Effectiveness of Vitamin A Supplementation in the Control of Young Child Morbidity and Mortality in Developing Countries – Nutrition policy discussion paper No. 13

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by

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United Nations – Administrative Committee on Coordination – Subcommittee on Nutrition (ACC/SCN)

The ACC/SCN is the focal point for harmonizing the policies and activities in nutrition of the United Nations system. The Administrative Committee on Coordination (ACC), which is comprised of the heads of the UN Agencies, recommended the establishment of the Sub−Committee on Nutrition in 1977, following the World Food Conference (with particular reference to Resolution V on food and nutrition). This was approved by the Economic and Social Council of the UN (ECOSOC). The role of the SCN is to serve as a coordinating mechanism, for exchange of information and technical guidance, and to act dynamically to help the UN respond to nutritional problems.

The UN members of the SCN are FAO, IAEA, IFAD, ILO, UN, UNDP, UNEP, UNESCO, UNFPA, UNHCR, UNICEF, UNRISD, UNU, WFP, WHO and the World Bank. From the outset, representatives of bilateral donor agencies have participated actively in SCN activities. The SCN is assisted by the Advisory Group on Nutrition (AGN), with six to eight experienced individuals drawn from relevant disciplines and with wide geographical representation. The Secretariat is hosted by WHO in Geneva.

The SCN undertakes a range of activities to meet its mandate. Annual meetings have representation from the concerned UN Agencies, from 10 to 20 donor agencies, the AGN, as well as invitees on specific topics; these meetings begin with symposia on subjects of current importance for policy. The SCN brings certain such matters to the attention of the ACC. The SCN sponsors working groups on inter−sectoral and sector−specific topics.

The SCN compiles and disseminates information on nutrition, reflecting the shared views of the agencies concerned. Regular reports on the world nutrition situation arc issued, and flows of external resources to address nutrition problems are assessed. State−of−the−Art papers arc produced to summarize current knowledge on selected topics. SCN News is normally published twice a year. As decided by the Sub−Committee, initiatives are taken to promote coordinated activities – inter−agency programmes, meetings, publications – aimed at reducing malnutrition, primarily in developing countries.

Foreword

In 1990, the Advisory Group on Nutrition presented a proposal to the SCN for reviewing the scientific evidence on the effectiveness of vitamin A supplementation on mortality and morbidity in children from developing countries. The idea was endorsed by the SCN and generous support from the Canadian International Development Agency made the meta−analysis possible. With Professors Beaton and Martorell as co−chairs, a multi−disciplinary committee presented its findings to the SCN at its 20th Session in February, 1993. We are pleased to now publish the report of these findings in the SCN's State−of−the−Art Series, as Nutrition Policy Discussion Paper No. 13.

The observations in 1986 by Sommer and colleagues, that vitamin A supplementation of pre−school children in areas of Indonesia prone to xerophthalmia produced a remarkable decline in mortality – a third or more – stimulated great debate in the international public heath community, with some finding such a large effect simply incredible. True to the scientific tradition, researchers soon launched a number of studies to replicate the findings in other settings, but the results which emerged, though largely confirmatory of the earlier report, were not always consistent. Also, the studies focusing on morbidity appeared to suggest lack of a clear effect, in sharp contrast to most of the mortality studies. Thus the need was clear for careful analysis of the evidence by an independent group. The UN member agencies of the SCN, as well as governments, bilateral agencies and NGOs felt the need for guidance. Was there really a mortality effect? Did it vary dependent upon age, gender or nutritional and demographic characteristics? What about cause−specific mortality? Did incidence or severity of respiratory and gastrointestinal infections change? These and many other questions needed well−founded answers.

The SCN is grateful to the AGN and to the members of the committee in particular for having undertaken the review so competently. The scientific evidence has been taken only as far as it goes, with caution expressed where warranted. It has been possible to adequately address many of the pertinent questions with the evidence at hand. There is a clear mortality reduction of 23% and this does not appear to be the result of a pharmacological effect. Any intervention which proves effective in improving vitamin A status in deficient populations will on average reduce mortality by 23%. Although it appears that vitamin A supplementation does not reduce the overall morbidity burden, it does appear to reduce severity and case fatality rates, as for example with measles. More details are found in the report – but these examples are enough to demonstrate the contributions made.

The report provided crucial background for the second phase of this project – as originally proposed by the AGN and accepted by the SCN – which examines the policy and programme needs for reducing vitamin A deficiency. This led to a meeting in Ottawa in July 1993 and substantial consensus, which will be published separately to this volume in 1994, thus completing the overall exercise.

We hope that these important results will stimulate and support expanded action to prevent vitamin A deficiency, thus, we now know, saving many young lives.

Dr Abraham Horwitz
Chairman, ACC Sub–Committee on Nutrition

Acknowledgements

We express our sincere appreciation to those original investigators who responded to our questions and provided us with access to unpublished reports and draft manuscripts, and who, in some cases, ran additional analyses of their data to provide us with specific information. We are fully cognizant of the fact that secondary reviewers can never fully appreciate the subtleties of original field studies and we can only say that we have tried to honour their data in our interpretations.

We are indebted also to Dr. Sonya Rabeneck of the Canadian International Development Agency (CIDA) who assisted us in many ways. The proposal for this review arose at the United Nations ACC/Subcommittee on Nutrition and its Advisory Group on Nutrition. Many of the United Nations and bilateral agency representatives in those discussions were anxious that the project go ahead. It was CIDA that accepted the responsibility for financing the work but we express appreciation to all for the wide base of support that has been given to us.

As co–Chairmen of the project, Dr. Martorell and I express our appreciation to all members of the Technical Advisory Group who struggled through the mountains of paper that came to us and contributed heavily to the development of this project. We are appreciative also of the specific contribution of Dr. Bart Harvey who served as Research Associate for the project. Finally we note that our first meeting we had the benefit of the participation of Dr. Barbara Underwood and Dr. Sue Horton as consultants. Dr. J–P Habicht was an original member of the TAG but was unable to attend any meetings. Although he felt obliged to withdraw from membership because of this, we appreciate his critical comments in the early stages of planning.

Above all, we appreciate and respect the contribution made by the more than 175,000 children, and their families, who participated in the mortality and morbidity trials reviewed in this report. We trust that their contribution to improved knowledge of the role of vitamin A in the health and survival of children now alive and yet to be born, will be judged to have been worthwhile.

It is to those children that we dedicate this report.

George H. Beaton
August 1993

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Reviewers of the Report

This report, in its final draft form, was sent to external reviewers who were not connected with the final report and its conclusions. Their summary assessments, criticisms, and comments, except those incorporated into the final revision of the report, are presented as a special annex to the Report. At the same time that the draft report was sent to reviewers, it was sent to representatives of the original projects with the request that they review our interpretations of their project data, drawing our attention to any technical errors, and an invitation to offer such comment as they might wish. A few responses were received and changes were made. We are indebted to all who have advised us of errors and omissions in our original report to CIDA.

Abstract

This report presents conclusive evidence that improving the vitamin A status of young children reduced mortality rates by about 23%. The evidence relates to population groups in which there was evidence that vitamin A deficiency was sufficiently prevalent and sufficiently severe to give rise to at least a low prevalence of clinical signs of deficiency. The observed effect of vitamin A supplementation, described in terms of the Relative Risk (RR) was RR = 0.77,95% C.I. 0.68 to 0.88; $p < 0.001$. This confidence interval takes into account variation among studies (a Random Effect model) and the impact of cluster sampling designs. A narrower interval (0.71 to 0.84) was obtained under the assumptions of a Fixed Effect model. In reaching these estimates and the associated main conclusion, 10 mortality trials were identified and considered; these included trials with reported results ranging from a 50% reduction to no detected effect. Only 8 of the trials could be examined in full detail and be incorporated in the overall summary estimate of effects. Of the two excluded trials, one (in Bombay slums) reported a very major effect while the other (in Haiti) failed to find an effect on mortality.

The analyses reported demonstrate that the relative effects of vitamin A were independent of gender and age at least between 6 months and five years. A recent study in Nepal has reported no effect under 6 months of

age. The relative effect was not demonstrably influenced by mortality rates (as seen in the control groups). Clear effects could be shown for deaths attributed to diarrhoea and measles but the effect in deaths attributable to respiratory infection was negligible or non−existent as was also the effect in deaths attributed to malaria (Ghana study).

Variability among the trials in relative effect of vitamin A, was apparent but attempts to explain this variation by descriptors of the population (baseline anthropometric status, prevalence of xerophthalmia, age profile, baseline mortality rate) were unsuccessful. Indeed the only evident explanation of differences in effect would be differences in cause−specific mortality profiles.

The report develops estimates of the magnitude of effect to be expected in a new program or study. The point estimate remains an RR of 0.77 but the limits of the prediction interval for expected true effect, recognizing observed, but unexplained, variation among past studies, widens to 0.60 to 0.99. Estimates of what might be seen, taking into account the sampling error associated with a particular design of a new program (as a function of population size, mortality rate and cluster effect) are also presented along with associated probabilities.

The above analyses relate to the *relative* effects of vitamin A. If one considers the *absolute* effects (e.g. lives saved per 1000 children covered) then the effect is dependent upon baseline mortality rate and, to the extent that that varies with gender and age, on these characteristics as well.

The review does raise some question about the adequacy of current recommendations for periodic high potency dosing (the dose x frequency combination may be marginally adequate).

None of the mortality studies had been conducted in population groups where there was biochemical evidence of depletion without associated evidence of at least a low prevalence of xerophthalmia (although one study, in Ghana, came close to this situation); thus, no firm conclusion could be reached about probable effectiveness in such situations. Conversely, a recent morbidity trial in Brazil has shown an impact of vitamin A on severe diarrhoea, suggesting that mortality effects might also exist (the study was not designed to examine mortality).

Unlike the explicit conclusions concerning mortality effects, the review of 20 studies providing information about morbidity outcomes is less clear. The report concludes that, based on existing evidence, there should be no expectation of an effect of improvement of vitamin A status on general morbidity. Conversely there is suggestion that severe morbidity is favourably affected. Further, and in the specific case of measles, there is evidence that improvement of vitamin A status even after the onset of infection can improve both the course of the episode and the case fatality rate.

It is concluded, from the review of morbidity and mortality outcomes, that the effect of vitamin A is more likely to be on the body processes relating to response to infection than on those relating to resistance to becoming infected. Either type of effect would have been consistent with the literature relating to the biological roles of vitamin A.

Summary

Specific Goals of the Review of Experience

Under the original contractual agreement, there were three goals specified. These are set forth below.

- to review and assess the available experience with regard to the effect of vitamin A supplementation on young child morbidity and mortality.

- to advise CIDA on the apparent effectiveness of vitamin A supplementation in young children in developing countries

- to estimate, to the extent possible, the range of effects for mortality and morbidity outcomes expected under various nutritional and ecological circumstances and for various subgroups of the population.

These goals were to be addressed in the connotation of informing policy decisions but the review, assessment and formulation of policy was not included in the assigned mandate. Another group, with different composition and with additional background documents, is addressing policy implications of the report. The following summary is presented under the headings of the three specific objectives, rephrased as questions that were addressed.

Identify and Review Controlled Trials

We were able to identify and examine 10 mortality trials (plus a recently released extension of one of these) and 17 community–based morbidity trials (including morbidity results from the 10 mortality trials; plus 7 controlled trials in hospital or other settings). These included both published and unpublished studies for which we were able to obtain descriptions from the primary investigators. For published studies, we often obtained supplementary information from original investigators. We are aware of additional morbidity trials still under way, and of plans for further analyses of existing trials. However, we are unaware of any further mortality trials now under way or approved for implementation in the near future. Therefore, for the mortality outcome, we think we have captured the total experience and our only shortfall is with regard to two studies, one in Bombay, India and one in Haiti, for which we could not obtain the level of detailed information needed for inclusion in our formal analyses. In contrast, for morbidity we expect that substantial additional information will be forthcoming in the next year or two and therefore urge that our morbidity conclusions be seen as a valid interpretation of experience to date but subject to possible modification when further information becomes available.

Did Vitamin A Supplementation Have an Effect on Young Child Morbidity and Mortality?

Mortality Effect

We have provided a definitive YES answer with regard to mortality. Vitamin A supplementation resulted in an average reduction of 23% in mortality rates of infants and children between 6 months and five years (see Figure S.1). The effect was highly significant under two conceptual models examined: a *fixed effect* and a *random effect* model; RR = 0.77 (95% CI 0.71 to 0.84) for the former and RR = 0.77 (95% CI 0.68 to 0.88) for the latter. Also shown in Figure S.1 is the Prediction Interval relating to the effect to be expected in a future programme or study in a new setting. This is discussed later in this summary and is presented in Figure S.1 only to provide perspective.

An analysis was run for the small number of infants identified as being under the age of 6 months; this analysis also suggested a reduction of about 23% but it was not statistically significant. Subsequent to that analysis, the results of a trial of the effects of dosing between birth and 6 months on deaths under 10 months became available. Although the study included a very substantial number of infants, there was no detected effect. We are also advised that a group at the London School of Hygiene and Tropical Medicine, with newly obtained data from the projects we examined, cannot confirm our tentative finding about effectiveness of dosing under six months. They advise that there were some important errors in the aggregated reporting of ages in the data we were able to access. At this time, we are unable to reach a firm conclusion about short and long term benefits of vitamin A supplementation to infants under 6 months of age.

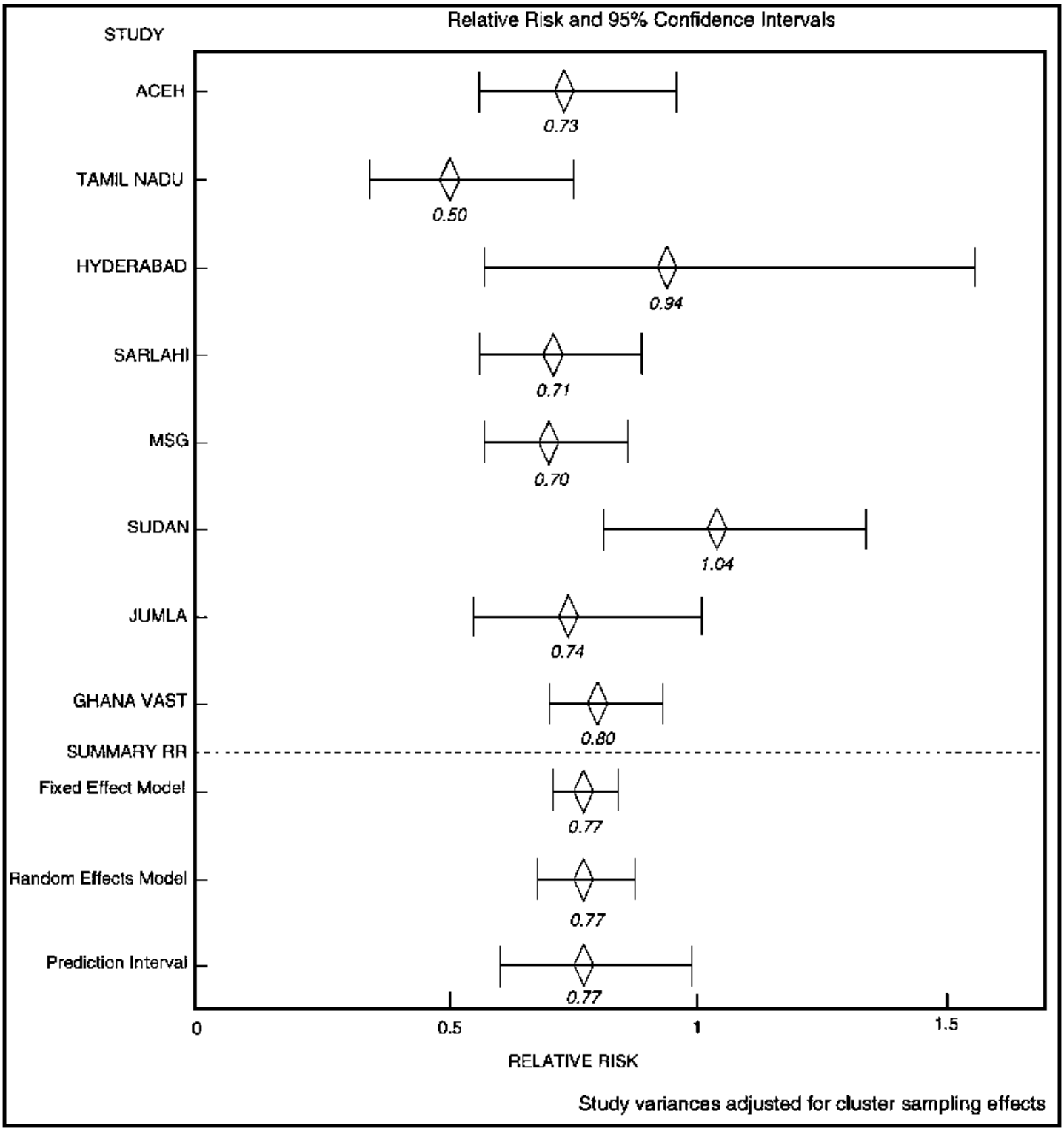

Figure S.1 Impact of Vitamin A Supplementation on Mortality of Infants and Children Six Months to Five Years

Note: Shown are the point estimates and 95% Confidence Intervals for the eight original studies reviewed in detail. Also shown are two summary estimates for the relative effect, taking into account all 8 studies. These have the same point estimates, a 23% reduction in mortality, but differ in the estimated Confidence Intervals. The second estimate (*random effects*) takes into account the between study variation that we believe exists. The first estimate (*fixed effect*) assumes that there is a single true RR for all studies. The Prediction Interval for a future programme or study is also presented. Again the predicted average effect is 23% but the interval describing possible actual effects is greatly expanded (see text for explanation).

Over 6 months of age, the relative effect of vitamin A (% reduction in mortality) was not influenced by age or gender. That is, one would expect to see comparable reductions in males and females and in infants over 6 months as well as children up to five years.

The mortality effect is pronounced for diarrhoeal disease, is demonstrable for deaths attributed to measles even though the number of cases is much smaller, and may be absent or very small for deaths attributed to respiratory disease (except in the case of pneumonia secondary to measles in hospitalized children) or to malaria (one study reporting).

A very important finding was that the effect on mortality was not dependent upon very high potency dosing. One trial was based on fortification of Monosodium Glutamate and another was based on the weekly administration of physiologic doses. This led us to the inference that it was improvement of vitamin A status rather than the method of improving it, that was the important determinant of effect.

Morbidity Effect

In contrast to the very clear effect of vitamin A on mortality, we were forced to conclude that improvement of vitamin A status cannot be expected to impact on incidence, duration or prevalence of general diarrhoeal and respiratory illness as seen in the community. Conversely, we conclude that it is likely that improvement of vitamin A status impacts upon the progression of illness to its severe forms, and to its severest form, mortality. This important conclusion about an impact on severity is explicitly documented in the recent GHANA VAST morbidity trial where it can be seen as having impact on referrals and clinical admissions as well as on reported occurrence of severe morbidity per se. It was documented also in a morbidity trial in Brazil where severe diarrhoea was reduced. The phenomenon is seen also in studies of vitamin A administration in children presenting with measles; both severity of the illness and case fatality rates are reduced. Since we know that hospital admission and clinical referral data were collected, but not yet analyzed, by other projects, we expect that further information, will be forthcoming. There is at least one well controlled study that fails to support the Ghana and Brazil observations. Given the indisputable effect on mortality, there has to be an effect on *severe* morbidity – however most morbidity trials may lack sufficient statistical power to pick up low incidence cases (and the incidence *of fatal* morbidity is low).

An implication of these findings is that for the control of young child morbidity, vitamin A is *not* a panacea. The attack will have to focus upon the environment in which morbidity occurs. We can only suggest that vitamin A status appears to affect the child's ability to respond appropriately and adequately once infection has developed and hence appears to impact on the course of morbidity. As for mortality, there may well be differentials in the effect across different types of illness. Available evidence did not permit a conclusion on this aspect of the morbidity effect.

One aspect of the morbidity analysis that has direct relevance to field programmes was the fact that vitamin A intervention *after* the onset of measles impacted favourably upon the development of severe complications and reduced the case fatality rate. In the main mortality trials reviewed, it was not possible to ascertain when the vitamin A had been administered in relation to measles onset. We infer that it is vitamin A status during infection that is important but infer also that this can be addressed before or after the onset of infection.

What Can be Expected in Future Programs?

The third goal specified in the contract is perhaps the most important. It addresses the important planning question of "what should we expect in a new programme in a new setting?" Below we divide our response to the third goal into two sub–questions: "Where (in what population setting(s)) can one expect vitamin A to be effective?" and "What is the range of effect to be expected?"

Where is Improvement of Vitamin A Status Most Likely to Affect Morbidity and Mortality?

The obvious answer to this question is "Where vitamin A deficiency is now a serious problem." For the mortality trials, all of which had been conducted in settings where it had been assumed vitamin A was a public health problem under the WHO definition, we attempted to ask about population–level predictors of the relative effect. For these analyses we had only 8 studies and with such a small sample, subtle effects might go undetected. However, any major effects should have been seen.

We found no relationship between the baseline prevalence of xerophthalmia and the relative effect of vitamin A. Thus we have to conclude that while the existence of clinically apparent deficiency was a marker for all programmes, the actual prevalence added very little further information in predicting outcome. One very

important question is unanswered. There were no mortality trials conducted in populations with biochemical evidence of vitamin A depletion but without associated evidence of clinical manifestations of deficiency (Ghana, with a xerophthalmia prevalence of only 0.7%, came closest to this situation). Thus we can offer no conclusion, based on the definitive mortality evidence, about the impact of vitamin A to be expected in populations where there is evidence of depletion but not evidence that depletion is severe enough to produce clinical lesions in at least a small proportion of individuals. This leaves as judgemental the potential impact of programmes in a very substantial part of the developing world. Our judgement is that mortality rates would likely be affected wherever vitamin A depletion is severe even in the absence of xerophthalmia. This judgement s based on three observations: i) the demonstrable effect in Ghana where xerophthalmia was very low; ii) the absence of a demonstrable relation between relative effect and prevalence of xerophthalmia; and iii) the demonstration in Brazil, where xerophthalmia is absent, that vitamin A supplementation reduced severe diarrhoea.

We found no impact of the prevalence of stunting or wasting or of the interaction with xerophthalmia prevalence on the prediction of the relative effect of vitamin A. We note however that all of the population groups studied exhibited a high prevalence of stunting and shared the common feature of representing the poorer segments of the population exhibiting the stigmata of early deprivations and undoubtedly also a common social/biological environment favouring high morbidity and mortality. Thus, stunting was seen more as a marker of the environment of early growth and development than as an index of current nutritional conditions.

We found no apparent association between the mortality rates of control groups and the relative effectiveness of vitamin A. The recorded mortality rates ranged between a low of about 5 per 1000 to a high of 126 per thousand.

As mentioned earlier, neither gender nor age appeared to influence relative effectiveness. The only factor we found that would serve to predict relative effectiveness of vitamin A was evidence that the effect depended on the attributed cause of mortality (Table S.1). From those analyses we conclude that a large relative effect is more likely to be seen where mortality attributed to diarrhoeal diseases or measles is predominant and that the relative effectiveness would be diminished where deaths attributed to respiratory infection or malaria became increasingly prevalent.

From these analyses we can add very little to the starting observations: *in populations like those studied* (*with evidence of poverty, general social and biological deprivation marked by stunting, and with evidence of existing vitamin A deficiency marked by the presence of xerophthalmia*)*, improvement in vitamin A status can be expected to have a beneficial effect on mortality.*

We can describe the apparent reason that two studies (Hyderabad and Sudan) failed to show an effect of vitamin A supplementation (Hyderabad reported a 6% reduction in mortality; Sudan reported a 4% increase in mortality,; neither was significant and the confidence bounds for both included the estimated average effect for all studies combined). In each case there was minimal difference in vitamin A status (marked by effect on xerophthalmia) generated between the treated and control groups. In the case of Sudan, it appears that the vitamin A administered was not biologically sufficiently effective although its chemical stability was demonstrated and night blindness was reduced. In the case of Hyderabad, the problem was an unexpected improvement in the vitamin A status of the control group. While these observations may explain why those trials failed to exhibit effects, it is extremely important to recognize that in neither case could the outcomes have been *predicted* on the basis of information available to us for examination. We treat these two trials and their reported effects as a part of the collective experience and as contributors to our Summary Estimate of the effect of Vitamin A supplementation. However, from the experience in these two studies, we conclude that it is essential that any future programmes monitor the impact of the programme on vitamin A status (e.g. by repeated clinical surveys or by monitoring serum retinol levels), at least until it is established that the administered vitamin A is biologically active in the particular setting.

Table S.1 Relative Risk for Vitamin A Supplementation by Attributed Cause of Death[a]

Attributed Cause of Death	*Estimated RR*
All causes	0.77
Diarrhoeal	0.71
Measles	0.46

Respiratory Other Malaria[b]	0.94 0.84 no effect

[a]Based on four trials reporting.
[b]Only one trial reporting.

What is the Range of Expected Effects for Future Programmes?

Given that we were unable to explain the variation in reported results among the 8 mortality trials, we must base any prediction on the total experience. In Figure S.1, we included a portrayal of the Prediction Interval applicable to a new study but based on the review of past experience. This interval includes the possibility that a new study will have no effect on mortality (such was a part of the experience). It includes also the possibility that a new study might have an effect much greater than the average 23% reduction expected. In the main report we developed this concept further and actually developed probabilities that could be attached to various levels of effect. These are portrayed in Table S.2. These might be interpreted in the following manner. If justification of a vitamin A control programme requires that there be a mortality reduction of at least 10%, then we suggest that there are about 9 chances in 10 (probability = 0.89) of an effect at least this large being present in a programme that does improve vitamin A status to a degree comparable to the reviewed programs. If a 20% reduction is needed, then the probability of achievement is 0.6 (3 chances in 5). However if reductions of 30% and 40 % are sought, the probabilities fall to 0.2 and 0.03. All of these may be contrasted to the probability of better than 97% that *some* effect will be produced.

We also cautioned, in our main report, that because of the predictable effects of sampling error, in a study of finite size, particularly in a population with low mortality rates, the investigator would not necessarily *see* an effect even if it were present. Table S.3 presents this warning in the form of probability that an effect will *not* be *seen* as a function of intervention group size and 'baseline' mortality rate. What this shows is that if one runs a pilot study in a population group of relatively small size (for mortality trials) and in the presence of a low mortality rate, there is a very high chance that one will fail to see any effect even though the probability that there is an effect remains high (see paragraph above). Interestingly the Hyderabad trial would fall into this category. The opposite also holds, there is a greater chance of seeing an effect as large as that reported for Tamil Nadu (50% reduction) even though it is unlikely that the real effect is that large. Care must be taken in interpreting any pilot studies that are run in the future.

Table S.2 Probability That a Vitamin A Effect of Specified Magnitude Will be Present in a Future Study

Mortality Reduction	***Probability***
Any effect	0.98
10%	0.89
20%	0.62
30%	0.23
40%	0.03

Note: Estimates assume a cluster effect (DEFF = 1.3). No new study sampling variance included in this model of the expected true effect.

We caution also that our estimation of future effects rests on comparison of control and treated groups. However, the mortality rates observed in the control groups was often much lower than expected (than previously believed to exist as a baseline mortality rate). There are several possible explanations for the discrepancy. These include at least: i) a possible non–specific effect of interventions such as increased awareness and use of health facilities (an effect operating in both control and treatment groups and unrelated to vitamin A); ii) an effect secondary to treatment of high risk xerophthalmic children with vitamin A (in both groups); iii) a phenomenon related to exclusion of high risk children (by design or by self selection); iv) the possibility that the study population was actually different from the regional population for which mortality rates had been described (perhaps the result of selecting a study area that had somewhat better health services or other infrastructure); or v) simply inaccuracies in previously reported local mortality rates (where not directly estimated by the research project). We did not have opportunity to test these hypotheses and warn only that we do not *know* whether vitamin A treatment is equally effective in children that might have been excluded – hence we do not *know* whether the predicted effect of vitamin A (23% reduction in mortality) is applicable to true baseline mortality rates. From those studies in which the baseline and control group mortalities appeared comparable, the reported effect of vitamin A appeared comparable. Therefore we *think* the relative effect is

applicable to true baseline mortality rates. It was also reported in the Tamil Nadu study that inclusion or exclusion of children treated for xerophthalmia (and then left in their original treatment group assignments) did not change the estimated relative effect of vitamin A. Thus, although that type of exclusion of a high risk group might alter apparent mortality rates (in both control and treated groups), it would not influence the estimate of effect of vitamin A. What the planner must recognize is that in a programme setting, without a concurrent control group, reductions from baseline mortality attributable to any of these causes might *appear* to be results of the intervention. In this sense our estimates of the real effect could be smaller than the apparent effect seen in an operating programme. Offsetting this, of course, would be lower 'compliance' rates expected in an operational programme as compared to a research study.

Table S.3 Probability of Failing to See an Effect of Vitamin A, as a Function of Group Size and Baseline Mortality Rate

	Mortality Rate/1000			
Group Size	***5***	***15***	***25***	***45***
5,000	0.239	0.135	0.096	0.064
10,000	0.172	0.085	0.060	0.042
50,000	0.061	0.034	0.029	0.025
100,000	0.041	0.028	0,025	0.023
250,000	0.029	0.024	0.023	0.022

Note: All estimates assume a cluster effect (DEFF =1.3) and provide for sampling variance as a function of group size and mortality rate. All estimates are based on average reduction of 23% (RR=0.77).

The Distinction Between Relative and Absolute Effects of Vitamin A on Mortality

All of the results described above refer to the *relative* effects of vitamin A, the proportional reduction in mortality. We have shown from those analyses that there was no apparent effect of gender, age or mortality rate. However, it is to be recognized that if the *relative* effect is unchanged, then the *absolute* effect (number of lives saved) must be directly proportional to the baseline mortality rate:

Lives saved per 1000 treated = RR x Baseline Mortality Rate per 1000.

Since mortality rates generally fall with age in young children, and perhaps differ by gender, it follows that one would expect an impact of age and perhaps gender on the *absolute* effect of vitamin A. The possible effect of age is illustrated in Figure S.2. Here, for purpose of illustration, the median mortality rates of studies contributing age specific data have been used. Actual rates in a new programme might be quite different but the phenomenon should be similar.

Some Implications for Programme Targeting

Although the present analyses were not designed to address operational programs, there are some apparent implications for targeting programs. In terms of *relative* effects of vitamin A, the only targeting that we identified as potentially making a difference was with regard to cause–specific mortality. Populations in which deaths attributable to diarrhoeal disease or measles where much higher than deaths attributed to respiratory disease or malaria would be expected to show higher relative effects of vitamin A than would be seen under the reverse condition.

In keeping with earlier reviews, we demonstrated also that intervention after the onset of measles was effective in reducing severe morbidity and mortality. This has implications for the design of treatment protocols in primary and secondary health care. It also suggests the importance of determining whether a similar phenomenon holds for diarrhoeal disease and other types of infection. It might have implications for the design of population level control programmes but this would imply the need for infrastructures capable of detecting and treating potentially severe illnesses.

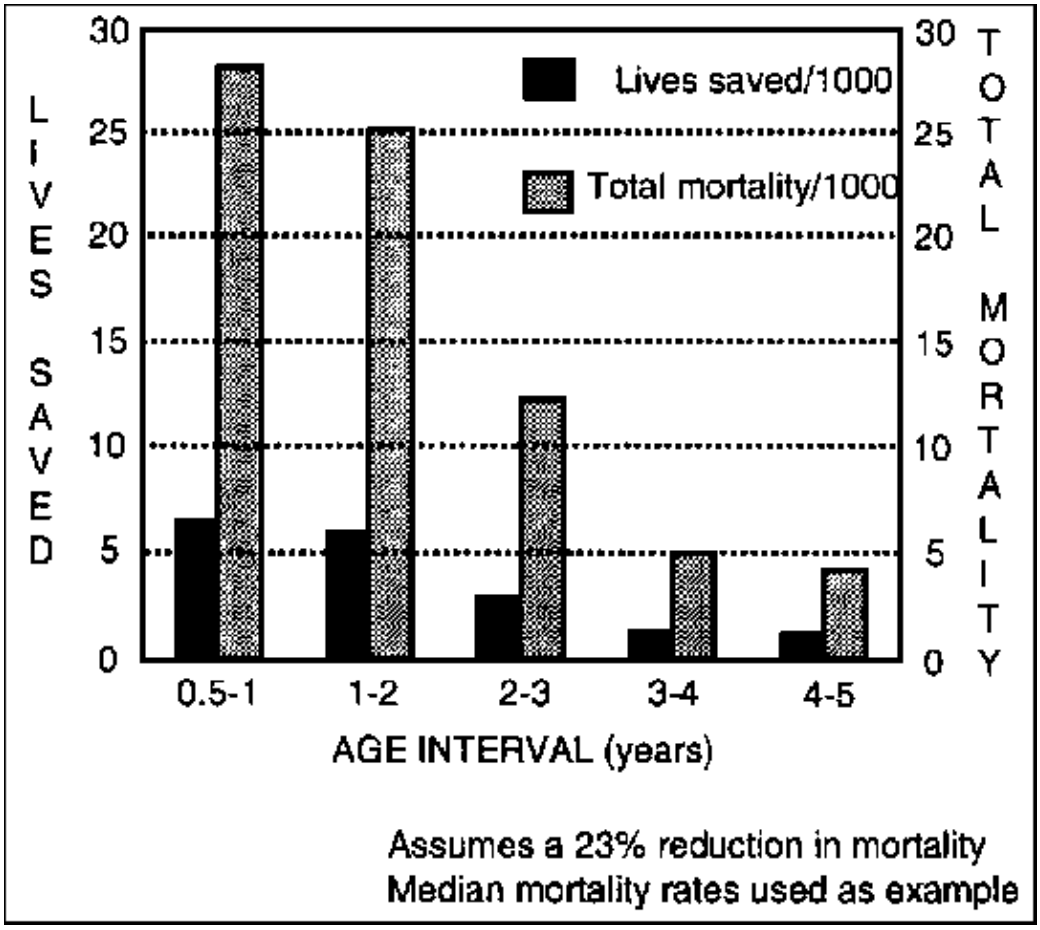

Figure S.2 Absolute Impact of Vitamin A Expressed as Lives Saved Per 1000 Subjects Covered

When one thinks of programmes in terms of their impact expressed as lives saved per 1000 infants/children covered, then it seems clear that the following baseline characteristics would increase the probable effect of the program:

- high baseline mortality rates, particularly for diarrhoeal disease or measles (the latter perhaps in conjunction with low measles immunization rates),

- young ages (but vitamin A may have little or no effect in breastfed infants under 6 months of age).

Of course, all of our analyses relate to populations determined in advance to likely benefit from vitamin A, thus our assessments apply to population groups characterized by:

- generalized poverty,

- high prevalence of stunting suggestive of disadvantageous social and biological environment and associated early growth failure,

- presence of clinical manifestations of vitamin A deficiency sufficiently prevalent to meet the WHO criteria of a public health problem.

A very important incompletely answered question is whether such populations, lacking evidence of clinical manifestations of vitamin A deficiency, but presenting biochemical evidence of major vitamin A depletion, would also be responsive to improvement of vitamin A status. We *think* the answer is “yes” but we lack hard evidence.

Programme Approaches

This analysis of experience was not designed to compare programme approaches, nevertheless some interesting observations relevant to the topic can be offered. First, it was demonstrated, without doubt, that daily (through fortification of monosodium glutamate, MSG) and weekly intakes of physiological levels of

vitamin A (Tamil Nadu) were just as effective as periodic high potency dosing. It follows, in the judgement of the authors that any approach to improving vitamin A status that effectively controlled xerophthalmia would have beneficial impact on mortality comparable to that reported. We noted also a recent report from an Indonesian study that one time dosing of women shortly after birth was effective in raising breast milk vitamin A levels and improving the vitamin A status of the infant for at least 8 months. This might be a strategy worthy of exploration if the target group is young infants or if it is accepted that the initial build up of vitamin A has longer term effects in young children.

Also evident was the fact, at least for complications of measles, that administration of vitamin A *after* infection was effective in improving prognosis (duration of hospitalization and mortality).

One important issue that could not be examined with the data available was whether the lives spared by improvement of vitamin A status were identical with lives that would be spared by improved health care or by immunization. Thus we do not *know* whether the effects of adding vitamin A improvement to *effective* immunization programmes would improve mortality experience or have greatly diminished impact. Similarly we cannot be sure whether improvement of vitamin A status would render immunization programmes more effective through enhancement of the immune response. These are important practical questions. It seems logical to assume that as public health measures significantly reduce young child deaths attributable to diarrhoea and measles, the relative impact of vitamin A on mortality will be diminished. Unfortunately, sharp reductions in deaths attributable to diarrhoea do not seem likely to occur soon. It follows that concern about vitamin A status will persist for some time to come. While the present review focused upon effects in very young children (to five years) we encountered evidence that effects are seen also in older children and clearly the adequacy of breast milk vitamin A levels and occurrence of night blindness in pregnant women are affected by the vitamin A status of the adult population. This is not a problem restricted to young children although they may be more susceptible due to the contribution of poor weaning practices (inadequate sources of vitamin A at a critical time of life).

Finally it must always be remembered that vitamin A is potentially toxic and may be teratogenic during pregnancy. In the studies reviewed there was some evidence of transient side effects of high potency dosing (e.g reports from Nepal and from GHANA VAST) but no evidence of actual toxicity. Conversely, there was some suggestion (Sudan, and perhaps also Hyderabad) that the 200,000 IU x 6 month interval for children over one year may have been inadequate to evoke a beneficia[1] response. That would be in keeping with an earlier review of oral dosing with vitamin A in the control of xerophthalmia. That review suggested that while the suggested dose level appeared adequate to prevent xerophthalmia, it did not appear adequate to sustain blood and tissue levels over 6 months. A more recent report suggests that the utilization of vitamin A from large doses may be conditioned by preexisting vitamin A status. It is suggested that there is need for continuing review of the norms for periodic high potency vitamin A dosing if that approach to intervention is chosen. Such review might focus upon the dose x frequency combination required to sustain blood levels (and presumably tissue stores) without necessarily having to document a mortality effect. We again reiterate our main conclusions:

In populations like those studied (with evidence of poverty, general social and biological deprivation marked by stunting, and with evidence of existing vitamin A deficiency) improvement in vitamin A status can be expected to have a beneficial effect on mortality.

*The effect is **not** dependent upon periodic high potency dosing. Rather, it can be expected with any effective means of improving vitamin A status in the population.*

1. Introduction, Statement of Purpose and Organization of the Report

Beginning in the 1950's periodic dosing with high levels of vitamin A was tested as a method of controlling xerophthalmia and blindness in children, particularly in India and Indonesia. Much experience was gained through those trials and operational programs (West and Sommer, 1987). At the same time descriptive epidemiologic studies documented the association between xerophthalmia and both morbidity and mortality. To test the causality of this association, Sommer and associates initiated a randomized (unblinded) field trial of the effect of vitamin A supplementation on young child mortality in Aceh province, Indonesia. In 1986, the investigators reported a 34% reduction in mortality in vitamin A supplemented preschool children (12–71 months at entry) in comparison to the control group. For the total study (all ages) the reduction was about 26% (Sommer et al., 1986). These findings prompted the United Nations Subcommittee on Nutrition to issue a statement citing the study and noting that young child mortality reduction *might* be an additional reason for

increasing efforts to control vitamin A deficiency.

In the 7 years that have followed this initial report, nine more field trials of vitamin A supplementation and mortality were initiated. Most involved high potency periodic dosing but one used weekly administration of a low−dose supplement and another was based on food fortification. At the time of preparation of the present report, the findings of all ten studies had been published in the open literature or were available to us in the form of draft manuscripts and other reports; one study had been extended and preliminary analyses based of the extension, relating to infants under 6 months, were reported in March, 1993. For two of the projects, we did not have sufficiently detailed data to permit inclusion in our formal analyses.

At the same time that these mortality trials were under way, much interest had been directed to morbidity as an outcome. Some of the mortality trials included morbidity measures. In general, the morbidity information gathered in those trials has been restricted to prevalence data. A number of smaller (in size) and more intensive (in data collection) morbidity trials also were initiated. We have been able to examine the results of twenty−three of these trials. We understand that by the end of 1993, the results of several more morbidity studies will have been reported.

When the present study was commissioned, although the mortality and morbidity trials were incomplete, there was already a sufficient volume of information to give rise to a number of serious questions about the effectiveness of vitamin A supplementation. The estimates of the reduction in mortality associated with vitamin A supplementation associated with those trials have ranged from a mortality reduction of over 50% (TAMIL NADU and BOMBAY) to no significant effect in three other trials (HYDERABAD, SUDAN, and unpublished results from HAITI). Understandably, the apparent divergence in results among the completed trials had led to both confusion and concern among potential users of the results. Most of the morbidity data examinations reported in the literature had failed to detect an effect of vitamin A supplementation [on incidence, duration and prevalence of illness] although a few had described beneficial effects (and subsequently−released preliminary analyses of at least one trial suggested detrimental effects of vitamin A supplementation). Recently a large morbidity trial (GHANA VAST) reported a beneficial effect on severe illness while at the same time seeing little or no effect on incidence or duration of general illness. This study gave an important clue as to the process by which vitamin A exerts its effect and provided also an important link between the morbidity and mortality trials.

Also emerging were suggestions that vitamin A administration may act differentially depending upon the nature of the illness; only a few of the mortality studies have reported results by attributed cause of death. The morbidity trials usually, but not always, present information classified by symptoms.

In 1992, the United Nations ACC−Subcommittee on Nutrition, acting on behalf of the interested UN agencies, as well as reflecting the interest of attending bilateral donor agencies, urged that there be an independent, objective, review of the experience to date. A similar recommendation was voiced by the International Vitamin A Consultative Group (IVACG) that year.

Against this background, the present study was commissioned by the Canadian International Development Agency (CIDA). The specific terms of reference were:

- to review and assess the available experience with regard to the effect of vitamin A supplementation on young child morbidity and mortality.

- to advise CIDA on the apparent effectiveness of vitamin A supplementation in young children in developing countries.

- to estimate, to the extent possible, the range of effects for mortality and morbidity outcomes expected under various nutritional and ecological circumstances and for various subgroups of the population.

Specifically, the mandate did not include the analysis of policy nor did it call for the development of proposed policy. Rather, the intent was to gather background information that CIDA and others might use in formulating policy which would then provide guidance in planning their own future programs.

When the present study was initiated, there were no other reported meta−analyses. Within a few months, an independent meta−analysis of the mortality trials was completed by the Johns Hopkins group and was reported at a vitamin A meeting held in Bellagio in 1992 (Tonascia, reported by Sommer, 1992; recently published in modified form, Tonascia, 1993). That analysis was based on the six then−published mortality

trials in S. E. Asia and reported an overall 30% reduction in mortality. After initial release of the present report, two more meta−analyses were published, and a third analysis directed specifically to the effects of vitamin A on lower respiratory disease, is due for release at any time. All of these addressed mortality outcomes and all drew on the same sets of field trials. Nevertheless they differed in their specific selections of trials/data to be included and in their analytical methodology. In spite of these differences, they reached similar general conclusions about the effectiveness of vitamin A. The series of meta analyses are compared and discussed later in this report.

The present report was first issued, and widely distributed, as a report to the Canadian International Development Agency (CIDA), in November−December, 1992. There was minor revision, again with wide distribution in January, 1993. The present revision was deferred so that results presented at the International Vitamin A Consultative Group (IVACG) meeting in Tanzania in March 1993 could be incorporated along with additional information provided by original investigators.

The report is organized in six chapters with two annexes. First we offer a very brief epidemiological overview of vitamin A deficiency. The primary purpose here is to describe the potential magnitude and general location of affected populations as well as the inferences drawn from past epidemiologic studies of associations between xerophthalmia and morbidity and mortality. The report then reviews the current state of knowledge concerning the function(s) of vitamin A *insofar as these might relate to susceptibility to infectious disease and hence to morbidity and mortality.* The next section of the report addresses experience to date with morbidity as the outcome. The following section undertakes an examination of studies that assessed the mortality outcome and the final section attempts a synthesis of this information and development of conclusions. The theoretical basis of our strategy of analysis of mortality data, all computer programs used, and the input data sets are presented in the Technical Annex. Upon completion of the draft of the final report, it was sent to a panel of reviewers who had expertise in relevant aspects of the work. In a Review Annex to this report we include a synopsis of each reviewer's remarks, excluding suggestions made that were incorporated into the final revision of the report. We express deep gratitude to those individuals who took the time to critically review this report.

In preparation of the report we have received extensive cooperation from a large number of the principal investigators of original studies, responding to our requests for specific information about their study design and results. A preliminary report on the analysis of mortality experience was distributed to investigators for comment and criticism in the spring of 1992[1].

> [1] Copies of the draft of the final report were sent to original investigators of the studies cited together with request that they notify us of any factual errors or interpretational errors in relation to their study as well as inviting general comment on the report. Prior to revision of this report, only the GHANA VAST morbidity trial had pointed out specific corrections to be made (these were done). A participant in the Tamil Nadu trial queried one of the number sets we had used and a notation has been added. A representative of the Hyderabad project offered important insight into that study and appropriate comment has been added. Other minor corrections were reported and have been corrected. We have been advised by a principle investigator in the London School of Hygiene meta analysis of Lower respiratory infections, that there are some errors in the reported age−specific mortalities that we used (that project had been in direct contact with original investigators and extracted new data tabulations from the individual projects). We did not have access to the new data and can only emphasize the cautionary statement previously included in our report.

The contract for this work was undertaken between CIDA and the University of Toronto (Program in International Nutrition, Department of Nutritional Sciences). Dr. George Beaton, University of Toronto, and Dr. Reynaldo Martorell, Cornell University, served as Co−Chairmen of the Technical Advisory Group (TAG) the members of which, in the final analysis, constitute the real authors of this report.

2. Epidemiology of Vitamin A Deficiency

Historical Background

The discovery of vitamin A is generally attributed to McCollum, although independently in 1913 both Osborne and Mendel (1913) and McCollum and Davis (1913) isolated a fat soluble growth factor which subsequently proved to be vitamin A. In 1917 McCollum and Simmonds reported that a deficiency of vitamin A caused rats to develop eye lesions known as xerophthalmia. The disease had been described in Japanese infants in 1904 and an outbreak among children in Denmark occurred in 1917. In each of the human occurrences, the disease had been attributed to a scarcity of food fats. The relationship of this fat soluble vitamin A to the plant pigment carotene was first demonstrated by Rosenheim and Drummond (1920) but it was Moore who established the chemical relationship between vitamin A and ?–carotene (Moore, 1957). In the early work with vitamin A, the only assays available were biological response tests and the unit of measure was defined as the International Unit (IU). In recent times the IU has been replaced by weights of the active components. The new expression *retinol equivalent* (RE) is defined as the amount of the substance having biological activity equivalent to that of 1 µg retinol. Considering estimated efficiencies of absorption and conversion, 6 µg of ß–carotene is taken as having biological activity equal to 1 RE. The true biological utilization of dietary sources of vitamin A may be conditioned by the level of fat in the diet, with very low fat diets potentially impairing the absorption and utilization of carotenoids or retinol or both. Conversely, conversion of carotenoids may be somewhat more efficient when intakes are very low (FAO/WHO, 1967, 1988). Other carotenoids have vitamin A activity but with lower potency than ß–carotene. Some derivatives of retinol (e.g. retinal and retinoic acid) also have at least some of the biological properties of retinol and may be on the pathway of biological utilization of vitamin A (see Chapter 3).

For infants and young children, current estimates of dietary vitamin A requirements, expressed as RE are presented in Table 2.1. For purpose of comparison these are also described in International Units (IU) under the assumptions that all is supplied as retinol or retinyl ester or all is supplied as ß–carotene.

Vitamin A can be stored in considerable quantity in the liver although excessive levels of intake and accumulation give rise to manifestations of toxicity. It is generally felt that the liver storage of the vitamin is extremely important in understanding the epidemiology of deficiency. If stores are at the levels commonly seen in industrialized countries, it may require several months of vitamin A deprivation before evidence of deficiency is detected. In developing country situations faced with major seasonal changes in level of vitamin A intake (largely as carotenoids rather than the preformed vitamin, retinol) liver storage accumulated in the “better” season may be very important in avoiding deficiency in the “bad” season. Because of these phenomena (major cycles in intake with season or other variables, the ability to increase and decrease stores in response to fluctuations in intake, and uncertainty about the conversion of carotenoids) it has been very difficult to examine the relationship between estimated vitamin A intake and evidence of clinical or biochemical deficiency in populations.

Table 2.1 Estimated Dietary Vitamin A Requirements[a]

Age	***Retinol Equiv. (µg RE)***	***International***	***Units (IU)***
		As Retinol[b]	*As Carotene*[b]
Basal Requirements[a]			
0–1	180	600	1,800
1–6	200	650	2,000
Normative Requirements[a]			
0–1	350	1,200	3,500
1–6	400	1,300	4,000

[a]FAO/WHO (1988); *basal requirement* is an estimate of amount needed to prevent signs of impaired *function. Normative requirement* is judged sufficient to maintain desirable levels of tissue stores. All estimates include allowance for individual variability of requirement.

[b]These estimates assume that all dietary vitamin A is in the form of retinol (1 µg RE = 3.3 IU) or ß–carotene (1 µg RE = 10 IU). For other carotenoids the conversion is lower (1 µg RE = 20 IU).

Note: The IU has been largely abandoned in favour of either RE or molar units because of confusion in interpretation of the IU and in keeping with SI rules.

By FAO food disappearance data (cited in FAO/WHO, 1988), the supply of food vitamin A is generally high in industrialized countries, with most derived from the highly available retinyl esters. Conversely, for most of the developing countries, the total supplies are appreciably lower and the major source is carotenoids, the utilization of which may be affected by dietary and other factors. The overall world supply (estimated to be about 800 µg RE per caput) would appear to be to meet at least basal requirements if distribution were proportional to needs. However, the per caput availability estimates for Europe and Oceania were about 1200 and 1100 µg RE. while those for Africa, South America, and Asia were approximately 900,600, and 650 respectively. This suggests major differences in the overall supplies by region. Even greater variation is seen when national estimates are examined. Thus, for example, within South America, national estimates ranged from 130 to 1800 µg RE per caput. In the inland countries of Africa, major seasonal variations were reported. In one rural area that had been examined, average family consumption increased from 109 µg RE per person in the dry season to 420 µg RE in the rainy season (cited in FAO/WHO, 1988). Even household level data mask problems of intra−household distribution.

National per caput data can be very misleading since they do not address problems of distribution. They do not offer a reliable predictor of the presence or absence of vitamin A deficiency except when apparent per caput intakes are very high or very low. As discussed below, vitamin A deficiency in its severe form is seen more frequently in very young children and appears to depend heavily on the specific patterns of food use and child feeding practices in the local situation.

The epidemiology of vitamin A deficiency has focused primarily upon the epidemiology of xerophthalmia, the clinical manifestation of acute deficiency without major attention to the distribution of intakes.

Much of the credit for developing current awareness of vitamin A deficiency and xerophthalmia in human populations must go to two individuals, H.A.P.C. Oomen and D.S. McLaren, who accumulated information and promoted awareness for many years. Working in FAO and then WHO, V.N. Patwardhan was strongly interested in vitamin A and xerophthalmia and did much to foster the interest of those agencies. For many years, as interest grew and population studies began to be reported, E. M. DeMaeyer, of WHO, took on the extremely important role of maintaining the documentation on the known prevalence of vitamin A deficiency and continuing a process started by Oomen, McLaren and Escapini (1964). It is this data base that has permitted the beginning of mapping of the geographic distribution. One such map, admittedly incomplete since little was known about many countries, is presented in Figure 2.1 (based on DeMayer, 1986; taken from ACC/SCN, 1987). By 1984 (DeMayer, 1984), it was estimated that at least 34 countries had serious vitamin A deficiency problems; some had initiated action to control the problem. Table 2.2 presents the criteria adopted by WHO in defining vitamin A deficiency as a public health problem (WHO, 1982). In the original presentation of the identification of the distribution of vitamin A problems, it was emphasized that this represented identification of countries with known or strongly suspected high prevalence of clinical vitamin A deficiency (category A in Figure 2.1). If, as some suspect, vitamin A depletion without clinical signs is also associated with functional deficits, the problem of vitamin A deficiency is much more widespread than suggested in Figure 2.1.

As interest grew, it was clear that there was need for a standardization of nomenclature and descriptions of manifestations (stages) of xerophthalmia. Such a classification scheme (Table 2.2) was given international recognition by a joint WHO/US AID committee in 1976. The scheme has undergone some modification since then but has served its original purpose very well. The International Vitamin A Consultative Group (IVACG) has played an active role in attempting to foster methods and criteria for the assessment of vitamin A status in the absence of clinical lesions which are, after all, a very late stage of deficiency (Arroyave et al., 1982). Until we have a broader base of data, it is difficult to associate the level of indices of depletion with functional significance (including the effect on risk for morbidity and mortality). There is need to continue the search for better indictors of vitamin A status as well as the need to better understand what existing indicators really mark (Sommer, 1993).

Table 2.2 Prevalence Criteria for Determining the Public Health Significance of Xerophthalmia and Vitamin A Deficiency[a]

Criteria	***Prevalence in Population at Risk*****(%)**

Night blindness (XN)[b]	>1.0
Bitot's spot (X1B)	>0.5
Corneal xerosis/corneal ulceration/keratomalacia (X2/X3A/X3B)	>0.01
Corneal Scar (XS)	>0.05
Plasma Vitamin A level <100 µg/L	>5.0

[a]Taken form DeMaeyer (1984) but based on WHO (1982). Prevalence levels (in one or more signs) above those shown are taken as indication that a public health problem exists.

[b]International classification of xerophthalmia.

