Population deworming every 6 months with albendazole in 1 million pre-school children in north India: DEVTA, a cluster-randomised trial

Shally Awasthi, Richard Peto, Simon Read, Susan M Richards, Vinod Pande, Donald Bundy, and the DEVTA (Deworming and Enhanced Vitamin A) team

Summary

King George's Medical
University, Lucknow, Uttar
Pradesh, India
(Prof S Awasthi MD, V Pande MD,
DEVTA team); Clinical Trial
Service Unit and
Epidemiological Studies Unit
(CTSU), University of Oxford,
Oxford, UK (Prof R Peto FRS,
S Read PhD, S M Richards PhD);
and Human Development
Network, The World Bank,
Washington, DC, USA
(D Bundy PhD)

Correspondence to:
Prof Shally Awasthi, Department
of Paediatrics, King George's
Medical University, Chowk,
Lucknow, Uttar Pradesh 226003,
India
shally07@gmail.com

Background In north India many pre-school children are underweight, many have intestinal worms, and 2–3% die at ages 1·0–6·0 years. We used the state-wide Integrated Child Development Service (ICDS) infrastructure to help to assess any effects of regular deworming on mortality.

Methods Participants in this cluster-randomised study were children in catchment areas of 8338 ICDS-staffed village child-care centres (under-5 population 1 million) in 72 administrative blocks. Groups of four neighbouring blocks were cluster-randomly allocated in Oxford between 6-monthly vitamin A (retinol capsule of 200 000 IU retinyl acetate in oil, to be cut and dripped into the child's mouth every 6 months), albendazole (400 mg tablet every 6 months), both, or neither (open control). Analyses of albendazole effects are by block (36 *vs* 36 clusters). The study spanned 5 calendar years, with 11 6-monthly mass-treatment days for all children then aged 6–72 months. Annually, one centre per block was randomly selected and visited by a study team 1–5 months after any trial deworming to sample faeces (for presence of worm eggs, reliably assessed only after mid-study), weigh children, and interview caregivers. Separately, all 8338 centres were visited every 6 months to monitor pre-school deaths (100 000 visits, 25 000 deaths at age 1·0–6·0 years [the primary outcome]). This trial is registered at ClinicalTrials.gov, NCT00222547.

Findings Estimated compliance with 6-monthly albendazole was 86%. Among 2589 versus 2576 children surveyed during the second half of the study, nematode egg prevalence was 16% versus 36%, and most infection was light. After at least 2 years of treatment, weight at ages 3·0–6·0 years (standardised to age 4·0 years, 50% male) was 12·72 kg albendazole versus 12·68 kg control (difference 0·04 kg, 95% CI –0·14 to 0·21, p=0·66). Comparing the 36 albendazole-allocated versus 36 control blocks in analyses of the primary outcome, deaths per child-care centre at ages 1·0–6·0 years during the 5-year study were 3·00 (SE 0·07) albendazole versus 3·16 (SE 0·09) control, difference 0·16 (SE 0·11, mortality ratio 0·95, 95% CI 0·89 to 1·02, p=0·16), suggesting absolute risks of dying between ages 1·0 and 6·0 years of roughly 2·5% albendazole versus 2·6% control. No specific cause of death was significantly affected.

Interpretation Existing ICDS village staff can be organised to deliver simple pre-school interventions sustainably for many years at low cost, but regular deworming had little effect on mortality in this lightly infected pre-school population.

Funding UK Medical Research Council, USAID, World Bank (albendazole donated by GlaxoSmithKline).

Introduction

Heavy worm infection can constrain physical development.[1,2] In areas where heavy infection is common, periodic deworming of school-age children can improve weight gain.[3–5] Of three studies of urban pre-school children in Lucknow, north India, two suggested little effect of deworming on growth and one showed a substantial effect, perhaps large enough to reduce mortality significantly in a much larger study.[6–9] The Integrated Child Development Service (ICDS) in Uttar Pradesh offered an opportunity to test the effects of deworming in children in rural areas.

The ICDS has staffed child-care centres serving all children up to age 6 years in one-third of the villages in Uttar Pradesh. These centres can deliver simple health interventions, as long as all the villages in the same administrative area are asked to give the same intervention.[10,11] We therefore planned a large cluster-randomised trial of whether the ICDS could inexpensively

and sustainably deliver anthelmintics at operational scale to rural pre-school children in Uttar Pradesh. The primary aim of the trial was to assess effects of a widely practicable periodic deworming regimen on mortality at ages 1·0–6·0 years.[12]

Plans for this deworming trial were eventually revised into plans for a factorial trial of albendazole, vitamin A (retinol), both, or neither that would assess the effects of each agent on child mortality. This report focuses on the albendazole results; an accompanying report gives the vitamin A results.[13]

Methods

Study design

This cluster-randomised study spanned seven adjacent districts (area 35 000 km², 3 degrees of latitude by 1 of longitude; figure 1). Excluding major municipalities, they consist of 118 largely rural administrative blocks (units that generally have a rural population of more than 100 000).

72 of these blocks could participate; 36 were cluster-randomly allocated albendazole every 6 months for 5 years and 36 open control (figure 2).

The study was based in Lucknow, the Uttar Pradesh state capital. The 72 participating blocks were those within a few hours drive that the ICDS director in Lucknow judged in 1998 to have a reasonably well functioning ICDS system with willing district and block ICDS directors and paid workers in most village anganwadi child-care centres (AWCs; anganwadi means courtyard). A typical rural AWC serves a village population of 1000 (10–15% aged 1–6·0 years); large villages can have more AWCs. The AWC workers, usually local women (plus assistants), give pre-school education, give nutritional supplements to malnourished children, and record births and pre-school deaths. AWCs register about two-thirds of under-5s (and one-third of 5-year-olds) for possible nutritional supplementation, although levels of AWC attendance and supplementary nutrition in Uttar Pradesh are often low.[10] AWC workers can help health workers to organise immunisation and pre-school health services. In one block, a court order closed down all AWCs, but treatment and follow-up continued via the local administration (known as the panchayat).

In these 72 blocks, 8511 AWCs were deemed functional in 1998 (or, in a few cases, were expected to become functional during the study), and 8338 (98%) of these remained functional for most or all of the study and so were included (figure 2). At any one time the study population for assessment of mortality was all pre-school children then aged 1·0–6·0 years in the defined catchment areas of these 8338 AWCs. Reported age was often rounded up or down to approximate whole numbers of years.

