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Clinical Research on Treatment of Measles: report of a meeting

Banjul, Gambia, 3-5 November 1993

Division of Diarrhoeal and Acute Respiratory Disease Control

Global Programme for Vaccines and Immunization
Expanded Programme on Immunization

World Health Organization
Geneva

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WORLD HEALTH ORGANIZATION

JOINT CDR/EPI CLINICAL RESEARCH CONSULTATION ON TREATMENT OF MEASLES

3-5 November 1993, Banjul, The Gambia

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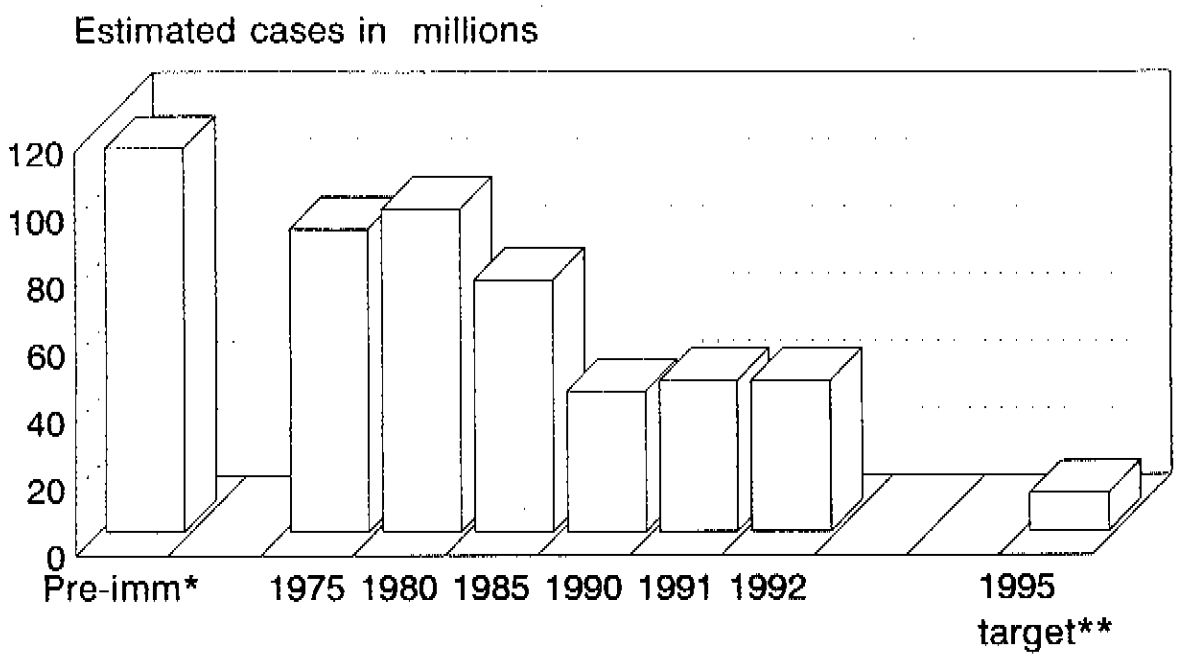
1. PURPOSE OF THE MEETING

The meeting was called by WHO (Division of Diarrhoeal and Acute Respiratory Disease Control, and Expanded Programme for Immunization) to examine the current state of knowledge on the clinical case management and treatment of complications of measles, to identify areas of lack of or deficient knowledge about treatment, and to plan studies in clinical research which would provide the missing information.

2. GLOBAL SITUATION

In 1989 the World Health Assembly declared the commitment of WHO to the global control of measles. The declaration included the goal of reducing measles by 90% compared with pre-immunization levels. Following this, on 30 September 1990, the World Summit for Children expanded the declaration to: "Reduction by 95 per cent in measles deaths and reduction by 90 per cent of measles cases compared with pre-immunization levels by 1995, as a major step to the global eradication of measles in the longer run." Progress towards reaching these goals is summarized in Figure 1).

Figure 1. Progress towards reaching the 1995 global goal of 95% reduction in estimated measles deaths



Source: EPI Information System, as of September 1993
* Pre-immunization rates of measles disease applied to projected 1995 population statistics
** 90% reduction target applied to projected 1995 population statistics

Many countries have already achieved 95% reduction in deaths. However in most developing countries, raising coverage with measles vaccine to even higher levels will not be sufficient to reduce deaths by 95% by 1995. Additional measures will be needed, including improvement of case management and treatment of complications.

3. INTEGRATED GUIDELINES FOR THE MANAGEMENT OF THE SICK CHILD

WHO and UNICEF are currently collaborating in the development of an integrated approach to the management of the sick child. Globally, acute respiratory infections (mostly pneumonia), diarrhoea, malaria, measles, and malnutrition cause seven out of 10 deaths in children under five years of age in developing countries. The integrated guidelines for the management of the sick child focus the health workers' training and attention not on one but on all of the leading killers of young children which can be effectively managed with simple, affordable treatments. These main contributors to death are also responsible for tremendous morbidity, accounting for a large proportion of outpatient clinic visits. In addition to addressing the leading killers of young children, the integrated guidelines also instruct health workers how to prevent serious disabilities, such as blindness resulting from measles and vitamin A deficiency, and to manage many of the common illnesses which cause mothers to seek care (e.g. otitis media, which is a common cause of fever in young children and the leading preventable cause of deafness, and anaemia).

The relevant technical programmes and units at WHO and UNICEF are working together to integrate their advice on clinical management and on the organization of health services. This developmental effort is coordinated by the WHO Division of Diarrhoeal and Acute Respiratory Disease Control (CDR) and involves the following WHO headquarters divisions, programmes and units: Programme for the Control of Acute Respiratory Infections (ARI), Diarrhoeal Disease Control Programme (CDD), Division of Communicable Diseases (CDS), Drug Action Programme (DAP), Expanded Programme on Immunization (EPI), Malaria Control (MAL), Maternal and Child Health (MCH), Nutrition (NUT), Oral Health (ORH), and the Programme for the Prevention of Blindness (PBL). It also involves the Child Survival and Bamako Initiative Units of UNICEF.

Previous separate disease-specific clinical guidelines and training activities leave the difficult task of integration to the health worker in his or her encounter with the sick child and caretaker. This new approach offers a substantial advantage in efficiency and economy in training, supervision and management of health facilities, including standard drugs and job aids. Efficient triage and case management of sick children in outpatient settings should ensure urgent referral or treatment of severely ill children and improve management of the major illnesses present.

Initial development efforts have been focused on the technical core of the clinical guidelines for the management of the sick child at first level health facilities. The integrated clinical guidelines for use with sick children aged 2 months up to 5 years by first-level facility health workers are summarized on three case management charts. The first, **Assess and Classify the Sick Child Age 2 Months Up to 5 Years**, summarizes how to assess the sick child and classify the illness. After the health worker checks for danger signs (convulsions during this illness, a child who is lethargic or unconscious, or not able to drink or breastfeed, a child who vomits everything), the caretaker is asked a series of key questions:

Does the child have cough or difficult breathing?
Does the child have diarrhoea?
Has the child had fever?
Does the child have an ear problem?

Depending on the answer to each question, further questions are asked and the child is examined for key clinical signs. Then all sick children are checked for signs of malnutrition and anaemia. This information is used to classify the illness using a colour-coded triage system already made familiar to health workers by the existing case management charts for diarrhoea and acute respiratory infections. The classification leads to treatment instructions which are summarized on a second chart, **Treat the Child**. A third chart, **Counsel the Mother**, summarizes the advice on home management that must be given to the caretaker.

In the integrated guidelines for the management of the sick child, a child is classified as having measles if he or she has a generalized rash <u>and</u> one of the following: cough, runny nose or red eyes. Children with measles are examined for mouth ulcers, pus draining from the eye and clouding of the cornea. All children with measles are given vitamin A. Urgent referral to hospital is recommended for those with severe pneumonia, stridor when calm (which may indicate life-threatening laryngotracheitis), corneal clouding, deep or extensive mouth ulcers, severe malnutrition or danger signs.

Mothers are taught how to manage at home a mouth complication (with gentian violet) and an eye complication (with tetracycline eye ointment) and how to administer antibiotics for otitis media and pneumonia. The management of diarrhoea complicating measles is unchanged from non-measles associated diarrhoeal disease, with the exception of a follow-up visit in two days for children with eye or mouth complication, or with dysentery. A follow-up visit is also recommended after five days if the child is not better.

4. PATHOGENESIS OF MEASLES

Measles is a widespread and severe viral infection of the lymphoid and epithelial tissues. The virus initially infects lymphocytes and macrophages, and multiplies greatly in these cells; it then escapes to infect the skin and epithelia of the eye, nasopharynx, lung and gut. The rash is caused by a massive allergic response due to the union of sensitized lymphoid cells and measles antibody with the virus in the skin. A similar reaction occurs in the epithelium producing conjunctivitis, stomatitis, pneumonitis and acute inflammation of the gastrointestinal tract. This allergic reaction which clears the virus is followed by a period of profound anergy during which delayed hypersensitivity and many other immune responses are diminished or completely abrogated.

The immune damage which may last for many weeks results in increased susceptibility to other infections such as the pneumococcus and to a recrudescence of endogenous microbes such as herpes virus in the eye or mouth and candida in the mouth and gut. These infections are often severe and may respond poorly to treatment as the child is still immunocompromised and may also be malnourished.

5. CASE FATALITY RATES

Case fatality rates (CFRs) vary tremendously between countries, between communities and even in the same community from one epidemic to another. Reports of CFRs as high as 50% have occasionally been reported in past outbreaks. However, WHO EPI allocates rates to countries based on literature reviews and feedback from countries. These values range from 6% in high-risk African countries to 0.1% in many industrialized countries. The goal is to reduce all CFRs globally to below 1% by 1995. Strategies for this include raising coverage rates, delaying age of onset of illness, and improving case management which includes assessment, classification and treatment.

