

# Effect of vitamin A supplementation in women of reproductive age on cause-specific early and late infant mortality in rural Ghana: ObaapaVitA double-blind, cluster-randomised, placebo-controlled trial

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## ABSTRACT

**Objectives:** To assess the effect of vitamin A supplementation in women of reproductive age in Ghana on cause- and age-specific infant mortality. In addition, because of recently published studies from Guinea Bissau, effects on infant mortality by sex and season were assessed.

**Design:** Double-blind, cluster-randomised, placebo-controlled trial.

**Setting:** 7 contiguous districts in the Brong Ahafo region of Ghana.

**Participants:** All women of reproductive age (15–45 years) resident in the study area randomised by cluster of residence. All live born infants from 1 June 2003 to 30 September 2008 followed up through 4-weekly home visits.

**Intervention:** Weekly low-dose (25 000 IU) vitamin A.

**Main outcome measures:** Early infant mortality (1–5 months); late infant mortality (6–11 months); infection-specific infant mortality (0–11 months).

**Results:** 1086 clusters, 62 662 live births, 52 574 infant-years and 3268 deaths yielded HRs (95% CIs) comparing weekly vitamin A with placebo: 1.04 (0.88 to 1.05) early infant mortality; 0.99 (0.84 to 1.18) late infant mortality; 1.03 (0.92 to 1.16) infection-specific infant mortality. There was no evidence of modification of the effect of vitamin A supplementation on infant mortality by sex (Wald statistic =0.07, p=0.80) or season (Wald statistic =0.03, p=0.86).

**Conclusions:** This is the largest analysis of cause of infant deaths from Africa to date. Weekly vitamin A supplementation in women of reproductive age has no beneficial or deleterious effect on the causes of infant death to age 6 or 12 months in rural Ghana.

**Trial registration number:** <http://ClinicalTrials.gov>: NCT00211341.

## ARTICLE SUMMARY

### Article focus

- This paper reports the results of planned (a priori) analyses of the effect of vitamin A supplementation in women of reproductive age on cause- and age-specific infant mortality in the ObaapaVitA trial.
- In addition, because of the recent interest in potential differential effects, we also assessed effects by sex and season.

### Key messages

- The analyses from this trial indicate that weekly vitamin A supplementation in women of reproductive age has no beneficial or deleterious effect on the causes of death in their babies of age 6 or 12 months, no effect on infection-specific infant mortality and no role for inclusion in child survival programs in Asia and Africa.
- We also failed to demonstrate any benefit or harm from vitamin A supplementation in women of reproductive age and in infant males or females in our study population. There was also no modification of the effect of vitamin A supplementation and mortality by season.

## INTRODUCTION

Vitamin A deficiency is a major public health problem. It is most prevalent in young children and pregnant women in low-income countries, especially in Africa and South-East Asia.<sup>1</sup> Clinical vitamin A deficiency can manifest as xerophthalmia, blindness and enhanced susceptibility to infections especially measles.<sup>2</sup>

Vitamin A supplementation in children aged 6–59 months substantially reduces

## ARTICLE SUMMARY

**Strengths and limitations of this study**

- There were some limitations to our trial. There was no direct observation of capsule taking; however, adherence was supported by an extensive Information, Education and Communication strategy, and we estimated that on average 75% of women both received and took all four capsules every month.
- We also used verbal postmortems (VPMs) and physician coders to assign cause of death, and it was not possible to use health facility records or postmortem examinations to verify the cause of death. Misclassification is common in VPM studies, but this can be minimised when broad categories such as 'infection', 'prematurity' and 'asphyxia' are used. Our VPM tools were also validated in similar study populations, and acceptable sensitivity and specificity were reported in comparison to a gold standard.
- Strengths included the fact that our study was large (62 000 infants) prospective and population-based. All resident women in the trial districts and their babies were enrolled, and loss to follow-up was low, even in women with babies who had died.

mortality<sup>3 4</sup>; these effects are apparent for deaths due to diarrhoea and measles but not respiratory infections or malaria.<sup>3 5</sup> However, the effect of vitamin A supplementation in children younger than 6 months is less clear. Trials of supplementation of 25 000 international units (IU) vitamin A linked to each of the first three doses of diphtheria–tetanus–pertussis immunisations demonstrated no significant effects on early or late infant mortality.<sup>6</sup> Early studies from Guinea Bissau suggested that there may be interaction with the season of birth with higher mortality occurring in the rainy season in neonates who were supplemented with vitamin A.<sup>7 8</sup> Findings from two trials in Guinea Bissau also suggested increased mortality among girls, but not among boys, in the second half of infancy following neonatal vitamin A supplementation.<sup>7 9</sup> However, a recent meta-analysis involving all trials to date indicated that there is no differential effect of neonatal vitamin A supplementation in boys and girls.<sup>10</sup>

A recent Cochrane review reported that vitamin A supplementation in women of reproductive age has no significant effect on maternal or infant outcomes.<sup>11</sup> This review included our recently reported findings from the Ghana ObaapaVitA cluster-randomised trial of the impact of weekly low-dose (25 000 IU) vitamin A supplementation given to women of reproductive age, which suggested no beneficial effect on the survival of their babies.<sup>12</sup> However, there have been no reports of the effect of vitamin A supplementation in women of reproductive age on cause-specific infant mortality or on mortality in early and late infancy. These outcomes were not included in our initial publication due to space limitations.

This paper reports the results of planned (a priori) analyses of the effect of vitamin A supplementation in women of reproductive age on cause- and age-specific

infant mortality in the ObaapaVitA trial. We hypothesised that vitamin A supplementation would have significant effects on all three groups (neonatal, early infant and late infant mortality). In addition, because of the recent interest in potential differential effects, we also assessed effects by sex and season.

**METHODS**

Methods are reported in detail elsewhere,<sup>12</sup> and the full protocol is available online (at [http://www.lshtm.ac.uk/eph/nphir/research/obaapavita/obaapavita\\_trial\\_protocol.pdf](http://www.lshtm.ac.uk/eph/nphir/research/obaapavita/obaapavita_trial_protocol.pdf)). In brief, all women aged 15–45 years living in seven, predominantly rural, districts in the Brong Ahafo region of Ghana, who were able to give informed consent and who planned to live in the trial area for at least 3 months were eligible for enrolment. Enrolment started in December 2000 and continued throughout the trial; fieldworkers recruited eligible women who migrated into their areas and girls who became fifteen. The trial ended in September 2008, with data collection continuing through October 2008. Verbal postmortems (VPMs) to ascertain cause of death were implemented for all infant deaths from June 2003. Analyses in this paper are therefore based on all live births that took place to study participants between June 2003 and September 2008.

There are two distinct seasons in the study area. October–March is the dry season with high temperatures (mean 30°C) and low rainfall (mean 100 mm). April–September is the rainy season with lower temperatures (mean 26°C) and high rainfall (mean 1270 mm).<sup>13</sup>

**Intervention**

Women were randomised, according to their cluster of residence, to receive either weekly vitamin capsules, containing 25 000 IU (7500 µg) of vitamin A in soybean oil in a dark red opaque soft gel, or identical-looking placebo capsules containing only soybean oil. The vitamin A dose was selected to deliver the recommended dietary allowance while being safe during pregnancy.<sup>14 15</sup> The capsules were manufactured by Accucaps Industries Limited, Windsor, Ontario, Canada; the vitamin A was donated by Roche. Women were visited at home every 4 weeks, and given four capsules to be taken over the next 4 weeks. Adherence was supported by an extensive Information, Education and Communication programme, based on formative research conducted before the trial began.<sup>16</sup>

**Randomisation and blinding**

The trial area was divided into clusters of compounds, with fieldworkers responsible for a fieldwork area (FWA) of four contiguous clusters, visiting women in one cluster per week over a 4-weekly cycle. There were a total of 272 FWAs and 1086 clusters. Randomisation was by cluster with two clusters in each FWA allocated to vitamin A and two to placebo to ensure geographic matching of vitamin A and control groups. A computer-generated

randomisation list was prepared for the capsule manufacturers by an independent statistician. The capsules were packaged in labelled jars, for each cluster for each week of the trial. No trial personnel (participants, care-providers, data collectors, data analysts, investigators) had access to the randomisation list or to any information that would allow them to deduce or change the cluster allocation.

### Data collection

Fieldworkers collected data during 4-weekly home visits on pregnancies, births, deaths, migrations, socio-demographic characteristics of pregnant women and number of capsules taken since the last visit. From June 2003, field supervisors conducted VPMs with close relatives or friends for all deaths reported among infants born to trial women; these included an open history, plus questions on signs, symptoms and the illness that lead to death. Standard WHO VPM tools and methods were used.<sup>17</sup> The methods have been presented and validated in earlier papers.<sup>18–20</sup> VPMs were reviewed by two experienced doctors, who independently assigned a single primary cause of death using identical tools. If the coders disagreed, the form was independently reviewed by a third doctor and a consensus coding accepted if two of the three agreed. If there was no consensus, the three coders met to determine whether they could reach agreement. The cause of death classi-

fication system had six major categories: congenital abnormalities, prematurity, birth asphyxia, infection (subdivided into neonatal, diarrhoea, pneumonia, malaria, measles, other), other specific cause of death and unexplained cause of death.