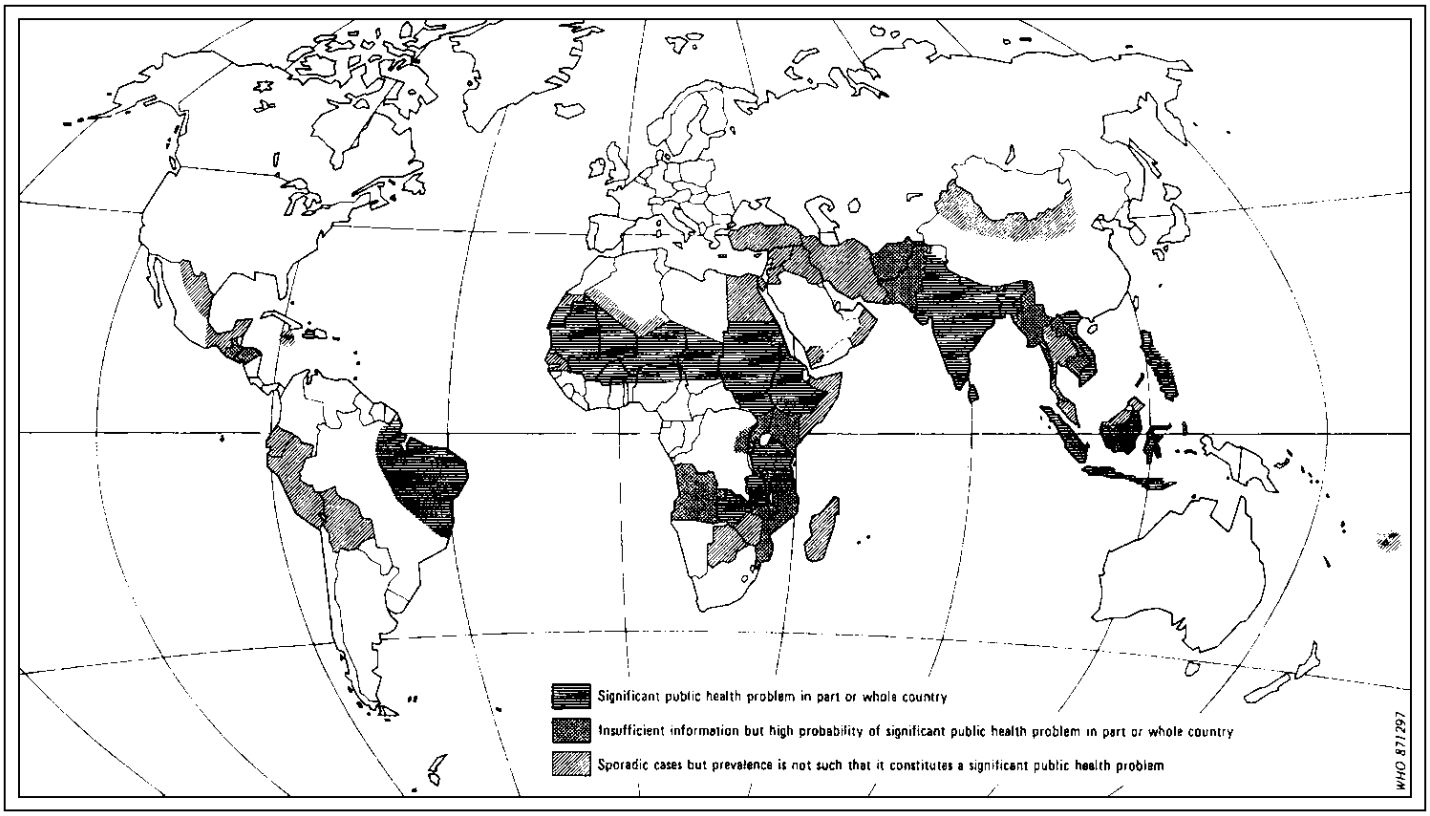

Figure 2.1 Geographical Distribution of Xerophthalmia, 1987

Source: **WHO (1987)**

Epidemiology: Localization of Deficiency and Identification of Groups at Risk

Quoting Oomen (1976), "Clinical hypovitaminosis A is essentially a condition, and perhaps even a parameter, of a poor socioeconomic environment. Retinol may be called 'the prosperity vitamin', particularly because of its close association with the consumption of cow's milk.... [although]... a vitaminosis A was present in Europe in the pre–industrial era." There is much evidence that as education levels and income increase and as diets become more diversified, vitamin A deficiency manifestations dwindle. This appears to have been the case in Hong Kong (Oomen, 1976) as well as in the earlier history of Europe. It has always been a matter of frustration to those concerned with vitamin A deficiency that in many settings there are abundant sources of vitamin A indigenous to the area while in villages 5% or more of young children may show clinical manifestations of deficiency. Obviously, child feeding practices as well as income are important factors to be considered.

As noted in the quote from Oomen, vitamin A deficiency is associated with poverty. As such it is also associated with anthropometric indices of undernutrition. However there is also evidence that the increased incidence of xerophthalmia among children with severe undernutrition as seen in clinical Protein Energy

Malnutrition (PEM) is more than an association of inadequate intakes. There is both experimental and clinical evidence to suggest that in *severe* PEM, conversion of carotene to retinol may be impaired and that the capacity to mobilize vitamin A from the liver to tissues where it is utilized is impaired (Arroyave et al., 1959, 1961). It was also noted, very early, that there was an association between infectious disease and xerophthalmia (Oomen, 1976) although it was not clear whether repeated or severe infections interfered with vitamin A deficiency or vitamin A deficiency increased the risk of morbidity (See update of experimental evidence in Chapter 3 and review of human intervention trials in Chapter 4). An association between xerophthalmia and morbidity (and mortality) was documented by Sommer and his colleagues (1983, 1984) in studies in Indonesia. The nature of the associations seen was consistent with the hypothesis that vitamin A deficiency was a risk (*implying causal*) factor for infections and mortality. With reference to mortality, the inference taken from observational epidemiology was apparently confirmed by the result of a direct intervention trial (Sommer et al., 1986), now confirmed by a number of other studies (see Chapter 5) although there remain inconsistencies and uncertainties in relation to the effect of vitamin A supplementation on morbidity (Feachem, 1987; see also Chapter 4).

Oomen (1967) described strong seasonal effects in the prevalence of xerophthalmia in several countries; in some tropical countries two seasonal peaks are reported roughly associated in time with peaks in diarrhoeal disease (summer peak) and respiratory disease (winter peak).

Age and Sex as Predictors of Risk of Xerophthalmia

Xerophthalmia is predominantly a problem of young children, typically under 5 years. In most countries where deficiency is seen, clinical manifestations are uncommon in the first year of life. This does not mean that 'deficiency' may not develop or that other functions of vitamin A are unaffected in the first year. The corneal lesions are thought to be a late stage of deficiency. Although liver vitamin A reserves are quite modest at birth even in well nourished industrialized countries, it is generally accepted that vitamin A levels build rapidly if dietary vitamin A is provided. This has led to considerable interest in the vitamin A secretion in breast milk and its protective effect against xerophthalmia in infants. Thus, an FAO/WHO (1967) committee considering vitamin A requirements noted an apparent relationship between the average concentration of vitamin A in breast milk and the typical age at which xerophthalmia was seen in the population. They used this observation in establishing target levels of vitamin A secretion and hence in estimating maternal requirements. Recently Stoltzfus et al. (1992,1993) reported that a single 300,000 IU vitamin A (equivalent of 90 mg retinol) supplement administered to mothers within a few weeks of birth was effective in raising milk vitamin A levels and in maintaining an improved level of vitamin A status in the infant for at least six months. Thus, the evidence continues to grow that maternal vitamin A status and hence breast milk vitamin A secretion is a risk factor to be considered in the epidemiology of vitamin A deficiency. Although active corneal lesions are seldom seen in adults, there are numerous reports in the early literature to suggest that the prevalence of functional night blindness (another manifestation of vitamin A deficiency, usually seen with less severe depletion than required to produce xerophthalmia) is increased in pregnant women.

In early surveys (Oomen, 1967) males were more likely to present with blindness attributable to vitamin A deficiency than were females. This is in contrast to the results of the vitamin A supplementation trials in which no major gender difference in relative effectiveness was detected (see Chapter 5).

Strategies of Intervention

All would likely agree that the goal for avoidance of vitamin A deficiency is improvement of dietary intakes through modification of eating practices and/or modification of the supply of foods available for consumption. This may require also that problems of poverty affecting food usage and problems of infectious disease affecting vitamin A needs, be addressed. Food fortification has been undertaken as an approach to modification of dietary intake without necessarily involving change in eating practices. More expedient approaches of direct intervention through supplementation have been undertaken in areas where clinical vitamin A deficiency is a known public health problem. In the prophylactic mode, the supplementation programs have relied on the fact that vitamin A can be stored and hence that periodic high potency doses can serve to prevent clinical manifestations over moderate periods of time (see previous reference to supplementation of mothers to improve vitamin A levels in breast milk as an approach to improvement of the vitamin A status of breast fed infants).

At the request of the ACC/SCN, West and Sommer prepared a comprehensive review of vitamin A supplementation procedures. While this review focused upon the oral dosing route, it included also experience with fortification approaches. West and Sommer noted that dosing with 200,000 IU of retinyl ester (210 µmol, equivalent to 60 mg retinol) every six months (after the age of one year) was the most common approach used in operational programs aimed at the control of xerophthalmia. They noted that this seemed to be effective in the avoidance of recurrence of xerophthalmia. On theoretical grounds (disappearance time calculated from estimated turnover rates) and observations on maintenance of serum retinol levels, this regimen may not be adequate to maintain tissue stores at commonly accepted minimum levels. The distinction between preventing xerophthalmia and maintaining tissue levels becomes critically important if one believes that important functions of vitamin A may be lost or seriously compromised at tissue levels above those associated with xerophthalmia. The theoretical calculations and observations did not take into account the intake of dietary vitamin A which may be an important variable of maximal effective interval (West and Sommer, 1987). West and Sommer also offered an important cautionary comment:

> *... the protective period [of a 200,000 IU dose] is likely to vary with the frequency and severity of precipitating and contributory factors such as infection and protein–energy malnutrition. Efficacy establishes the upper limit of effectiveness when large–dose vitamin A delivery is implemented through a routine program* (*West and Sommer, 1987, page 19*).

A recent report (Humphrey et al., 1993) has suggested that response to a large dose of vitamin A may depend in part on the preexisting vitamin A status of the subject. That is, in a trial of administration of a small 'priming dose' prior to a large therapeutic dose of the type commonly used in the control of vitamin A deficiency after onset of infection, Humphrey et al. showed that the net uptake and duration of maintenance of serum levels was significantly affected by the priming dose – and that this was not explained simply by the additional vitamin A provided by the priming dose. An inference *may* be that if the dose interval schedule used in operational programmes is such that near–total depletion occurs before the next dosing, utilization of that dose may be compromised – in turn this suggests that there *might* be advantage associated with more frequent dosing at somewhat lower levels in ongoing prophylactic programmes just as there appears to be advantage in a priming dose approach in the presence of illnesses such as measles. Interestingly they also showed that xerophthalmic children reverted to the vitamin a depleted state (low serum levels) more rapidly than did non–xerophthalmic children.

Hypervitaminosis A

There is clear evidence that vitamin A (as retinol or retinyl esters rather than as the ß–carotene precursor) can produce manifestations of toxicity in acute or chronic dosing with very high levels. Since this is an obvious concern in high potency dosing approaches to supplementation, or in long term fortification or oral supplementation approaches, the IVACG commissioned a review of the available literature (Bauernfeind, 1980). That review resulted in the recommendations show in Table 2.3. The schedules shown in that table refer to daily dosing, not periodic administration (see Table 2.4). The report also addressed the use of the commonly available capsules containing 200,000 IU of retinyl palmitate and 40 µg vitamin E in an oil solution. The final recommendations are summarized in Table 2.4. Relatively little is known about acute toxicity in young infants. Recently West et al. (1992) reported that, in Nepalese infants, there was no risk associated with a 50,000 IU dose (in first month of life) and a minimal risk of transient effects with a 100,000 IU dose given between 1 and 6 months. Arthur et al. (1992b), report only minor transient (in first 24 hours) gastrointestinal disturbances as a side effect of dosing with 200,000 IU in Ghana. The whole question of both risk and benefit of high potency vitamin A dosing of young infants has recently been reviewed by a WHO committee (Underwood, personal communication, 1992). A formal report addressing risks benefits and suggested dosing schedules for very young infants is expected soon.

Table 2.3 IVACG Proposals on Daily Vitamin A Maxima for Oral Prophylactic and Therapeutic Use[a]

Age Group	*Prophylaxis Daily Maximum*	*Therapeutic Daily Maximum*
Infant, 1–3 m	3,000 IU	6,000 IU
Child, 1–3 y	6,000 IU	12,000 IU
Child, 4–6 y	10,000 IU	25,000 IU

Child, 7–10 y	15,000 IU	50,000 IU
Adolescents, 11–17 y	20,000 IU	100,000 IU
Women, 18+ y	25,000 IU	125,000 IU
Men, 18–65+	30,000 IU	150,000 IU

[a]Levels were set as multiples of the then U.S. Recommended Daily Allowances.
[b]Not applicable to pregnant women.

Table 2.4 IVACG Assessment of Safe Use of Vitamin A Capsules (200,000 IU Vitamin A + 40 IU Vitamin E in Oil)

Age Group	***Prophylaxis Number and Interval***	***Therapeutic Number and Interval***
Infants under 1 year	Half at 3–6 month intervals	Half on diagnosis Half on second day Half on discharge
Others (except pregnant and lactating women)	1 at 3–6 month intervals	1 on diagnosis 1 on second day 1 on discharge
Lactating women	After delivery, nursing mothers may be given one capsule as an aid to maintaining milk levels	
Pregnant women	Supplements should not exceed 10,000 IU per day[a]	

[a] Based on concern about potential teratogenic effects; no strong human evidence available.

The IVACG report commented that while high doses of ß–carotene or other carotenoids produced blood and skin pigmentation (hypercarotinaemia), they do not produce vitamin A toxicity. The report did not address upper limits to ß–carotene intake/dosing.

Because of known teratogenicity in animal models, there is general agreement that high potency dosing should *not* be undertaken in pregnant women. In practice this has been interpreted to imply that the only safe period for such dosing is in the very short window of time after birth and before there is risk of conception of a new pregnancy. There is no indication that administration of a single high potency dose during that window of time is detrimental to the mother or infant. Conversely there is evidence that it is potentially beneficial to the breast fed infant.

Summary: Points Arising from the Epidemiology of Vitamin A

Available information about dietary vitamin A supplies suggests that there is a potential for problems of inadequacy in many of the developing countries. Information on intake distributions suggests that whether or not problems actually develop is conditioned very heavily by local patterns of infant and young child feeding as well as factors apparently affecting requirements.

From the epidemiologic data, it appears that the incidence of clinical vitamin A deficiency is likely to be higher in undernourished/malnourished children and particularly those who develop acute infectious disease (particularly measles) or acute PEM. Such considerations formed the basis of WHO guidelines on direct intervention on indication. However in the prophylactic mode, there is not a very distinct pattern by which risk groups can be identified other than that they tend to constitute the poorer segment of poor populations and to show the signs of multiple social and biological deprivation commonly seen in those segments of developing country populations. Dietary intakes (low vitamin A, probably also very low fat intake) are, of course, another

indicator of likely risk but the major marker for populations has been the demonstrated presence of xerophthalmia or low serum vitamin A levels suggestive of a public health problem. The problem is best documented in children under 5 years but it is now clear that pregnant and lactating women must be considered since the levels of vitamin A in breast milk appear to have very important influence on the status of the infant.

From a review of programs implemented for the control of xerophthalmia, recommendations have been developed concerning apparently safe and effective combinations of doses and intervals. There is, however, some ***uncertainty*** *about the adequacy of these regimens to maintain tissue levels of vitamin A and hence it is at least possible that although xerophthalmia can be controlled, other functional consequences of vitamin A depletion may not be as effectively controlled by the recommended regimens.*

The report by Humphrey et al. (1993) that preexisting vitamin A status may affect the efficiency of utilization of a high dose of vitamin A raises further question about the desirable interval between dosing as well as the level to be administered.

The epidemiologic data have not provided very clear markers for the selection of populations in which vitamin A supplementation is more likely to be effective. Existing control programs have used the presence of xerophthalmia in a population group as the marker of probable responsiveness (but note that existing vitamin A control programmes and research studies have been modelled on previous programmes designed for the control of xerophthalmia and night blindness).

3. Vitamin A and Biological Functions: Consideration of Possible Biological Bases of Morbidity and Mortality Effects

Introduction

Vitamin A is essential for a variety of biologic processes, many of which are related to growth, cellular differentiation and interactions of cells with each other or with the extracelluar matrix. Vitamin A deficiency, even in its relatively early stages, results in impairments in linear growth, cartilage and bone development, and epithelial cell differentiation and function (Roberts and Sporn, 1984; DeLuca, 1991), and in reduced vision in dim light (Underwood, 1984). If experimental vitamin A deficiency is allowed to persist, animals either succumb or, if they survive, progressively develop severe xerophthalmia leading to blindness.

The importance of vitamin A in maintaining the normal morphology and function of epithelial cells in many organs is now well recognized (Roberts and Sporn, 1984; DeLuca, 1991). This relationship suggests the hypothesis that breakdown of epithelial barriers may underlie the greater susceptibility to disease and greater mortality rate in vitamin A–deficient animals. Mortality may also plausibly be related to changes in the immune system and, hence, to a breakdown of the defense mechanisms which normally counteract environmental pathogens.

In this chapter, we will consider the effects of vitamin A deficiency and what is known regarding alterations which might be related to increased child morbidity or mortality. We will attempt to develop hypotheses or expectations regarding how vitamin A deficiency might affect resistance to infection or the response to infectious disease.

Most of the experimental evidence discussed below indicates that vitamin A deficiency causes pathological changes in epithelial tissues and reduces the resistance to or response to infection. Although it would be satisfying to conclude that the picture is entirely consistent, there are exceptions and inconsistencies even among well–controlled studies. For example, the response of epithelia to vitamin A deficiency differs with the organ and type of epithelium. Similarly, the immune response to infection is well known to be governed differently depending on the precise characteristics of the pathogen.

Retinol Accumulation and Transport

During gestation, the transfer of retinol from mother to young is limited even in well–nourished mothers and, as a consequence, neonates begin life with low reserves of retinol (Moore, 1971). The suckling neonates of well–nourished mothers accumulate retinol (as retinyl ester) in liver, the major storage organ for vitamin A, and in other tissues during the post–natal period (Davila et al., 1985; Smith, 1990). The quantity of retinol accumulated during the suckling period reflects maternal dietary vitamin A intake (Davila et al., 1985). Even rat dams with marginal vitamin A status transfer some retinol to their pups during gestation and lactation (Ross and Gardner, 1993). These observations are likely to explain why, in humans, clinical evidence of vitamin A deficiency is not often seen in breast–fed infants but generally ensues in the post–weaning period if the diet is nearly devoid of pro–vitamin A or retinol.

Liver retinyl ester concentration can vary widely and still be considered to be in the normal range. In the rat, concentrations exceeding 5–10 µ*g* retinol/g liver support a normal output of retinol on its transport protein, retinol–binding protein (RBP) (Goodman, 1984; Harrison et al., 1987). If liver retinol falls below this level, RBP synthesis continues but secretion is impaired unless additional retinol is provided (Smith et al., 1973). Thus it appears that these last retinol “reserves” are not readily mobilized for secretion into plasma. The retinol molecule is very well conserved: it is eliminated from the body only after several passages between liver and peripheral tissues (Green et al., 1985).

Signs and Symptoms of Vitamin A Deficiency

A number of signs and symptoms of vitamin A deficiency have been reported including inanition, change in cerebral spinal fluid pressure (CSF), growth cessation and ocular changes involving both the corneal epithelium and the retina.

Retinol must be converted in the retina to retinaldehyde to function in vision. In most other tissues, the active form of vitamin A is now recognized to be retinoic acid, a metabolite of retinol formed by intracellular oxidation. Retinoic acid acts in a hormone–like manner to control the expression of numerous genes which, in turn, are involved in maintaining cell morphology and function (DeLuca, 1991). Except in experimental conditions, retinaldehyde and retinoic acid do not contribute significantly to the dietary sources of vitamin A.

Work with experimental animals has demonstrated that chronic vitamin A deficiency results in a loss of taste, smell, and appetite leading to inanition (Wolbach and Howe, 1925; Underwood, 1984). Therefore, the later stages of experimental vitamin A deficiency are usually compounded by general malnutrition. Certain experimental paradigms, such as pair–feeding and cycling animals on and off of retinoic acid, have been used to attempt to isolate vitamin A deficiency from general malnutrition (Nauss, 1986; Nauss et al., 1990).

In a number of species of experimental animals made chronically vitamin A deficient, CSF pressure has been reported to be elevated (Underwood, 1984). However, in humans, this symptom (i.e. bulging of the fontanelles in young children or headache) has more often been associated with acute or chronic *hyper*vitaminosis A (Underwood, 1984).

A decreased rate of growth is a reliable marker of vitamin A deficiency in experimental animals where other variables can be controlled. Rats reach a weight plateau after all liver reserves are exhausted and plasma retinol concentration has fallen to 5–10 µg/dl. Within a few days of providing either retinol or retinoic acid to previously retinol–deficient animals, weight gain and growth are restored. Impaired growth may be related both to inanition and to metabolic changes such as disturbances in water balance and protein utilization. The weight plateau is probably not related to infection *per se* because germ–free or antibiotic–treated animals survived longer than conventionally housed rats while still exhibiting reduced growth (Bieri et al., 1968; Raica et al., 1970; Rogers et al., 1970; Anzano et al., 1979; Anzano et al., 1979; Underwood, 1984). Thus, vitamin A is required for sustained growth even in the absence of infection.

The role of vitamin A in the eye is two–fold: the retinaldehyde molecule functions as the chromophore for the visual pigment, rhodopsin. Vitamin A, probably in the form of retinoic acid, is also essential for the development of the neural tissue of the eye and for maintaining the ocular epithelial cells. Thus, night–blindness is caused by inadequate vitamin A to regenerate rhodopsin, involved in vision in dim light, in the photoreceptor cells after bleaching due to bright light. In contrast, xerophthalmia involving dryness of the cornea and progressive corneal deterioration is almost certainly due to a lack of retinol for conversion to retinoic acid necessary for normal differentiation of the corneal epithelium.

Changes in Epithelial Cells and Tissues

Many studies have now demonstrated that vitamin A (retinoic acid) is an important determinant of cell growth and differentiation. The classic studies of Wolbach and Howe (1925) established the necessity for vitamin A to maintain normal differentiation of tissues throughout the body. The specific pathology they described in the vitamin A–deficient rat was "widespread keratinization." Outward changes included encrustation around the eyes, change in hair lustre, and emaciation. These authors pointed out that many tissues besides the eye become involved during vitamin A deficiency: among the tissues noted to atrophy or to change histologically were the respiratory tract (nose, sinuses, larynx, trachea and bronchi); the glands of the alimentary tract; the genitourinary tract including bladder, ureter and pelvis, uterus and oviducts, and male reproductive organs; the cornea, conjunctiva, ducts and glands of the eye; the ductless glands including the thymus, spleen and lymph nodes. These changes occurred even in the absence of infection. As noted by these investigators, "infection and suppuration are very common, but not invariable and have nothing to do in initiating the epithelial change" (Wolbach and Howe, 1925). Instead, they emphasized tissue keratinization as the major, consistent pathological finding, independent of infection.

Subsequent studies at the light and electron microscope levels (Wong and Buck, 1971) examined the trachea in detail and revealed microscopic changes in epithelial structure due to vitamin A deficiency. In normal rats, the trachea is lined by a pseudostratified, organized layer of cells consisting of basal, ciliated, goblet (mucus–secreting), and brush–border types. In vitamin A deficiency, the trachea and bronchopulmonary airways develop a "squamous metaplasia" which is characterized by a flattened, less organized multi–layer of cells. The ciliated cells are lost during desquamation and the goblet cells disappear; concomitantly, there is an altered pattern of cytokeratin proteins. Wong and Buck (1971) highlighted the rapid change in tracheal morphology that occurred even in normal animals that were fed a vitamin A–deficient diet for a week or more, and the squamous metaplasia that resulted from chronic vitamin A deficiency.

Based on these studies, an expected effect of vitamin A deficiency in children, even with "mild" vitamin A deficiency, would be a change in the airways, e.g., decreased mucus secretion and loss of cilia. Given the importance of these processes in trapping and clearing airborne pathogens and irritants, an increase in the number of pathogens reaching further into the lungs would seem to be a reasonable expectation. Changes in the genitourinary epithelium would also be anticipated. Although some change in the intestinal goblet cells has been reported (DeLuca et al, 1969), the impression from morphological studies is that change in the intestine is far less dramatic than that seen in the trachea (Wolbach and Howe, 1925). Thus, based on experimental studies of a pure vitamin A deficiency, one may predict greater changes in the respiratory epithelia than in the intestinal lining.

Decreased Resistance to Infection

A WHO monograph by Scrimshaw et al. (1968) pointed out that several nutrient deficiencies, including that of vitamin A, may be synergistic with infection, or may have no effect or even appear to antagonize the infection. However, based on over 50 reports of experimental or human studies concerning vitamin A deficiency, Scrimshaw et al. (1968) summarized that "no nutritional deficiency is more consistently synergistic with infectious disease than that of vitamin A." It appears that vitamin A deficiency or marginal vitamin A status is often worsened by infectious disease (of bacterial, viral or parasitic origin) and, reciprocally, that poor vitamin A status is likely to prolong or exacerbate the course of illness.

Shortly after the discovery of vitamin A, Bloch (1924) described an association of vitamin A deficiency with malnutrition. Other investigators studying natural and experimental infections in animals began to correlate vitamin A deficiency with pathology in animals and humans. In 1923, Werkman (see Lassen, 1930) reported that rats fed a diet of natural components, described as vitamin A deficient, were less resistant to infection with typhoid or anthrax bacilli. He also reported no decrease in either the serum agglutination response or the opsonic activity which is now known to reflect the humoral (antibody) response. Thus, this early study supported decreased resistance to infection during vitamin A deficiency but it did not indicate that antibody production was decreased. Other investigators reported that mortality to mouse typhoid was greater in vitamin A–deficient mice than in mice fed an adequate diet (Lassen, 1930). Green and Mellanby (1928, 1930) showed that animals fed diets deficient in vitamin A and carotene often died with histopathologic evidence of infections, largely of the tongue, eyes and bladder. Such spontaneous infections were seen very rarely in animals fed the same diet plus vitamin A.

Lassen (1930) reported decreased resistance to a specific infection in vitamin A–deficient rats; in contrast to control rats which recovered following infection with paratyphoid bacilli, nearly all vitamin A–deficient rats died and, similarly, whereas few bacteriological cultures of normal rat tissues were positive, many of the cultures from vitamin A–deficient rats were positive, including those of the mesenteric lymph glands and submaxillary glands. Lassen (1930) commented that infection in vitamin A–deficient animals did not seem to differ qualitatively from that in normal rats, but rather that infection *persisted* in the vitamin A–deficient state. Since the pathogen itself was the same in both the vitamin A–sufficient and vitamin A–deficient groups, differences in outcome must have been related to host or environmental factors. In humans, such factors could include genetic susceptibility, concurrent or previous disease (infections or otherwise), differences in intestinal microflora, nutritional imbalances, and social factors such as stress due to crowding.

Based on these results, it is expected that vitamin A deficiency may either be associated with a greater rate of infection or that, once infected, vitamin A–deficient animals and humans may not respond effectively to the pathogen. Few experimental studies have addressed the incidence of infection separately from the severity of infection. A few studies have evaluated overall fatality or recovery in vitamin A–sufficient and –deficient groups. Other investigations have focused on specific aspects of infection such as phagocytosis and immune responses to antigens which are thought to be part of the host's normal defense mechanisms.

A number of potential biological mechanisms which normally limit infections could be altered during vitamin A deficiency. These include increased penetration of bacteria, viruses and parasites through altered epithelial barriers, changes in lymphoid cell maturation, abnormal production of the cytokines and lymphokines that regulate the immune response, and altered membrane structures that could affect the cell's receptors for antigens and regulatory molecules. The clearance of pathogens by cytotoxic and phagocytic cells might also be impaired.

Immune Responses

Generally, two basic forms of immunity have been distinguished: humoral immunity and cell–mediated immunity (CMI). In the humoral arm of the immune system, lymphocytes which produce specific antibody against invading pathogens are the main effector cells. The term CMI was originally used to describe localized reactions to pathogens, mediated by lymphocytes and macrophages, and is now more generally used to describe cellular responses in which antibody plays a subordinate role. The effector cells in CMI include cytotoxic T cells, macrophages and natural killer cells which destroy infected or foreign cells through some combination of direct contact, secretion of soluble factors and recruitment of other inflammatory cells such as neutrophils.

Lymphoid Cells and Organs

Vitamin A deficiency has been reported to cause changes in lymphoid organ mass, cell number, histology, and lymphocyte characteristics (reviewed in Nauss, 1986; Ross, 1992). There are, however, a number of inconsistencies. The exact pathological picture seems to depend on the duration of vitamin A deficiency, whether or not inanition also is present, and the species being examined. In experimental animals, a decrease in the weight of the thymus associated with marked atrophy often occurs late in vitamin A deficiency. Thymic atrophy has long been known to be associated with protein–energy malnutrition in children (Suskind, 1984). In contrast, enlargement of regional lymph nodes has also been observed (see Ross, 1992) and is thought to result from accumulation of cell debris and altered cellular composition.

One might anticipate that there would be major changes in the T or B cell lymphocytes in vitamin A–deficient animals. However, a comparison of cells from vitamin A–deficient and normal rats using fluorescent antibody labelling did not reveal significant changes in the distribution of T cell subsets (helper and suppressor/cytotoxic T cells) or in IgM– or IgD–positive B lymphocytes (Nauss et al., 1985; Pasatiempo et al., 1991). Therefore, cell population changes do not appear to offer an explanation for the functional changes which have been observed in the immune response (below). This picture contrasts to that reported for human protein–energy malnutrition in which the fraction of helper ($CD4^+$) T cells was reported to be decreased (Chandra, 1990).

Cell–mediated Immunity

CMI has been assessed in humans and animal studies by the delayed–type hypersensitivity reaction (Faherty and Bendich, 1990). In vitamin A–deficient mice, the delayed–type hypersensitivity reaction was significantly reduced (Smith et al., 1987; Ahmed et al., 1991). However, in a study of Bangladeshi children there was no difference in the delayed–type hypersensitivity response before and after vitamin A supplementation, although vitamin A status was not determined by serum vitamin A levels (Brown et al., 1980). This response in humans may be confounded by protein–energy malnutrition (Nauss et al., 1990) which generally impairs it. The function of cytotoxic T lymphocytes may also be reduced during vitamin A deficiency. When vitamin A–deficient chicks were challenged with Newcastle disease virus, the cytotoxic activity of spleen cells was low (Sijtsma et al., 1990). If the human cytotoxic T lymphocyte response is similarly depressed, these experimental results seem to imply that the recovery from viral infections may be poor in young children with marginal vitamin A status. As noted by Thurnham (1989) and others, humoral immunity develops slowly in young children and their reliance on CMI is greater than that of older children or adults. The proliferation of lymphocytes after stimulation with mitogens has frequently been used to assess CMI. The response to certain mitogens was reduced in vitamin A deficiency while the response to other mitogens was unchanged or even increased, depending on the anatomical site from which lymphocytes were obtained (Nauss et al., 1985; Nauss et al., 1979; Butera and Krakowka, 1986).

Vitamin A deficiency may also affect the functions of natural killer (NK) cells which mediate “natural cytotoxicity,” killing virus–infected cells. These cells also secrete a number of soluble factors [cytokines such as interferon (IFN)–gamma] which have regulatory roles in haematopoiesis and antibody formation. The released interferon can further increase the cytotoxic activity of NK cells and regulate the production of certain classes of immunoglobulin (Finkelman et al., 1990). Vitamin A deficiency has been associated with decreased NK cell cytotoxic activity in rat spleen cell preparations (Bowman et al., 1990; Nauss and Newberne, 1985), but not in cells from the cervical lymph nodes (Nauss and Newberne, 1985). After vitamin A–deficient rats were repleted orally with retinol, NK cell cytolytic activity of spleen returned to normal values. IFN production by spleen cells in vitro was also reduced in vitamin A–deficient rats (Bowman et al., 1990). Improvement of vitamin A status restored the ability of these cells to release IFN activity. It may be relevant that low NK activity was found in the peripheral blood mononuclear cells of young children with acute measles (Griffin et al., 1990). Although a connection to vitamin A status was not established in this work, serum retinol concentrations have been shown to be reduced during acute infection, and vitamin A therapy has been effective in reducing measles–related morbidity and mortality. Despite this low basal activity, the NK cells from children with measles or other infections could be activated by IL–2 in vitro, indicating that their potential for lytic activity was retained.

Antibody Responses

The antibody or humoral immune response, including the production of antibody–secreting plasma cells and memory B and T cells, is the mechanism by which the immune system provides highly specific protection of long duration against many pathogens and molecules recognized as non–self. Impaired antibody production might be expected to reduce the effectiveness of vaccinations. The relationship of vitamin A status to antibody production has been investigated for a number of antigens, some which are relevant to human vaccination programs while others are mainly of experimental interest.

*A generalization resulting from these studies is that the ability to produce antibody is usually not lost; rather, the ability to respond in a **specific** manner to antigen is often reduced.*

Vitamin A deficiency has been shown to reduce the response to certain types of antigens, principally heterologous cells, proteins and polysaccharides. Studies in the vitamin A–deficient rat have consistently shown a reduced primary antibody response (IgM and IgG) to the protein antigen tetanus toxoid (Lavasa et al., 1988; Pasatiempo et al., 1990; Krishnan et al., 1974). Despite this low antibody response, the kinetics of antibody production were normal (Kinoshita et al., 1991) and immunologic memory (demonstrated by the class switch from IgM to IgG) also developed normally during retinol deficiency. Memory cells could be activated after repletion with vitamin A, resulting in a normal secondary or “recall” response in rats repleted with vitamin A before reimmunization (Kinoshita et al., 1991). These data imply that the ability to produce specific antibody and the ability to establish cells which can later respond to antigen are not affected equally by a lack of vitamin A. The decreased levels of anti–tetanus toxoid antibodies observed in these studies were not a reflection of a generally low level of antibody production. Indeed, the concentration of plasma *total* IgG was elevated significantly in vitamin A–depleted rats (Kinoshita et al., 1991) and mice (Gershwin et al., 1984).

It may be noteworthy that circulating immunoglobulins are also elevated in children with protein–energy malnutrition (Suskind, 1984), despite the poor response to some antigens.

Human studies, which are fewer in number and less controlled in design, lead to a mixed assessment of the importance of vitamin A status for the antibody response. Brown et al. (1980) conducted a field study in Bangladesh to determine whether a large dose of vitamin A could be used to enhance the antibody response to tetanus toxoid. Young children matched by age and sex were assigned randomly to receive either a 60 mg dose of water–miscible vitamin A, delivered in at the time of immunization with tetanus toxoid, or tetanus toxoid only. A second dose of tetanus toxoid but no additional vitamin A was administered 4 weeks later. Baseline serum vitamin A levels averaged 14 µg/dl before supplementation but were not re–determined after treatment. Although antitoxin titers were measurable, there was no difference in the mean liters between children treated with vitamin A and the control group. Skin testing to monilia also revealed no difference. Semba et al. (1992) reported on a randomized placebo–controlled clinical trial with Indonesian children, ages 3–6, designed to determine whether the immune response in mild vitamin A deficiency is responsive to vitamin A supplementation. One–hundred eighteen children with mild xerophthalmia and an equal number of children with clinically normal eyes were randomly assigned to receive either 60 mg of vitamin A or a placebo. Baseline plasma vitamin A levels averaged 0.6 (µmol/L in the xerophthalmic group and 0.8 µmol/L in the clinically normal group, but 44% of children in the clinically normal group still had plasma vitamin A levels below 0.7 µ*mol/*L (20 (µg/dl), a cut–off often used to separate normal and clinically deficient children. Two weeks after treatment with vitamin A, children were immunized with diphtheria–pertussis–tetanus vaccine. After 5 weeks, plasma vitamin A levels increased to an average of 1.7 µmol/L in children who had received the vitamin A supplement, regardless of previous ocular condition, and remained al 0.7 µmol/L in the placebo group. After correction for previous immunization, there was a significant difference in anti–tetanus IgG liters between the vitamin A–supplemented and control groups. However, there was no difference in response between those children with pre–existing ocular signs of vitamin A deficiency and those without such signs.

The antibody response to bacterial antigens of the polysaccharide type has been examined in the vitamin A–deficient rat. In a study of the antibody response to pneumococcal poly–saccharide (from *Streptococcus pneumoniae,* type III, one of the more pathogenic strains of pneumococci), the antibody response was very low (< 20% of pair–fed control rats). Decreased antibody production was apparent before outward signs of vitamin A deficiency were manifest (Pasatiempo et al., 1990; Pasatiempo et al., 1991). In all experiments, repletion with vitamin A restored a normal level of antibody production. Similarly, vitamin A–deficient rats (either with or without symptoms of retinol deficiency) had almost no response following immunization with meningococcal polysaccharide, from *Neiserria meningitidis* type C (Pasatiempo et al., 1990). However, they responded normally after repletion with retinol (Pasatiempo et al., 1990). The effect of vitamin A status in humans on the response to these antigens has not been reported.

In contrast, when rats with the same low vitamin A status were immunized with the lipopolysaccharide antigens from either *Pseudomonas aeruginosa* or *Serratia marcescens,* antibody production was quantitatively normal (Pasatiempo et al., 1990). The contrasting effects of vitamin A deficiency on the response to polysaccharide and lipopolysaccharide antigens illustrate that the specific nature of the antigen or pathogen may determine whether or not vitamin A is a critical factor in the immune response.

A number of investigations have been carried out with other proteins, heterologous cells, and bacterial or viral antigens. Vitamin A–deficiency in mice was associated with a low response to foreign protein (Smith and Hayes, 1987) and a decreased frequency of helper T cells (Carman et al., 1989). Chicks fed a diet low in vitamin A developed a low agglutination response following challenge with the antigen from *Salmonella pullorum* (Panda and Combs, 1963). Morbidity and mortality rates after *Escherichia coli* infection were greater in chicks that were vitamin A–deficient but were also high in chicks that received an excess of vitamin A (Friedman et al., 1991).

The specific antibody response to viral antigens has been studied during vitamin A deficiency in several animal models. In chicks exposed to Newcastle disease virus the liter of virus–specific antibody was reduced (Sijtsma et al., 1990). The interaction of viral infection and vitamin A status on intestinal integrity was recently evaluated by Ahmed et al. (1990) in weanling mice infected by the oral route with rotovirus. Vitamin A–deficient mice showed a moderate reduction in the T cell area of the spleen, a significant reduction in thymus mass and, whether infected or not, had a reduced number of goblet cells per duodenal villus. In those mice with *both* vitamin A deficiency and rotovirus infection, there was marked destruction of the villus tips, but neither vitamin A deficiency nor rotovirus infection alone produced such a marked effect. This observation emphasizes the concept of synergy between a nutritional deficiency and infection as proposed by Scrimshaw et al. (1968). Vitamin A–deficient mice infected with rotovirus produced significantly lower levels of virus–specific antibody than mice pair–fed the control diet or fed ad libitum (Ahmed et al., 1991). Mice re–fed

the vitamin A–sufficient diet for 1 week before infection showed a partial restoration of antibody production, but little improvement in the delayed–type hypersensitivity response that was determined concurrently.

Nauss et al. (1985) developed the vitamin A–deficient rat as a model to study ocular infection with type 1 herpes simplex virus. The onset of herpetic keratitis was more rapid and clinical disease was more severe in vitamin A–deficient rats than control rats. The inflammatory response was significantly greater, as was the incidence of epithelial ulceration and necrosis. Similarly, after the conjunctiva of vitamin A–deficient rabbits had been inoculated with *P. aeruginosa,* infiltration of polymorpho–nuclear leucocytes, corneal ulceration and stromal melting followed although these changes were not observed in the controls (DeCarlo et al., 1981). Such studies emphasize the role of the epithelial barrier and inflammation in anti–viral defenses.

In nearly all studies of vitamin A deficiency and parasitic infections, the interaction has been synergistic (Beisel, 1982). Low plasma retinol levels are common in patients with parasitic diseases (Scrimshaw et al., 1968) and malabsorption of vitamin A has been demonstrated during a number of infections in humans (Nauss, 1986). An inverse relationship between plasma vitamin A levels and the pathogenicity of parasitic infections has been observed in rats or mice infected with a variety of parasites (reviewed in Parent et al., 1984; Darip et al., 1979). Low plasma retinol levels were associated with an inability to reject worm infestation. Parent et al. (1984) correlated nutrition, parasitological and immunological parameters in rats infected with *Schistosoma mansoni* and concluded that the humoral IgE immune response was markedly depressed during vitamin A deficiency while the cellular immune response was not significantly altered.

The importance of mucosal immunity is well recognized but this subject has received little experimental attention in relationship to vitamin A status. In malnourished children whose vitamin A status was not reported, Chandra (1975) observed that the secretory immune response (IgA) to live attenuated measles and polio vaccines was reduced significantly. Sirisinha et al. (1980, 1986) used the model of retinoic acid cycling in the vitamin A–deficient rat to investigate IgA production. The IgA levels in intestinal fluid and bile were significantly reduced, as was the transport of IgA into bile (Puengtomwatanakul and Sirisinha, 1986). Vitamin A deficiency has also been associated with a decreased number of Peyer's patches and fewer immunoglobulin–bearing cells in the gut–associated lymphoid tissues of the guinea pig (Majumder et al., 1987) and a reduced proliferative response to mitogens (Majumder and Abdus Sattar, 1987).

Influence of Vitamin A Administration on Immune Responses

A number of studies have revealed that retinol or retinoic acid can function as an adjuvant to enhance the antibody response to specific antigens, even in healthy animals with adequate vitamin A reserves. The adjuvant properties of retinol were first reported in 1968 by Dresser who showed that retinol–treated mice produced antibodies specific to soluble bovine gamma–globulin, which is not immunogenic in the mouse. Dresser speculated that macrophage activation might be responsible for the adjuvant properties of retinol, or that destabilization of cell membranes by retinol might stimulate lymphocytes to divide. Friedman (1991) has recently reported adjuvant effects of water–miscible forms of retinyl palmitate and retinoic acid admixed with protein antigens. This subject has recently been reviewed in greater detail elsewhere (Ross, 1992).

It is worthwhile to consider that supplementation with vitamin A may not only lead to nutritional rehabilitation but may also directly affect the immune response, perhaps through macrophage activation.

Although the mechanisms underlying adjuvant effects are not yet understood, a number of changes have been reported to follow administration of vitamin A. Cytokine production, lymphocyte transformation, resistance to tumour cells and CMI have all been reported to be greater in normal animals supplemented with high doses of vitamin A (Forni et al., 1986; Nuwayri–Salti and Murad, 1985). Cohen and Cohen (1973) reported that vitamin A treatment alone in normal mice enhanced the antibody response to a hapten–protein conjugate and to sheep red blood cells. Increased CMI as judged by lymphocyte proliferation in vitro was also demonstrated (Nuwayri–Salti and Murad, 1985). The authors speculated that vitamin A may enhance immune functions both by recruiting leucocytes and monocytes to the circulation and by altering membrane structure. Activation of naive or quiescent lymphocytes is often accompanied by increased expression of cell surface receptors for cytokines or other factors that function in the further expansion or maintenance of the activated state. Among the lymphocyte surface receptors that are expressed early and appear critical to further differentiation are various forms of the IL–2 receptor on activated T cells and NK cells and, on some cells, the transferring receptor. Retinoic acid added to cells in vitro increased the expression of IL–2 receptors on human T lymphoblasts (Sidell and Ramsdell, 1988).

In a rat model of sepsis, supplementation with vitamin A for 3 days prior to sepsis increased the survival rate (Demetriou et al., 1984). The number of white blood cells increased, with a greater percentage of lymphocytes and fewer neutrophils. T cell–mediated enhancement of the graft–versus–host reaction was increased in mice fed a high level of vitamin A (Malkovsky et al., 1983). In surgical patients who were treated with a large daily dose (90–135 mg) of vitamin A pre–operatively and for approximately 7 days following surgery the proliferation of lymphocytes was not different from the control group 1 day after surgery, but the response of cells from vitamin A–treated patients was significantly greater after 7 days (Cohen et al., 1979). Elderly nursing home residents given supplemental vitamins, including but not limited to vitamin A, for a month also showed increased CMI as measured by a greater number of T cells, an increased ratio of CD4 to CD8 T cells, and an increased mitogenic response to phytohemagglutinin (Penn et al., 1991).

There is evidence from studies of animals and humans that high doses of vitamin A stimulate phagocytosis or the cell–mediated killing of pathogens. Normal mice treated with vitamin A had sterile blood 5 hours after challenge with *P. aeruginosa* in comparison to control mice which developed a persistent bacteraemia. Survival time was extended in animals infected with *Listeria monocytogenes* or *Candida albicans* although mortality was not prevented (Cohen and Elin, 1974a; Cohen and Elin, 1974b). Because vitamin A treatment provided protection to three unrelated organisms, Cohen and Elin (1974a, 1974b) inferred that the nonspecific arm of the immune system was activated by vitamin A. Similarly, *hyper*vitaminosis A has been reported to enhance the resistance of mice to *Salmonella typhimurium* (Hof, 1981) and *L. monocytogenes* (Hof and Emmerling, 1979) presumably by activating mononuclear phagocytes. *S. typhimurium* was cleared at a significantly greater rate from blood as well as from the liver and spleen of vitamin A–treated rats (Hatchigian et al., 1989). Phagocytosis by peritoneal macrophages was also greater in mice fed diets high in retinyl palmitate (Moriguchi et al., 1985). This dietary treatment activated macrophages and T lymphocytes, as assessed by IL–2 receptor expression (Moriguchi et al., 1985). In patients with chronic lymphocytic leukaemia (Gergely et al., 1988) or lupus erythematosus (Vien et al., 1988) who were treated with 30 mg vitamin A/day for 2 weeks, NK cell activity, antibody–dependent cell–mediated toxicity and lymphocyte transformation were each reported to increase.

While these studies have focused on activation by retinal rather than on vitamin A deficiency, they nonetheless support the hypothesis that retinal has a positive influence on the clearance of pathogens. If the converse is true during vitamin A deficiency, one might expect the severity of infection to be greater during vitamin A deficiency, and significantly decreased following supplementation with retinol.

Summary and Hypotheses

Vitamin A deficiency in experimental animals has broad effects on metabolism, as shown by growth arrest, on the differentiation of epithelial tissues as exemplified by squamous metaplasia in the trachea, and on the immune system, including altered organ morphology, a decreased antibody response to many specific pathogens and antigens, decreased CMI and lower non–specific immunity. Repletion with retinol has nearly always rapidly reversed these changes. A number of investigations of antibody production and of phagocytosis also support a role of retinoids in immune stimulation in animals whose vitamin A nutritional status is normal or in patients whose immune response might be compromised. Nonetheless, not all data are consistent. In the case of some experimental infections or immunizations, no effect of vitamin A deficiency has been observed.

It seems clear that the precise features of an infection may determine whether or not vitamin A is critical and, if so, whether vitamin A has its greatest effect in preventing infection (*the barrier hypothesis) or in resolving an infection (the response or severity hypothesis).*

Based on the studies and observations reviewed in this chapter, it would be reasonable to predict that changes in epithelial structure occur in vitamin A–deficient children and that these would be more extensive in the respiratory tract than the intestine. Therefore, it may seem surprising that vitamin A supplementation has not been shown to have a greater effect in reducing mortality associated with respiratory infections.

Although the intestinal tract was not observed to be severely affected by experimental vitamin A deficiency (Wolbach and Ho we, 1925), the observations of Ahmed et al. (1990) that villus destruction occurred only when mice were both vitamin A deficient *and* infected with rotovirus may be highly relevant. Damage to the intestinal epithelium during infection in children with vitamin A deficiency may be greater than that in vitamin A–sufficient children.

It is obvious from the susceptibility of well nourished people to pathogens that infection per se is not prevented simply by a sufficiency of vitamin A. Thus, the types of infectious agent in the environment and other hygienic factors, rather than host factors, may predominate in determining the incidence of infectious disease.

Several lines of evidence indicate that host responses to challenge, whether with infectious organisms or purified antigens, is reduced during vitamin A deficiency. Collectively, these data provide strong support for the hypothesis that the response of the vitamin A–deficient child is sufficiently impaired to result in greater severity of disease.

Impaired responses could include decreased CMI and decreased functions of phagocytes, natural killer cells and lymphocytes. Decreased host responses may also be related to metabolic defects such as in protein utilization as have been reported in pure vitamin A deficiency in experimental animals. The ability of supplemental vitamin A to hasten bacterial clearance even in normal animals and its adjuvant properties in some immune responses also are consistent with the hypothesis that reactions (response) to infection could be improved following vitamin A supplementation. The therapeutic effect of high doses of vitamin A such as has been reported in children with measles might also result from stimulation of normal immune response mechanisms by supplemental vitamin A.

While there is ample experimental evidence to support an expectation that vitamin A deficiency should impact on morbidity and mortality associated with infectious disease in the human, the available evidence does not specifically predict whether vitamin A would be most likely to impact on the resistance to initial infection (*the barrier hypothesis*) *or on the response to infection* (*the response hypothesis*)*. Of course, the experimental evidence is consistent also with the notion that both are affected. One thing is clear from the studies reviewed. The influence of vitamin A status on morbidity and mortality may well be dependent upon the nature of the pathogen and perhaps also the biological environment in which infection occurs.*

4. Controlled Trials of Vitamin and Morbidity in Young Children

Introduction

Vitamin A was named the “anti–infective vitamin” on the basis of studies in animals linking deficiency to susceptibility to infection (Green and Mellanby, 1928). Nonetheless, a 1976 report of the Food and Nutrition Board (NRC, 1976) cautioned that investigations of vitamin A and morbidity and mortality might not yield conclusive results unless other concurrent infections, nutritional deficiencies, and environmental risk factors are taken into account. In effect, research in which a “simplistic single nutrient” approach is used, such as in vitamin A supplementation, was not recommended “for the purpose of demonstrating health effects other than those associated with the eye” (NRC, 1976).

The dramatic finding of the Aceh Study (Sommer et al., 1986), that periodic massive doses of vitamin reduced child mortality by one third or more, led to the implementation of other, similar studies in an attempt to replicate its findings (see Chapter 5). Also, the need for research on morbidity came to be recognized because of the strong expectation, based on epidemiologic observations of an association of xerophthalmia and infection (see Chapter 2), that reductions in the incidence and/or severity of respiratory and gastrointestinal infections were the presumed mechanisms behind the large mortality declines. In 1987, a committee of the Food and Nutrition Board set up to review studies of vitamin A and morbidity and mortality concluded that “ascertainment of effects on morbidity should be given high priority...” in part because “... demonstration of plausible mechanisms would add to the persuasiveness of the mortality findings” (NRC, 1987). The committee went on to issue specific research recommendations about vitamin A supplementation studies and morbidity and formulated the following hypothesis:

> *Vitamin A supplementation to populations in which vitamin A status is marginal increases immunocompetence and reduces the incidence and severity of diarrhoeal and respiratory infections* (Subcommittee on Vitamin A Prevention and Control, 1989).

The expectation of investigators was that large effects on morbidity were likely. For example, the MORVITA study (Dibley et al., 1992) in Indonesia was designed to detect a reduction of 25% in the incidence and severity of respiratory infections and diarrhoea.

In addition to the studies of vitamin A supplementation, there are prospective cohort studies which have examined whether the risk of increased morbidity is greater for children affected with xerophthalmia than for those unaffected. In Indonesia, children with mild xerophthalmia at the start and end of a three−month cycle had two to three times the risk of respiratory and diarrhoeal disease compared to controls (Sommer, Katz and Tarwotjo, 1984). A study in Hyderabad suggested an association between mild xerophthalmia at the onset of a six−month cycle of observation and respiratory but not diarrhoeal diseases (Milton, Reddy and Naidu, 1987). Associations with respiratory but not diarrhoeal diseases have also been reported by Bloem et al. (1989) who showed that Thai children with deficient (under 0.35 ?mol/liter) and marginal (0.35−0.70 ?mol/liter) levels of serum retinol at baseline were 3.6 and 2.4 times more likely than controls to develop respiratory diseases in 3 months of follow−up. This association remained significant after controlling for age and level of urbanization.

After reviewing the evidence, the subcommittee on Vitamin A Deficiency and Control concluded that “the literature suggests that marginal vitamin A deficiency is associated with increased incidence or severity of infections (or both)” (1989). It also pointed out “the interpretation of the results to date is difficult because studies have failed to fully document vitamin A status or to control for factors associated with both vitamin A deficiency and the risk of infection.” In a careful review of research results, Foreman (1989) expressed the same conclusion. Thus, the emphasis in this review on controlled vitamin A trials.

Objective and Approach of Present Review

The specific objective of this chapter is to review effects of controlled trials of vitamin A supplementation on morbidity, with emphasis on respiratory and gastrointestinal infections in children. Unlike the approach to examination of effects on mortality (Chapter 5), it was not possible to carry out a quantitative, pooled analysis of morbidity results. Marked differences in definitions of morbidity and in presentation of results made this impossible. Rather, a critical review of the findings, with particular consideration to design and analysis, was carried out.

Morbidity: Terminology and Methodologic Considerations

This brief section highlights the variation of morbidity methods which studies have used and also defines some of the terms used.

Some of the studies have taken place in hospitals and the morbidity data obtained have used clinical criteria and been collected by highly trained observers. Other studies have used a combination of clinical examinations and recall histories while many others have relied solely on recall histories. Yet another source of variation is the length of the recall period, from two days to six months.

A longitudinal design permits ascertainment of effects on incidence and on duration, *incidence being the number of episodes per child in a given period* (often expressed in reference to a year) and *duration, the number of days which an episode lasts.* Definitions of what is an episode of diarrhoea or of respiratory infection are variable and for this reason, an attempt is made in the review below to always specify the criteria used in each study. In addition to the presence of specific signs and symptoms as criteria, one or more symptom−free days are generally specified to demarcate the beginning or end of an episode. *Prevalence measures can also be generated from longitudinal data, most often as percent of time ill.* This is usually estimated as days ill in the period in question over days monitored in the period. This measure combines information about incidence and duration.

Cross−sectional data can provide incidence and duration data if recall information is obtained but data quality is generally poor for long recall intervals. Often, cross−sectional data are used to estimate *point or period prevalence* (*% of subjects exhibiting a symptom at a particular point in time*). In the field studies to be reviewed, there are many operational variants from these definitions. For example, “prevalence” may refer to the occurrence of symptomology at any time during a period of observation or recall such as the last week or the last two weeks. It will be apparent that such a variant in operational methodology would be expected to yield very different results from a study which reports the presence or absence of symptoms on a single survey day and very different again from the study that reports prevalence as % of observed days when illness was present. It is differences such as these, as well as nonstandardization of definition of diseases across studies that make comparisons very difficult and formal meta−analysis near impossible without access

to the original data or without requests for special analyses, using standardized definitions, by the original investigators. We are aware of a WHO−sponsored meta−analysis of experience with acute lower respiratory infection (ALRI) that plans to take such an approach.

Controlled Trials of Vitamin A Supplementation and Morbidity

Some two dozen studies of the impact of vitamin A supplementation on morbidity have been conducted recently or are being carried out. These studies have the following general characteristics:

- Children, almost in all instances of pre−school age, were given at least one large dose (usually 200,000 IU, equivalent to 60 mg retinol), or less powerful, but more frequent, doses (e.g. weekly or every other day), of vitamin A.

- A control, often a placebo−control, was included.

- Effects on respiratory and/or diarrhoeal infections were studied.

These studies are summarized in Tables 4.1−4.3. Table 4.1 is restricted to research carried out in free−living, largely unselected populations in developing countries; Table 4.2 is devoted to studies of children hospitalized for measles or diarrhoea; and Table 4.3 deals with studies in children at risk of respiratory infections. The characteristics of the studies selected for review include the site of the research, study design, measurement of morbidity and the nature of the findings. Comments are included as appropriate.

Review of Field Trials (Table 4.1)

Although many studies have been identified, results are not yet available from some of the studies. Among these are full details about the mortality trial in Sudan (Herrera et al., 1992) which collected 7−day recall data at baseline and after treatment, the Jumla study in Nepal which has information available about pneumonia (Daulaire et al., 1992) and a study from Delhi, India (Dr. Bhan) collecting detailed daily data, including severity indicators. Of the 16 studies included in Table 4.1, the authors have variously claimed to have found no effects of vitamin A supplementation on incidence and/or duration of episodes in seven instances, to have found at least some evidence that vitamin A reduces the morbidity burden in seven studies, and, in two studies, that vitamin A increases morbidity. Below the studies are grouped in terms of their overall finding. We then examine the studies as a whole, giving weight to the apparent quality of design and analysis in so far as this affects persuasiveness of the reported findings.

