Clinical problems in measles case management

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Summary Measles remains one of the leading causes of childhood morbidity and mortality in developing countries. The World Health Organization has identified effective case management as one of the specific strategies to reduce the burden of this disease. The purpose of this article is to review the aetiology, natural history, treatment and outcome of the common clinical problems associated with measles with a view to identifying possible deficiencies in case management. Complications such as pneumonia, diarrhoea, croup and malnutrition have been well defined in terms of their relative contribution to morbidity and mortality. However, there are few published data on the aetiology and natural history of these specific complications. Such data are crucial for rational case management strategies. Data on treatment of measles and its complications are limited and the role of antibiotic prophylaxis and therapy is unclear. The only specific research focus on case management during the last decade has been vitamin A therapy. There is a continuing need for community and hospital-based studies on the natural history of measles and its complications, the aetiology of these complications and intervention strategies that will improve measles case management.

Introduction

Measles remains one of the leading causes of childhood morbidity and mortality. As of August 1994, The World Health Organization (WHO) estimates that 1.15 million deaths occur annually in developing countries. Case fatality rates (CFR) exceed 1% in many of these countries. Most deaths follow complications such as pneumonia, croup and diarrhoea. In addition, countless thousands experience disability as a consequence of measles-related blindness, chronic lung disease and malnutrition. Recovery following acute measles may be delayed for many weeks and even months and is characterized by failure to thrive and recurrent infections. The death rate of children during this phase is also significantly increased.

In response to the 1990 World Health Assembly and the World Summit for Children’s call to control measles by the year 1995, the WHO’s Expanded Programme on Immunization (EPI) defined specific control objectives which included reducing the case fatality rate from measles to less than 1% in all countries by 1995 through effective case management.²

The objective of this paper is to review the clinical problems associated with measles infection. Deficiencies in knowledge of optimal treatment of complications are identified, and the need for more research in this area is demonstrated.

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### Table I. Complications of measles

<table>
<thead>
<tr>
<th>Common</th>
<th>Common Complications*</th>
<th>Uncommon Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>Encephalitis</td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Myocarditis</td>
<td></td>
</tr>
<tr>
<td>Laryngotracheobronchitis</td>
<td>Pericarditis</td>
<td></td>
</tr>
<tr>
<td>Eye complications</td>
<td>Pneumothorax</td>
<td></td>
</tr>
<tr>
<td>Malnutrition</td>
<td>Pneumomediastinum</td>
<td></td>
</tr>
<tr>
<td>Otitis media</td>
<td>Nephritis</td>
<td></td>
</tr>
<tr>
<td>Severe stomatitis</td>
<td>Appendicitis</td>
<td></td>
</tr>
<tr>
<td>Nosocomial infections</td>
<td>Subacute sclerosing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>panencephalitis (SSPE)</td>
<td></td>
</tr>
</tbody>
</table>

*Cancrum oris (noma, gangrenous stomatitis) is a well recognized complication of measles in West Africa—Ed.

### Pneumonia

Measles is estimated to account for 6–21% of all cases of pneumonia in children and for 8–93% of deaths from pneumonia.4 Pneumonia is a major complication in hospitalized cases, occurring in about 60–80% of cases, with CFRs varying from 5–20% (Table II).5,6,8,10,11,13,14,16 During measles outbreaks, pneumonia rates may rise dramatically, as in an unimmunized rural community in India where the reported incidence of pneumonia was 39.4% and the case fatality rate 46.3%.18

### Methods

A Medline search of the literature from 1966 to 1993 was undertaken. In addition, relevant articles prior to 1966 that were cited in these publications were also reviewed. The common complications of measles (Table I) are discussed, where appropriate, under the following headings: incidence, case fatality rate, aetiology, temporal association with onset of measles, management and issues of concern. Because they have a negligible effect on overall numbers of children dying from measles, the uncommon complications, with the exception of encephalitis, are not discussed. General management issues are also reviewed, particularly vitamin A and antimicrobial therapy.

