational data

Data and analyses

Comparison 1. NI versus placebo for prophylaxis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Influenza-like illness	4	3549	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.59, 1.44]
1.1 Oral oseltamivir 75 mg daily	2	1088	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.45, 3.66]
1.2 Oral oseltamivir 150 mg daily	1	779	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.25, 3.95]
1.3 Inhaled zanamivir 10 mg daily	2	1299	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.49, 1.19]
1.4 Intranasal zanamivir 0.32 mg daily	1	189	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.21, 2.95]
1.5 Inhaled and intranasal zanamivir 10 mg and 0.32 daily	1	194	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.07, 1.58]
2 Influenza (symptomatic)	4	3549	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.23, 0.48]
2.1 Oral oseltamivir 75 mg daily	2	1087	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.12, 0.48]
2.2 Oral oseltamivir 150 mg daily	1	780	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.11, 0.67]
2.3 Inhaled zanamivir 10 mg daily	2	1299	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.18, 0.59]
2.4 Intranasal zanamivir 0.32 mg daily	1	189	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.25, 2.37]
2.5 Inhaled and intranasal zanamivir 10 mg and 0.32 daily	1	194	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.17, 2.53]
3 Influenza (symptomatic and asymptomatic)	4	3549	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.49, 0.76]
3.1 Oral oseltamivir 75 mg daily	2	1087	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.31, 0.68]
3.2 Oral oseltamivir 150 mg daily	1	780	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.29, 0.80]
3.3 Inhaled zanamivir 10 mg daily	2	1299	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.50, 0.91]
3.4 Intranasal zanamivir 0.32 mg daily	1	189	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.54, 2.08]
3.5 Inhaled and intranasal zanamivir 10 mg and 0.32 daily	1	194	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.38, 1.56]
4 Influenza (asymptomatic)	3	2974	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.62, 1.12]
4.1 Oral oseltamivir 75 mg daily	2	1087	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.43, 1.26]
4.2 Oral oseltamivir 150 mg daily	1	780	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.35, 1.28]
4.3 Inhaled zanamivir 10 mg daily	1	1107	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.65, 1.47]

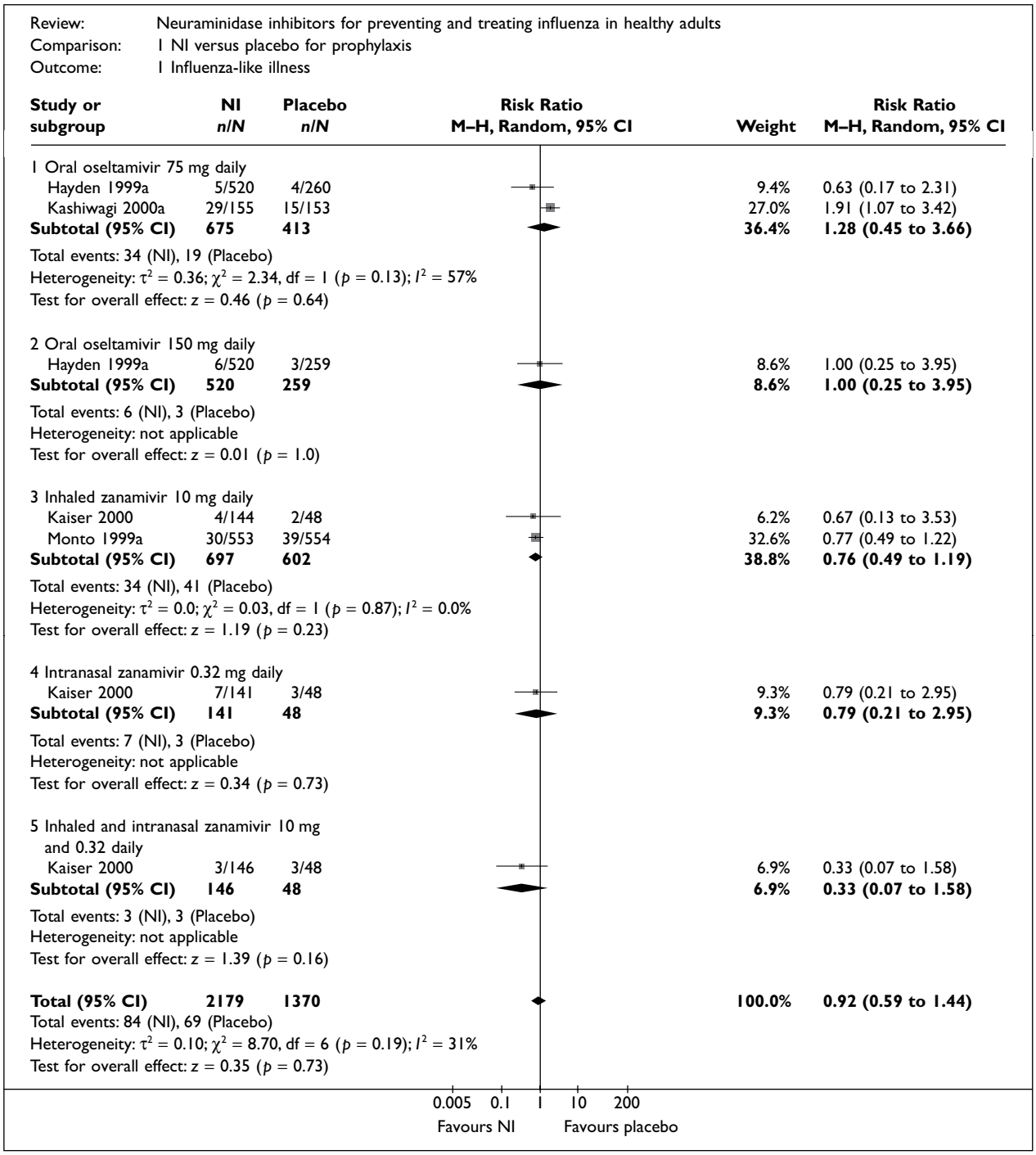
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Adverse events - nausea	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Oral oseltamivir 75 mg daily	2	1088	Odds Ratio (M-H, Random, 95% CI)	1.79 [1.10, 2.93]
5.2 Oral oseltamivir 150 mg daily	1	779	Odds Ratio (M-H, Random, 95% CI)	2.29 [1.34, 3.92]
6 Adverse events - vomiting	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Oral oseltamivir 75 mg daily	2	1088	Odds Ratio (M-H, Random, 95% CI)	2.28 [0.87, 5.95]
6.2 Oral oseltamivir 150 mg daily	1	780	Odds Ratio (M-H, Random, 95% CI)	3.57 [0.81, 15.82]
7 Adverse events - diarrhoea	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Oral oseltamivir 75 mg daily	1	308	Odds Ratio (M-H, Random, 95% CI)	0.58 [0.28, 1.20]
8 Adverse events - abdominal pain	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Oral oseltamivir 75 mg daily	1	308	Odds Ratio (M-H, Random, 95% CI)	0.99 [0.49, 1.97]
9 Adverse events - others	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 Oral oseltamivir 75 mg daily	1	308	Odds Ratio (M-H, Random, 95% CI)	0.95 [0.59, 1.55]
10 Adverse events – withdrawals due to gastrointestinal events	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 Oral oseltamivir 75 mg daily	1	779	Odds Ratio (M-H, Random, 95% CI)	3.51 [0.18, 68.21]
10.2 Oral oseltamivir 150 mg daily	1	780	Odds Ratio (M-H, Random, 95% CI)	3.52 [0.18, 68.47]

Comparison 2. NI versus placebo for treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time to alleviation of symptoms (ITT)	9	4985	Hazard ratio (Random, 95% CI)	1.22 [1.14, 1.31]
1.1 Zanamivir	6	3188	Hazard ratio (Random, 95% CI)	1.24 [1.13, 1.36]
1.2 Oseltamivir	3	1797	Hazard ratio (Random, 95% CI)	1.20 [1.06, 1.35]
2 Time to alleviation of symptoms (influenza cases only)	11	3491	Hazard ratio (Random, 95% CI)	1.32 [1.26, 1.38]
2.1 Zanamivir	7	2117	Hazard ratio (Random, 95% CI)	1.33 [1.29, 1.37]
2.2 Oseltamivir	4	1374	Hazard ratio (Random, 95% CI)	1.30 [1.13, 1.50]
3 Time to return to normal activity (ITT)	4	2454	Hazard ratio (Random, 95% CI)	1.26 [1.14, 1.40]
3.1 Zanamivir	3	1827	Hazard ratio (Random, 95% CI)	1.28 [1.13, 1.45]
3.2 Oseltamivir	1	627	Hazard ratio (Random, 95% CI)	1.23 [1.02, 1.48]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Time to return to normal activity (influenza cases only)	4	1234	Hazard ratio (Random, 95% CI)	1.22 [1.07, 1.39]
4.1 Zanamivir	3	860	Hazard ratio (Random, 95% CI)	1.17 [1.00, 1.37]
4.2 Oseltamivir	1	374	Hazard ratio (Random, 95% CI)	1.34 [1.07, 1.67]
5 Complications - all types (ILI cases only)	1	79	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.24, 1.19]
5.1 Zanamivir	1	79	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.24, 1.19]
6 Complications - all types (influenza cases only)	4	1122	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.46, 1.00]
6.1 Zanamivir	1	277	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.50, 1.06]
6.2 Oseltamivir	3	845	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.23, 1.37]
7 Complications - all types (ITT)	1	356	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.49, 0.96]
7.1 Zanamivir	1	356	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.49, 0.96]
8 Adverse events - cough	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Zanamivir	2	1043	Odds Ratio (M-H, Random, 95% CI)	1.40 [0.14, 13.49]
8.2 Oral oseltamivir 150 mg daily	1	273]	Odds Ratio (M-H, Random, 95% CI)	1.31 [0.53, 3.22
9 Adverse events - headache	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 Zanamivir	2	1352]	Odds Ratio (M-H, Random, 95% CI)	0.87 [0.39, 1.97
9.2 Oral oseltamivir 150 mg daily	2	586	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.44, 1.87]
10 Adverse events - diarrhoea	5		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 Zanamivir	4	2415	Odds Ratio (M-H, Random, 95% CI)	0.78 [0.37, 1.63]
10.2 Oral oseltamivir 150 mg daily	1	313	Odds Ratio (M-H, Random, 95% CI)	0.56 [0.28, 1.13]
11 Adverse events – nasal symptoms (congestion, rhinitis, dry or sore throat)	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 Zanamivir	3	2299	Odds Ratio (M-H, Random, 95% CI)	0.98 [0.47, 2.06]
11.2 Oral oseltamivir 150 mg daily	1	273	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.51, 1.44]
12 Adverse events - nausea	5		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
12.1 Zanamivir	3	2067	Odds Ratio (M-H, Random, 95% CI)	0.63 [0.36, 1.10]
12.2 Oral oseltamivir 150 to 300 mg daily	2	928	Odds Ratio (M-H, Random, 95% CI)	2.50 [1.49, 4.20]
13 Adverse events - vomiting (oseltamivir)	2	928	Odds Ratio (M-H, Random, 95% CI)	2.60 [0.77, 8.80]

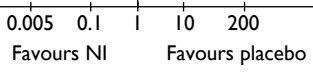
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14 Adverse events - bronchitis or pneumonia	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
14.1 Zanamivir	3	2299	Odds Ratio (M-H, Random, 95% CI)	0.73 [0.24, 2.26]
15 Adverse events - all types	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
15.1 Zanamivir	3	1159	Odds Ratio (M-H, Random, 95% CI)	0.88 [0.69, 1.14]
15.2 Oral oseltamivir 150 mg daily	1	313	Odds Ratio (M-H, Random, 95% CI)	0.67 [0.43, 1.05]
16 Use of relief medications and antibiotics	4	1830	Odds Ratio (M-H, Random, 95% CI)	0.82 [0.60, 1.11]
16.1 Zanamivir	2	838	Odds Ratio (M-H, Random, 95% CI)	0.64 [0.41, 1.01]
16.2 Oseltamivir	2	992	Odds Ratio (M-H, Random, 95% CI)	1.01 [0.67, 1.52]
17 Mean nasal viral titres (at 24 hours since randomisation)	4	1002	Mean Difference (IV, Random, 95% CI)	-0.62 [-0.82, -0.41]
17.1 Zanamivir 10 to 20 mg daily	2	441	Mean Difference (IV, Random, 95% CI)	-0.40 [-0.75, -0.06]
17.2 Oseltamivir 75 to 150 mg daily	2	561	Mean Difference (IV, Random, 95% CI)	-0.73 [-0.99, -0.47]
18 Mean nasal viral titres (at 48 hours since randomization)	3	659	Mean Difference (IV, Random, 95% CI)	-0.63 [-1.13, -0.13]
18.1 Zanamivir 10 to 20 mg daily	2	441	Mean Difference (IV, Random, 95% CI)	-0.71 [-1.58, 0.16]
18.2 Oseltamivir 150 mg daily	1	218	Mean Difference (IV, Random, 95% CI)	-0.44 [-0.74, -0.14]



