Effect of vitamin A supplementation on cause-specific mortality in women of reproductive age in Ghana: a secondary analysis from the ObaapaVitA trial

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Objective To determine the effect of weekly low-dose vitamin A supplementation on cause-specific mortality in women of reproductive age in Ghana.

Methods A cluster-randomized, triple-blind, placebo-controlled trial was conducted in seven districts of the Brong Ahafo region of Ghana. Women aged 15–45 years who were capable of giving informed consent and intended to live in the trial area for at least 3 months were enrolled and randomly assigned, according to their cluster of residence, to receive oral vitamin A (7500 µg) or placebo once a week. Randomization was blocked, with two clusters in each fieldwork area allocated to vitamin A and two to placebo. Every 4 weeks, fieldworkers distributed capsules and collected data during home visits. Verbal autopsies were conducted by field supervisors and reviewed by physicians, who assigned a cause of death. Cause-specific mortality rates in both arms were compared by means of random-effects Poisson regression models to allow for the cluster randomization. Analysis was by intention-to-treat, based on cluster of residence, with women eligible for inclusion once they had consistently received the supplement or placebo capsules for 6 months.

Findings The analysis was based on 581 870 woman–years and 2624 deaths. Cause-specific mortality rates were found to be similar in the two study arms.

Conclusion Low-dose vitamin A supplements administered weekly are of no benefit in programmes to reduce mortality in women of childbearing age.

Abstracts in عربي, 中文, Français, Русский and Español at the end of each article.

Introduction

Vitamin A deficiency is an important problem in low- and middle-income countries.[1] Although in these countries all-cause mortality among young children (i.e. children aged from 6 months to 5 years) can be reduced by administering vitamin A supplements,[2] there is little evidence that such supplements are beneficial among adults. In a meta-analysis of trials in which adults were given antioxidant supplementation, supplements of vitamin A (alone or combined with other antioxidants) were found to have either no effect on all-cause mortality or to increase such mortality.[3] However, none of the data considered in the meta-analysis came from a low-income country.

Among women of reproductive age, repeated pregnancies and prolonged lactation can heighten the risk of vitamin A deficiency.[4] However, trials in which women have been given vitamin A supplements during pregnancy[5] and in the postpartum period[6] have shown no effect on mortality. Prior to the ObaapaVitA trial in Ghana,[7] the published data on the effect of vitamin A supplementation among all women of reproductive age came from a single trial in Nepal.[8] In the Nepalese study, which was known as the Nepal Nutrition Intervention Project Sarlahi-2 (NNIPS-2) trial, pregnancy-related mortality was found to be 40% (95% confidence interval, CI: 3–63) lower in the vitamin A arm than in the placebo arm.[8] Although cause-specific mortalities could not be examined in detail, there was little evidence that the beneficial effect of supplementation seen in Nepal was limited to obstetric causes of death or to pregnant women.[9] Mortality in the "miscellaneous" category (including deaths associated with anaemia and asthma), direct maternal mortality and infection-related mortality were, respectively, 86% lower (95% CI: 24% lower to 97% lower), 12% lower (95% CI: 58% lower to 81% higher) and 6% lower (95% CI: 58% lower to 105% higher) in the supplement arm than in the placebo arm. No data were presented on the effects of vitamin A supplementation on non-pregnancy-related mortality.

The main goal of the ObaapaVitA trial, which was set up in Ghana in 2000, was to evaluate the effect of weekly vitamin A supplementation in women of reproductive age on pregnancy-related mortality in an African setting, and to compare this with the effect on overall mortality.[7] In this paper, we present the results of a secondary analysis of the effect of weekly vitamin A supplementation on cause-specific mortality in the ObaapaVitA trial. This appears to be the first time that such data from a low-income country have been published. The secondary analysis reported here was specified

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(*Submitted: 24 November 2011 – Revised version received: 3 October 2012 – Accepted: 11 October 2012 – Published online: 31 October 2012*)

a priori in the ObaapaVitA analysis plan. It is important to determine the effects of vitamin A supplementation on all deaths in women of reproductive age because it is not clear whether the beneficial effect seen in the NNIPS-2 trial was "specific to maternal mortality or part of a reduction in all cause adult female mortality".[9] Although several plausible ways in which vitamin A supplementation may reduce mortality have been suggested (e.g. reductions in the severity of infections and anaemia[10]), few appear to be restricted to pregnant women or to women who have recently given birth. Vitamin A supplementation might therefore be expected to cause a reduction in non-pregnancy-related mortality similar to the reduction seen in pregnancy-related mortality. In addition to discussing this possibility, we present population-based data on the causes of more than 3000 deaths among the women in the trial; such data from Africa are rare and often limited by small, selective samples.[11]

Methods

The ObaapaVitA trial ran between December 2000 and October 2008 and was both cluster-randomized and placebo-controlled. The general methods employed in the trial have been published elsewhere[7] and the protocol is available online.[12] The analysis plan, which was approved by an ad hoc data monitoring and ethics committee before the interim analysis of the trial results in June 2006, included a description of a series of planned secondary analyses. These analyses were designed to complement the results of the main trial analyses and to aid in the interpretation of those results. They included an analysis of the effect of vitamin A supplementation on cause-specific adult female mortality (in which both individual causes of death and groupings of such causes were considered).