Studies Reporting Null Results with Respect to Incidence, Duration or Prevalence

The mortality trial in Aceh, Indonesia included collection of morbidity data but the methods used, 1 week recall at baseline and 1 year later, do not provide good estimates of the usual morbidity experience of individuals through the seasons and permit only point prevalences to be compared (Abdeljaher et al., 1990). Prospective, continuous data collection, such as done in the Tamil Nadu study of Rahmathullah et al. (1991) provides better individual measures and allows for better characterization of group patterns in regards to incidence and infection. A more important concern is that in the Aceh study, the “post” assessment of point prevalence took place about 6 months after the second and last massive dose of vitamin A was given. As discussed in Chapter 2, experience suggests that a protective effect of vitamin A dosing on liver retinol stores may persist for about 4 months; stores could be approaching baseline levels six months after dosing. We do not know what level of vitamin A nutriture may be necessary before effects on morbidity, if any, should be expected. An Australian study indicates that the effect of weekly vitamin A supplementation on respiratory symptoms disappears in the six−month period following the last dose (Pinnock, Douglas and Badcock, 1986). On the other hand, a trial in children hospitalized for complicated measles, suggest residual effects on morbidity almost six months after the last dose (Coutsoudis et al., 1991). Certainly, it would have been interesting to also collect point prevalence data within 1−2 months of the high potency dose. In view of the above, the Aceh morbidity study may not have had a design adequate for testing morbidity effects. Admittedly, if an effect had been seen 1−2 months after dosing, it would have begged the very important operational question “Can the effects be expected to persist over the usual interval between dosing in the operational programs?” This

discussion may serve as an illustration of the difficulty of assessing experience. There are many differences between the individual studies. The differences in design certainly impact on interpretation.

Direct analyses of the strengths and weaknesses of studies are limited in a number of instances because of lack of information. Vijayaraghavan et al. (1990) and Vijayaraghavan and Reddy (1991) reported on the mortality results from the Hyderabad study and noted that there were no effects on morbidity; however, results were presented only by vitamin A status, not by treatment. The Sarlahi, Nepal (West et al., 1991) and GHANA VAST (Arthur et al., 1992; Ross et al., 1993) are better designed studies, but are not yet published in full. West et al. (1991) report in an abstract that in Sarlahi, Nepal vitamin A supplementation had no effect on the incidence or duration of diarrhoea, though the vitamin A group showed a decrease of 11% in dysentery. Information from this Nepalese study about respiratory infections has not yet been made available. For the Ghana study, we were afforded privileged access to a draft manuscript in preparation for publication. This provided greater detail to complement the two publications. Daily prevalence is compared between treatment and control and found to be similar for 19 of 21 symptoms. The unpublished report also provides information on incidence and duration of illness by class of disease. The Ghana study suggests that severity of illness is reduced among children receiving treatment. Specifically, rates of clinic attendance and hospital admissions were lower in the group receiving vitamin A. Though many studies have collected referral and clinic admission data, not all have analyzed this potentially important source of information; a good example is the Tamil Nadu study of Rahmathullah et al. (1991) which reported no differences between treatment and control in incidence and duration. A second study in Tamil Nadu (Ramakrishnan, 1993) assessed morbidity through weekly surveys. No differences in morbidity between treated an control groups were observed; data about clinic use are available but not yet analyzed.

The Iringa, Tanzania (Ndossi, 1992) and West Bengal (Sinha, 1972) studies are similar in terms of data presentation: figures are shown which present prevalence data in treated and control groups as a function of time. Simple inspection of these graphs suggests that there are no differences between groups. Appropriate analyses and statistical testing, which would at least stratify by age of subjects, were not carried out. In the Iringa, Tanzania study, the treatment may not have produced a sufficiently large contrast in vitamin A nutriture between treatment and control to show a morbidity effect, if one exists. A single dose of 200,000 I.U. was given at baseline but effects on morbidity were assessed as long as 8 months later.

Studies Reporting Reductions in Incidence, Duration or Prevalence

As presented, the results of the Bombay study are uninterpretable. Much more detailed information must be available before the study can be interpreted. This is particularly important because the design was non–randomized and non–blinded and therefore open to many types of biases (Khothari, unpublished and 1991). The study from Baroda, India (Bakshi and Gopaldas, unpublished) deals with school age children (9–15 years) unlike all of the other studies. Though it was implemented as a double–blind study, there are many concerns. Sample size losses were large, there is no information provided to assess data quality, and the construction of variables and the unit of analysis are unspecified. Thus, the conclusions of this study, that vitamin A lowers total morbidity, as well as upper respiratory infection (URI) and fever, but not diarrhoea, must be interpreted with caution. A Chinese study (Cheng et al., 1992) reports dramatic reductions in incidence and duration of diarrhoea and respiratory infections, by far the largest effects reported in any study. Although intended as a double–blind study, it may not have been such. A supervisor was in charge of capsule distribution to treated and untreated children but it is not specified whether colour codes were used to mark vitamin A and placebo capsules. This is important to clarify because the supervisor also checked the data collected by the local “village doctors” every 2–3 months. Another study reporting some benefit is that of Bloem et al. (1990) who reported a lower prevalence of respiratory disease but not diarrhoea in Thai children. The study was not placebo–controlled though it is reported that the paediatrician was not aware of which children received treatment. The morbidity method used was two–month recall surveys carried out twice; important errors of recall would be expected in this type of study but this imprecision would not necessarily bias the comparison of treatment and control groups. Barreto et al. (1993) have reported at the 1993 IVACG meetings in Arusha, Tanzania that the incidence of diarrhoea, particularly more serious diarrhoea, was reduced in Brazilian children who were treated with vitamin A. Full details about this study await publication.

Table 4.1 Experimental Studies of Vitamin A and Morbidity in Children from Developing Countries

Investigator and Country	*Research Design*	*Measurement of Morbidity*	*Mortality Effects*	*Morbidity Findings*	*Comments*

				Found?	
Abdeljaher et al. (1990) Aceh Province, Indonesia	Non−blinded, randomized, non−placebo controlled, community trial. 229 treated and 221 control villages. Children 12−71 months of age studied. Large doses used (200,000 IU). Treatment given at enrolment and 6 months later.	Recall of morbidity in previous week, collected at baseline and 9−13 months later. Cough & fever which occurred and lasted for at least 24 hrs. defined a respiratory infection. Diarrhoea defined as 4 loose or watery stools.	No differences found between groups in the percent of children reporting cough, fever and diarrhoea at either baseline or post−treatment.	Yes; reduced by 34%	Children with xerophthalmia in both groups treated with vitamin A. Prevalence of xerophthalmia declined from 1.9 to 0.3% in treated villages and from 2.3 to 1.2% in control villages. Crude measures of morbidity. Second assessment of morbidity carried out several months after 2nd vitamin A dose was provided.
Arthur et al. (1992) Ghana; also Ross et al. (1993)	Randomized (at level of individual), double−blind, placebo−controlled trial. 1,455 children (6−59 months) included. Large dose used: 200,000 I.U. in children 12 months or older and half in infants 6−11 months, given at 4 month intervals (*3* doses). An average *of* 94.7% of eligible children received the dose at each point. Subjects were followed for 14 months.	Weekly visits by field worker for 1 year. Frequency, duration and severity of illnesses collected. Recall by mother aided by use of pictorial daily health diary. Simple examinations, including observations of nasal flaring, noisy breathing and chest in−drawing and recording of breathing rate and axillary temperature, conducted by field workers. Children were referred to clinic if ill, where diagnosis and treatment was done by physician. Diarrhea was defined by mother. ALRI defined as reported cough or difficulty in breathing,	No difference in incidence or duration of diarrhea and ARI. Vitamin A group had significantly less severe diarrhea episodes (fewer signs of dehydration such as sunken eyes and drowsiness). Noisy breathing during episodes of ARI was significantly lower in vitamin A group. Vomiting and refusing food/breast lower by 13% and 15% respectively in vitamin A group. Rate of clinic attendance (12% lower) and hospital admissions (38% lower) favoured the vitamin A group.	Yes; reduced by 25%	15.8% had serum retinol levels 0.35 µmol/1 (severe deficiency) and 73.4% had levels below 0.70 µmol/1. Prevalence of xerophthalmia was 1.53%. The study provides strong evidence that the severity of diarrhoea was reduced. Effects on respiratory infections were not as great as those on diarrhoeal diseases.

		together with rapid breathing and/or “tight ribs”. Seriously ill children admitted to hospital and monitored. Morbidity information missing for 5.7% of weekly follow−ups and loss to follow up was 11.6%; treatment and control had similar rates.			
Bakshi and Gopaldas (unpublished) Baroda, India	School age children (9−15 yrs.) included a total of 210 children selected from 4 schools but only 124 completed study. Randomized to vitamin A (200,000 I.U.), vitamin A & antihelminthic dose, and placebo−control groups. Treatment every 4 months (chewable tablets) at 0, 4 and 8 months. Double− blind. Placebos received tablets resembling those given to treated children.	Physical examination and morbidity recall every 14 days. The examination provided data on fever (>=100° F) and URI (signs and symptoms of cough). The recall survey provided data for diarrhoea (>=4 stools per day), cough and colds, fever and passing of worms. Episodes defined as one or more days of illness preceded by at least one symptom free day in the last one week.	Vitamin A groups pooled and compared to placebo group. Morbidity differences found after second dose. Vitamin A group was lower in percent overall morbidity (episodes, days ill per subject and percent prevalence), URI (percent prevalence & episodes) and fever (episodes and days ill). No difference in diarrhoea (but infrequent symptom).	Not a study outcome	Vitamin A statu (serum retinol and clinical signs) of treate groups improv Details about data quality, variable construction, a analyses not clear. The unit analysis is not clear.
Barreto (1993) Bahia, Brazil	Randomized, double−blind, placebo−controlled trial in 1,240 children 6−48 months. Large doses (200,000 IU) given; children 12 months or less received half−dose. Doses given at start and every 4 months for 1 year (4 doses).	Data collected through household visits 3 times a week focusing on frequency and severity of diarrhoea and respiratory infections. In case of 3 or more liquid/semi−liquid stools/24 hrs, complete severity information collected (vomiting, blood/mucous, fever, health care	Total episodes of diarrhea fewer in vitamin A treated group. Frequency of short (1−2 days) episodes similar but that of long (>= 3 days) greater in control group. Frequency of episodes of long duration and 5 or more stools per day fewer in vitamin A group. Occurrence of symptoms	Not a study outcome	Exclusion crite included active xerophthalmia measles in previous mont vitamin A dose last 6 months and low weigh for age. No ca of xerophthalm at any point. About 65% measles vacci coverage. Vitamin A appears to reduce incider and severity o diarrhoeal

		1 treatment sought). Episodes of diarrhoea separated by 3 or more symptom free days. If cough reported, respiratory rate measured and if elevated (40 mc/min) or chest indrawing or nasal flaring observed, pediatrician examined the child (X–rays when indicated). Pneumonia defined as cough plus respiratory rate of 50 mc/min or greater for children under 12 months or 40 mc/min or greater for older children; episodes separated by 14 or more symptom free days.	(blood, mucous, vomiting) and medical care during episodes of diarrhoea were similar. There were differences in terms of mean daily prevalence of diarrhoea at certain cut–off points of stools per day (>=4, >=5 and >=6 day). No differences found in incidence or prevalence of pneumonia, cough, respiratory rate and other related indicators.		diseases but not that of respiratory infections.
Bloem et al. (1990) Northeastern Thailand	Randomized, non–placebo controlled trial in 166 children aged 1–5 years. Single dose (200,000 IU) given at baseline.	Morbidity interviews 2 and 4 months after treatment. Morbidity history in the previous 2 months collected through interviews by a paediatrician. Respiratory diseases were defined by history of clinically significant respiratory complaints, such as cough and runny nose, accompanied by fever. Diarrhoea was defined as a >4 stools/day.	The percent of children reporting symptoms at 2 and 4 months was compared in treated and control children. Sample divided into 1–2 and 3–5 years. Respiratory disease was consistently lower in the vitamin A group (significant only at 4 months in children 1–2 years; 13.2 and 33.3% of children affected respectively in treated and control groups). Diarrhoeal disease lower in treated group at 2 months but	Not a study outcome	The prevalence of night blindness in the rural area was 1.3% in children 1–5 years. 13% of rural children showed deficient serum retinol levels (< 0.35 µmol/L). In a companion observational study, serum retinol levels were found to predict respiratory but not diarrhoeal diseases. The paediatrician was not aware of which children had received the capsule.

			differences not significant. No apparent differences in diarrhea at 4 months.		
Cheng Lie et al. (1993) Hebei, China	Random assignment to vit A (n=98) or control (n=74) for 1 yr. (3:2 allocation to treatment). Children (6–36 mos.) came from 3 villages; allocation to treatment/control was within village. Capsules (200,000 IU) or placebo given 4 mos. & 10 mos. after baseline by study supervisor. Children less than 12 months received half dose. Double– blind; placebo–controlled.	Local “village doctors” recorded twice a month morbidity information as recalled by the mother on family’s diary. Diarrhoea was 3 or more stools per day. Respiratory infection was cough or nasal discharge with fever lasting more than 24 hrs. or evidence of bronchitis or pneumonia.	Incidence and duration of diarrhoea and respiratory infections markedly greater in control children. RR for incidence were 0.40 and 0.29 for diarrhoea and respiratory infections respectively. The corresponding values for days ill per child per year were 0.38 and 0.29. More hospitalization in control group (5 vs. 1 cases).	Not a study outcome	Quality of morbidity data not discussed. About 35% of children had retinol levels below 20 µg/dl baseline. Vitar A status improved in treated group. Neither parent or doctors awa of experimenta assignment. Supervisor checked the information ev 2–3 months ar also was responsible fo capsule distribution. Co coding of capsules not reported to hav been used. No clear if assignment to experimental group was kno to super– viso No effect on growth.
Dibley et al. (1992) Indonesia (known as the MORVITA study)	Randomized, double–blind, placebo–controlled trial in children 6–48 mos. Treated children received 200,000 IU (100,000 IU if < 12 mos) every 4 mos. (6 treatment cycles). Sample sizes were 691 children receiving vitamin A and 703 in placebo group.	Home visit every 2 days to monitor diarrhoea and acute respiratory illnesses. Ill children reexamined by field nurse. Diarrhoea defined as 3 or more loose stools per 24 hrs. Episodes of diarrhoea separated by at least 2 symptom–free days. Episodes of cough and ALRI (cough and 1 or more reports of	No differences in diarrhoea. Vitamin A group with adequate vitamin A stores (>20 µg/100 ml) had more cough. ALRI more common in vitamin A group but no differences in duration.	Not a study outcome	Incidence of diarrhoea declined in bot groups over tir perhaps becau of measles immunization. Though this is carefully done study, full deta are not availab at this time.

		elevated respiratory rate) separated by 3 or more symptom–free days.			
Herrera et al. (1992) Sudan	Randomized (at household level), double–blind, placebo–controlled trial. Large dose (200,000 IU) given three times every 6 months. 28,723 children 9 to 72 months included.	Recall survey for preceding seven days. Diarrhoea (3 or more loose or watery stools per 24 hrs.), fever, cough and measles recorded. Data collected at baseline and at 6, 12 and 18 months later.	Morbidity incidence (diarrhoea, fever, cough) decreased over intervention period. No differences between treatment and control.[a]	No effects found	All xerophthalmic children treated. De novo appearance of night blindness and Bitot's Spots only marginally reduced by treatment.
Kothari, G.A. (unpublished; 1991) Bombay, India	Non–randomized, non–blinded, controlled trial carried out in two slum areas of Bombay. Sample was about 200 children less than 1 yr. at baseline per area. 200,000 IU given every 6 months.	Six–month recall history by physician; health examination also carried out. Repeated every 6 months for 3 1/2 years. Methods not detailed.	Authors claim that the incidence of fever, respiratory infections and diarrhoea was reduced in the experimental area.	Some effects claimed	Xerophthalmia cases treated. Xerophthalmia prevalence declined in treated but not control area. Description of methods, data summarization, analyses and presentation of data are deficient.
Ndossi (1992) Iringa, Tanzania	Randomized, double–blind, placebo–controlled trial. 554 children less than 5 yrs. of age, from 14 villages participated for 8 months; 277 children allocated to each experimental group. Treatment occurred once at baseline (200,000 IU).	Mothers interviewed at baseline and at each of 4 subsequent visits (each 1 to 2 months apart). Mother was asked to recall the child's morbidity history for the previous seven days. Data collected for fever, skin infections, colds, cough, ear infection, measles and diarrhoea. Definitions used not provided. Data analyzed as prevalence (percent of children expressing	Key results presented in figures showing prevalences for each of the illness categories at baseline and at each visit for vitamin A and control groups. Sample sizes not given; statistical analyses not carried out. Consistent patterns not readily discernible except for fever and intestinal parasites which have lower prevalences in the vitamin A group at visits 3–5. Author	Not a study outcome	No children had Xerophthalmia. 4 weeks after treatment, serum retinol values in the placebo group had changed from 17.1 at baseline to 21.1 and in the vitamin A group from 18.4 to 23.4 µg/100 ml (sample sizes at 4 weeks are much reduced compared to baseline). Supplementation may not have created important differences in vitamin A status between groups. Later morbidity assessments

		symptom at each visit).	claims on the basis of these figures and other analyses that vitamin A supplementation did not influence morbidity.		carried out lon after the single dose was provided.
Rahmathullah et al. (1991) Tamil Nadu, India	Randomized, placebo−controlled, double−blind clinical trial in 15,419 children 6−60 months of age. Weekly doses used (2,500 µg).	Weekly recall during one year. Sick children referred to health unit. Diarrhoea was defined as at least 1 day with 4 or more watery or loose stools. URI and LRI recorded if symptoms occurred for 3 days or more. URI was cough with fever and LRI was cough, cold and fever with lung involvement. Episodes differentiated by 3 or more symptom free days.	No differences between treatment and control in incidence, or duration of diarrhoea or respiratory infections. There was a tendency for the percent of children who had chronic diarrhoea (one or more episodes lasting 15 or more days) to be greater in treatment than in control and this was statistically significant in stunted children 36 mos. or older.	Yes; reduced by 54%	11 % xerophthalmia baseline. All children with xerophthalmia treated with vit An extraordina large decline i stunting and wasting occurr Clinic referral data not analyzed in relationship to treatment.
Ramakrishnan (1993) Tamil Nadu, India	Randomized, double−blind, placebo−controlled trial. Children 6−36 months received three rounds of a liquid dose containing either 200,000 IU of vitamin or a placebo every 4 months. Morbidity sample was 583 children.	Weekly surveys of mothers for 1 year using trained village health workers. Variables were percent of time ill, incidence and duration of diarrhea and respiratory infections. Upper respiratory infection was defined as a cold or a cough accompanied by fever. Diarrhea was coded when reported by mother.	No effects of vitamin A treatment found on any of the morbidity outcomes or on physical growth. Controlling for covariates did not alter the conclusions.	Not a study outcome	Xerophthalmic children treate Unusually low levels of respiratory and diarrhea illness found. High compliance ra
Sinha (1972) West Bengal, India	310 children less than 5 yrs. enrolled. The children were studied for 1 yr. (Oct 71 to Dec 72). On Jan 73, the children were divided into two	Weekly history of illnesses collected and entered in a printed form by two data	Data expressed as prevalence (% of children affected each week). Detailed graphs showing	Not a study outcome	Low dietary intakes of vita A. Night blindness eliminated in treated group

	groups of 153 each. Matching was for age, sex and SES and allocation to treatment and placebo was at random; double−blind procedures followed. Treatment was 100,000 IU every 4 mos. on three occasions.	collectors who switched sectors every week. Detailed information collected for respiratory and gastrointestinal symptoms. URI defined as nasopharyngitis or pharyngitis. LRI defined as croup, bronchitis and/or pneumonia. A severity score was developed for diarrhoea based on stool frequency and stool consistency and the presence of mucus or blood.	prevalence by week for vitamin A and placebo groups for baseline and intervention periods suggest no differences between groups for upper respiratory infections, conjunctivitis (though tendency for prevalence to be lower in treated group), diarrhoeal diseases, and skin infections. Results for some variables (e.g., LRI) not given. Diarrhoea severity score and referral information not used in analyses of treatment effects.		changes in Bitot's spots unclear. Dose given is half that of many other studies. The unusual detail and apparent rigor of the study not exploited in analyses.
Stansfield et al. (unpublished) Haiti	Approximately 10,000 children 6−83 months entered a household−randomized, double−blind, placebo−controlled trial of vitamin A supplementation (200,000 IU at 4 m intervals; 100,000 IU for 6−11 molds). Study continued for 15 months with new entries and discharges by age. Checks on dosing records show fewer than 1.6% were mixed.	Two week morbidity histories collected in each round through household visits. ARI was recorded using local terms and concepts, which corresponded to signs of rhinitis, cold or flu, productive cough, and/or rapid breathing. Diarrhoea was a history of four or more loose or watery stools per day.	Reported that vitamin A administration *increased* the prevalence of morbidity with following risk ratios (vitA/control): diarrhoea, 1.18; rhinitis, 1.11; cold/flu, 1.15; cough, 1.14 and rapid breathing, 1.26. All risk ratios were statistically significant.	No effect seen. Cause−specific mortality rates also same	Baseline prevalence of xerophthalmia was lower than expected (0.4%). Response to supplementation not reported. The preliminary report does not provide all information needed. Analysis appears to be based on comparisons of the percent of two−week periods reporting a symptom in treated and control groups, with children being represented as often as included in each round (there were as many as 3 "full distribution

					cycles".
Vijayaraghavan et al. (1990) and Vijayaraghavan and Reddy (1991) Hyderabad, India	Randomized, double−blind, placebo−controlled community trial. Large doses (200,000 IU) given every 6 months (two doses). Children 1−5 years included; 7,691 in treatment and 8,084 in control groups.	Morbidity data collected every 3 mos. for 1 year. Mothers asked to recall morbidity history in previous month for diarrhoea (3 or more loose stools per day), respiratory infections (clinically significant cough with or without expectoration) and measles. "Incidence" of diarrhoea calculated for each 3−month interval. Data collected for 5 intervals. Pooled estimates of "incidence" also generated.	Risk of respiratory infections but not diarrhoea higher in xerophthalmic children compared to normal children. Vitamin A supplementation had not effect on morbidity; results not presented.	No effects found	All children wit corneal involvement treated. Xerophthalmia prevalence wa about 6.0% in both groups ar declined to 1.3 in treated children and 2.9% in contro children. Seriously ill children referr for treatment b data not analyzed in reference to treatment.
West et al. (1991) Sarlahi, Nepal	Randomized, double−blind, placebo−controlled vitamin A supplementation trial. Large dose (200,000 IU given) every 4 months for 1 year; infants 6− 11 months received half. 28,630 children 6−72 months included.	Recall survey for preceding seven days at baseline and every four months for 1 year. Episodes of at least 1 day duration of diarrhoea (>4 loose, watery stools), dysentery (blood in stools), high fever, and persistent cough recorded. 4−month history of measles collected at each visit.	No difference in incidence or duration of diarrhoea. 11 % decrease in vitamin A group in dysentery. Mortality risk related to severe diarrhoea and dysentery was lower in vitamin A group (RR=0.59).	Yes; 30% reduction	All xerophthalr children treate Published resu about diarrhoe not available i detail. Results respiratory infections not reported in any detail.

[a] Morbidity findings as reported in "Vitamin A mortality and morbidity studies." Report of a Joint WHO/USAID/NEI Consultation of Principal Investigators. Geneva, Switzerland, 1992.

Finally, as already noted the Sarlahi, Nepal study reported an 11% decrease in dysentery but no effects on the incidence or duration of total diarrhoea.

Studies Showing an Adverse Effect of Vitamin A on Incidence, Duration or Prevalence

The MORVITA study from Indonesia (Dibley et al., 1992) and that of Haiti (Stansfield et al., unpublished) are unique among all in that they report that vitamin A supplementation *increases* the risk of infections. The

Indonesian study (Dibley et al., 1992) reported an increased risk for respiratory infections but not diarrhoea. ALRI was more common in the vitamin A group and cough was more frequent in treated children with adequate vitamin A stores. This study is not yet reported in detail and its conclusions need to be viewed as tentative. The Haiti investigation, also unpublished, has a less persuasive research design. The study was mounted through existing infrastructures in an area that had been, and still was within a vitamin A control program. A preliminary report from that study suggests increased risks for several classes of symptoms, associated with periodic vitamin A supplementation (Stansfield, 1992). The morbidity data were collected through two−week recall morbidity surveys done within a few weeks of each of 3 rounds of treatment with vitamin A. The unit of analysis used was the two−week period report (presence or absence of any reported illness in the two weeks) and the prevalence of reports with symptoms in the treated group was compared to that in the control group. Other analyses, such as those based on percent of time ill per child in which data are aggregated per child from the various rounds, may yield different results.

The only other suggestions of harmful effects come from the Tamil Nadu study of Rahmathullah et al. (1991), which found more diarrhoea in stunted children 36 months or older, an Australian study which found weak evidence for more severe respiratory infections in the treatment group (Pinnock et al., 1988), and a study of newborns at risk of bronchopulmonary dysplasia in which the only four deaths (out of 40 infants in treated and control groups) occurred in the vitamin A treated group (Shenai et al., 1987). Another Australian study (Pinnock et al., 1986) found that treated children had fewer respiratory illness episodes but a tendency for more days with cough. The Tamil Nadu Study of Rahmathullah et al. (1991) found no differences between treated and control in other subgroups of children in the case of diarrhoea and in no subgroup in terms of respiratory infections. The single isolated finding may reflect the fact that multiple, unintended comparisons do result in occasional significant findings. Interestingly, following adjustment by Pinnock et al. (1988) for multiple comparisons, differences between treated and control children were non−significant; no such adjustment was done in the Tamil Nadu Study of Rahmathullah et al. (1991). As explained in Table 4.3, the four deaths in the bronchopulmonary dysplasia study may not be related to treatment; the authors, while expressing concern, did not attribute the deaths to the provision of vitamin A.

Vitamin A Supplementation in Children with Measles and Diarrhoea (Table 4.2)

Three studies have been carried out in children hospitalized for complicated measles (Barclay et al., 1987; Coutsoudis et al., 1991; Hussey and Klein, 1990). All three indicate that vitamin A supplementation is protective against complications, particularly from respiratory infections. Two of the studies also assessed mortality and found vitamin A to enhance survival. Recently Hussey and Klein (1993) reported a retrospective review of experience with routine supplementation of hospitalized measles cases; the findings were consistent with the controlled intervention studies.

Measles has been found to lower serum retinol concentrations but the low values are not necessarily due to low liver stores. Rather, they are due to impaired transport. This is the conclusion of Coutsoudis et al. (1990, 1991) who found that serum retinol of placebo cases rose markedly on day 8 after admission to the hospital. Vitamin supplementation led to even greater serum retinol levels and also improved specific IgG antibody levels and total number of lymphocytes. These findings suggest that vitamin A therapy during measles needs to be considered even in areas where vitamin A deficiency is not a public health problem. On the other hand, the single study of children hospitalized with diarrhoea (not associated with measles or cholera) did not find any benefit from vitamin A treatment in Bangladesh (Henning et al., 1992).

Vitamin A Supplementation in Children at Risk of Respiratory Infection (Table 4.3)

There are three studies of vitamin A supplementation in children at risk of respiratory infection: one in children with documented, recent history of frequent respiratory infections (Pinnock et al., 1986), another in children who had been hospitalized in infancy for bronchiolitis (Pin−nock et al., 1988) and one in very low birth weight babies at risk of bronchopulmonary dysplasia (Shenai et al., 1987). All three were carried out in developed countries. A clinical trial led by Dr. Kjolhede in children hospitalized for respiratory infections is underway in Guatemala City in collaboration with the Institute of Nutrition of Central America and Panama (INCAP).

Pinnock et al. (1988) found that in children who were hospitalized in infancy for bronchiolitis, treatment with weekly doses of vitamin A did not have consistent effects on respiratory morbidity later in the preschool years (i.e., 2−7 years). These Australian children were not vitamin A deficient though a few may have had marginal

serum retinol levels (Table 4.3). Also, there is no documentation, in spite of a history of hospitalization in early childhood, that the children were in fact prone to respiratory infections later in life.

In Australian children, recognized as being at high risk of respiratory infections but not vitamin A deficient, weekly supplementation with vitamin A led to 19% fewer episodes of respiratory illness (Pinnock et al., 1986). Foreman (1989) has criticized the analyses which are restricted to a comparison of control to treated children who received over 50% of the dosage. Such an analysis destroys "the randomization component of the study design". Another study, in very low birth weight babies at risk of bronchopulmonary dysplasia, supplementation with small, periodic doses reduced the occurrence of this disease (Shenai et al., 1987).

Discussion

The discussion is organized along three topics. The first focuses on whether the evidence points to an *important reduction* in the incidence or duration of diarrhoea and respiratory infections, the second on whether there is evidence of *increased* respiratory infections in children, and finally, the third deals with effects of vitamin A supplementation on *severity.*

What are the Effects on Incidence and Duration of Diarrhoea and Respiratory Infections?

The Indonesian study reported by Dibley et al. (1992) was designed to detect a reduction of 25% in the incidence and/or duration of diarrhoea and respiratory infections. A question worth posing is whether the methods used were capable of detecting such an effect.

The morbidity methods used in the reported studies varied widely in quality. Some used prospective and continuous data collection through household surveys with recall periods of one week or less (Arthur et al., 1992; Barreto et al., 1993; Dibley et al., 1992; Rahmathullah et al., 1991; Ramakrishnan, 1993; Sinha, 1972). In two other studies, household surveys were also continuous but spaced apart every two weeks (Bakshi and Gopaldas, unpublished; Cheng et al., 1992). Collection was variable in other studies. For example, West et al. (1991), Ndossi (1992) and Stansfield (1992) collected data about morbidity in the previous one or two weeks but not on a continuous basis (i.e., surveys were every few months).

There has been limited published discussion of the quality of the morbidity methods used in the studies reviewed, in reference to the ability of the studies to detect effects. However, it is possible to consider the general literature of morbidity trials directed toward other questions and gain some insight about the present studies. In Guatemala, 2–week household recall surveys of morbidity were found to result in substantial under–reporting. In each interview period, the number of days ill with diarrhoea was under–reported on average by 22% and for respiratory illnesses, by 12% (Martorell et al., 1976). Mothers' reports on the day of interview were compared with diagnoses made independently by a physician on the same day. Sensitivity values were found to be 66% and 92% for diarrhoea and respiratory infections, respectively, and corresponding specificity values were 99% and 64% (Martorell et al., 1975). Despite deficiencies in reliability and validity, the data generated were shown to be related, in the expected direction, to outcomes such as child growth (Martorell et al., 1975).

TABLE 4.2 Experimental Studies of Vitamin A and Morbidity in Children Hospitalized with Measles or Diarrhoea

Investigator and Country	*Research Design*	*Measurement of Morbidity*	*Morbidity Findings*	*Mortality Effects Found?*	*Comm*
Barclay et al. (1987) Tanzania	Random allocation of measles cases admitted to hospital to treatment (n=88) or control (n=92). Treated children received 200,000 IU	Children were hospitalized and records were kept for all subjects.	Complications somewhat more common in control group. Mortality from complications greater in control group, especially in children with croup or laryngotracheobronchitis.	Yes; of the 12 children who died, 10 were in the placebo group	Children v corneal ul excluded Treatmen known to paediatric not to stat

	orally immediately and one day later.				members. Retinol serum concentrations were about 9 ?g/100 ml (0.31 ?mol/L) at baseline.
Coutsoudis et al. (1991) Durban, South Africa	Double−blind, randomized, placebo−controlled trial in children 6−24 months hospitalized for complicated (by pneumonia and diarrhoea) measles. Sample sizes were 3 1 in placebo and 29 in vitamin A group. Xerophthalmic children treated and excluded. Treatment was on admission and on days 2 and 8 using dose “recommended by WHO”. A dose also given at 6 weeks (all children discharged by this time).	Patients assessed daily; clinical and radiological data used to define pneumonia. Mother asked to record symptoms in child card after discharge. An integrated morbidity score was estimated for diarrhoea, upper respiratory−tract infection, pneumonia and laryngotracheo−bronchitis by weighing various factors including source of information (mother vs. hospital) and severity of the episode. Each child assigned a score on day 1, day 8, and at 6 weeks and 6 months; all score computations done before the code was broken.	The scores were reduced by 82%, 61% and 85% on day 8, and at 6 weeks and 6 months respectively in the supplemented group. There was a tendency for duration of illnesses to be reduced in the vitamin A treated group (significant for pneumonia). Clinical recovery occurred within 7 days in 96% of treated children compared to 65% of placebo children ($p<.01$).	Not a study outcome	Baseline serum retinol levels were around 12 ?g/100 ml (0.42 ?mol/L). Follow−up at 6 weeks was 80% and at 6 months, 60% of the origina sample.
Henning et al. (1992) Bangladesh	Randomized, double−blind, placebo−controlled trial. Boys (1−5 yrs) with less than 48 h of watery diarrhea (non−cholera) received either 200,000 IU (n=46) or a placebo (n=37) during hospitalization at ICDDR. Groups similar in age, nutritional status and severity of diarrhea prior to admission.	Stools, urine and vomiting volumes collected and rectal temperature recorded every 8 hrs. Subjects discharged when diarrhea stopped (two normal stools or no stool in 24 hrs).	Duration of diarrhea and stool and emesis output similar. No differences in complications. Mean duration of diarrhea was about 2 days.	Not a study outcome	No adverse effect (e.g., nausea, vomiting) detected Exclusion criteria were serious illnesses, malnutrition, vitamin A capsule in past 3 months and history of vitamin A deficiency. More placebo children were excluded after enrollment (reasons: developed other illnesses, includin pneumonia and measles; laboratory diagnosis of treatable parasite (Giardia lamblia) and parent refusal). No changes in serum retinol between baseline and 24 hrs after treatmen

Hussey & Klein (1990) South Africa	Randomized, double−blind, placebo−controlled trial in children with severe measles to vitamin A (n=92) or placebo group (n=97). Treated children received 400,000 IU orally.	Patient records. Pneumonia defined as the presence of tachypnea (frequency of respiration > 40 per minute) with retractions, crackles, or wheezes. Diarrhoea was defined as the passage of four or more liquid stools a day.	Vitamin A group had reduced duration of pneumonia (6.3 vs. 12.4 days), diarrhoea (5.6 vs. 8.5 days) and had less croup (13 vs. 27 cases) and spent fewer days in the hospital. 52% of placebo children had an adverse outcome (death, pneumonia > 10 days, post−measles croup or transfer to ICU) compared to 25 of treated children.	Yes; differences significant for children < 2 years	Baseline s retinol lev 11.6 ?g/1 Xerophtha cases exc
Pinnock, Douglas & Badcock (1986) Adelaide, Australia	Randomized, double−blind, placebo−controlled trial in children (1−4 yrs.) with a history of frequent respiratory illness. Treated children received 1160 µg retinol equivalents three times weekly (equivalent to daily RDA) for 5 mos. Subjects were participants in double−blind trial of a pneumococcal vaccine which proved ineffective. The children selected were those experiencing more than 15 days of cough or 3 separate episodes of respiratory illness during the preceding 3 months. After sample size losses, 53 children remained in treatment and 54 in control group.	Respiratory symptoms recorded on daily diary by parents 6 mos. prior to supplementation, during the supplementation period and for 6 mos. after. Symptoms recorded were nose and/or throat soreness; pain in the sinus and/or runny nose (nose/throat); hoarseness and/or cough (cough); deep chest cough/wheezing (chest). Episodes defined as 1 or more days with any of above symptoms.	Treated children experienced 19% fewer episodes of respiratory illnesses during the 5 month period of supplementation. Effects were greater in children with a history of acute or chronic LRI (25% reduction). No effects seen in total days ill with respiratory infections, largely due to nonsignificant increase in treated children in days with cough.	Not a study outcome	Plasma re levels of t children d change (a µg/100 ml treatment placebo g Treatmen control gr similar in respirator infection c 6 months the 6 mon following month per supplemen Analyses treatment did not co child's pri
Pinnock et al. (1988) Adelaide, Australia	Double−blind, randomized, placebo−controlled trial in 2−7 yr. old children who had been hospitalized for bronchiolitis in the first two years of life. Treated group received 4.2 mg of retinyl palmitate weekly (equivalent to daily RDA). Cases meeting compliance criteria were 79 in	Symptoms of respiratory infections recorded daily by parents in diary. An episode defined as 1 or more days of symptoms preceded of succeeded by 2 or more symptom−free days. Clusters of symptoms were designated as probable, uncertain and doubtful episodes.	No effects on respiratory morbidity. Some comparisons favoured the placebo group (fewer number of doctor visits, fewer prescriptions for antibiotics, fewer days of sore throat). When adjustment is made for multiple comparisons, differences cease to be statistically significant.	Not a study outcome	Plasma re 39 µg/100 baseline a not chang supplemen Range of (11.7−73. ml) includ cases with marginal (actual nu given). Pl values unexpecte than in pr

	vitamin A group and 70 in placebo group.				study. No evidenc that the children were prone to respiratory infections at the time of the study.
Shenai et al. (1987) Tennessee, USA	Double−blind, randomized, placebo−controlled trial in very low birth weight babies at risk of broncho−pulmonary dysplasia (BPD). Treated neonates (n=20) received 2,000 IU on day 4 and every other day thereafter for a total of 14 injections over 28 days. Controls (n=20) received 0.9% saline solution at similar intervals.	Detailed clinical records kept. BPD based on clinical and radiologic criteria.	BPD diagnosed in 9/20 treated infants and in 17/20 control infants (p < 008). Mechanical ventilation on study day 28 was required by 4/19 treated infants and by 11/20 control infants (p < 029). The need for supplemental oxygen, mechanical ventilation, and intensive care was reduced in treated infants. Airway infections and retinopathy of prematurity were also reduced.	Not an outcome of study	Treated newborns had higher mean plasma concentrations of vitamin A (approximately 33 and 15 µg/100 ml on day 31 for treated and untreated infants respectively) and retinol−binding protein than controls. The authors conclude that vitamin A supplementation "...appears to promote regenerative healing from lung injury, as evidenced by a decrease in the morbidity associated with bronchopulmonary dysplasia." 4 infants who received vit A died 2 during the trial (one from preexisting causes and 2 from viral infections occurrin long after the completion of the study. Mortality differences were not statistically significant. Author do not attribute th deaths to the treatment.

Others have also found that data from morbidity surveys, particularly about diarrhoea, are consistently and negatively related to growth, as reviewed recently by Tomkins and Watson (1989).

Esrey, Feachem and Hughes (1985) have carried out a careful review of the literature on the improvement of water supplies and excreta disposal facilities on diarrhoeal diseases and mortality. On the basis of 67 studies from 28 countries, they concluded that the median reductions in diarrhoea morbidity rates were 22% from all studies and 27% from a few better−designed studies. They also concluded that the median reductions in mortality rates were 21% using all studies and 30% using only those with better designs. The studies reviewed by Esrey, Feachem and Hughes (1985) used methods similar to, and as variable in approach and apparent quality as, the studies included in this review.

*It seems reasonable to conclude that if there were a **major** effect of vitamin A supplementation on young child morbidity prevalence, the aggregation of studies reviewed should have been adequate to detect it. It is less certain that most studies could have detected subtle effects or effects on certain aspects of morbidity* (*e.g. cause specific morbidity with low incidence or severity*)*. It is noted that additional analyses of some of the existing studies might shed further light.*

A summary of the morbidity studies carried out in non−hospitalized children is given in Table 4.4. The studies are divided into three categories. The first includes studies with stronger design features. These involved double−blind and placebo−controlled designs, had large sample sizes and employed at least weekly, continuous monitoring of morbidity through household visits. The other two groupings simply distinguish between studies having more or less than 1,000 subjects included in treatment and control groups. No other distinctions, for example in quality of the research design, are implied between large and small studies.

The best studies generally indicate that vitamin A supplementation does not decrease morbidity rates in either diarrhoea or respiratory infections. Only the study in Bahia, Brazil found a reduction of 6% in the incidence of diarrhoea but no effects in the case of respiratory infections. Large but not as well−designed studies also do not generally support the hypothesis of declines in morbidity rates. The exception is the Nepalese study of West et al. (1991) which, while not finding reductions in overall diarrhoeal disease, reported an 11% decrease in dysentery. The smaller but less well designed studies are more variable in results but also indicate that vitamin A supplementation does not generally reduce morbidity rates. The exceptions are the Chinese study (Cheng et al, 1992) which stands truly alone in reporting consistent and dramatic reductions, in fact far greater than the anticipated 25% decline. The study is small (n = 174) and may not have been double−blind as noted earlier. The Bombay study (Kothari, unpublished) claims some effects but on the basis of a very poor study design and deficient analyses. The Thai study (Bloem et al, 1990) was small (n=166) and was not placebo−controlled. It reports a significant decline but only in respiratory infections and only in one age group and at 4 but not 2 months after dosing with vitamin A. A final exception is Pinnock et al. (1986) study in Australian children which found a 19% reduction in respiratory infections. Though the research design and methods (e.g., daily recording of symptoms by parents) are satisfactory, the analyses included only those children with the best participation rates.

Taking all the studies together, vitamin A supplementation does not appear to reduce morbidity rates. The lack of findings cannot be attributed to poor measurement of morbidity because studies of improvements in water supplies and excreta disposal were able to show declines in morbidity of the order of 22% using similar methods. Thus, the original expectation that vitamin A supplementation might be an important intervention for controlling infection has not been borne out. Other public health measures, such as environmental sanitation and health education, will need to be implemented to decrease the morbidity burden.

Does Vitamin A Supplementation Increase the Risk of Respiratory Infections?

If vitamin A supplementation does not decrease morbidity, one may ask “Is there any evidence that it increases it?” Reviewing the results, there is little or no indication that diarrhoea is increased; the only study reporting a significant finding in total diarrhoea is that in Haiti which also reports increased respiratory infections in the vitamin A treated group. This, but more so the results of the Indonesian study of Dibley et al. (1992) are the basis of concern about respiratory infections. An Australian study (Pinnock et al., 1986) hints at more severe respiratory infections in treated children and a later study, by the same authors suggest *fewer* episodes of respiratory illness but *more* cough in treated children.

Some studies of good to fair quality indicate no effect of vitamin A supplementation on respiratory infections (Arthur et al., 1992; Barreto et al., 1993; Rahmathullah, 1991; Ramakrishnan, 1993; Sinha, 1972) and some suggest reductions in respiratory infections (Bloem et al., 1990; Cheng et al., 1992; Pinnock et al., 1986).

A number of well designed studies in Guatemala and Delhi are being carried out and reports about respiratory infections have yet to appear from Sarlahi, Nepal (West et al., 1991), Jumla, Nepal (Daulaire et al., 1992) and Sudan (Herrera et al., 1992). Once these and other studies are published, the pattern may become clearer. We are aware also of a specific review of the effects of vitamin A supplementation on acute lower respiratory infection, now under way at the London School of Hygiene.

TABLE 4.4 Reported Effects of Vitamin A Supplementation on Incidence and Duration of Diarrhoea and Respiratory Infections in Non−hospitalized Children

Type of Study[a]	*Country and Author*	*Effects on Diarrhoea*	*Effects on Respiratory Infections*
Best Studies	a) Arthur et al. (1992), Ghana	None	None
	b) Barreto et al. (1993)	6% decrease	None
	c) Dibley et al. (1992), Indonesia	None	ALRI increased
	d) Rahmathullah et al. (1991), Tamil Nadu	India	None
Large Studies	a) Abdeljaber et al. (1990), Aceh, Indonesia	None	None
	b) Stansfield et al. (1992), Haiti	11% increase	15% increase
	c) Vijayaraghavan et al. (1990), Hyderabad, India	None	None
	d) West et al. (1991), Sarlahi, Nepal	None overall; 11 % decrease in dysentery	Not reported yet
Smaller Studies	a) Bakshi and Gopaldas (unpublished), Baroda, India	None	Claims reduction
	b) Bloem et al. (1990), Northeastern Thailand	None	60% reduction but only in children 1–2 years old and at 4 months after dosing
	c) Cheng Lie et al. (1993), Hebei, China	60% reduction	70% reduction
	d) Kothari (unpublished), Bombay, India	Claims reduction	Claims reduction
	e) Ndossi (1992), Iringa, Tanzania	None	None
	f) Pinnock et al. (1986), Adelaide, Australia	Not studied	19% reduction
	g) Pinnock et al. (1988), Adelaide, Australia	Not studied	None
	h) Ramakrishnan (1993), Tamil Nadu, India	None	None
	i) Sinha (1972), West Bengal, India	None	None

[a] Type of study: Best studies are those with double–blind and placebo–controlled designs, large sample sizes, and morbidity data collected prospectively at least weekly. Large and small studies are those with sample sizes above or below a thousand, respectively.

At the present time, there does not appear to be consistent evidence for expecting that vitamin A supplementation will increase the risk of respiratory infections, and even less so for expecting effects on severe respiratory infections. The study which most raises concerns is that of Indonesia (Dibley et al., 1992).

Should vitamin A supplementation not be undertaken there, at least? The answer is that improvements in vitamin A nutriture should be sought through direct supplementation or other means since two studies in Indonesia, one using large doses (Sommer et al., 1986) and one food fortification (Muhilal et al., 1988), have shown that mortality declines, as have most other studies elsewhere.

Does Vitamin A Supplementation Reduce the Severity of Infections?

Vitamin A supplementation does reduce childhood mortality in populations were xerophthalmia is observed (see Chapter 5). But, as the review of morbidity studies has suggested, incidence, duration and/or prevalence of respiratory infections and diarrhoea are not reduced by vitamin A supplementation. What then are the mechanisms explaining the mortality findings? The answer would seem to lie in severity. Vitamin A supplementation would be expected to lead to reduced severity and complications as well as reduced diarrhoea! and respiratory disease mortality.

Chapter 5 reviews the limited evidence available about effects of vitamin A supplementation on cause−specific mortality in field studies. Diarrhoea mortality and mortality attributed to measles are reduced but not respiratory disease mortality. The last finding may reflect the fact that respiratory infections are less frequent causes of mortality and consequently, that studies have less power to detect effects on respiratory than on diarrhoeal disease mortality. However, a vitamin A effect can be demonstrated in an even less frequent attributed cause of death in the field trials, measles.

Studies in children hospitalized for measles support strongly the notion that vitamin A supplementation reduces the severity of infections. These studies have shown that vitamin A supplementation reduces severity and complications as well as mortality from measles (Barclay et al., 1987; Coutsoudis et al., 1991; Hussey and Klein, 1990). These results should be weighed heavily because measles is an important cause of mortality in the poorest of countries and because good research designs were used in these investigations.

A study of neonates hospitalized for broncho−pulmonary dysplasia also indicates that vitamin A supplementation decreases complications and the need for medical interventions while hospitalized perhaps by promoting regenerative healing from lung injury (Shenai et al., 1987). On the other hand, there was no benefit to vitamin A supplementation in Bangladeshi children hospitalized for diarrhoea (Henning et al., 1992).

The field study providing the strongest support for a protective effect of vitamin A supplementation on severity is that conducted in Ghana (Arthur et al., 1992). They report evidence of less severe infections, particularly diarrhoeal ones, and reduced rates of clinic attendance and hospitalizations in the vitamin A treated group. The Brazilian study (Barreto et al., 1993) reported that the incidence of severe diarrhoea (but not that of respiratory infections), is decreased by vitamin A treatment. With the exception of the Chinese study (Cheng et al., unpublished) which reported less hospitalization in the vitamin A group and that of the Brazil study (Barreto et al., 1993) which reported no differences, none of the others looked for these effects even when data were available (Rahmathullah et al., 1991; Ramakrishnan, 1993; Vijayaraghavan et al., 1990). Though full accounts from the Indonesian study (Dibley et al., 1992) have not been issued, severity in treated children has not been reported to have been reduced in diarrhoea or respiratory infections, though hospitalizations appear to have been less frequent in treated children.

As noted earlier, a number of studies are still collecting data and many completed studies are only known from very preliminary reports. Not much information about severity, whether measured as signs and symptoms accompanying episodes such as fever, vomiting, mucous, blood, and high stool frequency in the case of diarrhoea or more generally in terms of visits to clinics and hospitalizations, is available. Future reports should assess these aspects carefully. It is also the case that a number of studies used methods which were unlikely to detect effects on severity (e.g., Abdeljaher et al., 1990; Herrera et al., 1992). Thus, future studies should use methods capable of detecting effects on severity, such as used in Ghana (Arthur et al., 1992) and Indonesia (Dibley et al., 1992).

A reasonable interim conclusion is that improvement of vitamin A status should result in less severe infections. These effects may be particularly important in some children, the frail and at greatest risk of dying from infections. Hence, effects on severity may be both hard to detect infield studies designed for much more frequent events, and to have minimal impact on the overall morbidity burden.

Major Conclusions

Vitamin A supplementation has no major effect on incidence or duration of diarrhoeal and respiratory infections.

• The lack of findings on incidence or duration cannot be attributed to poor methods since studies of the effects of improvements in water supplies and excreta disposal were able to detect a reduction of 22% in morbidity rates using similar methods.

• There does not appear to be consistent evidence that vitamin A supplementation increases the risk of diarrhoea! diseases and respiratory infections.

• Vitamin A supplementation appears to reduce the severity of infections: cause−specific mortality for diarrhoea is lower in vitamin A treated groups as are clinical complications and mortality from measles. Though not all studies have assessed severity, studies in Ghana and Brazil but not one in Indonesia, suggest reduced severity. Two of three studies that have examined hospitalization rates have detected decreased rates in treated children. Many studies used methods inappropriate for detecting effects on severity.

• No reports of differential effects by sex have appeared. Consistent, differential effects by age have not been reported.

• The findings are preliminary. Many studies are known from incomplete, unpublished results and some studies are still ongoing.

Research Recommendations

• Future studies should focus on detecting effects on severity using appropriate methods that collect signs and symptoms that can be used to scale the severity of episodes and rates of clinic visits and hospitalizations. The methodology should be competent also to assign consistent and internationally accepted “diagnoses” to infections.

• Studies of children hospitalized for respiratory infections and diarrhoea should be carried out to better detect the potential benefits of vitamin A supplementation.

5. Vitamin A and Young Child Mortality

Introduction: Studies Included

This report deals with the collective experience accrued through studies of vitamin A supplementation involving more than 172,000 children under the age of 6 years, of whom about 3,000 died, in Ghana, Haiti, India, Indonesia, Nepal, and Sudan. It is those children and their families that made this report possible; it is for them that we now attempt to interpret the experience.

When this project began we had access to reports by IVACG and by a meeting of investigators jointly sponsored by WHO and USAID. Together, these background documents provided a very comprehensive listing of projects addressing the effects of vitamin A on morbidity and morality. That background was complemented by the personal knowledge of field studies available through Dr. Barbara Underwood who had been monitoring this field for many years, by computerized literature searches, and by contacts with international and national agencies involved in the funding of vitamin A projects. Recently we were able to add information presented at the 1993 IVACG meeting in Arusha, Tanzania. The listing so obtained included completed studies and studies that were still under way, and included also both published and unpublished work. We think it was a very complete catalogue of studies, and that we have avoided the possible bias associated with review of only published (positive results) studies. From the aggregated list we selected projects that a) included control groups (coincident in time) and b) were specifically designed to examine mortality or morbidity (or both) effects of an intervention with vitamin A. This selection procedure, and particularly the demand for contemporary control groups, eliminated most evaluations of ongoing programmes from consideration and also eliminated uncontrolled studies that were designed to compare alternate approaches to improvement of vitamin A status.

From the above listing, ten controlled studies (including a recently reported extension of one) intended to address the effect of vitamin A supplementation on mortality have been identified. Eight are reviewed in detail. For the HAITI study, we have seen only early draft manuscripts providing too little detail to permit full inclusion in our analyses. For another study (BOMBAY) we lack definite records of the numbers of subjects and events; required further detail may be forthcoming. For several of the studies discussed in this report, supplementary information, not included in published reports, was provided by original investigators. The selected studies included:

1) The one year, village−randomised, non−blinded, non−placebo controlled, community trial examining the effect of six−monthly, large−dose vitamin A prophylaxis on preschool children's xerophthalmia status, morbidity, and mortality carried out in Aceh province, Indonesia by Sommer et al. (1986) [ACEH].

2) The one year, non−randomised, non−blinded, placebo controlled community study examining the effect of vitamin A−fortified monosodium glutamate (estimated average supplementary intake of vitamin A = 500 IU/d (Muhilal et al., undated)) on preschool children's growth, xerophthalmia status, morbidity, and mortality carried out near Bogor, Indonesia by Muhilal et al. (1988) [MSG];

3) The one year, cluster−randomised, double−blind, placebo controlled, community trial examining the effect of weekly, low−dose vitamin A prophylaxis on preschool children's morbidity and mortality carried out in Tamil Nadu, India by Rahmathullah et al. (1990,1991) [TAMIL NADU].

4) The one year, village−randomised, double−blind, placebo controlled, community trial examining the effect of six−monthly, large−dose vitamin A prophylaxis on preschool children's xerophthalmia status, morbidity and mortality carried out around Hyderabad, India by Vijayaraghavan et al. (1990, 1992) [HYDERABAD].

5) The ward−randomised, double−blind, placebo (1000 IU vitamin A) controlled, community trial examining the effect of four−monthly, large−dose vitamin A prophylaxis on preschool children's mortality carried out in Sarlahi, Nepal by West et al. (1991) (stopped at 1 year after a beneficial effect was detected) [SARLAHI]. Also available were the preliminary results of an extension of this study for 11,900 infants under 6 months of age (reported at IVACG, 1993).

6) The small three and one half year, non−randomised, non−blinded, controlled, community trial examining the effect of a single large dose vitamin A prophylaxis on preschool children's morbidity and mortality carried out in two slum areas of Bombay city by Kothari (1991) [BOMBAY].

7) The five month, non−randomised, non−blinded, controlled, community study examining the effect of a single, large−dose vitamin A prophylaxis on preschool children's mortality carried out in Jumla, Nepal by Daulaire et al. (1992) [JUMLA].

8) The eighteen month, household−randomized, blinded, placebo−controlled trial examining the effect of six−monthly, large−dose vitamin A prophylaxis on preschool children's malnutrition, morbidity, and mortality carried out in northern Sudan by Herrera et al. (1992) [SUDAN].

9) The recently completed large two year placebo−controlled cluster−randomized mortality trial undertaken in Ghana. A morbidity trial was undertaken in an adjacent area and is discussed in chapter 4 of this report. Binka et al. (1992); Smith (1992); The Ghana Study Team (Ross et al.) (1993) [GHANA VAST].

10) A 15 month randomized, blinded study conducted in North Haiti as an adjunct to an existing health care service. It involved large dose periodic administration of vitamin A. Children receiving vitamin A from other programs were excluded. Only preliminary manuscripts by Stansfield et al. (1992) were available for review [HAITI].

Analytical Objectives

The first objective was to ask the question, “Is there convincing evidence that vitamin A supplementation affects young child mortality?” This question is asked in a biological rather than programming sense. No distinction is made with reference to how the effect was achieved. Having answered that question and having subjected our answer to a series of sensitivity analyses to ensure the answer was robust, we then asked “Is the effect similar across gender and across age groupings? Is it the same across attributed causes of death?” We then attempted to address the question “Can one predict the situation in which a larger or smaller effect might be expected?” That is, we attempted to explain the observed variation among studies. Finally, drawing on these sets of answers, we attempted to address the planning question “What level of effect might one reasonably expect to see if a vitamin A control programme were mounted in a new setting?” That question is addressed on a theoretical basis, i.e. we ask what is the prediction interval that would be expected to hold for the forecast relative effect to be seen in another population. We do not, in this report, attempt to examine the factors of implementation (e.g. coverage, compliance, etc.) that might impact on observed effectiveness in an actual programme implementation. Clearly such matters must be considered in the development of any policy position.

Treatment of Data: Preparation for Analysis

Following identification of the mortality trials, published papers were examined and for each study we attempted to complete the information depicted in Figure 5.1 (here shown for HYDERABAD as an example). When the data were not available in published reports, original investigators were asked to fill in the boxes in the display. That process was seen as very important. The HYDERABAD project provides a very good example. Examination of the published description (Vijayaraghavan et al., 1990) led us to the same conclusion as had been drawn by Northrup (1991), i.e. that credibility of the study was very low given an apparent loss to follow–up of some 10–11 % of the children randomized into the trial. The authors were invited to provide further detail. It was not until October, 1992 that we received the data displayed in Figure 5.1 indicating that the “lost” children never actually entered the trial. Rather, they were excluded before dosing began; this is consistent with, but not obvious from, the published paper. In analyses we have used supplementary information from original investigators, rather than only original reports, where it provided important clarifications. Dr. Herrera undertook extensive examinations of the SUDAN data to provide us with clarifications of the original draft manuscript we had; a number of these clarifications were incorporated in the final published version of the manuscript (Herrera et al., 1992).

