Pneumonia in Children in Developing Countries

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1 Introduction

Pneumonia is the commonest cause of death in children [1, 2]. The World Health Organization (WHO) and UNICEF estimate that pneumonia is the primary cause of 19% of all deaths in children less than 5 years of age. In addition, most of the 10% of deaths caused by neonatal sepsis are associated with pneumonia and bacterial pneumonia is an important factor in many of the deaths caused by measles, pertussis and HIV [2]. Pneumonia therefore causes approximately one-third of all child deaths. Far too little effort has gone into research on pneumonia and its prevention and treatment.

Many factors are known to increase the risk of death from pneumonia. These include malnutrition, low birth weight, failure to breastfeed exclusively during the first four months of life, lack of measles immunisation, indoor air pollution and crowding [1].

2 Aetiology

Until the early 1980s, the conventional view was that "no specific causative agent is found in most patients" dying from respiratory tract infection and therefore that little could be done to reduce mortality from pneumonia [3, 4]. It was felt that attention should instead be focussed on diseases that could be treated, such as diarrhoea with dehydration and malaria. This view was based on studies that searched carefully for evidence of viral infection in children with pneumonia but did not involve bacterial cultures of percutaneous lung aspirates from children who had not received antibiotics [5–7].

Several lines of evidence suggest that most fatal pneumonia in children is caused by infection with *Streptococcus pneumoniae* or *Haemophilus influenzae* [8]. Firstly are findings from studies conducted in the United States and Europe during the

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N. Curtis et al. (eds.), *Hot Topics in Infection and Immunity in Children VII*,
Advances in Experimental Medicine and Biology 697, DOI 10.1007/978-1-4419-7185-2_5,

period before antimicrobial therapy was available. Bacteria were grown from percutaneous needle aspirates of the lung in 57% of children with pneumonia. Mortality was 65% in 99 children with a positive blood culture, compared to 17% of 826 children with a negative blood culture. Secondly, in controlled trials, the mortality rate from pneumonia was 2.3% in 824 children treated with sulphonamides, compared to 5.4% in 1491 control children. Thirdly, percutaneous needle aspirates of the lung yielded positive cultures in 71% of 321 children with pneumonia in developing countries in the pre-antibiotic era and in 58% of 705 children in the antibiotic era [8].

A detailed study of the bacteriology and virology of severe pneumonia was performed in 83 children in Papua New Guinea in the early 1980s [9]. Bacteria were grown from lung aspirate or blood in 68% of 71 children who had not received antibiotics, and viruses from 29% of 62 children; isolation of bacteria was strongly associated with mortality, but isolation of viruses was not. *Streptococcus pneumoniae* or *H. influenzae* or both were isolated from 52% of the children and from seven of the eight children who died. Among the *H. influenzae* isolated from lung or blood, 56% were non-serotypable strains, 25% were non-b serotypes (a, c, d, e or f), and only 19% were type b. Studies in several other developing countries have confirmed that strains of *H. influenzae* other than type b are an important cause of pneumonia in children [10]. In the early 1980s, this evidence convinced WHO to set up a programme to reduce mortality from acute respiratory infections in children [11–14].

The aetiology of pneumonia in children can only be determined reliably by doing needle aspirations of the lung in children who have no antibiotic activity present in blood or urine [15]. Studies that use blood culture and antigen detection without lung aspiration yield misleading results and studies that include children who have received antibiotics will grossly underestimate the proportion of cases caused by bacteria. The history is not a reliable indication of antibiotic use: the child's blood or urine must be tested for antibiotic activity [15].

3 Standard Management

Mortality from pneumonia caused by *S. pneumoniae* or *H. influenzae* can be substantially reduced by early treatment with antibiotics [8]. However, mortality is highest in the remote and disadvantaged regions of low-income countries [1] and early treatment will be possible only if we can train and support primary health-care workers to give antibiotic therapy in these regions. The antibiotics need to be effective, inexpensive, and suitable for use in primary health care. Since very few antibiotics meet all these criteria, their use needs to be restricted to limit the development of resistance.

In high-mortality areas, the guidelines for primary health-care workers should use the *minimum* number of criteria needed to decide on treatment reliably, and the *minimum* treatment needed to reduce *mortality* [16]. Unfortunately, these principles

have not always been observed and the WHO guidelines have become more complicated than necessary, and have sometimes been based on potentially misleading information from medium- or low-mortality areas [17, 18]. A clear distinction needs to be made between guidelines written for very high-mortality areas with minimal health-care resources and guidelines written for medium–low-mortality areas where more resources are available for health care and viruses cause a higher proportion of severe respiratory tract infection.

4 Which Children Need an Antibiotic?

Children with pneumonia have cough or difficulty in breathing. However, most children with cough or difficulty in breathing do not have pneumonia: they have only a mild respiratory infection and do not need an antibiotic. The best indication that children need antibiotics is their respiratory rate; in general, children without tachypnoea do not need an antibiotic and children with tachypnoea are more likely to benefit from antibiotic therapy [12, 19–21]. Fever is not a useful discriminator: children with viral infections often have a fever when they do not need antibiotics. Listening with a stethoscope is far less reliable than counting the respiratory rate and looking for chest indrawing and absence of prolonged expiration.

In high-mortality areas, it is important to decide which criteria for the use of antibiotics will save the most lives, while minimising the use of antibiotics (to delay the development of resistance). This is *not* the same as deciding which children have pneumonia; for example, young infants have a higher case fatality rate and are more likely to benefit from antibiotics than are older children with the same clinical findings. WHO suggests that antibiotics should be given to children aged 2–12 months if they have a respiratory rate $\geq$ 50 breaths/min and to children aged 12–59 months if they have a respiratory rate $\geq$ 40 breaths/min [18]. This age-dependent definition has a higher sensitivity for the diagnosis of pneumonia than using a rate $\geq$ 50 breaths/min for all children aged 2–59 months. However, children aged 15–59 months who present with a respiratory rate of 40–49 breaths/min have a low incidence of pneumonia and a low case fatality rate, so treating these children greatly increases the use of antibiotics with very little effect on total mortality [22]. For this reason, when deciding which children should receive antibiotics (rather than which children have pneumonia), tachypnoea should be defined as $\geq$ 50 breaths/min in all children aged 2–59 months.

