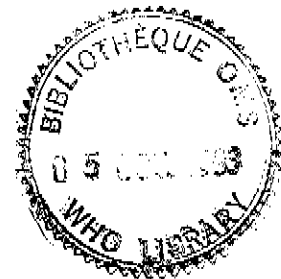


46966/770

WHO/CDR/93.2  
DISTR.: LIMITED  
ORIGINAL: ENGLISH

# Vitamin A Supplementation and Childhood Pneumonia: Report of a meeting (Geneva, 1-3 February 1993)



**Division of Diarrhoeal and  
Acute Respiratory Disease Control**

**World Health Organization  
Geneva**



## LIST OF PARTICIPANTS

Dr Paul Arthur	GHANA VAST (collaborative study between the London School of Hygiene and Tropical Medicine and the University of Science and Technology, Kumasi), Navrongo, Ghana
Dr Mauricio Barreto	Departamento Medicina Preventiva, Universidade Federal de Bahia, Salvador, Brazil
Dr M.K. Bhan	Department of Paediatrics, All India Institute of Medical Sciences, New Delhi, India
Dr Kenneth Brown	Director, Programme in International Nutrition, Department of Nutrition, University of California, Davis, California, USA
Dr Anna Coutsooudis	Medical Scientist, Department of Medicine Paediatrics & Child Health, University of Natal, Congelia, South Africa
Dr Nils Daulaire	The REACH Project/INTERCEPT, Norwich, Vermont, USA
Dr Michael Dibley	The Morvita Project, (collaborative study between the Gadjah Mada University and Johns Hopkins University), Yogyakarta, Indonesia
Dr Guillermo Herrera	Harvard School of Public Health, Boston, Massachusetts, USA
Ms Betty Kirkwood	Head, Maternal and Child Epidemiology Unit, London School of Hygiene and Tropical Medicine, London, United Kingdom
Dr Chris Kjolhede	Assistant Professor, Division of Human Nutrition, Department of International Health, School of Hygiene and Public Health, Johns Hopkins University, Baltimore, Maryland, USA
Dr Caryn Miller	Senior Technical Officer, Diarrhoea & Respiratory Disease Research, United States Agency for International Development (USAID), Washington DC, USA
Dr Roy Milton	Acting Associate Director, Biometry and Epidemiology Program, National Eye Institute, National Institutes of Health (NIH), Bethesda, Maryland, USA
Mr Saul Morris	Research Fellow, Maternal and Child Epidemiology Unit, London School of Hygiene and Tropical Medicine, London, United Kingdom
Dr Vinodini Reddy	Director, National Institute of Nutrition, Indian Council of Medical Research, Jamai - Osmania, Hyderabad, India
Dr Jon Rohde	Special Adviser, UNICEF, New York City, USA
Dr David Ross	Senior Lecturer in Epidemiology, Maternal and Child Epidemiology Unit, London School of Hygiene and Tropical Medicine, London, United Kingdom

Professor Alfred Sommer	Dean, Johns Hopkins School of Hygiene and Public Health, Baltimore, Maryland, USA
Dr Sally Stansfield	Evaluation Unit, Corporate Affairs and Initiative Division, International Development Research Centre (IDRC), Ottawa, Ontario, Canada
Dr Therese Stukel	Department of Community and Family Medicine, Dartmouth Medical School, Hanover, New Hampshire, USA
Dr Keith P. West	Associate Professor, Dana Center for Preventative Ophthalmology, Wilmer Eye Institute, Johns Hopkins School of Medicine and Public Health, Baltimore, Maryland, USA
<u>Secretariat</u>	
Dr John Clements	Medical Officer, Expanded Programme on Immunization, World Health Organization, Geneva, Switzerland
Dr Nicholas Cohen	Medical Officer, Expanded Programme on Immunization, World Health Organization, Geneva, Switzerland
Dr Sandy Gove	Research Coordinator, Programme for the Control of Acute Respiratory Infections, World Health Organization, Geneva, Switzerland
Dr Jose Martines	Medical Officer, Programme for the Control of Diarrhoeal Diseases, World Health Organization, Geneva, Switzerland
Dr Gretel Pelto	Scientist, Programme for the Control of Acute Respiratory Infections, World Health Organization, Geneva, Switzerland
Dr James Tulloch	Director, Division of Diarrhoeal and Acute Respiratory Disease Control (CDR), World Health Organization, Geneva, Switzerland
Dr Barbara Underwood	Scientist, Special Assistant for Vitamin A Programmes, Nutrition, World Health Organization, Geneva, Switzerland

## 1. THIS REPORT

This meeting report describes the conclusions and recommendations of the informal consultation held on 1-3 February 1993. The report includes the background and objectives of the meta-analysis and review of the impact of vitamin A supplementation on morbidity and mortality from childhood pneumonia, the methods and process, and its conclusion but not the full numerical data. A full report, including the detailed data results used in the meta-analysis, will be prepared, circulated for comment and finalized before the end of the year. The delay reflects a need to finalize preliminary results from several studies before presenting detailed numerical results.

## 2. MEETING BACKGROUND

Observational studies have shown that children with vitamin A deficiency (VAD) have an increased risk of respiratory morbidity and mortality (El Bushra, 1992; Bloem, 1990; Milton, 1987; Sommer, 1984; Sommer, 1983). Clinical studies have also demonstrated a relationship between vitamin A deficiency and severity of respiratory infections. Including vitamin A in the management protocol for children with measles reduces the duration and severity of illness, the incidence of complications, case fatality and subsequent morbidity from ARI and diarrhoea (Coutsoudis, 1991; Hussey, 1990; Barclay, 1987). A biologically plausible explanation can be found for the observed results.

Most of the field studies to date have demonstrated a large impact of vitamin A supplementation on overall childhood mortality (Sommer, 1986; Rahmathullah, 1990; West, 1991; Daulaire, 1992), and a recent meta-analysis of eight field studies yielded a 23% summary estimate of effect (RR=0.77; 95%CI: 0.71-0.84) (Beaton, 1992).

It is reasonable to expect that such a large beneficial impact on mortality cannot be obtained without impact on the leading causes of childhood deaths, namely pneumonia and diarrhoea, which together account for more than 60% of all childhood deaths in developing countries. However, whilst all the studies that have cause-specific mortality data all show a beneficial impact on deaths due to diarrhoea (summary estimate: RR=0.71; 95%CI: 0.57-0.88), and measles (summary estimate: RR=0.46; 95%CI: 0.22-0.98) (Beaton, 1992), none of them has demonstrated a beneficial impact on pneumonia mortality. This is a surprising finding, given the strong association between vitamin A deficiency and risk of ARI found in field studies, the observed clinical, pathological, and immunological effects of VAD on the respiratory system, and the beneficial impact of vitamin A on measles.