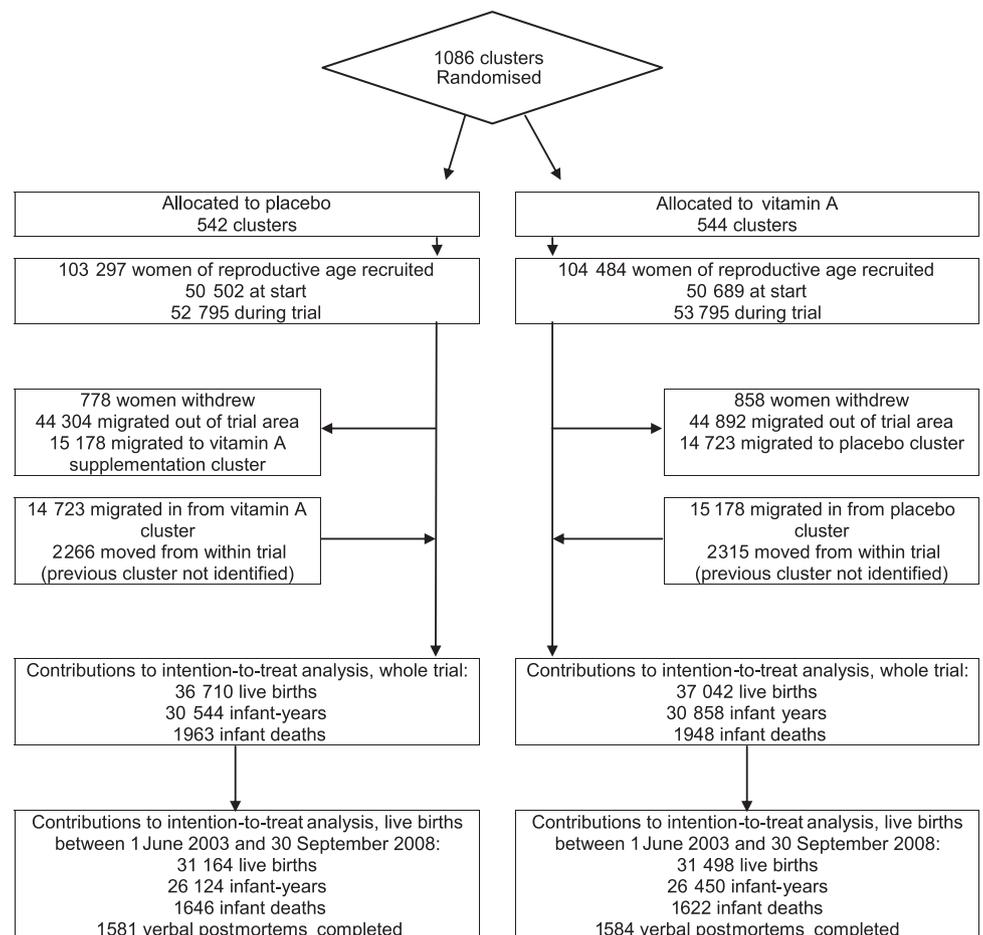
### Sample size

Sample size for the trial was determined by the rarest outcome, pregnancy-related mortality, to allow for the detection of a reduction of 33% in pregnancy-related mortality in the vitamin A arm, with 90% power and at 5% significance, and allowing for a 10% design effect. The sample size of 62 000 infants was also sufficient to detect at least a 15% effect of vitamin A supplementation on neonatal, early infant and late infant mortality.

### Statistical methods

Stata V.10.0 was used for all analyses. Infant mortality (deaths from 0 to 11 months of age), early infant mortality (deaths from 1 to 5 months of age) and late infant mortality (deaths from 6 to 11 months of age) were all expressed per 1000 infant-years of follow-up. Neonatal mortality (<1 month) was expressed per 1000 live births. Intention-to-treat analyses compared treatment groups using logistic regression for neonatal mortality and Cox regression for infant mortality. Random-effects regression (for logistic regression) or robust standard errors (for Cox regression) were used to

**Figure 1** Profile of trial and subjects included in analysis of all live births from 1 June 2003 to 30 September 2008.



take account of the clustered design. The proportional hazards assumption for all Cox regressions was assessed using visual inspection of the Nelson–Aalen log cumulative hazard curves. Interaction between vitamin A supplementation and season or gender was examined using the likelihood ratio test (when using logistic regression) or the Wald test (when using Cox regression).

Intention to treat was by cluster of residence. As previously described,<sup>12</sup> we accounted for the fact that vitamin A stores require some time to become replete or depleted by excluding the first 6 months of follow-up after recruitment or after any change of treatment group for the same reasons, and regarding women as belonging to their pre-move group for a period of 2 months after changing group. Infants were considered as belonging to the treatment arm of the mother at the time of delivery.

### Trial monitoring and ethical approval

The conduct of the trial was overseen by Trial Steering and Data Monitoring and Ethics Committees. It was approved by the ethics committees of the Ghana Health Service and the London School of Hygiene and Tropical Medicine and registered with <http://clinicaltrials.gov> (identifier NCT00211341). Full informed consent was obtained from all trial participants.

## RESULTS

### Participant flow

The trial profile is shown in [figure 1](#). One thousand and eighty-six clusters (542 placebo, 544 vitamin A) in 272 FWAs were randomised. Recruitment, withdrawals and migration patterns were similar in the vitamin A and placebo arms, as were socio-demographic characteristics ([table 1](#)). There were a total of 62 662 live births to 50 422 women of reproductive age in the trial from 1 June 2003 to 30 September 2008 with 52 574 infant-years of follow-up and 3268 infant deaths ([figure 1](#)). For babies born before 31 October 2007, follow-up to 1 year was 86%. Data collection for the trial ended on 31 October 2008, and 90% of the babies born after 31 October 2007 were seen in the last month of data collection or had died before then.

### Age at death

Overall, 58.9% (1925/3268) of the deaths occurred in the neonatal period, 21.3% (699/3268) occurred in early infancy (1–5 months) and 19.7% (644/3268) occurred in late infancy (6–11 months) ([table 2](#)). Mortality was comparable for the vitamin A and placebo groups during the neonatal period and in early and late infancy ([table 3](#)).

### Cause of death

A suitable respondent was found for the administration of 3129 VPMs out of the total 3268 deaths (95.7%). Coders were able to assign a cause for 2589 of these deaths (82.7%). Causes of death were markedly different in the neonatal ([table 4](#)) and postneonatal periods (1–11

**Table 1** Comparability of vitamin A and placebo groups, all live births from 1 June 2003 to 30 September 2008

Characteristic	Placebo, n (%*)	Vitamin A, n (%*)
Live births in study population (n)	31 164 (100)	31 498 (100)
Age group at the birth outcome, years		
<20	2404 (8)	2536 (8)
20–24	7645 (25)	7747 (25)
25–29	8866 (28)	8993 (29)
30–34	6848 (22)	6818 (22)
35–39	3784 (12)	3752 (12)
≥40	1617 (5)	1652 (5)
Previous live births (n)		
0	3463 (11)	3628 (12)
1	6032 (19)	6061 (19)
2	5812 (19)	5719 (18)
3	4628 (15)	4888 (15)
4	3664 (12)	3714 (12)
5+	7217 (23)	7179 (23)
Not known	348 (1)	309 (1)
Highest educational level		
None	12 142 (39)	12 280 (39)
Primary school	5812 (19)	5865 (19)
Secondary school	12 515 (40)	12 636 (40)
Technical college or university	262 (1)	281 (1)
Not known	433 (1)	436 (1)
Religion		
Christian	20 663 (66)	20 721 (66)
Muslim	7428 (24)	7594 (24)
Traditional African	1718 (6)	1803 (6)
Other	939 (3)	961 (3)
Not known	416 (1)	419 (1)
Ethnic group		
Akan	13 361 (43)	13 693 (43)
Other	17 392 (56)	17 386 (55)
Missing	411 (1)	419 (1)
Wealth quintiles		
1st (poorest)	8039 (26)	8339 (26)
2nd	6743 (22)	6666 (21)
3rd	5668 (18)	5768 (18)
4th	5177 (17)	5171 (16)
5th (richest)	4618 (15)	4670 (15)
Not known	919 (3)	884 (3)

\*Percentages may not add up to 100 due to rounding.

months) ([table 5](#)). Asphyxia was coded as the most common cause of neonatal death (37.0%; 568/1536), followed by infection (28.8%; 442/1536) and prematurity (18.3%; 281/1536). In contrast, infection was coded as the cause of 94.2% (992/1053) of the postneonatal deaths; 30% (298/992) of these infection deaths were due to pneumonia, 22.9% (228/992) to malaria, 14.1% (140/992) to diarrhoea, 0.6% (6/992) to measles and 32.3% (320/992) were due to other infection (meningitis, tetanus, HIV/AIDS or infection with an unknown cause).

The distributions of both neonatal and postneonatal causes of death were similar in the placebo and vitamin A groups ([tables 4 and 5](#)). There was no marked impact

**Table 2** Mortality by age and sex for infants born from 1 June 2003 to 30 September 2008

	Overall	Males*	Females*
<b>Neonatal deaths</b>			
Live births (n)	62 662	31 631	30 980
Total neonatal deaths	1925	1113	790
Total neonatal deaths/1000 live births	30.72	35.19	25.50
OR (95% CI)	—	1.00	0.72 (0.65 to 0.79)
p Value	—	—	<0.0001
<b>Infant deaths 1–5 months</b>			
Infant years of follow-up 1–5 months	23 660	11 886	11 772
Total 1–5 months deaths	699	362	334
Total 1–5 months deaths/1000 infant-years	29.54	30.46	28.37
HR (95% CI)	—	1.00	0.93 (0.80 to 1.08)
p Value	—	—	0.35
<b>Infant deaths 6–11 months</b>			
Infant years of follow-up 6–11 months	24 094	12 087	12 005
Total 6–11 months deaths	644	352	292
Total 6–11 months deaths/1000 infant-years	26.73	29.12	24.32
HR (95% CI)	—	1.00	0.84 (0.72 to 0.98)
p Value	—	—	0.02

\*Sex of baby unknown in 51 of 62 662 infants.

of vitamin A supplementation on any specific cause of mortality, either in the neonatal period (table 4) or in the postneonatal period (table 5). The overall HR for infection-specific infant mortality was 1.03 (95% CI 0.92 to 1.16).

### Sex

Mortality rates were considerably lower for females than males during the neonatal period and late infancy (table 2). Mortality was also lower in females than males in the early infant period, but this difference was marginal and non-significant. Mortality rates were similar for the vitamin A and placebo groups for both males and females in the neonatal period and early and late infancy. There was also no evidence of modification of the effect of vitamin A supplementation on infant mortality by sex (Wald statistic =0.07, p=0.80).

### Season

There was no obvious seasonality in mortality rates (figure 2). Fifty-three per cent (1729/3268) of infant deaths occurred in the rainy season (April–September) and 47% (1539/3268) in the dry season (October–March). Mortality rates were similar in both (HR 0.99 (95% CI 0.92 to 1.06), p=0.67), and there was no impact of vitamin A supplementation on infant deaths in either the rainy (HR 0.98 (95% CI 0.89 to 1.08), p=0.68) or the dry season (HR 0.97 (95% CI 0.87 to 1.08), p=0.56). There was also no evidence of modification of the effect of vitamin A supplementation on infant mortality by season (Wald statistic =0.03, p=0.86).

### DISCUSSION

This large-scale community-based trial provides the largest analysis of cause of infant deaths from Africa to date. Our analyses indicate that weekly vitamin A supplementation in women of reproductive age has no beneficial or deleterious effect on the causes of death in their babies of age 6 or 12 months in rural Ghana.

