REPORT OF THE WHO
TECHNICAL CONSULTATION ON
NEONATAL VITAMIN A
SUPPLEMENTATION RESEARCH
PRIORITIES

GENEVA, SWITZERLAND, 4-5 DECEMBER 2008
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Participants of the WHO Technical Consultation on Neonatal Vitamin A Supplementation Research Priorities reported the following:

Emily Wainwright reported being employed by an organization (USAID) that provided financial support to some of the research trials presented during the meeting.

Professor Keith P West Jr reported receiving a DSM, Ltd scholarship in micronutrient deficiency prevention that is awarded to one student each year in the Program for Human Nutrition at Johns Hopkins School of Public Health, where he is affiliated.

The other participants declared they had no conflicts of interest.
Vitamin A supplementation has been promoted as an essential child survival intervention for children 6-59 months of age. Studies that evaluated the effects of vitamin A supplementation in the 1-5 month period did not show any child survival benefits. Recently, there has been considerable interest in vitamin A supplementation during the neonatal period (0-28 days) with three trials, conducted in Indonesia, India, and Bangladesh, showing a reduction in mortality during infancy ranging from 15-64%. However, three other trials conducted in Nepal, Zimbabwe and Guinea-Bissau have shown no effect of this intervention on infant mortality, regardless of when vitamin A was given in the neonatal period.

In order to better understand these apparently contradictory results, a systematic review of randomized controlled trials (RCT) was commissioned by the World Health Organization’s (WHO) Department of Child and Adolescent Health and Development (WHO/CAH) and Department of Nutrition for Health and Development (WHO/NHD) to evaluate the effects of neonatal vitamin A supplementation on infant mortality, morbidity and adverse effects. The authors of this systematic review concluded that vitamin A supplementation during the neonatal period (0-28 days) was not associated with a reduced risk of infant mortality and morbidity and identified several issues that needed further research. WHO (CAH and NHD Departments) jointly with UNICEF (Nutrition Section) convened a Technical Consultation to discuss the WHO-commissioned systematic review and identify priorities for future research on neonatal vitamin A supplementation.

### Objectives of the meeting

i. To review the findings of the WHO-commissioned systematic review.

ii. To identify and discuss research gaps in the use of vitamin A supplements for neonates.

iii. To prioritize the research needs.

### Expected outputs of the meeting

i. List of research priorities for neonatal vitamin A supplementation.

ii. Recommendations for appropriate study design and methodology for the identified research priorities.

iii. Identification of potential academic and research institutions to implement priority research studies.
2. Neonatal Vitamin A Supplementation for the Prevention of Mortality and Morbidity in Infancy: Systematic Review of Randomized Controlled Trials (RCT) (Presented by HPS Sachdev)

The systematic review was commissioned by WHO’s Departments of Child and Adolescent Health and Development, and Nutrition for Health and Development, and conducted by Dr Siddhartha Gogia and Dr HPS Sachdev. The authors declared that they have no conflicts of interest. The authors alone are responsible for the views and conclusions expressed in this review which do not necessarily represent the decisions or policies of WHO.

The objectives of the systematic review were to evaluate the effect of prophylactic, synthetic vitamin A supplementation initiated in the neonatal period (< 1 month of age) on mortality and morbidity during infancy, and assess early adverse effects of this intervention. Randomized or quasi-randomized placebo-controlled trials, with randomization at the individual or cluster level, were eligible for inclusion. Trials conducted only on selected subgroups of neonates, such as those who were of very low birth weight (<1500 grams), HIV-positive, born to known HIV-positive mothers, or sick or hospitalized, were excluded. The comparison group was that in which placebo was administered to the neonate and either placebo or no supplementation was given to the mother during pregnancy or the postpartum period. The primary outcome measures were all-cause mortality during the period between initiation of the intervention and the last follow-up within the age of one year, and all-cause mortality during the neonatal period. Secondary outcome measures included cause-specific mortality, presence of diarrhoea; acute respiratory infection or respiratory difficulty; cough or running nose; fever and vomiting; clinic visits or hospitalizations in the period between initiation of intervention and the last follow-up within the age of one year; and early adverse effects including bulging fontanel; vomiting; irritability; diarrhoea; or fever within one week after receiving the intervention.

A search strategy included computerized bibliographic medical databases and clinical trials websites until July 2008 with no language restrictions. Subgroup analyses were performed only for the primary outcome on pre-specified characteristics. For computing the summary relative risk (RR), individual study RR and 95% confidence interval (CI) or standard error (SE) for intention to treat analysis was used if stated by authors, or was computed from the data in the publication, when available. For cluster-randomized trials, the stated cluster adjusted RR and 95% CI were used, irrespective of the method employed. In factorial trials and in multi-arm designs having two or more vitamin A intervention groups, the data in the intervention groups were pooled and compared against the single control group to prevent unit-of-analysis error. Pooled estimates were computed using both fixed effects and random effects model assumptions and the contribution of baseline characteristics to heterogeneity was explored by meta-regression.
Of the 72 references identified through the search strategy, 11 references corresponding to six trials were included (six trials provided mortality data, three trials had relevant morbidity data, and six trials provided adverse effects data). There was no evidence of publication bias (Egger’s method, P for bias=0.931). Data from six trials involving 42,508 infants suggest that there is no evidence of a reduced risk of mortality due to any cause during the first year of life in infants who were supplemented with vitamin A during the neonatal period in comparison to those who received placebo; pooled RR 0.92 (95% CI 0.75 to 1.12, P=0.393; I²=54.1%, P=0.053) by random effects model (Figure 1). The pre-specified sensitivity, subgroup, and meta-regression analyses for RR of all-cause mortality during infancy did not identify a consistent significant predictor of mortality during infancy. A stratified analysis of the limited data (three trials) suggests a greater reduction in infant mortality in infants from mothers who had reported night blindness most frequently (mothers with a reported prevalence of 5% or more versus those with less than 5% prevalence of night blindness).