There are important causes of false-positive and false-negative findings with tachypnoea. False-positive findings occur in children with bronchiolitis or asthma who often have tachypnoea when they do not need antibiotics. In very high-mortality areas, it is probably sensible to give antibiotics to infants with bronchiolitis and asthma is usually uncommon in these areas, so this is not an important problem. However, in medium–low-mortality areas, a high proportion of infants with tachypnoea have bronchiolitis or asthma, so tachypnoea (and chest indrawing) are unreliable indications of the need for antibiotics unless small airway obstruction

has been excluded. This is best done by observing the chest and looking for a prolonged active expiratory phase and *not* by listening for wheeze with a stethoscope. Separate guidelines are needed for medium–low-mortality areas when bronchiolitis and asthma are common.

False-negative findings with tachypnoea may occur in children with very severe pneumonia: such children sometimes have slow, laboured respiration. However, all these children will have chest indrawing (see below). Children without chest indrawing should be given antibiotics only if they have tachypnoea.

5 Which Children Need Admission?

Among children who do not have small airway obstruction, tachypnoea is a sign that the lungs are stiff (have reduced compliance) from inflammation and accumulation of pus in the alveoli. As lung compliance falls even further, chest retraction (or chest indrawing) develops; this is the best sign that a child has severe pneumonia and requires admission for intensive antibiotic treatment [16, 20, 21]. The WHO definition of the term chest indrawing was initially vague; it should be used to mean the presence of subcostal retraction plus either intercostal or supracostal retraction [16, 21]. False-positive chest indrawing may occur in the absence of pneumonia in children with airway obstruction (those with small airway obstruction will have prolonged expiration or audible wheeze) and in preterm babies (who all have a degree of chest indrawing).

Two controlled trials performed at tertiary-care facilities have suggested that children with chest indrawing could safely be treated at home with oral amoxicillin [23, 24]. However, it is likely that few of the children had bacterial pneumonia: lung aspirates were not cultured, only 14 of the 3,739 children died, and 63% had wheeze, so these results should not be extrapolated to areas with a high mortality from pneumonia.

6 Which Children Have Very Severe Pneumonia?

WHO defines very severe pneumonia as the presence of chest indrawing plus either central cyanosis or severe respiratory distress (for example, head nodding) or the inability to drink – providing small airway obstruction has been excluded [17, 18]. There is considerable evidence to support these criteria [21, 25]. Unfortunately, the clinical diagnosis of cyanosis is not reliable. When pulse oximetry is not available, it is helpful to compare the colour of the child's tongue to that of the mother's tongue. The lips look "cyanosed" in pigmented children, and all people look "cyanosed" in ordinary fluorescent lighting.

There is confusion about the measurement of hypoxaemia. In places fortunate enough to have pulse oximetry available, a clear distinction should be made between the use of saturation as an indication of the severity of pneumonia (less than 90% is associated with a much higher mortality) [21] and as a guide to when to give

oxygen. With normal cardiac output, haemoglobin concentration and pH, arterial oxygen saturations of 68% or more are not dangerous [26], which suggests that it might be sensible to give supplemental oxygen only when the saturation is less than 80% if oxygen supplies are limited. When comparing the effectiveness of different methods of giving oxygen, arterial oxygen tension is much more sensitive than oxygen saturation because of the sigmoid shape of the haemoglobin–oxygen dissociation curve [27].

7 Which Antibiotic for Outpatients With Non-severe Pneumonia?

Most children with bacterial pneumonia recover without antibiotic therapy [8]. Consequently, antibiotics and vaccines may have a substantial effect on mortality even if they tip the balance only slightly in favour of the host. For example, if 90% of children recover from pneumonia without antibiotics, an increase in survival of only 5% (to 95%) means that mortality has halved from 10 to 5%.

At the time that the WHO protocols were developed in the late 1970s and early 1980s, most strains of *S. pneumoniae* and *H. influenzae* were sensitive to benzyl penicillin (but not phenoxymethylpenicillin), amoxicillin, and cotrimoxazole. Pharmacokinetic studies performed in children in Papua New Guinea suggested that mean serum penicillin levels were greater than 1.0 μg/mL for about 11 h after 48 mg/kg (48,000 U/kg) of procaine penicillin given by intramuscular injection [28]. The early WHO protocols therefore suggested that children should be treated with intramuscular injections of 50 mg/kg of procaine penicillin given daily, or 15 mg/kg of amoxicillin orally three times a day, or cotrimoxazole (4 mg/kg of trimethoprim and 20 mg/kg of sulphamethoxazole) orally twice a day.

Cotrimoxazole is inferior to amoxicillin for the treatment of proven infections with *H. influenzae* or *S. pneumoniae* in bacterial pneumonia [29] and in otitis media [30, 31]. Otitis media provides useful information about the treatment of pneumonia because it is caused by the same organisms, and bacterial cultures can be performed using tympanocentesis before, during and after treatment. Two studies that were not supported by microbiological evidence concluded that cotrimoxazole is as effective as amoxicillin or procaine penicillin for pneumonia, but only 66 children received cotrimoxazole in the first study [32] and the other study involved only children with non-severe pneumonia where a very large sample size would have been needed to detect a difference in efficacy [33]. Cotrimoxazole should no longer be used as a first-line treatment for pneumonia in high-mortality areas [29–31] except as an adjunct to amoxicillin in HIV-affected areas when pneumocystis pneumonia is prevalent.

Streptococcus pneumoniae resistance to penicillin and other antibiotics is an increasing problem throughout the world and it is therefore surprising that WHO has recently recommended that amoxicillin be given fewer times a day and for fewer days to children with pneumonia. Amoxicillin remains an effective treatment for

pneumonia caused by strains of *S. pneumoniae* with an intermediate level of resistance (MIC 2–4 μg/mL), provided that amoxicillin levels remain above the MIC for at least 50% of the time between doses [34, 35]. To increase the proportion of time that the levels of amoxicillin are above the MIC, it is much more effective to give the same dose more often, rather than a higher dose at the same frequency [34]. Because of problems with compliance, the dose of amoxicillin recommended by WHO has been changed from 15 mg/kg three times a day to 25 mg/kg twice a day [36]. Unfortunately, the serum level remains above a given MIC for a smaller percentage of the time with the new regimen [37], so it will be less effective for the treatment of partially resistant strains of *S. pneumoniae*. In the management of otitis media caused by *H. influenzae* or partially resistant *S. pneumoniae*, 45 mg/kg amoxicillin twice a day is clearly superior to 20–25 mg/kg twice a day [38, 39]. In high-mortality areas, the best policy may be to recommend giving 45 mg/kg amoxicillin twice a day orally or (preferably) 30 mg/kg three times a day for greater efficacy.