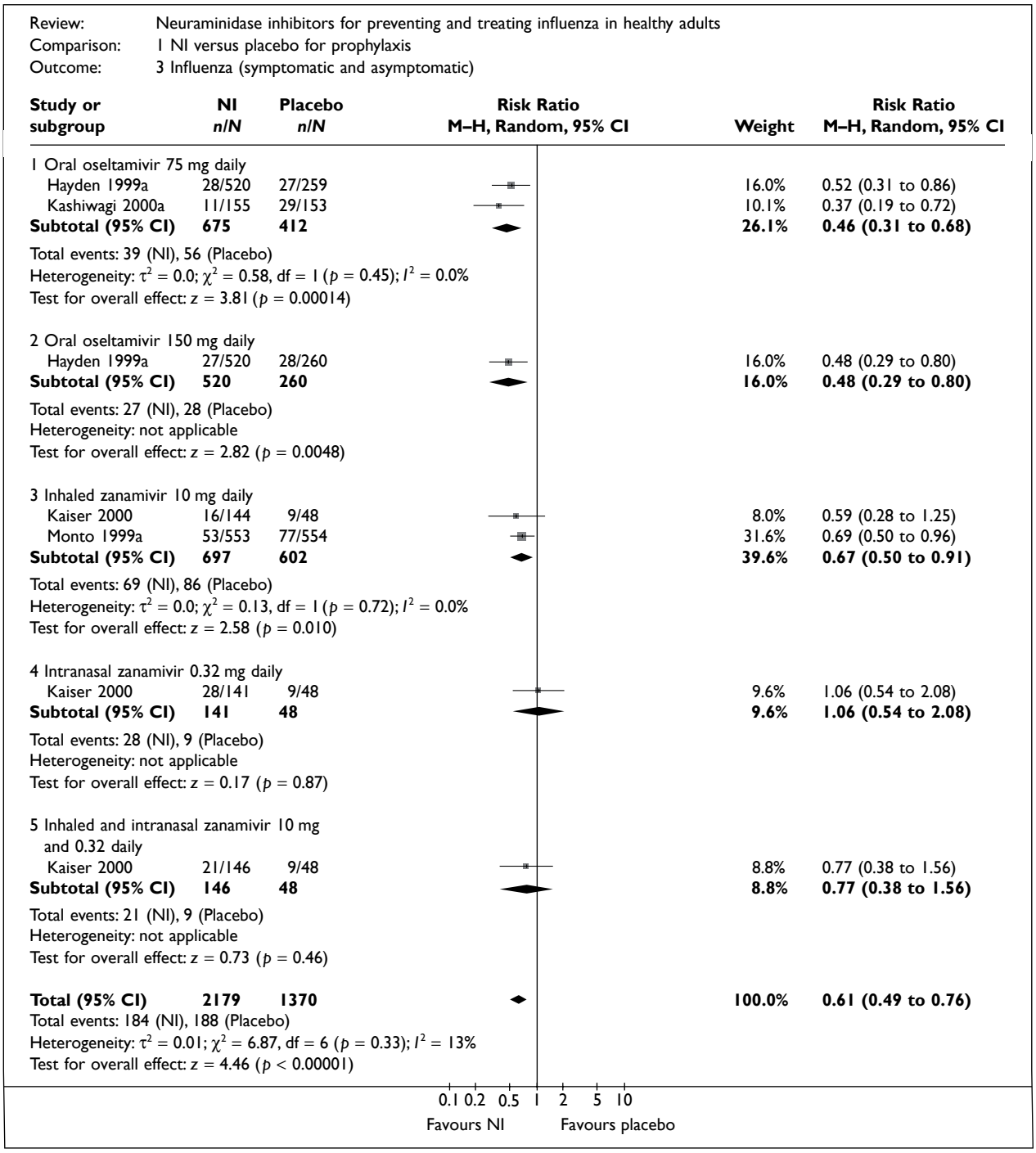
Analysis 1.1 *Comparison 1 NI versus placebo for prophylaxis, Outcome 1 Influenza-like illness.*

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults
Comparison: 1 NI versus placebo for prophylaxis
Outcome: 2 Influenza (symptomatic)

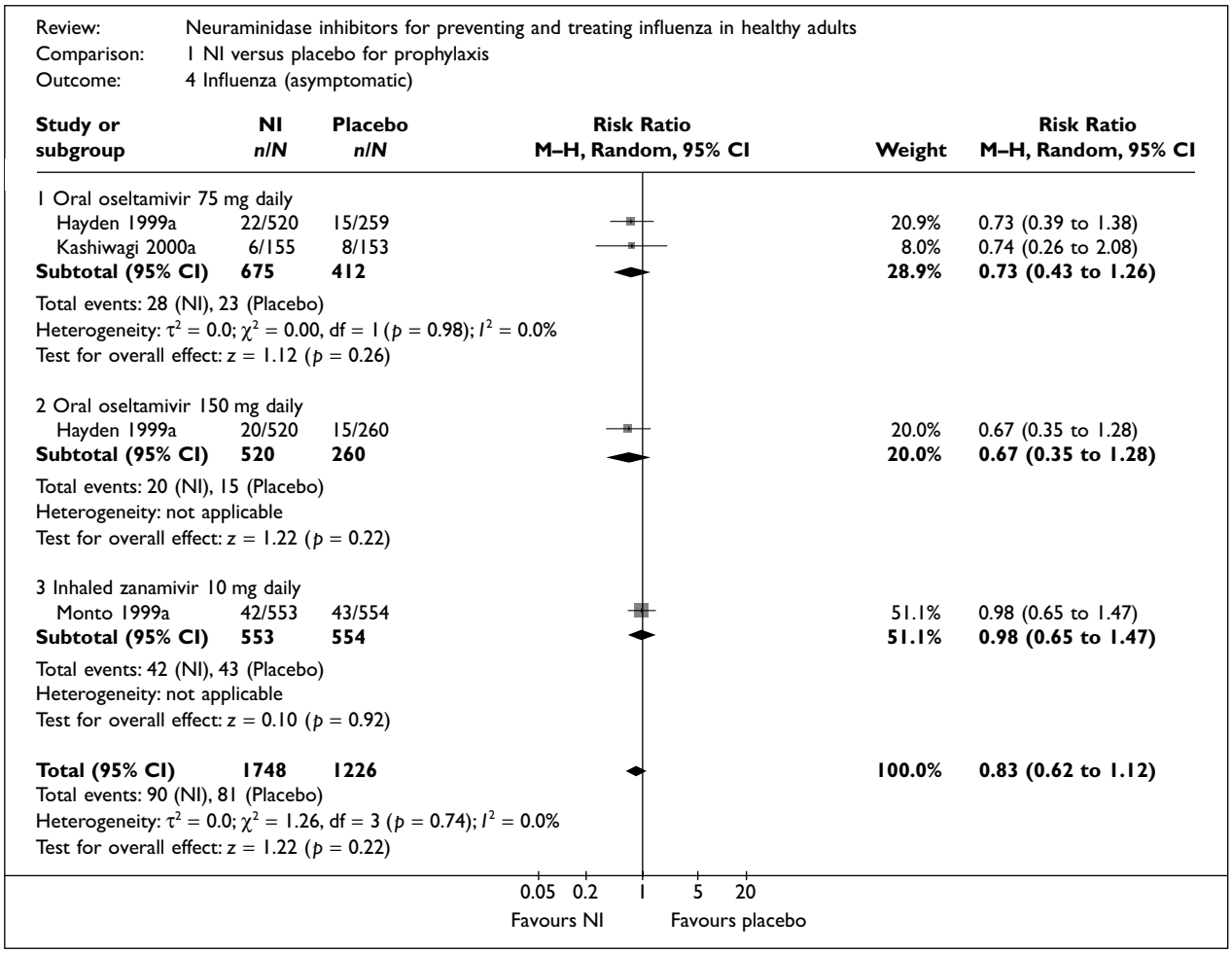
Study or subgroup	NI n/N	Placebo n/N	Risk Ratio M–H, Random, 95% CI	Weight	Risk Ratio M–H, Random, 95% CI
1 Oral oseltamivir 75 mg daily					
Hayden 1999a	6/520	12/259		14.2%	0.25 (0.09 to 0.66)
Kashiwagi 2000a	5/155	21/153		14.8%	0.24 (0.09 to 0.61)
Subtotal (95% CI)	**675**	**412**		**29.0%**	**0.24 (0.12 to 0.48)**
Total events: 11 (NI), 33 (Placebo)					
Heterogeneity: $\tau^2 = 0.0$; $\chi^2 = 0.01$, df = 1 ($p = 0.93$); $I^2 = 0.0\%$					
Test for overall effect: $z = 4.10$ ($p = 0.000041$)					
2 Oral oseltamivir 150 mg daily					
Hayden 1999a	7/520	13/260		16.2%	0.27 (0.11 to 0.67)
Subtotal (95% CI)	**520**	**260**		**16.2%**	**0.27 (0.11 to 0.67)**
Total events: 7 (NI), 13 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: $z = 2.84$ ($p = 0.0046$)					
3 Inhaled zanamivir 10 mg daily					
Kaiser 2000	4/144	4/48		7.3%	0.33 (0.09 to 1.28)
Monto 1999a	11/553	34/554		29.7%	0.32 (0.17 to 0.63)
Subtotal (95% CI)	**697**	**602**		**37.1%**	**0.33 (0.18 to 0.59)**
Total events: 15 (NI), 38 (Placebo)					
Heterogeneity: $\tau^2 = 0.0$; $\chi^2 = 0.00$, df = 1 ($p = 0.97$); $I^2 = 0.0\%$					
Test for overall effect: $z = 3.66$ ($p = 0.00025$)					
4 Intranasal zanamivir 0.32 mg daily					
Kaiser 2000	9/141	4/48		10.4%	0.77 (0.25 to 2.37)
Subtotal (95% CI)	**141**	**48**		**10.4%**	**0.77 (0.25 to 2.37)**
Total events: 9 (NI), 4 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: $z = 0.46$ ($p = 0.64$)					
5 Inhaled and intranasal zanamivir 10 mg and 0.32 daily					
Kaiser 2000	6/146	3/48		7.3%	0.66 (0.17 to 2.53)
Subtotal (95% CI)	**146**	**48**		**7.3%**	**0.66 (0.17 to 2.53)**
Total events: 6 (NI), 3 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: $z = 0.61$ ($p = 0.54$)					
Total (95% CI)	**2179**	**1370**		**100.0%**	**0.33 (0.23 to 0.48)**
Total events: 48 (NI), 91 (Placebo)					
Heterogeneity: $\tau^2 = 0.0$; $\chi^2 = 4.16$, df = 6 ($p = 0.66$); $I^2 = 0.0\%$					
Test for overall effect: $z = 5.90$ ($p < 0.00001$)					



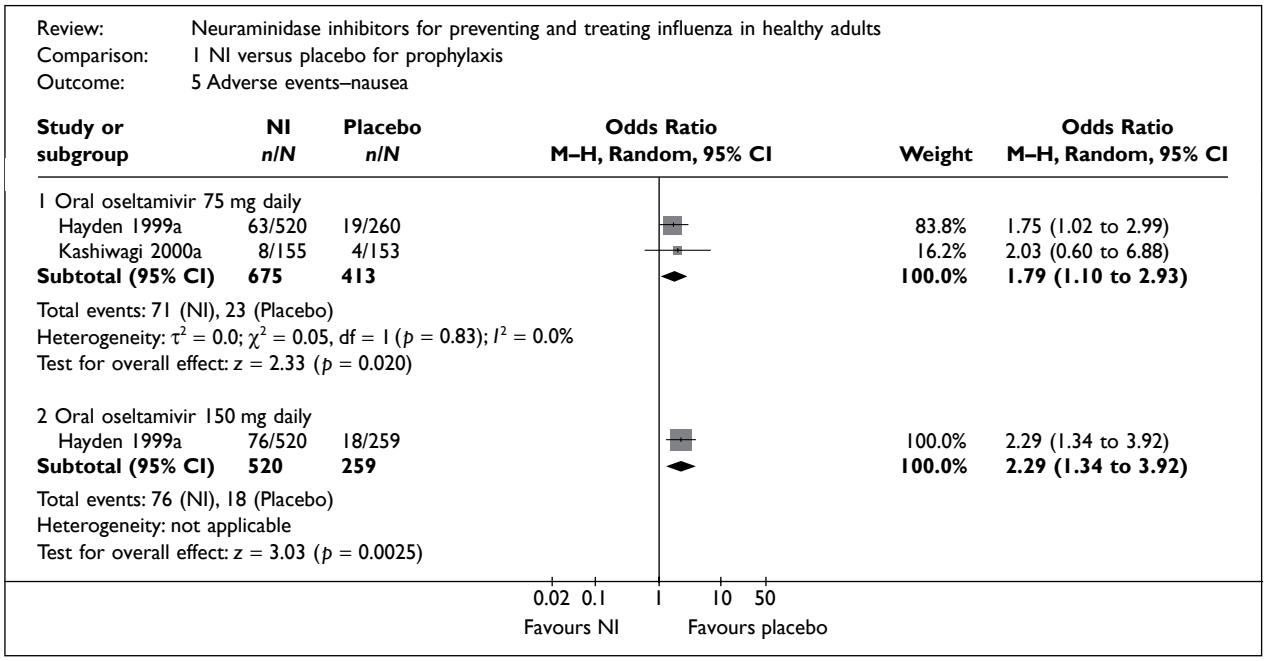
Analysis 1.2 *Comparison 1 NI versus placebo for prophylaxis, Outcome 2 Influenza (symptomatic).*



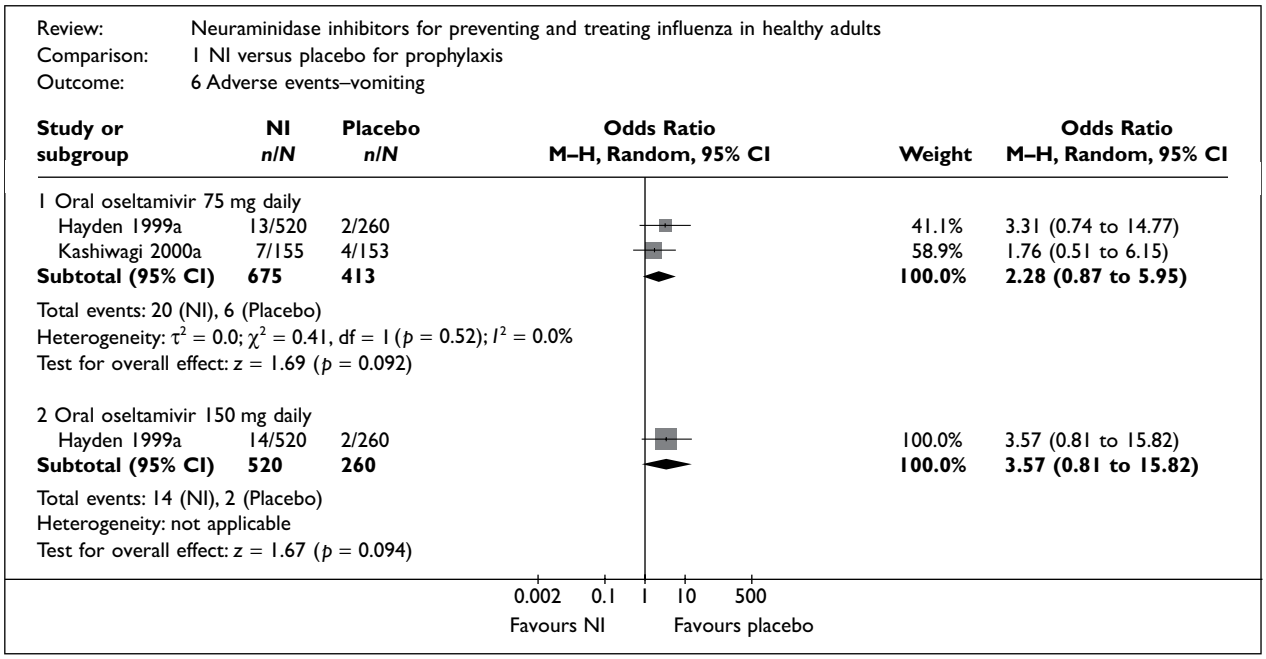
Analysis 1.3 *Comparison 1 NI versus placebo for prophylaxis, Outcome 3 Influenza (symptomatic and asymptomatic).*