Combined results from the three trials that had information on neonatal mortality (Indonesia, Guinea-Bissau and Bangladesh) suggest that neonates who received the vitamin A supplements were as likely to die during the neonatal period as those who received placebo (pooled RR for neonatal mortality 0.90, 95% CI 0.75 to 1.08). There was no evidence of an increased risk of early adverse effects, including bulging fontanel. The limited data available did not indicate a reduced risk of cause-specific mortality, morbidities (diarrhoea and others), and hospitalization; however, they do suggest an increased risk of acute respiratory infection and a reduced risk of clinic visits.

Some limitations of this review merit consideration. For example, all trials were conducted in developing countries and there were limited data on some high-risk groups (prevalence of maternal night blindness ≥5% and low-birth-weight infants). Also, follow-up duration was variable in the included studies, which precluded constitution of a uniform measure to explore baseline mortality as a predictor. Finally, multiple subgroup and meta-regression analyses were performed, with the possibility of false positive results.
Sensitivity analysis performed by altering the methodological decisions showed that the results related to the primary outcome were stable, e.g. changing the comparison group to the infants that received placebo irrespective of maternal supplementation status (RR 0.89; 95% CI 0.76 to 1.06); changing the outcome to mortality within the first six months (RR 0.91; 95% CI 0.76 to 1.09); or analysing the outcomes when the vitamin A supplementation intervention was provided only during the first 48 hours (RR 0.90; 95% CI 0.73 to 1.12) or during the first week of life (RR 0.90; 95% CI 0.73 to 1.11). Even in the absence of underlying biological plausibility, when the subgroup analysis was done by region, it was not found to be a significant predictor of heterogeneity (P=0.133) on meta-regression although the effect sizes appeared disparate (RR 1.13, 95% CI 0.90 to 1.43, I²=0% in Africa and RR 0.82, 95% CI 0.66 to 1.02, I²=45% in Asia).

The authors recommended that future research studies should examine the effect of neonatal vitamin A supplementation on mortality and morbidity in more settings in Asia and Africa to understand regional differences, if any. These studies should be designed to determine intervention effects in important subgroups (maternal vitamin A deficiency, low-birth-weight infants, boys/girls, and vaccinated/unvaccinated infants). Additionally, biological mechanisms of action of this intervention, and any subtle, long-term adverse effects should be further evaluated.
Summary of discussion on the presentation

Usefulness of a systematic review as the summary of evidence
Some participants were of the view that a meta-analysis or pooled analysis of all available data was not useful for preventive interventions because of differences in the underlying risk profiles of the various populations studied in the trials conducted to date. They felt that results from the studies conducted in Asia and Africa should not be combined given the differences in the risks of vitamin A deficiency and other measures of nutritional status, infectious diseases, health care access, and mortality. Further, some of the studies’ populations did not reflect the population of interest, e.g. Indonesia and Zimbabwe studies were conducted in low-mortality settings. However, it was pointed out that systematic reviews and meta-analysis of all available data is recommended in the WHO Handbook for Guideline Development (WHO, 2008). It was also pointed out that meta-regression in the available six trials did not find region (Asia/Africa) to be a significant factor that could explain the difference between the studies’ findings. The regional analysis did not control for timing of dosing or population differences.

The intervention
Most participants were of the view that the intervention under consideration should be vitamin A supplementation given within the first 2-3 days after birth, and not anytime during the neonatal period. Some participants argued that the effective interventions referred to the newborn, intending to mean an infant within the first 2-3 days of life. However, WHO uses the terms newborn and neonate as synonymous. According to WHO, the neonatal period refers to 0-28 days of life, dividing this period into the early (0-6 days) and late neonatal period (7-28 days). Some participants suggested that the Nepal trial should not have been included in the systematic review as none of the children were dosed with vitamin A within the first week of life. Others felt that the inclusion of trials should be based on the intended time to treat and not when the treatment was actually delivered. Some participants felt that there may be possible biological mechanisms that could result in different effects of vitamin A if received in the days immediately after birth, because this is the transition between fetal and postnatal life, and vitamin A could affect the maturation of organ systems. Results of the meta-analysis indicate that there is no clear evidence to show that the effect of the intervention given in the first 2-3 days is different from that of the intervention given later, and therefore this remains a hypothesis. It was suggested that a pooled analysis of raw data from existing studies may shed more light on these issues.