A controlled trial performed in four tertiary-care hospitals in Pakistan compared 45 mg/kg/day amoxicillin with 90 mg/kg/day in children with non-severe pneumonia [40]. The study failed to detect any benefit from using a higher dose of amoxicillin. However, it is likely that few of the children had bacterial pneumonia: lung aspirates were not performed, none of the 876 children died and 42% had wheeze, so these findings should not be extrapolated to regions with a high mortality from pneumonia.

WHO originally recommended that children with tachypnoea and no chest indrawing should be treated with antibiotics for 5 days, and this is still the case in areas where HIV infection is common [36]. In areas with low HIV prevalence, WHO now suggests that amoxicillin be given for only 3 days. This recommendation is based on the findings of three studies (one unpublished) in 5,763 children, where the relative risk of failure was 1.07 (95% CI 0.92–1.25) with 3 days compared to 5 days of treatment [41]. However, it is likely that few of the children had bacterial pneumonia: only nasopharyngeal bacteria were cultured, and there was only one death among the 4,188 children in the two published studies, so these results should not be extrapolated to areas with a high mortality from pneumonia.

8 Which Antibiotics for Severe Pneumonia?

Pharmacokinetic studies performed in children in Papua New Guinea found that the mean serum level of penicillin was more than 5 μg/mL for 3 h after a dose of 35 mg/kg of benzyl penicillin given by intramuscular injection. WHO recommends that children with chest indrawing who do not have signs of very severe pneumonia should be treated with 50 mg/kg of benzyl penicillin given by intramuscular injection every 6 h for at least 3 days and then 25 mg/kg of oral amoxicillin twice a day (which perhaps should be 30 mg/kg three times a day – see above). This high dose of benzyl penicillin is likely to provide effective treatment for most strains of

H. influenzae and *S. pneumoniae*, including strains with intermediate resistance to penicillin (MIC 2–4 μg/mL) [35].

When a child with severe pneumonia cannot be referred for treatment with intramuscular benzyl penicillin, WHO suggests that treatment can be safely given at home with 45 mg/kg amoxicillin orally twice a day for 5 days [36]. This recommendation is based on two controlled trials performed in urban tertiary centres [23, 24]. However, it is likely that few of the children had bacterial pneumonia: lung aspirates were not cultured, only 14 of the 3,739 children died and 63% had wheeze, so these findings should not be extrapolated to regions with a high mortality from pneumonia. As discussed above, 30 mg/kg of amoxicillin given three times a day is likely to be more effective than 45 mg/kg given twice a day [34].

9 Which Antibiotics for Very Severe Pneumonia?

Children are said to have very severe pneumonia if they have chest indrawing plus either central cyanosis or severe respiratory distress or an inability to drink. WHO recommends that these children be treated with ampicillin plus gentamicin, or with chloramphenicol. *Streptococcus pneumoniae* is increasingly resistant to chloramphenicol and two controlled trials suggest that penicillin (or ampicillin) plus gentamicin is more effective than chloramphenicol (the relative failure rate was 1.26, 95% CI 1.03–1.54). Gentamicin has a synergistic effect with β-lactams against many strains of *S. pneumoniae* that have reduced sensitivity to penicillin [42–47] and it has excellent activity against *H. influenzae*. There are advantages in giving 8 mg/kg of gentamicin intramuscularly on the first day followed by 6 mg/kg on subsequent days, rather than 7.5 mg/kg daily [48].

Penicillin plus gentamicin remains an effective treatment for pneumonia caused by strains of *S. pneumoniae* with an intermediate level of resistance, provided penicillin levels remain above the MIC for at least 50% of the time between doses [34, 35]. Penicillin resistance is *not* an indication for the use of third-generation cephalosporins to treat pneumonia, as they are no more effective than penicillin alone [35], let alone penicillin plus gentamicin. Third-generation cephalosporins and fluoroquinolones are much more expensive than penicillin and gentamicin, and they are more likely to induce antibiotic resistance [49].

WHO should recommend penicillin plus gentamicin, rather than ampicillin plus gentamicin, for the treatment of very severe pneumonia. Ampicillin has a much broader spectrum than oral phenoxymethylpenicillin (penicillin V), but there are fewer differences between ampicillin and parenteral benzyl penicillin (penicillin G); in particular, ampicillin and benzyl penicillin have similar activity against *H. influenzae* [28]. Some gram-negative bacilli are sensitive to ampicillin and resistant to benzyl penicillin, but these organisms are almost all sensitive to gentamicin so that organisms that are sensitive to ampicillin plus gentamicin can also be expected to be sensitive to penicillin plus gentamicin. Hospitals have to stock benzyl penicillin to treat severe pneumonia and it would be better just to add gentamicin for

very severe pneumonia, rather than requiring hospitals to stock ampicillin as well. Ampicillin is more expensive than penicillin and it has more side effects.

WHO recommends that treatment be changed if a child with pneumonia "does not improve within 48 h". It is unrealistic to expect that improvement will reliably occur as early as this in bacterial pneumonia; in adults with pneumococcal pneumonia, Robert Austrian noted no difference in mortality between treated and untreated patients in the first 5 days [50] and the controlled trials of both penicillin (or ampicillin) plus gentamicin vs. chloramphenicol for very severe pneumonia assessed the response to treatment after 5 days [51, 52]. It would be more logical to recommend that treatment be changed if the child is getting worse at any time from 48 h onwards or if there is no improvement after 5 days [21, 53].

10 Oxygen Therapy

Hypoxaemia is a major cause of mortality in pneumonia [54]. Studies in guinea pigs and adult humans in the 1920s and in children in Papua New Guinea in the 1970s all suggest that oxygen therapy approximately halves mortality from pneumonia [55]. A recent study found that an improved system for delivering oxygen reduced mortality from pneumonia by 35% among children in Papua New Guinea [56].