More than 60% of pneumonia deaths in pre-school children occur in infants, and up to 50% before 6 months of age. Except for two studies in NEPAL, all vitamin A trials have been conducted in children above 6 months of age (6-72 months), and individually they would not have sufficient numbers of children in the most vulnerable age group, to detect an impact on pneumonia. This can be addressed in a meta-analysis of data from all the field studies, examining in detail for age-specific pneumonia mortality, especially in infants.

In contrast to the observations on total childhood mortality, there is as yet no clear evidence of a similar impact on morbidity. One study in GHANA has produced evidence of an impact on severity of illness (Arthur, 1992), but results from two other studies (unpublished) indicate a possible increased risk of ALRI in children receiving vitamin A at levels of 100,000-200,000 IU four monthly (Dibley; Bhan, personal communication).

Given the high incidence of ALRI morbidity and mortality in infancy, small increases in risk could translate into a large population impact. These results require further examination, particularly given the suggestion that 25,000 IU vitamin A supplementation be given to young infants with vaccination at 6, 10 and 14 weeks of age in vitamin A deficient areas.

It was therefore proposed to address these concerns by a review and meta-analysis of all available data.

### **3. MEETING OBJECTIVES**

- 3.1 To complete the review and meta-analysis of the impact of vitamin A supplementation on morbidity and mortality from childhood pneumonia, based on published and unpublished field trials.
- 3.2 To explore the implications of these data for the safety and efficacy of two proposed approaches to vitamin A supplementation in young children in areas where xerophthalmia is a public health problem- including supplementation linked with vaccination contacts and with clinic visits for illness.

### **4. VITAMIN A AND PNEUMONIA: REVIEW AND META-ANALYSIS**

#### **4.1 Introduction**

The WHO Programme for the Control of Acute Respiratory Infections (WHO-ARI), in collaboration with the Maternal and Child Epidemiology Unit (MCEU) of the London School of Hygiene and Tropical Medicine (LSHTM), is engaged in a review of potential interventions for the prevention of childhood pneumonia. The aim is to produce a short list of selected nutritional, environmental, behavioural and vaccine interventions that can be expected to have a significant impact on childhood pneumonia. This is being achieved by a staged process of elimination. The first stage aims to evaluate the epidemiological and biological evidence of the contribution of the various risk factors to the burden of childhood pneumonia, to evaluate results from field intervention studies, and from these, to model the expected impact that might result from reduction of the prevalence of the risk factor. The second stage identifies potential interventions and assesses their potential impact on these risk factors. The third stage assesses the feasibility and the cost effectiveness of selected potentially high impact interventions. The review also aims to identify research needs. Vitamin A deficiency (VAD) has

been suggested as one of the important risk factors for childhood pneumonia, and is one of 23 risk factors being evaluated in the review.

A first stage review of the published literature on VAD and acute lower respiratory infections (ALRI) was conducted in the first phase of this project (Southwick and Tomkins, Feb 1992; unpublished). This review was preliminary, and in view of the paucity of data from field studies, focused on the biological plausibility of the observed associations. The data available from field studies at the time showed large reductions in overall childhood mortality following supplementation with vitamin A, as well as in deaths due to diarrhoea and measles. No impact on mortality from ALRI was, however, observed. This review was examined by an expert group meeting in March 1992, which recommended that "the (ARI) Programme should monitor ARI specific data from ongoing or completed trials, to update the initial review, and to conduct a more detailed evaluation of the data, particularly for infants" (WHO, 1992). Following this, investigators of vitamin A supplementation field studies that have data on childhood mortality and/or morbidity due to acute lower respiratory infections (ALRI) or pneumonia have been invited to contribute data to a meta-analysis of the impact on childhood pneumonia.

4.2 The objective of the review is to combine and compare the data on ALRI specific mortality and/or morbidity resulting from individual trials of the effects of vitamin A supplementation in order to:

4.2.1 obtain estimates of the effect of supplementation on pneumonia mortality during infancy, and during the second year of life;

4.2.2 examine whether vitamin A supplementation has any impact (positive or negative) on the incidence and severity of childhood pneumonia;

4.2.3 attempt to explain reasons for the apparently contradictory results emerging so far on the impact of supplementation on ALRI morbidity;

4.2.4 summarize the results in a review and meta-analysis.

4.3 Methods of the review and meta-analysis

Principal Investigators (PIs) of 12 completed large-scale field trials (published and unpublished) which collected data on ARI morbidity and/or mortality were invited to contribute data to the review. Participating studies are summarized in Table 1. Seven studies were conducted in Asia (in India (3), Indonesia (2), and Nepal (2)), three in Africa (in Ghana (2) and Sudan), and two in Latin America (in Brazil and Haiti).

At the meeting, data were also presented from an ongoing morbidity trial in China. This trial is collecting data from approximately 400 children on a limited number of symptoms, namely cough, fever and diarrhoea. In addition, this trial is collecting data on the incidence of clinical pneumonia, diagnosed by a

physician. Given the preliminary nature of the data and the lack of sufficient detail of symptoms to meet the meta-analysis requirements, these data were simply noted, and not formally included in the meta-analysis but will be included in the broader review.

#### 4.3.1 Review procedure

A detailed protocol, which specified the definitions for the various variables collected, endpoints to be evaluated, and the analyses to be performed was prepared in consultation with the investigators. In a pre-test, this protocol was applied to data from some of the studies and was finalized at a consultation of PIs in November 1992. Individual consultations were held to discuss specific situations where, on account of differences in study design or in data format, PIs were unable to meet the definitions and analyses specified. In such situations, agreed separate analyses in a format as closely compatible to the protocol as possible were requested, which were separately considered in the meta-analysis. The protocol was applied by the individual studies to their data, and tabulations of results returned to the coordinating group at the LSHTM. Where possible these results were summarized in a review and meta-analysis which were presented to this meeting of PIs. This consultation discussed results from the individual studies, comparisons across studies, and aimed to reach consensus conclusions from the results.