Choice of control group
Most participants felt that the appropriate control group in trials with a factorial design should be one in which the neonates receive placebo, instead of one in which both the neonate and the mother received placebo. They based their suggestion on the lack of a demonstrable interaction between
maternal and neonatal supplementation, evident by close and qualitatively comparable relative risk estimates and markedly overlapping confidence intervals. The author of the systematic review pointed out that the power to detect a significant interaction in the available data was low as a much larger sample size would be needed, and therefore the current choice of the comparison group was appropriate. It was noted that the choice of the control group resulted in reducing the effective sample size of the Bangladesh trial.

Further subgroup analysis to understand differences in results
Several participants expressed the view that it was not possible to fully explore if effects were different among subgroups with a meta-analysis that relied on published findings. They suggested that a pooled analysis of raw data from all trials would be useful. In particular there was interest expressed in examining the effect of the intervention in subgroups by time of dosing (first 24 hours; 0-48 hours; 0-96 hours; 2-6 days; 7-27 days), birth weight (low/not low), sex (male/female), vaccinations received during the follow-up period, and possible sources of vitamin A (time of initiation of breastfeeding, maternal vitamin A status).

3. Biological Issues Surrounding the Use of Vitamin A Supplements in Neonates (Presented by S. Tanumihardjo)

Vitamin A status for both mothers and infants is compromised in many developing countries. Most sources of vitamin A are derived from fruits and vegetables and the provitamin A carotenoids are thought not to be readily bioavailable. In general, vitamin A supplementation programs are highly successful in addressing deficiency but are not without risk. For example, the doses currently recommended for postpartum women are at toxic levels (e.g. 400,000 IU retinyl ester is 172 times higher than the Recommended Dietary Allowances; RDA). Acute toxicity may occur at dosages exceeding 100 times the RDA in adults. The supplements may be more toxic if consumed without a fat source. Information related to the following hypotheses surrounding the use of vitamin A supplements was presented:

Hypothesis: In primates, vitamin A is transferred from the pregnant mother to the fetus predominantly by chylomicra. In rhesus macaque monkeys, who have a gestation of 164 days, the fetuses generally have sufficient vitamin A stores by 50 days gestation. It is still not clear to what extent retinyl esters from chylomicra are taken up by the placenta and transferred to the fetus, nor whether all vitamin A is transferred by retinol binding protein.

Hypothesis: Supplements at birth do not make vitamin A deficient infants replete. The swine model has been used to look at this issue. Piglets are a good model for infants because of their similar size, gastrointestinal anatomy, and vitamin A requirements. Sows were put on vitamin A deficient diets and studied for three parities. Piglets born to them in the first and third
parity were given 0 IU; 25 000 IU; 50 000 IU or 100 000 IU vitamin A, and their hepatic retinol levels were compared. A main effect of parity (P = 0.038) and treatment (P < 0.0001) was seen. In piglets from the first parity (Parity A), the 50 000 and 100 000 IU treatment groups increased liver vitamin A concentrations above the deficiency level of 0.07 µmol/g liver. For piglets from the third parity (Parity B), only the 100 000 IU treatment group improved mean reserves above 0.07 µmol retinol equivalents/g.

**Hypothesis: Supplementing mothers gives ~48 hours of increased vitamin A in breast milk.** Oral doses of 0 (n = 3), 300 or 600 mg (n = 6/group) retinyl acetate were given to lactating sows. Blood and milk were collected up to 48 hours. Serum retinyl ester levels showed large peaks within two hours of supplementation. Retinyl esters, corresponding to chylomicra, accounted for most of the serum vitamin A in both groups at peak time points. Mean serum retinol concentrations changed little and accounted for most of the serum vitamin A at baseline (94% and 97% for the low- and high-dose groups, respectively) but for only 22% (and 14% at peak times) for the low- and high-dose groups, respectively. Total serum vitamin A showed large increases at 1, 2, 4, and 8 hours post-supplementation but there was no increase in serum retinol. Sow milk retinol levels rose rapidly peaking at about 24 hours after supplementation, but did not remain high after about 48 hours. It is unclear if hepatic vitamin A stored by supplemented mothers can be readily mobilized for long-term secretion into breast milk.

In a human study, 167 lactating Ghanaian women were given either 400 000 IU vitamin A (n = 85) in two divided doses or one 200 000 IU and a placebo dose (n = 82) 24 hours apart. Baseline serum retinol concentration and modified relative dose response (MRDR) values were 1.4 ± 0.5 µmol/l and 0.048 ± 0.037, respectively. Post-supplementation MRDR values were different from baseline (P < 0.0001), and there were no interactions or difference by treatment group. Therefore, a 200 000 IU dose of vitamin A was sufficient in this moderately deficient population of lactating women. It is not clear if this would be true in severely deficient mothers. Assuming an average milk intake of 700 ml/d, infants’ theoretical accrual of vitamin A over the first 48 hours is 710 µg from unsupplemented mothers, 5250 µg vitamin A from a 200 000 IU dose and 10 750 µg from a 400 000 IU dose.