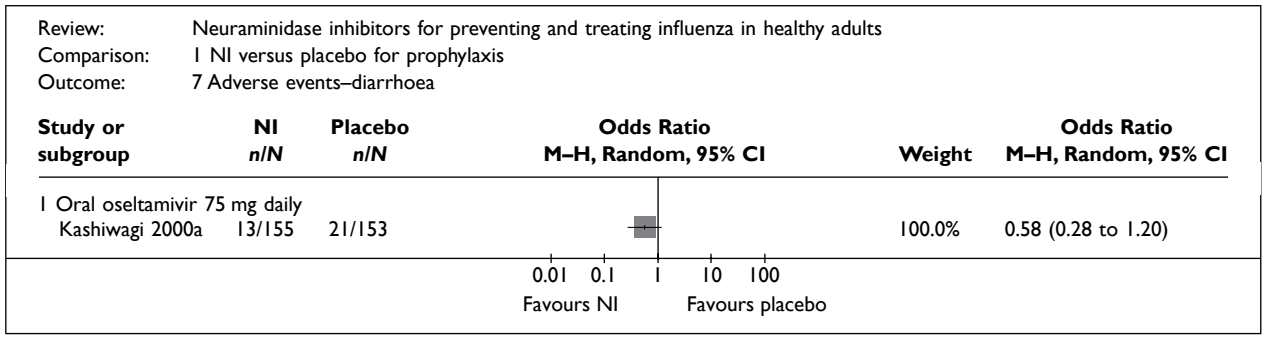
Analysis 1.4 *Comparison 1 NI versus placebo for prophylaxis, Outcome 4 Influenza (asymptomatic).*



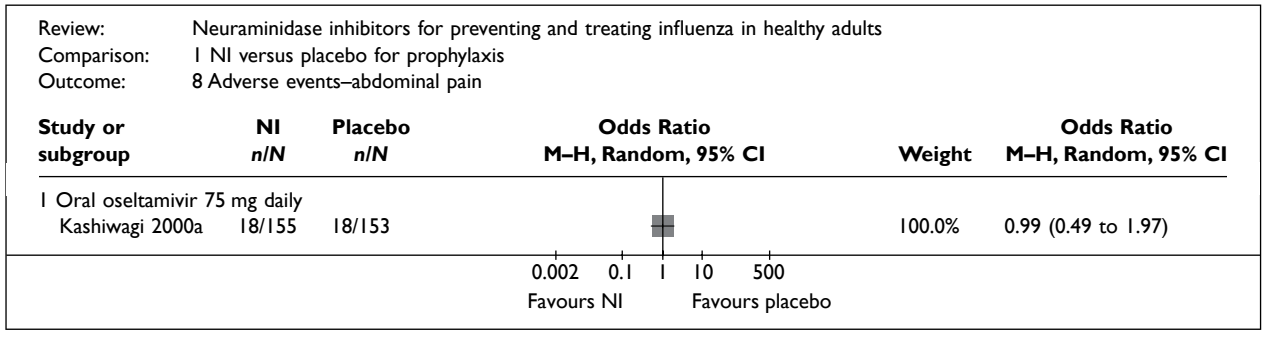
Analysis 1.5 *Comparison 1 NI versus placebo for prophylaxis, Outcome 5 Adverse events – nausea.*



Analysis 1.6 *Comparison 1 NI versus placebo for prophylaxis, Outcome 6 Adverse events - vomiting.*



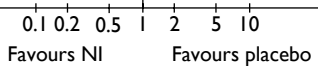
Analysis 1.7 *Comparison 1 NI versus placebo for prophylaxis, Outcome 7 Adverse events - diarrhoea.*



Analysis 1.8 *Comparison 1 NI versus placebo for prophylaxis, Outcome 8 Adverse events – abdominal pain.*

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults
Comparison: 1 NI versus placebo for prophylaxis
Outcome: 9 Adverse events events–others

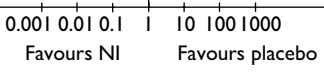
Study or subgroup	NI n/N	Placebo n/N	Odds Ratio M–H, Random, 95% CI	Weight	Odds Ratio M–H, Random, 95% CI
1 Oral oseltamivir 75 mg daily					
Kashiwagi 2000a	46/155	47/153		100.0%	0.95 (0.59 to 1.55)



Analysis 1.9 *Comparison 1 NI versus placebo for prophylaxis, Outcome 9 Adverse events - others.*

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults
Comparison: 1 NI versus placebo for prophylaxis
Outcome: 10 Adverse events–withdrawals due to gastrointestinal events

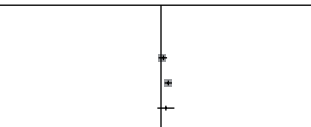
Study or subgroup	NI n/N	Placebo n/N	Odds Ratio M–H, Random, 95% CI	Weight	Odds Ratio M–H, Random, 95% CI
1 Oral oseltamivir 75 mg daily					
Hayden 1999a	3/520	0/259		100.0%	3.51 (0.18 to 68.21)
Subtotal (95% CI)	**520**	**259**		**100.0%**	**3.51 (0.18 to 68.21)**
Total events: 3 (NI), 0 (Placebo)					
Heterogeneity: no applicable					
Test for overall effect: $z = 0.83$ ($p = 0.41$)					
2 Oral oseltamivir 150 mg daily					
Hayden 1999a	3/520	0/260		100.0%	3.52 (0.18 to 68.47)
Subtotal (95% CI)	**520**	**260**		**100.0%**	**3.52 (0.18 to 68.47)**
Total events: 3 (NI), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: $z = 0.83$ ($p = 0.41$)					



Analysis 1.10 *Comparison 1 NI versus placebo for prophylaxis, Outcome 10 Adverse events – withdrawals due to gastrointestinal events.*

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults
Comparison: 2 NI versus placebo for treatment
Outcome: 1 Time to alleviation of symptoms (ITT)

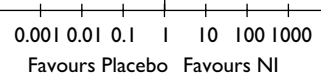
Study or subgroup	NI N	Placebo N	log [Hazard ratio] (SE)	Weight	Hazard ratio IV, Random, 95% CI
1 Zanamivir					
Hayden 1997	273	144	0.105 (0.1183)	8.9%	1.11 (0.88 to 1.40)
Makela 2000	174	182	0.405 (0.1183)	8.9%	1.50 (1.19 to 1.89)
Matsumoto 1999	77	39	0.288 (0.2449)	2.1%	1.33 (0.83 to 2.16)
MIST 1998	227	228	0.262 (0.1048)	11.4%	1.30 (1.06 to 1.60)
Monto 1999b	834	422	0.154 (0.0744)	22.5%	1.17 (1.01 to 1.35)
Puhakka 2003	293	295	0.207 (0.8366)	0.2%	1.23 (0.24 to 6.34)
Subtotal (95% CI)				**54.0%**	**1.24 (1.13 to 1.36)**
Heterogeneity: $\tau^2 = 0.0$; $\chi^2 = 4.41$, df = 5 ($p = 0.49$); $I^2 = 0.0\%$					
Test for overall effect: $z = 4.48$ ($p < 0.00001$)					
2 Oseltamivir					
Li 2003	216	235	0.049 (0.0969)	13.3%	1.05 (0.87 to 1.27)
Nicholson 2000	484	235	0.216 (0.0854)	17.1%	1.24 (1.05 to 1.47)
Treanor 2000	418	209	0.253 (0.0894)	15.6%	1.29 (1.08 to 1.53)
Subtotal (95% CI)				**46.0%**	**1.20 (1.06 to 1.35)**
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 2.67$, df = 2 ($p = 0.26$); $I^2 = 25\%$					
Test for overall effect: $z = 2.96$ ($p = 0.0031$)					
Total (95% CI)				**100.0%**	**1.22 (1.14 to 1.31)**
Heterogeneity: $\tau^2 = 0.0$; $\chi^2 = 7.32$, df = 8 ($p = 0.50$); $I^2 = 0.0\%$					
Test for overall effect: $z = 5.64$ ($p < 0.00001$)					



Analysis 2.1 *Comparison 2 NI versus placebo for treatment, Outcome 1 Time to alleviation of symptoms (ITT).*

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults
Comparison: 2 NI versus placebo for treatment
Outcome: 2 Time to alleviation of symptoms (influenza cases only)

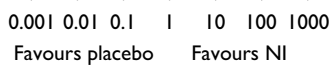
Study or subgroup	NI N	Placebo N	log [Hazard ratio] (SE)	Hazard ratio IV, Random, 95% CI	Weight	Hazard ratio IV, Random, 95% CI
1 Zanamivir						
Boivin 2000	17	10	0.642 (0.3987)		0.4%	1.90 (0.87 to 4.15)
Hayden 1997	173	89	0.223 (0.1483)		2.6%	1.25 (0.93 to 1.67)
Makela 2000	136	141	0.47 (0.1378)		3.0%	1.60 (1.22 to 2.10)
Matsumoto 1999	44	29	0 (0.2863)		0.7%	1.00 (0.57 to 1.75)
MIST 1998	161	160	0.288 (0.016)		64.6%	1.33 (1.29 to 1.38)
Monto 1999b	481	241	0.241 (0.1)		5.6%	1.27 (1.05 to 1.55)
Puhakka 2003	222	213	0.153 (0.0959)		6.0%	1.17 (0.97 to 1.41)
Subtotal (95% CI)					**83.0%**	**1.33 (1.29 to 1.37)**
Heterogeneity: $\tau^2 = 0.0$; $\chi^2 = 5.89$, df = 6 ($p = 0.44$); $I^2 = 0.0\%$						
Test for overall effect: $z = 18.52$ ($p < 0.00001$)						
2 Oseltamivir						
Kashiwagi 2000a	122	130	0.287 (0.1264)		3.6%	1.33 (1.04 to 1.71)
Li 2003	134	139	0.036 (0.124)		3.7%	1.04 (0.81 to 1.32)
Nicholson 2000	314	161	0.32 (0.1048)		5.1%	1.38 (1.12 to 1.69)
Treanor 2000	245	129	0.379 (0.1095)		4.7%	1.46 (1.18 to 1.81)
Subtotal (95% CI)					**17.0%**	**1.30 (1.13 to 1.50)**
Heterogeneity: $\tau^2 = 0.01$; $\chi^2 = 4.80$, df = 3 ($p = 0.19$); $I^2 = 37\%$						
Test for overall effect: $z = 3.61$ ($p = 0.00031$)						
Total (95% CI)					**100.0%**	**1.32 (1.26 to 1.38)**
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 10.77$, df = 10 ($p = 0.38$); $I^2 = 7\%$						
Test for overall effect: $z = 11.37$ ($p < 0.00001$)						



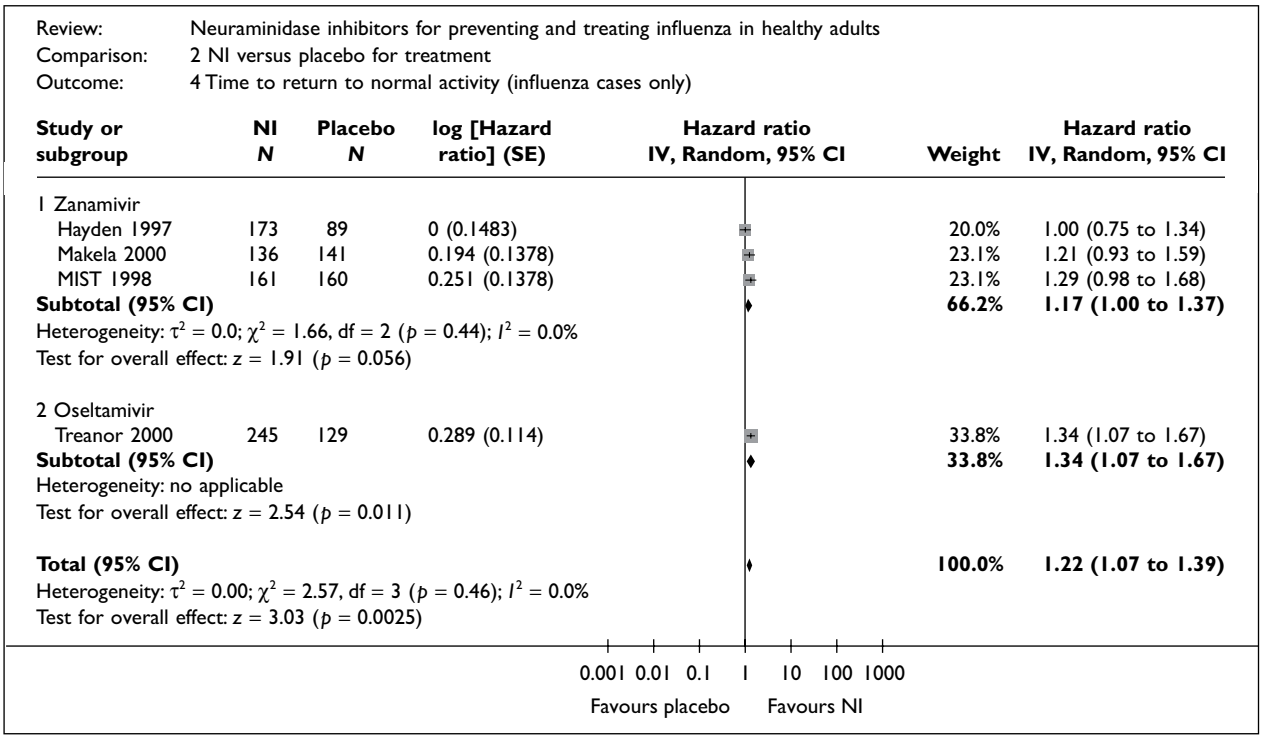
Analysis 2.2 *Comparison 2 NI versus placebo for treatment, Outcome 2 Time to alleviation of symptoms (influenza cases only).*

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults
Comparison: 2 NI versus placebo for treatment
Outcome: 3 Time to return to normal activity (ITT)