6. CLINICAL PROBLEMS ASSOCIATED WITH MEASLES

6.1 Literature review

It is well recognized that measles is associated with a significant number of complications. However the natural history of measles and its associated complications have not been well defined in the literature. Of particular importance is the lack of information on the temporal association between measles and associated complications, and the aetiology and management of these problems. Most of the information comes from retrospective hospital-based record reviews. These have been primarily descriptive in nature, focusing on major complications such as pneumonia, croup and diarrhoea. This is not unexpected, given that these are the leading causes of death in measles. In addition comparison of data between countries, and even between different regions within a country, is problematic because of the non-uniformity of the criteria used for defining the complications.

Data from the reviewed literature suggest that complications that occur early in the clinical course (during the first week of the illness), such as croup, diarrhoea and pneumonia, are probably due to the effects of the measles virus itself. Later complications (after the first week of the illness) are usually caused by secondary viral or bacterial infections. Post-measles pneumonia (frequently due to *Streptococcus pneumoniae*, *Staphylococcus aureus*, herpes virus and adenovirus), croup and diarrhoea are the most common life-threatening complications. Post-measles blindness may be the result of measles virus infection, secondary bacterial and herpes infection, vitamin A deficiency or a chemical conjunctivitis. Other common complications include malnutrition, otitis media, severe stomatitis (candida and herpes virus) and neurological problems.

Although measles is probably the most common childhood infectious disease worldwide, data on inpatient and outpatient management and on the associated complications of measles are virtually non-existent. The only recent publications on management relate to vitamin A therapy in hospitalized cases of measles. Of particular significance is the absence of good clinical trials relating to the prevention and treatment of the complications.

The literature review highlighs the urgent need for studies that address ways in which the morbidity and mortality of measles can be reduced. A number of proposals were put forward. These included the treatment of pneumonia, croup, diarrhoea, stomatitis, conjunctivitis and malnutrition. In addition the need was recognized for more detailed documentation of the natural history of the disease, as this would be informative in terms of the management of complications. The various proposals are discussed below in the section on research priorities.

6.2 Antibiotic usage in measles cases in Senegal

During a measles vaccine trial in Senegal between 1987 and 1993, measles cases were treated with prophylactic cotrimoxazole to evaluate the impact on frequency of respiratory complications. Results of the study showed that infants receiving prophylactic cotrimoxazole during the first week of illness developed less respiratory complications during their second week of illness compared with controls. Also, children aged three years and over who were not seen by the physician during their first week of illness presented with more respiratory complications in the second week than the group who were seen by the physician during their first week of illness. It was concluded that prophylaxis with cotrimoxazole diminished the frequency of respiratory complications following measles, but that a larger study was needed to confirm this.

7. ETHICAL ASPECTS OF MEASLES RESEARCH

Research on measles treatment in developing countries poses particular ethical problems. Ethical research on human subjects in general involves a balance between the ability of the consent-giver to understand a project, the element of trust which exists in the relationship between the consent-giver and the investigator, and the belief of the investigator that research will benefit the participant and the wider community. With measles research the site of the study is crucial. It may be tempting to carry out a study in a refugee camp in the midst of an epidemic, but such research would not be ethical unless accompanied by a vaccination program. Furthermore, the ability of refugees to give free consent is doubtful and is unlikely that a trusting relationship would exist between them and a prospective investigator.

Research into the treatment of measles falls into two broad categories: manipulation of existing treatments and the introduction of new treatments. The former may carry the risk that a useful treatment may be dropped. It is difficult to ethically justify the removal of an existing treatment (such as the routine use of antibiotic eye ointment) when it is hard to imagine any therapeutic gain from such a strategy. It is easier to justify the addition of a new strategy (such as routine antibiotic treatment for all cases) even though there is a possibility that this will have a negative effect. In all areas of measles treatment there are new treatment strategies which could be tried (such as hyper-immune globulin for intermediate complications). The most difficult ethical question facing such studies is how the follow-up should be conducted. Intensive follow-up may negate the outcome measures being assessed. It is probably reasonable to follow cases for the first month and then review them around six months later. Whatever regimen is chosen it needs to be carefully thought through, both in terms of the impact on the study and of its ethical acceptability.

8. RESEARCH PRIORITIES IDENTIFIED

Priorities (i)-(iv) listed below are brief outlines of the proposed clinical trials while (v)-(vii) are descriptive studies, components of which could be incorporated into the clinical trials. They are described in descending order of priority.

(i) Prophylactic antibiotics

Research question. Do prophylactic antibiotics in children with acute measles prevent complications?

Motivation. Bacterial infections in measles are responsible for considerable morbidity and may be the cause of death in many children. Research on the role of prophylactic antibiotics to prevent the bacterial complications of measles is extremely limited. Many clinicians prescribe broad spectrum antibiotics for children with measles. Is this valid? Indiscriminate antibiotic use may result in the emergence of drug resistant organisms. Additionally, there is concern that antibiotics given during the acute phase of measles may change the children's flora and put them at increased risk of serious infection when they become immunodeficient during the intermediate and late stage of measles.

Study design. There is a need for a randomized placebo controlled double-blind clinical trial. Children with acute measles will be randomly assigned to receive an antibiotic (cotrimoxazole, amoxycillin with probenecid, or chloramphenicol) or identical looking placebo for 7-10 days.

Setting. Outpatient clinic.

Inclusion criteria. All children aged less than 5 years, with a clinical diagnosis of acute measles (i.e. rash present for less than 7 days).

Exclusion criteria. Children with the following conditions:

- marasmus and kwashiorkor
- AIDS
- otitis media (a bulging drum, marked unilateral inflamed eardrum or pus draining from the ear)
- pneumonia (this requires further definition, since virtually all cases of measles are associated with a "pneumonitis". It is suggested that the definition should include clinical and radiological criteria).

If, during the trial, children develop a severe complication which would require antibiotic therapy under present standards of practice, they will be treated accordingly. They will not be excluded from the trial but will be regarded as a failure of prophylaxis.

Sample size. Assuming a 25% complication rate, a 50% reduction in complications would require a total of about 700 children, and a 30% reduction would require about 2000 children. A multicentre trial may be appropriate for this.

Follow up. Children will be reassessed clinically at 21 or 30 days. They should be asked to return before that time if they are not well. Children who fail to attend the follow-up clinic should be actively sought through, for instance, a home visit.

Outcome measures. These will be the following:

- nutritional status (i.e. weight)
- frequency of complications
- admission to hospital
- frequency of clinic visits
- frequency of persistent diarrhoea
- mortality.

Additional data. Where resources permit, monitoring of antimicrobial susceptibility patterns of isolates from the nasopharynx of children in the general population is advisable to detect antibiotic resistance that may occur following widespread antibiotic usage.

Description of natural history. The study should also allow for a description of the natural history of measles and the development of complications (i.e. the control group). The data could be stratified for children at risk of severe measles (i.e. those with HIV infection, malnutrition, tuberculosis).

(ii) Management of stomatitis

Research question. What is the natural history of stomatitis in acute measles, what is the impact on nutrition and what is the most effective therapy?

Motivation. Research on this subject is virtually non-existent. The reasons for the subsequent effects of stomatitis and its treatment are not well defined.

Study design. Randomized clinical trial. Children will be randomly assigned to receive one of the following:

- gentian violet
- an antiseptic/analgesic solution (to be defined, but possibly lidocaine/tannic acid) or
- no specific therapy except routine advice about mouth care.

Setting. Outpatient clinic or hospital inpatient setting.

Inclusion criteria. All children with acute measles (rash present for less than 7 days) attending the outpatient clinic or hospitalized.

Exclusion criteria. Children with oral candidiasis and herpes stomatitis.

Sample size. Based on nutritional outcome.

Follow up. Children will be reassessed clinically at 21 or 30 days. They should be asked to return before that time if they are not well. Children who fail to attend the follow-up clinic should be actively sought, for instance, a home visit.

Outcome measures. These will be the following:

- nutritional status (i.e. weight)
- development or persistence of severe stomatitis, specifically deep herpes ulcers, candidiasis, *cancrum oris* (where applicable encourage etiological diagnosis)
- mother's report of ability to feed the child.

Description of natural history. The study should also allow for a description of the natural history of measles and the development of complications (i.e. the control group). The data could be stratified for children at risk of severe measles (i.e. those with HIV infection, malnutrition, tuberculosis).

(iii) Nutritional management

Research question. What is the optimal method of providing nutritional support to children hospitalized with measles?

Motivation. The *association* between malnutrition and measles in both the acute and recovery phase has been well documented. However the management of nutrition in measles still requires further investigation.

Study design. A randomized controlled clinical trial of accelerated feeding. One group would be given additional tube feeds for the duration of hospitalization while the other group would be managed in the conventional manner (i.e. normal ward diet, or therapeutic feeding according to nutritional status).

Setting. Hospital-based study.

Inclusion criteria. All children aged less than 2 years admitted to hospital with measles (within 10-14 days of onset of rash). There is a need to review the admission data at study sites before deciding on criteria.

Exclusion criteria. Children with severe protein energy malnutrition (PEM) who would normally be given tube feeds; children who are eating normally.

Sample size. This will be based on the assumption that the weight of the intervention group is at least 5-10% greater than that of the control group.

Follow up. Children are to be reassessed clinically at 21 or 30 days. They should be asked to return before that time if they are not well. Children who fail to attend the follow-up clinic should be actively sought, for instance, a home visit.

Outcome measures. These will be the following:

- nutritional status
- duration of hospitalization
- frequency and severity of complications.

Description of natural history. The study should also allow for a description of the natural history of measles and the development of complications (i.e. the control group). The data could be stratified for children at risk of severe measles (i.e. those with HIV infection, malnutrition, tuberculosis).

(iv) Therapy for the very sick child

Research question. Will measles immunoglobulin have an impact on morbidity and mortality in children admitted to hospital with measles? The study should address both the treatment of measles virus infection (neutralization of measles virus) and the prevention of secondary infection.

Motivation. Children with measles are at significant risk of developing secondary complications. In addition there are few therapeutic modalities for the treatment of severe measles other than antibiotics and vitamin A.

Immunoglobulin has been shown to be effective in preventing measles and other infectious diseases. It has also been shown to be effective in reducing complications in children who are at risk of secondary infections (i.e. newborns, children with AIDS and other immunodeficient diseases, children with pertussis).