In a typical block these study catchment areas included 10 000–20 000 children aged 1·0–6·0 years, so at any one time the study included 1 million such children. During the study another million 1-year-olds joined as the 6-year-olds left, so at one time or another the study included about 2 million children. The study continued for 5 years, and recorded 25 000 child deaths during 5 million child-years of follow-up. The study was approved by King George's Medical University ethics committee (Lucknow, India) and by the ICDS directors, but no permissions were obtained from the population, except when faecal samples were sought.

Randomisation and masking

Neighbouring blocks (clusters), in groups of four, were randomly allocated in Oxford, UK, using a factorial design to: (1) usual care; (2) 6-monthly vitamin A; (3) 6-monthly albendazole; or (4) both. No placebos were used; the control was open. Randomisation was stratified in groups of four blocks, where possible in the same district. No other relevant details of the blocks were known at baseline. This report compares albendazole (36 blocks) versus not (36 blocks), largely
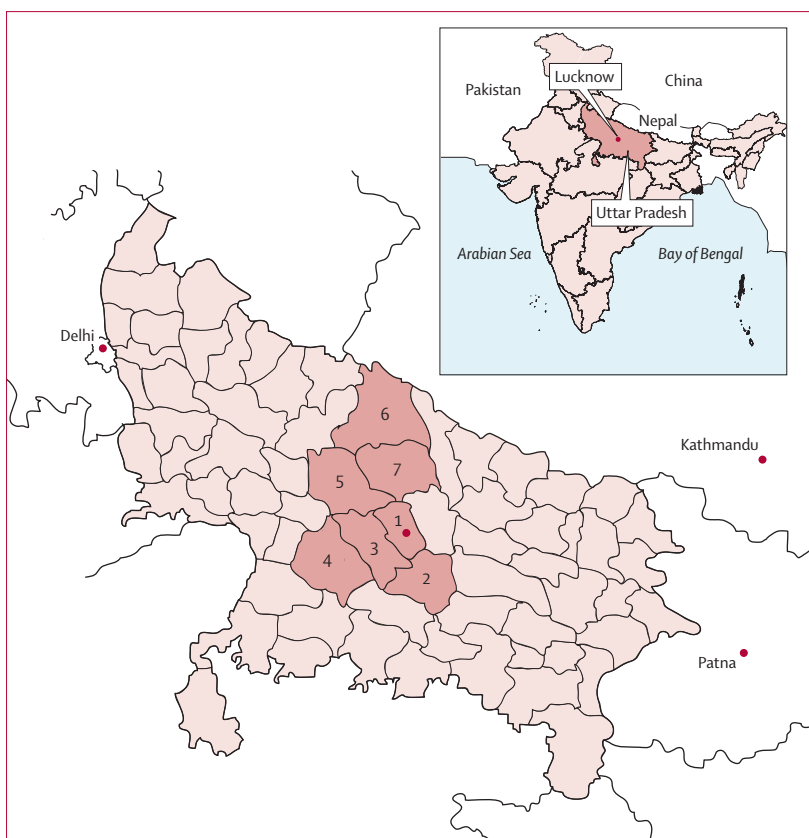

Figure 1: Location of the seven DEVTA study districts in the state of Uttar Pradesh in north India
1 Lucknow (study centre: Lucknow city), 2 Rae Bareli, 3 Unnao, 4 Kanpur, 5 Hardoi, 6 Lakhimpur, 7 Sitapur. Within the districts, the study areas were largely rural.

ignoring retinol allocation and stratum. Sensitivity analyses showed the main findings were unchanged when adjusted for district.

Procedures

GlaxoSmithKline donated albendazole in pots of 150 chewable tablets (400 mg Zentel). Dose was independent of age. When treatment became due (in April or October), in each treatment-allocated block a mass-treatment day was selected on which all children of apparent age 6–72 months in all study AWCs in that block would be given the trial treatment by their AWC worker. The few children missed were often treated soon afterwards.

Implementation of the mass-treatment days was encouraged and monitored independently by project staff and state government staff. At the previous monthly block meeting, each supervisor in the AWCs to be treated collected 150 tablets (plus extras, for large AWCs) and, on the selected day, administered treatment. Villagers were alerted beforehand.

To ensure AWC workers undertook mass-treatment on the chosen day, they were trained before the study (with refresher training in 45 blocks), discussed matters at their
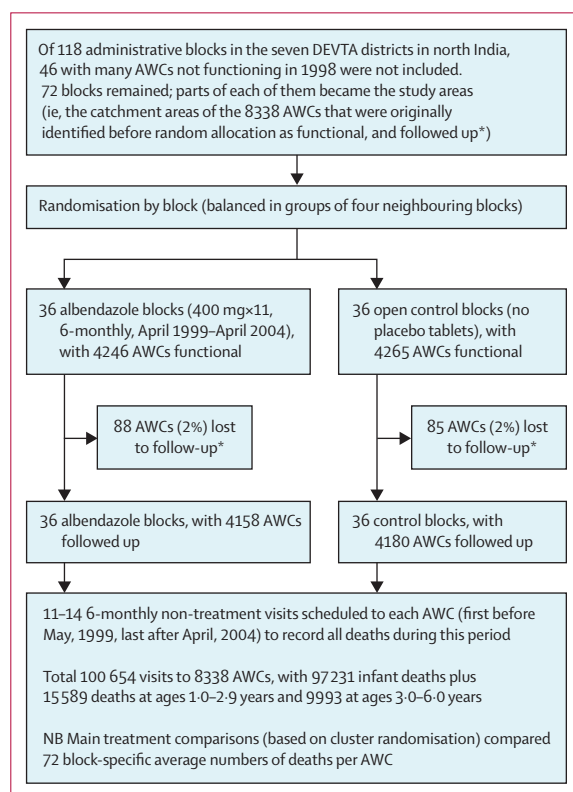
Of 118 administrative blocks in the seven DEVTA districts in north India, 46 with many AWCs not functioning in 1998 were not included. 72 blocks remained; parts of each of them became the study areas (ie, the catchment areas of the 8338 AWCs that were originally identified before random allocation as functional, and followed up*)

↓

Randomisation by block (balanced in groups of four neighbouring blocks)

↓

| 36 albendazole blocks (400 mg×11, 6-monthly, April 1999–April 2004), with 4246 AWCs functional | 36 open control blocks (no placebo tablets), with 4265 AWCs functional |