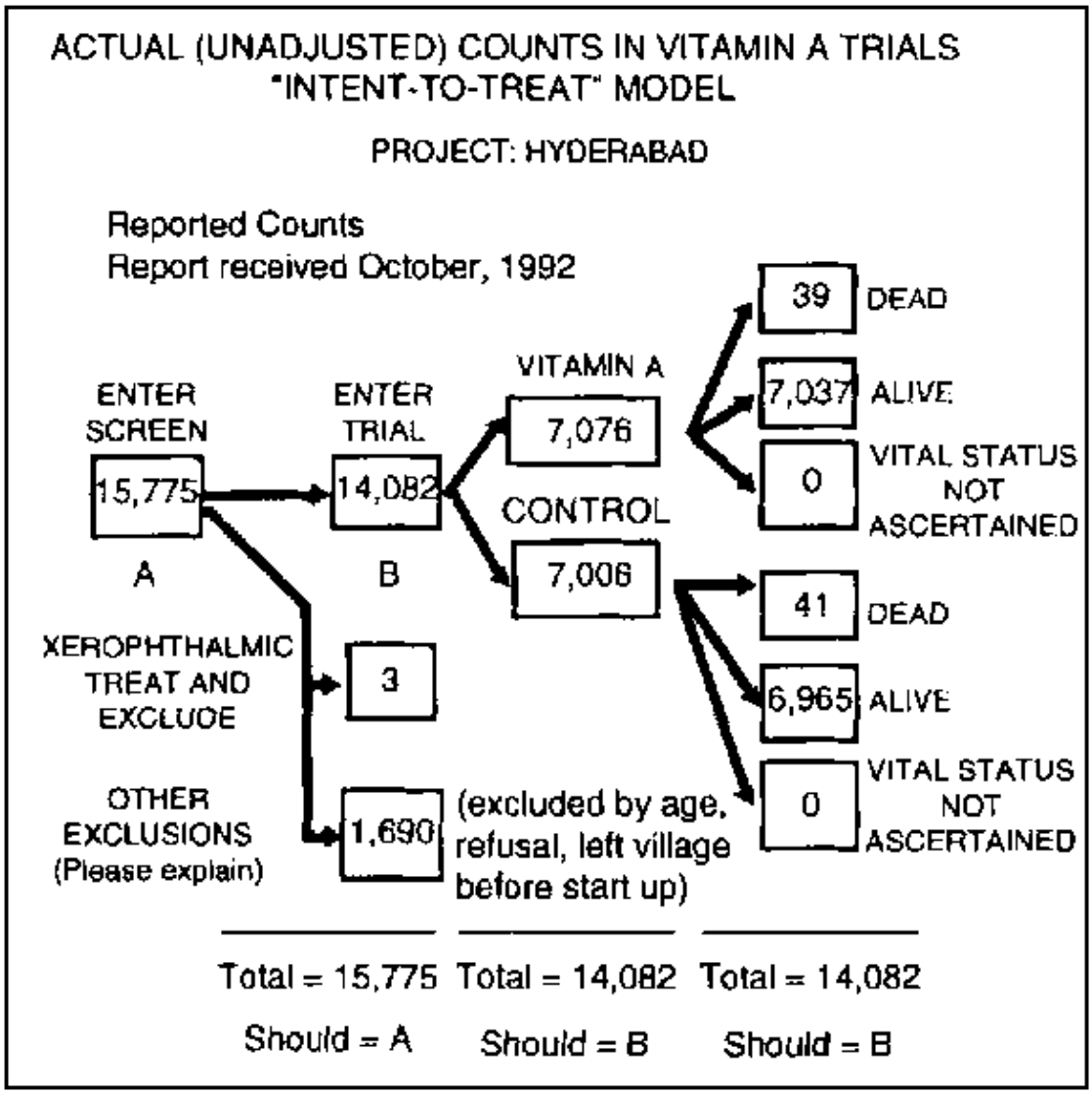

Figure 5.1 Example of Data Collection Format (Hyderabad Study Response)

An interim report on our mortality analyses was distributed to original investigators in March 1991 with an invitation for comment and correction.

In preparing data for analysis, we faced another problem. Most studies provided information on actual counts of children involved. However, because of design features (e.g. study durations of less than or more than one year or a dynamic sample with continuing entry and discharge by age) three studies (SARLAHI, JUMLA and GHANA VAST) reported part or all of the information only in terms of 'child–years' of exposure. Such an expression is very appropriate if one wishes to describe mortality rates which are conventionally expressed as deaths per year. However, for our purpose we were compelled to extract or convert all data to estimated counts of children, disregarding duration of exposure. We recognize that back calculating counts of children from child years of exposure undoubtedly led to some errors. We do not think they were serious errors and we are confident that they did not affect our main conclusions in important ways. It is critical to recognize that the actual count of deaths was always available (except in BOMBAY). There could be no error there. In our analyses, we used only the counts of children known to be alive (an estimate for the studies reporting in child years of exposure) or known to be dead (always known) at the end of the trial. Thus, children whose vital status at the end of the trial was not known were excluded from analysis. However, as suggested above, the proportion lost to follow–up was considered in evaluating the design and implementation of the study and reaching a judgement on the credibility and persuasiveness of the study findings.

Table 5.1 describes the total sizes of groups studied. Actual counts used in all analyses reported in the chapter are presented in the Technical Annex. Within the report, "child years" of exposure are used only in calculating mortality rates for descriptive purposes.

In one study (TAMIL NADU) accidental deaths had been excluded from consideration in the published paper. Using information provided by the investigators, we added these accidental deaths back into the counts for

consistency with other studies. We also obtained unreported information from the author concerning the number of children whose vital status was not ascertained at the end of the study. As far as we can ascertain all of the study data we present relate to total deaths (all causes) except when we specifically examine deaths attributed to particular causes.

Few of the studies intentionally included infants under the age of 6 months. Thus when we examine effects for infants less than one year of age, most are over the age of 6 months. We do reference a recent study of infants 0 to 6 months of age at entry (SARLAHI extension).

An unresolved problem arises in the reporting and analysis of deaths by age groups. Some studies (ACEH, TAMIL NADU, HYDERABAD, SUDAN) grouped the data by age interval at entry while others (SARLAHI, JUMLA, MSG) reported by age at death. This has relatively little impact after about two years of age, but it is an important issue when looking at deaths in the first two years and even more important when considering deaths in the under one year group. We were not able to obtain data expressed on a common basis.

Almost all studies treated any detected case of active xerophthalmia and then excluded them from the trial. At least one (TAMIL NADU) continued to collect data for such subjects and then reported analyses with and without their inclusion. We attempted to exclude such children from the counts used in the present analyses. Since other evidence establishes that mortality rates are higher among children with xerophthalmia, their exclusion from these analyses would imply that total mortality rates are somewhat underestimated. The TAMIL NADU project demonstrated that inclusion or exclusion of the xerophthalmic children did not change the overall RR estimate (note that the detected children were treated regardless of the group to which they had been assigned). The intentional or unintentional (self−selection) exclusion of high risk individuals may have contributed to a lower than expected mortality rate in the study groups.

Some of the general design characteristics of the studies selected for detailed consideration are summarized in Table 5.2.

It is clear that design and implementation vary among the studies. Non−blinded studies (e.g. ACEH and JUMLA) and studies with large proportions of subjects lost from follow−up [vital status not ascertained] (e.g. ACEH with a 12% loss and perhaps GHANA VAST and TAMIL NADU with 8% and 5.5% losses) must be seen as having a degree of uncertainty in interpretation. Further, not all reported studies were designed specifically as experimental trials. For example, the JUMLA study, was an opportunistic evaluation of the first phase of an operational program mounted by a non−governmental organization. The research phase was discontinued and a regular supplementation programme was continued, as soon as there was convincing evidence of effect. We have not attempted to assign ‘quality ratings’ to the studies for application in analyses. Rather, in the analyses reported we have asked whether the findings were similar in a subset of studies judged to have more adequate design features, and in the whole group of studies, a form of sensitivity analysis.

Table 5.1 Size of Population Groups Studied[a]

				Vital Status at End of Study		
Study	*Treatment*	*Number Screened[c]*	*Number Entered[d]*	*Dead*	*Alive*	*Unknown*
Aceh	Vitamin A	29,236	12,991	101	12,890	1,606
	Control		12,209	130	12,079	1,602
MSG	Vitamin A		5,775	186	5,589	n/s
	Control		5,445	250	5,195	n/s
Tamil Nadu	Vitamin A	16,024 (605 excluded)	7,764	42	7,255	467[e]
	Control		7,655	83	7,161	411[e]
Hyderabad	Vitamin A	15775 (1,693 excluded)	7,076	39	7,037	0

	Control		7,006	41	6,965	0
Sarlahi[b]	Vitamin A	Enrolled 96% of eligible	14,487	152	13,766	569[f]
	Control		14,143	210	13,400	533[f]
Extension for infants < 6 months[b]	Vitamin A	Not available	6,086	150	5,936	0
	Control		5,832	130	5,702	0
Bombay	Vitamin A Control	It is not clear whether mortality data are based on small samples (200 per group) or on the mortality experiences of the whole districts (2000 per group). Only rates are reported.				
Jumla[b]	Vitamin A		3,786	138	3,648	"under 1%"
	Control		3,411	167	3,244	
Sudan	Vitamin A	26,615	14,455	123	14,111	109(+112[g])
	Control		14,298	117	13,974	58 (+149[g])
Ghana Vast[b]	Vitamin A	Not available	21,906	397	9,638	8.4%
	Control			495	9,529	
Haiti	Vitamin A Control	From the draft manuscript it appears that approximately 5,500 children were entered into each group. 36 deaths were reported in each group.				

n/s = Not specified in available reports.

[a] See also Annex Tables for age and gender counts. Sources of data are listed at the end of chapter.

[b]Counts of subjects are shown. Either because of short duration of the study (less than one year) or continuing entry of subjects during the study, the original investigators reported data by "child years of exposure." Actual or derived *counts* were used in analyses presented except for estimated mortality rates.

[c]In several studies, some of the children potentially admissible to the study were excluded or the parent refused participation accounting for the difference between the number screened and number entered. In some studies () children with signs of active xerophthalmia were treated and excluded; in other studies they were treated and admitted to the trial. It was not possible to obtain actual counts of children screened for all studies.

[d]Total entered is the sum of live, dead and unknown vital status.

[e]This may require careful interpretation. It appears that almost all of these children were known to be alive within a few weeks of the end of the study even though they could not be located at the time of the final examination or after the study. Hence, it seems very unlikely that there were many if any unreported deaths.

[f]Recorded as withdrawals after study started.

[g]Noted as having developed active xerophthalmia and withdrawn from study. The true Moss to follow up' would be the first numbers presented, 109 and 58.

Because of data selections and manipulations, the results portrayed in the present report for individual studies are not identical with those in published reports. A comparison of the estimated RR and confidence intervals with published values is presented in the Technical Annex. Readers interested in the individual studies are encouraged to consult the published reports.

Analytical Methods

The analyses reported in this review are all based on an intent to treat model. We have not taken compliance into account. We do report crude compliance figures in Table 5.2A.

This section provides an overview of the methods used in this report. The theoretical basis is presented in the Technical Annex of the report. Analyses were implemented under the Categorical Modelling (CATMOD) procedure of SAS version 6.04 for the microcomputer (SAS, 1987). Actual SAS programs used are presented in the Technical Annex as are also the data files.

We have chosen to use relative risk (*RR*) *as the outcome measure for this project. It is defined as the proportion of deaths in the Vitamin A treated group divided by the proportion of deaths in the control group. Thus, an RR of 0.75 means that the mortality risk in the treated group is 75% of the risk in the control group or that the mortality rate has been reduced by 25% compared to that of the control group. The choice to examine* ***relative*** *effectiveness has important implications for interpretation. Because those implications may relate closely to field programming decisions, we include a section in which we compare and illustrate the distinction between looking at* ***relative*** *and* ***absolute*** *effects of vitamin A.*

Table 5.2A Some Features of Design of Studies Examined

Study	*Units of Study*	*Blinded?*	*Study Length*	*Follow– Up Frequency*	*Vitamin A Dosage*	*Dosing Frequency*	*Compliance*	*Loss to Follow* Up*
Aceh	Villages (n = 450) (m = 56)[b]	No	12 months	6–monthly	200,000 IU	6–monthly	78%: 2 doses 15%: 1 dose 7%: 0 dose	11.3%[c] (n = 3,208)
MSG	Subvillages (n = 83) (m=135)	No	11 months	At 11 months	Fortified MSG	Daily ingestion	n/s	n/s
Tamil Nadu	Sub–areas set by population (n = 206) (m = 76)	Yes	12 months	Weekly	8,333 IU	Weekly	88%: each week 42%: 52 doses 87%: 42+ doses	5.7% (n = 878) (see note, Table 5.1)
Hyderabad	Villages (n=84) (m=188)	Yes	12 months	3 –monthly	200,000 IU 6–11 months: 100,000 IU	6–monthly	58%: 2 doses 33%: 1 dose 9%: 0 dose	0%
Sarlahi	Wards (n = 260) (m=109)	Yes	12 months	4–monthly	12+ months: 200,000 IU 6–11 months: 100,000 IU	4–monthly	93%: each visit 74%: 3 doses 2%: no dose	3.8% (n = 1,102)
Bombay	Urban slums (n = 2)	No	42 months	6–monthly	200,000 IU	6–monthly	89% coverage of population compliance	n/s

							n/s	
Jumla	Subdistricts (n=16) (m = 450)	No	5 months	At 5 months	12+ months: 200,000 IU 6–11 months: 100,000 IU <6 months: 50,000 IU	At baseline	88%: Dosed	< 1%
Sudan	Households (n= 17,031)	Yes	18 months	6–monthly	200,000 IU	6–monthly	87%: 3 doses 5%: 2 doses 8%: 1 dose	0.6% (n = 167)
Ghana Vast	Groups of compounds (n=185) (m=114)	Yes	24 months (variable)	4–monthly	12+ months: 200,000 IU 6–11 months: 100,000 IU	4–monthly	89.5% average coverage for each round	8.4%
Haiti	Households (n = 7)	Yes	15 months	4–monthly	12+ months: 200,000 IU 6–11 months: 100,000 IU	4–monthly	n/s	n/s

n/s = Not specified in information available.
[a] 200,000 IU is equivalent to 60 mg of Retinol.
[b]Mean cluster size (rounded).
[c]Refers to proportion of individuals.

Table 5.2B Some Features of Design of Studies Examined

Study	*Active Xerophthalmia at Baseline*	*Effect on Xerophthalmia?*	*Baseline Anthropometry*	*Control Group Mortality Rate (/1, 000 child–year)*
Aceh	2.1%	Yes: 1.2% in control vs. 0.3% in programme villages	Height forage < 85% of median: <1.5% Weight for height < 80% of median: 3.4%	10.6
MSG	1.2% in program group and 0.8% in control (Bitot's Spots)	Yes: to 0.2% in program group; no change in control	52.5% stunted; 4.5% wasted,[a] 45.9	
Tamil Nadu	11.0%	Yes: approximately 50% reduction in	72% undernourished; 31% stunted; 23%	11.5

		treated vs. controls (count of cases detected and treated)	wasted; and 18% stunted and wasted	
Hyderabad	6.0%	Yes: 1.3% in treatment vs. 2.9% in control areas	19.5% stunted; 29.7% wasted; 17.7% both	5.9
Sarlahi	3.0%	n/s	Arm circumference < 11.5 cm: 3.6%	16.4
Bombay	4.7%	Yes: to 0.5% in experimental group; no change in control	n/s	Infants (<1): 60.2 1–5 year olds: 18.9
Jumla	13.2%	Not addressed	Arm circumference < 12.5 cm: 26%	126.2
Sudan	2.85% xerophthalmia	Modest: de novo incidence of xerophthalmia – 0.013% in treated; 0.015% in control de novo appearance of night blindness reduced by 50% compared to control group	Stunted: 37%; wasted: 6%; stunted and wasted: 6%; normal: 58%	5.3 (estimated)
Ghana Vast	0.7%	Not published	46.4% stunted; 17.5% wasted	30.0
	14% serum retinal < 0.35?M/L			
Haiti	0.4%	n/s	Weight < – 2 SD: 60%	5.4 (uncertain)

n/s = Not specified in available reports.
[a] Criteria not clear.

For a single study with subjects individually randomized to treatment and control groups, the calculation of RR is straightforward. Construction of a confidence interval for estimates of the *true* RR involves consideration of the group sizes, mortality rates and the design effect of cluster sampling discussed below. Because we have chosen to examine a ratio, the RR, it is necessary to work with logarithmic transformations (distributions are skewed). For presentation, the computed values are transformed back to the original, and much more familiar, linear scales where the upper and lower limits are unequally spaced from the RR point estimate (see Figure 5.2 for example).

Because we are combining results from many different studies, complications arise. Only two of the studies (SUDAN and HAITI) reported the use of the household as the unit of randomization. The others used villages or some other clustering unit. For example, in the ACEH study, 229 villages received supplementation and 221 villages served as controls. This influences the apparent variation and confidence intervals because individuals within a group or cluster can be expected to be more similar to one another than would be true for independent individuals. The 'effective group size' is reduced by the clustered randomization design and this must be taken into account in the analyses.

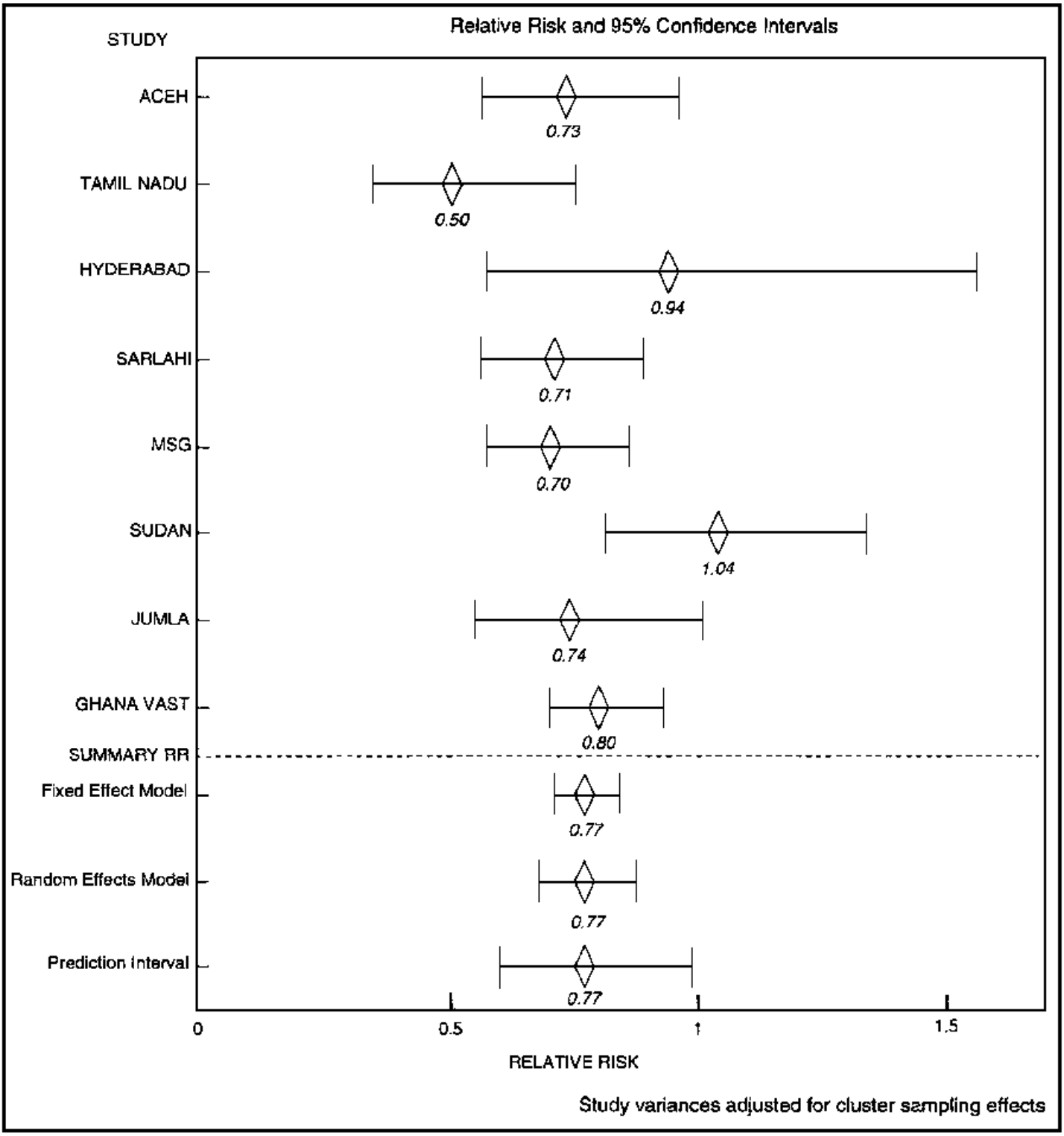

Figure 5.2 Study–Specific and Summary RR and 95% CI

Note: Shown are Fixed Effect (single true RR) and Random Effects (RR varies among studies) models. Prediction interval is for a new study or programme (see text).

The effects of clustering can be expressed in terms of a *design effect* (DEFF) (Cochran, 1977). This is a ratio of the variance that would be appropriate if randomization were done at the level of individuals rather than clusters over the variance as calculated directly from the counts presented ('observed' variance). The TAMIL NADU and SARLAHI studies reported design effects (1.3 and 1.23) and the ACEH, GHANA VAST and JUMLA studies reported confidence intervals that took this complication into account. We used information from these five studies to estimate design effects for all eight studies. Note (Table 5.3) that the design effects are all greater than or equal to one and have the effect of increasing the width of the confidence intervals relative to an analysis that would ignore these effects. The SUDAN and HAITI studies randomized treatment

at the level of the individual household. Here the DEFF would be very close to 1.0, the value we assign to SUDAN.

We have used these estimated design effects to produce *confidence intervals* that incorporate our best assessment, given the information available, of the true variability of individual study results. The method is described in a recent paper (Rao and Scott, 1992) and was independently developed by the authors of this report while working on this project. In operation, the group sizes are divided by the DEFF thereby reducing effective size and increasing the C.I.

As noted in the presentation of results, in case the answers were driven by the procedure of DEFF estimation, we also tested other variance adjustment procedures, and other weighting factors in a form of sensitivity testing.

Table 5.3 Estimated Design Effects (DEFF)

Study	*DEFF*
Aceh	1.11
Ghana	1.22
Hyderabad	1.34
Jumla	1.92
MSG	1.25
Sarlahi	1.22
Sudan	1.00
Tamil Nadu	1.14

Note: All DEFF estimates are derived indirectly rather than computed directly from cluster level data.

The CATMOD procedure (SAS Institute, 1987) was used to generate the RR estimates and the associated confidence intervals. We also used this procedure to model the logarithm of the mortality rate as a linear function of factors of interest. As appropriate to the question posed, these models included treatment group (vitamin A or control), study, age and gender. For the overall analyses (including only treatment group), this corresponds exactly to the traditional approach to this type of problem based on the Mantel–Haenszel method (Rothman, 1986; L'Abbé et al., 1987). For models involving age and gender, this approach allows us to test the null hypothesis that the effect of vitamin A does not depend on age or gender. In CATMOD, results are presented in the traditional form of an ANOVA (analysis of variance) table, but the test statistics are all based on chi–square distributions. Note that these results are not the same as those that would be obtained using logistic regressions (models for log odds or log of the rate divided by 1 minus the rate).

A major focus of this project is to combine results from several studies to produce *summary estimates with associated confidence intervals.* The basic idea is simple. The summary values are a weighted average of the individual study results (in log form). From a statistical point of view, it can be proved that the optimal weights are inverse functions of the variances of each log RR being combined. Unless noted otherwise, the results presented use these weights. Note that the weights are very dependent on the study characteristics and the estimated DEFF. We have compared the results produced by various weighting methods including equal weights for each study. The main conclusions are very consistent. In the next section of this report, we give the summary RR values and confidence intervals for several weighting schemes. By explicitly presenting the weights used in the summaries, we demonstrate that the major conclusions of this report do not depend on the choice of weights. Note that the Mantel–Haenszel summary of RR (with the design effect adjustments) is simply a special case of our approach.

In calculating variances, we ignore variability due to uncertainty in the weights. The effects on the conclusions are judged to be very small relative to other approximations that are used in these analyses.

Although it has been proposed that 'quality' factors can be incorporated into meta–analyses of the type we are performing, it has proven very difficult to actually implement such an approach (Detsky et al., 1992). We

adopted a different strategy. To study the robustness of the results with respect to specific characteristics that may be present in individual studies, we performed several analyses. Summary RR estimates computed after leaving−out one(study) at a time, excluding extreme values of RR, and including only high confidence studies, are presented.

We have attempted to relate study results (expressed as RR or logarithm of RR) to the reported prevalence of xerophthalmia and wasting. For these regressions we have used weights based on the variance of the relative risk (or log RR) for each study.

A major question for users of this report is *"What can we expect if we treat large numbers of children with vitamin A supplements?"* We have tried to address this question in the following way. Variability in what we expect is based on three components (of variance):

- variance due to the imprecision of our knowledge at the present time i.e. the variance of our estimated log RR;

- variance expressing study to study variability that we can estimate from the eight studies that we have available; and

- the within study, or sampling, variability of the proposed program. That is related to the number of children involved, the collective baseline mortality rate and the expected effect of treatment.

Our answer to the planner's question is expressed with *prediction intervals.* As with confidence intervals for relative risk, the prediction interval is constructed in the log scale and the results are transformed back to the linear RR scale. The centre of the interval (in log scale) is the estimate of log RR. The 95% boundaries are given by 1.96 times a standard error term, which is the square root of the sum of variances corresponding to the three components given above. The first two components are estimated from the data in the eight studies we analyzed. The last is calculated for particular study characteristics. We have done those calculations for each of the studies included in our primary analyses. In addition we can calculate the interval for a range of values of this variance. A value of zero corresponds to a situation where a very large number of children are treated or a study in which mortality rates were very high. In Figure 5.7, presented in the last section of this chapter, the prediction intervals are plotted as a function of this variance with a range from zero to a value a little larger than the largest value that we calculated for the studies we analyzed. We have also plotted the RR estimates from the eight studies we have examined. Note that the limits for the confidence interval as computed in the usual Mantel−Haensztel meta−analysis are based only on the first of the above components of variance.

The meaning of a summary estimate of relative risk and the interpretation of the prediction intervals relate to the models underlying the analyses. Under one model (*a 'fixed effects model'*)*, there is a universal common value of RR that we are trying to estimate. In a second model* (*a 'random effects model'*)*, the RR is assumed to vary from study to study and we are trying to estimate the average of these RR's. The homogeneity test of the Mantel−Haenszel approach, expressed as the study* treatment effect in the CATMOD ANOVA tables, is a statistical test that compares these two models. A significant chi−square value rejects the first model in favour of the second.* (*In some of our analyses, we found a statistically significant effect of this kind.*) *We prefer the second model on the grounds that it more accurately reflects reality. Even with much larger numbers of children we would not expect to see exactly the same RR in all such studies. It is not a question of which study or studies are wrong. Real study to study variation is reasonable and we have estimated this component of variation for inclusion in our prediction interval.*

"Does Vitamin A Supplementation Affect Mortality?"

Table 5.4 presents a summary of the estimated relative effects of vitamin A supplementation for the 8 individual projects and also a summary estimate for all projects. The p−value for the test of no effect (RR=1.0) is shown. It is clear that while 2 of the 8 projects failed to demonstrate an effect of vitamin A, as shown by the inclusion of an RR= 1.0 in the confidence interval, the overall experience suggests that vitamin A exerts a highly significant protective effect. That is, a summary RR = 0.77 means that vitamin A supplementation, on average, was associated with a 23% reduction in mortality.

Table 5.4 Estimated Relative Effects of Vitamin A Supplementation: Total Studies[a] (Variance Adjusted for Cluster Design Effects)

		95% *C.I.*			
Study	*RR*	*Lower*	*Upper*	Z	*Prob H_0: RR=1*
Aceh	0.73	0.56	0.96	–2.26	0.024
Ghana	0.80	0.70	0.93	–3.02	0.003
Hyderabad	0.94	0.57	1.56	–0.23	0.817
Jumla	0.74	0.55	1.01	–1.89	0.058
MSG	0.70	0.57	0.86	–3.34	0.001
Sarlahi	0.71	0.56	0.89	–2.96	0.003
Sudan	1.04	0.81	1.34	0.31	0.756
Tamil Nadu	0.50	0.34	0.75	–3.42	0.001
Summary (All Studies)					
Fixed Effect Model	0.77	0.71	0.84	–6.09	1.12×10^{-9}
Random Effect Model	0.77	0.68	0.88	–4.01	3.09×10^{-5}
	Test of homogeneity: p = 0.088				

[a] Details of counts were not available for the Bombay and Haiti projects. The authors reported effects as follows: Bombay RR = 0.19; Haiti RR = 1.0.

The same data are displayed in Figure 5.2. Although a statistical test failed to reject homogeneity of the results across studies (Table 5.4), the display makes it readily apparent that indeed the projects appear to exhibit somewhat different relative effects of vitamin A. This should not be surprising given that neither the study designs nor the study populations were standardized. In later sections, we examine possible sources of this variation. In the present section we review evidence that the conclusion drawn above is robust.

For the Summary RR shown in Figure 5.2, 95% confidence intervals computed on the basis of both the pooled within study variance alone and also with added variance contributed by between study variation, are shown. Statistically these might be described as “fixed effect” and “random effect” models. The estimates correspond to the two models described in the section on Analytical Methods. Computed either way, the effect remains highly significant (*p < 0.001*). The figure also includes a portrayal of the prediction interval discussed later in this chapter.

As a first test of our summary estimate, the analyses presented in Table 5.4 and Figure 5.2 were repeated without application of the derived DEFF estimates. That is, the cluster effect was ignored. In this analysis, the summary RR was 0.77 (C.I. 0.71 to 0.83) and the vitamin A effect was highly significant (*p < 0.001*). With the smaller variances assigned to individual projects, there was marginal evidence of heterogeneity among projects (*p = 0.050*). The analyses were rerun again assuming a DEFF of 1.3 for all projects except SUDAN. The value of 1.3 was taken from the authors of the TAMIL NADU study (Rahmathullah et al., 1990) who suggested that this might be an appropriate adjustment for cluster effect. In this analysis, the summary RR was 0.78 (C.I. 0.71 to 0.85) and the vitamin A effect remained highly significant (*p < 0.001*) without evidence of heterogeneity (*p = 0.099*). It may be concluded that the apparent effectiveness was not attributable to our estimation of the DEFF applicable to individual studies.

As noted in the methods section, the summary RR = weighted average of the logs of study RRs, converted back to the linear scale. To be certain of the operations within the CATMOD procedure, we tested the effect of generating weighted averages, using different weighting factors (see Program B in Technical Annex). The results are displayed in Table 5.5. These alternatives included a simple averaging (all weights = 1), weighting on the basis of unadjusted variances, variances adjusted for study–specific design effects and variances adjusted using DEFF = 1.3 (the general adjustment suggested in the Tamil Nadu study) except for SUDAN where DEFF was left at 1.0. The table displays the derived weights for each study and the summary statistics that resulted from the particular strategy. As shown, the summary RR estimates ranged from 0.76 for the

simple average to 0.78 for the averages weighted by all the various variance estimates. The estimated C.I. ranges differed slightly with the technique of averaging. All summary RR estimates were significantly different from 1.0 and were essentially similar to the output of the CATMOD programme (see above). This was reassuring since it can be argued that, given heterogeneity, simple averages are preferable to weighted averages; we found it makes little difference for our series. The DEFF adjustments are needed for other purposes; we retain them for this purpose as well.

Table 5.5 Derivation of Weighted Average, Summary RR Estimates

	*Basis of Weighting**			
Study	*Simple Average*	*Adjusted Variance*	*Actual Variance by DEFF*	*Variance Adjusted by 1.3*
	Relative weight assigned to each study			
Aceh	1.0	0.68	0.76	0.66
Ghana	1.0	2.73	2.78	2.66
Hyderabad	1.0	0.24	0.22	0.23
Jumla	1.0	0.93	0.60	0.91
MSG	1.0	1.31	1.31	1.28
Sarlahi	1.0	1.06	1.08	1.03
Sudan	1.0	0.72	0.89	0.91
Tamil Nadu	1.0	0.33	0.36	0.32
	Summary RR Estimates			
RR	0.766	0.770	0.772	0.78
95% C.I.[b]	0.68–0.84	0.71–0.83	0.71–0.84	0.71–0.85

[a] Weighting factors applied to log RR for each study and the weighted mean converted back to original scale.

[b]Fixed effect model shown.

Table 5.6 Sensitivity Testing: Effect of Omitting Single Studies (One at a Time)

		95% *C.I.*				
Study Omitted	*RR*	*Lower*	*Upper*	Z	*Prob H_0: RR=1*	*Chi Square Test of Homogeneity*
None	0.77	0.71	0.84	–6.09	< 0.001	0.088
Aceh	0.78	0.71	0.85	–5.52	< 0.001	0.051
Ghana	0.75	0.68	0.83	–5.33	< 0.001	0.064
Hyderabad	0.77	0.71	0.84	–5.99	< 0.001	0.058
Jumla	0.78	0.71	0.85	–5.65	< 0.001	0.048
MSG	0.79	0.72	0.87	–5.03	< 0.001	0.069
Sarlahi	0.79	0.72	0.86	–5.23	< 0.001	0.061
Sudan	0.75	0.68	0.82	–6.42	< 0.001	0.333
Tamil Nadu	0.79	0.73	0.86	–5.34	< 0.001	0.245

Note: Variances were adjusted by DEFF.

It may be concluded that the main finding, that vitamin A has an effect on mortality, is not driven by the particular technique of generating the summary RR estimate.

Having satisfied ourselves on the methodologic questions, we then asked whether the effect seen was driven by a particular study. This was examined by a simple procedure of rerunning the analyses with omission of single studies. If one study were unduly influential it would be expected that omission of that study would have noticeable impact on the summary RR estimate. The results of these analyses are shown in Table 5.6. While the effect of deleting individual studies on both the RR and the C.I. (and on the test of homogeneity) can be seen in the table it is also apparent that the Summary RR estimates do not vary over a wide range and in every instance, clear statistical significance is seen.

It may be concluded from this that no single study drives the conclusion of a protective effect of vitamin A supplementation on childhood mortality to an unwarranted degree.

We then examined the impact of excluding the outlying studies (HYDERABAD, SUDAN, TAMIL NADU) in varying combinations. Table 5.7 shows the impact of omitting two or three at a time. The table illustrates that deletion of outliers has some impact on the Summary RR estimate and associated C.I. but the effect is relatively modest. *It is not the outliers that drive the conclusion.*

Finally, we considered the design attributes of the eight studies. As noted, designs were not the same across projects. From a purely design and implementation standpoint, some projects may seem more credible than others. Application of the DEFF takes into account the effective reduction of study size because of clustering designs. The weighting procedure used in the estimation of the Summary RR then takes account of effective size of the studies but not other elements of design and implementation. If studies that were not blinded, and studies with a large proportion of subjects with unknown vital status are excluded, one is left with four (HYDERABAD, SARLAHI, SUDAN and TAMIL NADU) or five (previous + GHANA) studies in which one could have higher confidence. HYDERABAD might have been omitted from these selections on grounds that non–specific effects influences by the intervention team seriously compromised the design (see later discussion) but we chose to include it here. Analyses were run with these two groups of studies. With the four study group, the RR estimate was 0.79 (C.I. 0.68 to 0.92, $p < 0.001$). When GHANA was added to the group, the Summary RR changed to 0.80 (C.I. 0.72 to 0.88, $p < 0.001$). In each case, the vitamin A was highly protective and the effect was statistically significant. With only the small series of studies, heterogeneity among studies was evident (test of homogeneity, $p = 0.012$ for the four studies and 0.026 for the five).

Table 5.7 Sensitivity Testing: Effect of Omitting Outlying Studies (Groups of Studies)

		95% *C.I.*				
Studies Omitted	*RR*	*Lower*	*Upper*	Z	*Prob H_0:RR=1*	*Chi Square Test of Homogeneity*
None	0.77	0.71	0.84	–6.09	< 0.001	0.088
Sudan, Hyderabad	0.74	0.68	0.81	–6.48	< 0.001	0.302
Sudan, Tamil Nadu	0.76	0.70	0.84	–5.80	< 0.001	0.735
Sudan, Hyderabad, Tamil Nadu	0.76	0.69	0.83	–5.84	< 0.001	0.720

Note: Variances adjusted by DEFF.

Table 5.8 Impact of Gender on Effect of Vitamin A Supplementation (Data from Aceh, Hyderabad, Jumla, Sarlahi, Sudan and Tamil Nadu projects)

		95% *C.I.*			
Gender	*RR*	*Lower*	*Upper*	*Z*	*Prob H_0: RR = 1*
Female	0.76	0.64	0.90	–3.242	0.001
Male	0.79	0.67	0.95	–2.588	0.010

		Test of effect of gender on vitamin A effectiveness: p = 0.728 *Test of homogeneity: p = 0.031*

Note: Variance adjusted by DEFF.

While the specific estimate of the summary RR can be manipulated by selection of particular studies, the main conclusion, that vitamin A ***does*** *reduce young child mortality in developing country situations, at least as represented in these field trials, is very robust.*

Impact of Age and Gender

Individual field trials have limited power to examine the effects of age and gender on the effectiveness of vitamin A supplementation. However, through the meta–analysis approach to pooling, considerable power can be attained. Six trials (ACEH, HYDERABAD, JUMLA, SARLAHI, SUDAN, and TAMIL NADU) provided data (published or unpublished) by gender. These same trials provided data by age groups, except that the Hyderabad trial excluded infants under one year. It should be noted that the counts in the age and sex analyses do not coincide with each other or those in the total study analyses for two reasons: first, if age or gender was unknown, the child was excluded from the present analyses; second the present age analyses exclude children over 5 years while some are included in the total study and gender analyses. The discrepancies are relatively small. Table 5.8 presents the summary RR estimates by gender. Statistical testing confirmed that gender did not affect the relative effectiveness of vitamin A administration (*p = 0.728*). That is, the relative effect of vitamin A supplementation in reducing childhood mortality is virtually the same in girls and boys. GHANA VAST reported a somewhat greater effect in boys than in girls but the difference was not significant; counts were not reported. Further details of the gender and age analyses are included in the Technical Annex.

Table 5.9 presents the Summary RR estimates by age intervals. Although the youngest interval is described as under one year, there were few infants under 6 months in most studies (see below). As for gender, age group had no significant effect on the apparent effectiveness of vitamin A (*p = 0.863*). That is, the effect of vitamin A in reducing childhood mortality is virtually the same in different age groups from less that one year through five years of age. The GHANA VAST trial reported no age tends in the effect of vitamin A on total mortality. Since counts were not reported, that trial is not included in Table 5.9.

Table 5.9 Impact of Age on Relative Effectiveness of Vitamin A Supplementation (Data from Aceh, Hyderabad, Jumla, Sarlahi, Sudan, Tamil Nadu Studies)

		95% *C.I.*			
Age Group (*months*)	*RR*	*Lower*	*Upper*	Z	*Prob H_0: RR = 1*
0–11	0.76	0.60	0.96	–2.34	0.019
12–23	0.82	0.67	1.01	–1.86	0.063
24–35	0.77	0.57	1.04	–1.71	0.086
36–47	0.87	0.58	1.30	–0.68	0.497
48–59	0.59	0.36	0.97	–2.08	0.037
		Test of effect of age on relative effectiveness of vitamin A: p = 0.863 *Test of homogeneity: p* = 0.066			

Note: Variance adjusted by DEFF.

In the above analysis, age was treated as a categorical variable. The analyses were also run with age as a linear continuous variable. Again, no significant difference attributable to age was seen but the model did not fit well. It is not presented. The age analyses are complicated, particularly for very young infants, due to the fact that some projects reported age at entry while others reported age at death. We could not adjust data to standardize the classification.

In the original studies, very limited data were available for infants under the age of six months (JUMLA study – 233 child years or about 550 infants; TAMIL NADU – 425 infants; SUDAN study – 11 infants). These infants are included in the under one year group analyzed in Table 5.9. An analysis of this under 6 month group suggested a summary RR = 0.77 (C.I. 0.38 to 1.*54, p = 0.459*), identical with the overall estimate for older infants and children; it was not significantly different from 1. Not only was this analysis limited by the very small sample size, but more important, as noted above, we could not be sure whether studies were reporting age at dosing or age at death. It follows that interpretation is very difficult. Recently (March, 1993), West presented the results of a study of dosing infants under six months of age in Nepal (West et al., 1993). The dose used was 50,000 IU under 1 month and 100,000 IU after 1 month; the dosing interval was 4 months; controls received 250 or 500 IU vitamin A. Dosing was stopped at 6 months and the mortality outcome was followed through 10 months of age. No effect of vitamin A supplementation in this very young age group was detected in this large group (RR = 1.07, 95% C.I. = 0.83 to 1.52). Note that this new study was not included in our main analyses – only the original SARLAHI data were included.

No firm conclusions can be drawn about the effectiveness of vitamin A in infants under 6 months of age but it appears that the effect, if any, is much smaller than in older children, except, ***perhaps*** *in areas where maternal vitamin A depletion is extreme and breast milk vitamin A levels are very low* (*no evidence presented*).

A WHO committee is considering not only the level of benefit to be expected in the under 6 month age group but also the possible risk of detrimental effects. That report should be available shortly.

From the foregoing analyses it is appropriate to conclude that neither gender nor age (*at least after 6 months*) *have important impact upon the relative effectiveness of vitamin A supplementation. That is, vitamin A is equally effective in males and females and in infants and preschool children.*

Cause–specific Mortality

The review of the biology of vitamin A (Chapter 3) reported that, in animal models, the effect of vitamin A on morbidity and mortality differed between infective agents. The review of morbidity studies in humans (Chapter 4) also suggested that there *might* be cause–specific effects. There is obvious interest in examining this in terms of mortality effects in young children even though the data available are limited. Only 5 studies, GHANA VAST, JUMLA, SARLAHI, SUDAN and TAMIL NADU, have provided cause–specific mortality data (SUDAN had no deaths attributed to measles). While other attributed causes of death were reported in individual studies, only diarrhoea, respiratory disease and measles were defined in common across studies. Analyses for these three causes, and for 'other causes', are presented in Table 5.10.

The analyses suggest that the dominant effect of vitamin A is likely to be on mortality attributed to diarrhoeal disease. Conversely there may be little or no effect on respiratory disease. In keeping with studies reviewed in Chapter 4, an effect on mortality attributed to measles is suggested even though the number of cases is very small. These analyses must be seen as tentative. The total sample sizes are small. If and when additional studies report cause–specific mortality results, the picture could change.

Table 5.10 Cause–Specific Mortality Effects of Vitamin A Supplementation (Data from GHANA VAST, JUMLA, SARLAHI, SUDAN and TAMIL NADU projects)

		95% C.I.		*Z*	*Prob H_0: RR = 1*
Cause	*RR*	*Lower*	*Upper*		
All Causes	0.78	0.71	0.87	–4.763	0.000
Diarrhoea"	0.68	0.57	0.80	–4.462	0.000
Respiratory	0.99	0.73	1.34	–0.080	0.936
Measles[b]	0.74	0.53	1.04	–1.734	0.083
Other Causes	0.95	0.81	1.06	–0.680	0.497

[a] For Ghana, diarrhoea includes 'acute gastroenteritis' + 'chronic diarrhoea and malnutrition'; relative risks were almost identical for the two classes.

[b]Measles not reported for Sudan.

Note: Variance adjusted by DEFF.

Further, since it was not possible to probe the coding rules of the individual studies, it is not clear how primary and associated causes of death were distinguished. There is undoubtedly some 'blurring' in the data analyzed; we emphasize that our analyses are based on *attributed* cause of mortality.

The GHANA VAST study extended the findings in Table 5.10 by reporting the absence of an effect of vitamin A on mortality attributed to malaria – the attributed cause of 23.1% of deaths in that setting. When the Ghana data were recomputed omitting malaria deaths, the RR changed from 0.80 to 0.78. This shift had very little impact on the pooled point estimate for all studies (0.762 omitting malaria; 0.770 including malaria deaths).

Pending the publication of further data, it is reasonable to conclude that in humans, as in animals, the nature of the pathogen impacts on the effectiveness of vitamin A and that in the community, the clearest identified mortality effects are in the presence of diarrhoeal disease and measles. We note (*see later discussion of other meta analyses*) *that in studies of interventions in children hospitalized after measles, there was a significant reduction in mortality attributed to pneumonia but this could not be seen in the field studies, perhaps because there were too few deaths secondary to measles to impact on total respiratory disease mortality.*

When and Where is Vitamin A Likely to be More Effective?

The question is phrased and treated as a 'population' question. That is, interest is directed toward identification of population groups, not individuals, likely to be responsive to vitamin A. It has been noted already that there are many differences in the precise design and implementation of the studies reviewed. There are also differences among them in the baseline conditions of the populations. Only some of the potentially important population differences were captured by descriptive variables reported in common by the projects. In this section, we attempt to address some potential explanations of variation among the studies. Again we emphasize that in these analyses, we are comparing groups, not analysing individuals within groups. It follows that the *n* for the present analyses is only 8. Since the studies were not planned with this type of analysis in mind, there is another very serious limitation. The range for many of the potentially interesting variables is too limited to expect to detect subtle relationships even if they exist. With this constraint in mind we proceed to address some potential descriptive variables that a health planner might wish to use in deciding when and where vitamin A is likely to have a greater effect.

Demographic Profile

When expressed on a relative scale, age (over 6 months) and gender make no difference in the estimated relative effect of vitamin A. That is, as we have shown above, vitamin A is equally effective in all age groups between 6 months and five years and in girls and boys. It follows that demographic profile does not explain the differences in RR among projects.

Mortality Profile

Two aspects of pre–existing mortality profiles might influence the expected effectiveness of vitamin A. One has been examined above – the pattern of disease present. A greater effect would be expected where mortality attributable to diarrhoeal disease is more prevalent than where respiratory disease is the dominant cause of mortality. Similarly the presence of non–responsive malarial mortality in GHANA VAST undoubtedly explains a part of the lower RR reported for that project. The second consideration might be overall mortality rates. Figure 5.3 portrays the relative effectiveness of vitamin A supplementation in relation to control group mortality rates (a poor proxy for baseline mortality rate). No particular relationship is apparent and none could be detected in statistical analyses involving a variety of models in which individual projects were weighted (see Technical Annex).

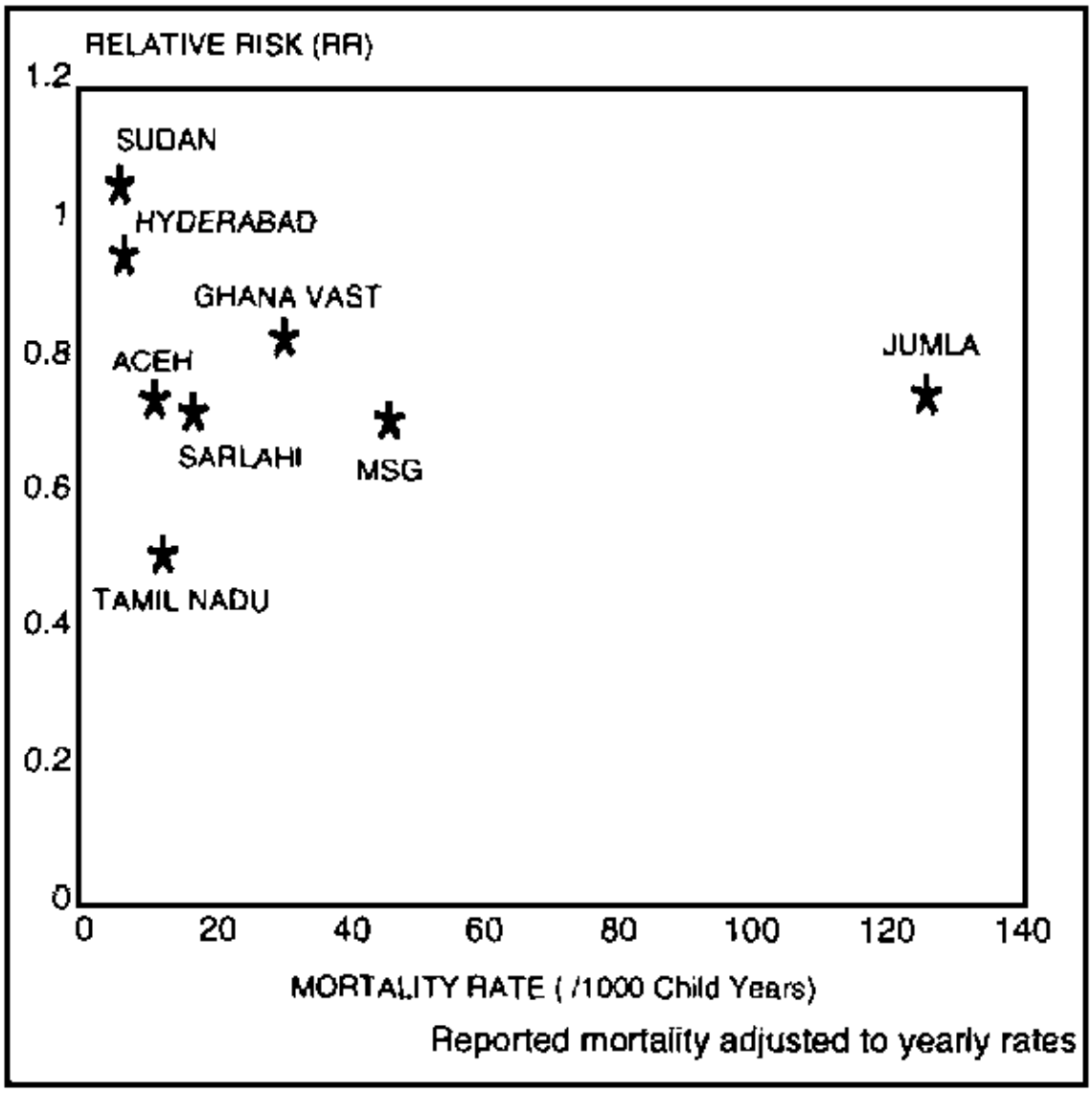

Figure 5.3 RR in Relation to Total Mortality Rate

Note: Mortality rates were those reported for control group in most cases. No relationship is seen.

There is a serious constraint on analyses of this type. We used mortality rates calculated from the control group counts. However, in most of the studies, observed mortality rates were lower, often much lower, than had been expected from pre−existing population−based information. It has been suggested that this may reflect a non−specific beneficial effect of interventions on mortality (Gopalan, personal communication). While such a nonspecific effect should not bias RR estimates in a blinded randomized trial, it does mean that the absolute mortality *rates* used in analyses are not the rates that a planner would customarily see. Given that studies can account for most of the children entering, we do not attribute the low rates to under−reporting of mortality. We do not know then whether we face over−reporting in the usual population statistics available to planners and others, a deviation between local mortality rates and national regional rates, an effect of intentional or unintentional exclusion of high risk children, an impact of treating the high risk xerophthalmic children in both groups (this would be expected to lower overall mortality rates though not necessarily bias the estimate of RR, as shown in the TAMIL NADU study where data were reported with an without exclusions), or a true *nonspecific* effect of intervention. Since we do not have a control for a non−specific effect phenomenon it is not possible to test the hypothesis that there is a nonspecific effect of intervention operating in these studies. It is of interest that the two studies with the highest reported mortality rates, JUMLA and MSG are also studies in which there was minimal additional intrusion into the communities. In the case of JUMLA, a basic health programme involving two−weekly visits to the household was already in place. The vitamin A supplementation trial added minimal additional involvement and was consistent for both control and treatment groups. The primary investigators of the HYDERABAD study have suggested that the frequent visits of conscientious health workers (on average 8 visits) may have motivated both experimental and control families to seek health care for illnesses that would otherwise have been fatal (Vijayaraghavan et al., 1992; Reddy,

personal communication). Indeed, in that project, the non–vitamin A effects of the intervention may have been so great that they overwhelmed any effect of vitamin A (addressed the same mortality sources?) thereby seriously compromising the study design. Certainly the observed mortality rates were extremely low.

Baseline Anthropometry

All of the population groups exhibited roughly comparable rates of stunting (Table 5.2.B), presumably reflecting early growth failure associated with general social and biological deprivation (Beaton et al., 1991). There is insufficient variability among populations to ask, in a meaningful way, whether this condition predicts effectiveness of vitamin A. An analysis was run and is described in the Technical Annex (Program G).

Conversely, there is a range in the reported prevalence of wasting (low weight for length). In the absence of true base–line data, we use the prevalence reported for the control groups. The estimated prevalence of wasting in the various projects was shown in Table 5.2B. In two cases (SARLAHI and JUMLA) wasting prevalence was not reported. In these cases we have assumed estimates from another study in the same country, reported at a WHO meeting of investigators (WHO, 1990). The prevalence assumed was 21.2%.

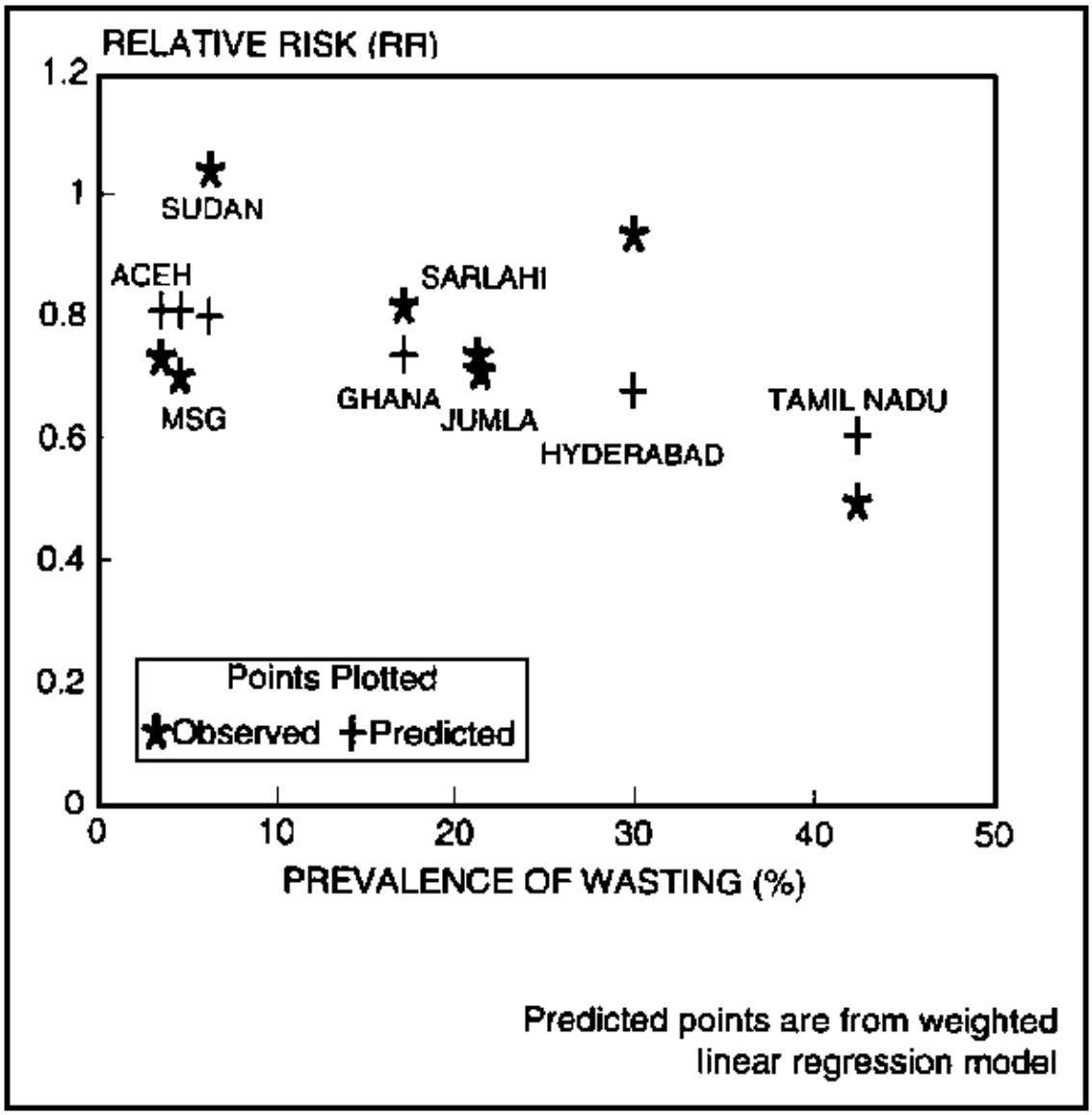

Figure 5.4 RR and Prevalence of Wasting (Low Weight for Length)

Note: Predicted points from one of the weighted regression models (not significant) are shown.