Study design. A randomized controlled clinical trial. One group would receive immunoglobulin and the other albumin (dose and route of administration to be defined).

Setting. Hospitalized inpatient setting.

Inclusion criteria. All children hospitalized with acute measles (within 7 days of onset of the rash).

Exclusion criteria. Children who die within 48 hours of admission will be excluded from the analysis, but will be reported.

Sample size. This will be based on results of other trials (e.g. newborns and AIDS).

Follow up. Children to be reassessed clinically on discharge from hospital and then again 1 month following discharge. They should be asked to return before that time if they are not well. In addition children who fail to attend the follow-up clinic should be actively sought, for instance, a home visit.

Outcome measures. These will be the following:

- frequency and severity of complications
- duration of hospitalization
- frequency of clinic or hospital visits
- frequency of side-effects
- immunological parameters

Description of natural history. The study should also allow for a description of the natural history of measles and the development of complications (i.e. the control group). The data could be stratified for children at risk of severe measles (i.e. those with HIV infection, malnutrition, tuberculosis).

(v) Description of the phenomenon of delayed mortality

The phenomenon of delayed mortality is reported in certain West African studies (e.g. Hull HF et al. Measles mortality and vaccine efficacy in rural West Africa, Lancet, 1983;I:972-975). Increased morbidity is also reported in the months following measles. In addition to events following measles infection, mortality has been reported as increased in females following administration of high titre measles vaccines for many months after administration of the vaccine. The meeting felt that it was important to document the phenomenon in multiple locations. If confirmed, there would be significant implications for measles case management which would need to be dealt with. Sites suggested for this included Senegal, northern Ghana, Guinea Bissau, Kenya and Bangladesh. Where possible, this could be combined with other studies.

(vi) Documentation of natural history of complications

The natural history of measles has not been well defined in the literature. Of particular importance is the temporal association between measles and its complications, which may be of significance in terms of possible etiology.

The group felt that there was a need for improved documentation of the natural history of the disease, particularly:

- assessment of risk factors for severe disease
- etiology
- standardization of definition of complications
- temporal relationships.

(vii) Operational issues

Motivation. The WHO/UNICEF training course *Management of Childhood Illness* teaches integrated clinical guidelines for management of the sick child at first-level (outpatient) health facilities. It would be important to compare the assessment, classification and treatment decisions of a health worker trained to use the sick child case management charts with those of an expert clinician, in a setting with endemic measles.

Study design. The study would be a comparison of the assessment of clinical signs, classification of illness and treatment of children presenting with acute measles by health workers and an expert paediatrician.

Setting. Outpatient clinic.

Outcome measures. These are successful classification and appropriate treatment choices by the health worker and the expert clinician. This study could be combined with the stomatitis treatment trial.

9. AREAS OF RESEARCH CURRENTLY DETERMINED TO BE UNSUITABLE FOR CONTROLLED CLINICAL TRIALS

A number of research proposals were discussed, as possible areas for fruitful research in terms of measles case management. On discussion during the meeting, however, it was felt that they were not appropriate at present because of ethical or practical issues. They were also regarded as related to areas of low priority.

(i) Treatment of pneumonia

The proposed study would determine whether duration of antibiotic therapy (i.e. 5 vs 10 days) and choice of antistaphylococcal regimen have an impact on pneumonia morbidity and mortality associated with measles.

The study was finally rejected by the group because:

- it would be unethical to have a placebo non-treatment group (all cases of pneumonia require antibiotics);

- there was no room for exploring the value of using alternative, suboptimal antistaphylococcal antibiotics within the trial.

(ii) Treatment of croup

The proposed study would evaluate the impact of nebulized epinephrine on outcome in patients with measles-associated croup. Nebulized epinephrine is used as therapy in children with croup in some countries. Efficacy data in developing countries and in children with measles are lacking. There is also some controversy as to the therapy's efficacy. An additional motivation for such a study is that there is no specific therapy for measles croup in most developing countries and it is a significant cause of both morbidity and mortality.

The study could be a randomized placebo controlled trial with one group receiving nebulized epinephrine and the other nebulized saline. This study would of necessity be carried out in hospital. The outcome indicator would be clinical improvement as measured by, for instance, croup score.

This study was finally rejected by the group because ethically it would be impossible to have a placebo arm of the trial, especially in situations where there was no access to intensive care or airway intervention. The treatment (even if there was controversy about its efficacy) could not be withheld from children with croup in such situations. It was however felt that there is need for documentation of the benefits of nebulized epinephrine, particularly in hospitals where there is the possibility of airway intervention. At minimum, a demonstration study to clarify guidelines for use in developing countries is needed. In addition, the potential benefit of acyclovir in herpes-associated croup needs investigation.

(iii) Prophylactic antibiotics in cases of conjunctivitis

The proposed study would determine the most effective way of treating conjunctivitis in children with measles. Conjunctivitis is part of the clinical presentation of measles. It is frequently aggravated by secondary infections, particularly bacterial ones. Current WHO recommendations on the sick child case management charts are that tetracycline ointment be prescribed for children with conjunctivitis with pus. However, many clinicians dispense ointment for all cases of conjunctivitis. Is this effective or not, and does it prevent further infections?

The group finally rejected this study on the basis that, if no topical therapy was offered, mothers would use alternative and often dangerous therapies. Therefore a second arm of topical therapy limited to children with conjunctivitis with pus was not a realistic research option. The adaptation guide for the sick child guidelines will mention the option of treating all children with measles conjunctivitis with tetracycline eye ointment.

(iv) Vitamin A prophylaxis

The proposed study would evaluate the efficacy of prophylactic vitamin A in uncomplicated cases of measles in an outpatient setting. It was noted that all the published studies on the efficacy of vitamin A therapy have been done in children hospitalized with severe measles.

The group felt this issue was already satisfactorily documented and there was no further need to document the value of vitamin A administration during the treatment of cases of measles. It was noted that the Zambian clinic- based prophylaxis study suggested benefit and the community-based supplementation trial has shown a reduction in measles-associated mortality. The current recommendation of WHO is that all children with measles should receive vitamin A when they present to clinic or hospital. The group noted that no data were available on active community-based case finding for vitamin A treatment of measles.

(v) Treatment of herpes stomatitis and conjunctivitis

If such a diagnosis were to be made, specific anti-herpetic therapy would be required (acyclovir). The group felt there was no need for research in this field given the current high cost of this therapy.

(vi) Treatment of persistent diarrhoea

The group felt this was a complex area which had already been extensively researched. Results of studies currently underway are awaited and may be helpful in developing further management guidelines for measles complicated by persistent diarrhoea.

(vii) Relationship between HIV/AIDS and measles

The proposed study would evaluate the consequences of measles in children with asymptomatic HIV infection and in children with AIDS.

The group felt the was no need to undertake specific additional studies but that some of the issues of concern could be evaluated in the antibiotic prophylaxis study. HIV status needs to be included as a variable in most of the above studies to permit adequate data interpretation in areas with significant HIV prevalence.

10. CONCLUSIONS

Measles remains a major cause of morbidity and mortality. Little is known about the etiology, prevention and management of measles-associated complications. The meeting identified a number of research areas that would possibly resolve many of these current uncertainties. Such research may result in more effective strategies for the case management of measles and thus contribute to a reduction of associated disability and death. The list of priorities is not exhaustive. It was felt that the ones proposed were at best the minimum necessary to possibly meet the WHO goal of reducing case fatality rates. It was also felt that the focus should be on carrying out a few well conducted clinical trials rather than attempting to do too many. Research activities that are not mentioned in this report are nevertheless also encouraged. This includes other related areas of research, including those directed towards primary prevention through vaccination, prevention of complications and prevention of long-term disability and mortality.

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Summary Table

Proposed randomized control clinical trials (RCT) in acute measles

Title	Prophylactic antibiotic therapy	Management of stomatitis	Nutritional intervention	Gammaglobulin
Study design	RCT	RCT	RCT	RCT
Setting	Outpatient	Outpatient or Inpatient	Inpatient	Inpatient
Intervention	Cotrimoxazole or Chloramphenicol or Amoxycillin & probenecid	Gential violet Antiseptic/ analgesic	Tube feeding	Intravenous immunoglobulin
Duration	7-10 days	3-5 days	Duration of hospitalization	One dose
Control group	Placebo	Normal mouth care	Normal ward diet	Albumin
Inclusion	All cases aged <5 yrs	All cases <5 yrs	All cases <2 yrs	All cases
Exclusion criteria	Severe PEM, AIDS, acute otitis, pneumonia	Candidiasis Herpes	Severe PEM	
Sample size	Assume 25% compliance 50% reduction-700 30% reduction-2000	Based on nutritional outcome	Based on 5-10% weight difference at outcome	Based on at least a 20-40% reduction in complications
Follow up	Day 21 or 30	Day 21 or 30	Day 7 and 30	Day 7 and 30
Outcome	Mortality Frequency of complications Weight Hospital admission Clinic attendance Persistent diarrhoea	Weight Frequency of severe stomatitis	Weight Other complications	Duration of hospitalization Frequency of complications Severity of complications Mortality Side-effects
Aditional activity	Monitor antibiotic susceptibility pattern			

ANNEX

REVIEW OF THE CLINICAL PROBLEMS ASSOCIATED WITH MEASLES

I. INTRODUCTION

The objective of this Annex is to review the clinical problems associated with measles infection. It provides a basis for identifying deficiencies in knowledge regarding optimal treatment of complications, and to demonstrate where more research may be needed. A Medline search of the literature from 1966-1993 was undertaken. Articles prior to 1966 were also reviewed.

II. RISK FACTORS FOR COMPLICATIONS AND SEVERE MEASLES DISEASE

Epidemiological factors

Severe disease with possible complications should be anticipated if the child with measles is from a high risk area or from a high-risk group[1].

High-risk areas include those with:

- vitamin A deficiency
- poor access to medical facilities (this results in children with complications possibly presenting late)
- high numbers of measles cases and/or deaths
- poor socioeconomic and educational status
- low immunization coverage.

These high-risk areas are frequently associated with high population density and overcrowding.