Participants

The ObaapaVitA trial was conducted in seven districts in the Brong Ahafo region of Ghana, where subsistence farming and small-scale trading are the main sources of income. Since 17% of the pregnant women previously investigated in the study area had < 0.70 μmol of retinol per litre of serum,[13] the study population was assumed to have moderate levels of vitamin A deficiency.[14]

All women aged 15–45 years who were capable of giving informed consent and intending to live in the study area for at least three months (including women who migrated into the trial area during the study period and girls in the study area who reached an age of 15 years during the same period) were eligible for enrolment in the trial. Fieldworkers visited all compounds in the study area and – using a standard information sheet and, if necessary, an interpreter – explained the trial's aims and methods to the householders. The women who were met by the fieldworkers during the visits were encouraged to ask questions. Informed consent, confirmed by signature or thumbprint, was obtained from each of the women who were recruited.

Randomization and masking

The trial area was divided into clusters of compounds. Each fieldworker was responsible for four contiguous clusters and visited the women in a different cluster every week, over a 4-weekly cycle. A study cluster consisted of all of the women living in the compounds visited by a fieldworker in a particular week. Randomization was blocked, with two of the clusters visited by each fieldworker allocated to vitamin A supplementation and two allocated to placebo. An independent statistician prepared a computer-generated randomization list. All staff members and participants were blind to treatment assignment throughout the trial.

Interventions

Women were randomly assigned, according to their cluster, to receive a vial containing either four vitamin A capsules or four placebo capsules every 4 weeks, with instructions to take one capsule each week. Adherence was supported by an information, education and communication programme, based on formative research before the trial.[15] Each vitamin A capsule contained 25 000 IU of retinol (7500 μg or retinol equivalents) in soybean oil in a dark red opaque soft gel; this dose delivered the recommended dietary allowance and was safe during pregnancy.[14] The placebo capsules only contained soybean oil but looked and tasted identical to the vitamin A capsules. Capsule distribution, which was phased by district, began between December 2000 and January 2003 and ended in September 2008. Data collection ended four weeks after the last capsule had been distributed.

Data collection

Data on pregnancies, births, deaths, migrations, hospital admissions, morbidity, sociodemographic characteristics and number of capsules taken were collected by the fieldworkers during the 4-weekly home visits. Each week, adherence was also assessed in detail (including observation of capsule vials) among a random sample of 10 women from each of four different clusters. For this, the four clusters were selected so that there was one cluster each from among those where each study subject should have had three, two, one and no capsules remaining in her vial. A sub-study, consisting of a random sample of 440 pregnant women and 440 non-pregnant women, was conducted in September 2008 to assess the vitamin A status of the trial population (by measuring the serum retinol concentrations of the women in the placebo arm) and to compare the serum retinol concentrations of the women in the vitamin A and placebo arms.

Adult female deaths were identified during the 4-weekly surveillance. Verbal autopsies were then conducted, by trained field supervisors, in interviews with close relatives and/or friends of the dead women. The autopsy data were collected using a questionnaire that was based on a validated instrument for adult deaths[16] and an instrument for maternal deaths developed for a previous study.[17] Two physicians independently reviewed the data and assigned a cause and up to two associated conditions for each recorded death, using standard methods of coding.[18] The physicians did not discuss the cases or the causes they had assigned at this stage. The cause of death was accepted if both physicians agreed. If the physicians did not agree, the data were reviewed by a third physician (who remained blind to the causes assigned by the previous physicians). If two of the three physicians who had then reviewed the case gave the same cause of death, that cause was accepted as accurate. If all three physicians disagreed, they were asked to discuss the case and either decide on a cause together or, if unable to reach consensus, to record the cause of death as "uncertain".

Outcomes

All deaths among the trial participants were classified as pregnancy-related (i.e. as having occurred during pregnancy or within 42 days of the end of pregnancy, irrespective of the cause)[19] or non-pregnancy-related. Data on the causes of pregnancy-related deaths will be presented elsewhere. Non-pregnancy-related deaths were grouped by cause according to the headings of the 10th revision of the International Classification of Diseases (ICD-10).[19] A "signs and symptoms not classified elsewhere" category was included to allow some information on cases of acute abdomen, instantaneous death, death within 24 hours of symptom onset, or unattended deaths to be presented. Deaths whose cause was uncertain (with no cause identified during the coding process) or unknown (with no respondent identified for the verbal autopsy) were pooled, since the number of deaths with unknown cause was low. Data on infection- and anaemia-associated deaths were analysed in detail because previous research has suggested that vitamin A can protect against such deaths. As in previous studies,[20,21] deaths initially coded as being from "fever of unknown origin" were re-classified as having been caused by malaria because malaria is endemic in the study area.