**Hypothesis: Chylomicra deliver substantial vitamin A to essential organs.** Piglets (n = 28, 11.6 ± 0.5 days) from vitamin A-depleted sows were weaned onto a vitamin A-free diet for one week, assigned to four groups, and dosed orally with 0; 26.2; 52.4; or 105 µmol vitamin A. After 10 days, 5.3 µmol 3,4-didehydroretinyl acetate (DRA) was administered to determine short-term uptake of 3,4-didehydroretinol (DR). Four hours later, the piglets were sacrificed; adrenal glands, kidney, lung, and spleen were collected and analysed for retinol and DR. In four hours, the minimum estimated chylomicron
contribution to tissue DR was 63-280% higher than the maximum DR exposure from retinol binding protein. Constant dietary intake may be important in maintaining vitamin A concentrations in extrahepatic tissues.

**Hypothesis: Food sources of provitamin A will help maintain liver reserves after supplementation.** By increasing the amount of β-carotene in the diet, one can see modulation of liver reserves of vitamin A after vitamin A concentrations are in the adequate range. There must be constant vitamin A intake from the diet to maintain vitamin A stores in lung and spleen, which are needed to maintain immune function.

**Hypothesis: Food sources of provitamin A will enhance tissue antioxidant status while vitamin A supplements do not.** The antioxidant potential and vitamin A bio-efficacy of four bio-fortified carrot varieties was examined in Mongolian gerbils (n = 73). Following a four week vitamin A depletion period and baseline kill (n = 7), freeze-dried carrot powders were mixed into purified feeds and fed to six groups (n = 11/group) for four weeks. Antioxidant capacity of liver extracts from the four coloured carrot-fed groups was significantly higher than the white carrot-fed control group and vitamin A-supplemented group. Liver retinol stores in the coloured carrot-fed groups were higher than the white carrot-fed control group (P <0.0001). Serum antioxidant capacity and retinol did not differ among treatment groups. Antioxidant activity is one of several proposed mechanisms by which plant foods, like bio-fortified carrots, may provide additional health benefits beyond maintenance of vitamin A status. Additionally, food-based approaches ensure gut integrity which has major a immune function in the body.

**Implications of mechanisms of vitamin A transport and metabolism**
In response to a question on what happens to a high-dose supplement, the presenter responded that some vitamin A is converted to glucuronides and excreted through urine and some may bypass the liver and, given the large dose, may be perceived by the body to be toxic; there may be an increased catabolism. In response to another question about the implications of chylomicra transport of vitamin A, the presenter was of the view that maternal supplementation would produce the largest increase in breast milk vitamin A if given at the time when breast milk comes in (e.g. on the third day after birth).

**Measurement of vitamin A status**
The presenter proposed that an appropriate way to measure population vitamin A status is to measure serum retinol in all subjects and then do a MRDR test on a subgroup, as the latter would help interpret the serum retinol values. She also proposed that it would be best to perform MRDR in the third trimester of pregnancy in order to assess maternal status in a field trial setting.
Biological plausibility of mortality benefit of neonatal vitamin A supplementation

Many participants expressed a view that the data presented did not address the issue of biological plausibility of the effect of neonatal vitamin A supplementation on mortality. They recommended studies to explore the imprint of such an intervention on the immune system in both male and female piglets, and to ascertain the role of vitamin A given during the first few days of life in tissue differentiation and maturation, especially with regard to the lung.

Use of piglet as a model for the newborn vitamin A supplementation

Some participants questioned the appropriateness of the piglet model for studying neonatal vitamin A supplementation. They felt that piglets are different in that they rapidly become totally vitamin A deficient if not given sow milk, and also they may not be a good model for studying the effects of vitamin A on immunity.

4. Brief Overview of Design of Previous Studies and Suggestions for Future Research

The Nepal Nutrition Intervention Project, Sarlahi
(Presented by K. West)

Study setting
The prevalence of vitamin A deficiency in the population was high, with about 3% of preschool-age children having xerophthalmia. Mortality in the control group was about 132 per 1000 infant-years during the period between enrolment and end of follow-up.

Study design
A cluster randomized, placebo-controlled trial with two study arms designed and executed to estimate the efficacy of vitamin A delivered in the community every four months in reducing preschool child mortality.

Intervention
Households were visited every four months and any surviving infants less than one month of age were given 50 000 IU vitamin A or placebo. Infants 1-11 months of age were given 100 000 IU or placebo. Among the 1621 infants supplemented less than one month of age, none were reached within first week of life, and virtually all were dosed after the first two weeks of life.

Outcomes
All-cause mortality with follow-up until six months of age.

Potential effect-modifiers examined
None.

What would the investigators do differently based on the lessons learned?
Had the question about newborn vitamin A supplementation been posed a decade earlier than it was, the investigators would have designed a trial to directly address the question of the impact of dosing infants in the first days of life on infant mortality.
Neonatal Vitamin A 
Trial in Bandung 
Indonesia
(Presented by J. Humphrey)

Study setting
There was no evidence of biochemical vitamin A deficiency in this population, and 80% of children were not exclusively breastfed. Mortality in the control group was about 20 per 1000 infant-years during the period between enrolment and end of follow-up.

Study design
The study was conducted in three stages to study the safety, mortality impact, and effect on growth and development when children were three years of age. The mortality study was an individually randomized placebo-controlled trial with two study arms.

Intervention
Enrolled infants were given 50 000 IU vitamin A or placebo within a few hours of birth.