High-risk groups include:

- the young, particularly those less than one year old
- the severely malnourished
- infants and children of HIV-infected women
- other immunocompromised children
- children who contract measles from another case in a household or a health centre
- displaced populations such as refugees living in camps
- children living in zones of armed conflict
- certain ethnic and religious subgroups
- migrant populations.

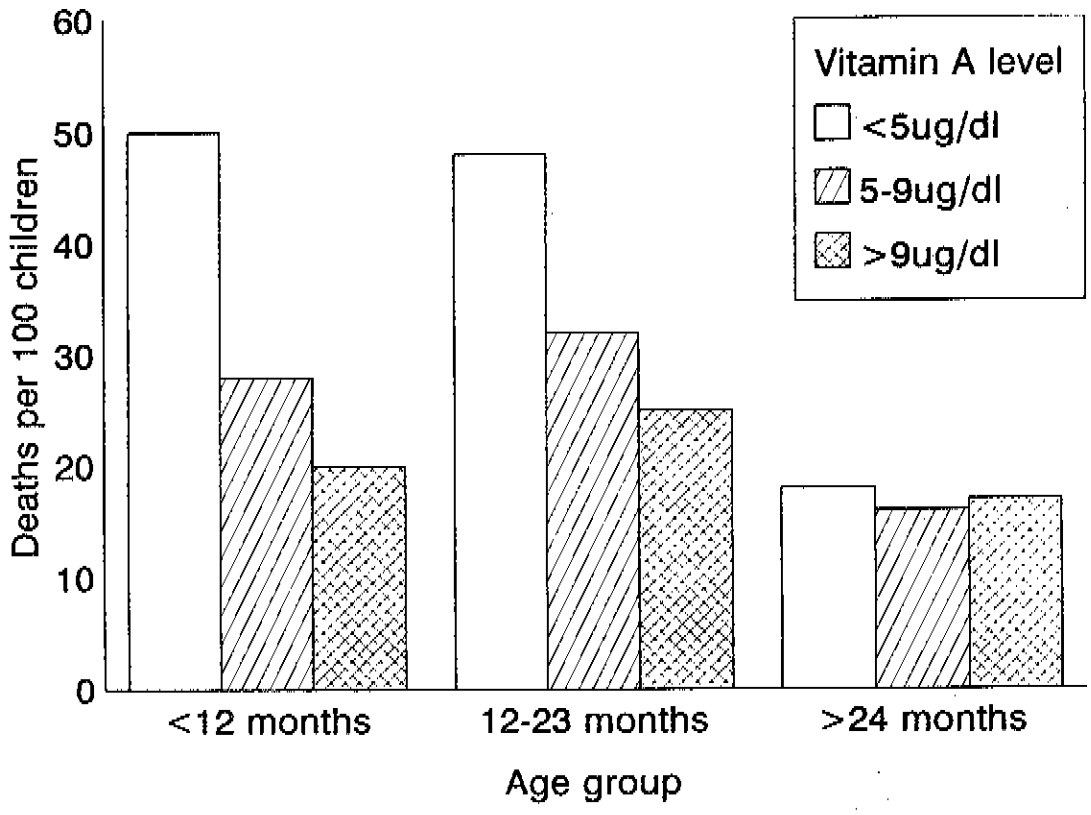
Pathophysiological factors

The clinical expression of infection and complications is influenced by the extent of virus-induced epithelial damage, by the degree of immune suppression,[2] and by the patient's vitamin A status.[3] The pathological effects of measles virus infection and vitamin A deficiency are remarkably similar in that both are responsible for epithelial damage and immune suppression. In addition measles induces vitamin A deficiency which may manifest itself biochemically or in the development of xerophthalmia.

The clinical significance of measles virus immunosuppression has been documented by Coovadia et al. who found that lymphopenia due to lower T and B cell levels impaired antibody response and that reduced C3 levels were predictors of the clinical severity of measles.[4]

Low vitamin A status has been associated with a higher rate of complications and a higher death rate. In Zaire, children with measles, especially those under two years of age and with a vitamin A level below 5μg/dl, had a risk of dying three times greater than children with higher levels (Figure 1).[5] In the United States where clinical vitamin A deficiency is virtually unheard of, low serum vitamin A levels have also been associated with an increased risk of hospitalization and severe disease.[6]

Figure 1
Deaths from measles by age and vitamin A status



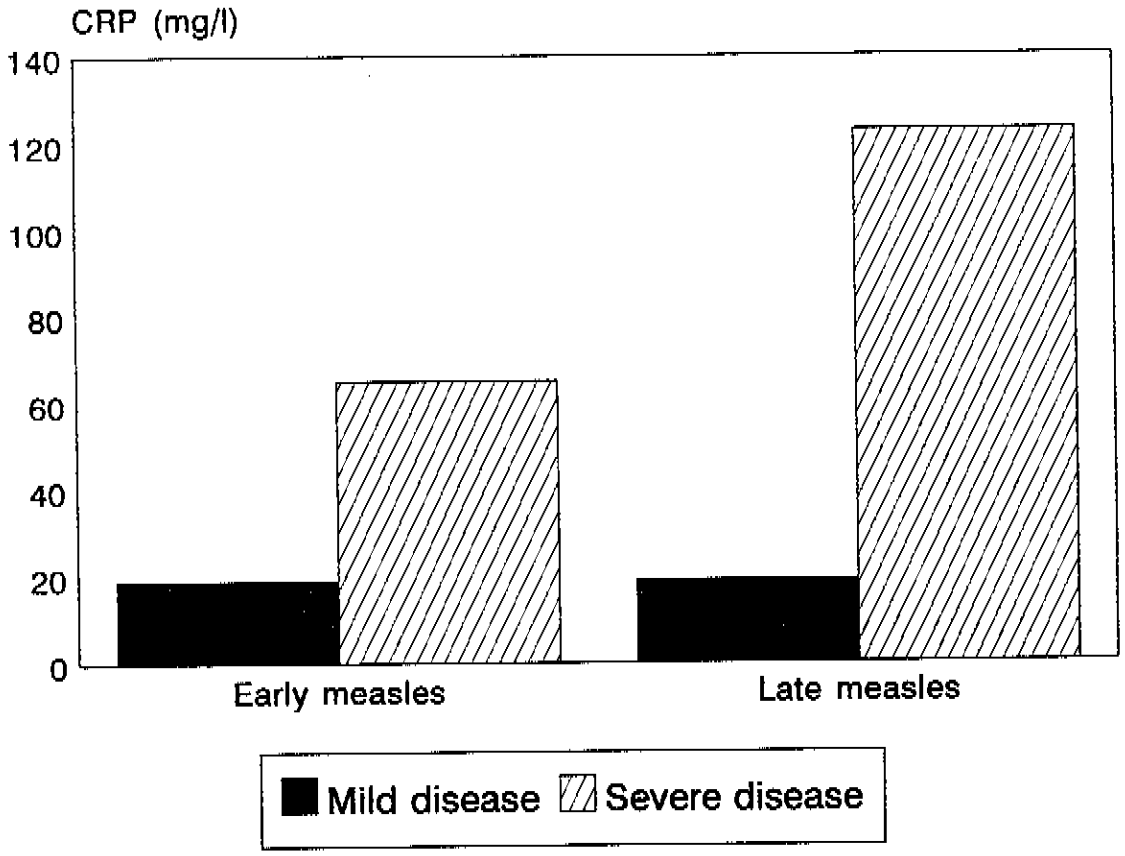
Adapted from Markowitz et al. J Trop Paeds 1989;35:109

Other determinants of severity

A recent study from Santiago, Chile, evaluated the use of C reactive protein (CRP) as a marker for disease severity.[7] This was done by nephelometry using a finger-prick blood sample.

Seventy-two children with early measles (first 3 days after rash) and 63 with late measles (more than 3 days after appearance of the rash) were studied. Both groups were classified as mild or severe in terms of their acute respiratory symptoms (Figure 2).

Figure 2
C reactive protein (CRP) levels in measles[7]



Roini et al. J Trop Ped 1992;38:149

There was no difference in CRP in terms of nutritional status. Sequential CRP levels in three children who subsequently developed complications showed dramatically increased levels. Patients with early mild measles but with intra-alveolar infiltrates had high levels. The researchers concluded that CRP is a simple and useful tool to indicate severity. A sharp increase in the level was indicative of a complicating pneumonia even before clinical signs become obvious.

Development of complications

Complications that tend to occur early during the clinical course (within a week of the appearance of the rash) such as croup, diarrhoea and pneumonia are usually due to effects of the measles virus itself and even though they may be severe, they are not usually life-threatening. Later complications are usually due to secondary viral or bacterial infections. Post-measles pneumonia, croup and diarrhoea are the most common life threatening complications. Corneal ulceration may result in blindness. Other common complications include malnutrition, otitis media and herpes gingivostomatitis (mouth ulcers).

The **frequency of complications** vary in different parts of the world. In the United States in 1989, complications were reported in 17.4% of cases. These included diarrhoea (6.4%), otitis media (6%), pneumonia (4.9%), and encephalitis (0.2%)[8]. The frequency of complications in developing countries is less well known because of less effective surveillance systems. However, hospital-based surveys have shown that the three major problems that are associated with a significantly higher mortality than others are pneumonia, diarrhoea and croup, occurring in up to 75%, 80% and 25% of hospitalized cases respectively.

Long-term complications may occur many weeks and even months following acute measles and are characterized by failure to thrive, recurrent infections, persistent pneumonia and diarrhoea. They are probably due to viral persistence with immune suppression. If present, vitamin A deficiency will aggravate these problems. The survival rate of children during this phase is also significantly reduced. These problems underscore the importance of long-term follow-up once the child with measles recovers from the acute illness.

Uncommon complications include acute encephalitis, nephritis, pneumomediastinum, myocarditis, pericarditis, hepatitis, ileocolitis and appendicitis. Subacute sclerosing panencephalitis is a rare long-term complication of measles. It is a degenerative disease of the brain due to a persistent measles virus infection. These complications are relatively uncommon so, with the exception of acute encephalitis, they will not be discussed.