Sample size

The sample size for the trial allowed for the detection of a 33% reduction in pregnancy-related mortality in the vitamin A arm with 90% power, a 5% significance level and a 10% design effect. The sample size also gave adequate power for the detection of a similar reduction in any specific cause of death that was at least as frequent as pregnancy-related deaths.

Statistical methods

Stata version 10 (StataCorp. LP, College Station, United States of America) and random-effects Poisson regression models (to account for the cluster-randomized design) were used to compare the age- and cause-specific mortality rates (in deaths per 100 000 woman–years of follow-up) recorded in the vitamin A and placebo arms. If a woman moved out of the trial area, data collected before that woman's migration were included in the analysis, with the woman's person–time censored on the date on which she was last seen.

All trial analyses were by intention to treat, based on cluster of residence. When women moved from one cluster to another during the trial, they received the same capsules as other women in their new cluster and so might change treatment arm. Four periods relating to these changes ("run in", "carry over", "lag" and "washout") were defined a priori; full definitions are given in the trial protocol. Briefly, for the primary analysis, the first 6 months following recruitment were excluded to allow the full impact of vitamin A supplementation to become apparent (lag). When women changed treatment group, they continued to be included in their former group for 2 months because vitamin A supplementation was likely to have little or no effect in this period (run in) or because the effect of such supplementation would be reduced only marginally (carry over). The following 4-month period was excluded, with the women contributing person–time again only 6 months after they had moved, to allow for a lag period or for the effect of vitamin A supplementation to abate (washout). Although biochemical data to define them do not exist, these periods were selected a priori in consultation with the members of the trial's data monitoring and ethics committee, on the basis of advice from experts. A "pure" intention-to-treat analysis, in which women were excluded from the time when they changed treatment arm, was also performed.

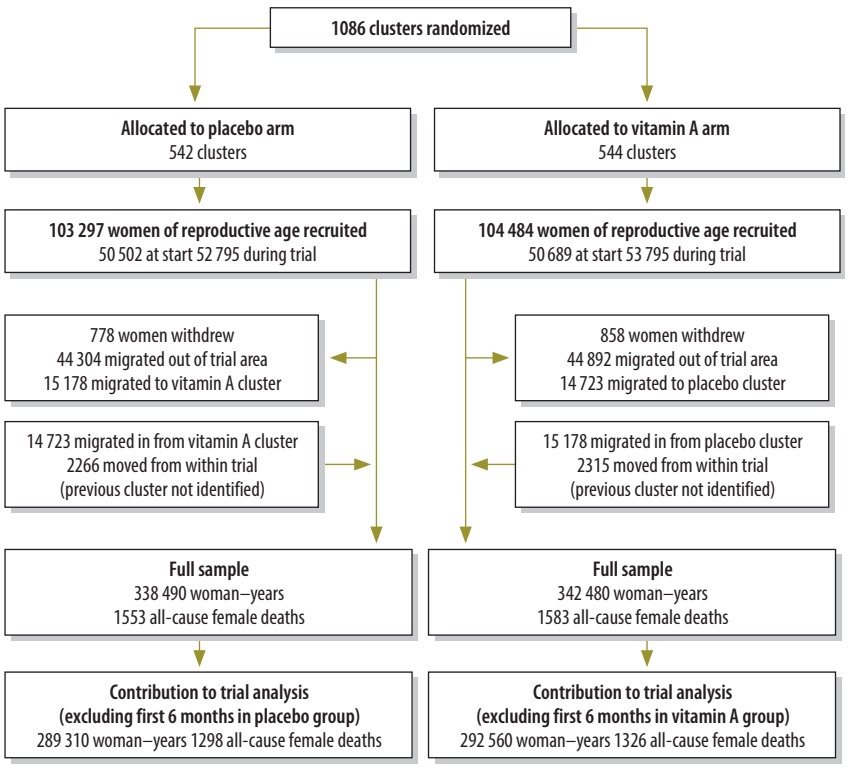
Ethics and trial monitoring

The trial was approved by the ethics committees of the Ghana Health Service and the London School of Hygiene and Tropical Medicine. Conduct was overseen by a trial steering committee and by the members of the trial's data monitoring and ethics committee, which undertook yearly blinded safety analyses and a full interim analysis in June 2006. The trial is registered with ClinicalTrials.gov as trial NCT00211341.

Results

The trial profile is shown in Fig. 1. Overall, 1086 clusters (544 allocated

Fig. 1. **Flowchart showing the numbers of women recruited, withdrawing, migrating and included in the final analyses of data, ObaapaVitA trial, Ghana, 2000–2008**



to the vitamin A arm and 542 to the placebo arm) in 272 fieldwork areas were randomized. Recruitment, withdrawals and migration patterns were similar in the two arms (Fig. 1), as were the sociodemographic characteristics that were investigated.[7] The 207 781 women who were recruited contributed 680 970 woman–years of follow-up and 3136 deaths. Although migration in and out of the study area was high, each woman enrolled was followed up for a mean of 3.3 years. The characteristics of the many women who migrated within the study area were similar to those of the women who migrated out of the study area (data not shown).