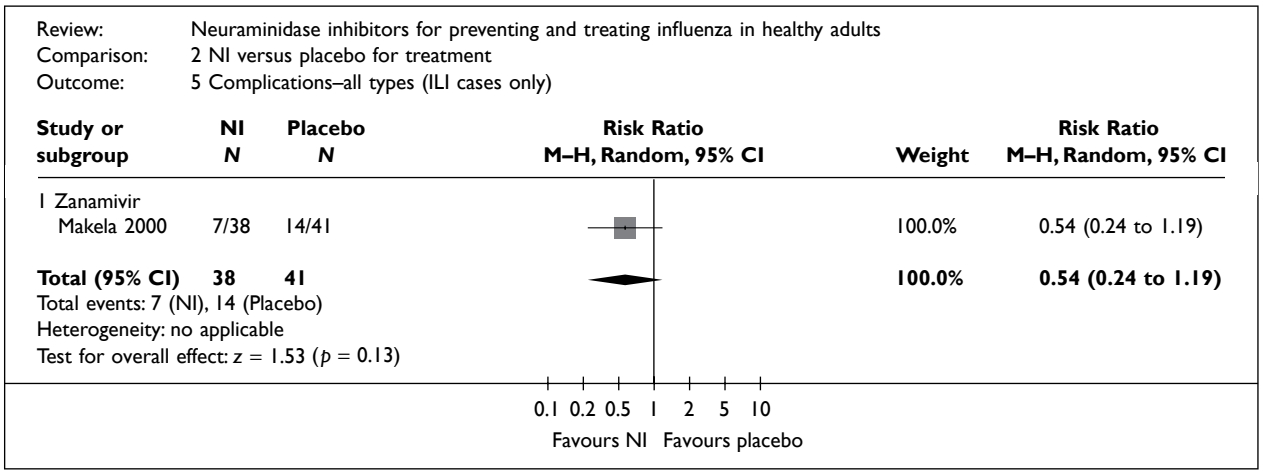
Study or subgroup	NI N	Placebo N	log [Hazard ratio] (SE)	Hazard ratio IV, Random, 95% CI	Weight	Hazard ratio IV, Random, 95% CI
1 Zanamivir						
Matsumoto 1999	77	39	0.405 (0.2664)		4.0%	1.50 (0.89 to 2.53)
MIST 1998	227	228	0.251 (0.1378)		15.0%	1.29 (0.98 to 1.68)
Monto 1999b	834	422	0.234 (0.0761)		49.2%	1.26 (1.09 to 1.47)
Subtotal (95% CI)					**68.3%**	**1.28 (1.13 to 1.45)**
Heterogeneity: $\tau^2 = 0.0$; $\chi^2 = 0.38$, df = 2 ($p = 0.83$); $I^2 = 0.0\%$						
Test for overall effect: $z = 3.83$ ($p = 0.00013$)						
2 Oseltamivir						
Treanor 2000	418	209	0.204 (0.0948)		31.7%	1.23 (1.02 to 1.48)
Subtotal (95% CI)					**31.7%**	**1.23 (1.02 to 1.48)**
Heterogeneity: no applicable						
Test for overall effect: $z = 2.15$ ($p = 0.031$)						
Total (95% CI)					**100.0%**	**1.26 (1.14 to 1.40)**
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.53$, df = 3 ($p = 0.91$); $I^2 = 0.0\%$						
Test for overall effect: $z = 4.38$ ($p = 0.000012$)						



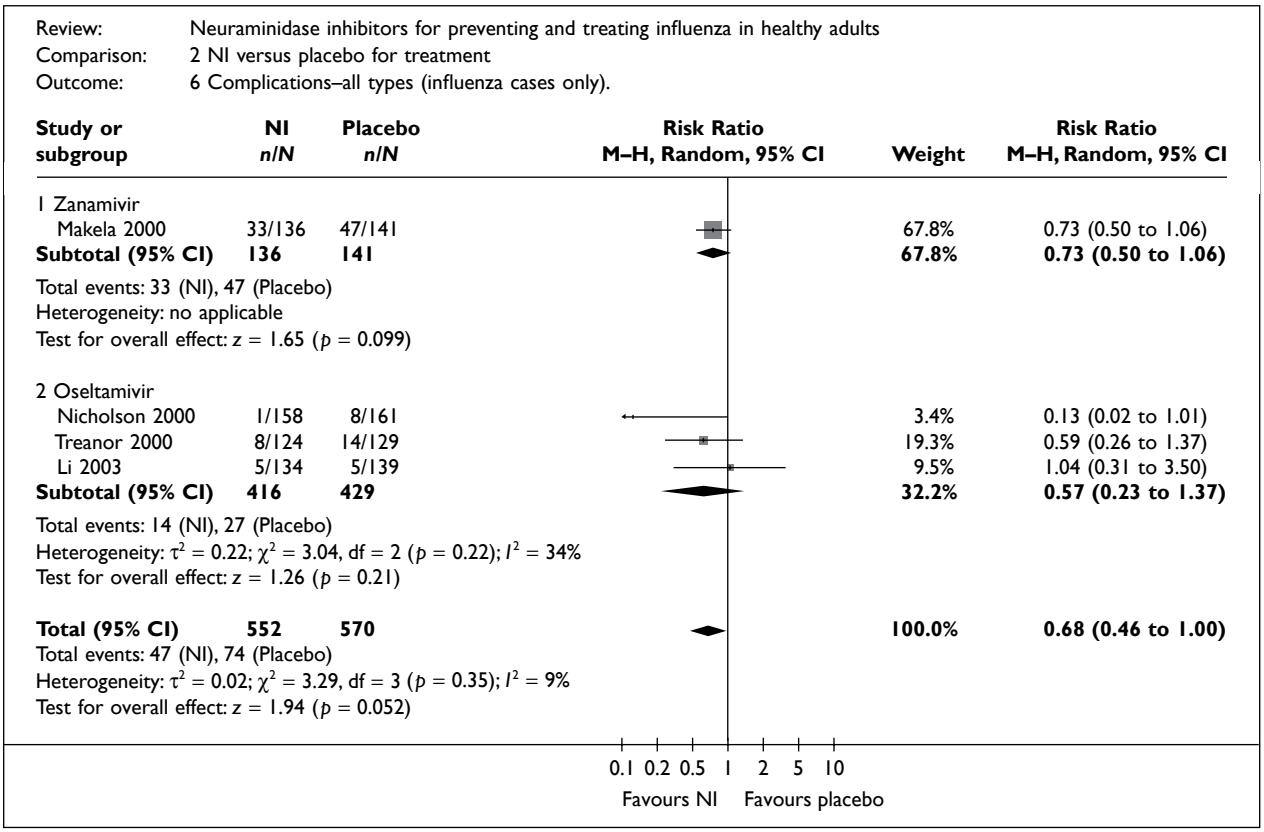
Analysis 2.3 *Comparison 2 NI versus placebo for treatment, Outcome 3 Time to return to normal activity (ITT).*



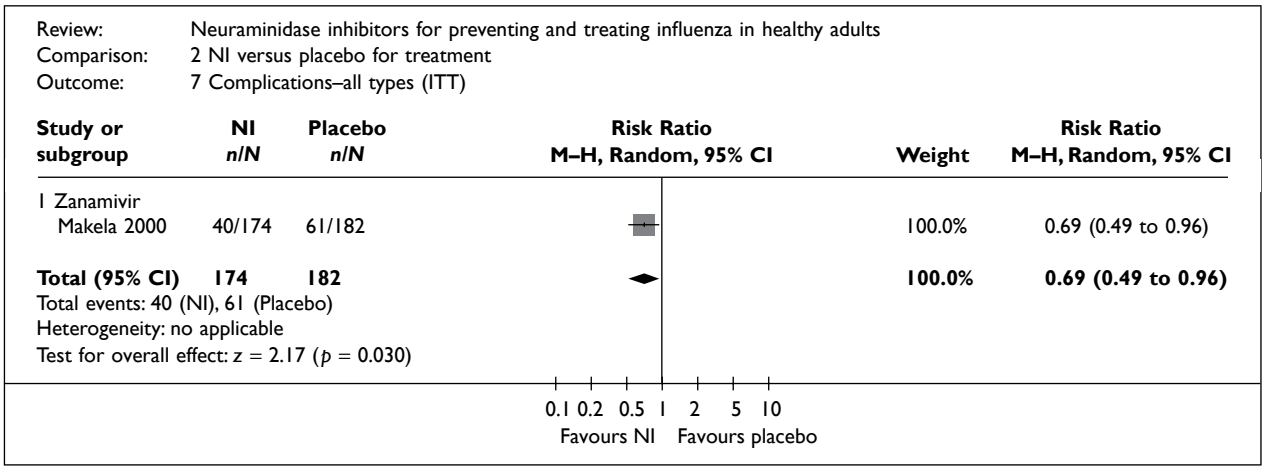
Analysis 2.4 *Comparison 2 NI versus placebo for treatment, Outcome 4 Time to return to normal activity (influenza cases only).*



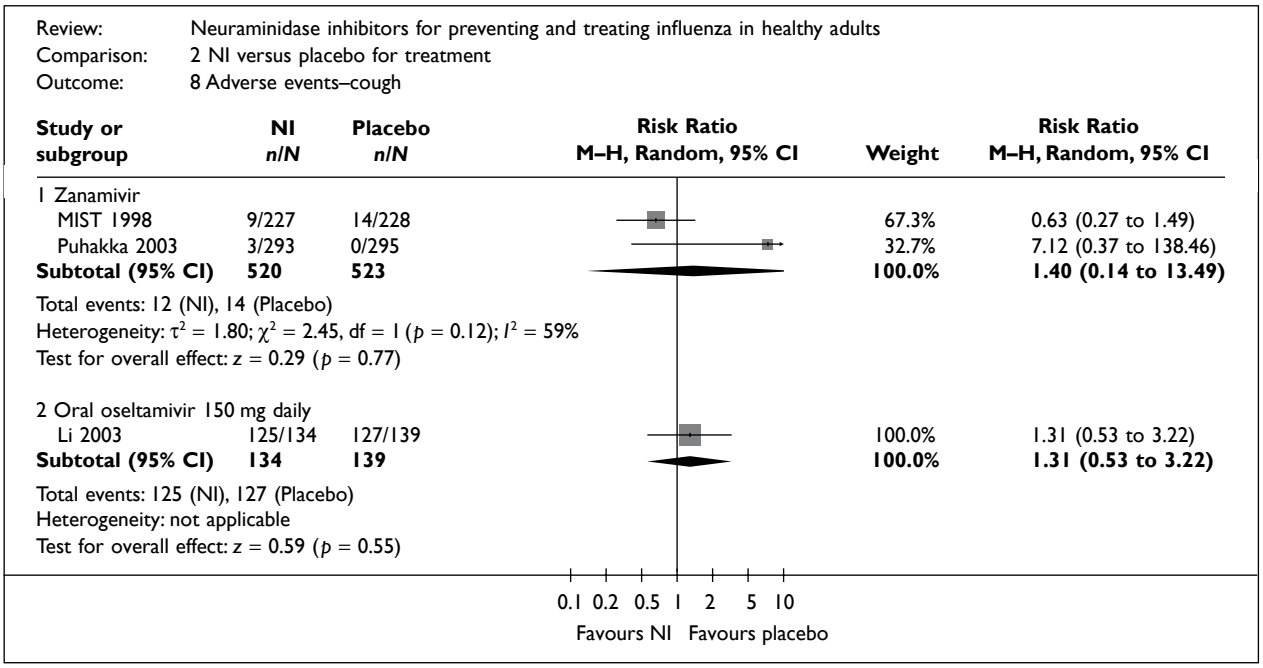
Analysis 2.5 *Comparison 2 NI versus placebo for treatment, Outcome 5 Complications – all types (ILI cases only).*



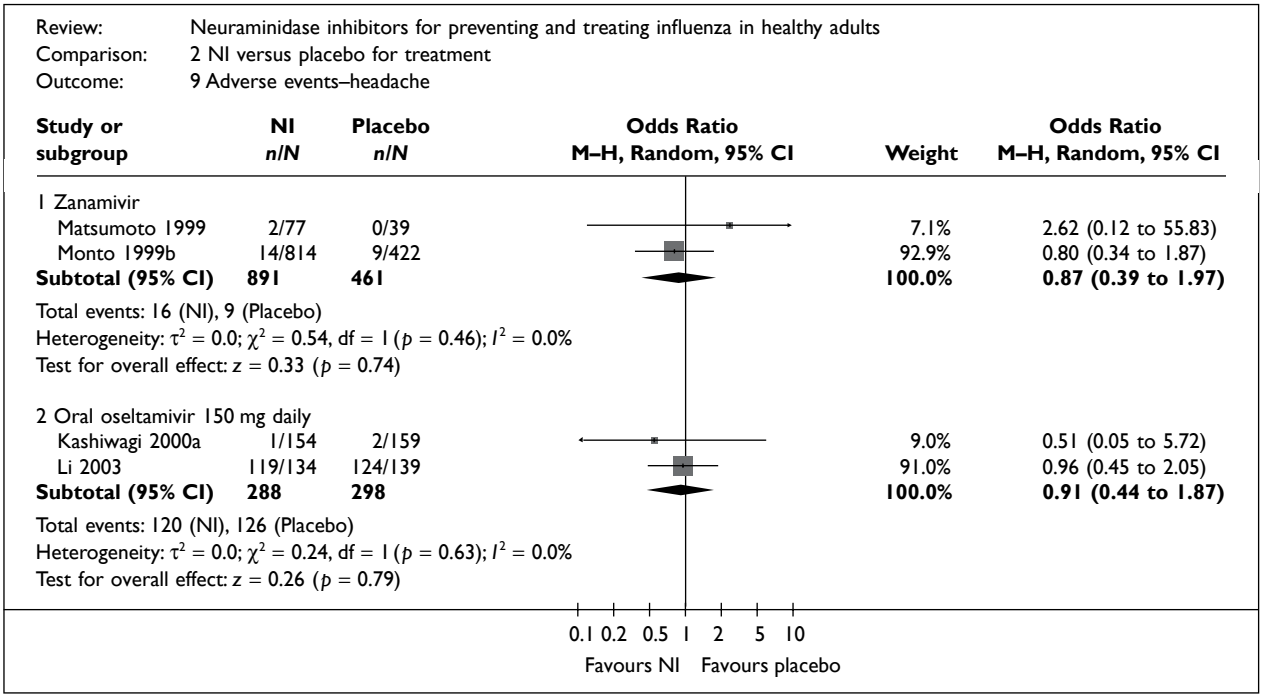
Analysis 2.6 *Comparison 2 NI versus placebo for treatment, Outcome 6 Complications - all types (influenza cases only).*