Using these data and the estimated relative effectiveness of vitamin A, Figure 5.4 was plotted to display the

data. Regression analyses were run with linear, log−linear and log−log models and included also models with both wasting and xerophthalmia prevalence and their interaction (see Technical Annex for models and results). None of the models tested detected a statistically significant relationship between the RR and the prevalence of wasting.

We must conclude that the prevalence of wasting is not a very useful indicator of situations in which vitamin A is expected to be more beneficial.

Prevalence of Xerophthalmia

The prevalence of xerophthalmia is commonly used as an indicator of both the magnitude and severity of the vitamin A deficiency problem in populations. It is logical to ask whether this indicator predicts relative response to vitamin A administration. In doing so, it is to be recognized that none of the studies were undertaken in populations without evidence of some clinical vitamin A deficiency.

Table 5.2B presents the available estimates of the prevalence of classified signs of xerophthalmia in the control group or in the whole study population at baseline. Figure 5.5 portrays the relationship of prevalence of xerophthalmia and the RR. As for wasting, a series of regression models were used to test for a relationship. No significant relationship was found with any of the tested models (see Technical Annex).

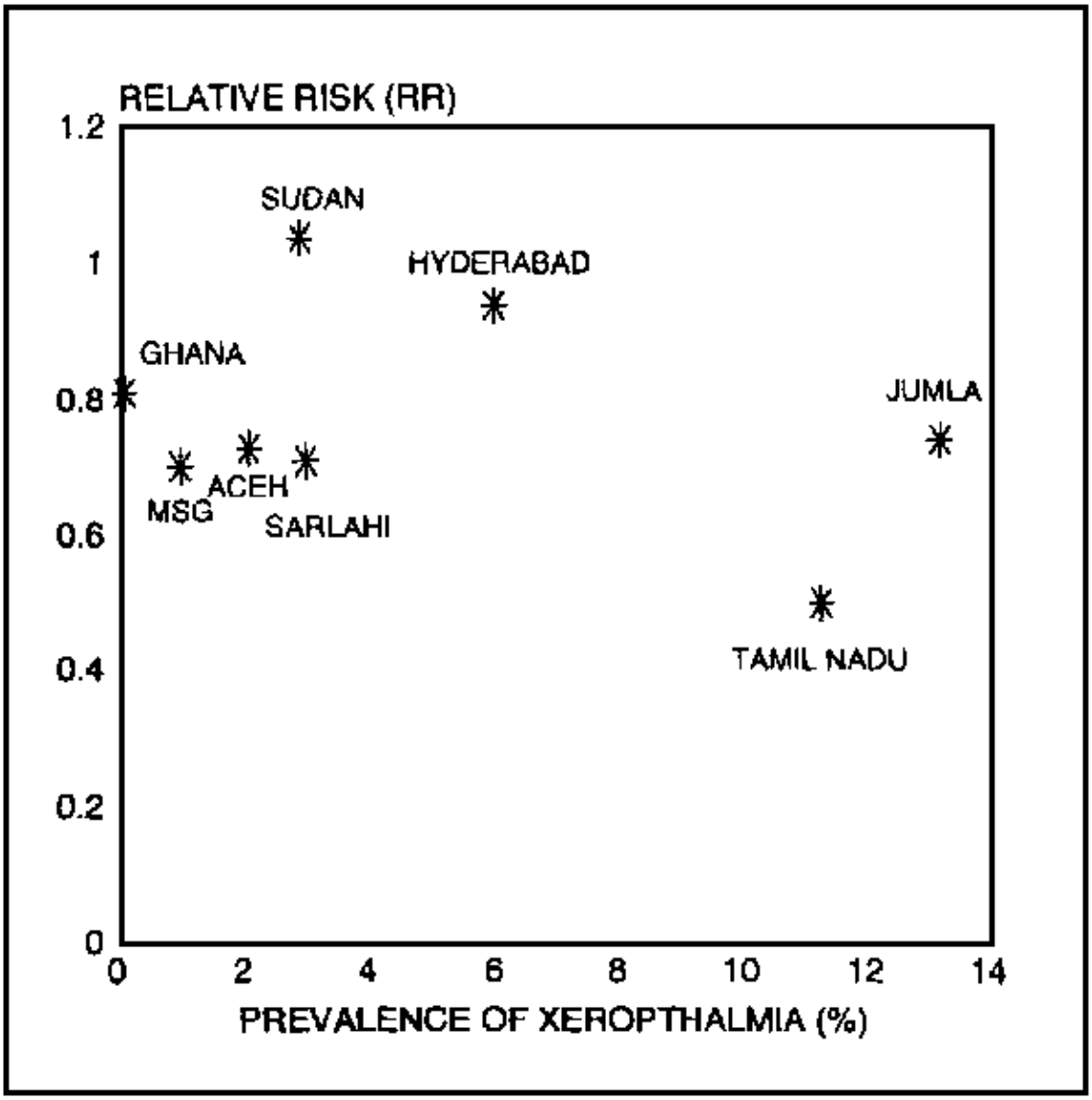

Figure 5.5 RR and Prevalence of Xerophthalmia

Note: No relationship could be established.

We conclude from this very limited data set that while the presence of xerophthalmia in a population is a useful indicator of vitamin A deficiency and potential responsiveness, the prevalence estimate adds little information useful for the selection of situations in which the response is likely to be greater or smaller. We note the very important caveat that we were unable to address a critically important question, "In the presence of biochemical evidence of vitamin A depletion, without evidence of actual xerophthalmia in the population, is vitamin A supplementation likely to have an effect on mortality?" None of the studies available for inspection fell into this category although the GHANA VAST study approached it.

Periodicity and Magnitude of Dosing

All studies provide evidence that the vitamin A preparations retained potency during the trials. This was not an explanation of variation among studies.

One important observation can be made with confidence. The effect of vitamin A on young child mortality is not a "pharmacologic" effect dependent upon the very high potency dose. Two studies (MSG and TAMIL NADU) involved low doses given daily (as fortified MSG) and weekly respectively. Vitamin A appeared to be highly effective in these studies.

An attempt was made to examine the association (if any) of periodicity and magnitude of the vitamin A dose with its apparent effectiveness (ignoring compliance). Dosages were adjusted under the age of one year. For comparative purposes, the doses used in older infants and young children are displayed in Table 5.11; see Table 5.2A for dosages used in infants under one year of age).

The SUDAN study exhibited a remarkably small effect of vitamin A dosing on the occurrence of clinical signs of deficiency other than night blindness (see Table 5.2B). Internal analysis of the SUDAN data (Hen−era et al., 1992) did not suggest that this was a function of compliance. The other "no−effect" study, HYDERABAD, showed an apparent reduction of signs of vitamin A deficiency in the treated group. However there was also an unexplained reduction in the control group (not supposed to be receiving vitamin A supplements from any source; but see previous comment on reported high level of non−specific intervention effect [Vijayaraghavan, personal communication, 1992]). In both of these studies, the effective utilization of the distributed vitamin A *may* be questioned. Perhaps more important for the present analysis is that, apparently for different reasons, these field studies did not generate the expected difference in vitamin A status between the treatment and control groups. This may have contributed importantly to the failure to detect an effect of vitamin A on mortality in these two studies. [No information is available with regard to the response of clinical signs to vitamin A supplementation in the 'negative' HAITI study, where xerophthalmia prevalence was reported to be very low at baseline.] Until and unless we can *predict* the situation of the Sudan and Hyderabad studies, we feel it is unjustified to omit them from our analyses and summary estimates.

Table 5.11 Relationship Between Dosing Schedule and Effect of Vitamin A

Project	***RR***	**95% *C.I.***
Dose = 200,000 IU at 6 month intervals		
Sudan	1.04	0.87 to 1.34
Hyderabad	0.94	0.61 to 1.46
Aceh	0.73	0.56 to 0.95
Bombay	0.19	0.09 to 0.41 (est)
Dose at baseline, follow for 6 months		
Jumla	0.74	0.60 to 0.87
Dose = 200,000 IU at 4 month intervals		
Sarlahi	0.70	0.57 to 0.87

Ghana Vast	0.83	0.73 to 0.94
Haiti (?)	1.00	0.63 to 1.59 (est)
Daily or weekly administration		
MSG	0.70	0.58 to 0.85
Tamil Nadu	0.50	0.35 to 0.72

In contrast, most of the other studies offered evidence that the vitamin supplementation effected expected changes in the prevalence/incidence of xerophthalmia. In addition, reasonable precautions seem to have been taken to ensure that dosing was not mixed up (i.e. that controls and treated regimes were not accidentally mixed). Herrera et al. (1992) suggested that the limited effect of vitamin A might have been a function of inadequate levels of dosing or too long an interval between doses (i.e. the net intake and utilization was below that needed in the SUDAN situation). There was no direct evidence for or against this hypothesis. Other studies with similar dosing regimens exhibit apparent effectiveness. In the five studies that administered this dosing schedule, 3 had positive effects and two (SUDAN and HYDERABAD) failed to see an effect on mortality and only a marginal effect, compared to controls, on signs of vitamin A deficiency. When studies are categorized by dosing regimen (Table 5.11), there is no readily apparent relationship between dosing schedule and relative response.

In an earlier communication it was suggested that, in the SUDAN setting, some other factor, perhaps inadequacy of zinc or other micronutrient intake, impaired the utilization of vitamin A (Herrera, personal communication). In the published paper it was suggested that high morbidity rates, affecting vitamin A utilization and need, might be an important factor (Herrera et al., 1992).

Earlier studies, conducted in connection with blindness control programs, had suggested that in the populations tested (most in Indonesia and India), 200,000 IU at 6 month intervals was apparently adequate to prevent xerophthalmia although it may not be adequate to maintain serum retinol levels or perhaps vitamin A tissue levels (West and Sommer, 1987). A recent study suggests that utilization of high potency doses may be conditioned by existing vitamin a status (Humphrey et al., 1993)

With the exception of the two studies discussed above, there is no grossly apparent association between dose x frequency and the RR of vitamin A supplementation (see Table 5.11).

Given the SUDAN experience, and perhaps also the HYDERABAD experience, there is an important message.

It is at least possible that the commonly used dosing schedule is marginally adequate for the purpose of reducing mortality, or that other unidentified factors interfere with the utilization of vitamin A. We have no basis for predicting situations in which this is more likely to be a problem.

Prediction of Effectiveness in a New Situation

On the basis of the detailed examination of 8 studies, we can say *with reasonable confidence* that if vitamin A supplementation of children under five years were under– taken in a similar population setting (poverty, evidence of general deprivation marked by stunting, evidence of the existence of xerophthalmia, high mortality rates typical of most developing countries), there is likely to be an effect on mortality. However, we have been unable to identify predictors of relative effectiveness other than differences in the profile of cause–specific mortality. We have to conclude that there were real, albeit not identified, sources of variation in response between the populations. The studies we examined themselves showed a range of effect ranging from no detected effect to a 50% reduction of mortality. Thus, it is appropriate to question what we mean by offering *reasonable confidence* that an effect would be seen in a future programme.

We have attempted to quantify this assurance by a statistical technique. In Table 5.4 and Figure 5.2 we presented confidence bounds associated with our estimate of the relative effect of vitamin A. Those bounds were the uncertainty of our estimate of the RR. One of these reflected only the sampling errors of the individual studies (the fixed effect model). The other (random effect model) recognized that there was also a variation among studies and included that effect in the confidence limits presented in Figure 5.2. We reproduce those limits, this time as the innermost band in Figure 5.6. Now, when we come to a new study, we

have to accept that its true RR could fall anywhere within the between study variation already estimated for the 8 studies. Thus, to generate a prediction interval for the true RR of a future program, we have to add the between study variance to the uncertainty variance of our existing estimate. Together, these give the interval bounds portrayed by the second set of bands in Figure 5.6.

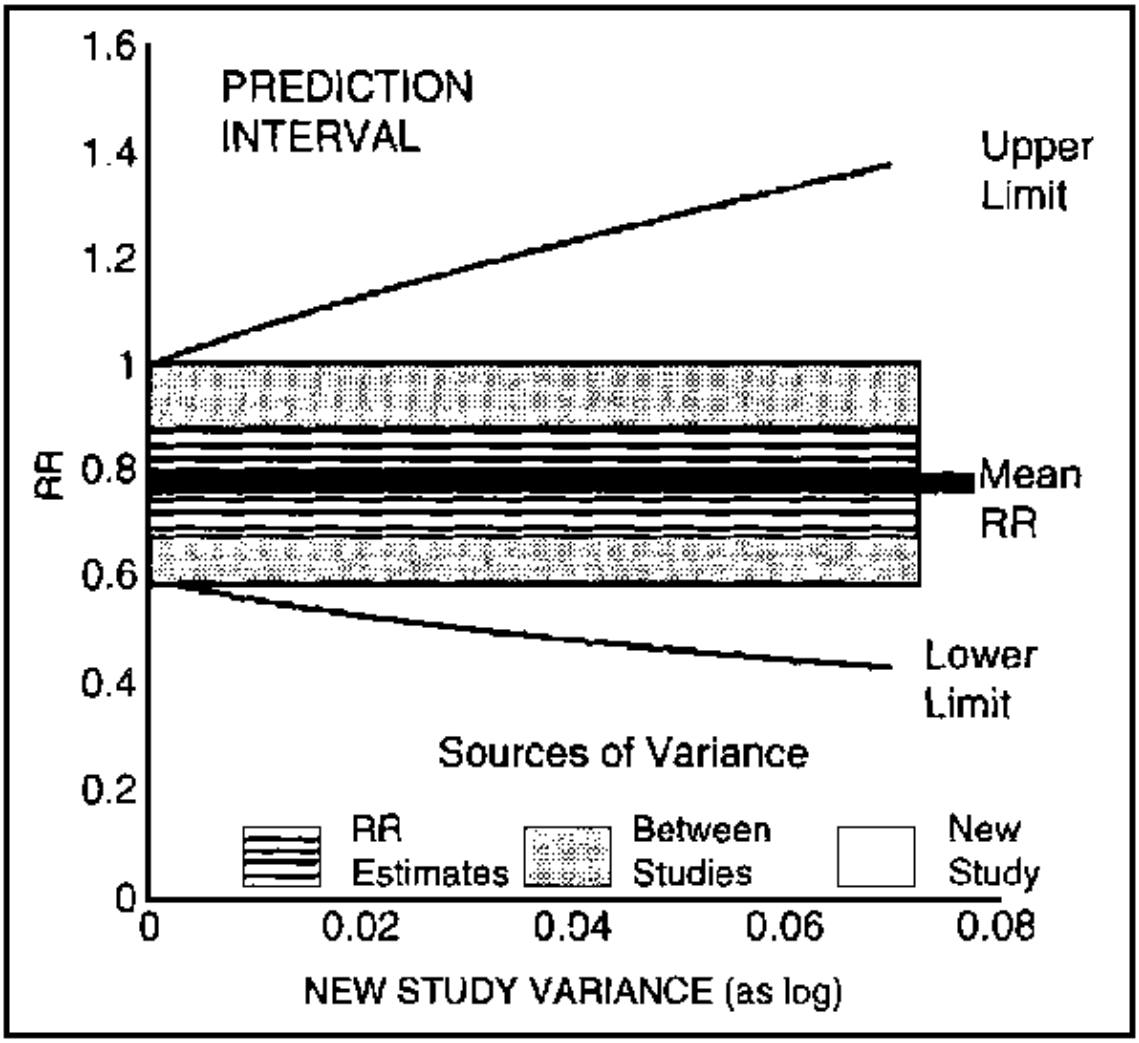

Figure 5.6 Portrayal of Prediction Interval

Note: Shown also are the components of variance included in the interval.

However, as was shown in the opening parts of this chapter, in any given field program, we have a confidence interval around the study's estimate of RR. That interval reflects the 'sampling error'. It suggests that the true RR of the studied population would fall within the C.I. *95%* of the time. If we accepted the principle of sampling error then, we must accept it also for a future study. Given sampling error of the new study (now we designate it 'NV') the prediction interval for the *observed RR* must be greater than for the true RR. Figure 5.6 portrays this concept graphically. Since the NV depends upon study size, baseline mortality rate and expected effect of vitamin A [average RR] as well as any cluster sampling effect, it will depend upon the particulars of the new study or program. The Prediction Interval for *observed* effect changes with the value of NV (Figure 5.6). The interval for the *true* effect is independent of design of the future study; it derives solely from past experience. For a very large population or for populations with very high baseline mortality rates, the value of NV will approach 0 and the two prediction intervals will be almost identical. Conversely with a small study or one having a very low mortality rate, the value of NV will be higher. We have plotted Figure 5.6 with NV ranging from 0 to 0.07 since that range captures the NVs that would hold for all of our individual studies. We replot the same intervals in Figure 5.7 but this time plot also the points for the observed RR is plotted in relation to the calculated NV for each study. Now it can be seen that there is a scatter of values. Most fall in the core band (the interval for the true RR but SUDAN and TAMIL NADU fall outside that range but within our prediction interval for observed RR. This illustrates the phenomenon. We expect with considerable certainty that there will be an effect of vitamin A; we expect that the observed effect will be about 23% reduction but we recognize the unlikely eventuality that it could have an RR as high as 1 (no effect) or as low as 0.5 (50% reduction).

Table 5.12 Components of Variance for Prediction Interval Sensitivity to Omission of Studies

		Variance Component (*as log*)	
Studies Omitted	*Estimated RR*	*Attached to the RR Estimate*	*Between Study*
None	0.77	0.00425	0.0124
Aceh	0.78	0.00596	0.0172
Ghana	0.75	0.00634	0.0202
Hyderabad	0.77	0.00492	0.0147
Jumla	0.78	0.00579	0.0170
MSG	0.79	0.00618	0.0164
Sarlahi	0.78	0.00613	0.0168
Sudan	0.75	0.00260	0.0023
Tamil Nadu	0.79	0.00290	0.0046
Sudan and Tamil Nadu	0.76	0.00050	–0.0065

Note: Lines marking variance components are shown. Also plotted are the 8 studies used in derivation of the interval.

Recognizing that the Prediction Limits depend upon the assessed experience. We have conducted sensitivity analyses to see if the variance components that enter into the PI are unduly influenced by individual studies. As in an earlier sensitivity analysis, this has been done by the technique of omitting individual studies and computing the variance components. The results are shown in Table 5.12. It is clear that, as implied in Figure 5.7 and as implied also by the earlier sensitivity analyses, SUDAN and TAMIL NADU are the two important outlying projects. When both are omitted (Table 5.12), the between study variance component disappears. That is where the heterogeneity is particularly manifest. As discussed earlier we have found no basis for prediction of these ‘unexpected’ outcomes and no basis for rejecting them from the analyses. We must, therefore, accept these two studies as part of our experience and they must be allowed to contribute to the estimate of between study variance and the prediction interval.

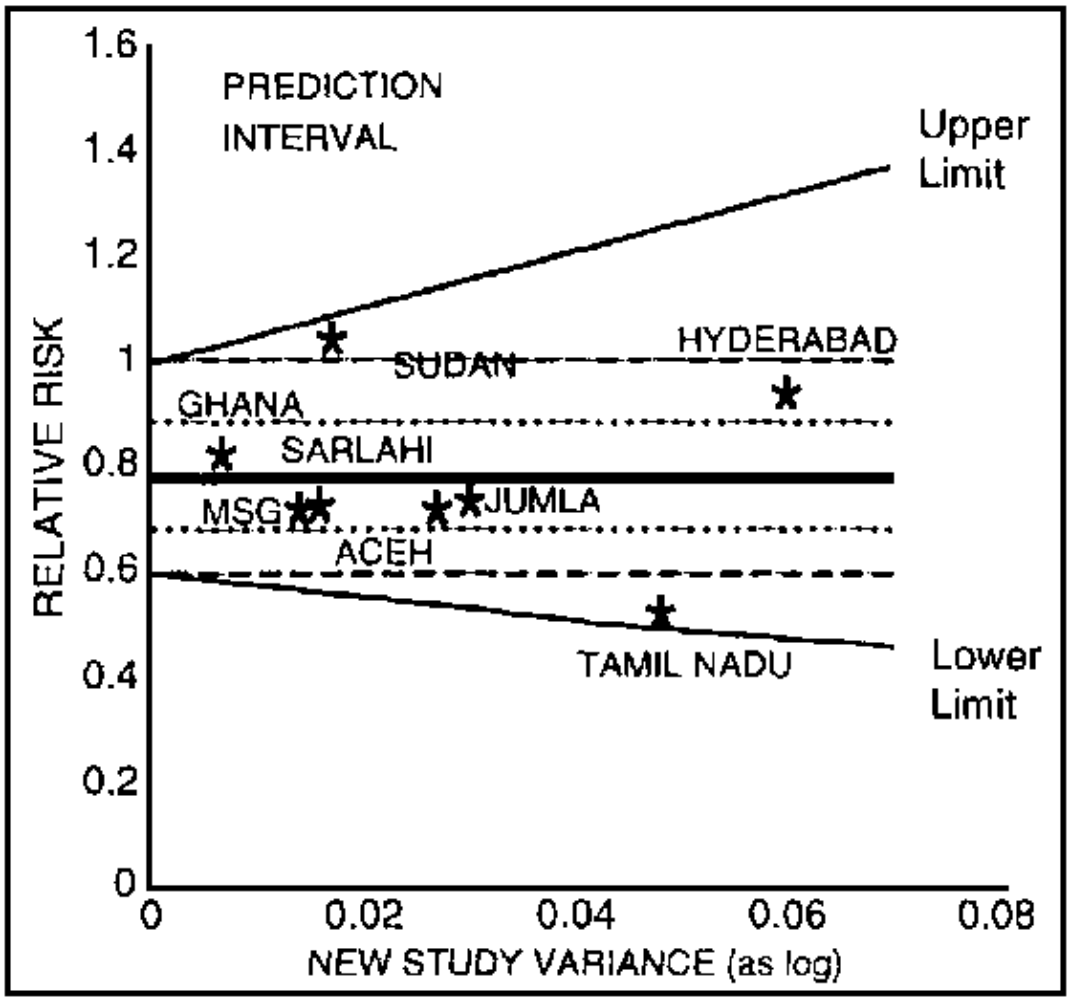

Figure 5.7 Portrayal of Prediction Interval

The interval portrayed in the figures appears very wide. In fact it is not unreasonable for planning purposes. If someone were to undertake a vitamin A supplementation programme in a setting (population size, mortality rate) that resembled that of the MSG trial, we would expect that there would be an approximately 23% reduction in young child mortality (RR=0.77) but we also recognize that there is about 1 chance in 20 that no effect would be *seen.* If the population size and mortality rate resembled that of the HYDERABAD study, then the expected effect would still be a 23% reduction but now we would have to accept also a one in five chance that there would be no *detected* effect. This interpretation comes directly from the plotted figures and represents a calculation of the probability of there being no *observed* effect (RR > 1). These probabilities can be generated by the SAS programme included in the Technical Annex. At the same time the prediction intervals can also be interpreted to mean that there is a 50% chance that the effect *seen* will be greater than 23%, but very little chance that it will be as great as was seen in the TAMIL NADU study (a 50% reduction). Please see chapter 6 for further discussion of this topic.

Beyond this, and until someone identifies population predictors of relative effectiveness, we can go no further. In our judgement, our confidence in the assertion that vitamin A supplementation is effective and is likely to have an effect in a new population having the same general characteristics as the study populations, is at least as great, if not greater than the confidence that might be attached to many other public health programs.

Relative and Absolute Effects: Implications of the Difference

In the analytical methods section of this chapter it was emphasized that a decision had been taken to conduct all analyses with *relative* effectiveness (RR) as the outcome. That was a correct decision for the analyses planned and led us to a position that, in effect, says that the RR is similar no matter how one selects the population group except with regard to the cause−specific mortality profile. There were no predictors of relative effect.

However, the reader may miss the realization that if one considers the absolute effect of vitamin A, mortality rate is the major predictor of effect. Consider for example two populations, one with a mortality rate of 25/1000 children and one with a rate of 100/1000. Our analyses suggest that in each group the RR would be about 0.77. Thus we expect a 23% reduction in each group but 23% of 25 means 6 lives saved per 1000 treated whereas 23% of 100 would mean 23 lives saved – an approximately four–fold difference in the absolute effect of vitamin A. this example may be generalized as:

Lives saved/1000 treated = (*1* – RR)
x mortality rate/1000.

Seen this way, one should immediately recognize that predictors of mortality rate also become predictors of absolute vitamin A effect. Consider another example portrayed in Table 5.13, the age effect.

Since mortality rates typically fall with increasing age, one would expect that the lives saved per 1000 treated would also fall with age. Using the age–specific control group mortality rates observed in the present studies (median estimate used as an example), the calculations in Table 5.13 can be made. One might find comparable differences across other groupings such as gender. (For additional estimates see output of programme K in Technical Annex.)

Table 5.13 Impact of Age and Mortality Rate on Vitamin A Effect Expressed as Lives Saved per 1000 Children Covered

Age months	*Mortality Rate/1000*[a]	*Lives Saved/1000 Covered*
6–11 (some < 6)	27.8	6.2
12–23	25.0	5.8
24–35	12.0	2.8
36–47	4.8	1.1
48–59	4.1	0.9

[a]Median rate for projects reporting ages.

The planner is likely to be more interested in the absolute rather than relative effects. It is important, therefore that the distinction in interpretation be understood.

Comparison of Present Results with Other Meta–Analyses

When the present study was initiated, no other meta–analyses had been reported although we were soon apprised by Dr. Herrera that an analysis was being conducted by his colleagues. To date three other meta–analyses have been published (Table 5.14). In this section we briefly compare results obtained and examine some likely explanations for the relatively small reported differences.

It is important to recognize that all of the reported analyses come to the same general conclusion – Vitamin A supplementation is effective in lowering young child mortality.

This should not be surprising since all analyses were based on selections from the same set often studies. What does differ among reports is the actual estimate of the Summary RR and the breadth of the confidence intervals assigned to the estimates. Table 5.14 presents a summation of the results of the analyses of community trials.

The first meta–analysis to be reported was presented at a meeting in Bellagio in the spring of 1992. That analysis, based on a fixed effect model, included the six then–published field trials (ACEH, MSG, TAMIL NADU, HYDERABAD, SARLAHI and JUMLA); SUDAN and GHANA VAST were not available at the time. The analysis was subsequently modified to exclude infants under 6 months and has recently appeared in print (Tonascia, 1993).

In February 1993, a few months after completion of our study, two more meta–analyses appeared in the literature (Glasziou and Mackerras, 1993; Fawzi et al, 1993). In each case, the projects selected for inclusion

differed and the analysis strategies themselves differed. Glasziou and Mackerras included 5 of the ten mortality trials: ACEH, TAMIL NADU, HYDERABAD, SARLAHI and JUMLA. The BOMBAY, MSG and SUDAN trials were omitted because of perceived design problems. In the analysis by Fawzi et al., again design quality was used in selecting studies for inclusion; actually they presented 3 analyses with sequential omission of weakest studies. The community study analyses were based upon SARLAHI, SUDAN, TAMIL NADU, ACEH, HYDERABAD, JUMLA, MSG and BOMBAY (presented in order of assigned design quality score). They presented both fixed and random effect models.

Table 5.14 Comparison of Published Meta–analyses

Authors	*Studies Included Relative to Present*	*Summary*		
	Analysis[a]	*Model*[b]	*RR*	95% *C.I.*
Tonascia(1992)	–Sudan, –Ghana	Fixed effect	0.70	0.64 to 0.78
Tonascia(1993)	Excluding infants under 6 months		0.64	Not published
Present analyses	Reference	Fixed effect adjusted[c]	0.77	0.71 to 0.84
		Random effect adjusted[c]	0.77	0.68 to 0.88
		Prediction adjusted[c]	0.77	0.60 to 0.99
Glasziou and Mackerras (1993)	–MSG, –Sudan, –Ghana	Fixed effect unadjusted[c]	0.70	0.62 to 0.79
Fawzi et al. (1993)	–Ghana, + Bombay	Fixed effect	0.72	0.66 to 0.79
		Random effect unadjusted[c]	0.70	0.58 to 0.85
		Adjusted[c]	0.70	0.56 to 0.95
London School of Hygiene and Tropical Medicine		Results not yet available		

[a] All analyses drew from the same set of 10 field trials but not all included in the same trials. This column shows inclusions relative to the 8 trials included in the present report.

[b]Refers to the analytical model used.

[c] 'Adjusted' refers to the adjustment of variance estimates for clustering design.

Both Glasziou and Mackerras (1993) and Fawzi et al. (1993) presented meta–analyses of hospital–based measles studies. Glasziou and Mackerras (1993) also examined the effect of vitamin A in very low birth weight infants in an industrialized country setting.

None of the other meta–analyses attempted to offer a prediction model for a future study or programme as was done in the present report.

It is clear, as was illustrated earlier in our own analyses, that the point estimate can be altered by selection of studies (see Table 5.6). That is the explanation of differences in RR seen in Table 5.14. The breadth of the confidence intervals is driven by two variations among the reported analyses – how individual analysts chose to deal with the cluster effect in adjusting, or not adjusting, variance, and whether the analysis model assumed a fixed effect (single true relative effect of vitamin A) or a random effect (true relative effect varying from study to study) model. We feel confident that our estimates are valid as a summation of world experience to date and as such represent a conservative estimate of the effect to be expected in a future programme.

It is important to note other areas of accord among the reported meta–analyses. Both Glasziou and Mackerras (1993) and Fawzi et al. (1993), attempted analyses by attributed cause of mortality as did we.

Each showed a highly significant effect for deaths attributed to diarrhoeal disease and no effect for deaths attributed to respiratory disease in the community studies. This is in keeping with our findings.

Even more interesting, both Glasziou and Mackerras (1993) and Fawzi et al. (1993) examined the measles intervention trials in relation to attributed cause of death. They both reported that in these post−measles cases, deaths attributed to respiratory infection (pneumonia) were significantly reduced (both analyses); deaths attributed to diarrhoea (a much smaller number) were not significantly affected although the point estimate suggested reduction (Glasziou and Mackerras, 1993). The effect on pneumonia is in sharp contrast to the reports from the examination of community studies. This *might* reflect differences in classification of attribution or it could imply real differences in the effect of vitamin A depending upon the nature of the actual pathogenic insult.

A fifth meta−analysis conducted at the London School of Hygiene and Tropical Medicine and focusing upon acute lower respiratory infection will be released in the very near future. Details are not yet available but it has been suggested that the results based on community studies are consistent with the present report.

Discussion and Conclusions: Mortality Effects

The most important conclusion to be drawn from the review of mortality studies in populations exhibiting signs of general deprivation marked by a high prevalence of stunting), and exhibiting at least a low prevalence of xerophthalmia are:

> • *On average a reduction of young child mortality by about 23%* (*RR=0.77*) *can be expected.*

The present analyses provide strong evidence for an association between supplementation with vitamin A and decreased risk of mortality among children. Six out of the eight studies reviewed display statistically significant inverse associations with mortality risk. Despite the evidence of some heterogeneity, the studies are extremely consistent in their finding of an inverse association (7 of 8 studies) and the results from the final study, SUDAN, are not inconsistent with an inverse association (the lower bound of the confidence interval in Table 5.4 is 0.81).

It would be reasonable to expect that where vitamin A deficiency exists, improvement of vitamin A status, by supplementation, fortification or modification of dietary intake, would have a beneficial effect.

> • *Vitamin A has a role in the determinants of young child mortality in developing countries. Further, this role is "biological" rather than "pharmacological." That is, it is not dependent upon the administration of periodic high potency doses of vitamin A. It is much more likely to be a function of vitamin A status.*

While recognizing that there is real variation among the studies reviewed, we have been unable to identify population−level predictors of responsiveness to vitamin A supplementation. We must assume that there are population characteristics that better predict responsiveness. Until these have been identified and examined, we can draw the following conclusions:

> • *The relative effectiveness of vitamin A supplementation is not gender dependent and is not dependent upon age* (*from 6 months to 5 years*)*. The effectiveness of vitamin A under 6 months of age remains uncertain but is likely to be much lower than in older infants and children.*
>
> • *Improvement of vitamin A status is more likely to impact upon diarrhoeal disease mortality and mortality attributed to measles than upon respiratory tract mortality or mortality attributed to malaria. Indeed the last two may be relatively unaffected by vitamin A status.*
>
> • *Positive predictors of population responsiveness have not been identified from the existing data base.*
>
> • *Until and unless more information becomes available and better predictors are developed, the prediction limits on expected effects in a new programme must take this into account. Of necessity they will be substantially wider than the C.I. of the original summary RR estimate. This does not detract from the main conclusion that an effect of vitamin A on young child*

mortality is expected.

A critically important question, potentially affecting a major population segment, remains unanswered. None of the studies available for examination involved population groups in which there was evidence of vitamin A depletion (e.g. low serum vitamin A levels) without evidence of xerophthalmia. This might characterize many population groups in, for example, Latin America.

> • *Available evidence does not permit any firm conclusion about the likely responsiveness of population groups presenting biochemical evidence of depletion without accompanying evidence of xerophthalmia.*

However, as discussed in the next chapter, the demonstration of an effect of vitamin A on severe diarrhoea in a population without xerophthalmia (Barreto, 1993) is very suggestive that mortality effects would also be seen.

We found no clear explanation for the fact that two studies failed to detect a statistically significant effect of vitamin A supplementation (HYDERABAD and SUDAN) but we note that in each case the difference in vitamin A status between treated and control groups appeared to be much smaller than expected. Two recommendations/conclusions arise directly from this.

> • *Any programme designed to improve vitamin A status must monitor response of the population* (*e.g. through estimation of serum vitamin A or monitoring clinical symptomatology depending upon circumstances*) *rather than assuming that the administered/ingested vitamin is exerting an effect.*

While there is no direct evidence that the commonly used dosing schedule of 200,000 IU at 6 month intervals is inadequate, earlier studies reviewed by West and Sommer suggest that it may be marginal. Since this *may* have been a contributing factor in the absence of an effect in the SUDAN study, it follows

> • *There is some uncertainty about the adequacy of currently recommended dosing schedules. This should be kept under continuing review.*

In keeping with earlier reviews of experience, we suggest:

> • *There would seem to be very strong evidence that the administration of vitamin A after the onset of severe illness as in complications of measles is effective in reducing mortality risk. This warrants attention in developing guidelines for infectious disease treatment centres.*

Research Recommendations

Given the clear demonstration of effectiveness (actually “efficacy”) of improvement of vitamin A status in the reduction of young child mortality in situations where there is clinical evidence of vitamin A deficiency, it may be unethical to undertake any additional mortality trials. There would seem to be very little benefit to be gained and the ethical consideration becomes overwhelming. There are two situations in which the ethical issues might be weighed against the possible benefit of further investigation. These are:

> • *Studies of the effectiveness of improvement of Vitamin A status of infants under 6 months whether this be achieved through improvement of maternal status and hence breast milk levels or through direct supplementation.*

A recent study in Nepal suggests that there is no effect in this age group. However, one can speculate that the presence or absence of effect might be dependent upon such factors as vitamin A content of breast milk and/or coexisting detrimental effects of the relatively large doses used in the Nepal study, the answer is not unequivocal as far as the rest of the world is concerned. Since this is a very high interest group given the drive to link direct vitamin A supplementation with the extended immunization programs, a clear answer *might* be deemed sufficiently important that it justifies a controlled trial in another setting. The second type of study that *might* be considered is:

> • *Studies designed to ascertain whether vitamin A–depleted* (*not clinically deficient*) *populations are responsive to vitamin A.*

This type of study assumes importance because such a large proportion of the population of developing countries appear to fall into this category and we have no mortality data on which to offer an objective assessment of likely effectiveness of improvement of vitamin A status. The recent report from Brazil (Barreto et al., 1993) that severe diarrhoea is reduced by vitamin A suggests that a mortality effect is likely and certainly must be considered in weighing the ethics of a mortality study.

Of course, given the demonstration of efficacy of improvement of vitamin A status, there is even greater justification for operational research designed to develop, test and improve cost–effective approaches to the improvement of vitamin A status. While the present report has focused primarily on trials involving periodic high potency dosing, we would not want our report to be seen as a specific endorsement of this approach to the control of vitamin A deficiency. It is but one of many potential alternatives.

Sources of Study Data

Aceh

Sommer, A., Tarwotjo, I, Djunaedi, E., West, Jr., K. P., Loeden, A. A., Tilden, R., Mele, L., and the Aceh Study Group (1986). Impact of vitamin A supplementation on childhood mortality: a randomised controlled community trial. *Lancet* 327: 1169–73.

West, Jr., K. P. (1992) Personal communication. A complete set of published and unpublished reports of the study were made available.

MSG

Muhilal et al. (undated) A pioneering project for combat–ting vitamin A deficiency and xerophthalmia with MSG fortified with vitamin A. Center for the Research and Development of Nutrition. Agency for the Research and Development of Health. Indonesia.

Muhilal, Permeisih D., Idjradinata, Y. R., Muher–diyantiningsih, Karyadi D. (1988). Vitamin A–fortified monosodium glutamate and health, growth, and survival of children: a controlled field trial. *American Journal of Clinical Nutrition* 48: 1271 –6.

Tamil Nadu

Rahmathullah, L., Underwood, B. A., Thulasiraj, R. D., Milton, R. C., Ramaswamy, K., Rahmathullah, R., Babu, G. (1990) Reduced mortality among children in southern India receiving a small weekly dose of vitamin A. *New England Journal of Medicine* 323:929–35.

Rahmathullah, L., Underwood, B. A., Thulasiraj, R. D., Milton, R. C. (1991) Diarrhoea, respiratory infections, and growth are not affected by a weekly low–dose vitamin A supplement: a masked, controlled filed trial in southern India. *American Journal of Clinical Nutrition* 54:568–77.

Rahmathullah, L. (1992) Personal communication, enclosing copies of responses to critiques of the study. In addition, copies of several other articles and of a report to the Ford Foundation were made available.

Hyderabad

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Vijayaraghavan, K. (1992) Personal communication.

Sarlahi

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Bombay

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Kothari, G. (1992) Personal communications.

Jumla

Daulaire, N.M.P., Starbuck, E. S., Houston, R. M., Church, M. S., Stukel, T. A., Pandey, M. R. (1992) Childhood mortality after a high dose of vitamin A in a high risk population. *British Medical Journal* 304: 207–10.

Daulaire, M.N.P. (1992) Personal communication.

Sudan

Herrera, M. G., Nestel, P., El Amin, A., Fawzi, W. W., Mohamed, K. A., Weld, L. (1992) Vitamin A supplementation and child survival. *Lancet* 340: 267–271.

Herrera, M. G. (1992) Personal communications and solicited additional analyses of data.

Ghana Vast

April 1990–March 1991 Annual survival study report of activities for the Ghana vitamin A supplementation trials (VAST) (A complete set of progress reports was made available. Sample sizes as well as population descriptions were derived from these.)

Binka, F. (1992) Personal communication. Summary of preliminary analyses presented at a seminar at IDRC, Ottawa, Canada in August 1992.

Dollimore, N. (1992) Personal communications. Details of unpublished results including ‘loss to follow up’ estimates and baseline xerophthalmia rates.

Ghana Vast Study Team (1993) Vitamin A supplementation in northern Ghana: effects on clinic attendances, hospital admissions, and child mortality. *Lancet* 342: 7–12.

Smith, P. (1992) Personal communications. Tabulation of mortality data at the level of individual clusters (as child years), total counts, and summary analysis made available.

Haiti

Stansfield, S., Pierre–Louis, M., Lerebours, G. (1992) Unpublished draft manuscripts: Vitamin A supplementation and increased prevalence of childhood diarrhoea and acute respiratory infections.

6. Discussion and Conclusions

While most of the studies reviewed involved the periodic administration of high potency doses, *we feel that our conclusions are relevant to Improvement of vitamin A status by any effective means.*

The major conclusions of this report are:

> • Improvement of vitamin A status in young child populations exhibiting evidence of vitamin A deficiency (at the population level) *does* lead to a reduction in all–cause mortality rates. On average, this reduction is about 23% (RR = 0.77).
>
> • There is a suggestion that improvement in vitamin A status can also be expected to reduce the chance of infectious diseases progressing to their severe forms.
>
> • Conversely, there is very little evidence to suggest that vitamin A status impacts on the prevalence of general morbidity in young children. It would be unreasonable to expect such an effect in operational programs.

Of the eight mortality studies reviewed in detail, only one (SUDAN) saw no effect of vitamin A on mortality (RR=1.04). Another (HYDERABAD) did not detect any significant effect but the Relative Risk was slightly reduced (RR=0.96). A third study (HAITI), not examined in detail, advises that no mortality effect was seen. The other six studies reported statistically significant effects of vitamin A supplementation on total mortality. A seventh study (BOMBAY), again not examined in detail, reported a very major reduction in mortality. A new study of infants under 6 months failed to detect any beneficial effect of large doses of vitamin A.

The present mortality findings are comparable to the results of a meta–analysis originally reported at a meeting in Bellagio and more recently cited in print (Sommer, 1992; Tonascia, 1993). However, that report suggested an average 34% reduction in mortality in children 6 months to five years of age, while we report only a 23% reduction. The major distinction is that the earlier report analyzed data from only 6 mortality trials in S.E. Asia while we had access to data from 8, including the SUDAN and GHANA studies. If we examine only the S.E. Asia studies, the estimated reduction in mortality is 30%. A further distinction between the meta–analysis by Tonascia and the present results is that the earlier analyses selected for age over 6 months while we have analyzed the total data provided by the original studies; no comparison has been attempted to assess the impact of this selection. In 1993, two more meta–analyses were published (Fawzi et al., 1993; Glasziou and Mackeras, 1993). Since each analysis included a different set of projects, the derived summary RR estimates differ somewhat from analysis to analysis. Nevertheless, all meta–analyses conclude that vitamin A supplementation had a highly significant effect in the studies reviewed.

Four other conclusions can be drawn from the mortality study review:

> • The effect of vitamin A is not dependent upon very high potency dosing (not a pharmacologic effect). Rather, it is reasonable to conclude that equivalent improvement in vitamin A status by any means would exert comparable effects.

This conclusion derives from the fact that one of the trials involved the use of fortified mono–sodium glutamate (MSG) resulting in a modest increase in daily intake and another (TAMIL NADU) administered a physiologic dose once per week. Both were demonstrably effective.

> • The effects of vitamin A supplementation appear to be comparable in males and females and, at least from age 6 months to 5 years, appear to be comparable across ages (no gender or age effect detected).

An examination of the very limited experience reported in the original 8 studies for infants under six months suggested a reduction that averaged about 23% but did not achieve statistical significance. Subsequently West (1993) reported on the extension of the SARLAHI study to examine the impact of vitamin A administration between birth and 6 months of mortality under 10 months. No beneficial effect was seen. The effect of vitamin A under 6 months may not yet be clear but it should likely be presumed that the effect, if any, is small.

> • In community–based programmes, it appears that there *is* a differential effect of vitamin A supplementation depending upon attributed cause of mortality. The effect is very pronounced for diarrhoeal diseases, may be absent in respiratory disease deaths and for deaths attributed to malaria, and was detectable in deaths attributed to measles.

This has important implications for planning since it implies that the effectiveness of vitamin A will be greatest in areas, and age groups where diarrhoeal disease is the major attributed cause of mortality. Given the uncertainties in the attribution of mortality, we do not feel this aspect of the analysis can be taken much

further.

> • It has also been shown that vitamin A administration after the onset of measles reduces severe complications and has a favourable effect on case mortality. *Interestingly, in these interventions, in contrast to community–based interventions, pneumonia deaths* ***were*** *reduced.*

These observations have great practical importance in considering treatment protocols.

Contrasting with these clear effects on mortality, in examining the available morbidity trials, and the morbidity results of studies designed primarily as mortality trials, we have come to the conclusions shown below. In offering these conclusions, we are cognizant of the fact that several morbidity studies have not yet published their final analyses and a few are still under way. Certain of our conclusions may be altered by further information that will become available within the next year or so.

> • Vitamin A supplementation has no *important* effect on the incidence or duration of diarrhoeal and respiratory tract infections.

In our judgement, the above finding cannot be attributed to poor study design or methods. We are aware of other morbidity studies, using similar designs to ask about the impact of improvements in water supply and excreta disposal, that detected with statistical significance a reduction of 20–25% in morbidity rates. While small effects on morbidity prevalence or incidence might have gone undetected, we are confident that no major impact of vitamin A on general morbidity is to be expected. Some individual trials have reported beneficial effects of vitamin A on morbidity rates but our judgement and conclusions are based on a review of all trials, taking into account important design features, and giving emphasis to those studies which seem more convincing from the design standpoint. We are quite confident in this conclusion.

> • While some studies have reported that vitamin A administration increases the risk of diarrhoeal diseases and respiratory infections, there does not appear to be consistent evidence for such an effect.

We do not place major credence in the few reports of a negative impact of vitamin A administration.

> • Vitamin A supplementation appears to reduce the severity of infections.

Not all studies have assessed severity. A study in Ghana and another in Brazil, but not a study in Indonesia, suggest reduced severity as an outcome of vitamin A supplementation. The few studies that have assessed hospitalization rates have detected a decrease among treated children. Since many studies appear to have collected data that could be used to assess markers of severity, but have not yet reported analyses of those data, we expect that future reports will offer clarification of this important question. An effect of vitamin A on severity even without an effect on incidence or duration of morbidity, would be consistent with the results from the mortality trials. It would also be consistent with the results seen in hospital–based trials of intervention after measles.

> • No reports of differential effects on morbidity by gender or by age (over six months) have appeared.

The pattern that seems to emerge from the review of morbidity and mortality trials is that vitamin A status impacts upon the response to infection rather than on resistance to becoming infected. The original expectation (when a number of the trials were being designed) was that general morbidity would show reductions in the same order of magnitude as the reported reductions in mortality. In hindsight, the pattern that has emerged is reasonably consistent with what is known about the biological roles of vitamin A (see chapter 3). There were two broad hypotheses about expected effects of vitamin A on morbidity and mortality. One focused upon the known role of vitamin A in epithelial tissues and postulated a barrier mechanism under which the vitamin A–deficient subject, would be more likely to become infected (seen as incidence). The other focused upon the roles of vitamin A in the immune system and hypothesized that the real effect of deficiency would be on the manner in which the organism responded to infection (seen as either or both of duration and severity). The morbidity and mortality results reviewed above would strongly favour the latter hypothesis – that vitamin A is influencing the child's ability to respond appropriately and successfully to infections. There remains an anomaly – the apparent absence of an effect on respiratory disease–related mortality (except in the case of pneumonia after measles) vs a clear effect on diarrhoeal mortality. Neither theory of action of vitamin A would seem to explain this difference. Indeed, the very well documented role of vitamin A in the

maintenance of epithelial tissue, linked to the barrier hypothesis, would also predict that respiratory disease would be more responsive to vitamin A status than would be diarrhoeal disease – the opposite of what has been seen.

There is ample evidence from animal studies that response to vitamin A can differ with infective agents and that may be what is involved here. The actual pathogens have not been identified in the reports available for review.

We conclude that the barrier hypothesis discussed in Chapter 3 is unlikely to be the most important path of effect. Instead we favour the "response hypothesis" suggesting that it is the body's ability to generate the normal and appropriate responses to infection that play an important role.

It is tempting to speculate that the degree of deficiency is an important determinant of which type of mechanism is involved in the effect of vitamin A. Such speculation would hold that significant epithelial changes and associated weakening of the body' s barrier system occur only in very severe deficiency while the immune system responses are affected by lesser degrees of depletion of tissue levels. It is emphasized that this is speculation. We do not have experimental data to test it. Interest arises because, in the studies we have examined, for ethical reasons, children who developed signs of xerophthalmia, severe vitamin A deficiency, were treated with vitamin A. This might have effectively removed, or at least reduced, very severe deficiency from the study groups (treatment and control) and hence diminished the chance of seeing effects that required a very severe state of depletion (impaired barrier function?) In turn that may help to explain why the epidemiologic experience suggested a linkage between xerophthalmia and incidence as well as outcome of infectious disease while the controlled trials failed to see the implied effect.

Having undertaken quantitative analyses of the mortality trials, we are able to offer some additional conclusions that are germane to the health planner. We did not attempt quantitative analyses of the morbidity trials because of substantive differences between projects in the way that morbidity data were collected, analyzed and reported. Nevertheless, some of our analyses of mortality data may be applicable also to severe morbidity (morbidity likely to lead to mortality).

Using all eight studies, including the two that failed to find significant effects (but omitting the recently reported extension of SARLAHI to examine dosing of infants under 6 months), we can provide estimates of the magnitude of effect that might be expected in a programme mounted in a new area.

- The average RR for the reported studies was 0.77. The 95% confidence interval attached to that estimate was only 0.71 to 0.84 and the p–value for the test of RR 1.0 (no effect) was 1.12 x 10"[9]. When this confidence interval is recomputed to allow for between study variation (i.e. accepting the Summary RR as an average value for the eight studies rather than as an estimate of a single true RR), the Confidence Interval increases to 0.68 to 0.87, but the effect remains highly significant. We are very confident that in this group of studies, vitamin A supplementation reduced mortality. We are confident also that in future programmes, conducted in populations like these (marked by poverty, evidence of widespread early growth failure ("stunting"), and exhibiting signs of vitamin A deficiency consistent with the international criteria of a public health problem), vitamin A is likely to have an effect. The expected effect, on average will be about a 23% reduction in mortality in pre–school children between 6 months and 5 years of age.

At the same time, we explicitly recognize that there were differences among the eight trials. We have to accept that the actual effect in a particular future programme may not be exactly a 23% reduction. Indeed, based on past experience it is possible, though unlikely, that no effect would exist in a particular program and a very large effect (e.g. 50% reduction) might be present in another. We have attempted to address this between project variation in two ways. First we attempted to identify population characteristics that would serve to predict a greater or smaller effect. In these analyses we only had an n of 8 (the 8 studies) so our power to detect subtle effects was very limited; major predictors should have been detectable. The results are presented below:

- Gender and age (over 6 months) profiles are unlikely to be predictors of effect since neither appears to influence the relative effectiveness of vitamin A (see above).

- The prevalence of wasting, prevalence of xerophthalmia and the interaction between these were not significant predictors. Since all study groups exhibited generally comparable degrees of stunting, it is not surprising that this was not an effective explanatory variable.

• No gross association between mortality rate (of the control group) and the *relative* effectiveness of vitamin A was seen. There *is* an association between mortality rate and *absolute* effect (the lives saved per 1000 treated is implicitly related to the basic mortality rate – see below).

• The observation that there appears to be a cause–specific differential in *the impact of vitamin A on mortality would suggest that important differences mortality profiles would predict differences in the relative effect on total mortality. This was not formally tested.*

From the above, we accept variation between studies but were unable to explain it. It follows that in offering predictions for the effect in future studies, we must allow for the between study variation that we have observed as well as the uncertainty of the estimate of the average RR for the 8 studies. In chapter 5 we presented, in graphic form, the prediction interval. It was in graphic form since a third variable to be considered in predicting the effect that would be seen is the size and mortality rates in the future programme or study. Below, in Figures 6.1 and 6.2 we present these intervals again but in a different form. Based on our analyses of eight studies we offer a portrayal of what a planner might reasonably expect. We do it as a probability statement – the probability of producing *any* effect, or of producing an effect exceeding a *10%, 20%, 30%, 40%* or *50%* reduction in young child mortality.

In Figure 6.1 we present probabilities that there would be a *real* effect of vitamin A in a new program. This display suggests that there is a 98% chance of there being some effect. The figure suggests also that there is an 89% chance that the real effect will be a reduction of at least 10%, 62% chance of a 20% reduction, and a 23% chance of reduction as great as 30%. We see the likelihood of a true reduction of 50% or more (reported in Tamil Nadu) as being effectively 0. These are predictions of the *real* effects to be expected. However a planner is more interested in knowing what effects s/he can expect to actually see. If s/he were working with a very large program with moderate to high mortality rates, the probabilities shown in Figure 6.1 might be expected to apply. However with smaller programmes or in programmes with very low mortality rates, the 'sampling error' is high. This means that the *observed* effect may not be the same as the *real* effect that would be seen with larger group sizes. We use the characteristics of the Hyderabad study (moderate sample sizes but extremely low mortality rates) to illustrate this situation in Figure 6.2. It will be noted that the probability of seeing any effect has fallen from 98% to 81%. The true effect is the same but there is less chance of seeing it. At the other end of the spectrum, the chance of seeing a 50% or greater reduction (an observed effect that would be greater than the real effect) has increased from 0 to about 6%. In the Technical Annex, programs (see Programmes J and K) are provided which compute these probabilities for given study characteristics. Information of this type may help the planner charged with choices in the allocation of resources.

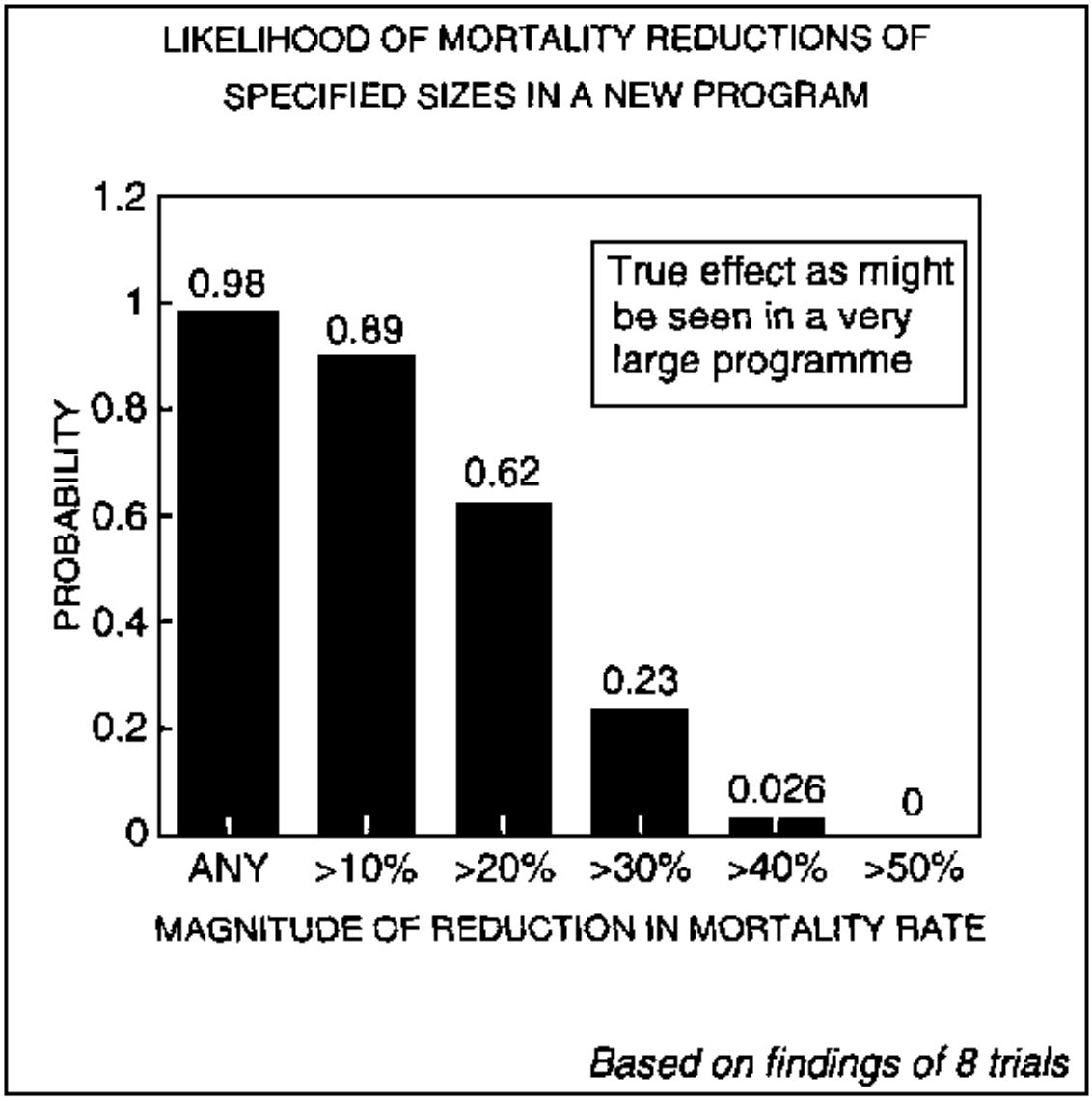

Figure 6.1 Probability that Effect of Vitamin A Supplementation Will be Greater Than Specified Mortality Reductions in a Very Large Field Program

Note: See text for explanation.