Adherence to capsule intake was high: 78.8% of the women given capsules took the expected number. In the placebo arm, 20 (15.4%) of the 217 pregnant women investigated and 18 (9.6%) of the 215 non-pregnant women investigated had < 0.70 µmol of retinol per litre of serum, confirming that the study population had moderate levels of vitamin A deficiency. Among the women in the vitamin A arm, the mean serum retinol concentration and prevalence of serum retinol levels of < 0.70 µmol per litre were similar to those recorded among the women in the placebo arm.[7]

Intention-to-treat analyses were based on 581 870 woman–years and 2624 deaths (Fig. 1). Mortality rates from specific causes were similar in the two arms (Table 1). For example, infection-attributed mortality in the vitamin A arm was 1.04-fold (95% CI: 0.92-fold to 1.18-fold) higher than in the placebo arm. Rates of death from uncertain or unknown cause did not differ significantly between the two arms either (Table 1). Nor were any significant between-arm differences recorded in the rates of death attributed to specific infections or anaemia (Table 2). Similar observations were made in the "pure" intention-to-treat analysis and in analyses using lag periods of 9 and 12 months (data not shown).

The all-cause mortality rate in the trial population was 461 deaths per 100 000 woman–years (Table 3). The causes of death in the whole sample (3136 deaths) were similar to those in the intention-to-treat sample (2624 deaths) (data not shown). More than one in every two deaths occurred at home and only one fifth of the women who died had been in hospital for more than 2 days in the 12 months before their death.

The cause of death was uncertain (no cause identified during coding; $n = 668$) or unknown (no respondent identified; $n = 60$) for 728 (23%) of the 3136 deaths recorded (Table 4). There were 375 pregnancy-related deaths (representing 16% of deaths once deaths with uncertain or unknown cause were excluded). The commonest causes of non-pregnancy-related deaths were infections (51%), particularly infection with human immunodeficiency virus (27%). About one in every four deaths was attributed to a non-infectious disease, most frequently circulatory (8% of deaths). Another 5% of deaths were injury-related and 3% were associated with "signs and symptoms not classified elsewhere".

Mortality rates increased with age (Table 5). Rates of pregnancy-related mortality were highest in women aged 25–29 years (because most pregnancies occurred in this age group). The youngest and oldest age groups suffered the highest numbers of deaths per 100 000 pregnancies. Although mortality from most other causes tended to increase with age, mortality rates for several causes were lowest in women aged 20–24 years.

Table 1. **Vitamin A supplementation and cause-specific mortality among women, Ghana, 2000–2008**

Cause	No. of deaths		RR (95% CI)[a]
	Placebo	Vitamin A	
All deaths	1298	1326	1.01 (0.93–1.09)
Pregnancy-related[b]	148	138	0.92 (0.73–1.16)
Non-pregnancy-related	1150	1188	1.02 (0.93–1.11)
Deaths caused by:			
All infections	512	540	1.04 (0.92–1.18)
Neoplasms	52	45	0.86 (0.57–1.28)
Disorders of blood and blood-forming organs	44	61	1.37 (0.93–2.02)
Endocrine, nutritional and metabolic diseases	15	15	0.99 (0.49–2.00)
Neuropsychiatric conditions	7	11	1.55 (0.60–4.01)
Circulatory diseases	81	75	0.92 (0.66–1.26)
Respiratory diseases	6	6	0.99 (0.32–3.05)
Digestive diseases	28	29	1.03 (0.60–1.76)
Genitourinary diseases	23	21	0.90 (0.50–1.63)
Other known cause	2	5	2.48 (0.48–12.80)
Signs and symptoms not classified elsewhere[c]	39	35	0.89 (0.56–1.40)
Injuries	55	43	0.77 (0.51–1.17)
Uncertain or unknown cause	286	302	1.04 (0.88–1.23)

CI, confidence interval; RR, rate ratio.
[a] Calculated, as the mortality rate in the vitamin A arm divided by that in the placebo arm, after adjusting for clustering by use of random-effects models. The data come from an intention-to-treat analysis.
[b] All deaths during pregnancy, labour or delivery or within 42 days of pregnancy, regardless of cause
[c] Includes deaths associated with an acute abdomen, instantaneous deaths, deaths within 24 hours of symptom onset and unattended deaths.