III. PNEUMONIA

Measles virus is a major cause of pneumonia in children. It has been estimated that it accounts for 6-21% of all cases of pneumonia and for 8-93% of the deaths.[9]

Incidence of measles associated pneumonia

Studies done in the last two decades indicate that pneumonia occurs in about 60-80% of children hospitalized with measles, and that the case fatality rates in developing countries may be in excess of 20% (Table 1).

Individual outbreaks have been reported with much higher case fatality rates, however. For instance, a recent paper describing a measles outbreak in an unimmunized rural community in India reported a 39.4% incidence of pneumonia, with a case fatality rate of 46.3%.[10]

Table 1
Incidence (%) of pneumonia and case fatality rate (CFR) (%) in hospitalized patients.

Country	Year	Incidence	CFR
Denmark[11]	48-62	26	0.9
UK[12]	63[a]	4	0.3
Uganda[13]	67-68	79	20.0
Ghana[14]	73-82	63	21.7
Tanzania[15]	81-83	75	8.0
Jakarta[16]	82-86	75	15.8
India[17]	86-87	16	NR
S Africa[18]	87-88	77	6.5
Ceylon[19]	90	68	4.3

a. Community based study - postal questionnaire
NR = not reported

Etiology

Measles-associated pneumonia may be the result of measles virus infection (this usually occurs early on in the clinical course) or secondary viral (particularly adenovirus and herpesvirus) and bacterial infections.

There is, however, little published data on the etiology of measles-associated pneumonia. The results of bacteriological investigations done in four descriptive studies in the last 20 years are shown in Table 2.

In addition, Ristori[20] reported that about 50% of the fatal cases of pneumonia seen in Santiago in 1962 were due to *S. aureus* superinfection. A Nigerian study[21] reported that isolation of bacteria was dependent on disease severity and nutritional status. In children with severe cases of pneumonia 18/19 (94.7%) isolates were positive compared to 14/37 (37.8%) of milder cases, $p = <0.01$. In the more malnourished children 21/32 (65%) of isolates compared to 10/24 (42%) in the better nourished children ($p = 0.07$) were positive.

Antimicrobial sensitivity patterns.

The only data available comes from two South African studies.[22,23] In the 1971 study of 22 children it was noted that:

- 50% of *S. aureus* isolates were resistant to cloxacillin.
- most gram negative organisms were resistant to ampicillin.

In the 1988 study:

- 55% of *S. pneumoniae* were penicillin-resistant and 33% were chloramphenicol-resistant;
- 73% of *S. aureus* were cloxacillin-resistant;
- 40% of *H. influenzae* were ampicillin- and chloramphenicol-resistant;
- All *E. coli* isolates were ampicillin- and septrin-resistant;
- 75% of *Klebsiella* species were gentamicin-resistant.

Table 2
Frequency of bacterial isolates (%) and complications (%) following lung and tracheal aspirates in measles-associated pneumonia.

	Nigeria[21] 1986	S. Africa[22] 1971	S. Africa[a23] 1988	Colombia[24] 1975	
Number	56[b]	22[b]	51[c]	21[b]	21[c]
Prior antibiotic therapy	43		84		
Positive cultures	55	68	100	10	62
S. pneumoniae	55	0	10	5	29
S. aureus	12	45	16	0	10
H. influenzae	9	0	10	5	19
S. pyogenes	3				
S. viridans		14			
Klebsiella spp	3		25		
E. coli		27	12		
Pneumothorax	21	23	14		
Case fatality rate	18	41	20	15	

a. The 51 patients included 27(53%) with measles-associated pneumonia (18 nosocomial measles pneumonia and 9 measles pneumonia); others were patients with severe PEM or pneumonia unresponsive to therapy.
b. Lung aspirates.
c. Tracheal aspirates.

Virology

Viral culture. Kipps et al. reported adenovirus in 6/18 (33%) and herpes virus in 4/18 (22%) of postmortem samples. Histology revealed bacterial superinfection in 9/18 (50%) and measles pneumonia in 5/18 (27.8%).[25]

Serology. Studies carried out by Morton (1986) indicated that 3/7 (42.9%) were positive for adenovirus. Cultures for herpes virus were negative.[21] Dover found seroconversion to adenovirus in 5/21 (23.8%) and to parainfluenzea in 3/21 (14.2%) patients.[24]

Pathology. In 1983, Kaschula reported that there was histological evidence for herpesvirus, adenovirus and measles virus in about 75% of postmortem cases (25% in each group). The rest were associated with bacterial sepsis.[26] It would appear that viral secondary pneumonias may be responsible for significant morbidity and mortality.

Temporal association of pneumonia and onset of measles

This has not been well documented. Morton reported from Nigeria that the more severe cases (significant consolidation on chest X-ray) manifested on day 11 of the illness, while the milder cases (less significant chest X-ray findings) presented on day 7.[21] In the Colombian study, children with pneumonia presented on average 7.4 days after onset of fever.[24]

In Uganda, of 34 children who died, 23 died within 24 hours of admission while 11 died later. The mean time from admission to death was 2.7 days. When the deaths were analysed in relation to the time of death from the onset of the rash, two peaks were noticed. One occurred on day 3 and the other on day 8. The authors suggest that the early deaths were due to measles virus (histological evidence in some cases) and the late deaths were due to secondary infection.[27] In the study by Kaschula from South Africa, the early deaths were due to measles virus pneumonia and the late deaths due to secondary viral and bacterial infections[26] (Table 3).

Table 3
Time of death in measles-associated pneumonia in relation to onset of rash.

		Duration from onset of rash to death (days)	
Diagnosis	**Number**	**mean**	**range**
Measles	5	5.4	2-15
Herpes	5	17.8	8-24
Adenovirus	6	18.8	13-27
Bacterial	5	18.4	15-21

Management

The issue of the management of measles-associated pneumonia has not been adequately addressed in the literature. This may be due to the fact that it is presumed that the basic principles of pneumonia management apply to measles-associated cases as well. This includes antibiotic therapy, oxygen and supportive care.

Summary of issues

- There is lack of good descriptive data on the natural history of measles-associated pneumonia.
- The etiology of pneumonia remains unclear (especially the late onset presumed bacterial infections), although the limited data does suggest that *S. pneumoniae* is probably the most important pathogen. Gram negative infections are probably of significance as well. This has important bearing on the choice of antibiotic.

IV. CROUP

Croup or laryngo-tracheo-bronchitis (LTB) is a common complication of measles and may result in potentially life-threatening airway obstruction.

Incidence of measles-associated croup

Recent data from both the United States and Africa indicate that croup occurs in approximately 10-25% of hospitalized cases of measles (Table 4). Case fatality rates vary from below 7% in the United States up to 40% in some areas of Africa. There are virtually no recent data on the incidence of measles-associated croup from Asia or South America. A study from Chile in 1960 reported occurrence of laryngitis in over 50% of children.

Etiology

There are extremely scant data on the etiology of this complication.

Measles virus infection. Many children with measles present with croup early in the clinical course and this is probably caused by the measles virus itself. The experience from Cape Town is that this measles croup is usually mild and not life-threatening, that it responds well to conservative therapy and seldom requires airway intervention. A study from Cape Town reported that 13/189 (6.9%) children had measles croup and none required airway intervention. In contrast, croup occurred some time after acute measles infection (post-measles croup) in 40/189 (21.2%) patients and 12.5% of these required an airway intervention.[18]

Secondary viral infection. Experience from Cape Town suggests that *herpes* virus is a common cause of post-measles croup. It may or may not be associated with oropharyngeal lesions. *Para-influenza* virus may also be responsible. *Herpes* virus (from the oropharynx) and *adenovirus* (from the lung) was cultured in 2 of 6 patients with croup in one study in the United States (Houston).[28]

Bacterial infection. Bacterial tracheitis (or membranous LTB) is uncommon and is usually due to *S. aureus, S. pneumoniae* or *H. influenzae* infection. Isolated cases have been reported.[29] It should be considered in patients who, in addition to stridor, are toxic, have purulent sputum or associated pneumonia. Secondary bacterial infections may contribute to the morbidity and mortality of the croup. In the two studies in the United States, *S. aureus, alpha haemolytic streptococcus* and *P. aeroginosa* were cultured from tracheal aspirates of 12/14 patients. One case of tracheitis was found on endoscopy.[28,30]

Table 4
Incidence (%) of croup in measles and case fatality rate (CFR - %) in hospitalized patients.

Country	Year	LTB/All[a]	Incidence	CFR
Denmark[11]	48-62	213/4824	4.1	
UK[12]	63[b]	17/53008	0.03	
Uganda[13]	70	19/171	14	21.1
Kenya[31]	72	74/800	9.5	39.2
Ghana[14]	73-82	494/2758	11.4	19.6
Tanzania[15]	81-83	164/913	17.9	22.6
S Africa[18]	87-88	13/189	6.9[c]	
		27/97	27.8[d])	
		13/92	14.1[e])	12.5[f]
USA/Houston[28]	88-89	27/124	21.8	7.4[f]
USA/Los Angeles[30]	90	82/440	18.6	1.2[f]

a. Ratio of children with LTB/total measles cases studied.
b. Community based study - postal questionnaire.
c. Measles croup, i.e. occurring within 3 days of the appearance of rash.
d. Post-measles croup, i.e. occurring 3 days after appearance of rash - no vitamin A therapy.
e. Post-measles croup, i.e. occurring 3 or more days after appearance of rash - given high dose vitamin A therapy.
f. Mortality primarily related to pneumonia; croup incidental finding.

Temporal association of croup and measles onset

It is assumed that early onset croup is probably due to measles virus itself and that late onset croup (post-measles) is due to secondary infections. However, this assumption has not been subjected to any formal study. In addition, hardly any studies have looked at the temporal association between the onset of croup and rash. A recent retrospective record review of 74 cases from Los Angeles, United States reported that 10.9% occurred during the prodromal period, 46% within 2 days, 37.8% between 3-5 days and 5.4% after day 5 of the rash.[30]

Severity of croup

There is no consistent classification of the severity of croup. Scoring systems have been used.[32] From a clinical point of view, mild croup is characterized by fever, hoarseness, a barking or hacking cough and stridor which is audible when the child is agitated. Severe croup is present when the child is calm. There is frequently tachypnoea, tracheal tug, subcostal indrawing and in extreme cases cyanosis and apathy. Children with severe croup may not have audible stridor in some instances ("silent stridor"); the stridor becomes softer with airway narrowing.