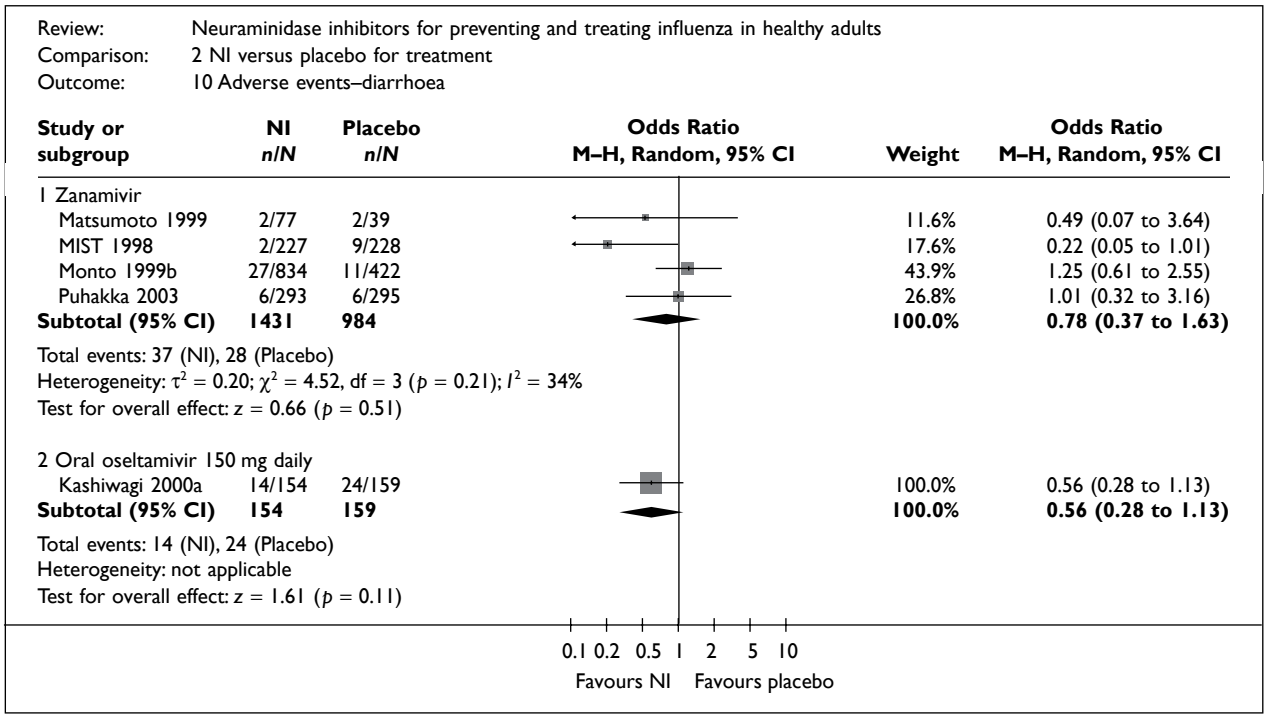
Analysis 2.7 *Comparison 2 NI versus placebo for treatment, Outcome 7 Complications – all types (ITT).*



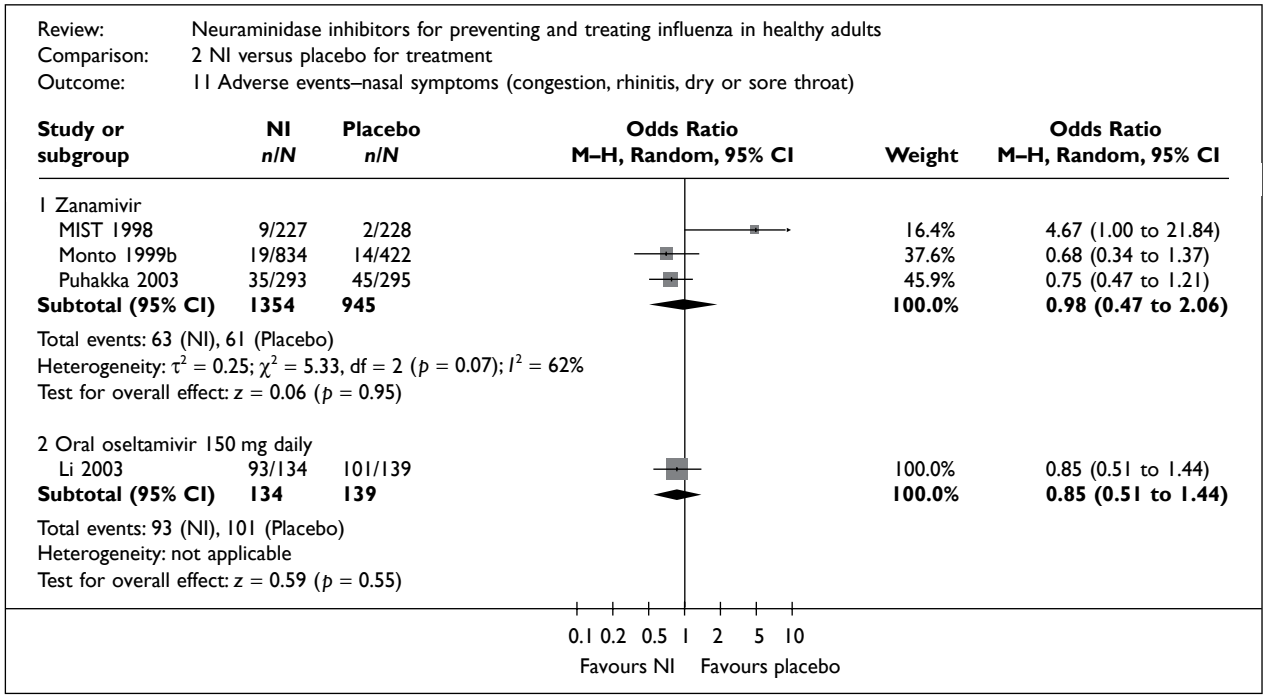
Analysis 2.8 *Comparison 2 NI versus placebo for treatment, Outcome 8 Adverse events - cough.*



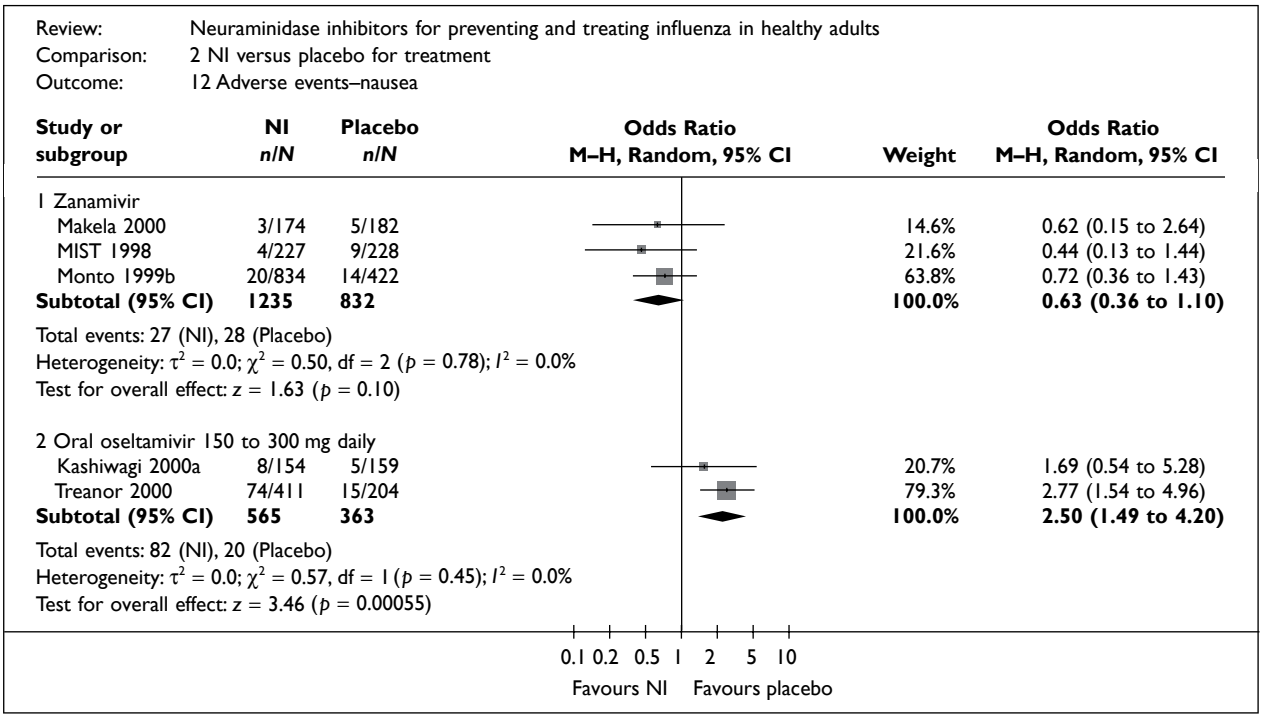
Analysis 2.9 *Comparison 2 NI versus placebo for treatment, Outcome 9 Adverse events – headache.*



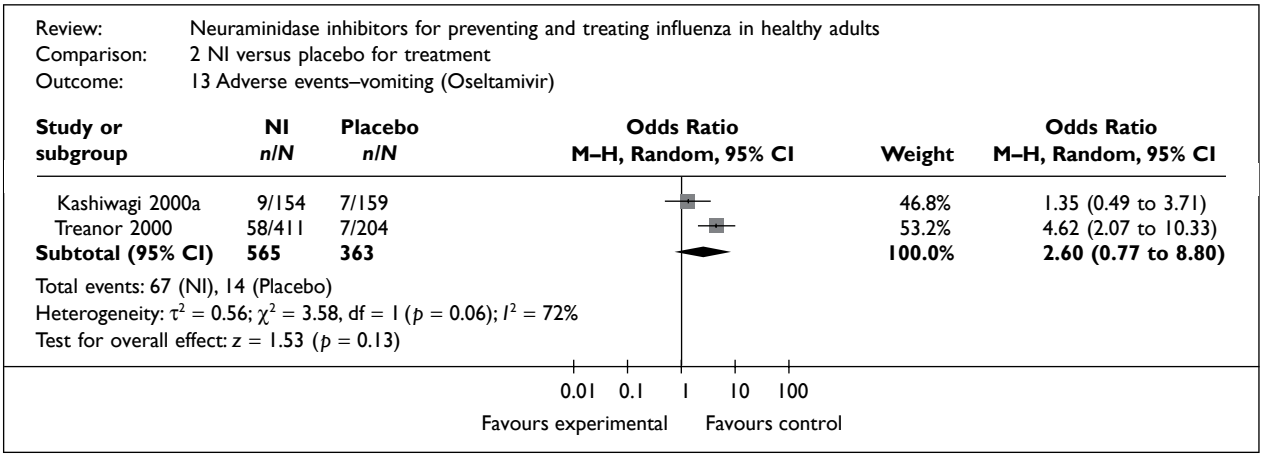
Analysis 2.10 *Comparison 2 NI versus placebo for treatment, Outcome 10 Adverse events - diarrhoea.*



Analysis 2.11 *Comparison 2 NI versus placebo for treatment, Outcome 11 Adverse events – nasal symptoms (congestion, rhinitis, dry or sore throat).*



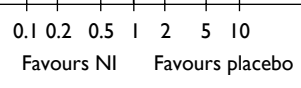
Analysis 2.12 *Comparison 2 NI versus placebo for treatment, Outcome 12 Adverse events - nausea.*



Analysis 2.13 *Comparison 2 NI versus placebo for treatment, Outcome 13 Adverse events – vomiting (Oseltamivir).*

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults
Comparison: 2 NI versus placebo for treatment
Outcome: 14 Adverse events–bronchitis or pneumonia

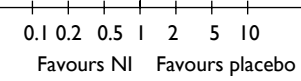
Study or subgroup	NI n/N	Placebo n/N	Odds Ratio M–H, Random, 95% CI	Weight	Odds Ratio M–H, Random, 95% CI
1 Zanamivir					
MIST 1998	7/227	16/228		35.6%	0.42 (0.17 to 1.05)
Monto 1999b	9/834	11/422		36.0%	0.41 (0.17 to 0.99)
Puhakka 2003	9/293	3/295		28.4%	3.08 (0.83 to 11.51)



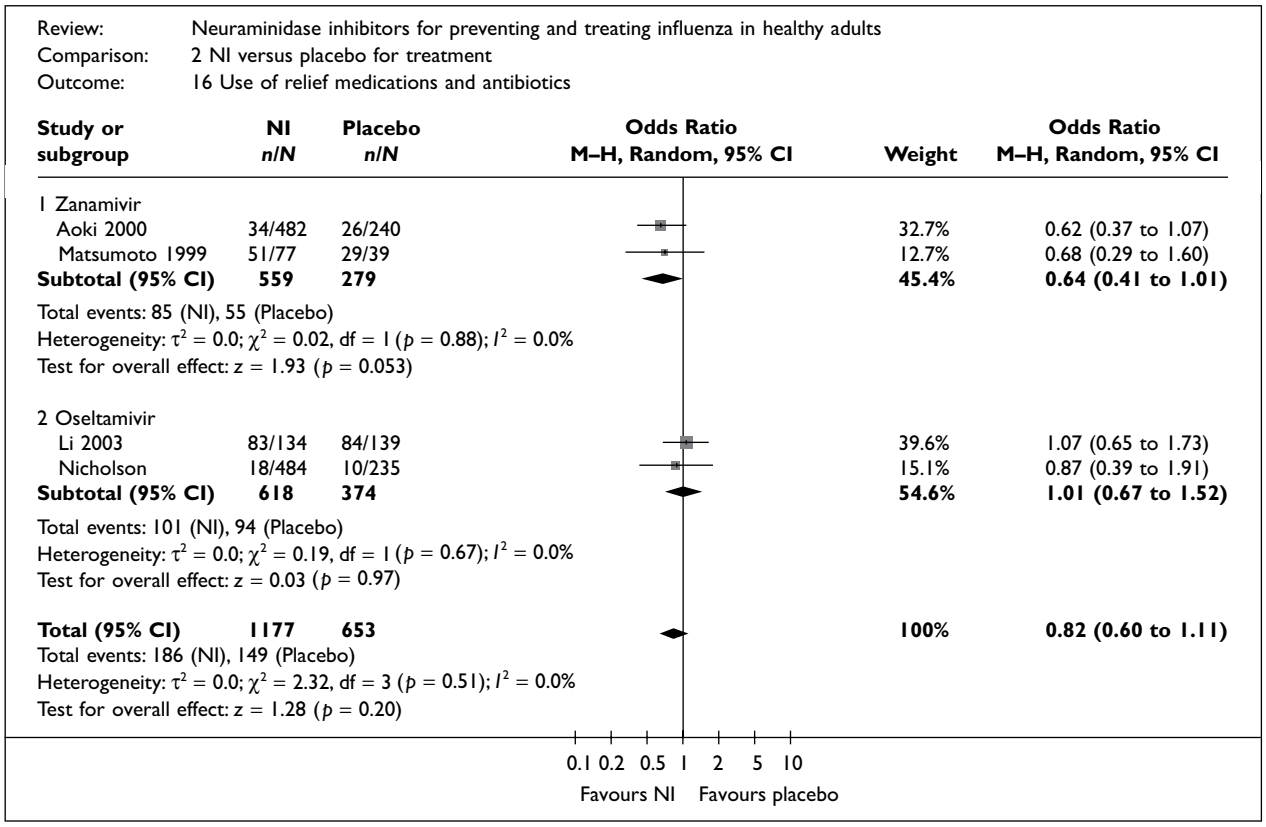
Analysis 2.14 *Comparison 2 NI versus placebo for treatment, Outcome 14 Adverse events - bronchitis or pneumonia.*