Discussion

The ObaapaVitA trial was large and adherence to the supplements was good.[7] The results indicate that low-dose weekly vitamin A supplementation has no effect on cause-specific mortality in women of reproductive age in rural Ghana. Most notably, there was no reduction in deaths from those causes against which vitamin A may have a plausible effect, such as infections. Given that the study population is deficient in vitamin A[13] and has a high burden of infections,[21] this apparent lack of benefit was unexpected, especially as vitamin A supplementation in children between the ages of 6 months and 5 years in similar populations has reduced all-cause mortality and mortality from diarrhoeal diseases.[2]

The trial had adequate power to examine the effect of vitamin A supplementation on pregnancy-related deaths. It also had adequate power to examine the effect of such supplementation on rates of infection, as these were more common, among

Table 2. **Vitamin A supplementation and mortality among women caused by specific infections or anaemia, Ghana, 2000–2008**

Cause	No. of deaths		RR (95% CI)[a]
	Placebo arm	Vitamin A arm	
Infection			
Malaria	21	24	1.13 (0.63–2.03)
Tuberculosis	51	63	1.22 (0.84–1.78)
Other respiratory infection	14	18	1.27 (0.63–2.57)
HIV/AIDS	258	276	1.06 (0.88–1.26)
Intestinal infection	59	48	0.80 (0.54–1.19)
Meningitis	45	38	0.84 (0.54–1.29)
Other infection[b]	64	73	1·13 (0·81–1·58)
Anaemia			
Haemolytic	15	25	1.65 (0.87–3.13)
Other	29	36	1.23 (0.76–1.99)

CI, confidence interval; HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome; RR, rate ratio.

[a] Calculated, as the mortality rate in the vitamin A arm divided by that in the placebo arm, after adjusting for clustering by use of random-effects models. The data come from an intention-to-treat analysis.

[b] Includes hepatitis, abscess, cellulitis, rabies, tetanus, chicken pox, and septicaemia/infection of unknown etiology.

Table 3. **Descriptive data on follow-up and deaths among the women enrolled in the ObaapaVitA, Ghana, 2000–2008**

Parameter	Value[a]
Number of women	207 781
Person–years of follow-up	680 970
Number of deaths	3136
All-cause mortality rate (deaths per 100 000 person–years)	461
Number and percentage of deaths occurring:	
At home	1733 (55)
In a heath facility	1136 (36)
On the way to a health facility	62 (2)
At another known location[b]	114 (4)
At an unknown location	91 (3)
After hospitalization for:	
> 2 days in previous 12 months	660 (21)
0–2 days in previous 12 months	2362 (75)
Unknown period	114 (4)
In rainy season (April–September)	1594 (51)
In dry season (October–March)	1542 (49)

[a] For full sample, before applying the exclusion criteria for the intention-to-treat analysis.

[b] At the home of a traditional birth attendant, traditional healer or spiritual healer.

the causes of death, than pregnancy-related deaths. Although it is difficult to draw firm conclusions on the effects of vitamin A supplementation on the less common causes of death, the relevant data have been included in this article because very little data have been published on the cause-specific effects of vitamin A supplementation in women of reproductive age. Our results are consistent with those of the NNIPS-2 trial in Nepal, in which vitamin A supplementation was also found to have no significant effect on rates of death resulting from infection or non-communicable diseases.[8] The Nepalese study was, however, focused on pregnancy-related deaths.[8]

Although verbal autopsies are known to have limitations,[22] they remain an important tool for assessing causes of death in populations where the complete and accurate registration of causes of death is not possible.[23] The cause of death may have been misclassified for some cases in this trial, but the frequency and type of such inaccuracy are likely to have been similar in the two arms. The potential misclassification cannot explain why, for many causes of death, vitamin A supplementation was associated with a marginally higher mortality rate than that recorded in the placebo arm.

Verbal autopsies could not be conducted for just 60 of the women who died during the trial. Cause could not be ascertained for another 668 deaths, but such failures to determine cause of death are not uncommon when only verbal autopsies are conducted. In another study based on verbal autopsies, no cause could be identified for > 20% of the deaths recorded in six of 12 demographic surveillance sites.[20] In the present trial, it is possible that vitamin A supplementation did significantly reduce rates of death attributable to a specific cause but that this trend was masked by the inclusion of such deaths among the "deaths with unknown cause". However, we do not think that this is likely. All staff collecting data and coding the results of the verbal autopsies were blinded to treatment allocation, as were the study subjects. Hence, the lack of an identified cause probably reflects the limitations of the questionnaire used to collect the autopsy data[22] rather than a differential bias in coding between the two treatment arms. This is supported by the fact that the rates of death from unknown cause were similar in the two arms.