#### 4.3.2 Analysis protocol and analysis performed

A detailed review and analysis protocol was used<sup>1</sup>. This contains definitions of specific ARI symptoms, the combination of symptoms constituting ALRI and pneumonia, agreed indicators of illness severity and definition of illness episodes. These definitions were based on those used by the ARI Programme, and where permitted by the data, different definitions were explored. The endpoints under evaluation and the statistical methods applied to the analyses of these endpoints were also specified. Vitamin A and placebo groups were compared with respect to the ratio of incidence of pneumonia, tendency to multiple episodes over a short block of time, and to the prevalence of symptoms of pneumonia and severe pneumonia. On account of significant differences in data format and doubts with respect to the quality of data on the duration of episodes, it was decided NOT to evaluate the impact on duration of illness. Differentials in impact by age, vitamin A status and anthropometric status were also examined.

Several indicators of severe illness were examined, although not all of the studies contained data on all of these. These included symptoms reported at interview, observations and measurements made at the time of visit and some indicators of care-seeking behaviour. Data on pneumonia deaths were based on cause of death as obtained by verbal autopsy, and although there were clear differences in the

---

<sup>1</sup> "Protocol for a review of the impact of vitamin A supplementation on childhood pneumonia" available from WHO-CDR or LSHTM/MCEU.

instruments applied, the data were accepted as provided by the various studies. This decision was made in view of the inability of studies to re-code for cause of death even if a consensus definition was reached. Studies were, however, requested to provide details on the instrument and method by which those data were obtained, so that this could be taken into account in the summary.

#### 4.3.3 Study characteristics

Studies have been classified into mortality or morbidity categories according to the primary endpoints they were designed to evaluate. There were eight mortality studies and four morbidity studies. One mortality study (MADURAI) which used a weekly dosing regime was able to obtain detailed morbidity data in addition to the mortality data.

The study design features and characteristics of the study populations are summarized in Tables 1 and 2. All the trials used oral doses of vitamin A, in a range of dosages and dosing intervals, from weekly low doses (MADURAI) to four-monthly and six-monthly high doses. Two trials (JUMLA and DELHI) gave only a single high dose supplement, with a much shortened follow-up of children (5 months and 3 months). The morbidity trials were all randomized on the individual child, whereas the mortality studies were randomized on larger units, such as households, villages, clusters of villages, or other administrative or geographic units. All of these were field trials with supplementation of the general child population, except for the DELHI trial which was restricted to children with acute diarrhoea who were recruited from a clinic. All of the trials included children from 6 months of age on, except for DELHI (12 months and above), but only two (SARLAHI and JUMLA) systematically included infants under 6 months of age. The mortality studies employed visits at long intervals (except for MADURAI) for the verification of status of the child, at which morbidity prevalence data were also obtained, but the morbidity studies employed a more intensive follow-up of children, at intervals of 48 hours to seven days.

The study sites were varied in terms of affluence and indicators of health, nutritional status and vitamin A profile, from areas of relatively high affluence and zero xerophthalmia prevalence (BAHIA) to extremely deprived areas with very high xerophthalmia rates (JUMLA).

#### 4.3.4 Data used

Pneumonia incidence data were obtained from the four detailed morbidity studies (DELHI, GHANA VAST-CHS, MORVITA, BAHIA, that had intensive follow-up of children), from the MADURAI study, and from another mortality study (JUMLA) which obtained data from an active case detection and treatment system that was already in place in the study area. Prevalence data were available from all the studies (both mortality and morbidity), although these were obtained for varying periods of time in the mortality studies (one week to four weeks), at varying intervals (three months to six months), and for different ARI symptoms. Illness severity data were obtained from the morbidity studies,

including rates of physician-diagnosed pneumonia, but only two studies (BAHIA and GHANA VAST-CHS) were able to provide data on health facility utilization. Three morbidity trials have data on radiologically confirmed episodes. In addition, the SARLAHI mortality study was able to contribute some data on the severity of illness episodes.

Data on pneumonia mortality were available from five out of the eight mortality studies; two of the remaining three (ACEH and HAITI) collected only limited data on cause-specific mortality, and the other (HYDERABAD) did not analyse the data owing to concerns about the instrument used.

## 5. MEETING RESULTS

### 5.1 Mortality

The variation observed in the pneumonia-specific mortality rate in the five mortality trials is not more than might reasonably be expected by chance if the true impact of vitamin A supplementation was uniform across study sites. The pooled estimate of the effect on pneumonia mortality indicates no significant difference between the supplemented and unsupplemented groups (rate ratio = 1.04; 95% confidence intervals 0.78-1.38).

In four of the five studies considered, vitamin A supplementation shows a markedly less protective effect on pneumonia mortality than on all-cause mortality. Indeed, in two of these studies, a detrimental effect on pneumonia mortality coexists with a positive impact on all-cause mortality. Whilst the small number of pneumonia deaths makes it unlikely that a significant difference between the impact on pneumonia mortality and that on mortality from other causes can be demonstrated in any individual study, the consistency of this relationship is striking.

It is not thought that the lack of impact of vitamin A supplementation on pneumonia-specific mortality can be explained by misclassification of deaths due to problems with the measurement instrument (verbal post-mortem). A non-systematic misclassification of cause of death would be expected to bring the estimate of the impact of supplementation on pneumonia deaths closer to the estimate of the impact on all-cause mortality, not towards a rate ratio of one. This was in fact observed in one of the mortality studies, when a less specific definition of "pneumonia-associated" deaths was used. Furthermore, similar verbal autopsy instruments have already been shown to be capable of demonstrating an impact on pneumonia mortality in trials of other interventions.

The summary estimates of the impact of vitamin A supplementation on pneumonia mortality were disaggregated by age, and showed no evidence of a differential impact by age. Given, however, that most pneumonia deaths occur in infancy, it was felt important to examine this age-group in greater detail. Rate ratios near one were observed in the 0-5 month and 6-11 month age-groups,

although confidence intervals were very wide since there were only just over 50 deaths in each age group (based on a dosage of 50,000 IU to neonates/100,000 IU to 1-11-month-old infants on a 4-monthly basis).