### Frequency of complications

The frequency of complications varies in different parts of the world. In the USA in 1989, complications were reported in 17.4% of cases, and these included diarrhoea (6.4%), otitis media (6%), pneumonia (4.9%) and encephalitis (0.2%).3 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 associated with significant mortality are pneumonia, diarrhoea and croup, occurring in up to 75%, 80% and 25% of hospitalized cases, respectively.

### Aetiology

There are few published data on the aetiology of measles-associated pneumonia. Results from three descriptive studies are given in Table III, and show that *Streptococcus pneumoniae* and *Staphylococcus aureus* were the predominant isolates.19-21 About 50% of the fatal cases of pneumonia seen in Santiago in 1962 were due to *Staph. aureus* superinfection.22 Additional evidence for the important role of bacterial superinfection comes from post-mortem studies on measles which report this problem in 25–50% of fatal cases.23

A study from Nigeria showed that a higher bacterial isolation rate was found in severe cases of pneumonia (94.7%) than in milder cases (37.8%, p = < 0.01), and in malnourished children (65%) than in well nourished children (42%),19 but the difference was not significant.

Limited studies suggest that viruses are also a significant cause of measles-associated pneumonia. Post-mortem studies (histology and virology) from Cape Town indicate that measles virus, herpes virus and adenovirus are each responsible for approximately 25% of cases.23,24 Serological studies from Nigeria19 and Columbia21 found that 3/7 and 5/21 (24%) cases, respectively, were positive for adenovirus.

### Temporal association

In Nigeria, the more severe cases of pneumonia (significant consolidation on chest X-ray [CXR]) manifested on day 11 after the rash appeared, while the milder cases (less significant CXR findings)
TABLE II. Incidence rates [IR] (%) of pneumonia, croup, diarrhoea and respective case fatality rates [CFR] (%) in hospitalized patients with measles

<table>
<thead>
<tr>
<th>Years</th>
<th>No.</th>
<th>Pneumonia</th>
<th></th>
<th>Croup</th>
<th></th>
<th>Diarrhoea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denmark(^5)</td>
<td>1948–62</td>
<td>4847</td>
<td>26</td>
<td>1</td>
<td>4.1</td>
<td>—</td>
</tr>
<tr>
<td>Uganda(^6)</td>
<td>1967–68</td>
<td>171</td>
<td>79</td>
<td>20</td>
<td>14</td>
<td>21</td>
</tr>
<tr>
<td>Kenya(^7)</td>
<td>1972</td>
<td>800</td>
<td>—</td>
<td>—</td>
<td>10</td>
<td>39</td>
</tr>
<tr>
<td>Ghana(^8)</td>
<td>1973–82</td>
<td>4317</td>
<td>63</td>
<td>22</td>
<td>11</td>
<td>20</td>
</tr>
<tr>
<td>Bangkok(^9)</td>
<td>1980–81</td>
<td>137</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>79</td>
</tr>
<tr>
<td>Tanzania(^10)</td>
<td>1981–83</td>
<td>913</td>
<td>75</td>
<td>8</td>
<td>18</td>
<td>23</td>
</tr>
<tr>
<td>Jakarta(^11)</td>
<td>1982–86</td>
<td>512</td>
<td>75</td>
<td>10</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Lima(^12)</td>
<td>1985–87</td>
<td>246</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>71</td>
</tr>
<tr>
<td>India(^13)</td>
<td>1986–87</td>
<td>150</td>
<td>16</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Cape Town(^14)</td>
<td>1987–88</td>
<td>97</td>
<td>77</td>
<td>7</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>Houston(^15)</td>
<td>1988–89</td>
<td>124</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>13</td>
</tr>
<tr>
<td>Ceylon(^16)</td>
<td>1990</td>
<td>69</td>
<td>68</td>
<td>4</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Los Angeles(^17)</td>
<td>1990</td>
<td>440</td>
<td>—</td>
<td>—</td>
<td>19</td>
<td>1</td>
</tr>
</tbody>
</table>