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults
Comparison: 2 NI versus placebo for treatment
Outcome: 15 Adverse events–all types

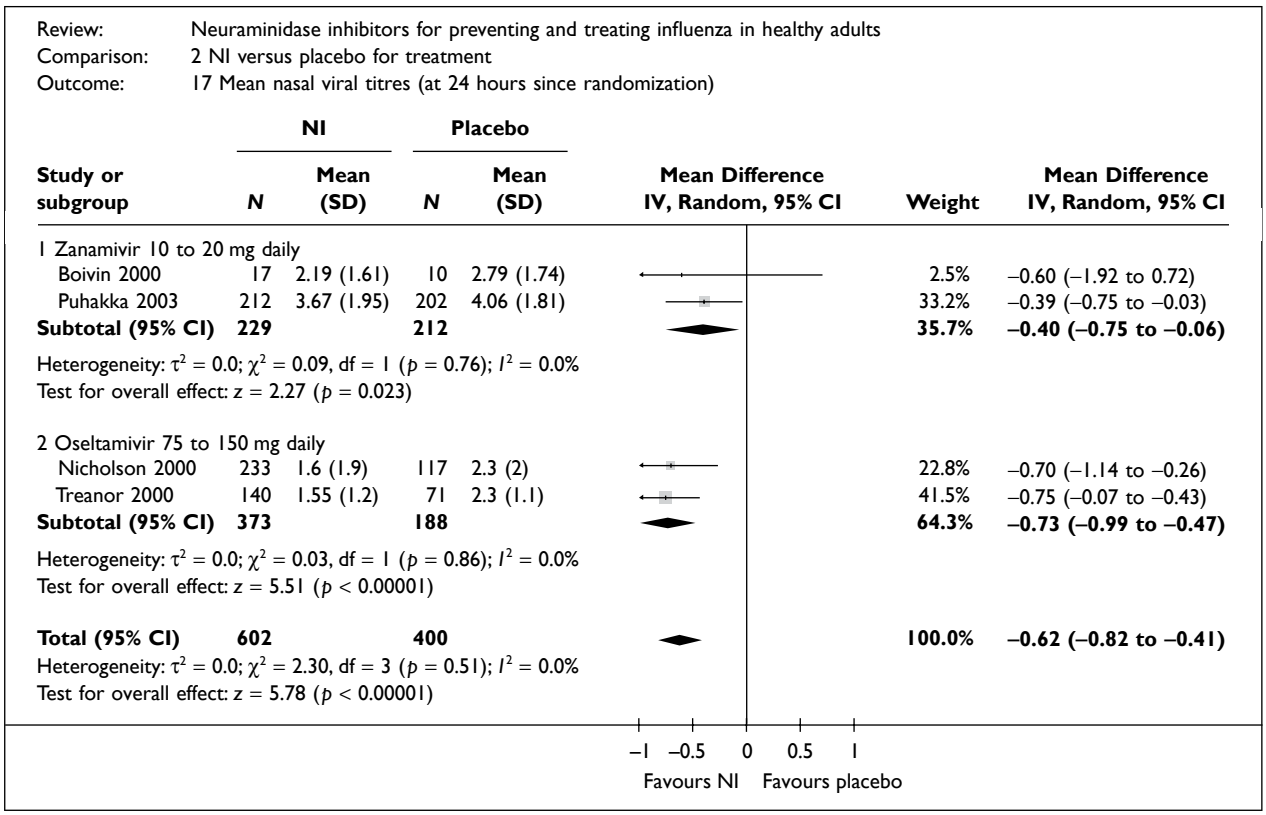
Study or subgroup	NI n/N	Placebo n/N	Odds Ratio M–H, Random, 95% CI	Weight	Odds Ratio M–H, Random, 95% CI
1 Zanamivir					
Matsumoto 1999	21/77	9/39		7.9%	1.25 (0.51 to 3.07)
MIST 1998	83/227	98/228		44.7%	0.76 (0.52 to 1.11)
Puhakka 2003	77/293	80/295		47.4%	0.96 (0.66 to 1.38)
Subtotal (95% CI)	**597**	**562**		**100.0%**	**0.88 (0.69 to 1.14)**
Total events: 181 (NI), 187 (Placebo)					
Heterogeneity: $\tau^2 = 0.0$; $\chi^2 = 1.33$, df = 2 ($p = 0.51$); $I^2 = 0.0\%$					
Test for overall effect: $z = 0.96$ ($p = 0.34$)					
2 Oral oseltamivir 150 mg daily					
Kashiwagi 2000a	71/154	89/159		100.0%	0.67 (0.43 to 1.05)
Subtotal (95% CI)	**154**	**159**		**100.0%**	**0.67 (0.43 to 1.05)**
Total events: 71 (NI), 89 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: $z = 1.74$ ($p = 0.081$)					



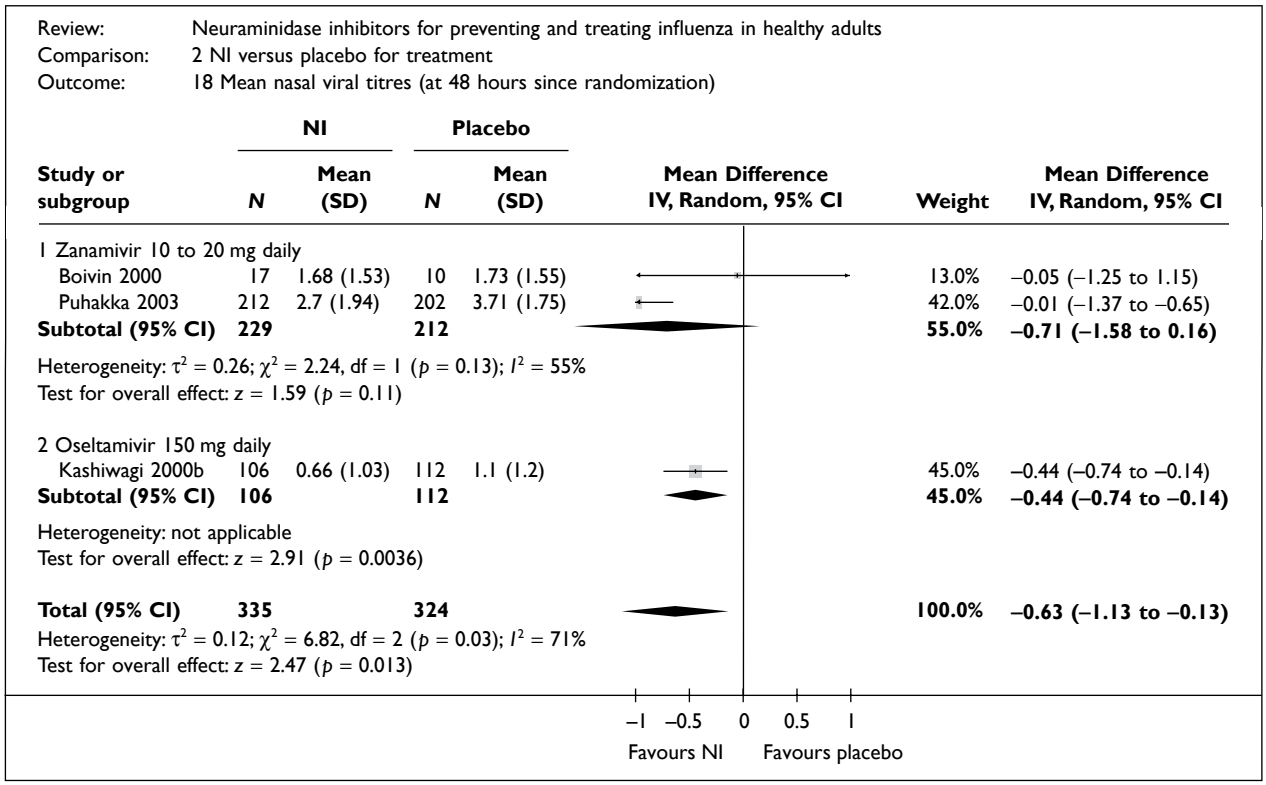
Analysis 2.15 *Comparison 2 NI versus placebo for treatment, Outcome 15 Adverse events – all types.*



Analysis 2.16 *Comparison 2 NI versus placebo for treatment, Outcome 16 Use of relief medications and antibiotics.*



Analysis 2.17 *Comparison 2 NI versus placebo for treatment, Outcome 17 Mean nasal viral titres (at 24 hours since randomisation).*



Analysis 2.18 *Comparison 2 NI versus placebo for treatment, Outcome 18 Mean nasal viral titres (at 48 hours since randomisation).*

Appendices

Appendix 1. EMBASE (WebSPIRS) search strategy

#1 explode 'influenza-' /

#2 (influenza* in ti) or (influenza* in ab)

#3 #1 or #2

#4 explode 'sialidase-inhibitor' /

#5 (neuraminidase inhibitor* in ti) or (neuraminidase inhibitor* in ab)

#6 explode 'oseltamivir-' /

#7 (oseltamivir in ti) or (oseltamivir in ab)

#8 explode 'zanamivir-' /

#9 (ozanamivir in ti) or (zanamivir in ab)

#10 #4 or #5 or #6 or #7 or #8 or #9

#11 #3 and #10

Appendix 2. Glossary of terms

- **Efficacy**: the impact of an intervention (drug, vaccines etc) on a problem or disease in ideal conditions - in this case the capacity of NIs to prevent or treat influenza and its complications.
- **Effectiveness**: the impact of an intervention (drug, vaccines etc) on a problem or disease in field conditions - in this case the capacity of NIs to prevent or treat ILI and its complications.
- **Influenza**: an acute respiratory infection caused by a virus of the Orthomyxoviridae family. Three serotypes are known (A, B and C). Influenza causes an acute febrile illness with myalgia, headache and cough. Although the median duration of the acute illness is three days, cough and malaise can persist for weeks. Complications of influenza include otitis media, pneumonia, secondary bacterial pneumonia, exacerbations of chronic respiratory disease and bronchiolitis in children. These illnesses may require treatment in a hospital and can be life-threatening especially in 'high-risk' people e.g. the elderly and people suffering from chronic heart disease. Additionally, influenza can cause a range of non-respiratory complications including febrile convulsions, Reye's syndrome and myocarditis. The influenza virus is composed of a protein envelope around an RNA core. On the envelope are two antigens: neuraminidase (N antigen) and hemagglutinin (H antigen). Hemagglutinin is an enzyme that facilitates the entry of the virus into cells of the respiratory epithelium, while neuraminidase facilitates the release of newly produced viral particles from infected cells. The influenza virus has a marked propensity to mutate its external antigenic composition to escape the hosts' immune defences. Given this extreme mutability, a classification of viral subtype A based on H and N typing has been introduced. Additionally, strains are classified on the basis of antigenic type of the nucleoprotein core (A, B), geographical location of first isolation, strain serial number and year of isolation. Every item is separated by a slash mark (e.g. A/Wuhan/359/95 (H3N2)). Unless otherwise specified such strains are of human origin. The production of antibodies against influenza beyond a conventional quantitative threshold is called **seroconversion**. Seroconversion in the absence of symptoms is called **asymptomatic influenza**.
- **Influenza-like illness (ILI)**: an acute respiratory illness caused by scores of different viruses (including influenza A and B) presenting with symptoms and signs which are not distinguishable from those of influenza. ILI does not have documented laboratory isolation of the causative agent and is what commonly presents to physicians and patients (also known as the flu)
- **Mean**: a measure of central tendency of a group of variables (such as age). It is calculated by adding all the individual values and then dividing by the number of values in the group.
- **Median**: a measure of central tendency of a group of variables (such as age). It is the

halfway mark of a set of variables, the dividing point between lower and upper.

- **Randomised study**: when it appears that the individuals (or other experimental units) followed in the study were definitely or possibly assigned prospectively to one of two (or more) alternative forms of health care using random allocation – **randomized controlled trial (RCT)**. When the unit of allocation is a group (such as a family, or a military unit) the design is that of a **Cluster Randomised Trial (C-RCT).**
- **Quasi-randomised study**: when it appears that the individuals (or other experimental units) followed in the study were definitely or probably assigned prospectively to one of two (or more) alternative forms of health care using some quasi-random method of allocation (such as alternation, date of birth or case record number) - **clinical controlled trial (CCT).**

Appendix 3. Details of previous searches

In the original review, we searched the Cochrane Controlled Trials Register (CCTR) (*The Cochrane Library* 1999, issue 1), MEDLINE (in May 1999), EMBASE (1991 to 1998). We read the bibliography of retrieved articles in order to identify further trials. We hand searched the journal *Vaccine* from its first issue to the end of 1997. Given that NIs were still at the pre-registration developmental phase, to locate unpublished trials, we contacted both manufacturers. See below for the original search strategy.

The following search terms or combined sets in any language were used:

Influenza Route (oral)

route (parenteral)

Neuraminidase inhibitors

Oseltamivir

RO/GS 4104

Zanamivir

In the 2005 update, we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2005, issue 3), MEDLINE (2004 to September, Week 4 2005), EMBASE (2003 to June 2005). We also contacted manufacturers, researchers in the field, and authors of studies evaluated in the review.