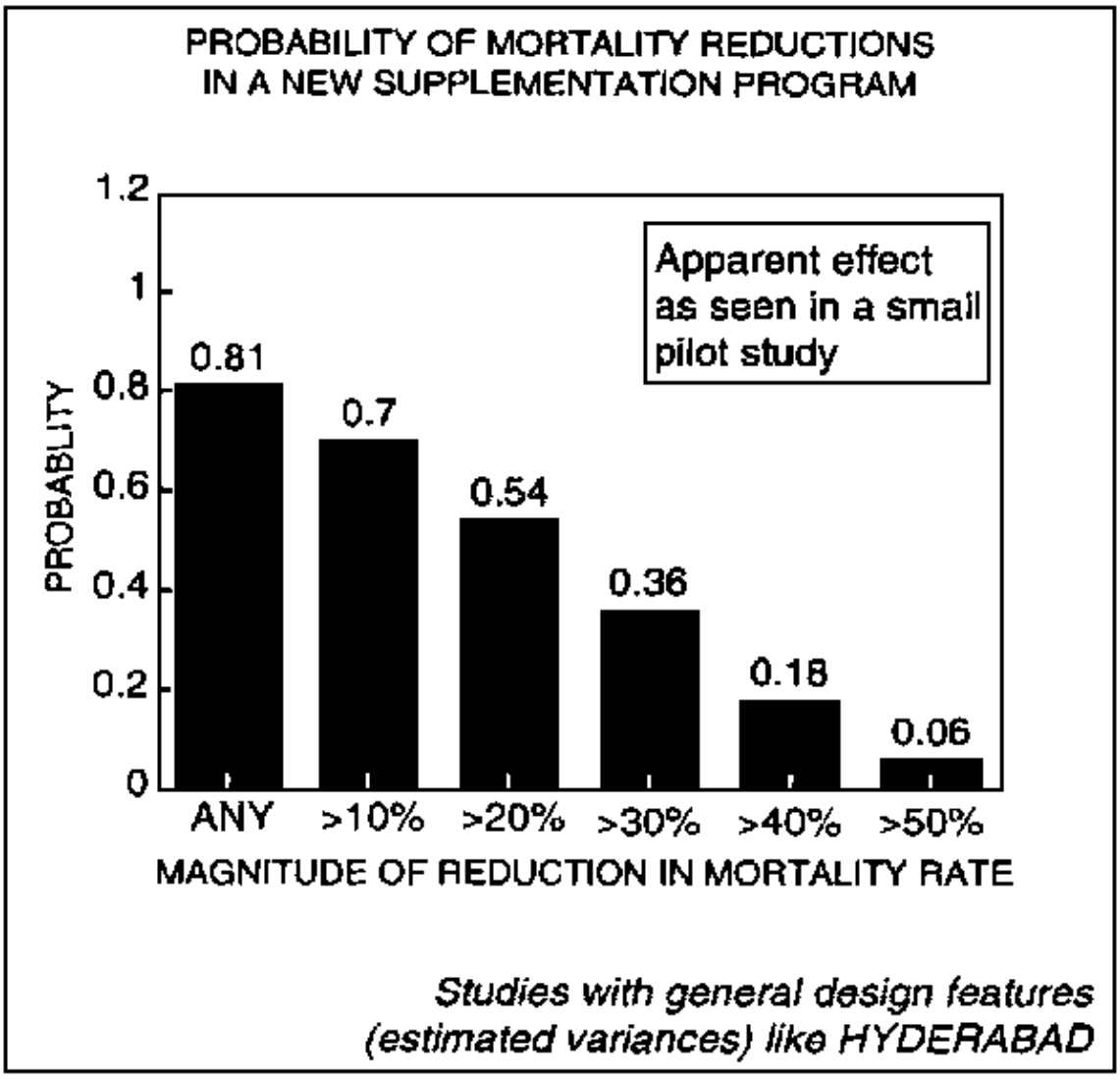

Figure 6.2 Probability of Effects of Specified Magnitudes – in a Moderately Small Pilot Study

Note: Modelled after the variance characteristics of the Hyderabad trial.

To illustrate the operation of two of the key variables in the determination of expected variance of new programs, and to keep the presentation consistent with the 'planning mode', we present Figure 6.3 which shows the likelihood of failing to see *any* effect in a new programme as a function of the population group size and baseline mortality rate. The calculations assumed that the summary RR of 0.77 operates for this new population (that the population selected generally resembles those studied) and that compliance and coverage were at least as good as in the research studies.

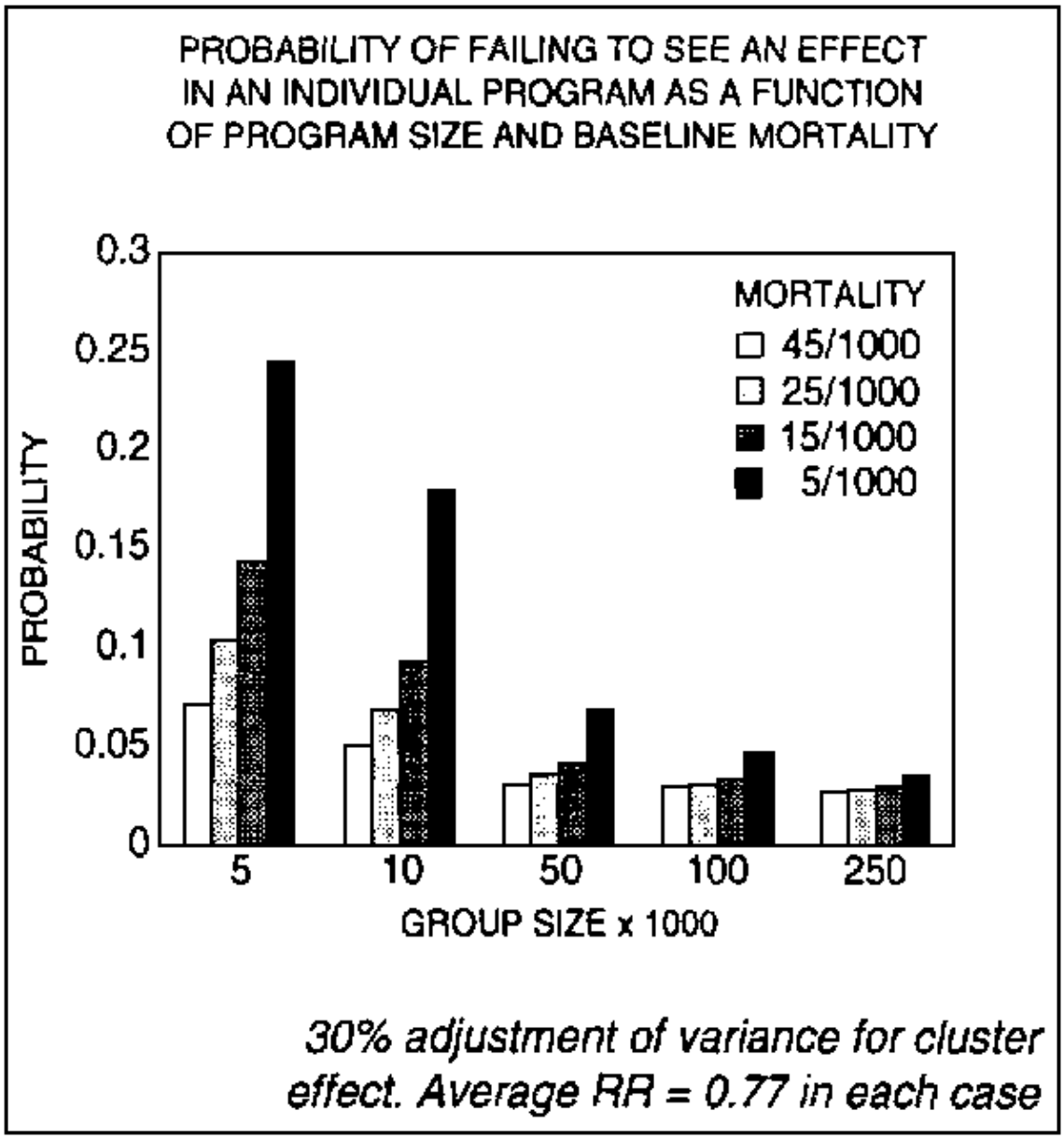

Figure 6.3 Estimated Chances of Failing to See an Effect in a New Program

The important message from Figure 6.3, is that the results seen in “small” pilot studies could be quite misleading. A negative pilot study is not inconsistent with a true positive effect if the programme were applied to a much larger population. Similarly, a very promising (large effect) pilot study might be expected to be associated with smaller overall effects when scaled up.

The planner may face a problem in applying this approach. The mortality rates that s/he has available in background documents may be higher than the rates on which we have built our analyses and predictions. As we indicate in our report, the observed mortality rates in control groups were often much lower than rates anticipated from background information available for the district, region or country. There are many possible explanations for such a discrepancy. Possible explanations include, but are not limited to:

- possible limitations of vital statistics reporting in the country or region.

- possible effect of excluding high risk individuals and groups in the selection of study subjects (or refusal of high risk individuals to participate).

- reduction of mortality risk by treatment of active xerophthalmia.

- a non–specific beneficial effect of interventions and household visiting by study workers (e.g. unintentional encouragement to seek health care).

We could not test any of these implied hypotheses since none of the studies had appropriate controls for these types of effect. It is interesting that the exceptions to the pattern of lower than expected mortality rates appeared to be in studies in which there was minimal additional contact with households (MSG and JUMLA). That observation is consistent with the hypothesis that increased contact with households, as occurred in most of the trials, exerts a non–specific beneficial effect on young child mortality. As long as there is a blinded control group, this should not bias the results of the study (unless the 'nonspecific' effects swamped out any demonstrable effect of vitamin A). However, if an uncontrolled pilot study or operational programme were undertaken, the *apparent* effect of supplementation might be much greater than we have predicted (non–specific effect + specific effect of vitamin A).

Conversely, the planner will recognize that compliance is likely to be much greater in research programmes and pilot studies than in operational field programmes. As a modest warning, we have included whatever information was presented about compliance in the research studies, but have not attempted any analyses. The planner must expect that because of compliance, the vitamin A–specific effect s/he is likely to find may be less than we suggest. Clearly s/he will wish to examine compliance and other logistical aspects of operational programmes in any pilot study that is undertaken.

Above we noted that there was no detected gender or age effect on the estimated RR. We mentioned also that in fact, since mortality rates typically differed with age and perhaps also with gender, one should expect that programme effects, estimated as lives saved per 1000 children treated, or similar measures, would differ with age. The higher the mortality rate, the greater will be this index even though the *relative* effect (RR) does not change. This was exemplified in Chapter 5, Table 5.13.

It follows from this that a planner *can* consider targeting of vitamin A program to groups where the absolute effects per 1000 covered are greater. The indicator variables for such targeting would seem to be total mortality rates (group specific) and relative contribution of diarrhoeal disease and measles to the overall mortality (in contrast to respiratory disease and malaria mortality).

Targeting at the level of the individual could include 'secondary prevention', i.e. administration of direct supplements when a child becomes seriously ill. We offer no guidance on the logistical feasibility of such an approach or the coverage that might be expected. We do voice a note of scepticism that this could be seen as an effective approach to population control unless the primary health system were reasonably advanced. However, we do note that it could be a valuable attachment to other intervention strategies. We have reviewed studies that indicate that vitamin A supplementation in the face of serious illness can be efficacious in reducing the risk of more severe illness and mortality.

We note that the two studies that failed to find an effect of vitamin A supplementation on mortality shared one thing in common. They failed to generate the expected difference in vitamin A status between treated and control groups. The explanation for this is not clear and seems to differ between the two studies. Although potency of the distributed supplement was confirmed in both, the authors of the SUDAN study have postulated that the size of dose and interval between doses may have been inadequate to produce an effect in that setting.

This suggests that there may be need to carefully review the existing dosing guidelines for operational programs.

In our analysis of mortality trials we were unable to offer a clear answer to the question "should an effect of vitamin A be expected in situations where there is biochemical evidence of vitamin A depletion but no xerophthalmia?" We think it likely that a mortality effect would be present. This is based on three observations: i) a mortality effect was demonstrable in Ghana even though the prevalence of xerophthalmia was very low; ii) the relative effectiveness of vitamin A was not demonstrably related to the prevalence of xerophthalmia; and iii) the recent report from Brazil (Barreto et al, 1993) serves to demonstrate and effect of vitamin A on severe diarrhoea in a population with biochemical evidence of vitamin A depletion but no xerophthalmia. The report from Brazil takes on great importance since it is the only real link between the many vitamin A–deplete populations, in Latin America and elsewhere, and the mortality trial results.

The possibility of linking vitamin A supplementation to immunization programmes is currently a matter of high interest (WHO, 1993). This has logistical appeal, at least for very young infants (to the time of the last measles immunization at 14 months) and may carry some advantage in terms of improved response to immunization as well as the protective effect of vitamin A on mortality as discussed in the present report. However, there is at Least the possibility that deaths prevented by immunization and deaths prevented by vitamin A overlap – i.e. under these circumstances the effects of immunization and vitamin A might not be fully additive. We can

offer some information pertinent to this with regard to measles. In Table 5.10 we presented an analysis by attributed cause of death. One can also compute, for the four studies reporting measles deaths (GHANA VAST, JUMLA, SARLAHI, and TAMIL NADU), the relative effects of vitamin A for all deaths, for measles deaths and for non−measles deaths. These are shown in Table 6.1. As can be seen, there is no detected effect of removing the deaths attributed to measles. This may be due to the very small number of cases identified (minimal impact on total mortality). One must interpret this with great caution – there is no way of ascertaining, from the data available, the number of deaths attributed to other causes that actually had measles as an underlying cause. One would expect that as measles immunization programmes take effect, there will be some reduction in the relative effectiveness of vitamin A even though it cannot be demonstrated in the present analyses. Precise figures are not available for the study projects but it was reported (personal communications) that measles immunization rates were very low in all four sites.

Table 6.1 Possible Effect of Specific Control of Measles on Relative Effect of Vitamin A (Ghana Vast, Jumla, Sarlahi and Tamil Nadu)

		95% *C.I.*			
Attributed cause	*RR*	*Lower*	*Upper*	*Z*	*Prob* H_0*:RR=1*
All	0.75	0.67	0.83	–5.294	< 0.000
Measles	0.74	0.53	1.03	–1.734	0.083
All, except measles	0.75	0.67	0.84	–4.945	< 0.000

In closing, the members of the Technical Advisory Group wish to be on record with the following statement:

We are very confident that vitamin A supplementation can effectively reduce mortality rates in young children, and probably also reduce the risk of severe morbidity. We believe that this is the result of improvement of vitamin A status. We expect that any other programme that effectively improved vitamin A status would have comparable effect.

Although the present review has been restricted to vitamin A supplementation programmes, usually involving the periodic administration of high potency doses, we do not wish to be interpreted as endorsing that as a preferred approach to the control of vitamin A deficiency.

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Review Annex: Assessments Offered by Invited Reviewers

A group of reviewers, highly qualified in their own fields, were invited to critically review the final draft of this report. Below we reproduce in full their general assessment and summarize also their detailed technical comments or indicate action taken. Between the draft on which the reviewers commented and the present version, there has been significant alteration; comments which were relevant to the copy they reviewed may no longer seem relevant. In particular, the Executive Summary they reviewed no longer exists. It was replaced by a separate Summary Report which, in turn, has been deleted from the present version. Major reorganization of chapter 5 was also undertaken in an attempt to give clarity to some of the more difficult conceptual issues developed there. We appreciate very much the constructive criticisms from these reviewers.

Reviewers were invited to review the whole report or those sections where their own technical competence was particularly relevant as they chose. It was requested that they indicate, in their assessment, the aspect(s) of the report that they had critiqued.

Reviewer

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General Assessment

This is an excellent report. It is focused and balanced in the background review of the literature. It offers some interpretive speculation that should stimulate research to further clarify some very basic issues regarding the differential effects of vitamin A on morbidity. While identifying areas for which more information is needed, however, the message is clear that programme decisions are justified now for interventions in endemic vitamin A deficient areas. It is clear also that those decisions should not be driven by a particular strategy of intervention, but that any strategy that improves and maintains an adequate vitamin A status should be effective in reducing mortality, thus giving national planners alternatives to match their resource availability for both the immediate situation and sustainable control of the problem.

It is also clear that vitamin A is no magic bullet to child health and survival – other interventions are needed concurrently to address the background of deprivation leading to high infection rates. In many national situations, there are on–going public health and community development programmes that provide an opportunity for integrating a vitamin A emphasis thus enhancing the potential effectiveness for family and particularly maternal–child health, e.g. immunization contacts, growth monitoring, regular MCH services, literacy programmes, etc.

I am very satisfied that the analysis of the mortality data has been adequately and fairly conducted and interpreted. I appreciate the respect given to the fact that some studies may fail to show effects, without necessarily attributing this to defects in implementation, even though the reasons for the lack of efficacy are not fully explained.

The *prediction interval* estimate is a useful development for planning purposes. I am not qualified to judge the statistical procedures used for arriving at the outcome but find it to be conceptually very useful, particularly when followed by the conclusion that improvement of vitamin A status by whatever appropriate strategy can be anticipated to have similar beneficial effects.

This analysis is a major contribution toward sorting through the confusion surrounding the issues of vitamin A and its role in child health and survival. Important researchable issues are identified, stimulating speculation regarding mechanisms have been suggested, and new interpretive insights for programme and policy decisions are given. In addition, the analysis provides a methodologic framework for continuing to refine the conclusions and programmatic implications as additional data become available.

I conclude by repeating my opening comment – congratulations for a task well executed.

Technical Comment: An additional reference was suggested and has been added.

Reviewer

Dr. Sue Horton
Institute of Policy Analysis
University of Toronto
Toronto, Ontario, Canada

General Assessment

Overall I found this to be a careful and thorough study. Most of my comments below relate to exposition. I did find that occasionally the discussion became a little repetitious, and at some points the result of efforts to write for a non–technical audience were a little unhappy (comments referred to chapter 5).

Some Specific Comments and Questions

1. I think it might be worth stressing that all the mortality trials were for populations with signs of xerophthalmia, and thus the evidence found and results predicted hold for those populations (the way this was stated, for example, in the first point of the Executive Summary, escaped my attention as a non–nutritionist).

2. Some questions struck me. I was disappointed that nothing seemed to explain the between–study variance (although I am convinced that your group did a very thorough job of investigating this). Would it be possible to examine RR by size of dose (is there a valid way of combining the daily or weekly administration cases with the ones at wider intervals?). Table 5.11 seemed mildly suggestive that the lower mortality responses were located in cases where dosage was marginally adequate.

3. I would also like to know if length of supplementation affected response: I might guess that response might fall over time in a program involving repeated high doses, if the initial dose helped the most vulnerable children in the study group, whilst the most vulnerable ones in the control group died. It seemed that there might be some variance among studies on this.

4. The literature survey hinted that giving vitamin A at the same time as providing immunizations might be beneficial, if I interpreted the statements correctly. This information might be worth bringing out more to advise policy makers considering the next stage.

> *Comment: Dr. Horton also offered a number of editorial suggestions most of which have been incorporated in the present revision. In keeping with her suggestion, the Executive Summary has been replaced by a different style of document prepared with a different audience in mind.*
>
> *On the comments offered above, it was not intended (#4) to suggest there was evidence that administering vitamin A along with immunization was more effective. Reference was to the fact that this has logistic appeal and is a topic of obvious interest. It was with this in mind that we attempted to examine the effects of vitamin A in very young infants. On another point (#3), also raised by Dr. Kramer, we agree that it would be valuable to ask whether, in sustained programs, the apparent effectiveness of vitamin A decreases over time (i.e. as the more susceptible individuals in the population are improved in vitamin A status. However, this was not deemed feasible of examination within the present series of relatively short term interventions. It is a question that might be addressed in the context of ongoing programmes.*

Reviewer

> Dr. Allan Donner
> Professor and Chairman
> Department of Epidemiology and Biostatistics
> University of Western Ontario, London, Ontario

General Assessment

I have reviewed the formal meta−analysis addressing the effect of vitamin A supplementation on mortality. It is both methodologically sound and thorough. The investigators have made every possible attempt to include all relevant trials (both published and unpublished), have developed clear criteria for considering the trials to be pooled, and have used appropriate statistical methods of conducting a pooled analysis. An unusual feature of the meta−analysis is that several of the randomized trials considered allocated intact units, such as wards, villages or households, to treatment groups rather than individuals. Standard statistical methods are not applicable to such designs, and this aspect of the analysis has been handled well. The investigators have also used a comprehensive sensitivity analysis to establish the robustness of their findings, and have carefully evaluated the strengths and weaknesses of the individual studies. Finally the possible impact of age and gender on the relative effectiveness of vitamin A supplementation has also been investigated. I conclude that the report provides a valid interpretation of the experience to date as well as a sound basis for policy formulation.

Technical Comments

I was impressed by the innovative approach used to handle the cluster randomization involved in several of the trials. Some points arising from this approach are as follows:

1. The estimated design effects for each individual study are presented. Since the design effect depends on both the average cluster size and the degree of within−cluster resemblance, it would also be useful to present the estimated degree of within−cluster correlation, at least where possible. This would provide information that could be very valuable in the assessment of sample size for future studies, and would also be of interest from the analytic point of view (e.g. how much stability is there in this estimate?). In the same vein, I would also recommend explicitly listing the average cluster size in the table of design features.

> *Comment: Data relating to intra−cluster correlation were not available to us. Average cluster size is now included in Table 5.2A.*

2. Because of the cluster randomization, it might be emphasized that the stated sample sizes for these trials are in a sense misleading since they might be taken to imply that a given study provides a greater degree of information than is actually the case. That is, the "effective" sample size for a given trial is really the stated sample size (no. of subjects) divided by the design effect. This is a particularly crucial issue in comparing the amount of information supplied by a study randomizing villages to, for example, a study randomizing households.

> *Comment: We agree. We have attempted to de−emphasize size and instead emphasize the variance. Since the variance estimates had been adjusted for cluster effects, and also took into account mortality rates as well as sample size, we hope we have accomplished the recommended emphasis.*

3. A test of homogeneity among the relative risks is presented on page 46 and elsewhere in chapter 5. It is not clear to me how the clustering involved in some of the studies combined for this test was accounted for, although the discussion on page 45 of chapter 5 is helpful in a general way. The explanation on page 81 of the Technical Annex is also helpful but does not completely explain how the variance inflation associated with the clustering is handled in testing homogeneity of the relative risks. Is it a matter of simply replacing observed counts by adjusted counts in the CATMOD procedure evaluating the statistical significance of the treatment X study effect?

> *Comment: Yes. We have reworded pages 44−45 to make this clearer and have noted in all relevant tables that variances have been adjusted by DEFF.*

4. Least squares prediction was used to estimate design effects for each of the studies, using empirical information on design effects reported in a subset. This is an innovative method of accounting for the cluster randomization for those trials which provide insufficient direct information. However there is very little rationale provided for the basic approach used. Specifically, what is the motivation for adopting equation (3) on page 80 of the Technical Annex as the basic model? Furthermore, the design effects as estimated from this model will clearly be correlated. Will this affect the validity of methodology used in the meta−analysis that depends on the assumption of independence among individual study effects which are combined? I do agree that the reported robustness of the conclusion to the different methods of estimating the design effects is very encouraging. But I would be interested to know what these other methods were. Finally, since the casual reader of Table 5.3 might assume the design effects reported are all internal estimates, a clarifying footnote might be useful.

> *Comment: A footnote was added to Table 5.3 to emphasize even further that the "Estimated Design Effects" are not internally estimated for each study. The rationale for choice of parameters in the estimation equation is briefly described in the Technical Annex. We plan a more detailed examination of this problem in future. However, as demonstrated through sensitivity testing, in fact the method of adjustment has very little impact on the overall results. It would impact much more on individual study results but examination of individual studies was not our main objective.*

Reviewer

Michael S. Kramer, M.D.
Professor, Department of Pediatrics and
of Epidemiology and Biostatistics
McGill University Faculty of Medicine
Montreal, Quebec, Canada

General Assessment

This review is based on my reading of the Executive Summary, Introduction (Chapter 1), the review and meta−analysis of studies of Vitamin A and Young Child Mortality (Chapter 5), the Discussion and Conclusions (Chapter 6), and the Technical Annex. Most of my comments bear on the meta−analysis of the child mortality studies.

In general, I found the meta−analysis to be a thorough and rigorous assessment of the available experimental evidence concerning the effects of vitamin A supplementation on mortality in young children from developing countries with high prevalences of child undernutrition and vitamin A deficiency. The statistical methods used are well described, particularly the assessment of potential effect modification (on the relative risk scale) by

gender, age, underlying child mortality rates, prevalences of stunting, wasting, and xerophthalmia, and periodicity and magnitude of dosing. The authors have also done an excellent job of examining the vitamin A effect on cause–specific mortality, although I would have preferred additional details on whether the three categories considered (diarrhoea, respiratory disease, and measles) were mutually exclusive. Does the category "respiratory disease" include all acute respiratory illnesses in children without a measles–like rash? If the three categories are mutually exclusive, I would have also liked to see results presented for a fourth category of deaths from "other" causes.

> *Comment: Dr. Kramer's comments concerning specificity of 'diagnosis' in the mortality data are well taken but unanswerable from data available to us. The aggregate total of attributed mortality is less than total mortality thus 'other causes' is a real group which we had not analyzed. We now present this category and also comment on malaria.*

Chapter 5 is stronger "biostatistically" than it is "epidemiologically". The authors do an excellent job of explaining how they analyzed the data once they obtained them, but the report would be strengthened by a better discussion of the design aspects of the meta–analysis. In particular, they should indicate how the studies reviewed (both published and unpublished) were identified, including the details of any computerized and/or manual literature searches. More information would also be helpful concerning selection criteria for studies included in the meta–analysis with respect to the use of concurrent vs. historical controls. Although it is clear from the very brief description of the studies on pages 38 and 39 that both randomized and nonrandomized studies were included, I would have preferred more detail on the various methods of treatment allocation, especially regarding the extent to which the individual study investigators ensured that treatment allocation was unbiased. It may well be that, since omission of individual studies had very little effect on the pooled estimate of the relative risk, taking treatment allocation into account would not alter the overall conclusions of the meta–analysis. Nonetheless, with no information on this design feature in the report, the reader who is unfamiliar with the individual studies may well question whether *all* the studies have produced a similar, but biased, effect estimate.

> *Comment: In response to this criticism, a new paragraph describing the method of identification and selection of studies has been added.*

Another potentially important design feature that is not taken into account explicitly in the meta–analysis is the overall duration of follow–up. Since, as shown in Table 5.2A, study length varied from 5 to 42 months, cumulative morality rates would also vary, even if there were the same underlying risk of mortality in each setting, to take an extreme example, if each of the studies had followed their subjects for 80 years, mortality would have been 100% in both the vitamin A and control groups, and no mortality reduction would have been seen with vitamin A. It may well be that, given the age group under study and the authors' assessment of effect modification by age categories, different durations of follow–up had little or no influence on the estimate of effect. But in addition to the analyses reported, the authors should examine mortality within, say, one year of beginning treatment. They should also consider including time–to–death types of analyses using life table techniques to adjust both for losses to follow up within studies and for differential durations of follow–up between studies.

> *Comment: We agree with the desirability of assessing the time course of mortality effects but we were unable to do this* (*see also comments in response to Dr. Horton*)*. We note that duration of the study* (*Table 5.2A*) *does not necessarily mean length of follow–up.*

The authors make a distinction between a pooled estimate of effectiveness based on the available studies, and prediction of effectiveness in a new treatment situation. It would be useful to discuss these differences in terms of fixed vs. random effect models, since some readers may ask why the variation in true effects among the reviewed studies was not taken into account in estimating the effectiveness from the reviewed studies or, conversely, why it was taken into account in predicting effectiveness in new situations.

> *Comment: Although originally we did not use this terminology, indeed we have presented 'fixed' and 'random' effect models. In our text, we describe these as two possible models – one in which there is a single true* RR *which we are attempting to estimate* (*the fixed effect model*) *and one in which we are attempting to estimate the average* RR *which varies among studies* (*the random effect model*)*. This is set out in the section in Chapter 5 on Analytical Methods and we now include a cross–identification for those more familiar with the fixed effect/random effect nomenclature. We accept that the variances of the summary* RR *estimates presented in tables are from the fixed effect model however in Figure 5.2 we now present also the* CI *that applies with a random effects model. Our Prediction Intervals*

explicitly accept the random effect model, as noted by Dr. Kramer.

Chapter 5 would be strengthened by having a separate section discussing the results in terms of relative risk and risk difference. It is true that the authors found no effect modification by gender, age, and a variety of study– and population–specific variables on the relative risk of mortality in vitamin A–treated vs. control children. Had they decided to perform a data–analysis based on the risk difference instead of the relative risk, however, such effect modification would have been observed. In fact, the insertion of Table 5.13, which clearly shows how the risk difference decreases with increasing age, will be difficult for most readers to understand, placed as it is in the middle of several paragraphs examining effect modification on the relative risk scale.

Comment: We have accepted this recommendation, also suggested by Dr. Horton, and now separate the discussion of relative and absolute effects. We feel that it is important that readers understand the distinction and its practical implication and we agree also that, as previously presented, all but the particularly astute reader might miss it.

Finally, the authors suggest that it might be ethical to study the effectiveness of improvement of vitamin A status in infants under 6 months of age (page 59, first paragraph of Research Recommendations). This appears to be based on a lack of statistically significant mortality reduction in this age group. But the point estimate of that risk reduction is very similar to the one obtained for older ages. Unless the authors have a biologically plausible explanation for why the effect should be absent in young infants (in which case they should cite the relevant evidence), it hardly seems any more ethical to study young infants than it does older children. The mere fact of insufficient sample size does not ethically justify such a study. To take an extreme but heuristic example, if the authors had examined the effect of vitamin A supplementation in infants between 21.0 and 21.5 months of age, their sample size might also have been inadequate to exclude a null result with high confidence. Would they then conclude it was ethical to study such children?

Comment: We accept this criticism and have modified the wording to indicate more clearly the original intent that since this was a very high interest group to programmers interested, for instance, in coupling vitamin A supplementation and extended immunization, we could not offer a definitive answer. The absence of an answer for such an important group might shift ethical considerations (*not resolve them*)*. We intended to make a strong contrast with the situation for older infants and children where we felt comfortable in giving a firm answer. We are pleased to reproduce Dr. Kramer's comment on ethics as a balancing view in a very difficult question. We note also that the report by West et al., on supplementation of very young infants in Nepal, did not become available until long after these comments were written.*

Dr. Kramer also offered a number of valuable detailed editorial comments and suggested modifications. Most have been accommodated in the present revision.

Reviewer

Dr. J.N.K. Rao
Professor of Statistics
Carlton University
Ottawa, Ontario, Canada

General Assessment

My review will focus on the theoretical basis of the analyses reported in Chapter 5.1 found the underlying theory, based on relative risk (RR), very sound and novel. In particular, the use of design effect to take account of clustering, the application of meta–analysis to combine results from several independent studies to produce summary estimates and associated confidence intervals, and the construction of prediction intervals for relative risk of a future study are noteworthy. Also, the procedure CATMOD is a good choice to model the logarithm of mortality rate as a linear function of factors of interest and to analyze the data on mortality rates. The analyses reported in Chapter 5 are carefully done and the conclusions clearly highlight the major results of the study.

Technical Comments: Dr. Rao offered valuable technical comment including suggestions of alternate strategies for derivation of estimates used in our analyses (*e.g. of estimation of variance components*)*. We value his suggestions and plan to take them up in a technical paper on our analytical methods now being planned. Through direct contact, it was*

established that the detailed comments presented by Dr. Rao would not have appreciable impact on the derived estimates that we used.

It was also clear from Dr. Rao's discussion, as well as from comments by other reviewers that the relatively novel development of Prediction Intervals and their relevance to actual use was not made clear. In Dr. Rao's comments this emerged as a challenge with reference to which components of variance should actually be included. We have attempted to address this and related comments by other reviewers by expanding the discussion of the prediction interval and by more clearly indicating that there are actually two intervals that have been constructed, each with different meaning and application. These are the intervals that relate to the real effect expected in a future study. As Dr. Rao pointed out this interval does not include sampling variance. The other interval which does include sampling variance relates to the effect that would be observed. We hope that the distinction is now clearer in our text. We think we have been responsive to Dr. Rao's comments and we thank him for his input which will help us move the whole new approach ahead in preparing a technical paper for publication.

Dr. Rao also identified some typographical errors in the statistical notations in the Technical Annex. These have been corrected.

Technical Annex

Theoretical Basis of Analyses Included

This annex gives the technical background that is the basis of the analyses presented in this report.

Variance of Relative Risk

Let $\hat{p}$ be an estimate of a mortality rate. If $\hat{p}$ is a binomial proportion with parameters n and p, the variance of $\hat{p}$ is $\sigma^2(\hat{p}) = pq/n$, where q = 1 – p.

The delta method can be used to approximate variances of functions of random variables. The variance of f (X) is approximated by $?^2(f'[\mu])^2$, where μ and $?^2$ are the mean and variance of X and f'(x) is the derivative of f (x) with respect to x. It follows that $\sigma^2(\log[\hat{p}])$ is approximately $\sigma^2(\hat{p})/p^2$.

Relative risk (R) is defined as the ratio of two rates, say p_a/p_c. (The subscripts here refer to the vitamin A group and the control group.) Because the distribution of R is skewed, it is standard practice to work with log(R). Let $\hat{R} = \hat{p}_a/\hat{p}_c$. We assume that $\hat{p}_a$ and $\hat{p}_c$ are independent. Since

$$\log(\hat{R}) = \log(\hat{p}_a) - \log(\hat{p}_c)$$

it follows that

$$\sigma^2(\log[\hat{R}]) = \sigma^2(\log[\hat{p}_a]) + \sigma^2(\log[\hat{p}_c])$$

Applying the delta method gives the approximation

$$\sigma^2(\log[\hat{R}]) = \sigma^2(\hat{p}_a)/p_a^2 + \sigma^2(\hat{p}_c)/p_c^2 \quad (1)$$

If we make the binomial assumption, this simplifies to

$$\sigma^2(\log[\hat{R}]) = q_a/n_a p_a + n_c p_c \quad (2)$$

We will need both of these forms in subsequent derivations. To obtain estimates of these variances from data, we simply substitute parameter estimates in place of unknown parameters.

Cluster Sampling and Design Effects

The randomizations in all but one of the studies analyzed in this report involve units larger than the individual. This is called *cluster sampling* (Cochran, 1977). The consequence is that equation (1) above is valid but (2) is not. Given information at the cluster level, the variances in equation (1) can be estimated. The ratio of the resulting variance to the variance in equation (2) is called the *design effect.* A recent paper (Rao and Scott, 1992) describes how to use the design effect to adjust sample counts to obtain correct variance estimates that account for cluster sampling. The idea is simple and elegant. The sample counts are divided by the design effect. We use this technique in our analyses.

Two studies report their results with design effects (Tamil 1.3, and Sarlahi 1.23) while two others (Aceh and Jumla) give information that we use to estimate these effects. For each of these four studies we estimate design effects appropriate for use in our analyses by the following method. First we transform the reported summary relative risk and confidence interval into an estimate of the cluster adjusted variance of the log relative risk. We divide this variance estimate by the variance calculated using equation (2) to get a design effect. In these calculations we use counts as reported by the studies. For Jumla, this means that we used numbers of children rather than the child−years of exposure. For the Ghana study we obtained data at the cluster level and used this information to calculate a design effect directly.

The calculated design effects for these five studies are used to estimate or predict design effects for all studies. A variety of approaches were tried. The approach we use is based on the following idea. We assume that the cluster−adjusted variance for each mortality rate is equal to the binomial variance plus a correction for the cluster design. We assume that the correction is proportional to the binomial variance with the number of children replaced by the number of clusters. Specially, we use

$$\sigma^2(\log[\hat{R}]) = q_a / n_a p_a + n_c p_c$$

for the binomial variance and

$$\sigma^2(\log[\hat{R}]) = q_a / m_a p_a + m_c p_c$$

where m_a and m_c are the numbers of clusters in the two samples, for the correction. If we allow the possibility that the coefficient for the binomial variance is not necessarily one, this gives an expression for d, the design effect.

$$d = (a[\frac{q_a}{n_a p_a} + \frac{q_c}{n_c p_c}] + b[\frac{q_a}{m_a p_a} + \frac{q_c}{m_c p_c}]) / (\frac{q_a}{n_a p_a} + \frac{q_c}{n_c p_c})$$

This simplifies to

$$d = a + bx \quad (3)$$

where

$$x = (\frac{q_a}{m_a p_a} + \frac{q_c}{m_c p_c}) / (\frac{q_a}{n_a p_a} + \frac{q_c}{n_c p_c})$$

Note that if $m_a = m_c$ and $n_a = n_c$ then $x = {}^{n}/_{m}$, the average cluster size.

When least squares is used to fit equation (3) to the data from the four studies, the intercept is very close to one. Therefore, we use the fit obtained by forcing a = 1. In this model, the P−value for the coefficient b is statistically significant; but the application of hypothesis testing in this circumstance is dubious. The Jumla study is a very influential point in this fit.

The fitted values of equation (3) were used to estimate design effects for all 8 studies. These design effects

are used to adjust the counts that we use in our study (these are not always the same as those reported, as noted elsewhere in this report) in the way described above.

Other approaches to estimate design effects were examined. The final results were relatively insensitive to the approach used.

Categorical Data Modelling

We use the SAS procedure CATMOD to analyze the counts. The link function is log(p) where p is the proportion dead. For a single study the model is

$$\log(p)=ß_0+ ß_1t$$

where t = 1 for the vitamin A group and t = 0 for the control group. The estimate of $ß_1$ is the estimate of the log relative risk. This estimate, b_1 and its associated standard error s are used to construct a 95% confidence interval for the relative risk using

$$e^{b_1 \pm 196s}$$

The test of the null hypothesis that $ß_1 = 0$ is equivalent to the test that the relative risk is one and the results are reported with a chi−square statistic.

More complex models are handled in a similar way. To combine information from studies, we use

$$\log(p)=ß_0 + ß_1t + s_i$$

where s, is a categorical variable representing the effect of the study i. The chi−square test associated with s_i has degrees of freedom equal to one less than the number of studies and tests the hypothesis that log(p) does not vary across studies. Examination of the data reveals that the mortality rates vary widely across studies so this hypothesis is not particular interesting.

The question of whether or not the relative risk varies across studies is examined by the residual for the above model. The degrees of freedom for this test are also equal to one less than the number of studies. A statistically significant residual indicates that there is evidence to conclude that the variation in study relative risks is more that would be expected by chance under the model that assumes a common true value of relative risk for all studies. This test is sometimes called the homogeneity test.

Note that we could rewrite the model as

$$\log(p) = ß_0 + ß_1t + s_i + ts_i$$

and the result would then appear as an interaction of treatment with study. In this case the model would be saturated and the degrees of freedom for residual would be zero. The results are equivalent.

The analyses for gender or age are handled similarly. To estimate gender specific relative risks for each study we run the model with t alone for each gender−study combination. To generate gender specific summaries across studies we use treatment and study in the model. To examine differences in relative risks across genders, we use a model with treatment, gender, study and the two way interactions of these terms. The equality of relative risks across genders is examined by the test for the treatment by gender interaction term in this model. Age is analyzed similarly.

Cause specific mortality is studied by analyzing each cause separately. Relative risk information is generated for each cause−study combination and summaries are computed using a model that includes treatment and study for each cause.

Weights

The combining of information from several studies can be viewed in terms of weighted averages. Specifically, let l_i, denote the log relative risk for study i. A general form of a summary is

$$\hat{L} = \frac{\sum w_i l_i}{n} \quad (4)$$

where ?w_i = n. The weights w_i represent the relative importance of each study in the summary. If w_i = 1 for all i then each study has equal weight.

Any set of weights satisfying the above condition will give a valid estimator in the sense that it will be an unbiased estimator of the mean. Different weights lead to different variances of the estimators, however. Weights that minimize this variance are called optimal weights and are inversely proportional to the variances of the l_i. These weights are

$$w_i = \frac{1/\sigma_i^2}{(1/n)\sum 1/\sigma_i^2}$$

where σ_i^2 is the variance of l. Estimated weights of this type are used in the Mantel–Haenszel summary of relative risk and in the CATMOD analyses. Note that the computational forms for these procedures do not necessarily explicitly use weights in this way. In general, the variance of a weighted estimator is

$$\sigma^2(\hat{L}) = \frac{\sum w_i^2 \sigma_i^2}{n^2} \quad (5)$$

In practice, variances are not known and must be estimated with the data. The estimated variances are used to estimate optimal weights and to calculate variances of the weighted estimators.

We have used different sets of weights to obtain summary relative risk estimates. Comparison of the results gives an indication of the insensitivity of the final estimates and confidence intervals to the particular choice of weights.

Weighted Regressions

We use the estimated optimal weights described above to perform regressions relating relative risk and log relative risk to the prevalence of xeropthalmia, stunting and wasting. We approximate the variance of relative risk using the delta method described above. The result is

$$?^2(r) = ?^2 (l)e^{2l}$$

where l denotes the log relative risk.

A Model

The following model is the basis for the prediction intervals generated in this report and serves as a framework for interpreting the results.

Let l_i, denote the observed log relative risk for study i. We assume that the l_i, are independently distributed normal random variables with means L, and variances τ_i^2. Furthermore, we assume that the L, are independently and identically distributed normal random variables with mean L and variance $?^2_i$ Here, the L_i represent the true log relative risk for each study and L represents the mean of these values averaged over the set of all possible studies of this kind.

It follows the El_i = L and

$$\sigma^2 = (l_i) = \tau^2 + \tau_i^2$$

Here and in what follows E denotes expectation. This model states that the variance of each study is composed of two components: (1) study to study variation represented by $?^2$ and (2) within study variation represented by τ_i^2.

Note that in the previous sections we have implicitly assumed that the first component is zero. The data suggest that this component is small; in most cases it cannot be distinguished from zero by the usual hypothesis testing methodology. Therefore, the conclusions drawn from the analyses based on this assumption are valid.

Let $\hat{L}=(1/n)\sum w_i l_i$, where $?w_i = n$, be a weighted estimator of L. It follows that

$$\sigma^2(\hat{L}) = \frac{\tau^2 \sum w_i^2 + \sum w_i^2 \tau_i^2}{n^2}$$

To obtain an estimator of $?^2$, we proceed as follows. First, let

$$s^2 = \frac{\sum w_i (l_i - \hat{l})^2}{n-1}$$

where $\hat{l}=(1/n)\sum w_i l_i$. Note that s^2 is simply the weighted variance estimator that views each l_i, as an observation.

It can be shown that

$$Es^2 = \frac{\tau^2 (n - \frac{1}{n}\sum w_i^2) + \sum w_i (1 - \frac{w_i}{n})\tau_i^2}{n-1}$$

Solving for $?^2$ and substituting sample estimators for unknown parameters gives the following estimator for the study to study variance $?^2$

$$\hat{\tau}^2 = \frac{(n-1)s^2 + \sum w_i (1 - \frac{w_i}{n}) s_i^2}{n - \frac{1}{n}\sum w_i^2} \quad (7)$$

where s_i^2 is the (design effect adjusted) estimated variance of the log relative risk for study i. Note that all of these formulas can be simplified in the special cases of equal weights and optimal weights.

Our model states that

$$\sigma^2(l_i) = \tau^2 + \tau_i^2$$

However, this is not the variance estimated by s_i^2, the estimated variance of log relative risk for study i. Each s_i^2 is an estimate of the variability of l_i about its study specific mean, i.e. it is an estimate of τ_i^2. Another way of viewing this is to note that τ_i^2 is the conditional variance of l_i, given the study.

Note that the estimator of $?^2$ is obtained from the variability among studies quantified by s^2. Equation (6), roughly speaking, expresses the idea that the true study to study variation is estimated by subtracting the within study variation from the observed study to study variation. This is the basic idea behind estimation of components of variance (Neter, Wasserman and Kutner, 1990).

For the SAS program that performs these calculations, we simplified the expression for $\sum w_i (1 - w_i/n) s_i^2$ in the variance formula above. It is equal to $\sum w_i s_i^2 - (1/n)\sum w_i^2 s_i^2$.

Prediction Intervals

Prediction intervals are most commonly encountered in a regression setting (see, for example, Neter, Wasserman and Kutner, 1990). The basic idea can be expressed in simple terms. Suppose we have X_i, X_2,...,

X , independent and identically distributed normal observations with mean μ and variance σ_i^2. We consider a new observation, say X_{n+1}. Let $\hat{X}$ denote the mean of the first n observations. Then, $\hat{X} - X_{n+1}$ is normal with mean zero and variance $?^2$ (1 + 1/n). Therefore, the probability that $\hat{X} - X_{n+1}$ is between $-1.96\sqrt{\sigma^2(1+1/n)}$ and $+1.96\sqrt{\sigma^2(1+1/n)}$ is .95, for example. This is equivalent to saying that X_{n+1} is in the interval

$$\hat{X} \pm 1.96\sqrt{\sigma^2(1+1/n)}$$

We call this interval a prediction interval. In the normal case, we generally use estimated variances and replace the normal critical values with values taken from the appropriate t distribution.

Note that the variance term $?^2(1 + 1/n)$ consists of two parts: the variance of X_{n+1} ($?^2$) and the variance of $\hat{X}(\sigma^2/n)$. Our inference with a prediction interval is based on the variability of our current estimator $(\hat{X})$ and the variability of the new value (X_{n+1}).

We apply this idea to the log relative risks. The role of $\hat{X}$ is played by

$$\hat{L} = (1/n)\sum w_i l_i \quad (8)$$

with variance $\sigma^2(\hat{L})$, given by equation (6). The role of X_{n+1} is played by l_{n+1} the log relative risk in a new program where children are supplemented with vitamin A. Our model states that its *unconditional* variance is $\tau^2 + \tau^2_{n+1}$. This is the variance that is appropriate to use when considering the variability of l_{n+1} about its unconditional mean L_{n+1}. (Recall that τ^2_{n+1} is the conditional variance of l_{n+1}, i.e. the variability of l_{n+1} about its conditional mean L_{n+1}).

Thus, to construct a prediction interval for l_{n+1}, the variance used in the limits is

$$\sigma^2(\hat{L}) + \tau^2 + \tau^2_{n+1}$$

The three terms in this expression represent

1. imprecision in our knowledge of L expressed as $\sigma^2(\hat{L})$,
2. study to study variation expressed as $?^2$,
3. within variance for the new program expressed as τ^2_{n+1}.

The above expression for the variance involves unknown parameters. We substitute estimates for these in our calculations. The estimate of the first term is obtained from equation (6).

$$s^2(\hat{L}) = \frac{\hat{\tau}^2 \sum w_i^2 + \sum w_i^2 s_i^2}{n^2}$$

The estimate of the second term is given in equation (7).

$$\hat{\tau}^2 = \frac{(n-1)s^2 - \sum w_i(1 - \frac{w_i}{n})s_i^2}{n - \frac{1}{n}\sum w_i^2}$$

In these expressions, s_i^2 is the (design effect adjusted) estimated variance of the log relative risk for study i.

The third term depends on the characteristics of the new program. It depends on the numbers of children supplemented and the control mortality rate. For a very large program this term would be close to zero and could therefore be neglected. We have calculated values for each of the 8 studies and these can be used as benchmarks to interpret the results.

To summarize, let s_p^2 denote the variance to be used in constructing the prediction interval. Then

$$s_p^2 = s^2(\hat{L}) + \hat{\tau}^2 + \tau_{n+1}^2$$

where τ_{n+1}^2 can be an estimated value from one of the studies we have or any other value that is plausible.

The 95% prediction interval in log form is

$$\hat{L} \pm 1.96 s_p$$

where

$$\hat{L} = (1/n) \sum w_i l_i$$

Exponentiation of the limits converts this interval to an interval in the relative risk scale. The prediction interval end–points are

$$e^{\hat{L} \pm 1.96 s_p}.$$

Comparison of Reported and Derived RR and C.I. Values

The following table compares the Relative Risk and Confidence Interval estimates published in the original papers (ACEH and MSG were expressed as odds ratios in inverse form in original; they have been inverted here) with the RR and adjusted Confidence Intervals presented in this report.

Comparison of Reported and Derived Estimates of Effects of Vitamin A (Total Study Population Estimates)

	Reported in Original Publication		***Derived in Present Report***	
Study	***RR***	***C.I.***	***RR***	***C.I.***
Aceh	0.74	0.54 to 0.99	0.73	0.56 to 0.96
Ghana	0.81	0.68 to 0.98	0.80	0.70 to 0.93
Hyderabad	N/R	N/R	0.94	0.57 to 1.56
Jumla	0.74	0.55 to 0.99	0.74	0.55 to 1.01
MSG	0.69	0.57 to 0.84	0.70	0.57 to 0.86
Sarlahi	0.70	0.56 to 0.88	0.71	0.56 to 0.89
Sudan	1.06	0.82 to 1.37	1.04	0.81 to 1.34
Tamil Nadu	0.46	0.29 to 0.71	0.50	0.34 to 0.75

N/R = Estimated RR and C.I. were not published.

In two studies, SUDAN and TAMIL NADU, the report–estimated RR appear to differ from the originally published estimate. In the case of SUDAN, this is likely due to the fact that we included the mortality among

'non−compliant' children (reported in original paper but not included in RR calculation). In the case of TAMIL NADU, the discrepancy arises from the fact that we included accidental deaths not originally included in the published paper. The confidence intervals are generally comparable for most studies. In the cases of SUDAN and TAMIL NADU, the intervals are shifted consequent to the difference in RR. Minor differences in the intervals for other studies probably arise from the derivation of the DEFF corrections for cluster effects applied in the present report, as well as from the fact that we excluded from the denominator the children with unknown vital status where this information was available. For JUMLA and GHANA, there has been some overestimation of variance, probably associated with the conversion between child years and counts.

The comparison confirms that our approach to derivation of RR and C.I. did not distort the inferences to be drawn about overall effect of vitamin A based upon originally reported analyses. *In every case, we recommend that the originally published confidence intervals and significance levels be used if interest is focused upon individual studies.*

SAS Programs Used and Outputs

NOTE THAT ALL PROGRAMS ARE WRITTEN FOR SAS PC, V 6.04. WITH VERY MINOR MODIFICATION (FILE DESIGNATIONS) THEY WILL RUN ON SAS MAINFRAME VERSION 6. ***THESE PROGRAMMES AND DATA FILES ARE AVAILABLE ON DISK. CONTACT G. H. BEATON.***

PROGRAMME A: First Part of Design Effect Estimation

```
*****************************************************************
** PROGRAMME TO DEVELOP REGRESSION FOR ESTIMATION OF **
** DESIGN EFFECT (FOR CLUSTERING) IN OTHER STUDIES **
** WITH UNSPECIFIED DESIGN EFFECT ADJUSTMENTS **
*****************************************************************
INPUT DESCRIPTORS OF REFERENCE STUDIES AND THEIR REPORTED (ADJUSTED) ESTIMATES OF
RR AND CI

************************************************
da na dc nc are counts of subjects by treatment and number dead (d..) and total count (n..)
rr lcl ucl are reported rr and confidence limits
cla and clc are reported numbers of clusters in design
preddeff is the estimated design effect for these studies

************************************************************;
** Note that for TAMIL NADU, the deaths reported do not include accidental deaths incorporated in later
analyses. This is done to permit direct use of the published RR and CI
Note also that total counts exclude children with vital status not known at end of study.
************************************************************;
data a1; input study $ da na dc nc rr lcl ucl cla clc;
cards;

 Aceh     101  12991  130  12209  .74  .54  .99  229  221
 Tamil     37   7302   80   7247  .46  .29  .71  103  103
 Sarlahi  152  14234  210  14091  .70  .56  .88  130  130
 Jumla    138   3786  167   3411  .74  .55  .99    8    8
 Ghana    397  10035  495  10024  .81  .68  .98   92   93
;
data a2; set a1;

ma = na/cla; mc = nc/clc;
pa = da/na; pc = dc/nc; qa = 1−pa; qc = 1−pc; rrcalc = pa/pc;
varpa = pa*qa/na; varpc = pc*qc/nc;
varlpa = varpa/(pa*pa); varlpc = varpc/(pc*pc);
```

```
varlrr = varlpa + varlpc;
lclc = exp(log(rrcalc)−1.96*sqrt(varlrr));
uclc = exp(log(rrcalc) + 1.96*sqrt(varlrr));
sup = (log(rr)−log(lcl))/1.96; slo = (log(ucl)−log(rr))/1.96;
sav = (sup + slo)/2; varadj = sav*sav;
if study = 'Jumla' then do; varadj = varadj*.95;
lcl = exp(log(rr)−1.96*sqrt(varadj));
ucl = exp(log(rr) + 1.96*sqrt(varadj));end;

wratio = (ucl−lcl)/(uclc−lclc); wratio2 = wratio*wratio;
deffcl = varadj/varlrr; deffsd = sqrt(deffcl);
x1 = ((qa/(cla*pa)) + (qc/(clc*pc)))/((qa/(na*pa)) + (qc/(nc*pc))); x2 = ((1/(cla*pa*pa)) +
(1/(clc*pc*pc)))/((qa/(na*pa)) + (qc/(nc*pc)));
proc plot; plot deffcl*(x1 x2) = study;
proc sort data = a2 out = a2; by study;
proc reg data = a2; model deffcl = x1; restrict intercept = 1;

output out = a3 p = preddeff;
proc print data = a3;
*************************************************************************
** THE REGRESSION COEFFICIENT GENERATED IN THIS PROGRAMME ***
** IS APPLIED IN SUCCESSIVE PROGRAMME TO ESTIMATE DESIGN EFFECT ***
** FOR OTHER STUDIES ***
*************************************************************************
run;
```

OUTPUT FROM PROGRAMME A

Model: MODEL1
NOTE: Restrictions have been applied to parameter estimates.
Dependent Variable: DEFFCL

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	ProbF
Model	0	.	.	.	.
Error	4	0.76867	0.19217		
C Total	4	0.42956			
Root MSE		0.43837	R−square	.	
Dep Mean		1.51507	Adj R−sq	.	
C.V.		28.93384			

Parameter Estimates

Variable	DF	Parameter Estimate	Standard Error	T for H0: Parameter = 0	Prob > |T|
INTERCEP	1	1.000000	0.00000000	.	.
X1	**1**	**0.002044**	0.00090182	2.267	0.0860
RESTRICT	−1	0.947081	0.66696016	1.420	0.2286

SAMPLE PARAMETER ESTIMATES

OBS	STUDY	DA	NA	DC	NC	RR	LCL	UCL	CLA	CLC	MA	MC

1	Aceh	101	12991	130	12209	0.740	0.54000	0.99000	229	221	56.729	55.244
2	Ghana	*Withheld pending pub*				0.814	0.68000	0.98000	92	93	109.076	107.785
3	Jumla	138	3786	167	3411	0.740	0.55568	0.98545	8	8	473.250	426.375
4	Sarlahi	152	14234	210	14091	0.700	0.56000	0.88000	130	130	109.492	108.392
5	Tamil	37	7302	80	7247	0.460	0.29000	0.71000	103	103	70.893	70.359

OBS	PA	PC	QA	QC	RRCALC	VARPA	VARPC	VARLPA
1	0.007775	0.010648	0.99223	0.98935	0.73016	.0000005938	.000000863	0.009824
2	0.039562	0.049381	0.96044	0.95062	0.80114	.0000037864	.000004683	0.002419
3	0.036450	0.048959	0.96355	0.95104	0.74450	.0000092767	.000013651	0.006982
4	0.010679	0.014903	0.98932	0.98510	0.71654	.0000007422	.000001042	0.006509
5	0.005067	0.011039	0.99493	0.98896	0.45902	.0000006904	.000001506	0.026890

OBS	VARLPC	VARLRR	LCLC	UCLC	SUP	SLO	SAV	VARADJ	WRATIO
1	0.007610	0.017434	0.56367	0.94582	0.16076	0.14850	0.15463	0.023909	1.17752
2	0.001920	0.004340	0.70410	0.91156	0.09177	0.09469	0.09323	0.008692	1.44608
3	0.005695	0.012677	0.59707	0.92833	0.15139	0.14850	0.14995	0.021359	1.29735
4	0.004691	0.011200	0.58231	0.88170	0.11385	0.11676	0.11530	0.013295	1.06884
5	0.012362	0.039252	0.31130	0.67682	0.23538	0.22145	0.22841	0.052173	1.14906

OBS	WRATIO2	DEFFCL	DEFFSD	**X1**	X2	PREDDEFF
1	1.38657	1.37139	1.17106	56.081	6432.96	1.11464
2	2.09114	2.00285	1.41522	108.505	2616.41	1.22181
3	1.68312	1.68489	1.29803	452.193	11535.11	1.92438
4	1.14242	1.18706	1.08952	109.032	9115.51	1.22288
5	1.32034	1.32918	1.15290	70.725	11663.14	1.14458

Note: From this programme it is the regression coefficient, X1, shown in **bold** that is carried forward to the next programme. The parameter estimates are for information only at this stage. PREDEFF is the factor to be used in adjusting for cluster effect.