Since respiratory illness is such an important cause of death in infants, it was thought desirable to complement the scarce data on pneumonia-specific mortality in this age-group with a re-examination of all-cause mortality in infants. The Beaton meta-analysis (Beaton, 1992) concluded that the observed effect is uniform across all ages. However, there were very few data on infants and no firm conclusions can be drawn for that age group, particularly for young infants (under 6 months of age). Since the compilation of the Beaton meta-analysis, the age attribution of both deaths and child-years of follow-up had been substantially revised in one of the studies, and additional data were available from two studies not included in the Beaton meta-analysis; it was therefore necessary to recalculate these data. Whilst the mortality reduction in the 6-11-month-olds was consistent with that observed in other age-groups (a 30% reduction), no reduction was observed in the 0-5-month-olds. The fact that the upper confidence interval from the very limited data in this age group corresponded to a 30% increase in mortality was viewed with some concern, and the urgent need for further studies was underlined.

## 5.2 Pneumonia incidence

Data on pneumonia incidence are available from the four studies in which children were visited at home on an intensive basis for the purpose of complete morbidity surveillance, and from JUMLA, where an existing case detection system was exploited. Only the JUMLA study showed a significant reduction in pneumonia incidence in the vitamin A supplemented group. In this analysis, pneumonia is defined in the four morbidity surveillance studies as cough plus respiratory rate over 50 for infants and over 40 for 1-4-year-olds. In JUMLA, however, a single respiratory rate cut-off of 50 was used for all children, and chest indrawing was also a sufficient condition for the diagnosis of pneumonia. The rate ratio and confidence limits in the JUMLA study have been adjusted to allow for the effect of the cluster-randomized design, and for baseline differences between the vitamin A and placebo clusters.

There is some statistical evidence that the impact of vitamin A supplementation on pneumonia incidence in JUMLA may be different from that in the other four studies. Many *a priori* considerations, relating to study design and physical environment, also suggest that JUMLA may not be directly comparable with the other studies. For this reason, summary estimates of the impact of vitamin A supplementation on pneumonia incidence are presented with and without the data from JUMLA. The ratio was near one, whether JUMLA was included or excluded. It appears therefore that vitamin A supplementation has no overall impact on pneumonia incidence as measured by cough and a measured increase in respiratory rate using age-specific cut-offs.

The results of the meta-analysis suggested a slight trend with age, with a possible

detrimental impact on pneumonia incidence in the 6-11-month-olds and a possible beneficial impact on the 48-59-month-olds. This trend is visually apparent to some degree in each of the four studies, but could not be demonstrated statistically. Confidence intervals in every age-group overlap unity, even when the different studies are combined, and it should be noted that most of the increased risk in the youngest age group is contributed by the data from MORVITA. A somewhat more pronounced trend is seen in the data from JUMLA. Only the JUMLA study provides information on children below 6 months of age, but since they are combined in the analysis with children up to 11 months of age, no statement on the effect of vitamin A supplementation on children 0-5 months of age may be made.

The same analyses were repeated using a 50 breaths per minute cut-off for all children, regardless of age. This resulted in a substantial reduction in the number of pneumonia episodes observed, especially in the children over 2 years of age, but did not alter the conclusions concerning overall pneumonia incidence.

Estimates were also obtained of the impact of vitamin A supplementation on pneumonia incidence as defined by a combination of cough plus maternally reported rapid breathing (GHANA VAST-CHS and MORVITA) or cough, cold and fever plus rapid breathing or chest indrawing (MADURAI). Since there is strong evidence of heterogeneity of effect between the different studies, no attempt has been made to summarize the results in a single estimate of the impact of vitamin A supplementation. Clearly, this heterogeneity is due to the discordance between the positive impact reported by the GHANA study and the detrimental impact reported by the other two studies. The baseline difference between the vitamin A and placebo groups in the prevalence of maternally reported rapid breathing in the GHANA study suggests caution in interpreting the results from this study. On balance, however, it appears unlikely that vitamin A supplementation has an important impact - either beneficial or detrimental - on pneumonia incidence based on maternally defined symptoms.

### 5.3 Pneumonia prevalence

In the case of pneumonia prevalence, data from the four studies with intensive morbidity surveillance are supplemented by data from other studies in which children were visited on a periodic basis. In the four studies with intensive morbidity surveillance, the age-specific impacts of vitamin A supplementation on pneumonia prevalence (as defined by cough plus raised respiratory rate) are almost identical to the impacts on pneumonia incidence described above. In the MORVITA and DELHI studies, however, stronger negative impacts are observed on pneumonia prevalence in the youngest age groups than are seen for incidence, with a rate ratio as high as 1.73 in the youngest age group in the MORVITA study ( $p=0.08$ ). Taken together, however, there is little evidence from these studies to suggest an important impact on pneumonia prevalence over the 6 to 59 months age range, and there is no consistent trend in this pattern with age.

Two other studies also contribute information on the combination of cough plus

(reported) rapid breathing. Data from the SARLAHI mortality trial, relating to one-week period prevalence and collected four months after the last dosing point, show no impact of vitamin A supplementation in any age group. Data from Haiti, however, relating to two-week period prevalence and collected two to six weeks after the last scheduled dose, show 20-25% increases in the risk of cough plus rapid breathing in most age-groups, reaching significance when the age-groups are combined. Interpretation of these results is complicated by the fact that both studies had significant differences between the two treatment groups in the baseline prevalence of these symptoms, with more morbidity in the vitamin A group in SARLAHI, and less in HAITI.

Findings on the impact of vitamin A supplementation on the combination of cough plus (reported) fever were also examined. Whilst this combination of symptoms is clearly not specific to pneumonia, it may shed further light on the patterns of respiratory morbidity in the various supplementation trials. None of these studies suggests any impact - beneficial or deleterious - of vitamin A supplementation on the combination of cough plus fever. The apparent reduction shown in the SUDAN study is almost certainly a reflection of the 34% lower morbidity from these symptoms shown in the vitamin A supplemented group at baseline.

Data on the prevalence of cough, irrespective of other symptoms, were also examined. Four of the nine studies contributing data show a 5-10% excess of cough in the vitamin A supplemented group, with a median estimate of the overall impact of 1.02. No trend with age is evident from these data.

#### 5.4 Pneumonia severity indicators

Since the selection of severity indicators available from each of the four intensive surveillance studies differs considerably, there is little scope for comparative analysis. No significant impact of vitamin A supplementation on any severity indicator is seen, and even the directions of the impacts shown are not consistent between studies. The following severity indicators showed agreement in the direction of impact between two or more studies: noisy breathing, reduced; fever, increased; and chest indrawing, unchanged.