However, it is very difficult to deliver oxygen therapy to children in the remote parts of many low-income countries and the cost is considerable. In Papua New Guinea, the improved oxygen delivery system cost US $51 per patient treated and $1,673 per life saved. The world's 49 low-income countries with a population of 1.3 billion had a total health expenditure of only US $22 per person in 2006 [57]. As discussed above, with normal cardiac output, haemoglobin concentration and pH, arterial oxygen saturations of 68% or more are not dangerous [26] and it might be sensible to give supplemental oxygen only when the saturation is less than 80% (rather than 90%) if oxygen supplies are limited.

11 Fluid Therapy

Some children with severe pneumonia present with sepsis and dehydration. If parenteral fluid therapy is available, hypovolaemia should be corrected rapidly with 10 mL/kg boluses of 0.9% saline. However, many patients with pneumonia have low maintenance water requirements because they have high levels of antidiuretic hormone [58]. Once hypovolaemia and hypoxaemia have been corrected, maintenance fluids should be restricted to 1–2 mL/kg/h [59, 60]. There is little evidence to support the widely offered advice that children with acute respiratory infections should be given extra fluids [61].

12 Fever

WHO recommends that paracetamol be administered to children with a temperature greater than 39°C if it "appears to be causing distress" [17]. This recommendation

may be harmful. In randomised trials in mammals with severe infection, antipyretic therapy *doubles* mortality, increases viral shedding and impairs the antibody response [62]. Antipyretics have been shown to prolong the illness in influenza, chickenpox and malaria [63–65]. It is potentially dangerous to recommend the administration of antipyretics to children with pneumonia in high-mortality areas.

13 Neonates, Malnutrition and HIV

Pneumonia, often with systemic sepsis, is common in neonates and infants with malnutrition, and it has a very high mortality rate in these children [66, 67]. Despite their high risk of dying, these children may not appear to be very ill – and the mortality rate is very high indeed in malnourished children with pneumonia if they are afebrile [25]. Gram-negative bacteria are a common cause of sepsis in neonates and malnourished children; so these children should be treated with gentamicin as well as penicillin (or ampicillin).

Children with HIV often present with pneumonia caused by *S. pneumoniae*, *H. influenzae* or *Staphylococcus aureus*. Other common causes of pneumonia in these children are *Pneumocystis jirovecii*, gram-negative bacteria, cytomegalovirus and tuberculosis [68, 69].

14 Overall Effect of Case Management

When case management can be properly delivered, it results in substantial reductions in child mortality. A meta-analysis of the effect of the case management of pneumonia in children in low-income countries found a reduction in total mortality of 27% (95% CI 18–35%) in neonates, 20% (11–28%) in infants and 24% (14–33%) in children 0–4 years of age [70]. There have been three recent reviews of the case management of pneumonia [21, 68, 71].

15 Immunisation

The WHO programme for the management of acute respiratory infections has led to substantial reductions in child mortality [70]. However, pneumonia remains the commonest cause of death in children [1, 2] despite the fact that the WHO programme has been going for almost 30 years [11]. This is largely because it has not been possible to deliver antibiotics reliably to children in the remote regions of many low-income countries, where most of the deaths from pneumonia occur. It is much easier to deliver vaccines at intermittent intervals to children in remote areas than it is to have antibiotics available for administration at all times. Unfortunately, none of the current Expanded Program on Immunization (EPI) vaccines provides specific protection against *S. pneumoniae* or *H. influenzae*, the main causes of fatal pneumonia.

Very substantial additional reductions in mortality would result from immunisation against *S. pneumoniae* and *H. influenzae* [72] and better utilisation of the non-specific effects of vaccines [73]. There is an urgent need for studies of the

effect of immunising mothers with the 23-valent polysaccharide pneumococcal vaccine before pregnancy, during pregnancy or immediately after delivery, in order to increase antibody transfer to the baby across the placenta or via breast milk [74–77]. Unlike the polysaccharide vaccine, the conjugated pneumococcal vaccines are immunogenic in the first few months of life, when most fatal pneumonia occurs, but they cover only a limited number of serotypes, and they are very expensive. Unfortunately, the three trials of conjugated pneumococcal vaccines in children in developing countries all used vaccines that are no longer available [78–80], only two studied the effects on clinical pneumonia [79, 80] and only one studied the effect on all-cause mortality [79]. The vaccines reduced radiological pneumonia by 17% (95% CI 4–28%) in South Africa, 37% (27–45%) in the Gambia, and 23% (–1 to 41%) in the Philippines.

The *H. influenzae* type b conjugate vaccine reduced radiological pneumonia by approximately 20% among children in trials in the Gambia and Chile [81, 82]. However, type b strains cause less than half the cases of *H. influenzae* pneumonia in children in low-income countries; approximately 40% of cases are caused by non-serotypable (unencapsulated) strains and 20% by types a, c, d, e and f [10]. This suggests that a vaccine that protected against all strains of *H. influenzae* would prevent approximately 40% of radiologically proven pneumonia. As with pneumococcal vaccine, there is a strong case for investigating the immunisation of mothers against *H. influenzae* in order to protect their infants through transfer of antibody across the placenta and via breast milk.

A new 10-valent pneumococcal conjugate vaccine has recently been licenced that provides some protection against non-serotypable strains of *H. influenzae* [83, 84]: eight pneumococcal serotypes are conjugated to *H. influenzae protein* D, one to tetanus toxoid and one to diphtheria toxoid. In a controlled trial of the 11-valent prototype, the per-protocol vaccine efficacy was 52% (95% CI 37–63%) against *S. pneumoniae* otitis media, and 36% (4–57%) against *H. influenzae* otitis media [85]. There is an urgent need to test the efficacy of this vaccine against radiological pneumonia in children in high-mortality areas; studies in Argentina, Columbia and Panama are expected to deliver results in the near future.

There is increasing evidence that vaccines have very substantial non-specific (heterologous) effects on mortality among children in low-income countries [73, 86]. For example, BCG and measles vaccines may reduce mortality from diseases other than tuberculosis and measles, and most of the benefits seem to be on mortality from pneumonia [87]. On the other hand, there are studies suggesting that, in some communities, diphtheria–tetanus–pertussis (DTP) vaccine may reduce mortality from diphtheria, tetanus and pertussis but *increase* mortality from pneumonia and diarrhoea [73, 86]. There is an urgent need for further research on the non-specific effects of vaccines in children in developing countries.