Presented on day 7.\(^19\) In a study from Columbia, children with pneumonia presented on average 7.4 days after the onset of the illness.\(^21\)

In Uganda, 68% of deaths occurred within 24 hours of admission and the mean time from admission to death was 2.7 days. When the time of death was analyzed in relation to the onset of the rash, two peaks were noticed. The first occurred on day 3 and the other on day 8 following appearance of the rash. The authors suggest that the early deaths were due to measles virus (there was histological evidence in some cases) and the late deaths to secondary infection.\(^6\) Post-mortem studies from South Africa support this hypothesis (Table IV).\(^24\)

The management of measles-associated pneumonia has not been adequately addressed in the literature. This complication should be given high priority in efforts to reduce the global impact of measles and in the management of individual children. The factors predisposing to pneumonia, its aetiology, natural history and progression require clarification. Should pneumonia occurring in the 1st few days be treated similarly to pneumonia arising after a week, or should prophylactic antibiotics be given to all cases of measles on diagnosis? There are other important matters which need to be clarified.

**Croup**

**Incidence.** Recent data from both the USA and Africa indicate that croup occurs in approximately 10–25% of hospitalized cases of measles (Table II).\(^6,8,10,14,15,17\) Case fatality rates reported vary from about 1% in the USA\(^17\) to an exceptional 40% in one report from Africa.\(^7\) There are no recently published data on measles-associated croup from Asia or South America.

**Aetiology.** Many children with measles present with croup early in the course of the disease and it is probably caused by the measles virus itself. In a Cape Town study, 13/189 (6.9%) children had early-onset measles croup and none required airway intervention. In contrast, late-onset croup, presumed to be herpes-associated, occurred in 40/189 (21.2%) of patients, five (12.5%) of whom required intubation.\(^14\) Unpublished data from Cape Town suggest that herpes virus is a common cause of post-measles croup.

Bacterial tracheitis is an uncommon cause of stridor and is usually due to *Staph. aureus, Strep. pneumoniae* or *Haemophilus influenzae* infection.\(^25\) Its presentation in measles is not much different from that in non-measles
TABLE III. Frequency of bacterial isolates and complications (%) following lung and tracheal aspirates in measles-associated pneumonia

<table>
<thead>
<tr>
<th>Aspirate (no.)</th>
<th>Nigeria\textsuperscript{19} (1986) Lung (56)</th>
<th>South Africa\textsuperscript{20} (1971) Lung (22)</th>
<th>Columbia\textsuperscript{21} (1975) Lung (21)</th>
<th>Columbia\textsuperscript{21} (1975) Tracheal (21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial isolates</td>
<td>Positive cultures (%)</td>
<td>55</td>
<td>68</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>\textit{S. pneumoniae}</td>
<td>55</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>\textit{S. aureus}</td>
<td>12</td>
<td>46</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>\textit{H. influenzae}</td>
<td>9</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>\textit{S. pyogenes}</td>
<td>3</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>\textit{S. viridans}</td>
<td>—</td>
<td>14</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Klebsiella spp.</td>
<td>3</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>\textit{E. coli}</td>
<td>—</td>
<td>27</td>
<td>—</td>
</tr>
<tr>
<td>Complications (%)</td>
<td>Pneumothorax</td>
<td>21</td>
<td>23</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>CFR</td>
<td>18</td>
<td>41</td>
<td>15</td>
</tr>
</tbody>
</table>

cases.\textsuperscript{26} Experience indicates that it should be considered in patients who, in addition to stridor, are toxic and have purulent sputum or associated pneumonia.

Temporal association of croup and measles onset. The assumption that early-onset croup is probably due to the measles virus itself and that late-onset croup is due to secondary infections remains unvalidated by formal study.