PROGRAMME B: Second Part of Design Effect Estimation

```
options ls = 80;
data a1a;

*****************************************************
** ESTIMATION OF DESIGN EFFECT FOR CLUSTERED SAMPLES **
** AND TEST ALTERNATE ESTIMATION OF SUMMARY RR * *
** USES REGRESSION COEFFICIENT DEVELOPED IN PROG A **
*****************************************************
************************************
INPUT STUDY COUNTS FROM REFERENCE FILE
************************************;
```

```
infile 'b:vita_cnt.all';
input study $ trtmnt $ surv $ count;
DATA A1A; SET A1A;
if trtmnt = 'A_admin' then do;

if surv = 'live' then faa = count;
if surv = 'dead' then fda = count;
END;
if trtmnt = 'control' then do;

if surv = 'live' then fac = count;
if surv = 'dead' then fdc = count;
END;
proc sort; by study;
proc univariate noprint; by study;
var faa fda fac fdc;
output out = a1 mean = aa da ac dc;
data a1; set a1;
na = aa + da;
nc = ac + dc;
drop aa ac;

*****************************************************************
INPUT CLUSTER COUNTS FROM REFERENCE FILE
*****************************************************************;
data cluster;
infile 'b:clusters.dat';
input study $ cla clc;
proc sort; by study;
data a1; merge a1 cluster; by study;
proc print data = a1;
data a2; set a1;

pa = da/na; pc = dc/nc; qa = 1–pa; qc = 1–pc; rr = pa/pc; lrr = log(rr);
varpa = pa*qa/na; varpc = pc*qc/nc;
varlpa = varpa/(pa*pa); varlpc = varpc/(pc*pc);
x1 = ((qa/(cla*pa)) + (qc/(clc*pc)))/((qa/(na*pa)) + (qc/(nc*pc)));
*****************************************************************************************
** ESTIMATE THE DESIGN EFFECT FROM A LINEAR REGRESSION **
** DEVELOPED FROM EXAMINATION OF STUDIES WITH INTERNALLY **
** REPORTED ADJUSTMENTS FOR CLUSTER EFFECT (ACEH, TAMIL, **
** SARLAHI, JUMLA, GHANA) **
*****************************************************************************************;

preddeff = 1 + .002044*x1; **<<<<Carried forward from programme A;
proc print round;
var study preddeff;
title 'ESTIMATED DESIGN EFFECT FOR INDIVIDUAL STUDIES';
run;
*****************************************************************************
** ESTIMATE THE RELATIVE RISK BY ALTERNATE STRATEGIES **
*****************************************************************************;

data a2; set a2;
vlrr = varlpa + varlpc; vlrrp = vlrr*preddeff; vlrrt = vlrr*1.3;
if study = 'SUDAN' then vlrrt = vlrr;
wt1 = 1; wtv = 1/vlrr; wtp = 1/vlrrp; wtt = 1/vlrrt;
lcl_nadj = exp(lrr–1.96*sqrt(vlrr))
ucl_nadj = exp(lrr + 1.96*sqrt(vlrr))
lcl_padj = exp(lrr–1.96*sqrt(vlrrp))
ucl_padj = exp(lrr + 1.96*sqrt(vlrrp))
lcl_tadj = exp(lrr–1.96*sqrt(vlrrt))
```

```
ucl_tadj = exp(lrr + 1.96*sqrt(vlrrt))
proc print data = a2 round;

var study preddeff rr
lcl_nadj ucl_nadj lcl_padj ucl_padj lcl_tadj ucl_tadj;
proc univariate data = a2 noprint; var wt1 wtv wtp wtt;

output out = s1 mean = mwt1 mwtv mwtp mwtt;
data a3; set a2; if _n_ = 1 then set s1;

wt1 = wt1/mwt1; wtv = wtv/mwtv; wtp = wtp/mwtp; wtt = wtt/mwtt;
vp1 = wt1*wt1*vlrrp/64; vpv = wtv*wtv*vlrr/64;
vpp = wtp*wtp*vlrrp/64; vpt = wtt*wtt*vlrrt/64;
proc print data = a3;

var study rr wt1 wtv wtp wtt;
proc univariate data = a3 noprint; var vp1 vpv vpp vpt;

output out = s2 sum = svpl svpv svpp svpt;
proc univariate data = a3 noprint; var lrr; weight wt1;

output out = m1 mean = lrr1;
proc univariate data = a3 noprint; var lrr; weight wtv;

output out = m2 mean = lrrv;
proc univariate data = a3 noprint; var lrr; weight wtp;

output out = m3 mean = lrrp;
proc univariate data = a3 noprint; var lrr; weight wtt;

output out = m4 mean = lrrt;
data a4; merge s2 m1 m2 m3 m4;

rr1 = exp(lrr1); rrv = exp(lrrv); rrp = exp(lrrp); rrt = exp(lrrt);
lcl1 = exp(lrr1−1.96*sqrt(svp1))
ucl1 = exp(lrr1 + 1.96*sqrt(svp1))
lclv = exp(lrrv−1.96*sqrt(svpv))
uclv = exp(lrrv + 1.96*sqrt(svpv))
lclp = exp(lrrp−1.96*sqrt(svpp))
uclp = exp(lrrp + 1.96*sqrt(svpp))
lclt = exp(lrrt−1.96*sqrt(svpt))
uclt = exp(lrrt + 1.96*sqrt(svpt))
proc print data = a4;

var rr1 rrv rrp rrt lcl1 lclv lclp lclt ucl1 uclv uclp uclt;
run;
```

OUTPUT FROM PROGRAMME B

OBS	STUDY	DA	DC	NA	NC	CLA	CLC
1	ACER	101	130	12991	12209	229	221
2	GHANA	397	495	10035	10024	92	93
3	HYDER	39	41	7076	7006	42	42
4	JUMLA	138	167	3786	3411	8	8
5	MSG	186	250	5775	5445	48	44

6	SARLAHI	152	210	13918	13610	130	130
7	SUDAN	123	117	14234	14091	8515	8515
8	TAMIL	42	83	7297	7244	103	103

ESTIMATED DESIGN EFFECT FOR INDIVIDUAL STUDIES

OBS	**STUDY**	**PREDDEFF**
1	**ACEH**	**1.11**
2	**GHANA**	**1.22**
3	**HYDER**	**1.34**
4	**JUMLA**	**1.92**
5	**MSG**	**1.25**
6	**SARLAHI**	**1.22**
7	**SUDAN**	**1.00**
8	**TAMIL**	**1.14**

OBS	STUDY	PREDDEFF	RR	LCL_NADJ	UCL_NADJ	LCL_PADJ	UCL_PADJ	LCL_TADJ	UCL_TADJ
1	ACEH	1.11	0.73	0.56	0.95	0.56	0.96	0.54	0.98
2	GHANA	1.22	0.80	0.71	0.91	0.70	0.93	0.69	0.93
3	HYDER	1.34	0.94	0.61	1.46	0.57	1.56	0.57	1.55
4	JUMLA	1.92	0.74	0.60	0.93	0.55	1.01	0.58	0.96
5	MSG	1.25	0.70	0.58	0.85	0.57	0.86	0.57	0.87
6	SARLAHI	1.22	0.71	0.58	0.87	0.56	0.89	0.56	0.90
7	SUDAN	1.00	1.04	0.81	1.34	0.81	1.34	0.81	1.34
8	TAMIL	1.14	0.50	0.35	0.73	0.34	0.75	0.33	0.77

COMPARISON OF WEIGHTING METHODS

OBS	STUDY	RR	WT1	WTV	WTP	WTT
1	ACEH	0.73016	1	0.67925	0.75804	0.66148
2	GHANA	0.80290	1	2.72884	2.77856	2.65747
3	HYDER	0.94181	1	0.23805	0.22057	0.23182
4	JUMLA	0.74450	1	0.93415	0.60409	0.90972
5	MSG	0.70149	1	1.31296	1.30786	1.27863
6	SARLAHI	0.70779	1	1.05777	1.08142	1.03011
7	SUDAN	1.04072	1	0.71616	0.88774	0.90666
8	TAMIL	0.50235	1	0.33281	0.36174	0.32411

OBS	RR1	RRV	RRP	RRT	LCL1	LCLV

1	0.75600	0.76585	0.77000	0.77201	0.67790	0.71022

OBS	LCLP	LCLT	UCL1	UCLV	UCLP	UCLT
1	0.70789	0.70921	0.84310	0.82583	0.83756	0.84038

Notes The DEFF estimates shown in **bold** are carried forward for use in later programs.

In the above programme listing, showing outcome of alternate weighting strategies, the suffixes identify the weighting system applied: (WT.. RR.. LCL.. UCL..) where LCL and UCL are the lower and upper bounds of the 95% Confidence Interval, RR is the Relative Risk and WT is the weighting factor.

..1 indicates unweighted simple average.
..V indicates weighting by unadjusted variance.
..P indicates weighting by variance adjusted using DEFF.
..T indicates weighting using variance adjustment suggested by the Tamil Nadu project (1.3 for all but SUDAN)

PROGRAMME C: Estimation of RR and Confidence Intervals for Total Study Population

```
*********************************************************************************
** PROGRAMME TO COMPUTE RR AND CI FOR INDIVIDUAL STUDIES**
** AND SUMMARY RR AND CI FOR ALL STUDIES. USES **
** ADJUSTED VARIANCES, ALSO USES A SET OF PROGRAMME **
** STATEMENTS TO RUN ANALYSES EXCLUDING SPECIFIED **
** STUDIES **
*********************************************************************************;
options ls = 80;
title1 'Overall analysis';
data a1;
infile 'B: VITA_CNT.ALL'; **< File containing counts for each study;
input study $ group $ surv $ count;
if group = 'control' then treat = 0; else treat = 1;
%include 'B:vitadeff.sas'; *** Rem: Design effect adjustment factors;
count = count/deff;
%include 'B:vitaxno.sas';

*************************************************************************
** The above %include is used to exclude studies as follows **
** %include vitaxz where z = no, a, g, h, j, m, d, l, t, dh, dt, th, tdh, 4. **
** no excludes no studies single letters letters correspond **
** to the first letter of each study with the d = Sudan and **
** l = Sarlahi pairs of letters excluded the indicated pairs of **
** studies tdh excludes t d and h 5 includes tlghd 4 includes lghd.**
*************************************************************************
** Sample of the %include statement (vitaxdh): **
** if study eq 'SUDAN' or study eq 'HYDER' then delete; **
** title3 'Sudan and Hyder excluded'; **
*********************************************************************;
proc sort data = a1; by study;
proc printto new print = 'vitatras.h'; ** Rem: gets rid of unused output;
proc catmod data = a1;

response 1 0 log/outest = a2; weight count; direct treat;
model surv = treat/nodesign noiter noparm noprofile noresponse;
```

```
by study;
proc printto;
data a3; set a2; if _type_ = 'PARMS'; lrr = b2;
data a4; set a2; if _type_ = 'COV' and _name_ = 'B2'; var = b2;
data a5; merge a3 a4; keep study rr llimit ulimit se z P;

rr = exp(lrr); se = sqrt (var); llimit = exp (lrr−1.96*sqrt (var));
ulimit = exp(lrr + 1.96*sqrt (var)); z = lrr/se; P = 2*(1−probnorm(abs(z)));
proc print data = a5;
proc catmod data = a1;

response 1 0 log/outest = a2; weight count; direct treat;
model surv = treat study/
nodesign noiter noparm noprofile noresponse;
data a3; set a2; if _type_ = 'PARMS'; lrr = b2;
data a4; set a2; if _type_ = 'COV' and _name_ = 'B2'; var = b2;
data a5; merge a3 a4; keep rr llimit ulimit se z P;

rr = exp (lrr); se = sqrt (var); llimit = exp (lrr−1.96*sqrt (var));
ulimit = exp(lrr + 1.96*sqrt (var)); z = lrr/se; P = 2*(1−probnorm(abs (z)));
proc print data = a5;
run;
```

OUTPUT OF PROGRAMME C

Overall analysis
Variances calculated using estimated design effect adjustments
All studies included

ESTIMATED RR AND C.I. FOR INDIVIDUAL STUDIES

OBS	STUDY	RR	SE	LLIMIT	ULIMIT	Z	P
1	ACEH	0.73016	0.13911	0.55591	0.95903	−2.26075	0.02377
2	GHANA	0.80290	0.07276	0.69619	0.92597	−3.01699	0.00255
3	HYDER	0.94181	0.25819	0.56779	1.56220	−0.23220	0.81638
4	JUMLA	0.74450	0.15601	0.54836	1.01080	−1.89116	0.05860
5	MSG	0.70149	0.10618	0.56969	0.86378	−3.33915	0.00084
6	SARLAHI	0.70779	0.11687	0.56289	0.88999	−2.95718	0.00310
7	SUDAN	1.04072	0.12859	0.80886	1.33904	0.31039	0.75627
8	TAMIL	0.50235	0.20141	0.33851	0.74550	−3.41828	0.00063

CATMOD PROCEDURE

Response: SURV	Response Levels (R) = 2
Weight Variable: COUNT	Populations (S) = 16
Data Set: A1	Total Frequency (N) = 126022
	Observations (Obs) = 32

ANALYSIS OF VARIANCE TABLE

Source	DF	Chi−Square	Prob

INTERCEPT	1	14697.09	0.0000
TREAT	1	37.11	0.0000 <<< Effect of Vitamin A
STUDY	7	1221.87	0.0000
RESIDUAL	7	12.41	0.0879 <<< Test of homogeneity
			If significant, then heterogeneity
			_is present. In other runs this is
			tested by TREAT*STUDY interaction.

SUMMARY ESTIMATE OF RR (Note: Fixed Effect Model)

OBS	RR	SE	LLIMIT	ULIMIT	Z	P
1	**0.77007**	0.042887	**0.70799**	**0.83760**	**−6.09196**	**.0000000011154**

Note 1: Z is (RR−1)/Standard Deviation. P assumes normal distribution when RR and standard deviation are in log form.

Note 2: See Programme H for Prediction Interval and the Summary Estimate C.I. adjusted to take into account between study variation (i.e. a Random Effect model).

PROGRAMME D: Examination for Gender Effect

```
*********************************************************
** PROGRAMME TO EXAMINE IMPACT OF GENDER ON VITAMIN A **
** EFFECT **
*********************************************************;
options ls = 72;
title1 'Gender analysis';
data a1;

infile 'B:vita_cnt.gen'; ** Rem: input study counts;
input study $ group $ surv $ gender $ count;
if group = 'control' then treat = 0; else treat = 1;
%include 'B:vitadeff.sas'; ** Rem: adjustment for cluster effect;
count = count/deff;
proc sort data = a1; by gender study;
proc printto new print = 'vitatras.h';
proc catmod data = a1; response 1 0 log/outest = a2; weight count;

direct treat; by gender study;
model surv = treat/nodesign noiter noparm noprofile noresponse;
proc catmod data = a1; response 1 0 log/outest = a2x; weight count;

direct treat; by gender;
model surv = treat study/nodesign noiter noparm noprofile noresponse;
proc printto;
data a3; set a2; if _type_ = 'PARMS'; lrr = b2;
data a4; set a2; if _type_ = 'COV' and _name_ = 'B2'; var = b2;
data a5; merge a3 a4; keep gender study rr llimit ulimit se z P;
rr = exp(lrr); se = sqrt(var); llimit = exp(lrr−1.96*sqrt(var));
ulimit = exp(lrr + 1.96*sqrt(var)); z = lrr/se; P = 2*(1−probnorm(abs(z)));
proc print data = a5;
data a3x; set a2x; if _type_ = 'PARMS'; lrr = b2;
data a4x; set a2x; if _type_ = 'COV' and _name_ = 'B2'; var = b2;
data a5x; merge a3x a4x; keep gender rr llimit ulimit se z P;
```

```
rr = exp(lrr); se = sqrt(var); llimit = exp(lrr−1.96*sqrt(var));
ulimit = exp(lrr + 1.96*sqrt(var)); z = lrr/se; P = 2*(1−probnorm(abs(z)));
proc print data = a5x;
proc catmod data = a1; response 1 0 log; weight count;

model surv = treat gender treat*gender

study study*gender study*treat/
nodesign noiter noparm noprofile noresponse;
run;
```

OUTPUT OF PROGRAMME D

Variances calculated using estimated design effect adjustments

INDIVIDUAL PROJECTS BY GENDER

OBS	GENDER	STUDY	RR	SE	LLIMIT	ULIMIT	Z	P
1	female	ACEH	0.92355	0.20675	0.61585	1.38499	−0.38468	0.70047
2	female	HYDER	0.90036	0.36547	0.43987	1.84293	−0.28720	0.77396
3	female	JUMLA	0.76227	0.22394	0.49146	1.18230	−1.21220	0.22544
4	female	SARLAHI	0.65170	0.15805	0.47809	0.88835	−2.70905	0.00675
5	female	SUDAN	0.94683	0.17680	0.66954	1.33897	−0.30900	0.75732
6	female	TAMIL	0.45327	0.26868	0.26770	0.76747	−2.94505	0.00323
7	male	ACEH	0.59111	0.19742	0.40144	0.87040	−2.66307	0.00774
8	male	HYDER	0.98520	0.36503	0.48173	2.01486	−0.04084	0.96743
9	male	JUMLA	0.72823	0.21747	0.47550	1.11529	−1.45827	0.14477
10	male	SARLAHI	0.77459	0.17413	0.55062	1.08966	−1.46685	0.14242
11	male	SUDAN	1.23056	0.18974	0.84838	1.78490	1.09344	0.27420
12	male	TAMIL	0.56959	0.30482	0.31339	1.03522	−1.84646	0.06483

Gender analysis
Variances calculated using estimated design effect adjustments

POOLED ANALYSES BY GENDER

OBS	GENDER	RR	SE	LLIMIT	ULIMIT	Z	P
1	female	0.75781	0.085531	0.64085	0.89612	−3.24234	.0011855
2	male	0.79400	0.089148	0.66670	0.94559	−2.58757	.0096656

CATMOD PROCEDURE

Response: SURV	Response Levels (R) = 2
Weight Variable: COUNT	Populations (S) = 24
Data Set: A1	Total Frequency (N) = 100771
	Observations (Obs) = 48

ANALYSIS OF VARIANCE TABLE

Source	DF	Chi−Square	Prob	
INTERCEPT	1	15963.04	0.0000	
TREAT	1	14.68	0.0001	
GENDER	1	2.51	0.1133	
TREAT*GENDER	1	0.12	0.7277	<< gender effect on vitamin A
STUDY	5	355.21	0.0000	
GENDER* STUDY	5	7.05	0.2170	
TREAT* STUDY	5	12.33	0.0305	<< homogeneity test
RESIDUAL	5	4.24	0.5148	

PROGRAMME E: Examination for Age Effect

```
*************************************************************************************************
** PROGRAMS TO EXAMINE RELATIVE EFFECTIVENESS OF VITAMIN A **
** CONSIDERING AGE. TWO PROGRAMME MODELS ARE PROVIDED. THE **
** FIRST TREATS AGE AS A CATEGORICAL VARIABLE AND THE **
** SECOND CONSIDERS AGE AS A CONTINUOUS LINEAR VARIABLE. **
** SUBPROGRAMS EXAMINE IMPACT OF MISSING DATA FOR 0−11 m **
** IN HYDERABAD STUDY POPULATION. SOME OUTPUTS ARE DISCARDED*
** TO TRASH FILE IN VERSION PRESENTED − DELETE PROC PRINTTO *
** IF OUTPUT WANTED **
*************************************************************************************************;
options ls = 80;
title1 ‘Age analysis’;
data a1;

infile ‘b:vita_cnt.age’; *** Rem: input of study counts;
input study $ group $ surv $ age $ count;
if group = ‘control’ then treat = 0; else treat = 1;
if age = ‘0−11’ then ag = 0; if age = ‘12−23’ then ag = 1;
if age = ‘24−35’ then ag = 2; if age = ‘36−47’ then ag = 3;
if age = ‘48−59’ then ag = 4;
%include ‘b:vitadeff.sas’; *** Rem: input of DEFF;
count = count/deff;
proc sort data = a1; by age study;
proc printto new print = ‘vitatras.h’;
proc catmod data = a1; response 1 0 log/outest = a2; weight count;

direct treat; by age study;
model surv = treat /nodesign noiter noparm noprofile noresponse;
data a1x; set a1; if age = ‘0−11’;
proc catmod data = a1x; response 1 0 log/outest = a2x; weight count;

direct treat; by age;
model surv = treat study /nodesign noiter noparm noprofile noresponse;
data a1y; set a1; if age ne ‘0−11’;
proc catmod data = a1y; response 1 0 log/outest = a2y; weight count;

direct treat; by age;
```

```
model surv = treat study/nodesign noiter noparm noprofile noresponse;
proc printto;
data a2x; set a2x a2y;
data a3; set a2; if _type_ = 'PARMS'; lrr = b2;
data a4; set a2; if _type_ = 'COV' and _name_ = 'B2'; var = b2;
data a5; merge a3 a4; keep age study rr llimit ulimit se z P;

rr = exp(lrr); se = sqrt(var); llimit = exp(lrr−1.96*sqrt(var));
ulimit = exp(lrr + 1.96*sqrt(var)); z = lrr/se; P = 2*(1−probnorm(abs(z)));
proc print data = a5;
data a3x; set a2x; if _type_ = 'PARMS'; lrr = b2;
data a4x; set a2x; if _type_ = 'COV' and _name_ = 'B2'; var = b2;
data a5x; merge a3x a4x; keep age rr llimit ulimit se z P;

rr = exp(lrr); se = sqrt(var); llimit = exp(lrr−1.96*sqrt(var));
ulimit = exp(lrr + 1.96*sqrt(var)); z = lrr/se; P = 2*(1−probnorm(abs(z)));
proc print data = a5x;
proc catmod data = a1; response 1 0 log; weight count;

model surv = treat ag treat*ag study study*ag treat*study/
nodesign noiter noparm noprofile noresponse;
proc catmod data = a1; response 1 0 log; weight count; direct ag;

model surv = treat ag treat*ag study study*ag treat*study/
nodesign noiter noparm noprofile noresponse;
run;
```

OUTPUT FROM PROGRAMME E

Variances calculated using estimated design effect adjustments

INDIVIDUAL STUDIES AND AGES

OBS	AGE	STUDY	RR	SE	LLIMIT	ULIMIT	Z	P
1	0−11	ACEH	0.83275	0.20545	0.55671	1.24566	−0.89081	0.37303
2	0−11	JUMLA	0.68142	0.26688	0.40387	1.14971	−1.43727	0.15064
3	0−11	SARLAHI	0.78375	0.23580	0.49370	1.24420	−1.03338	0.30143
4	0−11	SUDAN	0.74964	0.36043	0.36987	1.51934	−0.79951	0.42399
5	0−11	TAMIL	0.64706	0.35588	0.32212	1.29980	−1.22321	0.22125
6	12−23	ACEH	0.84705	0.32824	0.44515	1.61182	−0.50570	0.61307
7	12−23	HYDER	1.02188	0.33601	0.52891	1.97432	0.06442	0.94863
8	12−23	JUMLA	0.80012	0.23067	0.50911	1.25748	−0.96673	0.33368
9	12−23	SARLAHI	0.69032	0.19617	0.46997	1.01398	−1.88923	0.05886
10	12−23	SUDAN	1.25576	0.21908	0.81738	1.92926	1.03955	0.29855
11	12−23	TAMIL	0.40468	0.35023	0.20370	0.80396	−2.58303	0.00979
12	24−35	ACEH	0.55624	0.35017	0.28002	1.10493	−1.67506	0.09392
13	24−35	HYDER	0.84486	0.54772	0.28877	2.47176	−0.30781	0.75823
14	24−35	JUMLA	0.75270	0.42735	0.32573	1.73937	−0.66476	0.50620
15	24−35	SARLAHI	0.82881	0.28932	0.47009	1.46127	−0.64897	0.51636
16	24−35	SUDAN	1.09076	0.30437	0.60069	1.98066	0.28543	0.77531

17	24–35	TAMIL	0.38762	0.56043	0.12923	1.16265	−1.69109	0.09082
18	36–47	ACEH	1.21900	0.48849	0.46794	3.17550	0.40539	0.68519
19	36–47	HYDER	0.84565	0.69998	0.21446	3.33449	−0.23950	0.81071
20	36–47	JUMLA	0.83733	0.58607	0.26548	2.64100	−0.30292	0.76195
21	36–47	SARLAHI	0.63692	0.33243	0.33198	1.22196	−1.35701	0.17478
22	36–47	SUDAN	2.05727	0.54692	0.70428	6.00947	1.31900	0.18717
23	36–47	TAMIL	0.50127	0.65273	0.13946	1.80171	−1.05804	0.29004
24	48–59	ACEH	0.65259	0.61591	0.19515	2.18226	−0.69299	0.48832
25	48–59	HYDER	0.86148	1.15647	0.08930	8.31094	−0.12893	0.89742
26	48–59	JUMLA	0.63636	1.26219	0.05362	7.55274	−0.35810	0.72027
27	48–59	SARLAHI	0.50501	0.37656	0.24142	1.05641	−1.81426	0.06964
28	48–59	SUDAN	0.49952	0.70642	0.12509	1.99466	−0.98258	0.32582
29	48–59	TAMIL	0.81754	0.59303	0.25569	2.61399	−0.33971	0.73407

POOLED BY AGE GROUP

OBS	AGE	RR	SE	LLIMIT	ULIMIT	Z	P
1	0–11	0.75799	0.11842	0.60098	0.95601	−2.33988	0.01929
2	12–23	0.82392	0.10431	0.67158	1.01082	−1.85680	0.06334
3	24–35	0.76975	0.15269	0.57065	1.03830	−1.71383	0.08656
4	36–47	0.87020	0.20463	0.58269	1.29957	−0.67946	0.49685
5	48–59	0.59347	0.25070	0.36308	0.97005	−2.08131	0.03741

CATMOD PROCEDURE

Response: SURV — Response Levels (R) = 2

Weight Variable: COUNT — Populations (S) = 58

Data Set: A1 — Total Frequency (N) = 86818

Observations (Obs) = 116

ANALYSIS OF VARIANCE TABLE

Source	DF	Chi–Square	Prob	
INTERCEPT	1	436.82	0.0000	
TREAT	1	9.82	0.0017	
AG	4	190.84	0.0000	
TREAT*AG	4	1.29	0.8633	<< effect of age on vitamin A effect
STUDY	5	71.27	0.0000	
AG*STUDY	19*	36.85	0.0083	
TREAT*STUDY	5	10.34	0.0663	<< homogeneity test

RESIDUAL	19	8.31	0.9833

NOTE: Effects marked with * contained 1 or more singularities (i.e., redundant parameters). (arises because of missing data for one project x age group)

TREATING AGE AS A CONTINUOUS LINEAR VARIABLE

CATMOD PROCEDURE

Response: SURV Response Levels (R) = 2

Weight Variable: COUNT Populations (S) = 58

Data Set: A1 Total Frequency (N) = 86818

Observations (Obs) = 116

ANALYSIS OF VARIANCE TABLE

Source	DF	Chi−Square	Prob	
INTERCEPT	1	3262.69	0.0000	
TREAT	1	3.96	0.0466	
AG	1	215.36	0.0000	
AG*TREAT	1	0.33	0.5653	< effect of age on vitamin A
STUDY	5	105.37	0.0000	
AG*STUDY	5	5.49	0.3589	
TREAT*STUDY	5	11.91	0.0360	< test of homogeneity
RESIDUAL	39	55.10	0.0453	<< model does not fit well

PROGRAMME F: Examination of Mortality by Attributed Cause

```
*********************************************************************************************
** PROGRAMME TO EXAMINE CAUSE−SPECIFIC MORTALITY EFFECTS **
** OF VITAMIN A. **
** AS WRITTEN, THE PROGRAMME DOES NOT COMPARE EFFECTS **
** ACROSS CAUSES. RATHER, IT PROVIDES POOLED ESTIMATES **
** ACROSS STUDIES BY CAUSE **
*********************************************************************************************;
options ls = 80;
title1 'Cause Specific Mortality';
data a1;

infile 'B:vita_cnt.cas'; ** Rem: input study counts;
input study $ group $ surv $ cas $ count;
if group = 'control' then treat = 0; else treat = 1;
%include 'B:vitadeff.sas'; ** Rem: input DEFF
count = count/deff;
proc sort data = a1; by cas study;
proc printto new print = 'vitatras.h';
proc catmod data = a1; response 1 0 log/outest = a2; weight count;
```

```
direct treat; by cas study;
model surv = treat /nodesign noiter noparm noprofile noresponse;
data a1x; set a1; if cas = 'measles';
proc catmod data = a1x; response 1 0 log/outest = a2x; weight count;

direct treat; by cas;
model surv = treat study /nodesign noiter noparm noprofile noresponse;
data a1y; set a1; if cas ne 'measles';
proc catmod data = a1y; response 1 0 log/outest = a2y; weight count;

direct treat; by cas;
model surv = treat study /nodesign noiter noparm noprofile noresponse;
proc printto;
data a2x; set a2x a2y;
data a3; set a2; if _type_ = 'PARMS'; lrr = b2;
data a4; set a2; if _type_ = 'COV' and _name_ = 'B2'; var = b2;
data a5; merge a3 a4; keep cas study rr llimit ulimit se z P;

rr = exp(lrr); se = sqrt(var); llimit = exp(lrr−1.96*sqrt(var));
ulimit = exp(lrr + 1.96*sqrt(var)); z = lrr/se; P = 2*(1−probnorm(abs(z)));
proc print data = a5;
data a3x; set a2x; if _type_ = 'PARMS'; lrr = b2;
data a4x; set a2x; if _type_ = 'COV' and _name_ = 'B2'; var = b2;
data a5x; merge a3x a4x; keep cas rr llimit ulimit se z P;

rr = exp(lrr); se = sqrt(var); llimit = exp(lrr−1.96*sqrt(var));
ulimit = exp(lrr + 1.96*sqrt(var)); z = lrr/se; P = 2*(1−probnorm(abs(z)));
proc print data = a5x;
run;
```

OUTPUT FROM PROGRAMME F

INDIVIDUAL STUDIES AND CAUSES

Cause Specific Mortality
Variances calculated using estimated design effect adjustments

OBS	CAUSE	STUDY	RR	SE	LLIMIT	ULIMIT	Z	P
1	all	GHANA	0.80114	0.07276	0.69466	0.92394	−3.04714	0.00231
2	all	JUMLA	0.74450	0.15601	0.54836	1.01080	−1.89116	0.05860
3	all	SARLAHI	0.70779	0.11687	0.56289	0.88999	−2.95718	0.00310
4	all	SUDAN	1.04072	0.12859	0.80886	1.33904	0.31039	0.75627
5	all	TAMIL	0.50235	0.20141	0.33851	0.74550	−3.41828	0.00063
6	diarr	GHANA	0.61973	0.14650	0.46505	0.82586	−3.26602	0.00109
7	diarr	JUMLA	0.65651	0.18504	0.45681	0.94351	−2.27424	0.02295
8	diarr	SARLAHI	0.61511	0.22535	0.39549	0.95670	−2.15644	0.03105
9	diarr	SUDAN	1.01016	0.20067	0.68168	1.49692	0.05036	0.95984
10	diarr	TAMIL	0.48133	0.32478	0.25467	0.90970	−2.25140	0.02436
11	measles	GHANA	0.83653	0.19097	0.57534	1.21630	−0.93465	0.34997
12	measles	JUMLA	0.67571	1.05779	0.08499	5.37249	−0.37057	0.71096

13	measles	SARLAHI	0.24447	0.71285	0.06045	0.98858	−1.97611	0.04814
14	measles	TAMIL	0.57910	0.50749	0.21418	1.56579	−1.07645	0.28172
15	other	GHANA	0.85993	0.10594	0.69869	1.05837	−1.42451	0.15430
16	other	JUMLA	1.21893	0.44198	0.51257	2.89870	0.44793	0.65421
17	other	SARLAHI	1.41887	0.20058	0.95765	2.10221	1.74428	0.08111
18	other	SUDAN	1.07652	0.17435	0.76491	1.51508	0.42289	0.67238
19	other	TAMIL	0.48219	0.31515	0.25999	0.89428	−2.31456	0.02064
20	resp	GHANA	1.04559	0.22984	0.66638	1.64060	0.19397	0.84620
21	resp	JUMLA	0.95395	0.46748	0.38159	2.38480	−0.10085	0.91967
22	resp	SARLAHI	1.30383	0.28089	0.75184	2.26107	0.94453	0.34490
23	resp	SUDAN	0.43310	0.45301	0.17823	1.05245	−1.84716	0.06472
24	resp	TAMIL	0.66182	0.97452	0.09800	4.46961	−0.42355	0.67190

POOLED ESTIMATES BY ATTRIBUTED CAUSE OF DEATH

Cause Specific Mortality
Variances calculated using estimated design effect adjustments

OBS	GAS	RR	SE	LLIMIT	ULIMIT	Z	P
1	measles	0.74324	0.17108	0.53150	1.03935	−1.73442	0.08284
2	all	0.78528	0.05075	0.71093	0.86740	−4.76321	0.00000
3	diarr	0.67596	0.08777	0.56913	0.80285	−4.46182	0.00001
4	other	0.94798	0.07856	0.81270	1.10578	−0.67998	0.49652
5	resp	0.98770	0.15411	0.73020	1.33599	−0.08033	0.93597

PROGRAMME G: Regression models Examination of Association Between RR and Anthropometric Measures, Xerophthalmia

```
**********************************************************************************************
** REGRESSION ANALYSIS PROGRAMME (WEIGHTED REGRESSION) **
** PROGRAMME RUNS ANALYSES FOR LOG AND NON LOG EXPRESSIONS **
** WAS MODIFIED TO ALSO LOOK AT INTERACTIONS OF **
** ANTHROPOMETRY * XEROPHTHALMIA **
** AND TO LOOK AT LOG EXPRESSIONS OF ANTHROPOMETRY AND **
** XEROPTHALMIA **
**********************************************************************************************;
** FIRST PART OF PROGRAMME GENERATES VARIANCES FOR USE IN REGRESSIONS **;
options ls = 72;
title1 'Overall analysis';
data a1;

infile 'B:vita_cnt.all'; ** Rem: input study counts;
input study $ group $ surv $ count;
if group = 'control' then treat = 0; else treat = 1;
%include 'B:vitadeff.sas'; **Rem: input DEFF;
count = count/deff;
proc sort data = a1; by study;
proc printto new print = 'vitatras.h';
proc catmod data = a1;

response 1 0 log/outest = a2; weight count; direct treat;
```

```
model surv = treat /nodesign noiter noparm noprofile noresponse;
by study;
proc printto;
data a3; set a2; if _type_ = 'PARMS'; lrr = b2;
data a4; set a2; if _type_ = 'COV' and _name_ = 'B2'; var = b2;
data a5; merge a3 a4;

keep study rr lrr vlrri vrresti;
rr = exp(lrr); selrr = sqrt(var);
srrest = (rr*(exp(1.96*selrr)−exp(−1.96*selrr)))/(2*1.96);
vrresti = 1/srrest**2; vlrri = 1/var;
**** INPUT ANTHROPOMETRY AND XEROPTHALMIA PREVALENCE DATA ***;
data a6; input study $ xerop waste stunt; cards;

 ACEH        2.1    3.4   34.3

 MSG         1.0    4.5   52.5

 TAMIL      11.3   42.3   50.6

 HYDER       6.0   29.8   19.5

 SARLAHI     3.0   21.2   65.5

 JUMLA      13.2   21.2   65.5

 SUDAN       2.9    6.1   44.0

 GHANA       0.1   17.0   46.0
;
proc sort data = a6; by study;
data a7; merge a5 a6;
proc univariate data = a7 noprint; var vlrri vrresti;

output out = a8 mean = mvli mvi;
data a7; set a7; if _n_ = 1 then set a8; wtl = vlrri/mvli; wt = vrresti/mvi;

keep study rr wt lrr wtl xerop waste stunt;
proc print data = a7;
********** START REGRESSION RUNS **********
******* MODIFY THE MODELS IF INTERACTIONS WANTED **********;
** (note that the interaction term must be constructed outside model **;
proc reg data = a7; model rr = xerop; weight wt;
proc reg data = a7; model rr = waste; weight wt;
proc reg data = a7; model rr = stunt; weight wt;
proc reg data = a7; model rr = xerop waste stunt; weight wt;
proc reg data = a7; model lrr = xerop; weight wtl;
proc reg data = a7; model lrr = waste; weight wtl;
proc reg data = a7; model lrr = stunt; weight wtl;
proc reg data = a7; model lrr = xerop waste stunt; weight wtl;
proc plot; plot (rr lrr)*(xerop waste stunt);
run;
```

OUTPUT FROM PROGRAMME G
REGRESSION ANALYSES
(Variances calculated using estimated design effect correction)

OBS	STUDY	LRR	RR	XEROP	WASTE	STUNT	WTL	WT
1	ACEH	−0.31450	0.73016	2.1	3.4	34.3	0.76036	0.80331

2	GHANA	−0.21952	0.80290	0.1	17.0	46.0	2.77928	2.47229
3	HYDER	−0.05995	0.94181	6.0	29.8	19.5	0.22074	0.13201
4	JUMLA	−0.29504	0.74450	13.2	21.2	65.5	0.60455	0.61044
5	MSG	−0.35455	0.70149	1.0	4.5	52.5	1.30514	1.50935
6	SARLAHI	−0.34561	0.70779	3.0	21.2	65.5	1.07732	1.22007
7	SUDAN	0.03991	1.04072	2.9	6.1	44.0	0.88986	0.46442
8	TAMIL	−0.68846	0.50235	11.3	42.3	50.6	0.36275	0.78811

REGRESSION OUTPUTS _ LINEAR SCALES FOR RR AND VARIANCES

Model: MODEL1 **XEROPHTHAMIA**

Dependent Variable: RR

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	ProbF
Model	1	0.02214	0.02214	1.600	0.2528
Error	6	0.08300	0.01383		
C Total	7	0.10514			
Root MSE		0.11761	R−square	0.2106	
Dep Mean		0.74399	Adj R−sq	0.0790	
C.V.		15.80847			

Parameter Estimates

Variable	DF	Parameter Estimate	Standard Error	T for H0: Parameter = 0	Prob |T|
INTERCEP	1	0.784346	0.05240919	14.966	0.0001
XEROP	1	−0.012319	0.00973820	−1.265	0.2528

Model: MODEL1 **WASTING**

Dependent Variable: RR

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	ProbF
Model	1	0.02738	0.02738	2.113	0.1963
Error	6	0.07776	0.01296		
C Total	7	0.10514			
Root MSE		0.11384	R−square	0.2604	
Dep Mean		0.74399	Adj R−sq	0.1371	
C.V.		15.30123			

Parameter Estimates

Variable	DF	Parameter Estimate	Standard Error	T for H0: Parameter = 0	Prob |T|
INTERCEP	1	0.829571	0.07132161	11.631	0.0001
WASTE	1	−0.005248	0.00361052	−1.453	0.1963

Model: MODEL1 **STUNTING**

Dependent Variable: RR

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	ProbF
Model	1	0.01080	0.01080	0.687	0.4389
Error	6	0.09433	0.01572		
C Total	7	0.10514			
Root MSE		0.12539	R−square	0.1028	
Dep Mean		0.74399	Adj R−sq	−0.0468	
C.V.		16.85333			

Parameter Estimates

Variable	DF	Parameter Estimate	Standard Error	T for H0: Parameter = 0	Prob |T|
INTERCEP	1	0.926397	0.22446606	4.127	0.0062
STUNT	1	−0.003618	0.00436484	−0.829	0.4389

Model: MODEL1 **WASTING, STUNTING AND XEROPHTHALMIA**

Dependent Variable: RR

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	ProbF
Model	3	0.03300	0.01100	0.610	0.6432
Error	4	0.07214	0.01803		
C Total	7	0.10514			
Root MSE		0.13429	R−square	0.3139	
Dep Mean		0.74399	Adj R−sq	−0.2007	
C.V.		18.05008			

Parameter Estimates

Variable	DF	Parameter Estimate	Standard Error	T for H0: Parameter = 0	Prob |T|
INTERCEP	1	0.914624	0.24982919	3.661	0.0216
XEROP	1	−0.004564	0.01502297	−0.304	0.7764
WASTE	1	−0.003664	0.00559229	−0.655	0.5481
STUNT	1	−0.001903	0.00499017	−0.381	0.7224

REGRESSION OUTPUTS – LOG of RR and Variances

Model: MODEL1 **XEROPHTHAMIA**

Dependent Variable: LRR

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	ProbF
Model	1	0.01757	0.01757	0.639	0.4546
Error	6	0.16501	0.02750		
C Total	7	0.18257			
Root MSE		0.16583	R−square	0.0962	
Dep Mean		−0.26127	Adj R−sq	−0.0544	
C.V.		−63.47257			

Parameter Estimates

Variable	DF	Parameter Estimate	Standard Error	T for H0: Parameter = 0	Prob |T|
INTERCEP	1	−0.227221	0.07247245	−3.135	0.0202
XEROP	1	−0.012162	0.01521661	−0.799	0.4546

Model: MODEL1 **WASTING**

Dependent Variable: LRR

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	ProbF
Model	1	0.03065	0.03065	1.211	0.3134
Error	6	0.15192	0.02532		
C Total	7	0.18257			
Root MSE		0.15912	R−square	0.1679	
Dep Mean		−0.26127	Adj R−sq	0.0292	
C.V.		−60.90427			

Parameter Estimates

Variable	DF	Parameter Estimate	Standard Error	T for H0: Parameter = 0	Prob |T|
INTERCEP	1	−0.163836	0.10491532	−1.562	0.1694
WASTE	1	−0.006566	0.00596778	−1.100	0.3134

Model: MODEL1 **STUNTING**

Dependent Variable: LRR

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	ProbF
Model	1	0.02751	0.02751	1.065	0.3419
Error	6	0.15506	0.02584		
C Total	7	0.18257			
Root MSE		0.16076	R−square	0.1507	
Dep Mean		−0.26127	Adj R−sq	0.0091	
C.V.		−61.52994			

Parameter Estimates

Variable	DF	Parameter Estimate	Standard Error	T for H0: Parameter = 0	Prob |T|
INTERCEP	1	0.014766	0.27349563	0.054	0.9587
STUNT	1	−0.005599	0.00542615	−1.032	0.3419

Model: MODEL1 **WASTING, STUNTING AND XEROPTHALMIA**

Dependent Variable: LRR

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	ProbF
Model	3	0.04686	0.01562	0.460	0.7250
Error	4	0.13572	0.03393		
C Total	7	0.18257			
Root MSE		0.18420	R−square	0.2567	
Dep Mean		−0.26127	Adj R−sq	−0.3009	
C.V.		−70.50140			

Parameter Estimates

Variable	DF	Parameter Estimate	Standard Error	T for H0: Parameter = 0	Prob |T|
INTERCEP	1	0.027477	0.32642492	0.084	0.9370
XEROP	1	−0.001787	0.02047875	−0.087	0.9347
WASTE	1	−0.005015	0.00809479	−0.620	0.5691
STUNT	1	−0.004246	0.00666157	−0.637	0.5586

Programme also generates plots. Not reproduced here. Variances calculated using estimated design effect adjustments.

PROGRAMME H. Generation of Prediction Intervals.

```
**************************************************************************
** PROGRAMME FOR PREDICTION INTERVALS FOR THE EFFECT OF VITAMIN A **
** IN A NEW SITUATION. THE PROGRAMME FIRST ESTIMATES THE **
** BETWEEN STUDY VARIANCE FROM THE EXISTING 8 STUDIES, RECOMPUTES **
** THE VARIANCE THAT SHOULD BE ASSOCIATED WITH THE POOLED RR **
** ESTIMATE, INCLUDING THE APPROPRIATE PORTION OF BETWEEN STUDY **
** VARIANCE, AND THEN COMPUTES THE VARIANCE SUM THAT WOULD APPLY **
** TO THE BOUNDS FOR THE PREDICTED OBSERVED EFFECT IN A FUTURE **
** PROGRAMME – AS THE SUM OF THE UNCERTAINTY OF THE EXISTING ESTIMATE**
** OF RR + THE BETWEEN STUDY VARIANCE (THESE TWO GIVE BOUNDS FOR **
** THE TRUE RR OF THE FUTURE STUDY) + THE DESIGN–ASSOCIATED VARIANCE **
** THAT WOULD ASSOCIATE WITH THE NEW PROGRAMME (AS A FUNCTION OF THE **
** PROGRAMME SIZE AND MORTALITY RATES – THIS IS ALLOWED TO VARY) **
**************************************************************************
** THIS IS FUNDAMENTALLY DIFFERENT FROM THE CONCEPT OF THE CONFIDENCE *
** INTERVAL GENERATED EARLIER FOR THE POOLED RR ESTIMATE WHICH USED, **
** IN EFFECT, ONLY THE FIRST COMPONENT OF VARIANCE (THE POOLED **
** ESTIMATE OF WITHIN STUDY VARIANCE **
**************************************************************************
options ls = 72;
title1 'Prediction Intervals';
data a1;

infile 'B:vita_cnt.all';
input study $ group $ surv $ count;
if group = 'control' then treat = 0; else treat = 1;
%include 'B:vitadeff.sas';

count = count/deff;
proc sort data = a1; by study;
proc printto new print = 'vitatras.h';
proc catmod data = a1;

response 1 0 log / outest = a2; weight count; direct treat;
model surv = treat /nodesign noiter noparm noprofile noresponse;
by study;
proc printto;
data a3; set a2; if _type_ = 'PARMS'; lrr = b2;
data a4; set a2; if _type_ = 'COV and _name_ = 'B2'; var = b2;
data a5; merge a3 a4; keep study rr lrr var wt;

rr = exp(lrr); wt = 1/var;
proc univariate data = a5 noprint; var wt;

output out = s1 mean = mwt n = n;
data a6; set a5; if _n_ = 1 then set s1; wt = wt/mwt;
```

```
vp = wt*wt*var/n**2; wt2 = wt*wt; wt2v = wt2*var; wtv = wt*var;
proc univariate data = a6 noprint; var wt2 wtv wt2v;

output out = s2 sum = swt2 swtv swt2v;
proc univariate data = a6 noprint; var lrr; weight wt;

output out = s3 mean = lrr var = s2 n = n;
data a7; merge s2 s3;

studyv = ((n−1)*s2−(swtv−swt2v/n))/(n−swt2/n);
lhatv = (studyv*swt2 + swt2v)/n**2; rr = exp(lrr);
lcltrue = exp(lrr−1.96*sqrt(lhatv)); ucltrue = exp(lrr + 1.96*sqrt(lhatv)); proc print data = a7; var rr lhatv studyv
lcltrue ucltrue;
run;
**********************************************************
```

Rem: STUDYV is the estimate of the between study variance LHATV is the variance associated with the RR estimate derived for the 8 studies. It differs from the output of CATMOD procedures by including the portion of between study variance that would be attached to the estimate as well as the within study variance (see programme lines above for definition of proportion included) lcltrue and ucltrue are the upper and lower 95% CI bounds for the pooled RR estimate, taking into account the between study variance component.

```
**********************************************************
title1 ' ';
data a8; set a7; keep rrhat lpl upl nv z prob;

do nv = 0 to .07 by .005; *** Rem: can set to 0.001 for plotting;
sp = sqrt(studyv + lhatv + nv); moe = 1.96*sp;
rrhat = exp(lrr); lpl = exp(lrr−moe); upl = exp(lrr + moe);
z = lrr/sp; prob = probnorm(z);

output; end;
*****
```

Rem: moe is the variance associated with predicted effect for a new study. It includes LHATV, STUDYV and a design variance expected for a single study of finite size. This component of variance is allowed to change [as a function of characteristics of the new study]

```
*****
proc print data = a8;
data a9; set a5; keep study rr1−rr8 nv;

array r(i) rr1−rr8; i = _n_; r = rr; nv = var; output;
proc print data = a9;
run;
```

OUTPUT FROM PROGRAM

VARIANCE ATTACHED TO POOLED STUDIES ESTIMATE OF RR AND ADJUSTED CI OF RR FOR POOLED STUDIES

OBS	RR	LHATV	STUDYV	LCLTRUE	UCLTRUE
1	0.77007	.0042545	0.012361	0.67766	0.87509

RR is the average Relative Risk estimate based on existing studies LHATV is the variance attached to that estimate (including the between study variance that would be associated with the pooled estimate of the average RR)

STUDYV is the estimate of between study variance LCLTRUE and UCLTRUE are the lower and upper 95% CI bounds for the pooled estimate of RR, now including the between study variance component in LHATV (omitted in output from earlier estimates of C.I., programme C) Note that the effect of vitamin A remains highly

significant with upper bound = 0.88. The range for the true RR of the new programme must still include, in addition, the full between study variance.

PROJECTED PREDICTION INTERVALS FOR EFFECT TO BE SEEN IN A NEW STUDY

Note that NV is a variable representing the variance that would be associated with the design (mortality rates and population size) of the new study or field program. This is the only input variable that changes below. RR, LHATV and STUDYV are constants, all based on the existing experience.

LPL and UPL are the derived 95% lower and upper boundries of the prediction interval. The observed RR of the new study or field programme would be expected to fall within this range 95% of the time. RRHAT is the central predicted value. Recognize that variances and RR are used in log form and then converted back to linear scale for presentation in output of estimated limits.

The Z and PROB values are NOT significance testing in the usual sense. The purpose is to offer a statement of the likelihood that no effect (RR > 1) would be seen.

ESTIMATED PREDICTION INTERVALS AS FUNCTION OF DESIGN CHARACTERISTICS OF NEW PROGRAM

OBS	NV	RRHAT	LPL	UPL	Z	PROB
1	0.000	0.77007	0.59815	0.99142	–2.02686	0.02134
2	0.005	0.77007	0.57728	1.02726	–1.77705	0.03778
3	0.010	0.77007	0.55932	1.06024	–1.60146	0.05464
4	0.015	0.77007	0.54347	1.09115	–1.46938	0.07086
5	0.020	0.77007	0.52924	1.12051	–1.36537	0.08607
6	0.025	0.77007	0.51628	1.14863	–1.28073	0.10014
7	0.030	0.77007	0.50437	1.17575	–1.21010	0.11312
8	0.035	0.77007	0.49334	1.20205	–1.14999	0.12507
9	0.040	0.77007	0.48305	1.22764	–1.09804	0.13609
10	0.045	0.77007	0.47341	1.25264	–1.05254	0.14627
11	0.050	0.77007	0.46434	1.27712	–1.01227	0.15570
12	0.055	0.77007	0.45576	1.30115	–0.97630	0.16446
13	0.060	0.77007	0.44763	1.32479	–0.94390	0.17261
14	0.065	0.77007	0.43990	1.34807	–0.91453	0.18022
15	0.070	0.77007	0.43253	1.37104	–0.88774	0.18734

EXISTING STUDY DATA FOR PLOTTING

In the output below, data from the 8 studies are presented together with the NV that would apply for their population characteristics. The purpose of this output is simply to provide data for plotting and hence to provide a basis for visualizing the meaning of NV as it applies to existing studies.

OBS	STUDY	RR1	RR2	RR3	RR4
1	ACEH	0.73016	.	.	.
2	GHANA	.	0.80290	.	.
3	HYDER	.	.	0.94181	.