→ 88 AWCs (2%) lost to follow-up*   → 85 AWCs (2%) lost to follow-up*

| 36 albendazole blocks, with 4158 AWCs followed up | 36 control blocks, with 4180 AWCs followed up |

↓

11–14 6-monthly non-treatment visits scheduled to each AWC (first before May, 1999, last after April, 2004) to record all deaths during this period

Total 100 654 visits to 8338 AWCs, with 97 231 infant deaths plus 15 589 deaths at ages 1·0–2·9 years and 9993 at ages 3·0–6·0 years

NB Main treatment comparisons (based on cluster randomisation) compared 72 block-specific average numbers of deaths per AWC

Figure 2: **Flow diagram for the 72 mainly rural administrative blocks randomly allocated five years of six-monthly albendazole or open control**
AWC: anganwadi (ie, courtyard) child-care centre. In these 72 blocks, 8338 child-care centres were followed up, with a total population at ages 1·0–6·0 years of 1 million at any one time (hence 2 million ever in the study, May, 1999–April, 2004). *AWC catchment areas correspond approximately to villages; it was determined before randomisation which AWCs were then functional, and hence potential study areas; loss of an AWC to follow-up was defined by having only 1–6 follow-up visits (mean only 3, as against 12 in included AWCs), and was generally because the AWC had ceased to function.

monthly block meetings before and afterwards, and knew that on all mass-treatment days unannounced visits were made to every fourth AWC on a numbered list for each block to check that distribution had started, followed by visits 1 week later to check numbers dispensed and interview focus groups about receiving treatment.

During the third study year, study monitors abstracted from local records name, sex, age, and father's name for all (just over 1 million) pre-school children in the study areas. There should have been little undercount of children, but numbers by month of age showed, as expected, substantial undercount of young infants, and ages were often approximate. After removal of apparently duplicated records (about 1% at ages 1·0–6·0 years), this mid-study census was used before each subsequent treatment day to list all in 25 AWCs per block with predicted age 12–70 months (ie, well within the range to be treated). Monitors established soon after whether the children listed had actually been treated (and whether they were currently registered with the AWC).

Annually, Oxford randomly selected one AWC per block for teams (one phlebotomist, two fieldworkers, one driver) to survey 1–5 months after a mass-treatment day 30 pre-school children (six per year of age; if fewer were available, a neighbouring AWC was included), seeking from them blood and faecal samples. In practice, full information with complete assay results was obtained for about 24 children per block. Children surveyed were not randomly chosen, and tended to be selected by AWC workers from those registered with the AWC. Villagers decided after public discussion whether the village would cooperate; if it did, no caregiver then chose to refuse consent. Only one selected village refused; an adjacent village replaced it.

After marking consent, caregivers were asked whether the previous mass-treatment had been received (and, if so, whether diarrhoea, vomiting, or fever had followed) and about recent (past 4 weeks) fast or difficult breathing suggesting WHO-defined pneumonia,[14] diarrhoea (≥3 loose stools per day), measles, conjunctivitis, fever, and skin infection. Fieldwork teams were trained to measure height (to 1 mm; stadiometer), weight (to 0·1 kg; electronic scales, calibrated daily) and finger-prick haemoglobin.[15] Blood and faecal samples were collected for central retinol assay[16] and central formalin-ether-concentration helminth egg assay[17] (useable only after mid-study, when egg-counting methodology greatly improved).

Deaths were recorded by 18 full-time motorcycle village-to-village monitors. Monitors covered four neighbouring blocks at a time, one in each treatment group, and within 6 months visited all (about 500) study AWCs in those blocks to identify and visit households where in the past year a liveborn infant or child younger than 10 years had died, recording age, sex, name, parental names, and (by simple verbal autopsy) likely cause.

Monitors were literate, but not medically trained (except by the study and experience during it). Identification of households where a death had occurred was from AWC workers, from their records, and from key informants (eg, village head, other village leaders, teacher, auxiliary nurse midwife). There was digit preference; ages were often rounded up or down, so we analyse deaths at age 1·0–6·0 years. Monitors knew supervisors would, with 5% probability, randomly re-study selected villages shortly afterwards to ensure the relevant households had all been visited (and to help consolidate monitors' discipline and methods).

6 months later a different monitor visited the same blocks, again to record all deaths in the past year, so each death should have been reported twice, independently. Duplicates were eliminated manually, then by computer, in Lucknow, consulting monitors where necessary. The 238 remaining duplicates at ages 1·0–6·0 years were eliminated in Oxford by computer matches (199 with the same AWC, sex, first three letters of father's name, and date of death from a disease, 23 with matching for approximate date but closer other similarities, 16 with

the same death reported in adjacent AWCs), leaving 25 582 child deaths for analysis. During the third study year, monitors further undertook house-to-house surveys in every AWC to identify any missed deaths.

Statistical analysis

Data were checked manually and (apart from our mid-study census) double-entered; any obvious errors were corrected in the primary records. The FoxPro database was sent monthly to Oxford and extensively queried, leading to interactive corrections. Faecal egg counts, anthropometry, blood assays, and recent morbidity rates were standardised (by multiple regression) for age, sex (50% male) and 6-month season (50% May–October: height and weight were further standardised for study half-year). Age standardisation was to 3·0, 2·0, or 4·0 years, respectively, for age ranges 1·0–6·0, 1·0–2·9, or 3·0–6·0 years.

The prespecified primary analysis (see appendix of accompanying report[13]) was of pre-school child mortality, operationalised because of digit preference in stating ages as mortality at reported ages 1·0–6·0 years during the 5-year study period. This outcome was secondarily

subdivided into ages 1·0–2·9 and 3·0–6·0 years, and into study years 1–2 and 3–5. Analyses of the effects of albendazole allocation on any category of mortality (or on any other outcomes—eg, faecal egg counts, blood biochemistry, anthropometry, or morbidity) derived only from the 72 block averages for the outcome or explanatory factors of interest, giving all blocks equal weight (as they were of similar size). If albendazole did nothing, the mean of the 36 albendazole block averages would have been the mean of 36 selected randomly from these 72 values. Equivalently, the 72 values were regressed on two yes/no indicator values for retinol and albendazole allocation and on any explanatory factors.