The mortality patterns observed in the ObaapaVitA trial were broadly consistent with those described in the Global Burden of Disease (GBD) study.[24] The percentages of deaths attributed to neuropsychiatric, digestive and genitourinary causes and injuries were similar in the trial and the GBD study. However, differences were noted, in the specific percentages of deaths by cause, between the "Africa D" region defined in the GBD study (i.e. a region comprising 26 countries with generally similar mortality rates, including Ghana) and the population investigated in the ObaapaVitA trial, in Ghana. In the trial, for example, mortality from maternal conditions, neoplasms and endocrine, nutritional, metabolic, circulatory and respiratory diseases was relatively low, whereas mortality from some other causes, such as infectious diseases and blood disorders, was relatively high. These differences may be real, both because of differences in the methods

Table 4. **Causes of death among the women enrolled in the ObaapaVitA trial, Ghana, 2000–2008**

Cause or type of death	No. of deaths	Percentage of all deaths ($n = 3136$)	Percentage of all deaths with known and certain cause ($n = 2408$)
Pregnancy-related:	375	12	16
Direct maternal deaths	202	6	8
Infectious disease:	1240	40	51
Malaria	54	2	2
Tuberculosis	125	4	5
Other respiratory infections	37	1	1
HIV/AIDS	647	21	27
Intestinal infection	125	4	5
Meningitis	92	3	4
Other infection[a]	160	5	7
Neoplasm	107	3	4
Disorders of blood and blood-forming organs	114	4	5
Endocrine, nutritional and metabolic diseases	35	1	1
Neuropsychiatric conditions	21	1	1
Circulatory diseases	183	6	8
Respiratory diseases	12	< 1	< 1
Digestive diseases	66	2	3
Genitourinary diseases	48	2	2
Injuries and external causes	113	4	5
Other diseases	10	< 1	< 1
Signs and symptoms not classified elsewhere:	84	3	3
Acute abdomen	21	< 1	< 1
Instantaneous death	15	< 1	< 1
Death within 24 h of symptom onset	37	1	1
Unattended death	14	< 1	< 1
Uncertain or unknown[b]	728	23	–

AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.
[a] Includes hepatitis, abscess, cellulitis, rabies, tetanus, chicken pox and septicaemia/infection of unknown etiology.
[b] Includes 668 deaths for which a cause could not be identified by using the information collected in the verbal autopsy and 60 deaths for which respondents for the verbal autopsies could not be identified.

Table 5. **Age-specific all-cause and cause-specific mortality rates among women enrolled in the ObaapaVitA trial, Ghana, 2000–2008**

Parameter	Age (years)				
	< 20	20–24	25–29	30–34	≥ 35
Person–years of follow-up	108 989	144 522	132 363	108 226	186 870
Deaths,[a] by cause:[b]					
All causes	315	306	483	572	585
Pregnancy-related	49	57	73	67	37
Infectious diseases	99	110	230	265	234
Neoplasms	3	10	10	18	33
Circulatory diseases	19	9	19	35	49
Injuries	16	12	19	20	21
Other known causes	50	44	51	56	77
Uncertain or unknown cause	86	73	100	122	141
Pregnancy-related deaths[c]	422	293	339	402	549

[a] Per 100 000 person–years.
[b] As a consequence of rounding, the rates of cause-specific mortality do not exactly equal the corresponding all-cause mortality rate when they are added together.
[c] Per 100 000 pregnancies.

used in the two studies and because of marked differences in cause-specific mortality rates between some of the countries that were grouped together to give the Africa D region (for example, the maternal mortality ratio – i.e. the number of maternal deaths per 100 000 live births – is estimated to be 970 in Sierra Leone but only 350 in Ghana).[25] The women enrolled in the ObaapaVitA trial differed slightly in age from the women considered in the GBD study. Furthermore, the causes of some deaths in the ObaapaVitA trial were simply categorized as "signs and symptoms not classified elsewhere", whereas the corresponding deaths recorded in the GBD study were reassigned to specific causes.[26] The mortality rates given in reports on the GBD study are also simulated estimates based on several data sources (including censuses and surveys), whereas those reported here for the ObaapaVitA trial are based on data that were collected regularly and directly from the study population.

Despite the intensive approach to supplementation in the present trial (with home visits every 4 weeks and an ongoing information, education and communication campaign), the serum retinol concentrations of the women in the vitamin A arm who were tested were found to be very similar to those of the women in the placebo arm who were tested. This lack of effect was observed even though the women tested had been in the trial for a mean of 4.5 years when sampled and had an estimated compliance of > 90%.[7] It therefore appears that the dose of vitamin A used in the trial, which was selected to deliver the recommended dietary allowance while also being safe during pregnancy, was not sufficient to improve serum retinol levels in the trial area.

In conclusion, low-dose vitamin A supplementation appears to have no beneficial effect on cause-specific mortality in women of reproductive age in rural Ghana. The data from the ObaapaVitA trial add to the body of evidence indicating that, in programmes that aim to reduce mortality, weekly, low-dose vitamin A supplementation for women has no useful role. Little is known about the effects of vitamin A supplementation on morbidity in adults; this is an area for further exploration because, although vitamin A supplementation had no apparent effect on deaths from those causes most likely to be affected by vitamin A, it remains

possible that vitamin A reduces the morbidity resulting from the same conditions. ■

Acknowledgements

We acknowledge the support of the chiefs, elders and opinion leaders in the study area, and the substantial contribution of all the women who participated in the trial. We thank Angela Vega, for administrative support, all staff at the Kintampo Health Research Centre who were involved in the trial, and the trial steering and data monitoring and ethics committees, for their continuing support and guidance. We also thank the physicians who coordinated and undertook the coding of the verbal autopsies, for their much-valued contribution.