4	JUMLA	.	.	.	0.74450
5	MSG	.	.	.	.
6	SARLAHI	.	.	.	.
7	SUDAN	.	.	.	.
8	TAMIL	.	.	.	.

OBS	RR5	RR6	RR7	RR8	NV
1	.	.	.	.	0.019352
2	.	.	.	.	0.005294
3	.	.	.	.	0.066661
4	.	.	.	.	0.024340
5	0.70149	.	.	.	0.011274
6	.	0.70779	.	.	0.013659
7	.	.	1.04072	.	0.016536
8	.	.	.	0.50235	0.040564

PROGRAMME I: Infants under 6 months

```
************************************************************
** INFANTS UNDER 6 MONTHS OF AGE **
** PROGRAMME TO COMPUTE RR AND CI FOR INDIVIDUAL STUDIES**
** AND SUMMARY RR AND CI FOR ALL STUDIES. USES **
** ADJUSTED VARIANCES. ** CAUTION: SOME INFANT DATA **
** REFER TO AGE OF ENTRY, OTHERS TO AGE OF DEATH **
************************************************************
options ls = 80;
title1 'Overall analysis';
data a1;

title3 'INFANTS UNDER 6 MONTHS';
input study $ group $ surv $ count;
if group = 'control' then treat = 0; else treat = l;
%include 'B:vitadeff.sas'; *** Rem: Design effect adjustment factors;
count = count/deff;
cards;

TAMIL A_admin live 186
TAMIL A_admin dead 3
TAMIL control live 225
TAMIL control dead 9
SUDAN A_admin live 7
SUDAN A_admin dead 1
SUDAN control live 2
SUDAN control dead 1
JUMLA A_admin live 268
JUMLA A_admin dead 20
JUMLA control live 271
JUMLA control dead 19
;
proc sort data = al; by study;
proc printto new print = 'vitatras.h'; *Rem: gets rid of unused output;
proc catmod data = a1;
```

```
response 1 0 log/outest = a2; weight count; direct treat;
model surv = treat/nodesign noiter noparm noprofile noresponse;
by study;
proc printto;
data a3; set a2; if _type_ = 'PARMS'; lrr = b2;
data a4; set a2; if _type_ = 'COV' and _name_ = 'B2'; var = b2;
data a5; merge a3 a4; keep study rr llimit ulimit se z P;

rr = exp(lrr); se = sqrt(var); llimit = exp(lrr−1.96*sqrt(var));
ulimit = exp(lrr + 1.96*sqrt(var)); z = lrr/se; P = 2*(1−probnorm(abs(z)))
proc print data = a5;
proc catmod data = a1;

response 1 0 log/outest = a2; weight count; direct treat;
model surv = treat study/

nodesign noiter noparm noprofile noresponse;
data a3; set a2; if _type_ = 'PARMS'; lrr = b2;
data a4; set a2; if _type_ = 'COV and _name_ = 'B2'; var = b2;
data a5; merge a3 a4; keep rr llimit ulimit se z P;

rr = exp(lrr); se = sqrt(var); llimit = exp(lrr−1.96*sqrt(var));
ulimit = exp(lrr + 1.96*sqrt(var)); z = lrr/se; P = 2*(1−probnorm(abs(z)))
proc print data = a5;
run;
```

OUTPUT OF PROGRAMME I

INFANTS UNDER 6 MONTHS ESTIMATES BY INDIVIDUAL STUDY

Variances calculated using estimated design effect adjustments

OBS	STUDY	RR	SE	LLIMIT	ULIMIT	Z	P
1	JUMLA	1.05994	0.42868	0.45749	2.45573	0.13580	0.89198
2	SUDAN	0.37500	1.24164	0.03289	4.27499	−0.78995	0.42956
3	TAMIL	0.41270	0.70410	0.10382	1.64051	−1.25697	0.20876

CATMOD PROCEDURE

Response: SURV	Response Levels (R) = 2
Weight Variable: COUNT	Populations (S) = 6
Data Set: A1	Total Frequency (N) = 683.09
	Observations (Obs) = 12

ANALYSIS OF VARIANCE TABLE

Source	DF	Chi−Square	Prob
INTERCEPT	1	78.87	0.0000
TREAT	1	0.55	0.4598
STUDY	2	9.94	0.0069
RESIDUAL	2	1.68	0.4326

POOLED ESTIMATE ACROSS STUDIES

OBS	RR	SE	LLIMIT	ULIMIT	Z	P
1	0.77137	0.35120	0.38754	1.53536	−0.73915	0.45981

PROGRAMME J: Estimation of Probability of Effects of Specified Magnitudes.

```
************************************************************
** PROGRAMME TO COMPUTE PROBABILITY THAT A NEW FIELD PROGRAM OR **
** PILOT STUDY WILL SHOW AN EFFECT (1−RR) GREATER THAN SPECIFIED**
** LEVELS **
** ASSUMPTIONS: FOR TRUE RR OR INFINITE POPULATION, **
** VARIANCE FOR PI IS 0.0042545 + 0.012361 **
** FOR A PILOT STUDY WITH POPULATION CHARACTERISTICS LIKE **
** ACEH OR SUDAN. TAKE NV = 0.018 AND TOTAL VARIANCE = **
** 0.0042545 + 0.012361 + 0.018 **
** FOR A STUDY WITH CHARACTERISTICS LIKE TAMIL NADU, TAKE **
** NV = 0.0667 **
*****************************************************************;
OPTIONS LS = 75;
data CNTR_PRG;
do i = 1.0 to 0.5 by −0.025;
SD = (0.0166755)**0.5;
RR = i;
z = (log(0.77)−log(rr))/sd; **< convert variance to sd ;
prob_RR = 1−probnorm(z);
output; end;
proc print data = cntr_prg;
title 'PROBABILITY THAT RR WILL BE LESS THAN SPECIFIED _VERY LARGE POPULATION';

data PILOT1;
do i = 1.0 to 0.5 by −0.025;
SD = (0.0166755 + 0.015)**0.5;
RR = i;
z = (log(0.77)−log(rr))/sd; **< convert variance to sd ;
prob_RR = 1−probnorm(z);
output; end;
proc print data = pilot1;
title 'PROBABILITY THAT RR WILL BE LESS THAN SPECIFIED _FINITE ACEH TYPE';

data PILOT2;
do i = 1.0 to 0.5 by − 0.025;
SD = (0.0166755 + 0.0667)**0.5;
RR = i;
z = (log(0.77)−log(rr))/sd; **< convert variance to sd ;
prob_RR = 1−probnorm(z);
output; end;
proc print data = pilot2;
title 'PROBABILITY THAT RR WILL BE LESS THAN SPECIFIED _FINITE HYDERABAD TYPE';
RUN;
```

OUTPUT OF PROGRAMME J

PROBABILITY THAT RR WILL BE LESS THAN SPECIFIED − VERY LARGE POPULATION

OBS	I	SD	RR	Z	PROB_RR
1	1.000	0.12913	1.000	−2.02399	0.97851
2	0.975	0.12913	0.975	−1.82793	0.96622
3	0.950	0.12913	0.950	−1.62678	0.94811
4	0.925	0.12913	0.925	−1.42026	0.92223

5	0.900	0.12913	0.900	−1.20808	0.88649
6	0.875	0.12913	0.875	−0.98993	0.83890
7	0.850	0.12913	0.850	−0.76545	0.77800
8	0.825	0.12913	0.825	−0.53427	0.70342
9	0.800	0.12913	0.800	−0.29598	0.61638
10	0.775	0.12913	0.775	−0.05012	0.51999
11	0.750	0.12913	0.750	0.20380	0.41926
12	0.725	0.12913	0.725	0.46633	0.32049
13	0.700	0.12913	0.700	0.73807	0.23023
14	0.675	0.12913	0.675	1.01970	0.15393
15	0.650	0.12913	0.650	1.31196	0.09477
16	0.625	0.12913	0.625	1.61568	0.05308
17	0.600	0.12913	0.600	1.93180	0.02669
18	0.575	0.12913	0.575	2.26138	0.01187
19	0.550	0.12913	0.550	2.60561	0.00459
20	0.525	0.12913	0.525	2.96586	0.00151
21	0.500	0.12913	0.500	3.34369	0.00041

PROBABILITY THAT RR WILL BE LESS THAN SPECIFIED – FINITE ACEH TYPE

OBS	I	SD	RR	Z	PROB_RR
1	1.000	0.18621	1.000	−1.40358	0.91978
2	0.975	0.18621	0.975	−1.26761	0.89753
3	0.950	0.18621	0.950	−1.12812	0.87037
4	0.925	0.18621	0.925	−0.98491	0.83767
5	0.900	0.18621	0.900	−0.83777	0.79892
6	0.875	0.18621	0.875	−0.68649	0.75380
7	0.850	0.18621	0.850	−0.53082	0.70223
8	0.825	0.18621	0.825	−0.37050	0.64450
9	0.800	0.18621	0.800	−0.20525	0.58131
10	0.775	0.18621	0.775	−0.03476	0.51386
11	0.750	0.18621	0.750	0.14133	0.44381
12	0.725	0.18621	0.725	0.32339	0.37320
13	0.700	0.18621	0.700	0.51183	0.30438
14	0.675	0.18621	0.675	0.70713	0.23974
15	0.650	0.18621	0.650	0.90981	0.18146
16	0.625	0.18621	0.625	1.12043	0.13127
17	0.600	0.18621	0.600	1.33965	0.09018

18	0.575	0.18621	0.575	1.56820	0.05842
19	0.550	0.18621	0.550	1.80692	0.03539
20	0.525	0.18621	0.525	2.05674	0.01986
21	0.500	0.18621	0.500	2.31875	0.01020

PROBABILITY THAT RR WILL BE LESS THAN SPECIFIED – FINITE HYDERABAD TYPE

OBS	I	SD	RR	Z	PROB_RR
1	1.000	0.28875	1.000	–0.88275	0.81131
2	0.975	0.28875	0.975	–0.79507	0.78671
3	0.950	0.28875	0.950	–0.70511	0.75963
4	0.925	0.28875	0.925	–0.61275	0.72998
5	0.900	0.28875	0.900	–0.51786	0.69772
6	0.875	0.28875	0.875	–0.42030	0.66287
7	0.850	0.28875	0.850	–0.31991	0.62548
8	0.825	0.28875	0.825	–0.21652	0.58571
9	0.800	0.28875	0.800	–0.10995	0.54378
10	0.775	0.28875	0.775	0.00000	0.50000
11	0.750	0.28875	0.750	0.11356	0.45479
12	0.725	0.28875	0.725	0.23097	0.40867
13	0.700	0.28875	0.700	0.35250	0.36223
14	0.675	0.28875	0.675	0.47845	0.31617
15	0.650	0.28875	0.650	0.60915	0.27121
16	0.625	0.28875	0.625	0.74498	0.22814
17	0.600	0.28875	0.600	0.88636	0.18771
18	0.575	0.28875	0.575	1.03375	0.15063
19	0.550	0.28875	0.550	1.18770	0.11748
20	0.525	0.28875	0.525	1.34881	0.08870
21	0.500	0.28875	0.500	1.51778	0.06453

PROGRAMME K: Prediction of Programme Effects to be Seen in a Future Study

```
******************************************************
** PROGRAM TO ESTIMATE NV (VARIANCE OF LOG RR) AS A **
** FUNCTION OF GROUP SIZE MORTALITY RATE AND DEF AS **
** WELL AS RR **
** PROGRAM ALSO COMPUTES PROBABILITY OF FAILING TO **
** SEE ANY EFFECT AS A FUNCTION OF ABOVE **
** [Note that this is NOT the probability of failing **
** to achieve statistical significance.] **
** FINALLY, THE PROGRAM COMPUTES LIVES SAVED PER **
** 1000 COVERED BY POPULATION SIZE AND MORTALITY **
** RATE DESCRIBING THE 95% INTERVAL FOR THE ESTIMATES *
******************************************************
```

```
*******************************************************
** INPUT ARBITRARY STUDY DESIGN PARAMETERS **
*******************************************************
options ls = 72;
data a1;

** Rem: assumption is that na = nc = count;
** mortality rate in deaths/1000;
** RR is taken from actual analyses;
** LHATV and STUDYV are taken from prog H;
input count rr lhatv studyv;
cards;

 5000    0.77  0.0042545  0.012361

 10000   0.77  0.0042545  0.012361

 50000   0.77  0.0042545  0.012361

 100000  0.77  0.0042545  0.012361

 250000  0.77  0.0042545  0.012361;
data a1a; set a1;
do i = 5 to 45 by 10;
mortrate = i;
output;
end;
data a2; set a1a;

na = count; nc = count; dc = (count/1000)*mortrate;
da = dc*rr;
pa = da/na; pc = dc/nc; qa = 1−pa; qc = 1−pc; rr = pa/pc; lrr = log(rr);
varpa = pa*qa/na; varpc = pc*qc/nc;

varlpa = varpa/(pa*pa); varlpc = varpc/(pc*pc);
data a3; set a2;
do i = 1.0 to 1.9 by 0.3;

deff = i;
vlrr = varlpa + varlpc; vlrrp = vlrr*deff;
nv = VLRRP;
moe = 1.96*(lhatv + studyv + nv)**0.5; lrr = log(rr);
lpi = exp(lrr−moe); upi = exp(lrr + moe);
z = lrr/((lhatv + studyv + nv)**0.5); prob = probnorm(z);

output;
end;
PROC PRINT; VAR na da nc dc RR DEFF NV lhatv studyv lpi upi;
TITLE 'ESTIMATES OF NV AND PI BOUNDS FOR HYPOTHETICAL STUDIES';
proc print; var na da nc dc rr deff prob;
title 'PROBABILITY OF FAILING TO SEE AN EFFECT IN A STUDY OF DEFINED CHARACTERISTICS';
data a4; set a3;

ulsave = (1−lpi)*dc; llsave = (1−upi)*dc; aversave = (1−rr)*dc;
if llsave le 1.0 then llsave2 = 'none'; else llsave2 = llsave; proc print; var na da nc dc rr deff ulsave aversave
llsave llsave2;
title1 'ESTIMATES OF LIVES SAVED AS FUNCTION OF POPULATION SIZE,';
title2 'BASELINE [CONTROL] MORTALITY RATE AND DEFF';
RUN;
```

OUTPUT OF PROGRAMME K

ESTIMATES OF NV (Sampling variance) AND PI (Prediction Interval) BOUNDS

FOR HYPOTHETICAL STUDIES

NA = count, vit A group
NC = count control group or baseline
DA = deaths, vit A group
ND = deaths control group or expected deaths from baseline mortality
DEFF = design effect (from clustering)
NV = sampling variance (as log)
LHATV = variance associated with RR estimate
STUDYV = between study variance LPI, UPI = 95% limits for RR

OBS	NA	DA	NC	DC	RR	DEFF	NV
1	5000	19.25	5000	25	0.77	1.0	0.09155
2	5000	19.25	5000	25	0.77	1.3	0.11901
3	5000	19.25	5000	25	0.77	1.6	0.14648
4	5000	19.25	5000	25	0.77	1.9	0.17394
5	5000	57.75	5000	75	0.77	1.0	0.03025
6	5000	57.75	5000	75	0.77	1.3	0.03932
7	5000	57.75	5000	75	0.77	1.6	0.04840
8	5000	57.75	5000	75	0.77	1.9	0.05747
9	5000	96.25	5000	125	0.77	1.0	0.01799
10	5000	96.25	5000	125	0.77	1.3	0.02339
11	5000	96.25	5000	125	0.77	1.6	0.02878
12	5000	96.25	5000	125	0.77	1.9	0.03418
13	5000	134.75	5000	175	0.77	1.0	0.01274
14	5000	134.75	5000	175	0.77	1.3	0.01656
15	5000	134.75	5000	175	0.77	1.6	0.02038
16	5000	134.75	5000	175	0.77	1.9	0.02420
17	5000	173.25	5000	225	0.77	1.0	0.00982
18	5000	173.25	5000	225	0.77	1.3	0.01276
19	5000	173.25	5000	225	0.77	1.6	0.01571
20	5000	173.25	5000	225	0.77	1.9	0.01865
21	10000	38.50	10000	50	0.77	1.0	0.04577
22	10000	38.50	10000	50	0.77	1.3	0.05951
23	10000	38.50	10000	50	0.77	1.6	0.07324
24	10000	3850	10000	50	0.77	1.9	0.08697
25	10000	115.50	10000	150	0.77	1.0	0.01512
26	10000	115.50	10000	150	0.77	1.3	0.01966
27	10000	115.5	10000	150	0.77	1.6	0.024199

28	10000	115.5	10000	150	0.77	1.9	0.028737
29	10000	192.5	10000	250	0.77	1.0	0.008995
30	10000	192.5	10000	250	0.77	1.3	0.011693
31	10000	192.5	10000	250	0.77	1.6	0.014392
32	10000	192.5	10000	250	0.77	1.9	0.017090
33	10000	269.5	10000	350	0.77	1.0	0.006368
34	10000	269.5	10000	350	0.77	1.3	0.008278
35	10000	269.5	10000	350	0.77	1.6	0.010188
36	10000	269.5	10000	350	0.77	1.9	0.012099
37	10000	346.5	10000	450	0.77	1.0	0.004908
38	10000	346.5	10000	450	0.77	1.3	0.006381
39	10000	346.5	10000	450	0.77	1.6	0.007853
40	10000	346.5	10000	450	0.77	1.9	0.009326
41	50000	192.5	50000	250	0.77	1.0	0.009155
42	50000	192.5	50000	250	0.77	1.3	0.011901
43	50000	192.5	50000	250	0.77	1.6	0.014648
44	50000	192.5	50000	250	0.77	1.9	0.017394
45	50000	577.5	50000	750	0.77	1.0	0.003025
46	50000	577.5	50000	750	0.77	1.3	0.003932
47	50000	577.5	50000	750	0.77	1.6	0.004840
48	50000	577.5	50000	750	0.77	1.9	0.005747
49	50000	962.5	50000	1250	0.77	1.0	0.001799
50	50000	962.5	50000	1250	0.77	1.3	0.002339
51	50000	962.5	50000	1250	0.77	1.6	0.002878
52	50000	962.5	50000	1250	0.77	1.9	0.003418
53	50000	1347.5	50000	1750	0.77	1.0	.0012735
54	50000	1347.5	50000	1750	0.77	1.3	.0016556
55	50000	1347.5	50000	1750	0.77	1.6	.0020377
56	50000	1347.5	50000	1750	0.77	1.9	.0024197
57	50000	1732.5	50000	2250	0.77	1.0	.0009816
58	50000	1732.5	50000	2250	0.77	1.3	.0012761
59	50000	1732.5	50000	2250	0.77	1.6	.0015706
60	50000	1732.5	50000	2250	0.77	1.9	.0018651
61	100000	385.0	100000	500	0.77	1.0	.0045774
62	100000	385.0	100000	500	0.77	1.3	.0059506
63	100000	385.0	100000	500	0.77	1.6	.0073238

64	100000	385.0	100000	500	0.77	1.9	.0086971
65	100000	1155.0	100000	1500	0.77	1.0	.0015125
66	100000	1155.0	100000	1500	0.77	1.3	.0019662
67	100000	1155.0	100000	1500	0.77	1.6	.0024199
68	100000	1155.0	100000	1500	0.77	1.9	.0028737
69	100000	1925.0	100000	2500	0.77	1.0	.0008995
70	100000	1925.0	100000	2500	0.77	1.3	.0011693
71	100000	1925.0	100000	2500	0.77	1.6	.0014392
72	100000	1925.0	100000	2500	0.77	1.9	.0017090
73	100000	2695.0	100000	3500	0.77	1.0	.0006368
74	100000	2695.0	100000	3500	0.77	1.3	.0008278
75	100000	2695.0	100000	3500	0.77	1.6	.0010188
76	100000	2695.0	100000	3500	0.77	1.9	.0012099
77	100000	3465.0	100000	4500	0.77	1.0	.0004908
78	100000	3465.0	100000	4500	0.77	1.3	.0006381
79	100000	3465.0	100000	4500	0.77	1.6	.0007853
80	100000	3465.0	100000	4500	0.77	1.9	.0009326
81	250000	962.5	250000	1250	0.77	1.0	.0018310
82	250000	962.5	250000	1250	0.77	1.3	.0023802
83	250000	962.5	250000	1250	0.77	1.6	.0029295
84	250000	962.5	250000	1250	0.77	1.9	.0034788
85	250000	2887.5	250000	3750	0.77	1.0	.0006050
86	250000	2887.5	250000	3750	0.77	1.3	.0007865
87	250000	2887.5	250000	3750	0.77	1.6	.0009680
88	250000	2887.5	250000	3750	0.77	1.9	.0011495
89	250000	4812.5	250000	6250	0.77	1.0	.0003598
90	250000	4812.5	250000	6250	0.77	1.3	.0004677
91	250000	4812.5	250000	6250	0.77	1.6	.0005757
92	250000	4812.5	250000	6250	0.77	1.9	.0006836
93	250000	6737.5	250000	8750	0.77	1.0	.0002547
94	250000	6737.5	250000	8750	0.77	1.3	.0003311
95	250000	6737.5	250000	8750	0.77	1.6	.0004075
96	250000	6737.5	250000	8750	0.77	1.9	.0004839
97	250000	8662.5	250000	11250	0.77	1.0	.0001963
98	250000	8662.5	250000	11250	0.77	1.3	.0002552
99	250000	8662.5	250000	11250	0.77	1.6	.0003141

100	250000	8662.5	250000	11250	0.77	1.9	.0003730

OBS	LHATV	STUDYV	LPI	UPI
1	.0042545	0.012361	0.40415	1.46704
2	.0042545	0.012361	0.37412	1.58480
3	.0042545	0.012361	0.34892	1.69923
4	.0042545	0.012361	0.32727	1.81164
5	.0042545	0.012361	0.50375	1.17697
6	.0042545	0.012361	0.48436	1.22410
7	.0042545	0.012361	0.46714	1.26921
8	.0042545	0.012361	0.45164	1.31276
9	.0042545	0.012361	0.53474	1.10876
10	.0042545	0.012361	0.52029	1.13956
11	.0042545	0.012361	0.50713	1.16912
12	.0042545	0.012361	0.49504	1.19767
13	.0042545	0.012361	0.55038	1.07726
14	.0042545	0.012361	0.53884	1.10033
15	.0042545	0.012361	0.52817	1.12256
16	.0042545	0.012361	0.51823	1.14408
17	.0042545	0.012361	0.55989	1.05896
18	.0042545	0.012361	0.55029	1.07742
19	.0042545	0.012361	0.54132	1.09528
20	.0042545	0.012361	0.53289	1.11261
21	.0042545	0.012361	0.47193	1.25634
22	.0042545	0.012361	0.44837	1.32234
23	.0042545	0.012361	0.42789	1.38563
24	.0042545	0.012361	0.40976	1.44695
25	.0042545	0.012361	0.54305	1.09180
26	.0042545	0.012361	053011	1.11846
27	.0042545	0.012361	0.51823	1.14409
28	.0042545	0.012361	0.50724	1.16887
29	.0042545	0.012361	0.56269	1.05369
30	.0042545	0.012361	0.55370	1.07080
31	.0042545	0.012361	0.54526	1.08738
32	.0042545	0.012361	0.53730	1.10349
33	.0042545	0.012361	0.57206	1.03642
34	.0042545	0.012361	0.56518	1.04904

35	.0042545	0.012361	0.55864	1.06133
36	.0042545	0.012361	0.55240	1.07333
37	.0042545	0.012361	0.57758	1.02653
38	.0042545	0.012361	0.57202	1.03651
39	.0042545	0.012361	0.56668	1.04627
40	.0042545	0.012361	0.56155	1.05582
41	.0042545	0.012361	0.56214	1.05472
42	.0042545	0.012361	0.55303	1.07210
43	.0042545	0.012361	0.54448	1.08892
44	.0042545	0.012361	0.53643	1.10527
45	.0042545	0.012361	0.58506	1.01341
46	.0042545	0.012361	0.58140	1.01979
47	.0042545	0.012361	0.57784	1.02606
48	.0042545	0.012361	0.57438	1.03225
49	.0042545	0.012361	0.59017	1.00462
50	.0042545	0.012361	0.58790	1.00851
51	.0042545	0.012361	0.58566	1.01237
52	.0042545	0.012361	0.58346	1.01618
53	.0042545	0.012361	0.59243	1.00079
54	.0042545	0.012361	0.59079	1.00358
55	.0042545	0.012361	0.58916	1.00635
56	.0042545	0.012361	0.58756	1.00909
57	.0042545	0.012361	0.59371	0.99864
58	.0042545	0.012361	0.59242	1.00080
59	.0042545	0.012361	0.59115	1.00296
60	.0042545	0.012361	0.58989	1.00510
61	.0042545	0.012361	0.57886	1.02426
62	.0042545	0.012361	0.57362	1.03362
63	.0042545	0.012361	0.56857	1.04278
64	.0042545	0.012361	0.56372	1.05177
65	.0042545	0.012361	0.59140	1.00253
66	.0042545	0.012361	0.58946	1.00583
67	.0042545	0.012361	0.58756	1.00910
68	.0042545	0.012361	0.58568	1.01233
69	.0042545	0.012361	0.59407	0.99803
70	.0042545	0.012361	0.59289	1.00002

71	.0042545	0.012361	0.59172	1.00200
72	.0042545	0.012361	0.59056	1.00396
73	.0042545	0.012361	0.59523	0.99608
74	.0042545	0.012361	0.59438	0.99750
75	.0042545	0.012361	0.59355	0.99891
76	.0042545	0.012361	0.59271	1.00032
77	.0042545	0.012361	0.59588	0.99500
78	.0042545	0.012361	0.59522	0.99609
79	.0042545	0.012361	0.59457	0.99719
80	.0042545	0.012361	0.59392	0.99828
81	.0042545	0.012361	0.59004	1.00485
82	.0042545	0.012361	0.58772	1.00881
83	.0042545	0.012361	0.58545	1.01273
84	.0042545	0.012361	0.58321	1.01661
85	.0042545	0.012361	0.59537	0.99585
86	.0042545	0.012361	0.59457	0.99720
87	.0042545	0.012361	0.59377	0.99854
88	.0042545	0.012361	0.59297	0.99987
89	.0042545	0.012361	0.59647	0.99402
90	.0042545	0.012361	0.59598	0.99483
91	.0042545	0.012361	0.59550	0.99563
92	.0042545	0.012361	0.59502	0.99643
93	.0042545	0.012361	0.59694	0.99323
94	.0042545	0.012361	0.59660	0.99381
95	.0042545	0.012361	0.59625	0.99438
96	.0042545	0.012361	0.59591	0.99495
97	.0042545	0.012361	0.59720	0.99280
98	.0042545	0.012361	0.59694	0.99324
99	.0042545	0.012361	0.59667	0.99368
100	.0042545	0.012361	0.59641	0.99412

PROBABILITY OF FALLING TO SEE AN EFFECT IN A STUDY OF DEFINED CHARACTERISTICS

OBS	NA	DA	NC	DC	RR	DEFF	PROB
1	5000	19.25	5000	25	0.77	1.0	0.21339
2	5000	19.25	5000	25	0.77	1.3	0.23895
3	5000	19.25	5000	25	0.77	1.6	0.25876
4	5000	19.25	5000	25	0.77	1.9	0.27467

5	5000	57.75	5000	75	0.77	1.0	0.11365
6	5000	57.75	5000	75	0.77	1.3	0.13457
7	5000	57.75	5000	75	0.77	1.6	0.15267
8	5000	57.75	5000	75	0.77	1.9	0.16847
9	5000	96.25	5000	125	0.77	1.0	0.08001
10	5000	96.25	5000	125	0.77	1.3	0.09564
11	5000	96.25	5000	125	0.77	1.6	0.10998
12	5000	96.25	5000	125	0.77	1.9	0.12309
13	5000	134.75	5000	175	0.77	1.0	0.06356
14	5000	134.75	5000	175	0.77	1.3	0.07564
15	5000	134.75	5000	175	0.77	1.6	0.08709
16	5000	134.75	5000	175	0.77	1.9	0.09788
17	5000	173.25	5000	225	0.77	1.0	0.05396
18	5000	173.25	5000	225	0.77	1.3	0.06364
19	5000	173.25	5000	225	0.77	1.6	0.07300
20	5000	173.25	5000	225	0.77	1.9	0.08200
21	10000	38.50	10000	50	0.77	1.0	0.14769
22	10000	38.50	10000	50	0.77	1.3	0.17174
23	10000	38.50	10000	50	0.77	1.6	0.19163
24	10000	38.50	10000	50	0.77	1.9	0.20837
25	10000	115.50	10000	150	0.77	1.0	0.07118
26	10000	115.50	10000	150	0.77	1.3	0.08500
27	10000	115.50	10000	150	0.77	1.6	0.09788
28	10000	115.50	10000	150	0.77	1.9	0.10986
29	10000	192.50	10000	250	0.77	1.0	0.05121
30	10000	192.50	10000	250	0.77	1.3	0.06016
31	10000	192.50	10000	250	0.77	1.6	0.06887
32	10000	192.50	10000	250	0.77	1.9	0.07728
33	10000	269.50	10000	350	0.77	1.0	0.04235
34	10000	269.50	10000	350	0.77	1.3	0.04881
35	10000	269.50	10000	350	0.77	1.6	0.05520
36	10000	269.50	10000	350	0.77	1.9	0.06149
37	10000	346.50	10000	450	0.77	1.0	0.03741
38	10000	346.50	10000	450	0.77	1.3	0.04240
39	10000	346.50	10000	450	0.77	1.6	0.04737
40	10000	346.50	10000	450	0.77	1.9	0.05232

41	50000	192.50	50000	250	0.77	1.0	0.05175
42	50000	192.50	50000	250	0.77	1.3	0.06084
43	50000	192.50	50000	250	0.77	1.6	0.06968
44	50000	192.50	50000	250	0.77	1.9	0.07821
45	50000	577.50	50000	750	0.77	1.0	0.03109
46	50000	577.50	50000	750	0.77	1.3	0.03413
47	50000	577.50	50000	750	0.77	1.6	0.03718
48	50000	577.50	50000	750	0.77	1.9	0.04025
49	50000	962.50	50000	1250	0.77	1.0	0.02705
50	50000	962.50	50000	1250	0.77	1.3	0.02882
51	50000	962.50	50000	1250	0.77	1.6	0.03061
52	50000	962.50	50000	1250	0.77	1.9	0.03240
53	50000	1347.50	50000	1750	0.77	1.0	0.02534
54	50000	1347.50	50000	1750	0.77	1.3	0.02658
55	50000	1347.50	50000	1750	0.77	1.6	0.02783
56	50000	1347.5	50000	1750	0.77	1.9	0.029087
57	50000	1732.5	50000	2250	0.77	1.0	0.024404
58	50000	1732.5	50000	2250	0.77	1.3	0.025351
59	50000	1732.5	50000	2250	0.77	1.6	0.026305
60	50000	1732.5	50000	2250	0.77	1.9	0.027265
61	100000	385.0	100000	500	0.77	1.0	0.036298
62	100000	385.0	100000	500	0.77	1.3	0.040940
63	100000	385.0	100000	500	0.77	1.6	0.045587
64	100000	385.0	100000	500	0.77	1.9	0.050214
65	100000	1155.0	100000	1500	0.77	1.0	0.026116
66	100000	1155.0	100000	1500	0.77	1.3	0.027596
67	100000	1155.0	100000	1500	0.77	1.6	0.029088
68	100000	1155.0	100000	1500	0.77	1.9	0.030590
69	100000	1925.0	100000	2500	0.77	1.0	0.024140
70	100000	1925.0	100000	2500	0.77	1.3	0.025007
71	100000	1925.0	100000	2500	0.77	1.6	0.025879
72	100000	1925.0	100000	2500	0.77	1.9	0.026756
73	100000	2695.0	100000	3500	0.77	1.0	0.023303
74	100000	2695.0	100000	3500	0.77	1.3	0.023911
75	100000	2695.0	100000	3500	0.77	1.6	0.024523
76	100000	2695.0	100000	3500	0.77	1.9	0.025137

77	100000	3465.0	100000	4500	0.77	1.0	0.022840
78	100000	3465.0	100000	4500	0.77	1.3	0.023307
79	100000	3465.0	100000	4500	0.77	1.6	0.023776
80	100000	3465.0	100000	4500	0.77	1.9	0.024246
81	250000	962.5	250000	1250	0.77	1.0	0.027154
82	250000	962.5	250000	1250	0.77	1.3	0.028957
83	250000	962.5	250000	1250	0.77	1.6	0.030776
84	250000	962.5	250000	1250	0.77	1.9	0.032607
85	250000	2887.5	250000	3750	0.77	1.0	0.023202
86	250000	2887.5	250000	3750	0.77	1.3	0.023779
87	250000	2887.5	250000	3750	0.77	1.6	0.024360
88	250000	2887.5	250000	3750	0.77	1.9	0.024943
89	250000	4812.5	250000	6250	0.77	1.0	0.022426
90	250000	4812.5	250000	6250	0.77	1.3	0.022767
91	250000	4812.5	250000	6250	0.77	1.6	0.023109
92	250000	4812.5	250000	6250	0.77	1.9	0.023452
93	250000	6737.5	250000	8750	0.77	1.0	0.022096
94	250000	6737.5	250000	8750	0.77	1.3	0.022336
95	250000	6737.5	250000	8750	0.77	1.6	0.022577
96	250000	6737.5	250000	8750	0.77	1.9	0.022818
97	250000	8662.5	250000	11250	0.77	1.0	0.021912
98	250000	8662.5	250000	11250	0.77	1.3	0.022097
99	250000	8662.5	250000	11250	0.77	1.6	0.022282
100	250000	8662.5	250000	11250	0.77	1.9	0.022468

ESTIMATES OF LIVES SAVED AS FUNCTION OF POPULATION SIZE, BASELINE [CONTROL] MORTALITY RATE AND DEFF

OBS	NA	DA	NC	DC	RR	DEFF	ULSAVE	AVERSAVE	LLSAVE	LLSAVE2
1	5000	19.25	5000	25	0.77	1.0	14.896	5.75	−11.6759	none
2	5000	19.25	5000	25	0.77	1.3	15.647	5.75	−14.6200	none
3	5000	19.25	5000	25	0.77	1.6	16.277	5.75	−17.4808	none
4	5000	19.25	5000	25	0.77	1.9	16.818	5.75	−20.2909	none
5	5000	57.75	5000	75	0.77	1.0	37.219	17.25	−13.2726	none
6	5000	57.75	5000	75	0.77	1.3	38.673	17.25	−16.8075	none
7	5000	57.75	5000	75	0.77	1.6	39.964	17.25	−20.1908	none
8	5000	57.75	5000	75	0.77	1.9	41.127	17.25	−23.4573	none
9	5000	96.25	5000	125	0.77	1.0	58.157	28.75	−13.5951	none

10	5000	96.25	5000	125	0.77	1.3	59.964	28.75	−17.4454	none
11	5000	96.25	5000	125	0.77	1.6	61.608	28.75	−21.1402	none
12	5000	96.25	5000	125	0.77	1.9	63.119	28.75	−24.7088	none
13	5000	134.75	5000	175	0.77	1.0	78.684	40.25	−13.5212	none
14	5000	134.75	5000	175	0.77	1.3	80.703	40.25	−17.5580	none
15	5000	134.75	5000	175	0.77	1.6	82.570	40.25	−21.4475	none
16	5000	134.75	5000	175	0.77	1.9	84.309	40.25	−25.2134	none
17	5000	173.25	5000	225	0.77	1.0	99.025	51.75	−13.2667	none
18	5000	173.25	5000	225	0.77	1.3	101.184	51.75	−17.4204	none
19	5000	173.25	5000	225	0.77	1.6	103.202	51.75	−21.4378	none
20	5000	173.25	5000	225	0.77	1.9	105.100	51.75	−25.3382	none
21	10000	38.50	10000	50	0.77	1.0	26.404	11.50	−12.8170	none
22	10000	38.50	10000	50	0.77	1.3	27.581	11.50	−16.1170	none
23	10000	38.50	10000	50	0.77	1.6	28.605	11.50	−19.2817	none
24	10000	38.50	10000	50	0.77	1.9	29.512	11.50	−22.3475	none
25	10000	115.50	10000	150	0.77	1.0	68.543	34.50	−13.7695	none
26	10000	115.50	10000	150	0.77	1.3	70.484	34.50	−17.7685	none
27	10000	115.50	10000	150	0.77	1.6	72.266	34.50	−21.6133	none
28	10000	115.50	10000	150	0.77	1.9	73.914	34.50	−25.3307	none
29	10000	192.50	10000	250	0.77	1.0	109.328	57.50	−13.4225	none
30	10000	192.50	10000	250	0.77	1.3	111.576	57.50	−17.7009	none
31	10000	192.50	10000	250	0.77	1.6	113.686	57.50	−21.8444	none
32	10000	192.50	10000	250	0.77	1.9	115.676	57.50	−25.8713	none
33	10000	269.50	10000	350	0.77	1.0	149.778	80.50	−12.7481	none
34	10000	269.50	10000	350	0.77	1.3	152.186	80.50	−17.1649	none
35	10000	269.50	10000	350	0.77	1.6	154.477	80.50	−21.4660	none
36	10000	269.50	10000	350	0.77	1.9	156.662	80.50	−25.6641	none
37	10000	346.50	10000	450	0.77	1.0	190.091	103.50	−11.9394	none
38	10000	346.50	10000	450	0.77	1.3	192.593	103.50	−16.4295	none
39	10000	346.50	10000	450	0.77	1.6	194.993	103.50	−20.8196	none
40	10000	346.50	10000	450	0.77	1.9	197.301	103.50	−25.1190	none
41	50000	192.50	50000	250	0.77	1.0	109.465	57.50	−13.6803	none
42	50000	192.50	50000	250	0.77	1.3	111.743	57.50	−18.0248	none
43	50000	192.50	50000	250	0.77	1.6	113.879	57.50	−22.2312	none
44	50000	192.50	50000	250	0.77	1.9	115.893	57.50	−26.3183	none
45	50000	577.50	50000	750	0.77	1.0	311.208	172.50	−10.0554	none

46	50000	577.50	50000	750	0.77	1.3	313.952	172.50	−14.8391	none
47	50000	577.50	50000	750	0.77	1.6	316.620	172.50	−19.5474	none
48	50000	577.50	50000	750	0.77	1.9	319.216	172.50	−24.1853	none
49	50000	962.50	50000	1250	0.77	1.0	512.282	287.50	−5.7721	none
50	50000	962.50	50000	1250	0.77	1.3	515.131	287.50	−10.6405	none
51	50000	962.50	50000	1250	0.77	1.6	517.928	287.50	−15.4587	none
52	50000	962.50	50000	1250	0.77	1.9	520.678	287.50	−20.2286	none
53	50000	1347.50	50000	1750	0.77	1.0	713.239	402.50	−1.3745	none
54	50000	1347.50	50000	1750	0.77	1.3	716.122	402.50	−6.2582	none
55	50000	1347.5	50000	1750	0.77	1.6	718.97	402.5	−11.1045	none
56	50000	1347.5	50000	1750	0.77	1.9	721.78	402.5	−15.9146	none
57	50000	1732.5	50000	2250	0.77	1.0	914.16	517.5	3.0635	3.06
58	50000	1732.5	50000	2250	0.77	1.3	917.05	517.5	−1.8100	none
59	50000	1732.5	50000	2250	0.77	1.6	919.91	517.5	−6.6539	none
60	50000	1732.5	50000	2250	0.77	1.9	922.74	517.5	−11.4691	none
61	100000	385.0	100000	500	0.77	1.0	210.57	115.0	−12.1287	none
62	100000	385.0	100000	500	0.77	1.3	213.19	115.0	−16.8099	none
63	100000	385.0	100000	500	0.77	1.6	215.71	115.0	−21.3915	none
64	100000	385.0	100000	500	0.77	1.9	218.14	115.0	−25.8825	none
65	100000	1155.0	100000	1500	0.77	1.0	612.90	345.0	−3.7997	none
66	100000	1155.0	100000	1500	0.77	1.3	615.80	345.0	−8.7436	none
67	100000	1155.0	100000	1500	0.77	1.6	618.67	345.0	−13.6434	none
68	100000	1155.0	100000	1500	0.77	1.9	621.49	345.0	−18.5008	none
69	100000	1925.0	100000	2500	0.77	1.0	1014.83	575.0	4.9206	4.92
70	100000	1925.0	100000	2500	0.77	1.3	1017.78	575.0	−0.0509	none
71	100000	1925.0	100000	2500	0.77	1.6	1020.71	575.0	−4.9946	none
72	100000	1925.0	100000	2500	0.77	1.9	1023.60	575.0	−9.9112	none
73	100000	2695.0	100000	3500	0.77	1.0	1416.69	805.0	13.7032	13.7
74	100000	2695.0	100000	3500	0.77	1.3	1419.65	805.0	8.7443	8.74
75	100000	2695.0	100000	3500	0.77	1.6	1422.59	805.0	3.8055	3.81
76	100000	2695.0	100000	3500	0.77	1.9	1425.51	805.0	−1.1136	none
77	100000	3465.0	100000	4500	0.77	1.0	1818.54	1035.0	22.5071	22.5
78	100000	3465.0	100000	4500	0.77	1.3	1821.49	1035.0	17.5750	17.6
79	100000	3465.0	100000	4500	0.77	1.6	1824.42	1035.0	12.6584	12.7
80	100000	3465.0	100000	4500	0.77	1.9	1827.34	1035.0	7.7573	7.76
81	250000	962.5	250000	1250	0.77	1.0	512.45	287.5	−6.0622	none

82	250000	962.5	250000	1250	0.77	1.3	515.35	287.5	−11.0137	none
83	250000	962.5	250000	1250	0.77	1.6	518.19	287.5	−15.9132	none
84	250000	962.5	250000	1250	0.77	1.9	520.98	287.5	−20.7630	none
85	250000	2887.5	250000	3750	0.77	1.0	1517.36	862.5	15.5681	15.6
86	250000	2887.5	250000	3750	0.77	1.3	1520.37	862.5	10.5163	10.5
87	250000	2887.5	250000	3750	0.77	1.6	1523.37	862.5	5.4839	5.48
88	250000	2887.5	250000	3750	0.77	1.9	1526.35	862.5	0.4708	none
89	250000	4812.5	250000	6250	0.77	1.0	2522.08	1437.5	37.3741	37.4
90	250000	4812.5	250000	6250	0.77	1.3	2525.10	1437.5	32.3362	32.3
91	250000	4812.5	250000	6250	0.77	1.6	2528.11	1437.5	27.3100	27.3
92	250000	4812.5	250000	6250	0.77	1.9	2531.11	1437.5	22.2956	22.3
93	250000	6737.5	250000	8750	0.77	1.0	3526.78	2012.5	59.2064	59.2
94	250000	6737.5	250000	8750	0.77	1.3	3529.79	2012.5	54.2000	54.2
95	250000	6737.5	250000	8750	0.77	1.6	3532.79	2012.5	49.2020	49.2
96	250000	6737.5	250000	8750	0.77	1.9	3535.78	2012.5	44.2124	44.2
97	250000	8662.5	250000	11250	0.77	1.0	4531.47	2587.5	81.0476	81
98	250000	8662.5	250000	11250	0.77	1.3	4534.46	2587.5	76.0788	76.1
99	250000	8662.5	250000	11250	0.77	1.6	4537.44	2587.5	71.1164	71.1
100	250000	8662.5	250000	11250	0.77	1.9	4540.42	2587.5	66.1605	66.2

Input Data

The following listings represent the data used in analyses throughout this report. Where other data have also been used (e.g. prevalence estimates for anthropometry and xerophthalmia, data for infants under 6 months) they can be read from the appropriate SAS programme code in previous section. The datasets below are in format of the input files for SAS programs. They are identified by their nature and by the file name used in SAS programs in previous section. For some studies, actual counts (live) were not available and were back−calculated from reported child−years; this creates some error in the counts of live individuals below but not the counts of the dead.

TOTAL COUNTS BY STUDY AND TREATMENT

SAS: VITA_CNT.ALL

ACEH	A_admin	dead	101
ACEH	A_admin	live	12890
ACEH	control	dead	130
ACEH	control	live	12079
TAMIL	A_admin	dead	42
TAMIL	A_admin	live	7255
TAMIL	control	dead	83

TAMIL	control	live	7161
HYDER	A_admin	dead	39
HYDER	A_admin	live	7037
HYDER	control	dead	41
HYDER	control	live	6965
SARLAHI	A_admin	dead	152
SARLAHI	A_admin	live	13766
SARLAHI	control	dead	210
SARLAHI	control	live	13400
MSG	A_admin	dead	186
MSG	A_admin	live	5589
MSG	control	dead	250
MSG	control	live	5195
SUDAN	A_admin	dead	123
SUDAN	A_admin	live	14111
SUDAN	control	dead	117
SUDAN	control	live	13974
JUMLA	A_admin	dead	138
JUMLA	A_admin	live	3648
JUMLA	control	dead	167
JUMLA	control	live	3244
GHANA	A_admin	dead	397
GHANA	A_admin	live	9638
GHANA	control	dead	495
GHANA	control	live	9529

COUNTS BY GENDER, STUDY AND TREATMENT

SAS: VITA_CNT.GEN

ACEH	A_admin	dead	female	51
ACEH	A_admin	live	female	6188
ACEH	control	dead	female	52
ACEH	control	live	female	5823
ACEH	A_admin	dead	male	46
ACEH	A_admin	live	male	6316
ACEH	control	dead	male	73
ACEH	control	live	male	5895

TAMIL	A_admin	dead	female	23
TAMIL	A_admin	live	female	3588
TAMIL	control	dead	female	49
TAMIL	control	live	female	3438
TAMIL	A_admin	dead	male	19
TAMIL	A_admin	live	male	3667
TAMIL	control	dead	male	34
TAMIL	control	live	male	3723
SARLAHI	A_admin	dead	female	80
SARLAHI	A_admin	live	female	6909
SARLAHI	control	dead	female	121
SARLAHI	control	live	female	6768
SARLAHI	A_admin	dead	male	72
SARLAHI	A_admin	live	male	7431
SARLAHI	control	dead	male	89
SARLAHI	control	live	male	7095
SUDAN	A_admin	dead	female	61
SUDAN	A_admin	live	female	6853
SUDAN	control	dead	female	66
SUDAN	control	live	female	7017
SUDAN	A_admin	dead	male	63
SUDAN	A_admin	live	male	7257
SUDAN	control	dead	male	49
SUDAN	control	live	male	6957
JUMLA	A_admin	dead	female	67
JUMLA	A_admin	live	female	1743
JUMLA	control	dead	female	81
JUMLA	control	live	female	1587
JUMLA	A_admin	dead	male	71
JUMLA	A_admin	live	male	1905
JUMLA	control	dead	male	86
JUMLA	control	live	male	1657
HYDER	A_admin	dead	female	19
HYDER	A_admin	live	female	3475
HYDER	control	dead	female	21
HYDER	control	live	female	3456

HYDER	A_admin	dead	male	20
HYDER	A_admin	live	male	3562
HYDER	control	dead	male	20
HYDER	control	live	male	3509

COUNTS BY AGE, STUDY AND TREATMENT

SAS: VITA_CNT.AGE

ACEH	A_admin	dead	0–11	48
ACEH	A_admin	live	0–11	2026
ACEH	control	dead	0–11	55
ACEH	control	live	0–11	1924
ACEH	A_admin	dead	12–23	19
ACEH	A_admin	live	12–23	1960
ACEH	control	dead	12–23	22
ACEH	control	live	12–23	1919
ACEH	A_admin	dead	24–35	14
ACEH	A_admin	live	24–35	2072
ACEH	control	dead	24–35	25
ACEH	control	live	24–35	2047
ACEH	A_admin	dead	36–47	11
ACEH	A_admin	live	36–47	2263
ACEH	control	dead	36–47	8
ACEH	control	live	36–47	2008
ACEH	A_admin	dead	48–59	5
ACEH	A_admin	live	48–59	1882
ACEH	control	dead	48–59	7
ACEH	control	live	48–59	1717
TAMIL	A_admin	dead	0–11	14
TAMIL	A_admin	live	0–11	938
TAMIL	control	dead	0–11	24
TAMIL	control	live	0–11	1032
TAMIL	A_admin	dead	12–23	13
TAMIL	A_admin	live	12–23	1273
TAMIL	control	dead	12–23	31
TAMIL	control	live	12–23	1210
TAMIL	A_admin	dead	24–35	5

TAMIL	A_admin	live	24–35	1404
TAMIL	control	dead	24–35	13
TAMIL	control	live	24–35	1407
TAMIL	A_admin	dead	36–47	4
TAMIL	A_admin	live	36–47	1571
TAMIL	control	dead	36–47	8
TAMIL	control	live	36–47	1571
TAMIL	A_admin	dead	48–59	6
TAMIL	A_admin	live	48–59	1985
TAMIL	control	dead	48–59	7
TAMIL	control	live	48–59	1892
SARLAHI	A_admin	dead	0–11	39
SARLAHI	A_admin	live	0–11	1493
SARLAHI	control	dead	0–11	47
SARLAHI	control	live	0–11	1400
SARLAHI	A_admin	dead	12–23	53
SARLAHI	A_admin	live	12–23	3016
SARLAHI	control	dead	12–23	75
SARLAHI	control	live	12–23	2923
SARLAHI	A_admin	dead	24–35	27
SARLAHI	A_admin	live	24–35	2969
SARLAHI	control	dead	24–35	31
SARLAHI	control	live	24–35	2820
SARLAHI	A_admin	dead	36–47	18
SARLAHI	A_admin	live	36–47	2905
SARLAHI	control	dead	36–47	28
SARLAHI	control	live	36–47	2868
SARLAHI	A_admin	dead	48–59	13
SARLAHI	A_admin	live	48–59	2901
SARLAHI	control	dead	48–59	25
SARLAHI	control	live	48–59	2805
SUDAN	A_admin	dead	0–11	13
SUDAN	A_admin	live	0–11	751
SUDAN	control	dead	0–11	18
SUDAN	control	live	0–11	775
SUDAN	A_admin	dead	12–23	46

SUDAN	A_admin	live	12–23	2536
SUDAN	control	dead	12–23	37
SUDAN	control	live	12–23	2571
SUDAN	A_admin	dead	24–35	23
SUDAN	A_admin	live	24–35	2423
SUDAN	control	dead	24–35	20
SUDAN	control	live	24–35	2300
SUDAN	A_admin	dead	36–47	10
SUDAN	A_admin	live	36–47	2225
SUDAN	control	dead	36–47	5
SUDAN	control	live	36–47	2294
SUDAN	A_admin	dead	48–59	3
SUDAN	A_admin	live	48–59	2067
SUDAN	control	dead	48–59	6
SUDAN	control	live	48–59	2062
JUMLA	A_admin	dead	0–11	44
JUMLA	A_admin	live	0–11	860
JUMLA	control	dead	0–11	60
JUMLA	control	live	0–11	780
JUMLA	A_admin	dead	12–23	62
JUMLA	A_admin	live	12–23	774
JUMLA	control	dead	12–23	71
JUMLA	control	live	12–23	695
JUMLA	A_admin	dead	24–35	19
JUMLA	A_admin	live	24–35	705
JUMLA	control	dead	24–35	22
JUMLA	control	live	24–35	609
JUMLA	A_admin	dead	36–47	11
JUMLA	A_admin	live	36–47	739
JUMLA	control	dead	36–47	11
JUMLA	control	live	36–47	617
JUMLA	A_admin	dead	48–59	2
JUMLA	A_admin	live	48–59	570
JUMLA	control	dead	48–59	3
JUMLA	control	live	48–59	543
HYDER	A_admin	dead	12–23	24

HYDER	A_admin	live	12–23	2247
HYDER	control	dead	12–23	23
HYDER	control	live	12–23	2201
HYDER	A_admin	dead	24–35	8
HYDER	A_admin	live	24–35	1722
HYDER	control	dead	24–35	10
HYDER	control	live	24–35	1817
HYDER	A_admin	dead	36–47	5
HYDER	A_admin	live	36–47	1957
HYDER	control	dead	36–47	6
HYDER	control	live	36–47	1985
HYDER	A_admin	dead	48–59	2
HYDER	A_admin	live	48–59	1117
HYDER	control	dead	48–59	2
HYDER	control	live	48–59	962

CAUSE–SPECIFIC MORTALITY COUNTS

SAS: VITA_CNT.CAS

GHANA	A_admin	dead	all	397
GHANA	A_admin	live	all	9638
GHANA	control	dead	all	495
GHANA	control	live	all	9529
JUMLA	A_admin	dead	all	138
JUMLA	A_admin	live	all	3648
JUMLA	control	dead	all	167
JUMLA	control	live	all	3244
SARLAHI	A_admin	dead	all	152
SARLAHI	A_admin	live	all	13766
SARLAHI	control	dead	all	210
SARLAHI	control	live	all	13400
SUDAN	A_admin	dead	all	123
SUDAN	A_admin	live	all	14111
SUDAN	control	dead	all	117
SUDAN	control	live	all	13974
TAMIL	A_admin	dead	all	42
TAMIL	A_admin	live	all	7255

TAMIL	control	dead	all	83
TAMIL	control	live	all	7161
GHANA	A_admin	dead	diarr	91
GHANA	A_admin	live	diarr	9933
GHANA	control	dead	diarr	147
GHANA	control	live	diarr	9888
JUMLA	A_admin	dead	diarr	94
JUMLA	A_admin	live	diarr	3692
JUMLA	control	dead	diarr	129
JUMLA	control	live	diarr	3282
SARLAHI	A_admin	dead	diarr	39
SARLAHI	A_admin	live	diarr	13879
SARLAHI	control	dead	diarr	62
SARLAHI	control	live	diarr	13548
SUDAN	A_admin	dead	diarr	50
SUDAN	A_admin	live	diarr	14184
SUDAN	control	dead	diarr	49
SUDAN	control	live	diarr	14042
TAMIL	A_admin	dead	diarr	16
TAMIL	A_admin	live	diarr	7281
TAMIL	control	dead	diarr	33
TAMIL	control	live	diarr	7211
GHANA	A_admin	dead	resp	47
GHANA	A_admin	live	resp	9977
GHANA	control	dead	resp	45
GHANA	control	live	resp	9990
JUMLA	A_admin	dead	resp	18
JUMLA	A_admin	live	resp	3768
JUMLA	control	dead	resp	17
JUMLA	control	live	resp	3394
SARLAHI	A_admin	dead	resp	36
SARLAHI	A_admin	live	resp	13882
SARLAHI	control	dead	resp	27
SARLAHI	control	live	resp	13583
SUDAN	A_admin	dead	resp	7
SUDAN	A_admin	live	resp	14227

SUDAN	control	dead	resp	16
SUDAN	control	live	resp	14075
TAMIL	A_admin	dead	resp	2
TAMIL	A_admin	live	resp	7295
TAMIL	control	dead	resp	3
TAMIL	control	live	resp	7241
GHANA	A_admin	dead	measles	61
GHANA	A_admin	live	measles	9963
GHANA	control	dead	measles	73
GHANA	control	live	measles	9962
JUMLA	A_admin	dead	measles	3
JUMLA	A_admin	live	measles	3783
JUMLA	control	dead	measles	4
JUMLA	control	live	measles	3407
SARLAHI	A_admin	dead	measles	4
SARLAHI	A_admin	live	measles	13915
SARLAHI	control	dead	measles	12
SARLAHI	control	live	measles	13598
SUDAN	A_admin	dead	measles	
SUDAN	A_admin	live	measles	
SUDAN	control	dead	measles	
SUDAN	control	live	measles	
TAMIL	A_admin	dead	measles	7
TAMIL	A_admin	live	measles	7290
TAMIL	control	dead	measles	12
TAMIL	control	live	measles	7232
GHANA	A_admin	dead	other	198
GHANA	A_admin	live	other	9837
GHANA	control	dead	other	230
GHANA	control	live	other	9794
JUMLA	A_admin	dead	other	23
JUMLA	A_admin	live	other	3763
JUMLA	control	dead	other	17
JUMLA	control	live	other	3394
SARLAHI	A_admin	dead	other	74
SARLAHI	A_admin	live	other	13844

SARLAHI	control	dead	other	51
SARLAHI	control	live	other	13559
SUDAN	A_admin	dead	other	66
SUDAN	A_admin	live	other	14168
SUDAN	control	dead	other	65
SUDAN	control	live	other	15026
TAMIL	A_admin	dead	other	17
TAMIL	A_admin	live	other	7280
TAMIL	control	dead	other	35
TAMIL	control	live	other	7209

DESIGN EFFECT FILE
(Derived file: see SAS programs A and B for source)

SAS: VITADEFF.SAS

```
title2 'Variances calculated using estimated design effect adjustments' ;

if study = 'ACEH' then deff = 1.11;
if study = 'GHANA' then deff = 1.22;
if study = 'HYDER' then deff = 1.34;
if study = 'JUMLA' then deff = 1.92;
if study = 'MSG' then deff = 1.25;
if study = 'SARLAHI' then deff = 1.22;
if study = 'SUDAN' then deff = 1.00;
if study = 'TAMIL' then deff = 1.14;
```

COUNT OF CLUSTERS BY STUDY
(First column are the Vitamin A treated clusters and second column are Controls)

SAS: CLUSTERS.DAT

ACEH	229	221
TAMIL	103	103
SARLAHI	130	130
JUMLA	8	8
HYDER	42	42
MSG	48	44
SUDAN	8515	8515
GHANA	92	93

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