Mortality analyses first calculated for each block the mean number of child deaths recorded per study AWC and the mean number of infant deaths recorded per study AWC. Analyses of effects on child mortality regressed child deaths per study AWC (72 values) on albendazole allocation (0/1), with simultaneous adjustment for retinol allocation (also 0/1), for an interaction term (±1, included only in simultaneous analyses of both treatments), and for infant deaths per AWC (an important explanatory factor that cannot have

	Ages 1·0–2·9 years			Ages 3·0–6·0 years			Ages 1·0–6·0 years		
	Albendazole (n=783)	Control (n=802)	95% CI for difference	Albendazole (n=1806)	Control (n=1774)	95% CI for difference	Albendazole (n=2589)	Control (n=2576)	95% CI for difference
Faecal worm eggs (% prevalence)									
Ascaris	15·7%*	27·0%	6·7, 15·9	11·9%*	28·8%	14·7, 19·0	12·9%*	28·1%	13·4, 17·0
Hookworm	4·7%†	8·0%	1·0, 5·6	3·5%*	9·3%	4·2, 7·4	3·8%*	8·9%	3·9, 6·3
Either nematode	19·8%*	33·9%	9·5, 18·7	15·3%*	36·5%	18·9, 23·5	16·4%*	35·6%	17·2, 21·1
Tapeworm‡	5·7%	4·9%	–3·1, 1·3	4·2%	6·2%	0·5, 3·5	4·5%	5·7%	–0·1, 2·4
Other biomedical measurements									
Weight (kg)	9·45	9·41	–0·22, 0·15	12·72	12·68	–0·21, 0·14	11·09	11·05	–0·19, 0·09
Height (cm)	74·2	74·6	–0·2, 1·0	88·7	88·6	–0·8, 0·6	81·6	81·6	–0·6, 0·6
BMI (kg/m²)	17·2	16·9	–0·6, 0·1	16·1	16·1	–0·2, 0·2	16·6	16·5	–0·3, 0·1
Haemoglobin (g/L)	94·6	95·6	–1·0, 2·9	103·8	103·2	–2·2, 1·0	99·6	99·4	–1·5, 1·2
Illness in past 4 weeks (% prevalence)									
Diarrhoea	40·6%	42·5%	–5·1, 8·8	33·5%	33·2%	–4·9, 4·3	37·6%	37·6%	–4·2, 4·3
Cough	19·1%	18·4%	–5·5, 4·1	18·0%	17·6%	–3·7, 2·9	18·5%	18·0%	–3·8, 2·8
Runny nose	15·2%	12·2%	–8·3, 2·3	11·4%	10·6%	–4·0, 2·4	12·6%	11·5%	–4·2, 2·0
Fast breathing	4·3%	4·4%	–2·4, 2·5	2·5%	3·9%	0·1, 2·7	3·1%	4·1%	–0·3, 2·2
Difficult breathing	4·1%	4·0%	–2·3, 2·2	2·5%	3·3%	–0·4, 2·1	3·1%	3·6%	–0·6, 1·7
Noisy breathing	2·8%	2·9%	–1·9, 2·1	2·2%	2·1%	–1·1, 1·0	2·4%	2·5%	–1·1, 1·1
Measles	1·9%	1·3%	–1·8, 0·7	0·9%	1·0%	–0·7, 1·1	1·3%	1·3%	–0·9, 0·8
Fever	35·7%	33·7%	–7·3, 3·4	28·5%	28·2%	–4·3, 3·7	31·1%	30·6%	–3·9, 2·8
Skin infection	15·1%	13·5%	–5·6, 2·3	13·4%	14·1%	–3·1, 4·5	14·1%	14·1%	–3·4, 3·4
Conjunctivitis	1·8%	2·3%	–1·0, 2·1	2·1%	2·2%	–1·2, 1·4	2·0%	2·2%	–0·9, 1·4

Biomedical visit to one random village per block per year: 5165 children with no data missing. *p<0·00001. †Two-sided p<0·01. ‡p=0·01 at ages 3·0–6·0 years only for tapeworm (but, tapeworm result is opposite at younger ages and is non-significant at all ages). *Trichuris* was not present. Each entry is the mean of 36 block-specific values. CIs are for the effects of choosing 36 out of the 72 such values. All results are standardised to ages 2·0, 4·0, or 3·0 years, respectively, for age groups 1·0–2·9, 3·0–6·0, or 1·0–6·0 years, and to 50:50 averages for half-year season and for sex. Height, weight, and body-mass index (BMI) are further standardised for study half-year. The sex-specific differences (not shown) do not differ materially from these sex-standardised differences.

Table 1: Effects of albendazole allocation on prevalence of worm infection, weight, height, haemoglobin, and recent ill health (generally as reported by the child's guardian) in a subsample from each of the 72 blocks during the second half of the study, by age

been materially affected by trial treatment, and varied two-fold between blocks). Sensitivity analyses explored the relevance of not adjusting for infant mortality or of additional adjustment for district (by which randomisation had been stratified). All these analyses did not depend on the mid-study census, but further sensitivity analyses explored the effect of adjustment for the census estimate of child population per AWC (an unimportant factor, since it varied little between blocks).

72 blocks were made available for this study by the ICDS. On the assumption that the 72 block-specific mortality rates observed in the study at ages 1·0–6·0 years would be about 2–3% with SD 0·5, the mean mortality reduction would have SE 0·12 (2SD/√72), so if treatment reduced mortality by 0·5% (ie, by about a fifth) the study would have a 95% chance of getting p<0·01. SAS version 9.1 was used. This trial is registered at ClinicalTrials.gov, NCT00222547.

Role of the funding source
Study sponsors had no role in design, conduct, analysis, or interpretation. SA, RP, DB, and SR had full data access and entirely controlled submission for publication.

Results
Compliance with treatment allocation was good. Unannounced visits to a quarter of the AWCs in the albendazole blocks on or just after each mass-treatment day confirmed that 98% (10 364/10 597 visits) were distributing treatment. Independently, enquiries a week after mass-treatment days about lists of named children from the mid-study census confirmed treatment of 95% (131 631/138 333) of those registered with the AWC and 73% (76 490/104 925) of those not. Because two-thirds of under-5s and one-third of 5-year-olds were AWC-registered, overall compliance was about 86%. Consistent with this finding, the biomedical surveys of randomly chosen AWCs, which tended to over-sample AWC-registered children, found caregivers reporting 92% (2388/2589) had received albendazole on the previous mass-treatment day. AWC workers in albendazole and control blocks held non-study mebendazole to treat

children with obvious worms; otherwise, there was little non-study anthelmintic treatment. Loss to follow-up was similarly uncommon in both groups (2% [88/4246] albendazole, 2% [85/4265] control; figure 2), and was generally due to AWC closures.