Management of croup

The management of croup[33] is dependent on the resources available. In most developing countries management is supportive only, i.e. humidification and oxygen if available.

Humidification. The value of humidification therapy (steam kettle, mist tents) is debatable. Only one small study in non-measles croup has evaluated its efficacy[34] where mist therapy was found not to be of benefit. Disadvantages include possible scalds to the face and oropharynx. Children in steam tents become anxious and this may aggravate the croup. Monitoring of children in misted tents may be visually difficult.

Corticosteroids. The role of steroids in croup is controversial. These have been shown to be of benefit in some cases of spasmodic croup, but are **contraindicated** in measles.[33]

Oxygen therapy. This must be provided to all severe cases since patients are frequently hypoxaemic.

Anti-microbial agents. Antiviral drugs such as acyclovir may be useful if herpes infection is suspected, and antibiotics if bacterial infection is suspected.

Nebulized adrenaline. This has been found to be extremely useful in a number of studies. However, the effect may be transient and repeated doses may be required.[32,35]

Airway Intervention. In patients with severe croup, an artificial airway (endotracheal tube or tracheostomy) may prevent death. However many countries lack the resources for these interventions. In addition, there are numerous problems associated with artificial airways, including:

- mortality associated with tracheostomy (0.5-5%);
- pneumothorax, pneumomediastinum and subcutaneous emphysema;
- obstruction or dislodgement (in Kenya and South Africa), 33% and 18% of deaths followed obstruction or dislodgement of the tracheostomy;
- secondary infection;
- tracheal stenosis.

The available data on the proportion of all measles patients requiring airways intervention are presented in Table 5.

Table 5
Percentage of children with croup requiring airway intervention

Country	Year	% requiring airway intervention
Kenya[31]	72	29.7
S. Africa[18]	87-88	30
USA (Houston)[28]	88-89	22.2
USA (Los Angeles)[30]	90	11

The overall mortality with airway intervention was generally high. In the Kenyan study (1972), of the 74 patients with croup, 12/22 (55%) who had a tracheostomy died, compared to 17/52 (30.9%) who did not.[31] An analysis of these data did not reveal a statistical difference in mortality; relative risk of death following tracheostomy was 1.67 (0.6-4.5), $p = 0.37$. In a descriptive study (South Africa, 1972) of 81 measles cases with croup who had nasotracheal intubation (15% subsequently had tracheostomies), the mortality rate was 44%.[36] In another study from South Africa (1978), which included 16 children with measles out of a total of 50, the case fatality rate was 16%, with all the deaths due to causes other than croup. The measles case fatality rate was not mentioned.[37]

Summary of issues

- There is lack of clarity with respect to the definition and etiology of early versus late croup.
- It is not clear how the etiology of croup should influence antimicrobial intervention.
- The value of nebulized adrenaline in the treatment of measles-associated croup requires clarification.

V. DIARRHOEA

Diarrhoea is a common complication of measles and has been reported to occur in up to 80% of hospitalized cases (Table 6). Case fatality rates of up to 25% have been reported. However, the high case fatality rate may have been due to complications other than diarrhoea. The Jakarta study showed a lower mortality for diarrhoea on its own than for diarrhoea associated with other complications such as pneumonia. In addition, it has been estimated that measles diarrhoea accounts for 1-7% of all diarrhoeal episodes and that 9-77% of diarrhoeal deaths are measles-associated.[38]

Table 6
Incidence (%) and case fatality rate (CFR) of diarrhoea (%) in hospitalized cases of measles.

Area	Year	Incidence	CFR
Ghana[14]	73-82	18.8	21.7
Bangkok[39]	80-81	79.6	NR (inpatients)
Bangkok[40]	85-87	33.8	0 (outpatients)
Tanzania[15]	81-83	13.8	21.4
Rangoon[41]	84-85	21	2.1
Jakarta[16]	82-86	2.5	7.7 (DDA)
		18.6	14.4 (DDC)
Lima[42]	85-87	71.1	8.1
S Africa[18]	87-88	80	0
Ceylon[19]	1990	13	0

NR - Not reported
DDA - Deaths due to diarrhoea alone
DDC - Deaths due to diarrhoea and other complications

A recent paper describing a measles outbreak in an unimmunized rural community in India reported a 32.2% incidence of diarrhoea and a 10.8% incidence of dysentery. The case fatality rates were 4.8% and 13.3% respectively.[10]

Temporal relationship

Diarrhoea may occur at any stage of measles. In Thailand 22% of cases occurred before rash, 14% with the rash and 64% after the rash had appeared. The average occurrence was on day 2 (range of 8 days before and after the rash).[39]

Measles and persistent diarrhoea

Few studies have evaluated the role of measles and persistent diarrhoea. A prospective community-based study from Bangladesh reported that 25% of measles-associated diarrhoea lasted for more than 7 days.[46] The CFR was significantly higher when associated with prolonged diarrhoea (Table 7). In addition, in acute diarrhoea, children with measles had a higher case fatality rate than those without diarrhoea.

Table 7
Mortality rates (%) due to measles and diarrhoea during a one-year period of surveillance, Bangladesh[43].

Group	Duration of diarrhoea		
	None	<7 days	>7days
Controls	-	0.1	9.7
Measles	4	1.0	11.9

In contrast, Dutta evaluated 383 patients hospitalized with acute diarrhoea. Only in 48 (12.5%) did the diarrhoea continue for more than 14 days. Included in the 383 children were 14 with post-measles diarrhoea, and 64 had a history of measles within 6 months prior to admission. All of these children recovered within 14 days.[44]

Table 8
The etiology (% isolates) of diarrhoea in measles

	Kenya, 92		Peru, 91		Thailand Hospital, 85			Thailand OPD, 89		
	MDD	NMDD	MDD	NMDD	MDD	NMDD	No DD	MDD	M only	NMDD
Cases of measles	300	303	87	77	75	93	90	36	75	70
E coli					16	11	9	3	0	10
EAEC	10	15								
EPEC	12	17	14	23						
Other bac	10	13								
Champhylobacter	8	8	31	16*	0	0	2	6	5	4
Shigella			6	9	13	14	1	0	1	9
Salmonella					7	12	0	0	0	14
Yersenia					0	0	1			
Aeromonas	12	7			5	2	9	0	8	4
Parasites	15	9*								
Cryptosporidium	10	7	6	6						
Glardia			21	7*						
Viruses										
Rotavirus	3	30*	0	28*				0	1	16*
Coronavirus								0	5	3
No pathogens	42	10*	18	10	58	58	78	86	73	40*

*0<0.05. M-Measles. DD-Diarrhoea. MDD-Measles diarrhoea. NMDD-Non-measles diarrhoea. OPD-Out-patient department.

Etiology

The etiology of measles-associated diarrhoea has been well defined in four case controlled studies (Table 8).

The Kenyan study[45] and the Thailand outpatient[40] study reported a lower prevalence rate of positive cultures in measles cases compared to controls (diarrhoea cases without measles). This suggests that many cases of diarrhoea were due to measles virus *per se*. The Peru study reported no overall difference although there were more cases of *C. jejuni* and *giardia* in measles cases[42]. The Thailand inpatient study looked only at bacterial isolates and found no difference.[39]

A descriptive study from Egypt (1986) reported that the bacterial stool cultures of children with mild diarrhoea were negative in 42% of cases compared to 27% in children with moderate diarrhoea and none in severe diarrhoea.[46] This would suggest that most cases of mild diarrhoea were due to measles virus. *P. mirabilis* was the commonest isolate.

Management of diarrhoea

Children with acute diarrhoea complicating measles should be treated like any other child with diarrhoea. The problem of persistent diarrhoea in measles needs investigation in terms of prevention and optimal treatment. Although anti-diarrhoeal agents are not advocated in the management of diarrhoea, consideration as to their use, particularly that of bismuth subsalicylate[47], merits investigation in cases of measles complicated by severe diarrhoea.

Summary of issues

- The contribution of measles as a cause of persistent diarrhoea is not clear.
- The prevention and treatment of measles-associated persistent diarrhoea requires investigation, particularly with regard to the possible beneficial effects of antibiotics.

VI. NUTRITION

Nutrition has generally been held to be a major predictor of mortality. Data derived mainly from hospital surveys show that children who are significantly malnourished have a higher morbidity and mortality rate (Table 9). This does not, however, necessarily imply a causal relationship. It has been shown that measles is an extremely catabolic event and children lose a significant amount of weight following infection. The amount of weight loss may be related to severity of infection (infecting dose). In addition, except for the Kenyan study,[48] most studies have not been controlled for dehydration (Table 9). The Kenyan study also reported a longer hospital stay for severely malnourished children.

Table 9
Association between nutritional status and frequency of complications (%) and deaths (%).

	Nutrition (% of the median of NCHS reference values)			
	>80	60-80	<60	All
Jakarta[16]				
Pneumonia	61.9	84.6	100	74.9
Diarrhoea	13.7	19.9	39.2	18.6
Convulsions	8.2	7.7	2.2	7.5
Otitis media	6.7	5.9	2.2	5.9
Deaths				
Jakarta[16]	5.9	12.7	23.9	10.3
Tanzania[15]	3.6	7.3	24.5	8.0
Kenya[48]	0.8	1.4	4	1.8

If malnutrition is a risk factor, the effects are probably mediated via immune suppression, viral persistence or vitamin A deficiency. Prolonged giant cell excretion, indicative of viral persistence, has been documented in malnourished children. On the other hand, a review by Aaby of risk factors for measles reported that, in community-based studies, no difference in mortality was noted in relation to nutritional status (except for one study from Bangladesh).[49] There are no published studies on the optimal management of nutritional problems associated with measles both in the short and long term.

VII. OTHER COMPLICATIONS

Measles conjunctivitis and keratitis.

Conjunctivitis and keratitis are hallmarks of measles and usually resolve within a few days. Treatment is supportive and topical antibiotics are frequently prescribed. Whether they are necessary or not is debatable.