#### 5.5 Differences in impact by characteristics of the study populations

An attempt was made to explain some of the observed variation in the impact of vitamin A supplementation on pneumonia morbidity and mortality by relating the observed effect estimates to a number of parameters describing the vitamin A and the general development status of the various study populations. Little or no relationship between the impact of vitamin A supplementation on pneumonia incidence and morbidity, and the proportion of children a) severely, or b) severely or moderately, vitamin A deficient as measured by serum retinol was found.

The two mortality trials with data on serum retinol show opposing results depending on whether the proportion of severely deficient or severely and

moderately deficient children is taken as the indicator of vitamin A status. GHANA and MORVITA studies desegregated by baseline serum retinol. In the MORVITA study, a marked detrimental effect was observed in the replete children (retinol 1.05-) and the least detrimental effect was seen in the moderately deficient children (retinol 0.35-0.69 umol/l). The opposite trend was seen in the GHANA study.

There is a suggestion of a trend of increasing impact of supplementation on overall mortality with increasing prevalence of xerophthalmia, including night-blindness, although this is not statistically significant. Similar relationships are seen with pneumonia mortality and pneumonia incidence (the latter reaching statistical significance).

There was also a suggestion of a trend of increasing impact of supplementation with increasing level of underdevelopment, using a crude score suggested by meeting participants. This will be explored further using more objective indices such as IMR, literacy rate, and gross national product (GNP) per capita.

No clear relationship could be seen with the prevalence of stunting.

#### 5.6 Impact of vitamin A supplementation of children presenting with measles

Six clinical studies have examined the impact of vitamin A given to young children presenting with clinical measles, three in Africa and three unpublished studies from the Philippines. Although five of the studies were consistent in showing benefit in reducing the case-fatality rate, a recent randomized trial in the Philippines which enrolled a significant number of children with very severe pneumonia requiring intensive care showed a significantly elevated case-fatality rate.

#### 5.7 Supplementation with 25,000 IU vitamin A at 6, 10 and 14 weeks of age with vaccination

##### 5.7.1 Efficacy

No data were available for review with this schedule and dose. Efficacy in preventing mortality in the second 6 months of life has been predicted based on improved liver stores of vitamin A; these calculations were not reviewed at this meeting. Preliminary analysis of very limited data from SARLAHI based on a small number of infants given a significantly higher dose, 150,000 or 200,000 IU during the first 6 months of life, showed a small reduction in mortality when these infants were 6-8 months of age.

##### 5.7.2 Safety

See sections 5.1 and 5.2 for summaries of the scant data available in this age group on safety in terms of morbidity and mortality. No data are available on the acute toxic effects of 25,000 IU given with immunization at 6, 10 and 14 weeks of

age. Preliminary reports of significantly increased rates of bulging fontanelle in infants given 50,000 IU with vaccination at 6, 10 and 14 weeks of age in Bangladesh require thorough review when available. In Nepal, 50,000 IU to neonates and 100,000 IU given to infants 1-5 months produced an absolute excess rate of bulging fontanelle of 0.5% (West, 1992).

## **6. CONCLUSIONS AND RECOMMENDATIONS OF THE META-ANALYSIS AND REVIEW**

### **6.1 Pneumonia-specific mortality**

6.1.1 Supplementation with vitamin A has no consistent overall detrimental or protective effect on pneumonia-specific mortality between 6 months and 5 years of age. This is in contrast to the demonstrated impact of vitamin A supplementation on total, diarrhoea-specific and measles-specific mortality.

Within this age range, there is no apparent effect of age on the linkage of vitamin A with pneumonia-associated mortality.

6.1.2 There are insufficient data on infants in their first 6 months of life to make any judgement about risk of pneumonia-specific mortality in this age-group.

### **6.2 Total mortality**

6.2.1 Supplementation with vitamin A decreases total mortality of children between 6 months and 5 years in areas where xerophthalmia is a public health problem.

Within this age range, there is no consistent effect of age on the relationship between vitamin A supplementation and mortality.

6.2.2 Limited available data from children aged under 6 months who were supplemented with 50,000 or 100,000 IU do not suggest the same protective effect on total mortality in this age-group. Current available data cannot rule out the possibility of either an increase or decrease in risk of mortality in the first 6 months of life.

Several members of the group were concerned about the possibility of a substantially increased risk of mortality associated with vitamin A supplementation in the first few months of life.

### **6.3 Pneumonia incidence**

6.3.1 Supplementation with vitamin A has no overall effect on pneumonia incidence as measured by cough plus a measured increase in respiratory rate among children between 6 months and 5 years of age.

The data suggest the possibility of a small trend with age, with a decrease in pneumonia incidence in older children and an increase in young children. This merits further exploration in future studies.

6.3.2 There are almost no data in infants under 6 months.

- 6.4 There is a suggestion of a trend of increasing beneficial impact of vitamin A supplementation on total mortality and on pneumonia incidence with increasing levels of population xerophthalmia rates and with increasing levels of underdevelopment (as assessed by a crude development score suggested during the meeting). This latter trend will be explored further using, for example, GNP or IMR, as indices of deprivation/underdevelopment, and reported in the detailed report of the meeting.

## 7. IMPLICATIONS OF THE DATA FOR VITAMIN A SUPPLEMENTATION

Although the primary objective of the meeting was to complete the meta-analysis and review, the group was also asked to explore the implications of these data for the safety and efficacy of two proposed approaches to vitamin A supplementation in young children in areas where xerophthalmia is a public health problem - supplementation linked with vaccination contacts and with clinic visits for illness.

- 7.1 Given the current interest in the possibility of giving small doses of vitamin A with immunization at 6, 10 and 14 weeks, it was considered that further data must be collected promptly, before programmatic recommendations on supplementation in the first few months of life can be made.
- 7.2 Given the wealth of data regarding the positive benefits of giving vitamin A supplements to children aged 6 months and above, and given that many of the trials for logistical reasons ended up including children aged five months, it was considered that vitamin A supplementation, linked to the third DPT and measles immunization, in areas where xerophthalmia is a public health problem, would potentially be of great benefit, provided that this was only given to children presenting at 20 weeks of age or later for immunization.

However, data regarding toxicity require further review to establish a recommended dosage at 20 weeks and the minimal interval between doses. It was emphasized that a recommendation of this kind would only apply to areas where xerophthalmia is a public health problem. The logistics and requirements for child records to assure adequate intervals between vitamin A doses require further examination before implementation.