We identified no other published studies of the effect of vitamin A supplementation in women of reproductive age on cause-specific infant mortality. In particular, no cause-specific data have been reported from the other two trials of maternal vitamin A supplementation in Nepal<sup>21</sup> and Bangladesh.<sup>22–23</sup> Studies of maternal multiple micronutrient supplementation have also not reported effects on cause-specific infant mortality.<sup>24–25</sup> The biological action of vitamin A and previous evidence from childhood vitamin A trials<sup>5–26</sup> led us to postulate a priori that vitamin A may have an effect on deaths due to infant infection. However, we found no effect of vitamin A on deaths due to infant infections in our study population. It was also possible that vitamin A could have had an effect on deaths due to prematurity-related complications (eg, bronchopulmonary dysplasia, necrotising enterocolitis, intraventricular haemorrhage) as vitamin A has effects on epithelial integrity, cellular differentiation and foetal surfactant synthesis.<sup>2–27</sup> However, we found no impact of vitamin A supplementation in women of reproductive age on prematurity-specific neonatal mortality.

**Table 3** Effect of maternal weekly vitamin A supplementation on infant deaths by age and sex; intention-to-treat analyses, all live births from 1 June 2003 to 30 September 2008 (n=62 662)

	Both sexes combined		Males*		Females*	
	Placebo	Vitamin A	Placebo	Vitamin A	Placebo	Vitamin A
Neonatal deaths						
Live births (n)	31 164	31 498	15 777	15 854	15 357	15 623
Total neonatal deaths	984	941	589	524	382	408
Total neonatal deaths/1000 infant-years	31.57	29.87	37.33	33.05	24.87	26.12
Adjusted OR† (95% CI)	1.00	0.95 (0.86 to 1.04)	1.00	0.88 (0.78 to 1.00)	1.00	1.05 (0.91 to 1.22)
p Value	—	0.26	—	0.05	—	0.49
Infant deaths 1–5 months						
Infant years of follow-up 1–5 months	11 796	11 936	5921	5965	5839	5934
Total 1–5 months deaths	341	358	166	196	174	160
Total 1–5 months deaths/1000 infant-years	28.91	29.99	28.04	32.86	29.80	26.97
Adjusted HRT† (95% CI)	1.00	1.04 (0.88 to 1.22)	1.00	1.17 (0.95 to 1.45)	1.00	0.91 (0.72 to 1.14)
p Value	—	0.65	—	0.15	—	0.39
Infant deaths 6–11 months						
Infant years of follow-up 6–11 months	12 004	12 161	6022	6065	5945	6060
Total 6–11 months deaths	321	323	170	182	151	141
Total 6–11 months deaths/1000 infant-years	26.74	26.56	28.23	30.01	25.40	23.27
Adjusted HRT† (95% CI)	1.00	0.99 (0.84 to 1.18)	1.00	1.06 (0.85 to 1.33)	1.00	0.92 (0.73 to 1.16)
p Value	—	0.94	—	0.59	—	0.46

p Value for interaction between vitamin A and sex for neonatal deaths =0.06 (Likelihood ratio statistic =3.48).

p Value for interaction between vitamin A and sex for infant deaths 1–5 months =0.10 (Wald statistic =2.75).

p Value for interaction between vitamin A and sex for infant deaths 6–11 months =0.33 (Wald statistic =0.96).

\*Sex of baby unknown in 51 of 62 662 infants.

† Adjusted for clustering by ObaapaVITA cluster of residence.

**Table 4** Effect of weekly vitamin A supplementation on neonatal deaths by cause of death; intention-to-treat analyses, all live births from 1 June 2003 to 30 September 2008

	Placebo	Vitamin A
All live births (n)	31 164	31 498
Total neonatal deaths	984	941
<b>Infection</b>		
Infection-specific deaths (n)	218	224
Infection-specific deaths/1000 live births	7.00	7.11
Adjusted OR* (95% CI)	1.00	1.02 (0.84 to 1.23)
p Value	—	0.86
<b>Prematurity</b>		
Prematurity-specific deaths (n)	149	132
Prematurity-specific deaths/1000 live births	4.78	4.19
Adjusted OR* (95% CI)	1.00	0.88 (0.68 to 1.14)
p Value	—	0.33
<b>Asphyxia</b>		
Asphyxia-specific deaths (n)	284	284
Asphyxia-specific deaths/1000 live births	9.11	9.02
Adjusted OR* (95% CI)	1.00	0.99 (0.83 to 1.19)
p Value	—	0.95
<b>Other deaths†</b>		
Other deaths (n)	128	117
Other specific deaths/1000 live births	4.11	3.71
Adjusted OR* (95% CI)	1.00	0.89 (0.69 to 1.17)
p Value	—	0.41
<b>Unexplained</b>		
Unexplained deaths (n)	175	156
Unexplained deaths/1000 live births	5.62	4.95
Adjusted OR* (95% CI)	1.00	0.88 (0.71 to 1.10)
p Value	—	0.26
<b>Cause of death not ascertained</b>		
Unascertained deaths (n)	30	28
Unascertained deaths/1000 live births	0.96	0.89
Adjusted OR* (95% CI)	1.00	0.92 (0.55 to 1.55)
p Value	—	0.76

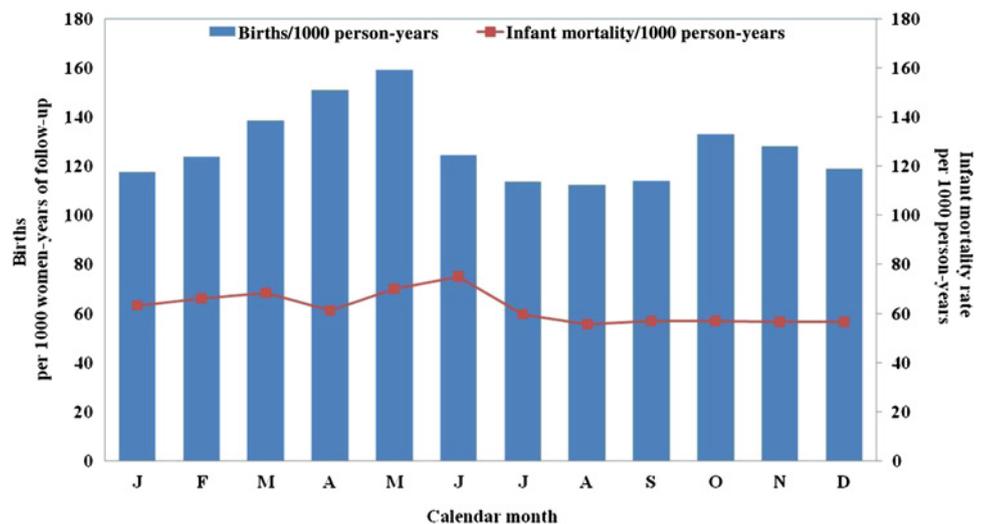
\*Adjusted for clustering by ObaapaVitA cluster of residence.

†Includes congenital abnormality, accident or injury, malignant tumours and neonatal jaundice.

The absence of an impact on early or late infant survival concurs with the findings of trials of maternal vitamin A supplementation from Nepal<sup>21</sup> and Bangladesh<sup>22 23</sup> and a pooled meta-analysis of the effects

of maternal multiple micronutrient supplements.<sup>24 25</sup> The results also concur with those of our main paper, which reported no effects of vitamin A supplementation in women of reproductive age on maternal mortality and

**Figure 2** Births and infant mortality per 1000 person-years, by calendar month.



**Table 5** Effect of weekly vitamin A supplementation on postneonatal deaths by cause of death; intention-to-treat analyses, all live births from 1 June 2003 to 30 September 2008

	Placebo	Vitamin A
Infant-years of follow-up	23 800	24 097
Total postneonatal deaths	662	681
<b>Infection</b>		
Infection-specific deaths (n)	479	503
Infection-specific deaths/1000 child-years	20.13	20.87
Adjusted HR* (95% CI)	1.00	1.04 (0.90 to 1.19)
p Value	—	0.61
<b>Pneumonia</b>		
Pneumonia-specific deaths (n)	152	146
Pneumonia-specific deaths/1000 child-years	6.39	6.06
Adjusted HR* (95% CI)	1.00	0.95 (0.75 to 1.21)
p Value	—	0.67
<b>Malaria</b>		
Malaria-specific deaths (n)	115	113
Malaria-specific deaths/1000 child-years	4.83	4.69
Adjusted HR* (95% CI)	1.00	0.97 (0.74 to 1.27)
p Value	—	0.83
<b>Diarrhoea</b>		
Diarrhoea-specific deaths (n)	60	70
Diarrhoea-specific deaths/1000 child-years	2.52	2.90
Adjusted HR* (95% CI)	1.00	1.15 (0.82 to 1.62)
p Value	—	0.42
<b>Measles</b>		
Measles-specific deaths (n)	4	2
Measles-specific deaths/1000 child-years	0.17	0.08
Adjusted HR* (95% CI)	1.00	0.49 (0.09 to 2.69)
p Value	—	0.41
<b>Other infection†</b>		
Other infection deaths (n)	148	172
Other infection-specific deaths/1000 child-years	6.22	7.14
Adjusted HR* (95% CI)	1.00	1.15 (0.91 to 1.45)
p Value	—	0.24
<b>Other deaths‡</b>		
Other deaths (n)	42	29
Other deaths/1000 child-years	1.76	1.20
Adjusted HR* (95% CI)	1.00	0.68 (0.42 to 1.10)
p Value	—	0.12
<b>Unexplained</b>		
Unexplained deaths (n)	106	103
Unexplained deaths/1000 child years	4.45	4.27
Adjusted HR* (95% CI)	1.00	0.96 (0.72 to 1.27)
p Value	—	0.78
<b>Cause of death not ascertained</b>		
Unascertained deaths (n)	35	46
Unascertained deaths/1000 child years	1.47	1.91
Adjusted HR* (95% CI)	1.00	1.30 (0.84 to 2.00)
p Value	—	0.24

\*Adjusted for clustering by ObaapaVitA cluster of residence.

†Includes meningitis, tetanus, HIV/AIDS or infection with an unknown cause.

‡Includes congenital abnormality, accident or injury and malignant tumours.

stillbirths.<sup>12</sup> However, none of these trials presented data separately for males and females. We recorded lower mortality rates in females than males throughout infancy and markedly so during the neonatal period and late infancy. We found no evidence of any differential effect of vitamin A supplementation in boys or girls, or by

season. This is in contrast to the recent Guinea Bissau trials which indicated that there may be an interaction between neonatal vitamin A supplementation and childhood immunisations by age, sex and season.<sup>7-9</sup>

There were some limitations to our trial. There was no direct observation of capsule taking; however, adherence

was supported by an extensive Information, Education and Communication strategy, and we estimated that on average 75% of women both received and took all four capsules every month.<sup>12</sup> We also used VPMs and physician coders to assign cause of death, and it was not possible to use health facility records or postmortem examinations to verify the cause of death. Misclassification is common in VPM studies, but this can be minimised when broad categories such as 'infection', 'prematurity' and 'asphyxia' are used.<sup>17 19</sup> Our VPM tools were also validated in similar study populations, and acceptable sensitivity and specificity were reported in comparison to a gold standard.<sup>17 18 20</sup> In addition, our study was prospective and population based. All resident women in the trial districts and their babies were enrolled, and loss to follow-up was low, even in women with babies who had died.