Significant corneal damage in children with measles can, in some cases, result in blindness. Measles-associated complications are regarded as one of the common causes of childhood blindness in Africa.[50] The causes of corneal damage include:

- measles virus infection
- secondary herpes or bacterial infection
- a chemical conjunctivitis as a result of harmful eye practices such as herbal remedies
- vitamin A deficiency.

Xerophthalmia

The relationship between infections and xerophthalmia is a well recognized observation and dates back to the late 19th century. Of all the infections linked to xerophthalmia, measles is the one where this synergism is most striking. In a global review of xerophthalmia, Oomen stated that "there appears to be a universal relationship between infectious diseases and xerophthalmia. This relates especially to measles...".[51] A number of cross-sectional and case controlled studies have evaluated the risk of xerophthamia following measles. The results are, however, conflicting. Two studies from Ethiopia[52] and Malawi[53] reported significant risk ratios (odds ratios of 4.6 and 1.6 respectively), but studies from the Philippines[54] and Bangladesh[55] found no significant association.

A prospective study from India[56] reported that conjunctival signs of xerophthalmia developed in 1.1% (3/281) of children in the six-month period following measles, compared to 0.5% (4/819) of children without measles. The relative risk of developing xerophthalmia was 2.19 times greater following measles, but the 95% CI were wide, (0.49-9.71, P=0.25). Children presenting with acute corneal xerophthalmia during the early stage of measles (10/318) were excluded from the analysis.

Acute encephalitis

Encephalitis is recognized as a significant complication in measles but its epidemiology has not been well described. A major problem relates to definitions. Confusion frequently arises between encephalitis, encephalopathy, convulsions and meningitis. Central nervous system manifestation may be a consequence of a number of measles-associated complications, including hyperpyrexia, hypoxaemia associated with pneumonia and croup, dehydration and electrolyte disturbance associated with diarrhoea. In a postal survey in the United Kingdom in 1964, neurological disturbances were reported in 0.4% of cases and 0.1% were regarded as having encephalitis.[12] In a Danish study in 1968 among hospitalized patients, encephalitis was seen in 1.4% of patients and the case fatality rate was 9%.[11] In a follow-up study, 68% had recovered completely. Reported central nervous system complications from developing countries are shown in Table 10. The major area of concern relates to the diagnostic criteria for encephalitis in developing countries.

Table 10
Frequency of central nervous system complications following measles in developing countries.

Area	Criteria	Percent
Ceylon (1992)[19]	Encephalitis	4.3
Ghana (1984)[14]	Convulsions/coma	3.2
Sudan (1988)[57]	Convulsions	7.2
Thailand (1992)[16]	Convulsions	7.1
	Encephalopathy	17.0
Bangkok(1985)[39]	Encephalitis	13.9
India(1992)[17]	Encephalitis	8.0
	Meningitis	3.3
	Convulsions	2.6

Otitis media and stomatitis

Although otitis media and ulcerative stomatitis are well recognized complications of measles, there are few publications dealing with their etiology, natural history, complications and management. A study from South Africa reported that *herpesvirus* infection was detected in 43% of hospitalized cases and 37% of outpatient children.[58]

Tuberculosis

It is generally believed that measles predisposes to the development or reactivation of tuberculosis. A review in 1976 of all the studies, both for and against the concept, concluded that the evidence for this assumption was not very strong.[59] A point is made that decreased tuberculin skin reactivity should not necessarily be equated with suppressed tuberculous immunity.

Super-added nosocomial infections

Children with measles are prone to secondary infections, particularly when hospitalized. However, hard data on the subject are lacking. A retrospective case controlled study from South Africa reported that nosocomial bacteraemia was six times more common in children with measles than in general paediatric patients.[60] The predominant organisms were gram negative (*Klebsiella* and *Salmonella*), accounting for 86.5% of the isolates, and 23% were multiply drug resistant.

Bronchiectasis

Measles has been associated with recurrent chest infections and bronchiectasis. In South Africa a number of cases have been shown to follow measles.[26]

VIII. POST-MEASLES MORBIDITY AND MORTALITY

A number of studies have indicated that children who have had measles have significantly increased morbidity and mortality in the ensuing months compared with community controls.

Mortality

Studies from West Africa have reported that children with measles had a 5-10-fold greater risk of dying compared to community controls.[61] The effect was most noticeable in those under one year of age (Table 11).

A more recent Kenyan study reported a mortality rate of 4.3% in children age 8-35 months living in compounds where there was a measles outbreak the previous year. The mortality rate in the compounds where there was no measles was much lower (1.1%) but was not statistically significant because of the small numbers.[62]

Table 11
Mortality during 9 months of follow-up for measles patients and community controls in the Gambia.[61]

Age at time of infection	Mortality (%) Measles Acute	Measles 1-9mths later	Control 0-9mths later
3-11 mths	18	56	3
1-2 yrs	9	13	2
3-4 yrs	6	7	1
5-6 yrs	0	6	1

Morbidity

A case controlled study from Lima, Peru, reported that episodes of diarrhoea in the ensuing month following measles were significantly greater in cases, as was the duration of episodes. No differences in pattern of weight gain were observed, which may have been ascribed to good home-based follow-up.[42]

In a prospective community-based study, Koster reported that children with measles complicated by diarrhoea for more than seven days failed to improve their nutritional status compared to controls with diarrhoea or to children with measles complicated by a brief attack of diarrhoea.[43]

Bhaskaram followed up children for a period of six months following hospitalization and found that hardly any weight was gained in the first month. Thereafter children gained weight, albeit more slowly than the controls. In addition the frequency of infections was 10 times that of controls in the six-month period.[63]

In a prospective community-based study of 281 cases of measles and 819 controls, Reddy found that in the six months following measles 34% of the children with measles developed chest infections compared to 6% of the control children.[56] In addition, the incidence of hospitalization was 2.9% versus 0.4% respectively.

In summary, the reasons for increased morbidity and mortality due to diarrhoea as a complication of measles are unclear but may be due to:

- viral persistence
- persistence of depressed immunity following measles
- vitamin A deficiency
- other factors not yet identified.

IX. TREATMENT WITH ANTIBIOTICS AND VITAMIN A

ANTIBIOTIC THERAPY.

Five studies have looked at the use of antibiotics in measles. The results of these are summarized below. Additional statistical calculations (risk ratios) have been done and the major problems of the respective studies are highlighted.

A. Weinstein, 1955, Boston, United States.[64]

The study looked at the cases of 428 individuals. All had clinical examinations, chest X-ray and throat cultures. Of the 428, 350 had no evidence of bacterial infections and 78 (24.6%) showed great evidence. 130 had received antibiotics prior to admission and 36 (30.4%) had secondary infections on admission. Of the 298 who had not received antibiotics, 42 (14.9%) had infection. The risk of infection following antibiotics was significantly greater than without antibiotics (odds ratio 1.96[1.3-2.9], $p = <0.001$)

Most patients had received penicillin and most complications were between days 3 and 5. Pneumonia, the commonest problem, developed in 22% of treated and 8% of untreated cases. In addition, of 78 patients who were treated with antibiotics after admission to hospital, 11% developed superinfection.

Problems

No data are provided with respect to the relationship between infection and other parameters such as the age or nutritional status of the patients, factors that may have influenced outcome.

The author claims that the individuals who were given antibiotics had a higher complication rate. The reasons for prescribing antibiotics before admission are, however, not given. Were these individuals possibly not already infected when antibiotics were prescribed?

The criteria for the definition of secondary bacterial infection do not appear very stringent and no information on the radiological findings is mentioned.

B. Prasad et al., 1967, Agra, India.[65]

This study enrolled 158 children in an outpatient setting (20% were <1 year, 48% <2 years and 90% <5 years). Children were randomized to receive tetracycline (15mg/lb for 7 days) or placebo. The number of patients enrolled in each stage of illness was as follows: prodrome 20, acute illness 42, and post-measles (within 1 month of rash onset) 111.

The complication rate was as follows: 27/80 (33.7%) in placebo versus 13/65 (16.6%) in cases; Relative risk (RR) 0.49 (0.28-0.89), p = 0.02. Eleven of the controls and none of the cases developed lobar or bronchopneumonia. In the treatment of 22 cases of consolidation, tetracycline therapy resulted in resolution.

The researchers concluded that tetracycline prevented complications and that it was an effective agent in the treatment of pneumonia.

Problems

There is an ethical issue in the use of tetracycline in young children. It is not recommended for use in children under 7 years.

There is little information on the actual methodology of the study. Was this a randomized controlled clinical trial? What was the method of randomization? Were the observers blinded to the intervention (i.e. the drugs used)?

The clinical parameters used as outcomes were vague.

The time sequence of the radiological investigations was not clear.

C. de Buse, 1969, Kampala, Uganda.[27]

Children in an outpatient setting were given (alternately) triplopen intramuscularly (n = 39) or vibramycin (n = 35); 71% were <1 year. No difference in clinical outcome was noted. In the triplopen and vibramycin groups respectively, 32 and 35 showed no signs, 1 and 2 improved, 5 and 4 were the same, and 1 on each antibiotic was worse.

In terms of chest X-ray findings, 9 and 8 were better, 16 and 17 were the same, and 8 and 7 were worse. They concluded that there was no difference in outcome in terms of the antibiotic used.

Problems

The study compared two different antibiotics and did not include a placebo arm to the trial.

The outcome measures were not detailed.

The results were based in part on the radiological appearances, which were performed only once after therapy, i.e. on day 8.

D. Lang, 1971, Port Elizabeth, South Africa.[66]

Fifty-nine children studied were admitted to hospital and graded for severity on the basis of a chest X-ray. They were given either ampicillin or doxycycline for 10 days and then reassessed. There were 8 deaths, 5 received doxycycline and 3 ampicillin. Duration of pyrexia and consolidation on chest X-ray was no different in the two groups. The author concluded that there was no difference in outcome with the two drugs.

Problems

This report did not provide sufficient information on the study design, particularly the process of randomization and matching. In addition, there was no placebo controlled group.