16 Conclusion

Although great progress has been made in reducing mortality from pneumonia, it remains the commonest cause of death among children in developing countries.

Further substantial reductions in mortality will require effective antibiotic therapy and immunisation against *S. pneumoniae* and *H. influenzae* to be made available to a high proportion of the children who live in the remote areas of low-income countries.

In recent years, several controlled trials have been performed that have suggested that non-severe pneumonia can be treated with 25 mg/kg amoxicillin twice a day for 3 days [40, 41], and that children with severe pneumonia who cannot be referred can be safely treated at home with 45–90 mg/kg/day amoxicillin [23, 24]. However, it is probable that a very low proportion of the children in these trials had bacterial pneumonia: the trials were performed in urban tertiary centres, no attempt was made to culture lung aspirates, very few children died and wheezing was common in many of the trials. Management based on the findings of these studies may considerably improve the management of children in communities with moderate–low mortality rates, but their findings should *not* be extrapolated to communities where there is a high mortality from pneumonia.

Table 1 outlines the optimal management of acute respiratory infection in children in high-mortality areas, and notes where this differs from the current WHO recommendations. Table 2 summarises the important considerations about pneumonia in high-mortality areas.

Table 1 Suggested management of children with cough or respiratory distress in high mortality areas (who do not have prolonged expiration – or audible wheeze)

Cough or cold
No chest indrawing, respiratory rate <50 breaths/min, age 2–59 months (WHO: <50/min, age 2–12 months; <40/min, 12–59 months)
No antibiotic
Pneumonia
No chest indrawing, respiratory rate ≥50 breaths/min, age 2–59 months (WHO: ≥50/min, age 2–12 months; ≥40/min, age 12–59 months)
Amoxicillin 30 mg/kg oral three times a day (or perhaps 45 mg/kg twice a day) for 5 days (WHO: 25 mg/kg twice a day for 3 days)
Cotrimoxazole should no longer be recommended (except for pneumocystis cover)
Severe pneumonia
Chest indrawing (without cyanosis or severe respiratory distress, and able to drink)
Admit, benzyl penicillin 50 mg/kg IM every 6 h for at least 3 days
When improving, change to amoxicillin 30 mg/kg oral three times a day (WHO: 25 mg/kg bd)
Give antibiotics for a total of 7 days (WHO: 5 days)
Very severe pneumonia
Chest indrawing (not required by WHO) plus either central cyanosis, or severe respiratory distress, or not able to drink
Admit, benzyl penicillin (WHO: ampicillin) 50 mg/kg IM every 6 h plus gentamicin 8 mg/kg IM day 1, then 6 mg/kg daily (WHO: 7.5 mg/kg daily) for 10 days
If getting worse at any time from 48 h onwards or not improving at 5 days (WHO: not improving at 48 h), change to cloxacillin 50 mg/kg IM every 6 h plus gentamicin IM daily for 3 weeks

Table 2 Important considerations about pneumonia in children in high-mortality areas

Epidemiology and aetiology
- Pneumonia is the commonest cause of death in children less than 5 years of age; it is a major factor in approximately 30% of deaths
- Most fatal pneumonia is caused by *S. pneumoniae* and *H. influenzae*

Case management
- Separate protocols are needed for children in medium–low-mortality areas, including children with a prolonged expiratory phase (caused by bronchiolitis or asthma)
- Guidelines for children in high-mortality areas should not be based on data from medium–low-mortality areas (so data from many urban areas should not be used even if they are in low-income countries)
- Guidelines for high-mortality areas should use the *minimum* necessary criteria to decide the *minimum* treatment needed to reduce *mortality*
- The current WHO guidelines are too complicated and influenced by data from medium–low mortality areas
- In children aged 2–59 months who do not have chest indrawing, it would be better to recommend antibiotics only if the respiratory rate is $\geq$50 breaths/min (WHO recommends that antibiotics be given to children aged 12–59 months taking $\geq$40 breaths/min)
- Non-severe pneumonia should be treated with amoxicillin 30 mg/kg oral three times a day for 5 days, or perhaps 45 mg/kg twice a day (WHO recommends 25 mg/kg twice a day for 3 days)
- Cotrimoxazole should no longer be used, except for pneumocystis (WHO policy is unclear)
- Antibiotics should probably be given for 5 days (WHO recommends 3 days) to outpatients in high-mortality areas (regardless of HIV status)
- Chest indrawing should be defined as subcostal plus either intercostal or supracostal retraction (WHO defines indrawing as retraction of the lower chest wall)
- If severe pneumonia cannot be treated with benzyl penicillin given intramuscularly, amoxicillin 30 mg/kg should be given orally three times a day for 7 days (WHO recommends 25 mg/kg twice a day for 5 days)
- Chest indrawing should be a requirement for the diagnosis of very severe pneumonia (WHO does not require this)
- Penicillin (WHO recommends ampicillin) plus gentamicin should be used to treat very severe pneumonia
- Third-generation cephalosporins should *not* be recommended for the treatment of pneumonia; they are no more effective than penicillin plus gentamicin (WHO agrees)
- Chloramphenicol should no longer be used to treat very severe pneumonia (WHO policy is unclear)
- Treatment failure should be defined as progression of disease at 48 h or later, or failure to improve at 5 days (WHO recommends failure to improve at 48 h)
- Fever should *not* be treated with an antipyretic in high-mortality areas (paracetamol is recommended by WHO)
- After correction of hypovolaemia, fluid intake should usually be 1–2 mL/kg/h
- Oxygen therapy for children with an oxygen saturation less than 80% is likely to halve mortality, but it is expensive (WHO recommends giving oxygen if saturation < 90%)

Immunisation
- Treatment with antibiotics reduces mortality from pneumonia, but it is difficult to deliver in remote areas in low-income countries, where most of the deaths occur
- Effective immunisation of mothers and infants against *S. pneumoniae* and *all* strains of *H. influenzae* would be likely to reduce mortality from pneumonia by at least 50% if it were available
- There should be urgent investigation of the evidence that BCG and measles vaccines reduce all-cause mortality (including mortality from pneumonia) in high-mortality areas, but that DTP vaccine may increase mortality from diseases other than diphtheria, tetanus and pertussis in some high-mortality areas

Consideration should be given to immunising mothers with polysaccharide pneumococcal vaccine and ensuring that all infants receive conjugated pneumococcal vaccine. *Haemophilus influenzae* type b causes less than half the cases of *H. influenzae* pneumonia, but the new protein D-conjugated pneumococcal vaccine may protect against pneumonia caused by non-serotypable *H. influenzae* as well as *S. pneumoniae*. Research is urgently needed on the evidence that BCG and measles vaccines may substantially reduce child mortality from diseases other than tuberculosis and measles (including mortality from pneumonia), and the weaker evidence that DTP vaccine may increase mortality from diseases other than diphtheria, tetanus and pertussis in some high-mortality communities.