Our findings have important implications for policy and program development. They indicate that vitamin A supplementation in women of reproductive age will not reduce infection-specific infant mortality, has no influence on any of the other causes of death in their infants and is not an effective strategy to improve neonatal or infant survival. It also appears that vitamin A supplementation in women of reproductive age has no role in reducing overall or cause-specific infant mortality in child survival programs. We also failed to demonstrate any harm from vitamin A supplementation in infant males or females in our study population. These findings add to the ongoing debate about the safety of vitamin A supplementation and whether vitamin A supplementation may have differential effects on mortality in boys and girls in early and late infancy.

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#### Author footnote

All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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**Competing interests** All authors have completed the Unified Competing Interest form at [http://www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) (available on request from the corresponding author) and we declare that all authors have no financial or non-financial interests that may be relevant to the submitted work.

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# Effect of vitamin A supplementation in women of reproductive age on maternal survival in Ghana (ObaapaVitA): a cluster-randomised, placebo-controlled trial

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## Summary

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**Background** A previous trial in Nepal showed that supplementation with vitamin A or its precursor (betacarotene) in women of reproductive age reduced pregnancy-related mortality by 44% (95% CI 16–63). We assessed the effect of vitamin A supplementation in women in Ghana.

**Methods** ObaapaVitA was a cluster-randomised, double-blind, placebo-controlled trial undertaken in seven districts in Brong Ahafo Region in Ghana. The trial area was divided into 1086 small geographical clusters of compounds with fieldwork areas consisting of four contiguous clusters. All women of reproductive age (15–45 years) who gave informed consent and who planned to remain in the area for at least 3 months were recruited. Participants were randomly assigned by cluster of residence to receive a vitamin A supplement (25 000 IU retinol equivalents) or placebo capsule orally once every week. Randomisation was blocked and based on an independent, computer-generated list of numbers, with two clusters in each fieldwork area allocated to vitamin A supplementation and two to placebo. Capsules were distributed during home visits undertaken every 4 weeks, when data were gathered on pregnancies, births, and deaths. Primary outcomes were pregnancy-related mortality and all-cause female mortality. Cause of death was established by verbal post mortems. Analysis was by intention to treat (ITT) with random-effects regression to account for the cluster-randomised design. Adverse events were synonymous with the trial outcomes. This trial is registered with ClinicalTrials.gov, number NCT00211341.

**Findings** 544 clusters (104 484 women) were randomly assigned to vitamin A supplementation and 542 clusters (103 297 women) were assigned to placebo. The main reason for participant drop out was migration out of the study area. In the ITT analysis, there were 39 601 pregnancies and 138 pregnancy-related deaths in the vitamin A supplementation group (348 deaths per 100 000 pregnancies) compared with 39 234 pregnancies and 148 pregnancy-related deaths in the placebo group (377 per 100 000 pregnancies); adjusted odds ratio 0.92, 95% CI 0.73–1.17;  $p=0.51$ . 1326 women died in 292 560 woman-years in the vitamin A supplementation group (453 deaths per 100 000 years) compared with 1298 deaths in 289 310 woman-years in the placebo group (449 per 100 000 years); adjusted rate ratio 1.01, 0.93–1.09;  $p=0.85$ .

**Interpretation** The body of evidence, although limited, does not support inclusion of vitamin A supplementation for women in either safe motherhood or child survival strategies.

**Funding** UK Department for International Development, and USAID.

## Introduction

Vitamin A deficiency is a well-recognised nutritional problem,<sup>1,2</sup> and the leading cause of preventable childhood blindness.<sup>3</sup> In the 1990s, vitamin A supplementation became a key child survival intervention<sup>4,5</sup> after a series of eight trials<sup>6–13</sup> showed a pooled reduction in mortality of 23% (95% CI 16–38) in children aged between 6 months and 5 years who were given the intervention compared with those given placebo.<sup>2–14</sup>

Findings from a randomised controlled trial in Nepal suggested that vitamin A supplementation might have a similar role in preventing maternal deaths; provision of supplements of vitamin A or its precursor (betacarotene) to women of reproductive age reduced pregnancy-related mortality by 44% (95% CI 16–63;  $p<0.005$ ).<sup>15</sup> If this reduction represents a real effect, then low-dose vitamin A

supplementation could become an important safe motherhood intervention. Vitamin A supplementation is safe (including during pregnancy), inexpensive, and potentially deliverable at community level, even in the absence of strong health systems advocated in existing safe motherhood strategies.<sup>16,17</sup>

However, changing policy without testing vitamin A supplementation in trials in other settings was deemed premature. Other evidence of the effect of vitamin A supplementation comes from two trials in which only pregnant women received supplements (table 1). Provisional results from the trial in Bangladesh suggested no effect of vitamin A supplementation on pregnancy-related mortality (relative risk 1.15, 95% CI 0.78–1.81).<sup>18</sup> The trial in Indonesia compared a daily multiple micronutrient supplement containing vitamin A with a

supplement consisting of just iron and folic acid; pregnancy-related mortality rates were similar in the two groups (relative risk 1.03, 95% CI 0.64–1.68).<sup>19</sup>

The ObaapaVitA trial assessed the effects of giving vitamin A supplementation to all women of reproductive age in an African setting, where maternal mortality ratios are among the highest in the world.<sup>20</sup> The trial attempted to replicate the findings of the Nepal trial by giving supplements to all women of reproductive age.

## Methods

### Participants

The main objective of the ObaapaVitA trial was to assess the effect of weekly, low-dose vitamin A supplementation in women of reproductive age on pregnancy-related mortality and all-cause female mortality. Secondary objectives were to assess the effects of vitamin A supplementation on maternal morbidity and perinatal and infant mortality, and to explore effects on cause-specific pregnancy-related mortality by meta-analysis with other trials.

All women aged 15–45 years living in seven predominantly rural districts in Brong Ahafo Region in Ghana, who were capable of giving informed consent and who planned to live in the trial area for at least 3 months were eligible for enrolment. Implementation was phased by district; fieldworkers visited all compounds over a 4–8 week period and explained the trial by reading from a standard information sheet in Twi (the most commonly spoken language), by use of an interpreter if necessary. Women were given the opportunity to ask questions and, if they provided consent, asked to sign the enrolment form or make a thumbprint. Enrolment continued throughout the trial; fieldworkers recruited eligible women who migrated into their areas and girls who reached 15 years of age. Once recruited, women continued in the trial even beyond 45 years of age.

Capsule distribution started in Kintampo North and Kintampo South in December, 2000, in Wenchi and Tain in June, 2001, in Techiman in June, 2002, and in Nkoranza North and Nkoranza South in January, 2003. Distribution ended in September, 2008, with data collection continuing until the end of October, 2008.

The trial was approved by the ethics committees of the Ghana Health Service and the London School of Hygiene and Tropical Medicine. Full informed consent (by signature or thumbprint) was obtained from all trial participants; a substudy explored their understanding of the trial.<sup>21</sup>

### Procedures

Women were randomly assigned, according to their cluster of residence, to receive a vitamin capsule or placebo capsule orally once every week. The vitamin A capsule consisted of 25 000 IU (7500 µg) retinol equivalents in soybean oil in a dark red opaque soft gel. The placebo capsule consisted of soybean oil only. The

dose of vitamin A was selected to deliver the recommended dietary allowance while being safe during pregnancy.<sup>22,23</sup> The capsules were manufactured by Accucaps Industries (Windsor, ON, Canada); Roche (Basel, Switzerland) donated vitamin A palmitate. Women were visited at home every 4 weeks, and given four capsules to be taken over the next 4 weeks; capsules were kept in vials, with cotton wool to absorb humidity in the rainy season.

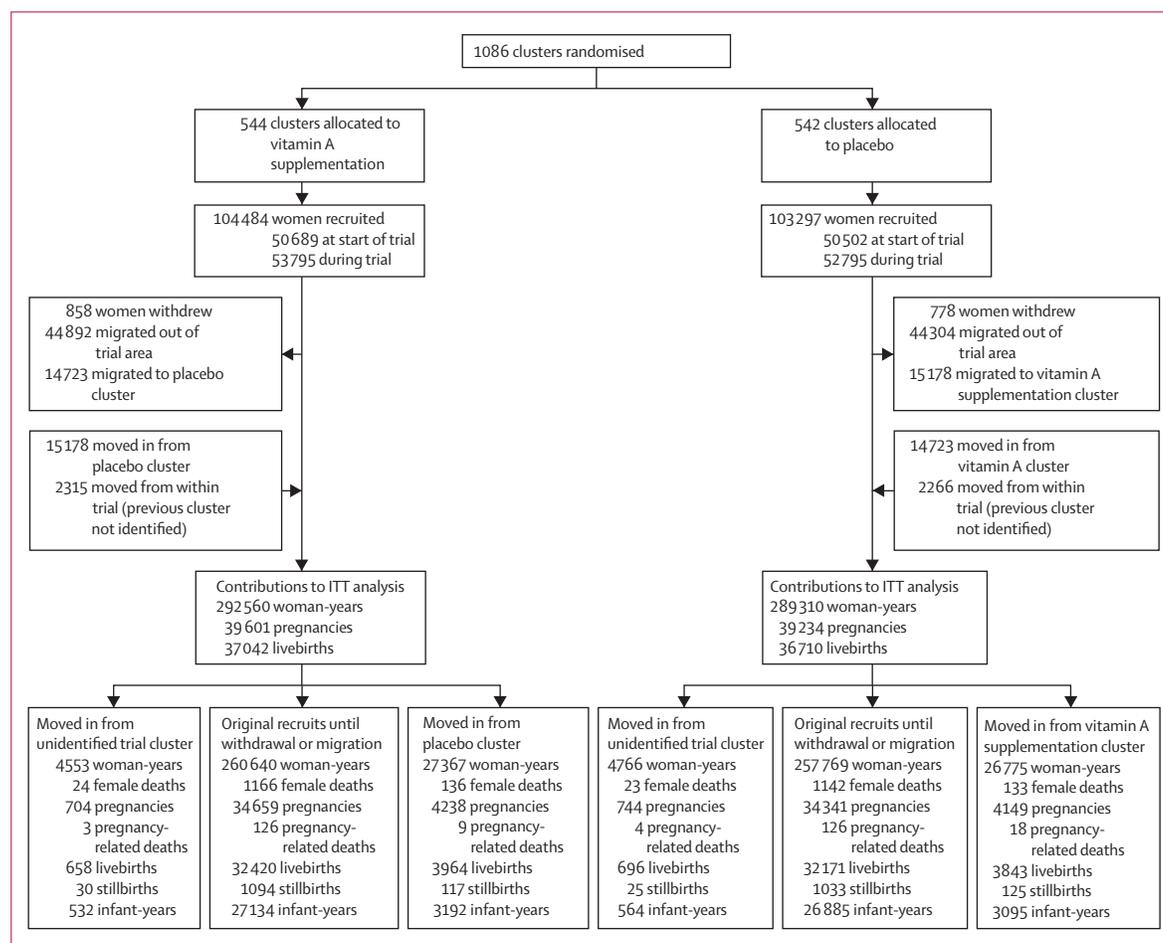
There was no direct observation of capsule taking during home visits. Instead, adherence was supported by an extensive Information, Education, and Communication (IEC) programme, based on formative research undertaken before the trial began<sup>24</sup> with women encouraged to take their capsules on the same day, Sunday, to foster social support and reduce forgetfulness. The IEC strategy also included reminder announcements on the radio and in the community (by means of loudspeaker vans and drum beaters), churches, and mosques; radio discussion programmes and community meetings to introduce the trial and answer questions; posters in all compounds; a book of frequently asked questions with answers for traditional healers, traditional birth attendants, drug sellers, and health workers in the trial area as well as fieldworkers; and a message of the month for fieldworkers to give women. A specially trained IEC team addressed any adherence issues through fieldworker reports and regular focus groups with community members, and identified possible solutions.