A recent retrospective review of 74 cases of stridor in measles from the USA reported that 11\% occurred during the prodromal period, 46\% within 2 days, 38\% within 3–5 days and 5\% later than day 5 of appearance of the rash.\textsuperscript{17}

Management of croup. The management of croup\textsuperscript{27} is dependent upon the resources available. Usually, supportive treatment with humidification and oxygen is adequate, but in severe croup, an endotracheal tube or tracheostomy may be needed to prevent death. Sadly, many hospitals in developing countries lack the resources for such interventions.\textsuperscript{28}

Two studies from the USA have respectively reported that 11\%\textsuperscript{17} and 22\%\textsuperscript{15} of patients with stridor required airway intervention, while studies from Kenya\textsuperscript{7} and South Africa\textsuperscript{14} reported that 30\% of patients required such intervention. In the Kenyan study, mortality rates with and without tracheostomy were 55\% and 31\%, respectively.\textsuperscript{7} A third of the tracheostomy deaths were associated with mechanical problems such as obstruction or dislodgement of the tracheostomy tube.

**TABLE IV. Time of death in measles-associated pneumonia in relation to onset of rash**\textsuperscript{24}

<table>
<thead>
<tr>
<th>Diagnosis of pneumonia</th>
<th>No. of cases</th>
<th>Mean (range) interval in days from onset of rash to death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles</td>
<td>5</td>
<td>5.4 (2–15)</td>
</tr>
<tr>
<td>Herpes</td>
<td>5</td>
<td>17.8 (8–24)</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>6</td>
<td>18.8 (13–27)</td>
</tr>
<tr>
<td>Bacterial</td>
<td>5</td>
<td>18.4 (15–21)</td>
</tr>
</tbody>
</table>

Issues of concern. The aetiology of early versus late croup is not clear. This has implications for possible interventions in that early croup tends to be mild compared with late croup which tends to be more severe. There is a need also to explore other interventions (such as nebulized adrenaline\textsuperscript{29,30}) where there are no facilities for airway intervention.

Diarrhoea

Incidence. It has been estimated that measles
diarrhoea accounts for 1–7% of all diarrhoeal episodes worldwide, and for 9–77% of deaths from diarrhoea.\textsuperscript{31} The proportion of measles cases presenting with diarrhoea varies greatly, as does the CFR (Table II). In a recent measles outbreak in an unimmunized rural community in India, the reported incidence (and case fatality rates) of diarrhoea and dysentery was 32.2% (4.8%) and 10.8% (13.3%), respectively.\textsuperscript{18}

\textit{Temporal relationship.} Diarrhoea may occur at any stage of measles. Data on temporal associations, as with pneumonia and croup, are scarce. In Thailand, 22% of cases occurred before the rash, 14% with the rash and 64% after the rash had appeared.\textsuperscript{9}

\textit{Measles and persistent diarrhoea.} Few studies have evaluated the role of measles in persistent diarrhoea. A prospective community-based study from Bangladesh reported that 25% of measles-associated diarrhoea was ‘prolonged’ (i.e. 7 or more days).\textsuperscript{32} The CFR was significantly higher for prolonged diarrhoea (11.9%) than for diarrhoea of less than 7 days duration (1%). Children with measles-associated acute diarrhoea had a higher CFR (1%) than those with acute diarrhoea without measles (0.1%).

In contrast, a prospective hospital-based study on persistent diarrhoea found no such cases among children who had had measles in the previous 6 months.\textsuperscript{33}

\textit{Aetiology.} The aetiology of measles-associated diarrhoea has been well defined in four case-controlled studies.\textsuperscript{9,12,34,35} In all studies, fewer pathogens were identified in measles-associated diarrhoea ‘cases’ than in non-measles-associated diarrhoea ‘controls’. This suggests that a significant proportion of diarrhoea (range 8–46%) was due to the measles virus \textit{per se}. Rotavirus was isolated in 16–30% of controls in three studies where it was sought, but was virtually never isolated in cases of measles.\textsuperscript{12,34,35} Parasitic infections were more frequent in cases than in controls where parasites were sought.\textsuperscript{12,34} Bacterial isolation rates were similar in cases and controls, except in one study which reported a higher rate of \textit{Helicobacter} isolation in cases than in controls.\textsuperscript{12} Support for the belief that measles virus causes mild diarrhoea is supplied by a descriptive study of measles from Egypt which reports negative bacterial stool cultures in 42% of children with mild diarrhoea (\textit{n} = 33), 27% of children with moderate diarrhoea (\textit{n} = 11) and none in children with severe diarrhoea (\textit{n} = 6).\textsuperscript{36}