Allocation to albendazole halved faecal worm egg prevalence 1–5 months after mass-treatment days. Faecal assays were available during the second half of the study for 5165 children with complete information on all assays and questionnaire replies, 2589 in albendazole-allocated versus 2576 in control blocks (table 1). Among them, the proportion with nematode (*Ascaris* or hookworm) eggs was 16% in the albendazole-allocated blocks versus 36% in control blocks, but in both albendazole and control groups any infection was generally light (median eggs per g faeces, if non-zero, *Ascaris* 96 [IQR 69–127], hookworm 83 [62–115]). The control prevalence matches previous estimates for north India.[18,19] *Trichuris* eggs were not found. The proportion with tapeworm eggs (*Hymenolepis* spp) was, as expected, not significantly reduced.

Albendazole remains almost wholly inside the intestine, and oral treatment was not significantly associated with any immediate adverse effects. In 36 albendazole-allocated blocks, 362 children died during the 7 days before mass-treatment was due and 366 during the next 7 days. Caregivers were asked at the biomedical surveys whether the previous treatment had been closely followed by acute illness. No significant differences in vomiting, diarrhoea, or fever were seen between retinol plus albendazole, retinol alone, and albendazole alone. Among 6290 children in 18 retinol-and-albendazole blocks, vomiting was reported for 29 children in five blocks, diarrhoea for ten children in two blocks, and fever for six children in three blocks; among 6686 children in 18 albendazole-only blocks, vomiting was reported for 15 children in six blocks, diarrhoea for 12 in three blocks, and fever for three children in one block; among 6433 children in 18 retinol-only blocks, vomiting was reported for 25 children in four blocks, diarrhoea for 14 children in two blocks, and fever for 37 children in two blocks (both with obvious outbreaks).

	Ascaris eggs			Hookworm eggs			Either type of nematode egg		
	No eggs (n=1858)	Eggs (n=718)	Difference (95% CI)*	No eggs (n=2336)	Eggs (n=240)	Difference (95% CI)*	No eggs (n=1660)	Eggs (n=916)	Difference (95% CI)*
Weight (kg)	11·07	11·02	0·05 (–0·08, 0·17)	11·06	11·02	0·04 (–0·15, 0·23)	11·08	11·01	0·07 (–0·04, 0·19)
Height (cm)	81·7	81·4	0·3 (–0·16, 0·76)	81·6	81·7	–0·1 (–0·84, 0·57)	81·7	81·4	0·3 (–0·11, 0·75)
BMI (kg/m²)	16·5	16·6	–0·1 (–0·20, 0·08)	16·5	16·4	0·1 (–0·13, 0·30)	16·5	16·5	0·0 (–0·17, 0·09)
Haemoglobin (g/L)	99·2	99·6	–0·4 (–1·42, 0·56)	99·3	99·0	0·4 (–1·17, 1·89)	99·2	99·4	–0·2 (–1·12, 0·74)

Biomedical visit to one random village per block per year (from mid-study): 2576 controls with no data missing. *Individual values for weight, height, body-mass index (BMI), and haemoglobin were standardised to age 3·0 years, 50% male, and 50% wet season (May–Oct), and then standardised for village (leaving the means unchanged). Hence, regressing the standardised individual values on the absence or presence of faecal eggs (0/1) effectively compares children in one village who do have eggs with others in the same village who do not.

Table 2: Associations within 116 of the 4180 control villages between faecal worm eggs (absent/present) and mean weight, height, and haemoglobin during the second half of the study (analyses of individuals)

Weight, height, and haemoglobin were not significantly improved by albendazole. After at least 2 years of treatment, mean weight at ages 3·0–6·0 years (standardised to age 4·0 years, half male, half female) in all surveyed children, infected or not, was 12·72 kg albendazole versus 12·68 kg control, difference 0·04 kg (95% CI –0·14 to 0·21 kg, p=0·66; table 2). This null result is statistically compatible with albendazole increasing weight by 0·5 kg in children who are actually infected. When, however, children in the same control village were compared with each other, the presence of faecal eggs was not associated with any significant differences in weight, height, or haemoglobin (table 2); the upper confidence limit for the weight difference associated with an individual having nematode eggs was only 0·2 kg. Likewise, there were no effects of allocation to albendazole on prevalence of ill health at the time of the visit (table 1). These null findings were independent of age and sex.

During the entire study, after exclusion of duplicated records and stillbirths, monitors recorded 97 231 deaths in infancy (86 084 before age 6 months), 15 589 at ages 1·0–2·9 years and 9993 at ages 3·0–6·0 years (figure 2). These numbers include any extra deaths identified by the special mid-study retrospective enquiry (which found similar numbers of missed child deaths in the two treatment groups, suggesting little ascertainment bias). Combined with our mid-study census listing a million children, this finding suggests at least 9% infant mortality and about 2·5% child mortality.

Figure 3 shows a 69% correlation between the numbers of infant and child deaths recorded per AWC. As any trial treatment in infancy began at 6–12 months of age and most infant deaths occur much earlier, overall infant mortality cannot have been materially affected by treatment. Hence, this strong correlation reflects differences not due to treatment between the numbers of infant deaths recorded per AWC. Confirming this conclusion, the correlation between infant and child mortality was equally strong among blocks that had all had the same treatment; figure 3. We therefore used number of infant deaths as an explanatory factor to reduce chance variation in our main analyses of the effects of treatment allocation on the number of child deaths.

Table 3 shows the findings for child mortality at ages 1·0–2·9 years, 3·0–6·0 years, and 1·0–6·0 years, along with the relative risk for the age range 1·0–6·0 years. Overall child mortality was 5% lower in albendazole than in control blocks, but because randomisation was by block rather than by AWC or by individual this 5% difference is not significant (risk ratio [RR] 0·95, CI 0·88–1·02, p=0·16).