References

1. Rudan I, Boschi-Pinto C, Biloglav Z, Mulholland K, Campbell H. Epidemiology and etiology of childhood pneumonia. Bull World Health Organ. 2008 May;86(5):408–16.
2. Wardlaw T, Salama P, Johansson EW, Mason E. Pneumonia: the leading killer of children. Lancet. 2006 Sep 23;368(9541):1048–50.
3. Chretien J, Holland W, Macklem P, Murray J, Woolcock A. Acute respiratory infections in children. A global public-health problem. N Engl J Med. 1984 Apr 12;310(15):982–4.
4. Walsh JA, Warren KS. Selective primary health care: an interim strategy for disease control in developing countries. N Engl J Med. 1979 Nov 1;301(18):967–74.
5. Bulla A, Hitze K. Acute respiratory infections: a review. Bull World Health Organ. 1978;56(3):481–98.
6. Monto AS, Johnson KM. Respiratory infections in the American tropics. Am J Trop Med Hyg. 1968 Nov;17(6):867–74.
7. Sobslavský O, Sebikari SR, Harland PS, Skrtić N, Fayinka OA, Soneji AD. The viral etiology of acute respiratory infections in children in Uganda. Bull World Health Organ. 1977;55(5):625–31.
8. Shann F. Etiology of severe pneumonia in children in developing countries. Pediatr Infect Dis. 1986 Apr;5(2):247–52.
9. Shann F, Gratten M, Germer S, Linnemann V, Hazlett D, Payne R. Aetiology of pneumonia in children in Goroka Hospital, Papua New Guinea. Lancet. 1984 Sep 8;2(8402):537–41.
10. Shann F. *Haemophilus influenzae* pneumonia: type b or non-type b? Lancet. 1999 Oct 30;354(9189):1488–90.
11. World Health Organization. Clinical management of acute respiratory infections in children: a WHO memorandum. Bull World Health Organ. 1981;59(5):707–16.
12. Shann F, Hart K, Thomas D. Acute lower respiratory tract infections in children: possible criteria for selection of patients for antibiotic therapy and hospital admission. Bull World Health Organ. 1984;62(5):749–53.
13. World Health Organization. Case management of acute respiratory infections in children in developing countries. Geneva: WHO; 1985.
14. World Health Organization. Respiratory infections in children: management at small hospitals. Background notes and a manual for doctors. Geneva: WHO; 1986.
15. Shann F. Bacterial pneumonia: commoner than perceived. Lancet. 2001 June 30;357(9274):2070–2.
16. Pio A. Standard case management of pneumonia in children in developing countries: the cornerstone of the acute respiratory infection programme. Bull World Health Organ. 2003;81(4):298–300.
17. World Health Organization. Pocket book of hospital care for children. Geneva: WHO; 2005.
18. World Health Organization. Integrated management of childhood illness chart booklet. Geneva: WHO; 2008.

19. Harari M, Shann F, Spooner V, Meisner S, Carney M, de Campo J. Clinical signs of pneumonia in children. Lancet. 1991 Oct 12;338(8772):928–30.
20. Shann F. The management of pneumonia in children in developing countries. Clin Infect Dis. 1995 Dec;21(Suppl 3):S218–25.
21. Ayieko P, English M. Case management of childhood pneumonia in developing countries. Pediatr Infect Dis J. 2007 May;26(5):432–40.
22. Shann F. WHO definition of tachypnoea in children. Lancet. 1992 Jan 18;339(8786):176–7.
23. Addo-Yobo E, Chisaka N, Hassan M, Hibberd P, Lozano JM, Jeena P, et al. Oral amoxicillin versus injectable penicillin for severe pneumonia in children aged 3 to 59 months: a randomised multicentre equivalency study. Lancet. 2004 Oct 25;364(9440):1141–8.
24. Hazir T, Fox LM, Nisar YB, Fox MP, Ashraf YP, MacLeod WB, et al. Ambulatory short-course high-dose oral amoxicillin for treatment of severe pneumonia in children: a randomised equivalency trial. Lancet. 2008 Jan 5;371(9606):49–56.
25. Shann F, Barker J, Poore P. Clinical signs that predict death in children with severe pneumonia. Pediatr Infect Dis J. 1989 Dec;8(12):852–5.
26. Nunn JF. Nunn's Applied Respiratory Physiology. 4th ed. Stoneham, MA: Butterworth-Heinemann; 1993. pp. 472–81.
27. Shann F. Oxygen delivery: nasopharyngeal catheter or nasal prongs? J Pediatr. 1996 Jul;129(1):185. Author reply 186.
28. Shann F, Linnemann V, Gratten M. Serum concentrations of penicillin after intramuscular administration of procaine, benzyl, and benethamine penicillin in children with pneumonia. J Pediatr. 1987 Feb;110(2):299–302.
29. Straus WL, Qazi SA, Kundi Z, Nomani NK, Schwartz B. Antimicrobial resistance and clinical effectiveness of co-trimoxazole versus amoxicillin for pneumonia among children in Pakistan: randomised controlled trial. Pakistan Co-trimoxazole Study Group. Lancet. 1998 July 25;352(9124):270–4.
30. Leiberman A, Leibovitz E, Piglansky L, Raiz S, Press J, Yagupsky P, et al. Bacteriologic and clinical efficacy of trimethoprim–sulfamethoxazole for treatment of acute otitis media. Pediatr Infect Dis J. 2001 Mar;20(3):260–4.
31. Dagan R, Schneider S, Givon-Lavi N, Greenberg D, Leiberman A, Jacobs MR, et al. Failure to achieve early bacterial eradication increases clinical failure rate in acute otitis media in young children. Pediatr Infect Dis J. 2008 Mar;27(3):200–6.
32. Campbell H, Byass P, Forgie IM, O'Neill KP, Lloyd-Evans N, Greenwood BM. Trial of co-trimoxazole versus procaine penicillin with ampicillin in treatment of community-acquired pneumonia in young Gambian children. Lancet. 1988 Nov 19;2(8621):1182–4.
33. Keeley DJ, Nkrumah FK, Kapuyanyika C. Randomized trial of sulfamethoxazole + trimethoprim versus procaine penicillin for the outpatient treatment of childhood pneumonia in Zimbabwe. Bull World Health Organ. 1990;68(2):185–92.
34. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis. 1998 Jan;26(1):1–10. Quiz 11–12.
35. Jacobs MR. Antimicrobial-resistant *Streptococcus pneumoniae*: trends and management. Expert Rev Anti Infect Ther. 2008 Oct;6(5):619–35.
36. World Health Organization. Technical updates of the guidelines on the integrated management of childhood illness (IMCI). Geneva: WHO; 2005.
37. Fonseca W, Hoppu K, Rey LC, Amaral J, Qazi S. Comparing pharmacokinetics of amoxicillin given twice or three times per day to children older than 3 months with pneumonia. Antimicrob Agents Chemother. 2003 Mar;47(3):997–1001.
38. Dagan R, Leibovitz E. Bacterial eradication in the treatment of otitis media. Lancet Infect Dis. 2002 Oct;2(10):593–604.
39. American Academy of Pediatrics Subcommittee on Management of Acute Otitis Media. Diagnosis and management of acute otitis media. Pediatrics. 2004 May;113(5):1451–65.
40. Hazir T, Qazi SA, Bin Nisar Y, Maqbool S, Asghar R, Iqbal I, et al. Comparison of standard versus double dose of amoxicillin in the treatment of non-severe pneumonia in children aged