- 7.3 Recommendations for vitamin A supplementation after 20 or 24 weeks of age linked to clinic visits for illness in areas where xerophthalmia is a public health problem should be explored further.
- 7.4 The safety of vitamin A supplementation at 6, 10 and 14 weeks of age with immunization in terms of (i) acute toxicity; (ii) response to immunization;

(iii) risks of increased morbidity and mortality; and (iv) the possible benefits of supplementation in improving vitamin A status, promoting growth and reducing the risks of morbidity and mortality should be examined in the context of randomized, controlled trials.

Plans for such trials were presented and briefly discussed. In the context of these trials, the significance of acute toxicity signs (particularly bulging fontanelle) in terms of neurological development during the first year of life and beyond should be explored.

IMPACT OF VITAMIN A SUPPLEMENTATION ON MORBIDITY AND MORTALITY FROM CHILDHOOD AND PNEUMONIA.

TABLE 1A: STUDY DESIGN PARAMETERS (MORTALITY STUDIES).

study	Trial population, recruitment and randomization.	Masking	Size of trial	Surveillance	ARI data collected
JUMLA (Nepal)	"Opportunistic trial", children 1-59 months, given single dose.	Not masked, 8 of 16 "panchayats" randomly selected.	7,197 children (3786 vit A), followed up for 127,135 child wks over 20 weeks.	Two-weekly active surveillance for pneumonia, with registration of vital events, VPMs for cause of death.	Pneumonia incidence and mortality.
MADURAI (India)	Children 4-72 months, weekly dosing, randomized by cluster. 286 clusters.	Double masked, 2 colours.	15,419 children (7,655 plac, 7,764 vit A), followed up for 670,740 child wks over 52 weeks, >90% received >70% of intended dose.	Weekly home visits for ascertainment of morbidity and mortality, VPMs to establish cause of death.	Pneumonia incidence and prevalence, pneumonia mortality.
SARLAHI (Nepal)	Children 0-72 months, continuous recruitment, randomized by "wards", 270 wards, 4-monthly dosing.	Double masked, 4 codes.	Approx 39,000 chn (11,918 0-5 mon), followed up for 31,416 child yrs over 16-24 months, <4% loss to follow up, 93% avr capsule coverage.	Weekly prevalence morbidity data obtained at 4-monthly mortality surveillance visits.	Prevalence of reported symptoms of pneumonia, pneumonia mortality.
VAST-CSS (Ghana)	Children 6-95 months, continuous recruitment at 4-monthly dosing, randomized by clusters, 185 clusters.	Double masked, coded by cluster.	21,906 children (10,990 plac, 10,916 vit A), followed up for 33,287 child yrs for up to 24 mon, 9% loss to follow up, 89% average capsule coverage.	4-monthly mortality surveillance, one-week and point morbidity prevalence data obtained, CKI notification of deaths, VPMs for cause of death.	Prevalence of reported symptoms of ARI and ALRI mortality.
HAITI.	Children 6-83 mon, recruited at start, randomized by household, 4-monthly dosing.	Double masked, 2 colours	Approx 11,124 chn (4,994 plac, 6,130 vit A), followed up for 12 months, 1.9% loss to follow up, 92% received at least one dose.	Two-week morbidity prevalence data obtained within 4-monthly surveillance visits.	Prevalence of ARI symptoms, no pneumonia mortality data.
ACER (Indonesia)	Children 12-71 mon, recruited at start, randomized by village, 450 villages, 6-monthly dosing.	Not masked	25,200 children (12,209 plac, 12,991 vit A), followed up for 9-13 months, 11% loss to follow up, 93% received at least one dose.	One week morbidity prevalence, and mortality surveys at baseline, and 9-13 months later.	Prevalence of cough lasting more than 24 hours.
HYDERABAD (India)	Children 12-59 mon, recruited at start, randomized by village, 84 villages, 6-monthly dosing.	Double masked, 2 colours	14,082 children (7,006 plac, 7,076 vit A), followed up for 12 months, 93% received at least one dose.	4-week morbidity prevalence data obtained within 3-monthly surveillance visits.	Prevalence of cough lasting more than 24 hours.
SUDAN	Children 9-72 months, recruitment at start, 6-monthly dosing, randomized by household	Double masked, 2 colours.	28,753 children (14,298 plac, 14,455 vit A), followed up for 18 months.	6-monthly mortality surveillance, with collection of one-week morbidity prevalence data.	Prevalence of reported symptoms of pneumonia, and symptoms associated with death.

NOTES: VPM: Verbal post-mortem; CKI: Community key informants

TABLE 1B: (MORBIDITY STUDIES):

study	Trial population, recruitment and randomisation.	Masking	Size of trial	Surveillance	ARI data collected
DELHI (India)	Children 12-60 months, presenting with acute diarrhoea at a clinic, continuous recruitment, individually randomized.	Double masked	900 children, (equal numbers vit A and plac), followed up for 90 days after a single dose of supplements, 5% loss to follow up.	Twice weekly home visits, with 72hr to maximum 7 day recall.	Incidence and duration of reported symptoms of pneumonia and measured breathing rate. No aetiology data. Clinic attendance data available.
VAST-CHS (Ghana)	Children 6-59 months, continuous recruitment at weekly home visits, individually randomized in blocks of 4.	Double masked, capsules individually packaged.	1455 children, (733 placebo 722 vitamin A), followed up for 61,602 child wks, 3 dosing rounds over 12 months. <5% loss to follow up, average 95% capsule coverage.	Weekly home visits with prompted daily recall over a 7-day period, recall aided by pictorial daily health diary kept by mothers. Monthly visits for anthropometric surveillance, and 4-monthly for vit A status.	Incidence and duration of reported symptoms of pneumonia, measured breathing rate and observed indicators of severity. No aetiology data. Clinic attendance and hospital admission data collected.
MORVITA (Indonesia)	Children 6-48 months, continuous recruitment at 4-monthly dosing, individually randomized in blocks of 4.	Double masked, coded by individual	1400 children, (approx equal numbers vit A and placebo), followed up for 78,202 child wks, 6 dosing rounds over a 24 month period. <2% loss to follow up.	Home visits every other day, with 48-hour prompted recall of morbidity. RR measured if cough reported, referral to pediatrician if RR>35/min.	Incidence and duration of reported symptoms of pneumonia and measured breathing rate. No aetiology data. Clinic attendance data can be obtained from health facilities in the study area.
BAHIA (Brazil)	Children 6-48 months, fixed cohort recruited at start, individually randomized.	Double masked,	1240 children, (equal numbers vit A and plac) followed up for 57,839 child wks, 3 dosing rounds over a 12 month period. <2% loss to follow up.	Thrice weekly home visits with 48/72hr prompted recall of morbidity. RR measured if cough reported, referral to pediatrician if RR>40/min.	Incidence and duration of reported symptoms of pneumonia and measured breathing rate. No aetiology data. Clinic attendance data available.