Sensitivity analyses (table 3) showed this RR was little changed (although its CI was narrowed) by adjustment for infant deaths, and would be little changed by use of 6-month mortality instead of infant mortality to correct for initial variation in prognosis, or by further adjustment for district or for mean number of children per AWC. There was no significant interaction between the effects of retinol
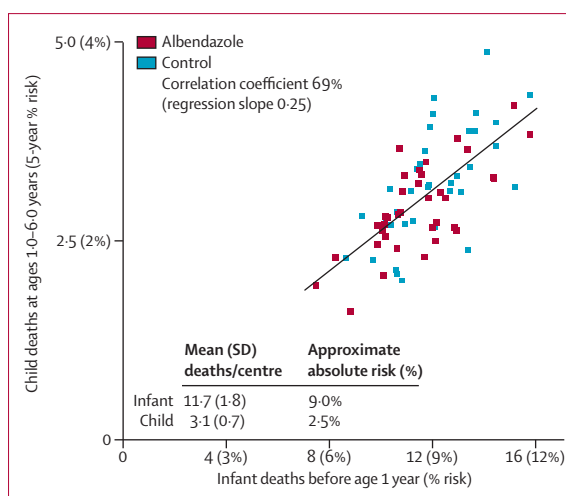

Figure 3: Correlation between 72 block-specific average numbers of infant and child deaths per child-care centre (AWC) during the entire study

The inter-block correlation (illustrated here) between numbers of infant and child deaths per AWC was 68·7% ignoring trial treatment allocation (or 68·4% given the four-way allocation to albendazole, retinol, both, or neither), and ranged from 66–71% within the four treatment groups. Mortality at ages 0–6 months had correlation 99·3% with infant and 68·2% with child mortality.

and albendazole (interaction p=0·83). So, RR was again little changed (although its CI was widened) by restricting attention to 18 albendazole-plus-retinol versus 18 retinol-alone blocks, where monitoring could not be biased by one group getting no treatment. Table 3 also provides the separate results in all four (2×2) treatment groups.

The main contributor to the overall mortality difference was diarrhoeal mortality, which was 9% lower with albendazole, but this 9% difference was also not significant (RR 0·91, 95% CI 0·80–1·03). If the difference in overall mortality was a chance finding, the RR would be expected to be similar in various subgroups, and it was similar in the first 2 years and last 3 years (see accompanying report for illustration of the trial timelines[13]) and in boys and girls. There was an 80% correlation between male and female child mortality rates in different blocks.

The annual number of deaths per AWC was greater at ages 1·0–2·9 than at 3·0–6·0 years (particularly for diarrhoea, pneumonia, and malnutrition), greater in girls than in boys, and greater in earlier than in later study years, but for no category of age, disease, or sex was there a significant effect of albendazole on mortality. Even for children who had been on treatment more than 2 years (ie, for mortality at ages 3·0–6·0 years during the last 3 study years) there was no significant difference in mortality between blocks allocated albendazole and control.

To convert numbers of deaths per AWC into risks, population estimates are needed. Our mid-study census enumerated about 119 children of age 1·0–6·0 years per AWC (65 male, 54 female). Because of strong digit

	Number of child deaths recorded per AWC during the whole study, albendazole versus control (A vs C) and 95% CI for the difference (C–A)*									Mortality rate ratio (RR=A/C), age 1·0–6·0 years		Absolute risk of death from age 1·0–6·0 years (%)	
	Age 1·0–2·9 years			Age 3·0–6·0 years			Age 1·0–6·0 years			RR	95% CI	Alben-dazole	Control
	A	C	CI for (C–A)	A	C	CI for (C–A)	A	C	CI for (C–A)				
Cause of death													
Diarrhoea	0·54	0·56	–0·04, 0·09	0·28	0·34	0·00, 0·11	0·82	0·90	–0·03, 0·19	0·91	0·80, 1·03	0·69%	0·76%
Pneumonia	0·33	0·32	–0·06, 0·03	0·12	0·12	–0·03, 0·02	0·45	0·44	–0·08, 0·05	1·03	0·89, 1·19	0·38%	0·37%
Measles	0·11	0·12	–0·02, 0·04	0·10	0·08	–0·04, 0·01	0·20	0·20	–0·06, 0·05	1·03	0·78, 1·35	0·17%	0·17%
Other infection/unknown	0·58	0·60	–0·07, 0·10	0·42	0·46	–0·02, 0·10	1·00	1·06	–0·08, 0·19	0·95	0·83, 1·08	0·84%	0·89%
Malnutrition	0·18	0·19	–0·03, 0·05	0·05	0·06	0·00, 0·03	0·23	0·25	–0·03, 0·08	0·91	0·73, 1·14	0·19%	0·21%
Other or external	0·11	0·11	–0·02, 0·03	0·18	0·20	–0·02, 0·05	0·29	0·31	–0·03, 0·07	0·94	0·80, 1·10	0·25%	0·26%
All causes, by subgroup													
Boys	0·84	0·86	–0·05, 0·10	0·56	0·62	–0·01, 0·14	1·39	1·48	–0·03, 0·21	0·94	0·86, 1·02	2·14%	2·28%
Girls	1·01	1·04	–0·06, 0·12	0·59	0·63	–0·02, 0·10	1·61	1·68	–0·05, 0·19	0·96	0·89, 1·03	2·97%	3·10%
May, 1999–April, 2001 (2 years)	0·85	0·86	–0·07, 0·09	0·54	0·60	0·00, 0·12	1·39	1·46	–0·04, 0·19	0·95	0·88, 1·03	2·91%	3·07%
May, 2001–April, 2004 (3 years)	1·00	1·04	–0·06, 0·15	0·61	0·65	–0·05, 0·13	1·61	1·70	–0·09, 0·26	0·95	0·85, 1·05	2·26%	2·38%
Trial retinol	1·77	1·92	–0·05, 0·35	1·15	1·18	–0·14, 0·20	2·92	3·10	–0·13, 0·50	0·94	0·85, 1·04†	2·45%	2·60%
No trial retinol	1·93	1·89	–0·24, 0·16	1·15	1·32	0·01, 0·34	3·08	3·21	–0·18, 0·45	0·96	0·87, 1·06†	2·59%	2·70%
All causes, total‡	1·85	1·91	–0·08, 0·20	1·15	1·25	–0·02, 0·22	3·00	3·16	–0·06, 0·38	0·95	0·88, 1·02§	2·52%	2·65%

*Reduction (C–A) in number of child deaths per AWC and its standard error, s, were calculated by regression of 72 block-specific numbers of child deaths per AWC on albendazole allocation (0/1), vitamin A allocation (also 0/1), and on the block-specific numbers of infant deaths per AWC (to help correct for any pre-existing variation in prognosis. RR is then A/C with 95% CI (A–x)/(C+x) to (A+x)/(C–x), where x=1·96s/2. Assuming approximately 119 (65 male, 54 female) children per AWC at ages 1·0–6·0 years, approximate absolute 5-year risks were calculated as five times (annual deaths per AWC)/(119, 65, or 54, as appropriate). Sensitivity analyses: further inclusion of district (as six indicators) or child population per AWC (which varied little) had no material effect. †Interaction p=0·83. ‡6-month mortality had correlation 99·3% with infant mortality and 68·2% with child mortality, so results were unchanged if it was used instead of infant mortality to correct for initial variation in prognosis; without either correction, numbers of child deaths per AWC at ages 1·0–2·9, 3·0–6·0, and 1·0–6·0 years would have been, respectively, 1·80 versus 1·96 (p=0·11), 1·13 versus 1·27 (p=0·031), and 2·92 versus 3·23 (p=0·045); RR=0·90 (0·82–1·00); absolute risks 2·46% versus 2·72%. §Two–sided p=0·16.