Outcomes
The trial was not designed as a mortality trial since the investigators did not expect to observe an impact on mortality. The purpose of the trial was to assess safety, using the rationale that if it were safe, birth would be a convenient time to augment vitamin A stores. Short-term safety outcomes were plasma retinyl ester concentrations in normal- and low-birth-weight infants, and incidence of bulging fontanelle, incidence of vomiting, irritability, fever, loose stools, and measurement of the resistive index (RI) of the anterior cerebral artery using duplex Doppler, a non-invasive indicator of intracranial pressure. All-cause mortality was measured at 12 months of age (n=1597) and at four, six, and 12 months in a subgroup (n=470). The child development study, conducted in those who had developed bulging fontanelle after supplementation (n=107) and those who had not developed it (n=428) used Bayley Scales of Infant Development II for assessing developmental outcomes when participants were three years of age.

Potential effect-modifiers examined
Birth weight.

What would the investigators do differently based on the lessons learned?
The investigators would measure breast milk vitamin A concentrations in mothers and would assess exclusivity of breastfeeding from birth to six months.
Vitamin A Supplementation in Newborns: A Community-Based, Randomized Trial in South India

(Presented by J. Tielsch)

Study setting
There was a high prevalence of vitamin A deficiency in this population. The intake of vitamin A was poor and vaccination coverage was low (30%). Mortality in the control group was about 69 per 1000 infant-years during the period between enrolment and end of follow-up.

Study design
The study was an individually randomized placebo-controlled community trial with two study arms.

Intervention
Enrolled infants were given two doses of 24 000 IU vitamin A or placebo within 48 hours of birth.

Outcomes
All-cause mortality was measured between the time of enrolment and six months of age. Vital status and morbidity were assessed every two weeks through six months of age. Infants were visited for the first three days after supplementation to monitor side-effects.

Potential effect-modifiers examined
Birth weight.

What would the investigators do differently based on the lessons learned?
The investigators would conduct the study in a setting with a smaller number of sources of health care, as a large private medical sector posed significant logistical issues. The investigators would collect information on a sensitive measure of maternal vitamin A status. They would perhaps conduct a cluster-randomized trial so as to be able to conduct valid subgroup analyses.

Zimbabwe Vitamin A Study

(Presented by J. Humphrey)

Study setting
Zimbabwe is classified as a country at high risk for vitamin A deficiency. At the time of the study, there was no national supplementation programme for mothers or neonates. A national micronutrient survey showed that 35.8% of preschool children and 7% of women had serum retinol <0.7 µmol/l (20 µg/dl). Mortality in the control group was about 18 per 1000 infant-years during the period between enrolment and end of follow-up.

Study design
The study was an individually randomized placebo-controlled community trial. It had a 2x2 factorial design; Arm 1: Both mother and baby received vitamin A supplementation; Arm 2: Mother received vitamin A and baby received placebo; Arm 3: Baby received vitamin A and mother received placebo; Arm 4: Both mother and baby received placebo.
Intervention
Enrolled mothers received 400,000 IU vitamin A or placebo and enrolled infants received 50,000 IU vitamin A or placebo within 48 hours of birth.

Outcomes
All-cause mortality was measured between the time of enrolment and 12 months of age. Follow-up was conducted at six weeks, three months, and every three months thereafter until 12 months of age. All mothers were tested for HIV status.

Potential effect-modifiers examined
Maternal HIV status

What would the investigators do differently based on the lessons learned?
The investigators would conduct the study in a setting with greater prevalence of maternal vitamin A deficiency. They would conduct a trial on newborn supplementation only, rather than a study with factorial design.

Guinea-Bissau Neonatal Vitamin A Supplementation Trial
(Presented by C. Stabell Benn)

Study setting
Guinea-Bissau is classified as a country having subclinical vitamin A deficiency. Within the trial, 9% of infants had serum retinol ≤0.7 µmol/l (adjusted for CRP) at four months of age and all but one mother had serum retinol >0.7 µmol/l. Mortality in the control group was 46 per 1000 infant-years during the period between enrolment and end of follow-up. It is noted that the number of infant deaths would have been considerably higher if the children had been enrolled at birth rather than at discharge from the maternity ward.

Study design
The study was an individually randomized placebo-controlled community trial with two study arms.

Intervention
Normal-birth-weight infants received 50,000 IU vitamin A supplementation or placebo in addition to BCG vaccination with the intent to investigate the effect on infant mortality overall and by sex. Post hoc the investigators also examined potential differences in effect by vaccination status and season.

Outcomes
Adverse effects included bulging fontanelles, vomiting, irritability, infections, fever, skin problems, and health care contacts. All-cause mortality was measured between the time of enrolment and 12 months of age. Follow-up was conducted every three months until 12 months of age. A verbal autopsy was conducted by a trained local physician and based on the questionnaire. The causes of death were determined by a panel of three doctors.
Potential effect-modifiers examined
The investigators strongly believe that sex, vaccination status, and season of supplementation are important effect modifiers.