TABLE 2A: BASELINE CHARACTERISTICS (MORTALITY STUDIES):

Social/ Economic status	Availability of Health services	Age distribution	Vitamin A status/intake	ARI morbidity	Nutrition status	Xerophthalmia rates
<b>JUMLA (Nepal):</b> Rural agricultural, dry, small farmers with pci<USD70/year, extremely poor sanitation and water availability, about 5% maternal literacy.	Poorly served by govt. health facilities, no pre- existing vitamin A supplementation, low immunization coverage (msl=15%)	1 - 24.2% 12 - 22.3% 24 - 18.8% 36 - 19.1% 48+- 15.5%	serum ret. not determined	pneumonia incidence 1.6 epi/chdyr (0-11mo), 0.86/chdyr (0-4 years).	26% of children have MUAC <12.5cm	4.7% XN 8.2% X1B 0.3% X2, X3 0.5% X8
<b>MADURAI (India):</b> Dry and severely drought prone, rural farmers, poor water and sanitation, 35% maternal literacy.	Poorly served, no regular vitamin A distribution, 44% use mid-day feeding pro., low immunization coverage (BCG and msl=5%-15%, DPT/OPV=47%).	4 - 1.7% 6 - 8.4% 12 - 19.2% 24 - 23.1% 36 - 21.1% 48 - 21.4% 60+- 5.1	serum ret. (umol/L): <0.35 - 19% 0.35 - 17% 0.70 - 17% 1.05 - 48%	4-week prevalence: URI <sup>1</sup> = 34% LRI <sup>2</sup> = 6.7%	Ht./age: 31% <2SD Wt./age: 23% <2SD Wt./ht: 17% <2SD	3.7% XN 7.2% X1B 0.1% X2, X3, X8.
<b>SARLAHI (Nepal):</b> Rural, flat plains; fairly good water availability and sanitation; 10% maternal literacy; poor economic status.	Fairly well served; vit A available for treating xero.; approx 60% vacc for measles.	0 - 19.6% 12 - 20.4% 24 - 20.0% 36 - 18.9% 48+- 21.0%	serum ret. not determined	pneumonia incidence 1.14 epi/chdyr.	mean Z score: Ht./age = -2.2; Wt./age = -2.1 Wt./ht = -0.9	2.8% XN + X1B
<b>VAST-CSS:</b> Mainly rural, small- scale subsistence farming; poor sanitation and available water, maternal literacy less than 10%	Poorly served in study area, no pre-existing vitamin A prog., 57% children 12-23 months vacc for BCG, 45% for measles, 31% for DPT3.	6 - 24% 12 - 18% 24 - 15% 36 - 15% 48 - 14% 60+- 26%	serum ret. (umol/L): <0.35 - 14.4% 0.35 - 43.1% 0.70 - 42.5%	63% weekly prevalence of cough or difficulty in breathing	Ht./age: 46% <2 SD Wt./age: 44% <2 SD Wt./ht.: 17% <2 SD	<1% XN 0.02% X1B 0.02% X2, X3 0.09% X8
<b>HAITI</b> Mountainous region, over 80% rural, mainly subsistence farming; poor sanitation and water availability.	Poor access, 8.2% coverage for vitamin A distribution; very low immunization coverage.	0 - 5.8% 6 - 9.2% 12 - 11.0% 18 - 11.2% 24 - 21.8% 36 - 21.2% 48+- 19.9%	serum ret not determined	prevalence: rhinitis 74%, cold/flu 68%, cough 53%, rapid breathing, 26%.	30% <90% ht./age median, 6.3% <80% ht/wt median.	0.3% X1A 0.14% X2, X3, X8.
<b>ACEH:</b> Predominantly rural agricultural area, generally poor sanitation and water availability	Well served, minimal pre- existing vitamin A prog.; no immunization coverage data.	<12 - 16.1% 12 - 15.6% 24 - 16.5% 36 - 17.0% 48 - 14.3% 60+- 20.5%	serum ret. not determined	20% prevalence of cough.	2.1% of children severely malnourished.	0.7% XN 2.7% X1B
<b>HYDERABAD (India)</b> Rural agricultural area with pci <USD5/month; poor sanitation and water availability, about 9% maternal literacy. IMR = 50/1000	Fairly well served, in study area, no pre-existing vitamin A prog., 30-35% average immunization coverage.	<12 - 22.6% 12 - 22.3% 24 - 22.9% 36 - 23.2% 48-59 9.1%	intake: 75-100 URE in preschool children.	not available	Wt./age: 6%-9% <60% NCHS; 95% <90% NCHS standard.	2.0% XN 4.0% X1B 0.02% X2, X3
<b>SUDAN:</b> Arid rural area with variable sanitation and water availability, maternal literacy about 30%.	Scarce government services, no pre-existing vitamin A prog., immunization coverage low.	9 - 46% 36 - 50% 72+- 4%	some data on intake obtained; not yet available	20% prevalence of cough.	Ht./age: 38% <2 SD Wt./age: 6% <2 SD Wt./ht.: 6% <2 SD	0.7% XN 2.7% X1B

NOTES: pci: per capita income; msl: Measles  
<sup>1</sup> URI = cough and/or nasal discharge with/without fever.  
<sup>2</sup> LRI = cough, nasal discharge and fever with chest indrawing.

IMPACT OF VITAMIN A SUPPLEMENTATION ON MORBIDITY AND MORTALITY FROM CHILDHOOD AND PNEUMONIA.