Table 3: Effects of albendazole allocation on pre-school child mortality: absolute numbers of deaths per anganwadi child-care centre (AWC) by allocated treatment, albendazole versus control (A vs C), and, from these, mortality rate ratio (A/C) and approximate absolute risk of death from age 1·0 to 6·0 years

preferences in describing ages and possible undercount, particularly of young infants and children not registered with the AWC, this number is only approximate. Nevertheless, ignoring any uncertainties in enumeration, 11·7 infant deaths (6·2 male, 5·5 female) and 119 children per AWC suggests at least 9% infant mortality (11·7/[11·7+119] plus some undercounted mortality in early infancy). Likewise, 3·1 child deaths per AWC (1·4 male, 1·6 female) suggests about 2·5% child mortality at ages 1·0–6·0 years (3·1/119). These infant and child mortality rates are consistent with published estimates for rural Uttar Pradesh.[20,21]

Discussion

Some but not all previous studies of periodic population deworming have suggested appreciable weight gain.[1–3] The stated aims of the present albendazole trial were to establish whether twice-yearly deworming would be practicable within existing ICDS structures and, if so, whether it would provide sustainable benefits in terms of improved physical growth and (the primary outcome) survival of pre-school children.[12] In terms of assessing effects on weight gain, this trial (which weighed only a representative few thousand children in a few dozen clusters) is no better powered than several previous

studies, but in terms of assessing effects on survival it is unique (enumerating 25 000 child deaths).[3,6–8,22,23] Because of digit preference in recording ages, the primary endpoint was operationalised as mortality at recorded ages 1·0–6·0 years. This outcome was secondarily subdivided into 1·0–2·9 and 3·0–6·0 years, and into the first 2 and last 3 study years. A major subsidiary aim was to establish whether the ICDS system could provide a cost-effective and sustainable delivery mechanism for this or other simple health interventions in pre-school children.

The subsidiary aim was fully achieved; 86% compliance was maintained over 5 years (with 95% compliance among the many children who were registered with the AWC). Focus group discussions attributed this compliance to political support, sustained and predictable drug supply, minimum additional work for AWC staff (who did not themselves have to report on compliance), helpful staff training meetings, and the knowledge that coverage might well be monitored. Excluding donated drug, the total cost was US$100 000 per year (US$0·10 per child), but this expense was mostly for evaluating the intervention. This suggests that, in villages with functioning ICDS anganwadi centres, delivery costs for simple pre-school interventions could be as low as for school-based health interventions.[1,24,25]

Panel: **Research in context**

The recently updated Cochrane Review[3] of previous trials showed that intermittent deworming of school-age children can improve weight gain in some high-prevalence areas. No previous trial was large enough to assess effects on mortality.

The present study shows that in a lightly infected rural Indian population routine deworming of pre-school children had little effect on weight gain or on mortality. This finding does not rule out effects of deworming on mortality in other populations, although any such effects are generally likely to be small.

For the primary aim, however, despite good compliance for 5 years and despite halving the prevalence of worm infection, the randomised comparison did not provide significant evidence of an effect of deworming on survival (mortality RR 0·95, 95% CI 0·89–1·02). Although the confidence interval does not exclude a mortality reduction of about 10%, such an effect is unlikely since there was no significant increase in weight gain—the proxy for better nutrition, our postulated mechanism for mortality reduction.

The absence of a significant increase in weight is consistent with two previous studies of deworming this age group in north India,[6,7] but discrepant with a third.[8] These three previous studies were in urban areas in which the prevalence of *Ascaris* eggs among controls would have been about twice as great as in the present study.[6] The upper confidence limit for the average weight gain in the second half of the present study was 0·2 kg, much less than the lower confidence limit of 0·7 kg for the 2-year gain in the third study.[8] The weight for age of the children in these two studies was similar, suggesting similar nutritional status, and we led both trials and are confident of the reliability of each. This substantial discrepancy between the apparent effects on weight gain in the two studies remains unexplained.

Previous studies of population mortality from soil-transmitted helminths have involved estimates of mortality from communities or hospital populations in unusual circumstances and offer little guidance as to the direct and indirect effects in large general populations.[26–29] Although further studies of the indirect effects on mortality in much more intensely infected or worse nourished populations could well be worthwhile, reductions in mortality might be difficult to demonstrate because of the age distribution of infection; for example, although the intensity of infection might be much greater in older child populations, they have lower overall mortality rates.[1]

Overall, the present study shows that in this lightly infected rural population routine deworming of pre-school children had little effect on mortality (panel). This finding does not rule out effects on mortality in other populations, but any such effects are generally likely to be small, so reduction in population mortality is unlikely to be a primary aim of deworming programmes.[30]

References

1   Bundy DAP, Shaeffer S, Jukes M, et al. Chapter 58: School-based health and nutrition programs. In: Jamison D, Breman JG, Measham AR, Alleyne G, Claeson M, eds. Disease control priorities in developing countries, 2nd edn (DCPC2). New York NY: World Bank and Oxford University Press, 2006: pp 1091–108. http://hdl.handle.net/Richards10986/7242 (accessed July 13, 2012).

2   Jukes M, Drake L, Bundy DAP. School health, nutrition and education for all: levelling the playing field. Cambridge MA: CAB International Publishing, 2007.

3   Taylor-Robinson D, Maayan N, Soares-Weiser K, Donegan S, Garner P. Deworming drugs for soil transmitted intestinal worms in children: effects on nutritional indicators, haemoglobin and school performance (July 2012 update). *Cochrane Database Syst Rev* 2007; **4:** CD000371.