What would the investigators do differently based on the lessons learned?
The investigators conducted a new non-blinded randomized controlled trial of vitamin A supplementation compared with the vaccine alone in low-birth-weight boys in 2008. The trial had to be stopped after an interim analysis because of higher mortality in the vitamin A group during the rainy season. The investigators therefore recommend conducting a pooled analysis of all existing datasets before undertaking any new trials. They believe that this pooled analysis should be aimed at understanding the differential effect of vitamin A by sex, season of supplementation, and vaccines received during the follow-up period.

JiVitA-2: Impact of Newborn Vitamin A on Infant Mortality in Bangladesh
(Presented by K. West)

Study setting
About 5% of mothers in Bangladesh had serum retinol concentrations <20 µg/dl in the first trimester of pregnancy. The majority of infants had a birth weight <2500 g and ~14% had a birth weight <2000 g. Mortality in the control group among infants who were reached with a placebo supplement was about 44 per 1000 infant-years from the time of supplementation to six months of age.

Study design
This was a cluster randomized, double-blinded, placebo-controlled newborn vitamin A supplementation trial (JiVitA-2), that was nested into an ongoing cluster-randomized, double-blind, placebo-controlled maternal weekly vitamin A or beta-carotene supplementation trial (JiVitA-1). A stratified randomization scheme assured that the two newborn supplement groups were balanced in their distributions across the three maternal supplement groups.

Intervention
Women received either β-carotene (42 mg), vitamin A (23 300 IU) or placebo supplements once each week from about nine weeks gestation through three months postpartum. Their live-born infants were dosed as soon as possible after birth with either 50 000 IU vitamin A or placebo. Median time from birth to dosing was seven hours.

Outcomes
All-cause mortality was measured between the time of dosing and six months of age. Infant vital status was assessed weekly at home for the first 12 weeks of life by field staff and then again at 24 weeks of age (six months).
Potential effect-modifiers examined
Birth weight, gestational age at birth, sex, place of delivery, type of birth attendant, newborn care practices, age (in hours) at receipt of supplement, and maternal supplement trial allocation group.

What would the investigators do differently based on the lessons learned?
Balanced nesting of the newborn trial into the maternal trial afforded a cost-efficient and timely way to launch a large confirmatory trial in January 2004, only five months following publication of the South Indian trial findings. However, the investigators would have preferred to have conducted a trial on newborn supplementation only, rather than a study with factorial design.

5. Research Questions Identified
Following review of the information provided in the above presentations, the participants identified the following research questions that need to be addressed:

i. Does newborn vitamin A supplementation, given within the first 48 hours of birth, reduce infant mortality in low-HIV prevalence settings with high infant mortality?

   Note: C. Benn was of the opinion that she would not consider doing another neonatal vitamin A supplementation trial in Guinea-Bissau because the intervention may be associated with an increased risk of mortality to children who later receive three doses of Diphtheria, Tetanus, Pertussis (DTP) vaccine.

ii. Does newborn vitamin A supplementation have differential effects on infant mortality in Asia and Africa?

iii. Is the effect of newborn vitamin A supplementation on infant mortality modified by (i) time of supplementation (first 24 hours, 48 hours, 72 hours, first week), (ii) maternal vitamin A status, (iii) gender, (iv) subsequent vaccines received, (v) birth weight, (vi) gestation, (vii) season of supplementation, (viii) time of initiation of breastfeeding?

iv. What are the biological mechanisms that might explain the postulated beneficial effects of vitamin A supplementation in the first days of life?

v. Does vitamin A supplementation given at birth have an impact on vitamin A status at three and six months of age?

vi. What are feasible approaches to reach newborns within the first two days after birth to deliver interventions like neonatal vitamin A supplementation?

vii. Is neonatal vitamin A supplementation safe and beneficial in those who are not vitamin A deficient?
6. **Priority Research Agenda**

The following priorities were proposed for implementing the research agenda:

1. A set of randomized placebo-controlled trials, at least two in Africa and one in Asia, to determine the effect of neonatal vitamin A supplementation given within the first two days after birth on mortality in the first six months of life. These trials should be conducted in settings with high infant mortality and should be individually powered to answer the research question.

2. A pooled analysis of all existing trials to explore the effects of neonatal vitamin A supplementation stratified by the following characteristics, subject to availability of information:
   - (i) time of supplementation (first 24 hours, 48 hours, 72 hours, or within the first week of life)
   - (ii) season of supplementation
   - (iii) sex
   - (iv) vaccines received during follow-up
   - (v) birth weight, and if possible, gestational age
   - (vi) maternal vitamin A status
   - (vii) time of initiation of breastfeeding

3. A set of studies on biological mechanisms that may explain the possible beneficial effects of vitamin A supplementation in the first days of life, focusing on improved immune response and/or organ maturation.