In the 2008 update, we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2008, issue 2), MEDLINE (2005 to May, Week 4 2008), and EMBASE (2005 to May 2008).

Appendix 4. Adverse effects search strategies

CENTRAL Issue 3, 2009

#1 MeSH descriptor Oseltamivir explode all trees

#2 MeSH descriptor Zanamivir explode all trees

#3 (oseltamivir or zanamivir or GS4071 or tamiflu or relenza):ti,ab,kw

#4 neuraminidase NEXT inhibitor*:ti,ab,kw

#5 (#1 OR #2 OR #3 OR #4)

#6 safe or safety:ti,ab,kw

#7 side NEXT effect*:ti,ab,kw

#8 (adverse or undesirable or harm* or serious or toxic) NEAR/3 (effect* or reaction* or event* or outcome*):ti,ab,kw

#9 MeSH descriptor Product Surveillance, Postmarketing explode all trees

#10 MeSH descriptor Adverse Drug Reaction Reporting Systems explode all trees

#11 MeSH descriptor Clinical Trials, Phase IV as Topic explode all trees

#12 MeSH descriptor Poisoning explode all trees

#13 MeSH descriptor Substance-Related Disorders explode all trees

#14 MeSH descriptor Drug Toxicity explode all trees

#15 MeSH descriptor Abnormalities, Drug-Induced explode all trees

#16 MeSH descriptor Drug Monitoring explode all trees

#17 MeSH descriptor Drug Hypersensitivity explode all trees

#18 (toxicity or complication* or noxious or tolerability):ti,ab,kw

#19 MeSH descriptor Case-Control Studies explode all trees

#20 MeSH descriptor Cohort Studies explode all trees

#21 (#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20)

#22 (#5 AND #21)

#23 MeSH descriptor Oseltamivir explode all trees with qualifier: AE

#24 MeSH descriptor Zanamivir explode all trees with qualifier: AE

#25 (#22 OR #23 OR #24)

EMBASE (Ovid)

1 exp sialidase inhibitor/

2 exp oseltamivir/

3 exp zanamivir/

4 (oseltamivir or zanamivir or GS4071 or tamiflu or relenza).tw.

5 neuraminidase inhibitor*.tw.

6 or/1-5

7 (ae or si or to or co).fs.

8 side effect*.tw.

9 (safe or safety).tw.

10 ((adverse or undesirable or harms* or serious or toxic) adj3 (effect* or reaction* or event* or outcome*)).tw.

11 exp adverse drug reaction/

12 exp drug toxicity/

13 exp drug safety/

14 exp drug monitoring/

15 exp drug hypersensitivity/

16 exp postmarketing surveillance/

17 exp drug surveillance program/

18 exp phase iv clinical trial/

19 (toxicity or complication* or noxious or tolerability).tw.

20 exp case control study/

21 exp cohort analysis/

22 or/7-21

23 6 and 22

Appendix 5. Doshi's description of the exclusion of one study (Kaiser 2003)

The story behind the review

Peter Doshi

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Adapted from a *BMJ* analysis (Doshi 2009)

Since August, our Cochrane review team tried to do one simple thing: obtain the data necessary to verify claims that Tamiflu lowers serious complications of influenza such as pneumonia. We failed, but in failing, discovered that the public evidence base for this global public health drug is fragmented, inconsistent, and contradictory. We are no longer sure Tamiflu offers a therapeutic and public health policy advantage over aspirin. If the public is to trust in public health policies, the scientific basis informing knowledge of the harms and effects of those interventions must be public and open to independent analysis.

How a Cochrane review turned controversial

Systematic reviews are designed to synthesize the most reliable evidence on the effects of interventions. In retrospect, our Cochrane review of neuraminidase inhibitors began on a naïve but excited note. I had just received from the FDA a response to my Freedom of Information

Act request, a CDROM containing thousands of postmarketing adverse event reports over the past decade for the two NI drugs Tamiflu (oseltamivir) and Relenza (zanamivir). The dataset was difficult to interpret, and analysis would require some time (1). Although the review had last been updated in 2008, our new task was to include a safety assessment component. Tom Jefferson, who led the review, wrote to the group then just being formed, "Dear Friends, I am writing to inform you that the NHS [National Institute of Health Research] has commissioned an update of our Cochrane review ... although it is always dangerous to pre-judge the issue, I expect no new effectiveness data but a lot of pharmacovigilance data." Two days later, a pediatrician from Japan submitted a comment to the Cochrane Collaboration that would end up bedevilling our analysis for months (See NI Review Web Extra: Hayashi criticism). Hayashi pointed out that while Jefferson et al's previous review (2) found Tamiflu effective in reducing important complications of influenza such as pneumonia, that conclusion was drawn from a single peer-reviewed study (Kaiser (3)) which itself had meta-analyzed 10 manufacturer-funded trials from the late 1990s, of which only 2 were published in peer reviewed journals (4,5). (The remaining eight were apparently either unpublished or published in abstract form.) The Hayashi comment exposed the fact that the conclusions of our review were based on taking the word of other papers on face value. Meeting Hayashi's challenge required we verify the data for ourselves.

A maze of inconsistencies

The Hayashi comment set off a series of perplexing discoveries. Despite funding the Kaiser meta-analysis which concluded that Tamiflu reduces complications, Tamiflu's manufacturer, Roche, apparently did not itself make any such claims about complications. A Tamiflu.com webpage reads, "Treatment with TAMIFLU has not been proven to have a positive impact on these outcomes," referring to pneumonia other respiratory diseases as well as influenza-related death (6).

Similarly, our Cochrane review of the literature also found both Tamiflu and competitor drug Relenza effective in reducing the duration of influenza-like illness symptoms. But here again, Roche's position is that Tamiflu is ineffective against influenza-like illnesses not caused by influenza (7). US, EU, and Japanese drug regulators agree: Tamiflu only works for true influenza virus infections. (Table) These inconsistencies were pointing to the uncomfortable conclusion that the Cochrane Collaboration had promoted-by trusting the validity of other work in the scientific literature-efficacy claims more optimistic than even the drug manufacturer's. Reality, however, proved more complex. Roche's statement that Tamiflu is not proven to reduce complications is apparently a message only meant for Americans. At the bottom of Tamiflu.com web pages is a bold-face note: "THIS [WEB] SITE IS INTENDED FOR U.S. AUDIENCES ONLY." On Roche.com, the global website, the manufacturer boasts that Tamiflu provides a "67 percent reduction in secondary complications such as bronchitis, pneumonia and sinusitis in otherwise healthy individuals" (8). Statements from regulatory agencies in Tamiflu's three chief markets are similarly inconsistent: the EU EMEA mentions benefit, the US FDA denies benefit, and Japanese PMDA does not discuss complications (Table), raising the question of whether these agencies have evaluated the same datasets. (Jefferson emailed the EMEA asking for the raw data underlying the endorsement but after three weeks was asked what he meant by "the raw data".)

Data pertaining to Tamiflu's safety were equally confusing. We discovered that FDA's postmarketing drug safety database known as AERS (which collects reports of adverse events worldwide of FDA approved pharmaceuticals approved) had fewer total entries than Roche's own database held of just neuro-psychiatric classified adverse events (NPAEs). (Of 2466 NPAEs in the Roche Global Safety Database between 1999 and September 15, 2007, Roche researchers classified 562 "serious" (9). Over this period, the AERS database only holds 1805 adverse event reports of any kind.)

In publications we trust

Analyzing and learning from publications in the scientific literature is central to contemporary scientific practice. Essential to this practice is the act of trust. Trust that trials are carried out properly and that published reports are a genuine reflection of that research. Trust that policymakers accurately read and interpret those reports to make evidence based decisions. Trust, in other words, that claims about a drug's performance are backed by hard data. Hayashi's comment challenging our conclusions revealed the degree to which Cochrane reviews are fundamentally based on the premise that the published literature can be trusted.

The Cochrane Collaboration was not alone in trusting publications. The Kaiser paper has for several years been the sole citation offered in US

CDC recommendations on influenza in support of the statement that Tamiflu reduces the risk of hospitalization and pneumonia (10-12). The claim also found its way into US national influenza preparedness documents. The United States HHS Pandemic Influenza Plan, for example, assumes that in a pandemic, neuraminidase inhibitors "will be effective in decreasing risk of pneumonia, will decrease hospitalization by about half (as shown for interpandemic influenza), and will also decrease mortality." (13) These statements were made despite US regulators saying the opposite.

Or, in secrecy we trust?

Obtaining raw data from properly carried out trials on complications is the only way to resolve the inconsistencies surrounding Tamiflu's effect on reducing complications. On behalf of the review team, Jefferson wrote to the authors of the Kaiser paper, but was told that they no longer had the files and to contact Roche. Jefferson also wrote to authors of the two peer-reviewed published trials used in Kaiser's meta-analysis. One responded but once again directed us to the manufacturer.

Jefferson first contacted Roche in early September. On October 2, Roche indicated a willingness to share data, but not openly. It furnished Jefferson with a "confidentiality agreement," containing a clause that says that the signee (Jefferson) agrees "not to disclose ... the existence and terms of this Agreement...." (Web Extra: Roche confidentiality agreement). Roche apparently intended to not only keep its data concealed, but additionally intended to conceal the fact that it was quieting people through a secrecy clause.

Jefferson never signed the confidentiality agreement, but wrote the next day asking for clarification which he never received. On October 7 the company asked Jefferson to restate which data he was seeking. After Jefferson's answer, Roche said it was unable to provide data because it had already provided it for a similar meta-analysis being started by an independent expert influenza group. The Cochrane request, Roche said, might conflict with that review. In return, Jefferson challenged Roche to outline its concerns and explain why multiple groups of independent researchers should pose a problem and lead to data exclusivity. Roche did not answer these questions, but eight days later (October 21), unexpectedly emailed Jefferson excerpts of company reports from all clinical trials used in the Kaiser meta-analysis. Our team analyzed the data, and Jefferson wrote to Roche explaining that the files were insufficient to verify the effects on complications claims in Kaiser and the methods used in the trials. Roche responded on October 28, saying it would send more information the next week. Jefferson informed them that our deadline was now past, but we would accept any additional information for future updates. (As of November 15, we have heard nothing.)

The 2008 Cochrane review placed its trust in publications, and included Kaiser's analysis, consequently endorsing the conclusion that Tamiflu reduces complications such as pneumonia and bronchitis. Once again incorporating the Kaiser paper data into the updated review, despite our inability to obtain data sufficient to perform an independent analysis of the data, would have shifted our position from that of trust in publication to that of trust in secrecy. We dropped Kaiser's paper from our analysis.

Implications

After four months of seeking the data used to support the claims of Kaiser, we have come up empty-handed. If one is to trust in the performance of Tamiflu to reduce important complications of influenza such as pneumonia, they must do so trusting that data supporting those claims exist. Our experience has left us with a doubtful feeling towards placing our trust in drug companies.

We feel equally wary over our conclusion that Tamiflu and Relenza reduce the symptoms of influenza-like illness (ILI), but this is what our review concludes, incorporating the published trial data. Lack of effectiveness against ILI would be bad news: ILI is the clinical syndrome usually consisting of fever with cough or sore throat, well known as "the flu." Without laboratory testing, one cannot know whether influenza virus or some other agent is causing the patient's discomfort (14). In past influenza seasons, United States virologic surveillance data suggest that at peak "flu season" the proportion of respiratory specimens testing positive for influenza reaches 25-35%, but over the entire season, influenza viruses are found in only a small minority (14%) of tested patients. By contrast, of the patients with influenza-like illness recruited into the Tamiflu and Relenza trials we analyzed, an incredible 57-80% had influenza (Figure). The discrepancy appears the likely outcome of a special patient inclusion methodology, in which "Centers were activated to recruit subjects during an influenza outbreak in the locality, detected using standardized surveillance techniques," according to the company trial report excerpts we obtained. This crucial detail, however, was not mentioned in

published Tamiflu trials (4,5). If Australia's winter experience with A/H1N1 is any guide, influenza is not a majority cause of ILI cases even during a pandemic, and thus NIs may be ineffective for most patients today (15).

If Tamiflu is no better than placebo in its ability to reduce the complications of influenza, and is also ineffective against non-influenza ILI, as US and Japanese regulatory documents indicate, Tamiflu's ability to treat the symptoms of influenza may be similar to that of an NSAID such as aspirin. This realization led us to call for a head-to-head trial of Tamiflu versus a NSAID.

With respect to safety concerns, FDA reporting rules turn out to have important limitations, namely that although manufacturers are under mandatory reporting requirements, adverse events occurring outside the United States judged to not meet the "both serious and unexpected" criteria are under no requirement to be reported. Thus the public AERS database relies on manufacturers to honestly and accurately judge whether adverse events reported in conjunction with their products are "serious" and therefore must be reported or not. In the case of Tamiflu, considering that 75% of Tamiflu's market has been in Japan, this has important implications on our knowledge of its safety.

Public Health Drugs

In the ten years since Tamiflu was approved for use in 1999, neither American nor Japanese regulators have approved statements that the drug lowers rates of influenza-related complications, and one may have in fact even required Roche to declare "Tamiflu has not been proven to have a positive impact on the potential consequences (such as hospitalizations, mortality, or economic impact) of seasonal, avian, or pandemic influenza."(16) Despite the work of these regulators, public health officials trusted the published literature, said Tamiflu could, and spent billions of dollars building drug stockpiles, elevating Tamiflu to the status of a public health drug.

Public health drugs-like vaccines-get deployed on a population basis, directed by national or international level policy decisions. As witnessed in the UK, when the government declared that Tamiflu may be used to treat all symptomatic cases even without a physician consult or laboratory diagnosis, hundreds of thousands of courses of the drug were used in a fortnight (17). Mass prescription carries serious responsibilities. While the evidence base for all approved drugs should be sound, the evidence base for public health drugs must be of the highest quality, publicly available and open to independent scrutiny.

Trust is a noble human quality, but evidence based medicine should not hinge upon a singular trust in any one institution, particularly not in profit-driven companies to report information about their own products free of bias, let alone truthfully. As John Abraham once observed, there seems a tragic irony in that as pharmaceutical companies do not trust each other, that the public or government should be asked to trust them. (18) If governments have the authority to purchase and govern the use of multi-billion dollar drug stockpiles, they should have the interest, time, and money to transparently and independently first verify and evaluate the effects of that drug. The Box contains some ideas on where to start.

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Competing Interest Statement: I am co-author of the Cochrane review about which this article is written.