\textit{Issues of concern.} The causes, natural history and management of persistent diarrhoea in measles need clarification. Anti-diarrhoeal agents are not advocated by WHO. Agents that have been shown to be effective in non-measles diarrhoea may require investigation in severe cases of measles-associated diarrhoea,\textsuperscript{37} given the known serious morbidity in this condition.

\textit{Malnutrition}

Data derived mainly from hospital surveys show that children who are significantly malnourished have a higher morbidity and mortality rate (Table V).\textsuperscript{10,11,38} This, however, does not necessarily imply a causal relationship. Measles is an extremely catabolic event and significant weight loss follows infection, the amount probably related to severity of infection (infecting dose). The presence of dehydration exacerbates weight loss and complicates nutritional assessment.

In a review of risk factors for measles, Aaby reported no difference in mortality in relation to nutritional status in community-based studies (except for one in Bangladesh).\textsuperscript{39}

\textit{Eye complications}

\textit{Measles conjunctivitis and keratitis.} Conjunctivitis is a hallmark of measles and usually resolves within a few days of onset. Significant corneal damage in children with measles can result in blindness.\textsuperscript{40} The causes of corneal damage include vitamin A deficiency (xerophthalmia), measles virus infection, secondary
TABLE V. Association between nutritional status and percentage of complications in measles

<table>
<thead>
<tr>
<th>Regional morbidity and mortality</th>
<th>All</th>
<th>&gt; 80%</th>
<th>60-80%</th>
<th>&lt; 60%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morbidity in Jakarta:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>74.9</td>
<td>61.9</td>
<td>84.6</td>
<td>100.0</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>18.6</td>
<td>13.7</td>
<td>19.9</td>
<td>39.2</td>
</tr>
<tr>
<td>Convulsions</td>
<td>7.5</td>
<td>8.2</td>
<td>7.7</td>
<td>2.2</td>
</tr>
<tr>
<td>Otitis media</td>
<td>5.9</td>
<td>6.7</td>
<td>5.9</td>
<td>2.2</td>
</tr>
<tr>
<td>Mortality in:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jakarta:</td>
<td>10.3</td>
<td>5.9</td>
<td>12.7</td>
<td>23.1</td>
</tr>
<tr>
<td>Tanzania</td>
<td>8.0</td>
<td>3.6</td>
<td>7.3</td>
<td>24.5</td>
</tr>
<tr>
<td>Kenya</td>
<td>1.8</td>
<td>0.8</td>
<td>1.4</td>
<td>4.0</td>
</tr>
</tbody>
</table>

herpes or bacterial infection, and a chemical conjunctivitis caused by harmful eye practices such as herbal remedies.

Xerophthalmia. In a global review of xerophthalmia, Oomen states 'there appears to be a universal relationship between infectious diseases and xerophthalmia. This relates especially to measles...'. The results from case control studies to confirm this are, however, conflicting. Studies from Ethiopia and Malawi reported significant risk ratios (odds ratios of 4.6 and 1.6, respectively), but studies from the Philippines and Bangladesh found no significant association.

A prospective study from India reported that conjunctival signs of xerophthalmia developed in 3/281 (1.1%) of children in the 6-month period following measles, compared with 4/819 (0.5%) of children without measles. The relative risk of developing xerophthalmia was 2.19 times greater following measles, but the 95% CIs were wide, 0.49 to 9.71.