Funding: This report is an output from a project funded by the United Kingdom's 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 the United States Agency for International Development. Vitamin A palmitate for the capsules was kindly donated by Roche.

Competing interests: None declared.

ملخص

تأثير مكملات فيتامين أ على الوفيات محددة السبب لدى النساء في سن الإنجاب في غانا: تحليل ثانوي من تجربة ObaapaVitA

الغرض تحديد تأثير جرعة منخفضة أسبوعية من مكملات فيتامين أ على الوفيات محددة السبب لدى النساء في سن الإنجاب في غانا.

الطريقة تم إجراء تجربة عنقودية عشوائية، ثلاثية التعمية، خاضعة لتلقي دواء غفل في سبع مناطق في إقليم برونغ أهافو بغانا. وتم تسجيل النساء اللاتي تتراوح أعمارهن بين 15 و45 عاماً واللاتي كن قادرات على تقديم موافقة مستنيرة وكانت لديهن النية على العيش في منطقة التجربة لمدة 3 أشهر على الأقل وتعيينهن بشكل عشوائي، وفقاً لمجموعة إقامتهن، لتلقي فيتامين أ عن طريق الفم (7500 ميكروغرام) أو دواء غفل مرة واحدة في الأسبوع. وتم حجب العشوائية، مع تعيين مجموعتين في كل منطقة عمل ميداني لفيتامين أ، واثنتين للدواء الغفل. وقام العمال الميدانيون، كل 4 أسابيع، بتوزيع كبسولات وجمع البيانات أثناء الزيارات المنزلية. وتم إجراء عمليات التشريح اللفظي بواسطة المشرفين الميدانيين ومراجعتها بواسطة الأطباء، الذين حددوا سبب الوفاة. وتم إجراء مقارنة لمعدلات الوفيات محددة السبب في كلا الطرفين عن طريق نماذج انحدار بواسون ذات الآثار العشوائية للسماح بالعشوائية العنقودية. وكان التحليل بقصد العلاج، استناداً إلى مجموعة الإقامة، مع النساء المؤهلات للإدراج بمجرد حصولهن باستمرار على كبسولات المكمل أو الدواء الغفل لمدة 6 أشهر.

النتائج استند التحليل على 581870 امرأة-سنة و2624 حالة وفاة. وتم التوصل إلى أن معدلات الوفيات محددة السبب متماثلة في طرفي الدراسة.

الاستنتاج الجرعة المنخفضة من فيتامين أ التي يتم تعاطيها أسبوعياً غير مفيدة في برامج الحد من الوفيات لدى النساء في سن الإنجاب.

摘要

对加纳育龄妇女死因别死亡率的影响：ObaapaVitA 试验的二次分析

目的 确定低剂量每周一次补充维生素A对加纳育龄妇女特因死亡率的影响。

方法 在加纳布朗阿哈福地区的七个区进行整群随机、三盲的安慰剂对照试验。招募能够给予知情同意并有意愿在受试地区生活至少3个月的15–45岁妇女，按照其居住地的整群将其随机分组，接受每周一次的口服维生素A（7500 μg）或安慰剂。采用区组随机化方法，安排每个现场调查地区的两个整群口服维生素A，两个整群口服安慰剂。现场调查人员在每4周一次的家庭访视过程中分发胶囊并收集数据。口头尸检由现场监督员进行，由医生进行审核并给出死亡原因。两个组的特因死亡率通过随机效应泊松回归模型进行比较，以实现整群随机化。使用意向性分析方法，以居住地整群为基础，妇女连续接受补充剂或安慰剂胶囊6个月即符合纳入条件。

结果 分析基于581870 妇女人年和2624 例死亡进行。发现两个研究组的特因死亡率相似。

结论 每周控制低剂量补充维生素A的方法在降低育龄妇女死亡率的计划中没有益处。

Résumé

Effet de la supplémentation en vitamine A sur la mortalité relative chez les femmes en âge de procréer au Ghana: une analyse secondaire de l'étude ObaapaVitA

Objectif Déterminer l'effet de la supplémentation hebdomadaire en vitamine A à faible dose sur la mortalité spécifique des femmes en âge de procréer au Ghana.