4   Taylor-Robinson D, Jones A, Garner P. Does deworming improve growth and school performance in children? *PloS Negl Trop Dis* 2009; **3:** e358. DOI:10.1371/journal.pntd.0000358.

5   Bundy DAP, Kremer M, Bleakley H, Jukes MCH, Miguel E. Deworming and development: asking the right questions, asking the questions right. *PLoS Negl Trop Dis* 2009; **3:** e362.

6   Awasthi S, Pande VK, Fletcher RS. Effectiveness and cost-effectiveness of albendazole in improving nutritional status of preschool children in urban slums. *Indian Pediatr* 2000; **37:** 19–29.

7   Awasthi S, Pande VK. Six-monthly de-worming in infants to study effects on growth. *Indian J Pediatr* 2001; **68:** 823–27.

8   Awasthi S, Peto R, Pande VK, Fletcher RH, Read S, Bundy DAP. Effects of de-worming on malnourished pre-school children in India: an open-labelled, cluster-randomised trial. *PLoS Negl Trop Dis* 2008; **2:** e223.

9   Pelletier DI, Frongillo EA Jr, Schroeder DG, Habicht JP. A methodology for estimating the contribution of malnutrition to child mortality in developing countries. *J Nutr* 1994; **124** (10S)**:** 2106S–22S.

10   Gragnolati M, Shekar M, Das Gupta M, Bredenkamp C, Lee Y-K. India's undernourished children: a call for reform and action. Washington DC: Health, Nutrition and Population Division, World Bank, 2006. https://openknowledge.worldbank.org/bitstream/handle/10986/7241/368050REVISED0101OFFICIAL0USE0ONLY1.pdf?sequence=1 (accessed July 13, 2012).

11   Integrated Child Development Service. National consultation to review the existing ICDS guidelines scheme in the field of health and nutrition: recommendations. *Indian J Pediatr* 2001; **38:** 721–31.

12   Awasthi S, Peto R, Bundy D. Short protocol for DEVTA, 1998. http://www.ctsu.ox.ac.uk/research/research-archive/devta-de-worming-and-enhanced-vitamin-a (accessed July 13, 2012).

13   Awasthi S, Peto R, Read S, Clark S, Pande V, Bundy D, and the DEVTA (Deworming and Enhanced Vitamin A) team. Vitamin A supplementation every 6 months with retinol in 1 million pre-school children in north India: DEVTA, a cluster-randomised trial. *Lancet* 2013; published online March 14. http://dx.doi.org/10.1016/S0140-6736(12)62125-4.

14   World Health Organization Department of Child and Adolescent Health and Development (WHO CAH). Cough and difficult breathing. In: WHO CAH. Handbook: IMCI Integrated Management of Childhood Illnesses. Geneva: WHO CAH, 2005: pp 19–24. www.who.int/entity/maternal_child_adolescent/documents/9241546441/en/ (accessed July 13, 2012).

15   Alstead S. Observations on Sahli's haemoglobinometer. *Postgrad Med J* 1940; 278–86. www.ncbi.nlm.nih.gov/pmc/articles/PMC2477104/pdf/postmedj00716-0007.pdf (accessed July 13, 2012).

16   Sommer A. Vitamin A deficiency and its consequences: a field guide to detection and control (3rd edition). Geneva: World Health Organization, 1995. www.who.int/nutrition/publications/vad_consequences.pdf (accessed July 13, 2012).

17   World Health Organisation SEARO. Parasitological Examination of Faeces. *Guidelines on standard operating procedures for microbiology,* Chapter 20. New Delhi, World Health Organization, 2006. http://www.searo.who.int/en/section10/section17/section53/section482_1804.htm (accessed July 13, 2012).

18   Nitin S, Venkatesh V, Husain N, Masood J, Agarwal GG. Overview of intestinal parasitic prevalence in rural and urban populations in Lucknow, North India. *J Commun Dis* 2007; **39:** 217–23.

19   Awasthi S, Verma T, Kotecha PV, Venkatesh V, Joshi V, Roy S. Prevalence and risk factors associated with worm infestation in pre-school children (6–23 months) in selected blocks of Uttar Pradesh and Jharkhand, India. *Indian J Med Sci* 2008; **62:** 484–91.

20   Registrar-General of India. Population projections for India and States, 2001–2026. New Delhi: Office of the Registrar-General of India, 2006.

21   Saika N, Singh A, Ram F. Has child mortality in India really increased in the last two decades? *Econ Polit Wkly* 2010; **45:** 62–70.

22   Alderman H, Konde-Lule J, Sebuliba I, Bundy D, Hall A. Effect on weight gain of routinely giving albendazole to pre-school children during child health days in Uganda: cluster-randomised controlled trial. *BMJ* 2006; **333:** 122.

23   Sur D, Saha DR, Manna B, Rajendran K, Bhattacharya SK. Periodic de-worming with albendazole and its impact on growth status and diarrhoeal incidence among children in an urban slum of India. *Trans R Soc Trop Med Hyg* 2005; **99:** 261–67.

24   Miguel EA, Kremer M. Worms: identifying impacts on education and health in the presence of treatment externalities. *Econometrica* 2004; **72:** 159–217.

25   Bleakley H. Disease and development: evidence from hookworm eradication in the American South. *Q J Economics* 2007; **122:** 73–117.

26   Pawlowski ZS, Davis A. Morbidity and mortality in ascariasis. In: Crompton DWT, Nesheim MC, Pawlowski ZS, eds. Ascariasis and its prevention and control. London: Taylor & Francis, 1989: pp 71–86.

27   de Silva NR, Chan MS, Bundy DAP. Morbidity and mortality due to ascariasis: re-estimation and sensitivity analysis of global numbers at risk. *Trop Med Internat Health* 1997; **2:** 519–28.

28   Krey W. Der Darmstaedter spulwurmbefall und seine bekaempfung [Infestation with the Darmstaedt worm and its treatment]. *Zeitschrift fuer Hygiene* 1949; **129:** 507–18.

29   Thein H. A profile of ascariasis morbidity in Rangoon children's hospital, Burma. *J Trop Med Hyg* 1987; **90:** 165–69.

30   Bundy DAP, Walson JL, Watkins KL. Worms, wisdom and wealth: why deworming can make economic sense. *Trends Parasitol* 2013; published online Jan 14. http://dx.doi.org/10.1016/j.pt.2012.12.003.