Contributor: PD is sole author and guarantor of the paper.

Study funding: The authors' own resources.

Table

Table *Contradictory statements made about the potential benefits of Tamiflu*

Effect	For	Against
Complications of influenza	Roche (roche.com): "Tamiflu delivers ... [a] 67 percent reduction in secondary complications such as bronchitis, pneumonia and sinusitis in otherwise healthy individuals" (8) Kaiser: "Our analysis found that early treatment of influenza illness with the neuraminidase inhibitor oseltamivir significantly reduced influenza-related LRTCs, associated antibiotic use, and the risk of hospitalization. This effect was observed in both at-risk subjects and otherwise healthy individuals" (3) EU: "The proportion of subjects who developed specified lower respiratory tract complications (mainly bronchitis) treated with antibiotics was reduced from 12.7% (135/1063) in the placebo group to 8.6% (116/1350) in the oseltamivir treated population (p = 0.0012)." (19) CDC: "In a study that combined data from 10 clinical trials, the risk for pneumonia among those participants with laboratory-confirmed influenza receiving oseltamivir was approximately 50% lower than among those persons receiving a placebo and 34% lower among patients at risk for complications ($p < 0.05$ for both comparisons) [(3)]" (12) HHS: "Treatment with a neuraminidase inhibitor (oseltamivir [Tamiflu®] or zanamivir [Relenza®]) will be effective in decreasing risk of pneumonia, will decrease hospitalization by about half (as shown for interpandemic influenza), and will also decrease mortality" (13)	Roche (tamiflu.com): "Treatment with TAMIFLU has not been proven to have a positive impact on [asthma, emphysema, other chronic lower respiratory diseases, pneumonia, other respiratory diseases, pneumonitis, and influenza-related death]" (6). FDA: "Serious bacterial infections may begin with influenza-like symptoms or may coexist with or occur as complications during the course of influenza. TAMIFLU has not been shown to prevent such complications" (20) Japan PMDA: *no mention of complications on drug product information sheet* (21)
Influenza-like illness (ILI)	Nicholson: "The duration of illness was significantly lower in the intention-to-treat [ILI] population than in the other subgroups because of the high proportion of influenza-infected patients in this population" (5) Treanor: "As expected, the greatest benefit of therapy was seen in individuals with evidence of influenza virus infection. However, analysis of the entire population also demonstrated a significant benefit of treatment" (4) Previous Cochrane review: "Time to alleviation of symptoms [for ILI were] … in favour of the [neuraminidase inhibitor] treated group …(hazard ratio 1.20, 95% CI 1.06 to 1.35)" (22)	Roche: "We acknowledge that oseltamivir is ineffective against influenza-like illness caused by viruses other than influenza" (7) EU EMEA: "Oseltamivir is effective only against illness caused by influenza viruses. There is no evidence for efficacy of oseltamivir in any illness caused by agents other than influenza viruses" (19) FDA: "There is no evidence for efficacy of TAMIFLU in any illness caused by agents other than 254 influenza viruses Types A and B." (20) Japan PMDA: "Tamiflu has no effect against infections except those caused by influenza A and B viruses" (21)

Box

Clarify expectations and provide evidence for them. Public health policies aiming to employ mass interventions should clearly state and identify (before approving the policy) the expected harms and benefits of that intervention. For every claim, raw data should be made available to aid independent analysis of the data. Clarity regarding the expectations of a drug can help reveal important inconsistencies, flagging them as areas of uncertainty that require better evidence.

Strengthen trial registration processes. All trials should be centrally registered (perhaps with the government in initiatives like ClinicalTrials.gov) with the names of all key study investigators and

their affiliations to help reduce the potential for ghost authorship. A field for publications resulting from a given trial, as well as a field explaining why a study was not/never published one year past its completion would help third party investigators match clinical trial to publication, and bring more awareness of the importance of publishing "negative" results.

Make patient level data available. Individual patient data is often the only way to resolve questions about the effects of a drug. Publicly available anonymized patient level datasets on regulator websites would increase transparency and enable independent reanalyses of trial results.

Reduce the reliance on trust. Data collecting methodologies (such as adverse events reporting systems) that rely on companies to selfevaluate potential harms caused by their drug may lead to bias. Reduce this potential by making mandatory reporting requirement apply to all known adverse events, allowing the importance of a given adverse event to be determined by anybody who cares to analyze the publicly accessible post marketing surveillance database. Internet-only based reporting of adverse events would lessen the workload and help facilitate all known adverse events rapidly find their way into regulatory agency public databases.

Box-A short list of higher standards for evidence-based public health decision making

Figure

Figure-Proportion of respiratory specimens testing positive for influenza during influenza seasons (week 40 to week 20), 1997-98 to 2008-09, and comparison to proportion of intention-to-treat (ITT) population with influenza enrolled in ten Roche clinical trials reported by Nicholson, Treanor, and Kaiser. Peak weekly influenza positivity rate also shown. Seasonal data are from US CDC.

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Feedback

Neuraminidase inhibitors for preventing and treating influenza in healthy adults, 16 July 2009

Summary

Dear Mr Jefferson

We have some questions on the conclusion in your Oseltamivir review especially about the prevention of complication. You described that Oseltamivir 150 mg daily prevented lower respiratory tract complications (OR 0.32, 95% CI 0.18 to 0.57).

However, we have found that this conclusion is based on the other review (Kaiser 2003) and not on your own data analysis. The authors of the review were four employees of F. Hoffman-La Roche Ltd, one paid consultant to F. Hoffman-La Roche Ltd and Kaiser. We cannot find any raw data about this conclusion from your review. Kaiser's review included 10 RCTs; two RCTs (Nicholson 2000 and Treanor 2003) were published as articles in the peer-reviewed medical journal (JAMA and Lancet), but other 8 RCTs were proceedings of congress (5 RCTs), abstracts of the congress (one RCT) and meeting (one RCT) and data on file, Hoffmann-La Roche, Inc, Nutley, NJ (one RCT). The lower respiratory tract complication rates of these articles were summarized on table: there was no significant difference between Oseltamivir and placebo, and their Odds Ratio's (ORs) were 1.81. But ORs of other 8 RCTs were 4.37. We strongly suppose that the reviewer's conclusion about the complications was mainly determined by these 8 RCTs, we should appraise the 8 trials rigidly. Without this process it's difficult to conclude that Osltamivir can prevent lower respiratory tract complications.

Submitter agrees with default conflict of interest statement: I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Table *All lower respiratory tract complications (influenza case only)*

Nicholson 2000 + Treanor 2003	
Complications Placebo Oseltamivir 150 mg	
+ 13	7
- 277	270
Other 8 RCTs	
Complications Placebo Oseltamivir 150 mg	
+ 22	10
- 350	695
Kaiser (Cochrane)	
Complications Placebo Oseltamivir 150 mg	
+ 35	17
- 627	965

Reply

Response to Hayashi's Feedback comment: critical analysis of Kaiser et al (2003)

Kaiser et al (2003) combined 10 randomised control trials (RCTs) comparing oseltamivir with placebo in the treatment of influenza. They focused on risk of complications leading to antibiotic use. A limitation of their analysis was the combining of bronchitis, pneumonia and lower respiratory tract infections which they labelled as lower respiratory tract complications (LRTC). In the original trials complications studied also included sinusitis and otitis media however these were ignored in the Kaiser et al study. In addition bronchitis is a very general diagnosis whereas pneumonia is more specific and a much more serious condition. Combining of these two outcomes is questionable. Another limitation of the Kaiser et al study involves their choice of analysis strategy: Fishers exact test. This analysis does not stratify by trial but treats the whole 10 trials as one study. Therefore the benefit of randomisation is

lost, resulting in a non-randomised comparison. To confirm that they did indeed use Fishers exact test two analyses where the actual P value is reported can be checked.

Hospitalisations: 18/1063 versus 9/1350 P = 0.019 (Kaiser et al report P = 0.02)

LRTC in high risk patients: 74/401 versus 45/368 P = 0.021 (Kaiser et al report P = 0.02)

The resulting P values are the same (to two decimal places) therefore it is highly likely that they did indeed use Fishers exact test to compare the overall groups (without stratification). Normally in a meta-analysis of individual RCTs, separate comparisons by trial are made and then combined in an appropriate way to obtain the overall effect of treatment. A "correct" analysis is especially important in this case because of the following facts reported in Kaiser et al:

1. The populations studied in each trial are different: healthy adults in four studies; elderly patients in four studies, and adults with chronic obstructive airways disease (COAD) in two studies.
2. Overall there are more oseltamivir patients compared to placebo patients (2023 versus 1541) hence at least one trial did not have a 1:1 allocation ratio.
3. The trials had different proportions of influenza infected patients (ranging from 50% to 73%).
4. Overall there were more high risk patients in the placebo group compared to the oseltamivir group (38% versus 27%) hence (overall) groups are not comparable.

The Kaiser et al study did not report the numbers of patients randomised to the two groups for each of the 10 trials; they just reported overall numbers. The following hypothetical meta-analysis of two trials illustrates why a correct analysis is critical.

This meta-analysis shows two trials with no effect. However, the two trials have recruited much different patient groups (e.g. elderly patients in trial 1 and the general population in trial 2). Also trial 2 has not allocated with a ratio of 1:1 (as in at least one of the Kaiser et al trials). Like the Kaiser et al study there is a higher proportion of high risk patients overall in the placebo group (56% versus 33%). A naïve analysis that does not stratify by trial (Fishers exact test) shows a significant difference between treatment (20% events) and placebo (30% events) with P = 0.01 (odds ratio = 0.58). Conversely an analysis that stratifies for trial (logistic regression) shows no difference (P = 1.0, odds ratio = 1.0). In the case of the Kaiser et al data, a random-effects meta-analysis that takes into account heterogeneity between trials may be most appropriate.

Note that the hypothetical example shown above is "extreme". However, it does illustrate what could happen with a naïve analysis that does not stratify by trial. The important point is that with a naïve analysis there is no guarantee of an unbiased estimate of treatment effect or a realistic 95% confidence interval and P value.

Tom Jefferson, Mark Jones, Peter Doshi, Chris Del Mar, Liz Dooley

Date of inclusion: 10 November 2009

Contributors

Keiji Hayashi

Date of inclusion: 16 July 2009

Table of proportions of adverse events by (hypothetical) trial

Trial number	Adverse events		
	Treatment	Placebo	Total
Trial 1 (high risk patients)	50/100 (50%)	50/100 (50%)	100/200 (50%)
Trial 2 (low risk patients)	10/200 (5%)	4/80 (5%)	14/280 (5%)
Total	60/300 (20%)	54/180 (30%)	

Neuraminidase inhibitors for preventing and treating influenza in healthy adults, 30 July 2009

Summary

The last sentence under Results, preceding Discussion is: 'Finally, use of relief medications and antibiotics is unaffected by assumption of NIs (OR 0.81, 95% CI 0.59 to 1.12).' Here 'assumption' makes no sense, so should the words in bold be 'consumption of an NI'? Submitter agrees with default conflict of interest statement: I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Reply

Thanks you, we have re-written this part of the review to make it clearer.

Tom Jefferson, Mark Jones, Peter Doshi, Chris Del Mar, Liz Dooley

Date of inclusion: 15 November 2009

Contributors

Andrew Herxheimer

Date of inclusion: 30 July 2009

What's new

Last assessed as up-to-date: 6 August 2009.

12 November 2009	New citation required and conclusions have changed	1. We excluded two new studies (Blumentals 2007 and Toovey 2008) 2. We now study pharmacovigilance data 3. We excluded a previously included study (Kaiser 2003) as we could not answer the Hayashi comment by reconstructing the Kaiser 2003 data set. Hayashi prompted us to more carefully evaluate the Kaiser2003 study. More critical evaluation of it leads essentially to a retraction of our 2006 and 2009 updates of this review. It results in changed conclusions: excluding the Kaiser 2003 data, and failing to identify sufficient toxicity data from pharmacovigilance sources, we conclude that there is insufficient evidence to describe the effects of oseltamivir on complications of influenza and its toxicity 4. There is a change in authors of the review team 5. The review was published in a print journal in a shortened form, December 2009 (Jefferson 2009e)
7 August 2009	New search has been performed	Safety/adverse effects searches conducted
30 July 2009	Feedback has been incorporated	Feedback added to review
16 July 2009	Feedback has been incorporated	Feedback added to review
14 July 2009	New search has been performed	Effectiveness searches conducted

History

Protocol first published: Issue 1, 1999

Review first published: Issue 2, 1999

20 May 2008	New search has been performed	Searches conducted in May 2008. For this update we assessed 688 possible studies, retrieved 17 and excluded all of them. Our conclusion did not change but we found non-comparative phase IV evidence from a thorough review of the evidence on harms by Hama which we mentioned in the Discussion section. Updated review published in Issue 2, 2009
29 April 2008	Amended	Converted to new review format
19 May 2006	New citation required and conclusions have changed	Substantive amendment published in Issue 3, 2006
13 October 2005	New search has been performed	Searches conducted in October 2005. We completely revised the text and added a section on evidence from an avian influenza epidemic that took place in the Netherlands in 2003 and claimed one life. We also added a section on post-exposure prophylaxis (PEP). We dropped studies looking at the effects of neuraminidase inhibitors (NIs) on experimental influenza cases (that is to say, on subjects who had been deliberately infected as part of an experiment) and concentrated on the now numerous studies of naturally-acquired influenza cases. The terms "laboratory-confirmed influenza" and "clinically confirmed influenza" have been changed for the more correct terms "influenza" and "influenza-like-illness" (ILI). We believe these words to reflect the difference between real influenza (caused by influenza A and B viruses) and what is colloquially known as "the flu". The two are rarely clinically distinguishable in real-time unless a very good surveillance apparatus is in place, as in most of the trials in our review. Updated review published in Issue 3, 2006
24 February 1999	New search has been performed	Review first published in Issue 2, 1999

Contributions of authors

For the 2009 update Tom Jefferson (TOJ) applied inclusion criteria.

Liz Dooley (ED) and TOJ independently read all titles and studies retrieved in the search and applied inclusion criteria. All authors except Ruth Foxlee (RF) reappraised and investigated extracted data while Chris DelMar (CDM) supervised the process and arbitrated when necessary.

Mark Jones (MJ) and Peter Doshi (PD) checked and transformed data and supervised the revised meta-analysis.

TOJ and CDM edited the text and together with ED, MJ and PD, contributed to the final draft.

RF developed and conducted the searches for adverse effects studies.

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The HTA programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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