Acute encephalitis

Central nervous system (CNS) manifestations 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 the 1963 UK community-based survey, neurological disturbances were reported in 0.4% of cases, and 0.1% were regarded as having encephalitis. In a subsequent hospital-based study from Denmark, encephalitis was seen in 1.4% of patients, with a CFR of 9%. At follow-up, 32% of survivors had some neurological dysfunction. The epidemiology of this complication in developing countries has not been well described. CNS complications reported from developing countries are shown in Table VI. The major area of concern relates to the diagnostic criteria for encephalitis in developing countries. The lack of standard case definitions makes comparison of data difficult.

Otitis media and stomatitis

Although otitis media and severe stomatitis are well recognized complications of measles, there are hardly any recent publications directed at these. A study from South Africa reports that herpes virus infection was detected in 43% of hospitalized and 37% of out-patient children with measles.

Nosocomial infections

Children with measles are prone to secondary infections, particularly when hospitalized. A retrospective case controlled study from South Africa reported that nosocomial bacteraemias were six times more common in children with measles than in general paediatric patients.
Gram-negative (Klebsiella and Salmonella) organisms accounted for 86.5% of the isolates, of which 23% were multiply drug-resistant.

**Post-measles morbidity and mortality**

A number of studies show that in the months following infection with measles children have significantly increased morbidity and mortality compared with community controls. There is an increase in the frequency and duration of diarrhoea, nutrition may be compromised and susceptibility to infection may be ten times greater than in controls. In a prospective community-based study of 281 cases of measles and 819 controls, 34% of the children with measles compared with 6% of the controls developed chest infections in the 6 months following measles, and the incidence of hospitalization for measles compared with controls was 2.9% and 0.4%, respectively.

**Tuberculosis.** It is generally acknowledged that measles predisposes to tuberculosis or its reactivation as a consequence of immune suppression. An American review in 1976 which concluded that the evidence for this assumption was not very strong does not reflect the experience in developing countries where evidence of this association is abundant.

**Bronchiectasis.** Measles has been associated with recurrent chest infections and bronchiectasis and a number of cases have been shown to follow measles in South Africa. The magnitude of the problem has, however, not been quantified.

**Delayed mortality.** Studies from West Africa report that children with measles, particularly those under 1 year of age, have a five-to-tenfold greater risk of dying in the ensuing year than community controls. A recent Kenyan study reported a mortality rate of 4.3% in children aged 8–35 months living in compounds where a measles outbreak had occurred the previous year. In the compounds without measles the mortality rate was 1.1%. The difference is not statistically significant because of small numbers.

Increased morbidity and mortality following measles may theoretically be due to viral persistence (this has never been demonstrated), but is more likely to be due to persistent immune suppression which is often associated with vitamin A deficiency.

**Management**

**Vitamin A therapy.** Four hospital-based clinical trials (UK 1932, Tanzania 1987, Republic of South Africa (RSA) 1990 and 1991) have evaluated the effect of vitamin A supplementation on morbidity and mortality. In Cape Town and Tanzania the children received 200 000 IU of vitamin A on 2 successive days, while in Durban 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 UK study received approximately 20 000
IU daily for 1–3 weeks (140,000–400,000 IU altogether). In all four trials, vitamin A was shown to protect against the effects of infections in measles. In the UK trial the CFR in the treated group was 3.7% compared with 8.7% in the untreated group. The relative risk (RR) of dying from measles following supplementation with vitamin A was 0.46 (0.26–0.81; \( p = 0.018 \)) compared with those not supplemented. The effect was most noticeable with respect to deaths from pneumonia.

In the Tanzanian double-blind clinical trial, six of 88 (7%) vitamin A-supplemented children and 12 of 92 (13%) controls died. The difference is not significant. There was, however, a significant difference in mortality in children less than 2 years of age.

In the Cape Town study (a prospective, double-blind, placebo-controlled trial on children with severe measles), vitamin A therapy had a significant effect on mortality. There were 10/97 (10%) deaths in the placebo group and only 2/92 (2%) deaths in the vitamin A-treated group (relative risk 0.21, 0.05–0.94; \( p = 0.046 \)).