### Randomisation and masking

The trial area was divided into clusters of compounds, with fieldworkers responsible for a fieldwork area of four contiguous clusters, visiting women in one cluster per week over a 4-weekly cycle; clusters were designed

For the full protocol for this study see [http://www.lshtm.ac.uk/nphiru/research/obaapavita/Obaapa\\_Trial\\_Protocol.pdf](http://www.lshtm.ac.uk/nphiru/research/obaapavita/Obaapa_Trial_Protocol.pdf)

	Country	Supplement tested	Approximate number of pregnancies per group	Deaths per 100 000 pregnancies in control group
<b>All women of reproductive age</b>				
NNIPS-2 <sup>15</sup>	Nepal	Vitamin A supplementation once every week (23 333 IU RE)	7000	704
NNIPS-2 <sup>15</sup>	Nepal	Betacarotene once every week (23 333 IU RE)	7000	704
ObaapaVitA	Ghana	Vitamin A supplementation once every week (25 000 IU RE)	39 000	377
<b>Pregnant women</b>				
JiVitA-1 <sup>18</sup>	Bangladesh	Vitamin A supplementation once every week (23 333 IU RE)	20 000	209
JiVitA-1 <sup>18</sup>	Bangladesh	Betacarotene once every week (23 333 IU RE)	20 000	209
SUMMIT <sup>9</sup>	Indonesia	Daily multiple micronutrients (including 2667 IU RE)	7000	278
<small>NNIPS-2=Nepal Nutrition Intervention Project Sarlahi 2. RE=retinol equivalents. SUMMIT=Supplementation with Multiple Micronutrients Intervention Trial.</small>				
<b>Table 1: Trials assessing the effect of vitamin A supplementation on maternal mortality, by target group</b>				



**Figure 1: Trial profile**

Intention-to-treat (ITT) analysis excludes first 6 months after recruitment. See Methods section for details.

to contain an initial maximum of 120 enrolled women. A computer-generated randomisation list was prepared for the capsule manufacturers by an independent statistician on the data monitoring and ethics committee. The capsules were packaged in labelled jars, for each cluster for each week of the trial. Trial personnel had no access to the randomisation list or to any information that would allow them to deduce or change the cluster allocation.

Randomisation was by cluster to keep the possibility of women receiving the wrong capsules to a minimum; fieldworkers only ever had one jar in their possession, which contained the capsules to be given to women they were visiting that week. All women in a compound received the same capsules to avoid any allocation errors should their vials accidentally get mixed up. Randomisation was blocked with two clusters in each fieldwork area allocated to vitamin A supplementation and two clusters allocated to placebo to ensure geographical matching of intervention and control groups. Two fieldwork areas contained three rather than four clusters; their randomisation was undertaken in

exactly the same way but the allocation of the fourth cluster was ignored.

All participants and trial personnel (including those distributing capsules and collecting, processing, and analysing data) were masked to treatment assignment for the duration of the trial. Placebo capsules were identical in taste and appearance to the vitamin A capsules.

#### Data collection

At home visits undertaken every 4 weeks, fieldworkers gathered data for pregnancies, births, deaths, migrations, hospital admissions, pregnancy and post-partum morbidity, sociodemographic characteristics of pregnant women, and number of capsules taken since the last visit. Each year, there were scheduled breaks of 4 weeks' duration over Christmas; eight rather than four capsules were distributed at the last visit before the break.

Field supervisors undertook verbal post mortems with close relatives or friends for deaths of trial participants and infants; these interviews included questions about the circumstances surrounding the death, an open history, and questions on signs and symptoms. Verbal

post mortems were reviewed by two experienced doctors, who independently coded the likely cause of death and (for women) whether it was pregnancy-related. If the doctors disagreed, the form was independently reviewed by a third doctor, and a consensus coding accepted if two of the three agreed. If there was no consensus on the cause of death, the three doctors met to see whether they could reach agreement. If, however, there was no consensus on a woman's pregnancy status, the form was reviewed by an experienced obstetrician, who assigned pregnancy status and cause of death.

Field supervisors were based at the four main district hospitals (in Kintampo, Nkoranza, Techiman, and Wenchi) from January, 2004, to capture data on hospital diagnosis, clinical signs, and management for any trial participants admitted while pregnant, delivering, or postpartum.

A random sample of 40 women was visited every week by specially trained IEC supervisors to gather data on sociodemographic characteristics, adherence to study capsules (including observation of capsules in their vial), exposure to IEC activities, and any perceived side-effects. The sample was selected to consist of ten women who should have had three capsules remaining in their vial, ten who should have had two, ten who should have had one, and ten who should have had none.

A substudy was undertaken during September and October, 2008, to assess vitamin A status of women in the trial, measured by serum retinol concentration. 440 pregnant women were selected at random from the trial database together with 440 women recorded as not pregnant for at least 12 months. Women were visited at home, and if they gave informed consent by signature or thumbprint, 5 mL of venous blood was taken by a trained phlebotomist. Serum retinol concentrations were measured by reverse-phase high-performance liquid chromatography at Kintampo Health Research Centre. Standard reference serum samples (SRM 968B, National Institute of Standards and Technology, Gaithersburg, MD, USA) were used to construct standard curves for determining retinol concentrations. Precision and accuracy between batches were checked by regular inclusion of samples from a designated control serum sample.

A survey was undertaken between March and May, 2003, to assess the extent of nightblindness in study participants. 200 women were selected at random for clinician review from 1466 women who reported problems with their vision during the monthly surveillance in February, 2003.

### Outcomes

The primary outcomes of the trial were pregnancy-related mortality and all-cause female mortality. We used the International Classification of Diseases (ICD)-10 definition of pregnancy-related mortality (all deaths occurring during pregnancy, at delivery, or up

	Placebo group	Vitamin A supplementation group
Number of women recruited	103 297	104 484
Age (years)*		
<20	27 968 (27%)	28 779 (28%)
20–24	24 338 (24%)	24 541 (23%)
25–29	18 311 (18%)	18 475 (18%)
30–34	13 156 (13%)	12 975 (12%)
35–39	8840 (9%)	9098 (9%)
40–44	6669 (6%)	6551 (6%)
≥45	4015 (4%)	4065 (4%)
Number of women in random sample	4800	4640
Livebirths		
0	678 (14%)	658 (14%)
1	624 (13%)	616 (13%)
2	549 (11%)	560 (12%)
3	435 (9%)	465 (10%)
4	452 (9%)	385 (8%)
≥5	1139 (24%)	1079 (23%)
Not known	923 (19%)	877 (19%)
Highest educational level		
None	1274 (27%)	1284 (28%)
Primary school	739 (15%)	705 (15%)
Secondary school	1817 (38%)	1720 (37%)
Technical college or university	46 (1%)	51 (1%)
Not known	924 (19%)	880 (19%)
Marital status		
Married	2455 (51%)	2379 (51%)
Living together	418 (9%)	423 (9%)
Widow or divorced	345 (7%)	301 (6%)
Single, unmarried	646 (13%)	643 (14%)
Not known	936 (20%)	894 (19%)
Religion		
Christian	2901 (60%)	2820 (61%)
Muslim	693 (14%)	713 (15%)
Traditional African	103 (2%)	99 (2%)
Other	180 (4%)	131 (3%)
Not known	923 (19%)	877 (19%)
Ethnic group		
Akan	2075 (43%)	2042 (44%)
Other	1802 (38%)	1721 (37%)
Not known	923 (19%)	877 (19%)

Data are number or number (%). \*On Jan 1, 2004.

**Table 2: Sociodemographic characteristics of study participants**

to 42 days after delivery, irrespective of the cause or site).<sup>25</sup> Pregnancy-related mortality, expressed per 100 000 pregnancies, was chosen in preference to maternal mortality (which excludes coincidental deaths)<sup>25</sup> to enable comparison with the Nepal trial, and because pregnancy-related mortality does not require clinical diagnoses or post mortems to be undertaken. A pregnancy was eligible for inclusion provided both its outcome (livebirth, stillbirth, ectopic pregnancy, or pregnancy lost before 6 months) and the status of the

	Placebo group	Vitamin A supplementation group	Total
<b>Home visits (every 4 weeks)</b>			
Total number	4 215 234	4 265 396	8 480 630
Visits in which women were seen and capsules distributed (%)	3 587 164 (85.1%)	3 629 852 (85.1%)	7 217 016 (85.1%)
<b>Adherence</b>			
Visits in which capsule taking was checked (restricted to women seen both this month and previous month)	3 265 827	3 305 266	6 571 093
All four capsules taken last month (%)*			
Reported	88.2%	88.2%	88.2%
Based on capsules left in vial	84.1%	84.3%	84.2%
At least three capsules taken last month (%)*			
Reported	95.7%	95.8%	95.7%
Based on capsules left in vial	90.6%	90.9%	90.8%
<b>Estimated adherence</b>			
All four capsules taken last month (%)†			
Reported	75.1%	75.1%	75.1%
Based on capsules left in vial	71.6%	71.7%	71.7%
At least three capsules taken last month (%)†			
Reported	81.4%	81.5%	81.4%
Based on capsules left in vial	77.1%	77.4%	77.3%

\*Percentage of visits with information on capsule taking. †Percentage of visits with capsules distributed multiplied by percentage of women taking capsules.