4. Operational research on how to reach most babies in developing countries within two days of birth should be conducted in general, not exclusively in the context of neonatal vitamin A supplementation.
The participants made the following recommendations for study design:

**Randomized controlled trials of newborn vitamin A supplementation:**

The recommendations resulting from group work and plenary discussions are summarized below.

| Population/setting | - At least two studies in Africa and one in Asia  
|                    | - High infant mortality rate (≥50/1000)  
|                    | - Low HIV prevalence (<5% among women attending antenatal services)  
|                    | - Exclude populations that are known to have adequate vitamin A status  
|                    | - Exclude sites with high levels of vitamin A fortification  
|                    | - Include all newborn infants in the population (minimal exclusions, if any) |
| Intervention       | - 50 000 IU vitamin A within 48 hours of birth, at the first postnatal visit  
|                    | - No maternal supplementation as part of trial  
|                    | - Document if maternal postpartum vitamin A given as part of routine care |
| Comparison         | - Double-blind placebo-controlled trials |
| Outcomes           | **Primary outcome:**  
|                    | - All-cause mortality from enrolment (i.e. age at dosing) to six months of age |
|                    | **Secondary outcomes:**  
|                    | - All-cause mortality between enrolment and one month, six and 11 months of age  
|                    | - Hospitalization  
|                    | - Adverse effects that concern parents in the three days after supplementation  
|                    | **Substudies:**  
|                    | - Immunological responses (antibody, T-cell)  
|                    | - Vitamin A status |
| Timing             | - Follow-up up to six months of age  
<p>|                    | - Recruitment to cover at least one full year (all seasons) |</p>
<table>
<thead>
<tr>
<th>Study design</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Double-blind randomized placebo-controlled trials, one intervention arm</td>
</tr>
<tr>
<td>- Cluster randomization (large number of clusters, e.g. ≥100)</td>
</tr>
<tr>
<td>- Multi-centre, but each centre powered to answer the study question</td>
</tr>
<tr>
<td>- Most participants preferred an efficacy study at this stage</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each study site should have enough participants to have adequate power to detect a 15% reduction in mortality between enrolment and six months of age</td>
</tr>
</tbody>
</table>

**Studies to understand biological mechanisms that may explain the possible beneficial effect of vitamin A supplementation**

<table>
<thead>
<tr>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is no knowledge on vitamin A metabolism in the first day of life and effects of early supplementation on organ maturation and immune responses</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Animal model:</strong> newborn piglets, stratified by sex and maternal vitamin A status (as determined by liver vitamin A levels). Include piglets from different parity from the same sows.</td>
</tr>
</tbody>
</table>

Some participants questioned the appropriateness of a piglet model. They were not sure whether piglets absorb vitamin A differently than humans or whether a primate model may be better. However, a problem is that primates are more prone to vitamin A toxicity.

<table>
<thead>
<tr>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supplementation with 0; 25,000; or 50,000 IU at birth</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unsupplemented piglets</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Absorption of vitamin A as measured by chylomicra response</td>
</tr>
<tr>
<td>- Serum metabolites: retinoic acid, retinyl glucuronide, retinoyl glucuronide</td>
</tr>
<tr>
<td>- Vitamin A distribution in the essential organs</td>
</tr>
<tr>
<td>- Organ maturation as measured by pathology</td>
</tr>
<tr>
<td>- Immunological responses (blood/tissue; needs more discussion with experts)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>First days of life</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study type</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Controlled trials, block by sows</td>
</tr>
<tr>
<td>- Siblings get same treatment with different doses</td>
</tr>
</tbody>
</table>
Pooled analysis of existing trials: Individual participant characteristics of interest for the pooled analysis are summarized below.

<table>
<thead>
<tr>
<th>Characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timing of vitamin A supplementation</td>
</tr>
<tr>
<td>Age at death</td>
</tr>
<tr>
<td>Infant vitamin A status</td>
</tr>
<tr>
<td>Maternal vitamin A status</td>
</tr>
<tr>
<td>Maternal exposure to vitamin A in supplements/diet</td>
</tr>
<tr>
<td>Infant vaccination history</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Timing of breastfeeding initiation, pre-lacteal feeds</td>
</tr>
<tr>
<td>Duration of exclusive breastfeeding</td>
</tr>
<tr>
<td>Timing of complementary food introduction</td>
</tr>
<tr>
<td>Season when supplemented (e.g. high/low disease transmission)</td>
</tr>
<tr>
<td>Birth weight (very low birth weight, low birth weight, normal)</td>
</tr>
</tbody>
</table>

The meeting participants were informed that R. Klemm at John Hopkins University is conducting a pooled analysis of three of the four trials conducted in Asia, but this would not interfere with making arrangements for a pooled analysis of all studies. The participants felt that such an analysis would take longer than a few months. There was no discussion on the mechanism of facilitating and conducting the proposed pooled analysis.

8. OVERVIEW OF WHO’S NEW POLICY FOR DEVELOPING GUIDELINES (PRESENTED BY S. WALLESER)

The aim of this presentation was to inform the participants about the process of development of policy recommendations on newborn vitamin A supplementation. This process is overseen by the WHO Guideline Review Committee (GRC) established in 2008 and is described in the Handbook for the Development of WHO Guidelines (http://www.searo.who.int/LinkFiles/RPC_Handbook_Guideline_Development.pdf).

In brief, the following steps are recommended:

a. Initial definition of scope and target audience.

b. Development of questions the guideline wants to address.

c. Systematic and comprehensive evidence retrieval and synthesis. This includes quality appraisal of the evidence and it is standard to use the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system.

d. Development of recommendations based on interpretation of this evidence. The GRADE system provides a systematic approach of moving from evidence to recommendations. The group that
develops recommendations must not have any conflicts of interest, must represent all regions, have gender balance, and include content and methodological experts.

e. Management of conflict of interest: Conflicts of interest are disclosed at the start of the process of development of guidelines; those with conflicts may be excluded from all or part of discussion.

f. Standards for reporting.

g. Plan for implementation and update.