The second RSA study in Durban was in a small sample (\( n = 60 \)) 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 an impressive 67% (\( p = 0.004 \)).

A meta-analysis of three large-scale community-based intervention trials, one in South India and two in Nepal, to evaluate the effect of vitamin A supplements on childhood mortality showed a 36% reduction in mortality, which is consistent with findings in the hospital-based studies.

The two South African trials specifically studied the impact of vitamin A on morbidity. In Cape Town the treated children had a significantly shorter hospital stay, recovered more rapidly from pneumonia and diarrhoea, and fewer developed croup, persistent pneumonia or persistent diarrhoea. In Durban, the vitamin A-treated children 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.

These benefits of vitamin A therapy have been confirmed by an evaluation of vitamin A supplementation used in the routine management of all children hospitalized with measles in Cape Town. The morbidity (hospital stay and intensive care admissions) and mortality in children hospitalized after the implementation of the programme were significantly less than that in the children admitted prior to the implementation of vitamin A therapy.

A study in Zambia that evaluated the effect of vitamin A therapy in an out-patient setting showed beneficial effects in line with observations in in-patients.

**Antibiotic therapy.** Five published studies, done between 1955 and 1973, have evaluated the role of antibiotics in measles.

A descriptive study done to evaluate the relationship between the use of prophylactic antibiotics and the development of complications involved 428 in-patients whose answers to questions about prior antibiotic usage were correlated with the development of complications. There was evidence of secondary infections on admission in 36 of 130 (30.4%) patients who received antibiotics prior to admission, while only 42 of the 298 (14.9%) patients who did not receive antibiotics had evidence of secondary infection. The risk of infection following prior antibiotic use was significantly greater than without antibiotics (odds ratio 1.96, [95% confidence interval 1.3–2.9], \( p < 0.001 \)). The major problem with this study is that the characteristics of the treated and untreated groups are not detailed, particularly the severity of disease, age group and duration of illness. Additionally, reasons for prescribing antibiotics are not detailed.

Three studies have compared the efficacy of different antibiotics, viz: triplofen and vibramycin; ampicillin and doxycycline; and penicillin and chloramphenicol. These studies found no differences in outcome in any of the groups compared. There were, however,
significant methodological defects in all of these studies. Inclusion criteria, the process of randomization and outcome measures were all vague and results would have been more meaningful if a placebo arm had been included. An out-patient study from India randomized children with measles to receive either tetracycline or a placebo. The complication rate in the placebo group was virtually double that in the treated group—27/80 (33.7%) compared with 13/65 (16.6%), respectively, \( p = 0.02 \). The ethics of using tetracycline and failure to define complications detract from the value of this study.

**Conclusion**

This literature review confirms that measles is still a major cause of childhood morbidity and mortality, especially in developing countries. What is surprising and not a little disturbing is the lack of hard data on a range of issues which are central to the development of a sound basis for case management of this disease. The papers reviewed are mainly reports of retrospective descriptive studies of records of hospitalized children that concentrate for the most part on just three major complications (pneumonia, croup and diarrohoea). Other complications responsible for significant morbidity are largely ignored. Additionally, comparison of data between and within countries is problematic because of the variability and inconsistency of definitions. Data from community-based studies are scant.

Review of these studies has not clarified time relationships between onset of measles and its various complications, nor has the aetiology of these been better defined. The measles virus appears to be directly responsible for many of the early complications which may be severe, but seldom kill. Complications occurring after the 1st week of illness are usually due to secondary viral and bacterial infections.

The management of measles and its complications are poorly documented. The only recent publications on management relate to beneficial effects of vitamin A therapy. There are no reports of clinical trials which have attempted to define optimal management of the common complications.

This review demonstrates the continuing need for community- and hospital-based studies which address issues such as the natural history of measles, its complications and the aetiology of these and intervention strategies, (e.g. antibiotic prophylaxis and therapy) which will lead to more effective measles case management.

**References**