Table 3: Adherence to study treatment

	Placebo group	Vitamin A supplementation group	p value
<b>Pregnant women</b>			
Women sampled	217	223	..
Women tested*	130 (59.9%)	148 (66.4%)	..
Serum retinol (µmol/L)	1.18 (0.52)	1.12 (0.56)	0.15
<0.70 µmol/L	20 (15.4%)	37 (25.0%)	0.048
<b>Non-pregnant women</b>			
Women sampled	215	225	..
Women tested†	187 (87.0%)	197 (87.6%)	..
Serum retinol (µmol/L)	1.52 (0.77)	1.56 (0.77)	0.60
<0.70 µmol/L	18 (9.6%)	16 (8.1%)	0.60

Data are number, number (%), or mean (SD). \*162 women were not tested: 123 pregnant women were not eligible because they had given birth between selection and testing; 13 refused consent; one had died; six had moved; seven were temporarily absent; and the reason was not recorded for 12 women. †56 women were not tested: seven were not eligible because they had become pregnant between selection and testing; 28 refused consent; one had died; two had moved; 14 were temporarily absent; and the reason was not recorded for four women.

Table 4: Effect of weekly vitamin A supplementation on serum retinol concentration in pregnant and non-pregnant women

woman 6 weeks after it ended were known. All-cause female mortality included all deaths in trial participants (including pregnancy-related deaths), expressed per 100 000 women-years of follow-up.

Secondary outcomes were severe maternal morbidity and perinatal and infant mortality. Serious maternal morbidity was defined as hospital admission during pregnancy or up to 42 days after delivery with the following diagnoses: severe pre-eclampsia, eclampsia, obstructed labour, emergency caesarean section, instrumental delivery, puerperal sepsis, spontaneous abortion, clinically significant malaria, clinically significant anaemia, antepartum haemorrhage, postpartum haemorrhage, or shock.

Perinatal and infant mortality consisted of stillbirth rate (babies born dead at 6 months of gestation or later) and perinatal mortality (number of stillbirths plus deaths in the first 7 days of life), both expressed per 1000 births (livebirths plus stillbirths); neonatal mortality (deaths in the first 28 days of life), expressed per 1000 livebirths; and infant mortality (deaths in the first year of life), expressed per 1000 infant-years of follow-up rather than per 1000 livebirths to take into account losses to follow-up during infancy. No changes were made to the study outcomes after commencement of the trial.

### Trial monitoring

The conduct of the trial was overseen by the trial steering committee, which had 12 members chosen to facilitate uptake of any findings within Ghana and to provide technical support. The data monitoring and ethics committee had six members with expertise in cluster-randomised trials, epidemiology, medical statistics, obstetrics, community medicine, and maternal, newborn, and child health; they undertook yearly blinded safety analyses to check for any excess in primary or secondary mortality or severe morbidity outcomes in the vitamin A supplementation group, and a full interim analysis in June, 2006.

The data monitoring and ethics committee also monitored capsule content. 56 randomly selected batches of capsules (28 vitamin A and 28 placebo) covering all yearly consignments received from the manufacturers were tested at an independent laboratory in Cambridge, UK, and randomisation accuracy was confirmed. These samples included 14 batches of unused capsules (seven vitamin A and seven placebo) returned from the field that had been stored in uncontrolled conditions for at least 4 weeks. All vitamin A capsules tested, including those returned from the field, had at least 95% of the required retinol content (most had 100%), apart from three batches that were tested after substantial periods of storage; two batches of unused capsules tested more than 2 years after manufacture had 79% and 83% of their retinol content, and a batch tested after 4 years had 53%.

### Statistical analysis

Sample size was determined by the rarest outcome, pregnancy-related mortality. Initial calculations suggested that data for 82 000 pregnancies would give 90% power to

detect a 33% reduction in pregnancy-related mortality in the vitamin A supplementation group (and 76 000 pregnancies an 80% power to detect a 30% reduction) from a baseline of 450 deaths per 100 000 pregnancies, at the 5% significance level. These calculations conservatively included a 10% design effect, which was expected to be negligible in view of the small cluster size and rare outcome. The data monitoring and ethics committee did conditional power calculations in 2003 and recommended that the trial be continued until October, 2008.

We undertook intention-to-treat analyses to compare treatment groups with random-effects regression to account for the cluster-randomised design. We used logistic models for outcomes where the denominator was pregnancies or births, and Poisson models where the denominator was person-years.

Intention to treat was defined by cluster of residence. When women moved residence, they received the same capsules as other women in their new residence, which might have resulted in them changing treatment group. We considered four periods to guide decisions for inclusion of data in the analysis. Lag referred to the period in which a woman was taking vitamin A supplements but the full effects of the intervention were not seen. During this period, events did not contribute to the analysis. Run-in was a shorter period at the start of the lag period during which vitamin A supplementation was likely to have little or no effect. Carry-over was defined as the period after cessation of vitamin A supplementation, when the effect was expected to be little reduced. During this period, women that changed from vitamin A supplementation to placebo could continue to contribute data to the vitamin A supplementation group. Wash-out, which was longer than the carry-over period, was the period after cessation of vitamin A supplementation, during which any effect would have worn off.

To ensure balanced lengths of follow-up between treatment groups, the same inclusion and exclusion rules needed to be applied whichever direction the change of group; equal values were therefore used for the lag and wash-out periods (6 months), and the run-in and carry-over periods (2 months). Since biochemical data do not exist to inform these values, they were decided in consultation with the data monitoring and ethics committee on the basis of responses from vitamin A experts.

Primary analyses therefore excluded the first 6 months after recruitment, and the 6 months after any change of treatment group, and regarded women as belonging to their pre-move group for a period of 2 months after changing group. Pure intention-to-treat analyses excluded data from the point that a woman changed group. Modified versions of both intention-to-treat and pure intention-to-treat analyses, undertaken for pregnancy-related mortality, included only women seen by their fieldworker (and given capsules) in at least three

	Placebo group	Vitamin A supplementation group
<b>Intention-to-treat analysis*</b>		
Number of pregnancies	39 234	39 601
Number of pregnancy-related deaths	148	138
Number of deaths per 100 000 pregnancies	377	348
Adjusted odds ratio† (95% CI)	1.00	0.92 (0.73–1.17)
p value	..	0.51
<b>Modified intention-to-treat analysis‡</b>		
Number of pregnancies	37 725	38 117
Number of pregnancy-related deaths	131	125
Number of deaths per 100 000 pregnancies	347	328
Adjusted odds ratio† (95% CI)	1.00	0.94 (0.74–1.21)
p value	..	0.65
<b>Pure intention-to-treat analysis§</b>		
Number of pregnancies	34 341	34 659
Number of pregnancy-related deaths	126	126
Number of deaths per 100 000 pregnancies	367	364
Adjusted odds ratio† (95% CI)	1.00	0.99 (0.77–1.28)
p value	..	0.95
<b>Modified pure intention-to-treat analysis¶</b>		
Number of pregnancies	33 031	33 379
Number of pregnancy-related deaths	110	115
Number of deaths per 100 000 pregnancies	333	345
Adjusted odds ratio† (95% CI)	1.00	1.04 (0.79–1.35)
p value	..	0.80

\*Intention-to-treat analysis excludes first 6 months after recruitment or change of treatment group. †All odds ratios adjusted for clustering by use of random effects models. ‡Excluding women seen less than three times in the 6 months before end of pregnancy. §Excluding women after change of treatment group. ¶Excluding women after change of treatment group and excluding women seen less than three times in the 6 months before end of pregnancy.

**Table 5: Effect of weekly vitamin A supplementation on pregnancy-related deaths**

	Placebo group	Vitamin A supplementation group
Woman-years of follow-up*	289 310	292 560
All-cause adult female deaths	1298	1326
Mortality rate (per 100 000 years)	449	453
Adjusted rate ratio† (95% CI)	1.00	1.01 (0.93–1.09)
p value	..	0.85

Data are number unless otherwise indicated. \*Woman contributed after 6 months in consistent treatment group, and continued to contribute to that group for a further 2 months if she moved. †Rate ratio adjusted for clustering by use of random effects models.

**Table 6: Effect of weekly vitamin A supplementation on all-cause female mortality (intention-to-treat analysis)**

of the 6 months before the end of the pregnancy to increase the likelihood of detecting any true effect of vitamin A supplementation.

Mean serum retinol concentrations were compared by use of a *t* test and the proportions in each group with serum retinol concentrations of less than 0.70 µmol/L were compared with  $\chi^2$  tests. Analyses were done with Stata version 9.0.

	Placebo group	Vitamin A supplementation group
Pregnancies since Jan 1, 2004	30 380	30 055
Admissions in four main hospitals*	2342	2332
Adjusted odds ratio† (95% CI)	1.00	0.98 (0.89–1.09)
p value	..	0.74

Data are number unless otherwise indicated. \*Admissions due to the following 12 causes: severe pre-eclampsia, eclampsia, obstructed labour, emergency caesarean section, instrumental delivery, sepsis after delivery, spontaneous abortion, clinically significant malaria, clinically significant anaemia, antepartum haemorrhage, postpartum haemorrhage, shock. †Odds ratios adjusted for clustering by use of random effects models.

**Table 7: Effect of weekly vitamin A supplementation on pregnancy-related hospital admissions (intention-to-treat analysis)**

	Placebo group	Vitamin A supplementation group
Livebirths	36 710	37 042
Infant-years of follow-up	30 544	30 858
Stillbirths	1183	1241
Stillbirths (per 1000 births*)	31.2	32.4
Adjusted odds ratio† (95% CI)	1.00	1.04 (0.96–1.13)
p value	..	0.36
Perinatal deaths (stillbirths and deaths in first 7 days)	2083	2117
Perinatal mortality (per 1000 births*)	55.0	55.3
Adjusted odds ratio† (95% CI)	1.00	1.01 (0.94–1.08)
p value	..	0.85
Neonatal deaths (days 1–28)	1187	1140
Neonatal mortality (per 1000 livebirths)	32.2	30.8
Adjusted odds ratio† (95% CI)	1.00	0.95 (0.87–1.04)
p value	..	0.27
Infant deaths (0–11 months)	1963	1948
Infant mortality (per 1000 child-years)	64.3	63.1
Adjusted rate ratio† (95% CI)	1.00	0.98 (0.91–1.05)
p value	..	0.58

Data are number unless otherwise indicated. \*Livebirths plus stillbirths. †All odds ratios and rate ratios adjusted for clustering by use of random effects models.

**Table 8: Effect of maternal weekly vitamin A supplementation on rate of stillbirth and perinatal, neonatal, and infant mortality (intention-to-treat analysis)**

This trial is registered with ClinicalTrials.gov, number NCT00211341.

### Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

### Results

Figure 1 shows the trial profile. 1086 clusters in 272 fieldwork areas were randomised. 207781 women were recruited, 101191 (49%) at the start of the trial in their district, and the rest during the trial. In the last month of the trial (October, 2008), the mean cluster size

was 108 women (SD 29.6; range 31–232). 1636 (1%) women withdrew consent and 89 196 (43%) moved out of the study area during the trial. Intention-to-treat analyses are based on 581870 woman-years, 78 835 pregnancies, and 73 752 livebirths (figure 1). The number of participants recruited and followed up were similar between groups. Table 2 shows sociodemographic characteristics of study participants.

8480630 4-weekly home visits were made, with fieldworkers finding on average 85.1% of active women each cycle. Adherence to all four capsules was high (table 3) and similar for reports and vial observation (88.2% and 84.2%, respectively). Combination of the successful visit and adherence rates gives an overall estimated adherence of more than 70%. This level was stable throughout the trial and confirmed by random home visits; 7533 (80%) of 9440 women selected were successfully seen, 5936 (79%) of whom had taken their expected number of capsules.

Vitamin A supplementation did not seem to result in improved serum retinol concentrations in either pregnant or non-pregnant women (table 4), despite mean duration in the trial of 4.5 years (SD 2.3), and estimated mean compliance over 90% in the previous 12 months. Overall, 57 (21%) pregnant women and 34 (9%) non-pregnant women had moderate retinol deficiency (serum retinol concentration <0.70 µmol/L). 1466 (2%) of the 81385 women seen in February, 2003, reported problems with their vision. None of the 124 women reviewed had clinical signs of xerophthalmia; four gave a history compatible with night blindness.

In the intention-to-treat analysis, there were 138 pregnancy-related deaths in the vitamin A supplementation group compared with 148 in the placebo group (adjusted odds ratio 0.92, 95% CI 0.73–1.17; table 5). Modified intention-to-treat, pure intention-to-treat, and modified-pure intention-to-treat analyses of pregnancy-related mortality are shown in table 5. The point estimates and lower confidence intervals increase as the analyses are restricted (with point estimates remaining close to 1.0). This pattern contrasts with what would be expected if vitamin A supplementation reduced pregnancy-related mortality, since both restrictions aim to remove potential sources of underestimation, by exclusion of data from women after they changed treatment groups and exclusion of women who had not been seen (and given capsules) regularly during pregnancy.

1326 women died of any cause in the vitamin A supplementation group compared with 1298 in the placebo group (adjusted rate ratio 1.01, 95% CI 0.93–1.09; table 6). There were no differences between groups in rates of pregnancy-related hospital admissions (table 7) or stillbirths, or in perinatal, neonatal, or infant mortality (table 8). All point estimates of adjusted rate ratios or odds ratios were close to 1.0, with narrow

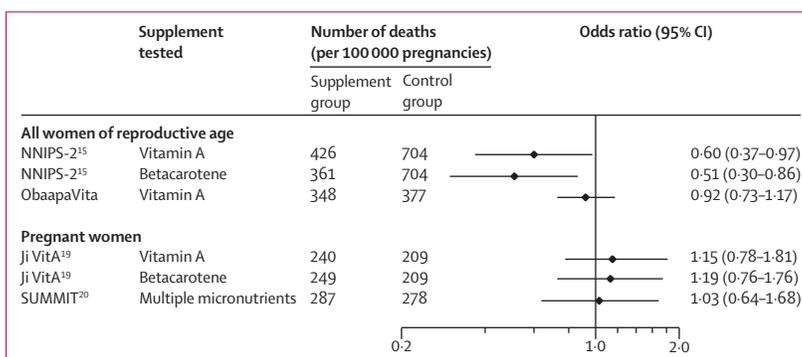
95% CIs. Results are shown only for the primary intention-to-treat analyses; the restricted versions gave similar results. Adverse events were synonymous with the trial outcomes.

## Discussion

Our results suggest that vitamin A supplementation once a week in women of reproductive age has no beneficial effect on their survival or on the survival of their babies in rural Ghana. The absence of an effect on stillbirth rate, neonatal survival, or infant survival accords with the findings of trials undertaken in Nepal<sup>26</sup> and Bangladesh.<sup>18,27</sup> However, the absence of an effect of vitamin A supplementation on pregnancy-related mortality contrasts with the substantial reduction in mortality reported in the Nepal trial, the only other trial in which all women of reproductive age were given supplements.

There are several possible reasons why our results differ from those of the Nepal trial. Night blindness (a sign of clinical vitamin A deficiency) was rare in participants in our trial, by contrast with the trial in Nepal, with approximately 10% of pregnant women in the placebo group affected.<sup>28</sup> There is also no word for night blindness in any of the local languages in Ghana, unlike in Nepal. This finding is unlikely to be the explanation for the difference between trial outcomes because subclinical levels of vitamin A deficiency were similar in the two trials (in our trial, 15% of pregnant women in the placebo group had moderate vitamin A deficiency compared with 19% in the Nepal trial).<sup>15</sup> Furthermore, there was no association between observed effect and vitamin A deficiency in trials of vitamin A supplementation in children;<sup>14</sup> reductions in mortality, hospital admissions, and severe diarrhoea were reported in children who received vitamin A supplements in Ghana,<sup>7</sup> where vitamin A deficiency was largely subclinical.

Vitamin A supplementation did not improve serum retinol concentrations in Ghanaian women. In fact, moderate vitamin A deficiency was more frequent in pregnant women in vitamin A supplementation clusters than in women in placebo clusters. The dose of retinol used in the vitamin A capsules was recommended as safe for pregnant women<sup>22</sup> and was slightly higher than the dose used in the Nepal trial. Analyses of capsules and high adherence rates suggest that women were receiving the intended dose; however, our results suggest that this dose was not sufficient to improve serum retinol concentrations in this setting. In Nepal, vitamin A supplementation substantially reduced moderate deficiency to 3% (compared with 19% in the placebo group), but supplementation with betacarotene did not (14% moderate vitamin A deficiency), although the reduction in mortality seen was higher in the betacarotene group than in the vitamin A group (figure 2).



**Figure 2: Effect of vitamin A supplementation on maternal mortality in cluster-randomised trials**

NNIPS-2=Nepal Nutrition Intervention Project Sarlahi 2. SUMMIT=Supplementation with Multiple Micronutrients Intervention Trial.

Although capsule taking was not directly observed in our trial, as it was in Nepal, levels of adherence achieved by the IEC strategy seem to be similar. Both the random household visits to check adherence and formative research confirm that Ghanaian women were taking their capsules; in general, women attributed a range of positive benefits to the capsules irrespective of type (eg, being good for strength, protective against illness, and ensuring safe delivery<sup>21</sup>) and were concerned that they would no longer receive them after the trial. We estimated that on average 75% of women both received and took all four capsules every month; this proportion was higher (82%) for women in the serum retinol survey during the 12 months before blood samples were taken.

The high rates of migration recorded in our trial might have resulted in shorter participation times than those in the Nepal trial. However, women included in the main intention-to-treat analysis had been receiving the same type of capsules for a mean 31.8 months, with 80.6% of women receiving them for at least 12 months.

Migration within the trial area and the use of small geographical clusters resulted in a substantial proportion of women changing treatment groups during the course of the trial. This occurrence contrasts with the design of the trial in Nepal, in which arrangements were made to ensure women received the same type of supplements if they moved. Such an approach was not logistically feasible in Ghana because of the low population density and large area involved. Exclusion of data obtained after change of treatment group increased the adjusted odds ratio from 0.92 to 0.99, opposite to what would be expected if migration was causing an underestimation of the effect of vitamin A supplementation on mortality.

The reduction in pregnancy-related deaths seen in the trial in Nepal could be an anomalous finding even though the reduction was substantial and the p value small. This suggestion accords with the fact that the highest reductions were seen in deaths related to injury or of unknown or uncertain causes, with smaller

reductions recorded for deaths from obstetric causes or infection. We would be interested to know whether there were reductions or increases in the number of deaths unrelated to pregnancy in the Nepal trial, and whether there was a similar lack of any effect on all-cause adult female mortality, as seen in our trial.

Figure 2 summarises results of trials assessing the effects of vitamin A supplementation on pregnancy-related mortality. The Bangladesh trial tested the same supplements as did the Nepal trial, but only enrolled pregnant women; provisional results presented at the Micronutrient Forum in 2007 show non-significant increased mortality in women assigned to vitamin A or betacarotene supplementation compared with controls.<sup>18</sup> In the Supplementation with Multiple Micronutrients Intervention Trial in pregnant women in Indonesia, vitamin A supplementation had no effect on mortality compared with placebo.<sup>19</sup> The primary focus was, however, on fetal loss and early infant mortality, and the trial was not powered to detect an effect on maternal deaths; although the point estimate for the relative risk was close to 1, the confidence interval was wide.

Further trials to assess the effect of vitamin A supplementation on maternal mortality are unlikely to be undertaken because of their size and cost. The body of evidence, although limited, does not support inclusion of low-dose vitamin A supplementation for women in either safe motherhood or child survival strategies.

#### Contributors

The report was drafted by BRK and reviewed by all members of the ObaapaVitA Trial Team. It is dedicated to the late Paul Arthur who established Kintampo Health Research Centre and initiated the trial. PA, BRK, and OC designed the study. ZH and CT participated in design of the Information, Education, and Communication component of the trial. SAE, SD, BRK, and CH participated in design of the data management system. KE and LH designed the hospital data capture system. KE, LH, GTA, and SOA were responsible for trial conduct. CZ coordinated the fieldwork. CT managed the Information, Education, and Communication component. SAE, SD, CH, and JF managed the database. LH, CH, and JF undertook the statistical analyses.

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#### Conflicts of interest

We declare that we have no conflicts of interest.

#### Acknowledgments

This report is an output from a project funded by the UK Department for International Development (DFID) for the benefit of developing countries; the views expressed are not necessarily those of DFID. The trial also received some contribution from USAID. Vitamin A palmitate for the capsules was kindly donated by Roche. We acknowledge the support of the chiefs, elders, and opinion leaders in the trial area, and the substantial contribution of all women who participated in the trial. We thank the administrative support provided by Angela Vega throughout the trial; all staff at Kintampo Health Research Centre involved in the trial, especially site leaders, coordinators, supervisors, fieldworkers, data managers, data supervisors, data entry clerks, and administrative support staff; and the trial steering committee and data monitoring and ethics committee for their continuing support and guidance.