2–59 months: a multi-centre, double blind, randomised controlled trial in Pakistan. Arch Dis Child. 2007 Apr;92(4):291–7.
41. Haider BA, Saeed MA, Bhutta ZA. Short-course versus long-course antibiotic therapy for non-severe community-acquired pneumonia in children aged 2 months to 59 months. Cochrane Database Syst Rev. 2008;2:CD005976.
42. Haynes J, Hawkey PM, Williams EW. The in-vitro activity of combinations of penicillin and gentamicin against penicillin-resistant and penicillin-sensitive *Streptococcus pneumoniae*. J Antimicrob Chemother. 1986 Sep;18(3):426–8.
43. Friedland IR, Paris M, Shelton S, McCracken GH. Time-kill studies of antibiotic combinations against penicillin-resistant and -susceptible *Streptococcus pneumoniae*. J Antimicrob Chemother. 1994 Aug;34(2):231–7.
44. Gross ME, Giron KP, Septimus JD, Mason EO, Musher DM. Antimicrobial activities of beta-lactam antibiotics and gentamicin against penicillin-susceptible and penicillin-resistant pneumococci. Antimicrob Agents Chemother. 1995 May;39(5): 1166–8.
45. Darras-Joly C, Bédos JP, Sauve C, Moine P, Vallée E, Carbon C et al. Synergy between amoxicillin and gentamicin in combination against a highly penicillin-resistant and -tolerant strain of *Streptococcus pneumoniae* in a mouse pneumonia model. Antimicrob Agents Chemother. 1996 Sep;40(9):2147–51.
46. Schlegel L, Sissia G, Fremaux A, Geslin P. In-vitro killing activity of combinations of beta-lactam agents with aminoglycosides against penicillin-resistant pneumococci. J Antimicrob Chemother. 1997 Jan;39(1):95–8.
47. Anadiotis L, Maskell JP, Sefton AM. Comparative in-vitro activity of penicillin alone and combined with gentamicin against clinical isolates of *Streptococcus pneumoniae* with decreased susceptibility to penicillin. Int J Antimicrob Agents. 2002 Mar;19(3): 173–81.
48. English M, Mohammed S, Ross A, Ndirangu S, Kokwaro G, Shann F, et al. A randomised, controlled trial of once daily and multi-dose daily gentamicin in young Kenyan infants. Arch Dis Child. 2004 Jul;89(7):665–9.
49. Sanders CC. Novel resistance selected by the new expanded-spectrum cephalosporins: a concern. J Infect Dis. 1983 Mar;147(3):585–9.
50. Austrian R, Gold J. Pneumococcal bacteremia with especial reference to bacteremic pneumococcal pneumonia. Ann Intern Med. 1964 May;60:759–76.
51. Duke T, Poka H, Dale F, Michael A, Mgone J, Wal T. Chloramphenicol versus benzylpenicillin and gentamicin for the treatment of severe pneumonia in children in Papua New Guinea: a randomised trial. Lancet. 2002 Feb 9;359(9305):474–80.
52. Asghar R, Banajeh S, Egas J, Hibberd P, Iqbal I, Katep-Bwalya M, et al. Chloramphenicol versus ampicillin plus gentamicin for community acquired very severe pneumonia among children aged 2–59 months in low resource settings: multicentre randomised controlled trial (SPEAR study). BMJ. 2008 Jan 12;336(7635):80–4.
53. Hazir T, Qazi SA, Nisar YB, Maqbool S, Asghar R, Iqbal I, et al. Can WHO therapy failure criteria for non-severe pneumonia be improved in children aged 2–59 months?. Int J Tuberc Lung Dis. 2006 Aug;10(8):924–31.
54. Subhi R, Adamson M, Campbell H, Weber M, Smith K, Duke T. The prevalence of hypoxaemia among ill children in developing countries: a systematic review. Lancet Infect Dis. 2009 Apr;9(4):219–27.
55. World Health Organization. Oxygen therapy for acute respiratory infections in young children in developing countries. Geneva: WHO; 1993.
56. Duke T, Wandi F, Jonathan M, Matai S, Kaupa M, Saavu M, et al. Improved oxygen systems for childhood pneumonia: a multihospital effectiveness study in Papua New Guinea. Lancet. 2008 Oct 11;372(9646):1328–33.
57. World Health Organization. World health statistics 2009. Geneva: WHO; 2009.