Méthodes Une étude randomisée, en triple aveugle, contrôlée contre placebo, a été menée dans sept districts de la région de Brong Ahafo au Ghana. Les femmes âgées de 15 à 45 ans, capables de donner un consentement éclairé et amenées à vivre dans la région de l'étude pendant au moins 3 mois, ont été incluses et il a été déterminé qu'elles recevraient une fois par semaine, au hasard selon leur groupe de résidence, de la vitamine A par voie orale (7 500 µg) ou un placebo. La randomisation a été fixée par deux groupes dans chaque zone recevant la vitamine A et deux groupes recevant le placebo. Toutes les 4 semaines, les agents de terrain distribuaient les capsules et recueillaient les données lors de visites à domicile. Des autopsies orales ont été effectuées par les superviseurs sur le terrain et analysées par des médecins, qui déterminaient la cause du décès. Les taux de mortalité spécifique dans les deux groupes ont été comparés à l'aide d'une régression de Poisson pour valider la randomisation des

groupes. L'analyse, basée sur l'intention de traiter, était basée sur le groupe de résidence, pour des femmes éligibles à l'étude ayant reçu les capsules de supplément ou de placebo de manière constante pendant 6 mois.

Résultats L'analyse s'est basée sur 581 870 années-femmes et 2624 décès. Les taux de mortalité spécifique ont été jugés similaires dans les deux groupes de l'étude.

Conclusion Les suppléments en vitamine A à faible dose administrés hebdomadairement ne sont d'aucune utilité dans les programmes visant à réduire la mortalité chez les femmes en âge de procréer.

Резюме

Влияние добавок витамина А на смертность, вызванную конкретной причиной, у женщин репродуктивного возраста Ганы: вторичный анализ исследования ObaapaVitA

Цель Определить влияние еженедельной низкодозированной добавки витамина А на смертность, вызванную конкретной причиной, у женщин репродуктивного возраста Ганы.

Методы Было проведено кластерное рандомизированное, тройное слепое, контролируемое плацебо исследование в семи районах региона Бронг Ахафо, расположенного в Гане. В исследование были зачислены и распределены в произвольном порядке согласно своему местожительству для перорального приема раз в неделю витамина А (7500 мкг.) или плацебо женщины в возрасте от 15 до 45 лет, способные дать осознанное согласие и намеревавшиеся проживать в опытной зоне не менее 3-х месяцев. Рандомизация являлась блочной при назначении приема витамина А и плацебо в двух группах в каждой зоне исследования. Каждые 4 недели исследователи распределяли капсулы и производили сбор данных во время домашнего обхода. Опросы об обстоятельствах смерти проводились руководителями исследования и рассматривались врачами, определявшими причину смерти. Показатели смертности, вызванной конкретной причиной, в обоих группах сопоставлялись с помощью моделей регрессии Пуассона случайного воздействия для проведения кластерной рандомизации. Анализ проводился по принципу исходно назначенного лечения, с учетом местожительства, с участием женщин, допущенных к включению в исследование, при условии постоянного приема капсул с добавкой или плацебо в течении 6 месяцев.

Результаты Анализ проводился на основе данных по 2624 смертям и 581 870 пациенто-годам. Было установлено, что показатели смертности, вызванной конкретной причиной, являются схожими в двух исследуемых группах.

Вывод Добавки витамина А, назначаемые еженедельно, не оказывают благоприятного влияния по программам сокращения смертности среди женщин репродуктивного возраста.

Resumen

El efecto de los suplementos de vitamina A en la mortalidad por causas específicas de mujeres en edad reproductiva en Ghana: un análisis secundario del ensayo Obaapa VITA

Objetivo Determinar el efecto de la administración semanal de dosis bajas de vitamina A en la mortalidad por causas específicas de mujeres en edad reproductiva en Ghana.

Métodos Se realizó un ensayo aleatorio de grupos, triple ciego y controlado por placebo en siete distritos de la región de Brong Ahafo, en Ghana. Se inscribieron mujeres de entre 15 y 45 años de edad capaces de dar su consentimiento informado y que tuvieran previsto vivir en el área de ensayo durante al menos tres meses. De acuerdo con el grupo de residencia al que habían sido asignadas de forma aleatoria, recibieron semanalmente vitamina A por vía oral (7500 µg) o placebo. La distribución aleatoria se limitó en cada área de trabajo a dos grupos a los que se les administró vitamina A y dos grupos que recibieron placebo. Cada cuatro semanas, los investigadores de campo distribuyeron cápsulas y recogieron datos durante las visitas a los hogares. Las autopsias verbales realizadas por los supervisores de campo fueron revisadas por médicos, quienes determinaron la causa de la muerte. Se compararon las tasas de mortalidad por causas específicas de ambos brazos mediante los modelos de regresión de Poisson con efectos aleatorios para facilitar la distribución aleatoria de los grupos. El análisis fue por intención de tratar, según el grupo de residencia y con mujeres que cumplieron las condiciones de inclusión una vez habían recibido de forma constante las cápsulas de suplemento o placebo durante seis meses.

Resultados El análisis se basó en 581 870 años-mujer y 2624 muertes. Se descubrió que las tasas de mortalidad por causas específicas fueron similares en ambos brazos del estudio.

Conclusión Los suplementos de dosis bajas de vitamina A administrados semanalmente no presentan ninguna ventaja en los programas para reducir la mortalidad de las mujeres en edad reproductiva.

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