TABLE 2B: BASELINE CHARACTERISTICS (MORBIDITY STUDIES):

social/ Economic status	Availability of Health services	Age distribution	Vitamin A status/intake	ARI morbidity	Nutrition status	Xerophthalmia rates
<b>DELHI (India):</b> Urban slum,	Good access to health facilities, pre-existing vit A capsule prog. had been suspended past 2 years,	12 - 49.6% 24 - 25.1% 36+- 25.3	serum ret. (umol/L): very few samples taken	not available	not available	3.76% XN, XIa and XIb
<b>VAST-CBS (Ghana)</b> Mainly rural, small-scale subsistence farming; poor sanitation and available water, maternal literacy less than 10%	No health facility in study area, no pre-existing vitamin A prog., 60% children 11-23 months vacc for BCG, 51% for measles, 30% for DPT3, 25% fully immunized.	6 - 18.0% 12 - 30.2% 24 - 25.8% 36 - 19.0% 48+- 7.1%	serum ret. (umol/L): <0.35 - 15.3% 0.35 - 57.1% 0.70 - 21.1% 1.05+ 6.5%	4.8% probable pneumonia (1 week period prevalence)	Ht./age: 52% <2 SD Wt./age: 43% <2 SD Wt./ht.: 5.4% <2 SD	1.36% XN 0.17% XIb
<b>MORVITA (Indonesia):</b> Rural, coastal Java; ample water but not always safe; maternal literacy about 80%, mainly farmers with land, most with a monthly household income of US\$10-39.	Well served; no feeding prog., 17% children had received vit. A capsules in the past year; 30% vacc for measles 40%-50% for OPV1-3.	6 - 14.0% 12 - 12.7% 18 - 13.7% 24 - 27.7% 36 - 29.8% 48+- 2.9%	serum ret. (umol/L): <0.35 - 6.4% 0.35 - 52.3% 0.70 - 37.0% 1.05+ 4.2%	not available	Ht./age: 42% <2 SD Wt./age: 41% <2 SD Wt./ht.: 9% <2 SD	No cases noted at baseline.
<b>BAHIA (Brazil):</b> Small urban town, jute plantation and gold mining activity, >66% adult literacy levels, 96,2% houses with piped water, 73% with toilets.	Well served with easy access to hospitals and health centres, no pre-existing vit A prog, approx 85% vacc for BCG, 65% measles, 65% for OPV1-3.	6 - 12.7% 12 - 13.4% 18 - 14.0% 24 - 25.8% 36-47 30.8%	serum ret. not determined in study popu. Survey in neighbouring area showed approx 50% children 0-59 months with <0.7umol/L.	not available	mean Z scores: Ht./age = -1.15 Wt./age = -0.80 Wt./ht. = -0.07	No cases noted

NOTES: pci: per capita income; msl: Measles

REVIEW OF THE IMPACT OF VITAMIN A SUPPLEMENTATION ON MORBIDITY AND MORTALITY FROM CHILDHOOD AND PNEUMONIA.

Table: DATA CONTRIBUTED BY FIELD STUDIES:

Type of study	Studies	Incidence	Period prevalence	Severity	Clinical assessments	Health facility utilisation	Pneumonia mortality
<b>MORTALITY STUDIES:</b>							
Single dose	JUMLA	X					X
Weekly dose	MADURAI	X	X				X
4-monthly dose	SARLAHI		X	X			X
	VAST-CSS		X				X
	HAITI		X				
6-monthly dose	ACEH		X				
	HYDERABAD		X				
	SUDAN		X				X
<b>MORBIDITY STUDIES:</b>							
Single dose	DELHI	X	X	X			
4-monthly dose	VAST-CHS	X	X	X	X	X	
	MORVITA	X	X	X		?	
	BAHIA	X	X	X	X	X	

## REFERENCES

- Arthur P, Kirkwood B, Morris S, Gyapong J, Tomkins A, Addy H. Letter: Impact of vitamin A supplementation on childhood morbidity in northern Ghana. *Lancet* 1992; 339:361-2.
- Barclay AJG, Foster A, Sommer. Vitamin A supplements and mortality related to measles: a randomised clinical trial. *Br Med J* 1987; 294-96.
- Beaton GH, Martorell R, L'Abbe KA et al. Effectiveness of vitamin A supplementation in the control of young child morbidity and mortality in developing countries. Report submitted to CIDA. December, 1992.
- Bloem MW, Wedel M, Egger RJ, et al. Mild vitamin A deficiency and risk of respiratory tract diseases and diarrhoea in preschool and school children in Northeastern Thailand. *Am J Epidemiol* 1990; 131:332-39.
- Coutsoudis A, Broughton M, Coovadia HM. Vitamin A supplementation reduces measles morbidity in young African children: a randomized, placebo-controlled, double-blind trial. *Am J Clin Nutr* 1991; 54:890-95.
- Daulaire NMP, Starbuck ES, Houston RM, et al. Childhood mortality after a high dose of vitamin A in a high risk population. *Br Med J* 1992; 54:890-95
- El Bushra HE, Ash LR; Coulson AH, Neumann CG. Interrelationship between diarrhoea and vitamin A deficiency: is vitamin A deficiency a risk factor for diarrhoea? *Ped Inf Dis J* 1992; 11:380-84
- Hussey GD, Klein M. A randomized, controlled trial of vitamin A in children with severe measles. *N Eng J Med* 1990; 323:160-64.
- Milton RC, Reddy V, Naidu AN. Mild vitamin A deficiency and childhood morbidity - An Indian experience. *Am J Clin Nutr* 1987; 46:829-29.
- Muhilal, Permeisih D, Idjradinata YR, et al. Reduced mortality among children in southern India receiving a small weekly dose of vitamin A. *N Engl J Med* 1990; 323:929-35.
- Rahmathullah L, Underwood BA, Thulasiraj RD, et al. Reduced mortality among children in Southern India receiving a small weekly dose of vitamin A. *N Engl J Med* 1990; 323:929-95.
- Sommer A, Katz J, Tarwotjo I. Increased risk of respiratory disease and diarrhoea in children with pre-existing vitamin A deficiency. *Am J Clin Nutr* 1984; 40:1090-95.
- Sommer A, Tarwotjo I, Hussaini G, Susanto D. Increased mortality in children with mild vitamin A deficiency. *Lancet* 1983; ii:585-88.

Sommer A, Tarwotjo I, Djunaedi E, et al. Impact of vitamin A supplementation on childhood mortality: a randomised controlled community trial. *Lancet* 1986; i:1169-73.

West KP Jr, Pokhrel RP, Katz J, et al. Efficacy of vitamin A in reducing preschool child mortality in Nepal. *Lancet* 1991; 338:67-71.

West KP, Khatri SK, Leclerc SC et al. Tolerance of young infants to a single, large dose of vitamin A: a randomized community trial in Nepal. *Bull WHO* 1992; 70(6):1-10.

World Health Organization, 1992. Potential interventions for preventing pneumonia among young children, Report of a Meeting, Geneva 2-4 March 1992 unpublished.