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## **BMJ RESPONSE 20 Nov 2011**

**Re: BMJ.2011.000387 entitled "Effect of vitamin A supplementation to women of reproductive age on cause specific early and late infant mortality in rural Ghana; ObaapaVitA double blind cluster randomised placebo controlled trial"**

### **Editors comments**

Our main problem with the paper was that we did not think it added enough, for general readers, to what is already known about supplementation with vitamin A. The committee was puzzled that the findings on the two prespecified secondary outcomes weren't included in the original paper published in the Lancet. You also present two post-hoc analyses done in response to the Guinea Bissau paper, showing no effects of sex or season on the findings. I'm afraid the committee decided this was not enough for a BMJ paper, and that we were under no obligation to keep pursuing your paper, since the Guinea Bissau paper tested a different intervention from that studied in your paper (ie infant dosing after birth vs maternal treatment during pregnancy). We did not have any specific criticism of the design or methods.

- We did not include the two prespecified secondary outcomes (cause and age specific infant mortality) in our initial publication due to space limitations. This information has now been included on Page 4 Paragraph 3 of the revised manuscript.
- We believe that the data from the prespecified secondary outcomes should be published as these data elucidate important elements in the causal pathway of vitamin A using a large sample of over 60,000 infants in rural Africa. Vitamin A reduces infection and improves epithelial integrity in older children thus it is of importance to assess whether the same causal pathway could be affected in younger infants; and to look specifically at effects on infection specific mortality and prematurity specific mortality. We have emphasised these points on Page 9 Paragraph 5 and Page 10 Paragraph 1 of the revised manuscript.
- We also believe that the data from the post hoc analyses provide important new evidence about the effects of vitamin A supplementation in male and female infants in Africa. Our findings contrast with the only other African study which has considered these factors (Guinea Bissau). In particular, we failed to demonstrate any harm from vitamin A supplementation to women of reproductive age in infant males or females in our study population in either early or late infancy. These findings add to the ongoing debate about the safety of vitamin A supplementation and add important information about whether vitamin A supplementation may have differential effects on infant mortality in boys and girls. Neither the Cochrane review nor our Lancet paper examined these issues. We have highlighted these issues on Page 11 Paragraph 2 of the revised manuscript.

## **Reviewer Comments:**

### **Reviewer: 1 H.P.S. Sachdev**

Comments:

For the authors

This manuscript presents important information on infant deaths from a well conducted Vitamin A supplementation trial in pregnancy in Africa. Although a very small proportion of the results were encapsulated in the earlier main publication in the Lancet and included in systematic reviews, the detailed results in this manuscript are relevant as: (i) causes of deaths are reported from a large sample in Africa to evaluate the impact on cause specific mortality; (ii) these provide evidence regarding the differential mortality effects in relation to gender and the season, which is important in relation to the ongoing controversy on this subject particularly in the media; and (iii) would be relevant to the ongoing WHO supported trials on neonatal Vitamin A supplementation.

I have only a few relatively minor comments:

The authors appear to be focusing disproportionately higher on the safety aspect in the box "We also failed to demonstrate any harm from vitamin A supplementation to women of reproductive age in infant males or females in our study population". In reality, there is no evidence of either benefit or harm and this should be stated accordingly only.

- We agree with the reviewer and we have changed the text in the last paragraph of the box to read "We also failed to demonstrate any benefit or harm from vitamin A supplementation to women of reproductive age in infant males or females in our study population. There was also no modification of the effect of vitamin A supplementation and mortality by season."

The number of Tables may need reduction.

- We are happy to reduce the number of tables if requested by the editors.

### **Reviewer: 2 Parul Christian**

Comments:

This is a well written paper of a secondary outcome from a large RCT conducted in Ghana, which examined vitamin A (VA) supplementation effects on maternal mortality. As with the maternal mortality outcome, the findings are negative, i.e. there was no effect of the intervention on infant mortality by cause or age.

There are some issues that need to be addressed as follows:

- a. Include a brief explanation as to why this outcome, albeit secondary, was not included in the first paper, especially as both outcomes were linked, and were planned a priori.

- We did not include these outcomes in our initial publication due to space limitations. This information has now been included on Page 4 Paragraph 3 of the revised manuscript.

b. It would be important to explain how evaluating the effect of maternal VA supplementation during pregnancy on infant survival speaks to findings from the study providing a large dose of VA at birth? This is important because the stratified analyses are motivated by the findings in the newborn vitamin A supplementation study.

- We agree with the reviewer. The data from the post hoc analyses provide important new evidence about the effects of vitamin A supplementation in male and female infants in Africa. Our findings contrast with the only other African study which has considered these factors (Guinea Bissau). In particular, we failed to demonstrate any harm from vitamin A supplementation to women of reproductive age in infant males or females in our study population in either early or late infancy. These findings add to the ongoing debate about the safety of vitamin A supplementation and add important information about whether vitamin A supplementation may have differential effects on infant mortality in boys and girls. Neither the Cochrane review nor our Lancet paper examined these issues. We have highlighted these issues on Page 11 Paragraph 2 of the revised manuscript.

c. Add information about the minimum detectable HR given the sample size estimated for the rarer outcome of pregnancy-related mortality.

- We agree with the reviewer that this information is important. The sample size of 62,000 infants was sufficient to detect at least a 15% effect of vitamin A supplementation on neonatal, early infant and late infant mortality. We have added this information on Page 7 Paragraph 1 of the revised manuscript.

d. Which of the outcomes (neonatal, 1-5 mo, 5-11 mo) were hypothesized to be different between group. Is there value in providing total infant mortality rate as well, i.e. adding a panel for that in Table 3?

- We hypothesised that vitamin A supplementation would have significant effects on all three groups. We have included this information on Page 5 Paragraph 1 of the revised manuscript. The effect on total infant mortality is presented in the initial Lancet paper thus we do not feel we need to present this data again in this paper. However, we would be happy to do this if the editors wish this.

e. The main issue is that maternal weekly 25,000 IU of VA during pregnancy is not the same intervention as a direct dose of 50,000 IU given to a newborn soon after birth. The efficacy (and safety) of maternal vitamin A supplementation at the dosage used demonstrated previously in a trial Nepal in the mid 1990's and again in Bangladesh, recently, although not in Africa. However, it is unclear if any safety concern related to infant mortality with maternal supplementation has been raised. Rather the purported harm to infants in the Guinea Bissau study was related to newborn dosing. Thus, this needs some clarification in the discussion.

- We agree with the reviewer. This is a similar point to that raised in point 'b'. The data from the post hoc analyses provide important new evidence about the effects of vitamin A supplementation in male and female infants in Africa. Our findings contrast with the only other African study which has considered these factors (Guinea Bissau). In particular, we failed to demonstrate any harm from vitamin A supplementation to women of reproductive age in infant males or females in our study population in either early or late infancy. These findings add to the ongoing debate about the safety of vitamin A supplementation and add important information about whether vitamin A supplementation may have differential effects on infant mortality in boys and girls. Neither the Cochrane review nor our Lancet paper examined these issues. We have highlighted these issues on Page 11 Paragraph 2 of the revised manuscript.

Minor:

Not sure why "VPM - verbal post-mortems" is introduced as a term, when the reference (#17) refers to these as verbal autopsies.

- We are happy to refer to these questionnaires as either verbal post mortems or verbal autopsies. We are happy to change the name to verbal autopsies if the editors wish it.

CONSORT - CHECKLIST OF ITEMS TO INCLUDE WHEN REPORTING A CLUSTER RANDOMISED TRIAL	
DETAILS	REPORTED ON PAGE NO
<b>Title and abstract</b>	
Design 1* How participants were allocated to interventions (eg random allocation, randomised, or randomly assigned), <i>specifying that allocation was based on clusters</i>	2
<b>Introduction</b>	
Background 2* Scientific background and explanation of rationale, <i>including the rationale for using a cluster design</i>	3, 5
<b>Methods</b>	
Participants 3* Eligibility criteria for participants <i>and clusters</i> and the settings and locations where the data were collected	4,5
Interventions 4* Precise details of the interventions intended for each group, <i>whether they pertain to the individual level, the cluster level, or both</i> , and how and when they were actually administered	4
Objectives 5* Specific objectives and hypotheses <i>and whether they pertain to the individual level, the cluster level, or both</i>	3,4
Outcomes 6* Report clearly defined primary and secondary outcome measures, <i>whether they pertain to the individual level, the cluster level, or both</i> , and, when applicable, any methods used to enhance the quality of measurements (eg multiple observations, training of assessors)	3,4
Sample size 7* How <i>total</i> sample size was determined ( <i>including method of calculation, number of clusters, cluster size, a coefficient of intracluster correlation (ICC or k), and an indication of its uncertainty</i> ) and, when applicable, explanation of any interim analyses and stopping rules	6
Randomisation:	
Sequence generation 8* Method used to generate the random allocation sequence, including details of any restriction (eg blocking, stratification, <i>matching</i> )	5
Allocation concealment 9* Method used to implement the random allocation sequence, <i>specifying that allocation was based on clusters rather than individuals</i> and clarifying whether the sequence was concealed until interventions were assigned	5
Implementation 10 Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups	5
Blinding (masking) 11 Whether participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. If done, how the success of blinding was evaluated	5
Statistical methods 12* Statistical methods used to compare groups for primary outcome(s) <i>indicating how clustering was taken into account</i> ; methods for additional analyses, such as subgroup analyses and adjusted analyses	6
<b>Results</b>	
Participant flow 13* Flow of <i>clusters and</i> individual participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of <i>clusters and</i> participants randomly assigned, receiving intended treatment, completing the study protocol, and analysed for the primary outcome. Describe protocol deviations from study as planned, together with reasons	7, 13
Recruitment 14 Dates defining the periods of recruitment and follow up	7
Baseline data 15* Baseline information for each group <i>for the individual and cluster levels as applicable</i>	7,15

Numbers analysed 16* Number of <i>clusters and</i> participants (denominator) in each group included in each analysis and whether the analysis was by intention to treat. State the results in absolute numbers when feasible (eg 10/20 not 50%)	7,13, 16-19
Outcomes and estimation 17* For each primary and secondary outcome, a summary of results for each group <i>for the individual or cluster level as applicable</i> , and the estimated effect size and its precision (eg 95% confidence interval) <i>and a coefficient of intracluster correlation (ICC or k) for each primary outcome</i> .	7,8, 16-19
Ancillary analyses 18 Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those prespecified and those exploratory	3,4
Adverse events 19 All important adverse events or side effects in each intervention group	7,8
<b>Discussion</b>	
Interpretation 20 Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes.	8-10
Generalisability 21* Generalisability (external validity) <i>to individuals and/or clusters (as relevant)</i> of the trial findings	10
Overall evidence 22 General interpretation of the results in the context of current evidence	9-10

\*Addition to CONSORT guidelines 2001