The GRC provides oversight to this process and approves the final guidelines. It provides its recommendations to Assistant Directors General and the Director General.

The implications of this process in developing guidelines for neonatal vitamin A supplementation were discussed. The WHO Department of Nutrition for Health and Development is currently setting up (possibly jointly with UNICEF) a project on an evidence-based nutrition guidelines “warehouse” with various internal and external partners including the Cochrane Collaboration and WHO Departments of Reproductive Health; Child and Adolescent Health; and Information, Evidence and Research. With regard to vitamin A, the priority areas for development and update of guidelines are (i) neonatal vitamin A supplementation, (ii) maternal postpartum vitamin A supplementation, and (iii) vitamin A supplementation for children 6-59 months of age. An advisory group will be created to follow the GRC process using available systematic reviews. WHO expects to develop a guideline statement within the next six months, based on the available evidence on neonatal vitamin A supplementation.
9. Comments from Funding Agencies

The representative from CIDA remarked that the agency has had a long-term interest in vitamin A supplementation for the reduction of mortality in children under five years of age. It was observed that the discussions at the meeting indicated a need for more research before going ahead with global programs for neonatal vitamin A supplementation. It was felt that CIDA would need more details about the planned research before it could commit to considering funding for the projects.

The representative from USAID expressed some reluctance in funding additional studies in Asia. It was noted that the newborn care community is interested in this intervention and is currently looking at operational issues in case neonatal vitamin A supplementation becomes a policy in the future. It was indicated that this meeting’s discussions would be shared with the USAID research group to see if there may be a way to support activities related to the pooled analysis.

The representative from the Bill and Melinda Gates Foundation informed that the Foundation’s Nutrition Strategy focuses on three areas: 1) better understanding of mechanisms of action; 2) nutritional status and biomarkers; and 3) development of new interventions. The Foundation would like to work with WHO and with other funding agencies to move forward the agenda with this intervention if it reduces infant mortality. The Foundation asked WHO to facilitate a meeting of funding agencies interested in this area to discuss ways to move forward.
10. **Next Steps**

The meeting was successful in reaching its proposed objectives of obtaining a consensus on the priority research agenda on neonatal vitamin A supplementation. Recommendations on the appropriate design of research studies were developed, and suggestions were provided for possible research sites.

Participants will use the results of the meeting to solicit support for the implementation of the priority research studies. Concurrently, WHO will move forward with development of guidance to countries based on the available evidence, following the process described in the WHO Handbook for Guideline Development.
ANNEX

List of Participants

Dr Christine Stabell Benn, Bandim Health Project, Statens Serum Institut, Copenhagen, Denmark.


Dr Karen Edmond, Infectious Disease Epidemiology Unit, London School of Hygiene and Tropical Medicine, London, the United Kingdom of Great Britain and Northern Ireland.

Ms Alison Greig, Micronutrient Initiative (MI), Ottawa, Canada.

Dr Jean Humphrey, ZVITAMBO, Borrowdale, Harare, Zimbabwe.

Dr Erin McLean, Canadian International Development Agency (CIDA), Gatineau, Canada.

Dr Ellen G. Piwoz, Bill & Melinda Gates Foundation, Seattle, WA, the United States of America.

Professor Harshpal Singh Sachdev, Sitaram Bhartia Institute of Science and Research, New Delhi, India.

Dr Laurence Grummer-Strawn, Centers for Disease Control and Prevention, Atlanta, GA, the United States of America.

Dr Sherry Tanumihardjo, Department of Nutritional Sciences University of Wisconsin, Madison, WI, the United States of America.

Dr James Tielsch, Global Disease Epidemiology and Control Program Baltimore, MD, the United States of America.

Mr Arnold Timmer, UNICEF, New York, NY, the United States of America.


Dr Keith West Jr., Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, the United States of America.
**WHO Secretariat**

Dr Rajiv Bahl, Newborn and Child Health and Development (NCH), Child and Adolescent Health and Development (*Rapporteur*).

Dr Francesco Branca, Nutrition for Health and Development (NHD).

Ms Tracey Goodman, Expanded Programme on Immunization (EPI), Immunization, Vaccines and Biologicals (IVB).

Dr Jose Martines, Newborn and Child Health and Development (NCH), Child and Adolescent Health and Development.

Dr Elizabeth Mason, Child and Adolescent Health and Development (CAH).

Dr Juan Pablo Pena-Rosas, Reduction of Micronutrient Malnutrition (MNM), Nutrition for Health and Development (NHD).

Dr Sonya Rabeneck, Partnership for Maternal, Newborn and Child Health (NMC).

Dr Lisa Rogers, Reduction of Micronutrient Malnutrition (MNM), Nutrition for Health and Development (*Rapporteur*).

**Observers**

Ms Kelly M. Randels, Bill and Melinda Gates Foundation in Seattle, WA, the United States of America.

Ms Silvana Faillace, Micronutrient Forum, Washington, DC, the United States of America.