E. O'Donovan and Barua, 1973, Nairobi, Kenya.[67]

Children with pneumonia were graded in terms of clinical severity from 1 - 4, with 1 being mild and 4 most severe. Grade 1 was given either penicillin or no therapy, while grades 2 - 4 were treated with penicillin or chloramphenicol orally. Children were matched for nutrition and age (39% were < 1 year, 77% were <2 years and all were <5 years). Chest X-rays were done within 24 hours of admission and graded from 1 - 4 (mild to severe). The case fatality rate in the children (grades 2 - 4) with chloramphenicol was 20% compared to 10% with penicillin; RR 0.45 (0.-1.1), p = 0.07. Most deaths (over 70%) occurred in the severely ill group (i.e. group 4). In group 1, the mild cases, there were three deaths in those who did not receive penicillin and one in the treated group. In addition, 17 of the untreated children developed prolonged fever or increasing signs of respiratory distress. They were given penicillin; 16 recovered abruptly while one died.

Problems

The results of this study are questionable since most deaths were in the severe cases. In the mild cases, no data are provided for the untreated cases.

Summary of the five studies

The five published studies evaluating the value of antibiotics in patients with measles were all carried out prior to 1973. All of them have significant methodological problems. Inclusion criteria, the process of randomization (except the Weinstein study) and outcome measures were all rather vague. Three studies compared the efficacy of one antibiotic versus another and the conclusions were that there was no difference in outcome. Three studies failed to shed light on the value of antibiotics in preventing complications. The results would have been more meaningful if a placebo arm had been included in the study design. One study (Prasas et al.) compared tetracycline with a placebo; the results suggested that the antibiotic prevented complications. In a descriptive study of antibiotic usage in measles, Weinstein argued that patients who received antibiotics had a higher risk of complications. The major problem with this study is that the reasons for prescribing antibiotics are not detailed. Were these patients already infected when given the antibiotic? The lack of good data highlights the need for more rigorous and well designed controlled clinical trials in the management and prevention of measles-related complications.

VITAMIN A THERAPY

Influence of vitamin A on mortality

Four clinical trials (in the United Kingdom in 1932[66], Tanzania in 1987[69], and South Africa in 1990[18] and 1991[70]), have evaluated the effect of vitamin A supplementation on morbidity and mortality. In Cape Town[18] and Tanzania[69], the children received 200,000 IU on two successive days, while in Durban[70] they received 100,000 IU (<1 year of age) or 200,000 IU (>1 year) on days 1, 2 and 8. The children in the United Kingdom study received approximately 20,000 IU daily for 1-3 weeks (140,000-400,000 IU altogether).

In the United Kingdom trial the case fatality rate in the treated group was 3.7% compared to 8.7% in the untreated group. The relative risk of dying from measles following supplementation with vitamin A was 0.46 (0,26-0.81; P=0.018) compared to those not supplemented. The effect was most noticeable with respect to deaths due to pneumonia, RR 0.46 (0.26,0.81).

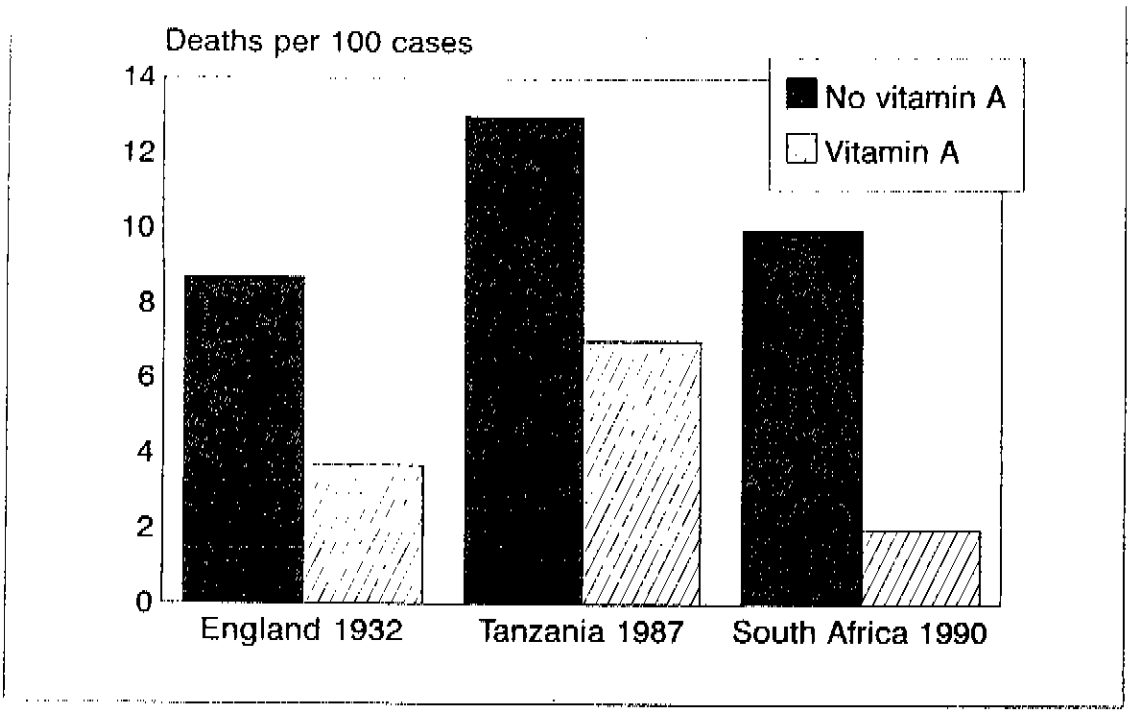
In the Tanzanian double-blind clinical trial, 6 (7%) of the 88 vitamin A-supplemented children who were admitted to a rural hospital died, while there were 12/92 (13%) deaths in the control group. Although there were twice as many deaths in the placebo group, the difference was not significant (RR 0.52, 0.21-1.33; P=0.25). There was, however, a significant difference in mortality in children less than 2 years old (RR 0.15, P = 0.03) and for the cases who were complicated by croup.

The Cape Town study was a prospective double-blind placebo controlled trial on children with severe measles who were admitted to an urban regional hospital. Vitamin A therapy had a significant effect on mortality, with 10/97 (10%) of deaths occurring in the placebo group and only 2/92 (2%) of deaths in the group treated with vitamin A (RR 0.21, 0.05-0.94; P=0.046).

The mortality data of these three clinical trials are summarized in figure 3. The Durban study consisted of a small sample size (n=60) and only one death was reported in the placebo group. A recent meta-analysis of these four studies showed that vitamin A therapy reduced mortality by 67% (P = 0.004)[71]

Three large-scale community intervention trials, one in South India[72] and two in Nepal,[73,74] have evaluated the effect of vitamin A supplements on childhood mortality and have included in their analysis the effect on measles-related mortality. A meta-analysis of these studies showed a 54% reduction in mortality with a RR 0.46 (0.22 - 0.98), p = 0.043. These findings are consistent with those from the hospital-based studies.

Figure 3
Mortality from measles in three clinical trials
the impact of vitamin A



Hussey & Klein, Ann NY Acad Sc 1992;669:188

Influence of vitamin A on morbidity

The two South African[18,70] trials specifically studied the impact of vitamin A on morbidity. In Cape Town, the treated children had a significantly shorter hospital stay, and recovered more rapidly from pneumonia and diarrhoea; fewer children developed croup, persistent pneumonia and persistent diarrhoea.[18] In Durban, the children treated with vitamin A also recovered more rapidly overall and specifically from pneumonia. In addition, the integrated morbidity scores (determined by clinical findings and chest radiograph) at 1, 6 and 26 weeks following infection were reduced by 82%, 61% and 85% respectively in the supplemented group.[70]

In both South African studies, vitamin A levels were below 20ug/dl in 90% of patients. These findings are important since vitamin A deficiency is not a public health problem in either of these areas. In Cape Town no child with a vitamin A level greater than 20ug/dl died, but the small numbers involved (n=14) leave the significance of this finding in doubt.

The beneficial effect of vitamin A therapy reported in the above-mentioned clinical trials has been confirmed in an evaluation of a vitamin A supplementation programme implemented as part of the routine case management of all children hospitalized with measles in Cape Town. The morbidity (hospital stay and intensive care admissions) and mortality in children hospitalized during 1989 and 1990, after the implementation of the programme, was significantly less than that in the children admitted during 1985 and 1986, the period prior to the implementation of vitamin A therapy. The children treated with vitamin A had a significantly shorter hospital stay (mean 10 vs 13 days; $P<0.001$), fewer intensive care admissions (4.3% vs 10.5%; $P<0.001$), and fewer deaths (1.6% vs 5%; $P<0.001$) when compared to the unsupplemented children. These findings strongly support the administration of vitamin A therapy in everyday hospital practice.[74]

Vitamin A therapy in an outpatient setting

All the clinical trials on vitamin A therapy in acute measles have been carried out in a hospital setting. There has been one study from Zambia reported at the recent International Vitamin A Consultative Group meeting.[76] In a blinded placebo controlled trial, children attending an outpatient clinic were given a single high dose of vitamin A. At baseline, 63% and 68% of treated and placebo-treated children had acute lower respiratory infection (ALRI). After four weeks, ALRI was absent in the treated group but occurred in 12% of controls.

X. CONCLUSIONS

The literature review has highlighted that measles is a major cause of childhood morbidity and mortality. However, most of the data referring to complications are from hospital-based studies, with many of them being retrospective descriptive record reviews. Most of the studies focused on three of the major complications, i.e. pneumonia, croup and diarrhoea. Other complications such as encephalitis, otitis media and stomatitis, which are responsible for significant morbidity, are not discussed in depth. In addition, comparison of data between different countries and within countries is problematic because of the irregularity of definitions. Data from community-based studies are scant. The natural history of measles, particularly the temporal association between measles infection and associated complications and its etiology are neither well defined nor sufficiently researched. Of particular concern is the fact that data on the inpatient and outpatient management of measles and its associated complications are virtually non-existent. The only recent publications on management relate to vitamin A therapy in hospitalized cases. Nor does the literature reveal any clinical trials that have attempted to define the optimal method of therapy of common complications.

In conclusion, this review has highlighted the urgent need for community and hospital-based studies that address issues such as the natural history of measles and its complications, the aetiology of complications and intervention strategies relating to more effective measles case management.

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