58. Dreyfuss D, Leviel F, Paillard M, Rahmani J, Coste F. Acute infectious pneumonia is accompanied by a latent vasopressin-dependent impairment of renal water excretion. Am Rev Respir Dis. 1988 Sep;138(3):583–9.
59. Singhi S, Sharma A, Majumdar S. Body water and plasma volume in severe community-acquired pneumonia: implications for fluid therapy. Ann Trop Paediatr. 2005 Dec;25(4): 243–52.
60. Shann F. Paediatric fluid and electrolyte therapy. In: Berston AD, Soni N, editors. Oh's intensive care manual. Philadelphia, PA: Elsevier; 2008. p. 1117–24.
61. Guppy MPB, Mickan SM, Del Mar CB. "Drink plenty of fluids": a systematic review of evidence for this recommendation in acute respiratory infections. BMJ. 2004 Feb 28;328(7438):499–500.
62. Shann F. Antipyretics in severe sepsis. Lancet. 1995 Feb 11;345(8946):338.
63. Plaisance KI, Kudaravalli S, Wasserman SS, Levine MM, Mackowiak PA. Effect of antipyretic therapy on the duration of illness in experimental influenza A, *Shigella sonnei*, and *Rickettsia rickettsii* infections. Pharmacotherapy. 2000 Dec;20(12):1417–22.
64. Doran TF, De Angelis C, Baumgardner RA, Mellits ED. Acetaminophen: more harm than good for chickenpox? J Pediatr. 1989 Jun;114(6):1045–8.
65. Brandts CH, Ndjavé M, Graninger W, Kremsner PG. Effect of paracetamol on parasite clearance time in *Plasmodium falciparum* malaria. Lancet. 1997 Sep 6;350(9079): 704–9.
66. Thaver D, Zaidi AKM. Burden of neonatal infections in developing countries: a review of evidence from community-based studies. Pediatr Infect Dis J. 2009 Jan;28(1 Suppl): S3–9.
67. Chisti MJ, Tebruegge M, La Vincente S, Graham SM, Duke T. Pneumonia in severely malnourished children in developing countries – mortality risk, aetiology and validity of WHO clinical signs: a systematic review. Trop Med Int Health. 2009 Oct;14(10):1173–89.
68. Graham SM, English M, Hazir T, Enarson P, Duke T. Challenges to improving case management of childhood pneumonia at health facilities in resource-limited settings. Bull World Health Organ. 2008 May;86(5):349–55.
69. McNally LM, Jeena PM, Gajee K, Thula SA, Sturm AW, Cassol S, et al. Effect of age, polymicrobial disease, and maternal HIV status on treatment response and cause of severe pneumonia in South African children: a prospective descriptive study. Lancet. 2007 Apr 28;369(9571):1440–51.
70. Sazawal S, Black RE. Effect of pneumonia case management on mortality in neonates, infants, and preschool children: a meta-analysis of community-based trials. Lancet Infect Dis. 2003 Sep;3(9):547–56.
71. Grant GB, Campbell H, Dowell SF, Graham SM, Klugman KP, Mulholland EK, et al. Recommendations for treatment of childhood non-severe pneumonia. Lancet Infect Dis. 2009 Mar;9(3):185–96.
72. Scott JAG, English M. What are the implications for childhood pneumonia of successfully introducing Hib and pneumococcal vaccines in developing countries? PLoS Med. 2008 Apr 22;5(4):e86.
73. Shann F. The non-specific effects of vaccines. Arch Dis Child. 2010 Sep;95(9):662–7.
74. Healy CM, Baker CJ. Prospects for prevention of childhood infections by maternal immunization. Curr Opin Infect Dis. 2006 Jun;19(3):271–6.
75. Quiambao BP, Nohynek HM, Käyhty H, Ollgren JP, Gozum LS, Gepanayao CP, et al. Immunogenicity and reactogenicity of 23-valent pneumococcal polysaccharide vaccine among pregnant Filipino women and placental transfer of antibodies. Vaccine. 2007 May 30;25(22):4470–7.
76. Almeida VDC, Mussi-Pinhata MM, De Souza CBS, Kubo CA, Martinez EZ, Carneiro-Sampaio MM, et al. Immunogenicity of 23-valent pneumococcal polysaccharide vaccine in HIV-infected pregnant women and kinetics of passively acquired antibodies in young infants. Vaccine. 2009 Jun 12;27(29):3856–61.
77. Shann F. Giving pneumococcal vaccine to mothers. Vaccine. 2007 Aug 14;25(33):6147.

78. Klugman KP, Madhi SA, Huebner RE, Kohberger R, Mbelle N, Pierce N. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. N Engl J Med. 2003 Oct 2;349(14):1341–8.
79. Cutts FT, Zaman SMA, Enwere G, Jaffar S, Levine OS, Okoko JB, et al. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial. Lancet. 2005 Apr 26;365(9465):1139–46.
80. Lucero MG, Nohynek H, Williams G, Tallo V, Simões EAF, Lupisan S, et al. Efficacy of an 11-valent pneumococcal conjugate vaccine against radiologically confirmed pneumonia among children less than 2 years of age in the Philippines: a randomized, double-blind, placebo-controlled trial. Pediatr Infect Dis J. 2009 Jun;28(6):455–62.
81. Levine OS, Lagos R, Muñoz A, Villaroel J, Alvarez AM, Abrego P, et al. Defining the burden of pneumonia in children preventable by vaccination against *Haemophilus influenzae* type b. Pediatr Infect Dis J. 1999 Dec;18(12):1060–4.
82. Mulholland K, Hilton S, Adegbola R, Usen S, Oparaugo A, Omosigho C, et al. Randomised trial of *Haemophilus influenzae* type-b tetanus protein conjugate vaccine [corrected] for prevention of pneumonia and meningitis in Gambian infants. Lancet. 1997 Apr 26;349(9060):1191–7.
83. Forsgren A, Riesbeck K, Janson H. Protein D of *Haemophilus influenzae*: a protective nontypeable H. influenzae antigen and a carrier for pneumococcal conjugate vaccines. Clin Infect Dis. 2008 Mar 1;46(5):726–31.
84. Croxtall JD, Keating GM. Pneumococcal polysaccharide protein D-conjugate vaccine (Synflorix; PHiD-CV). Paediatr Drugs. 2009;11(5):349–57.
85. Prymula R, Peeters P, Chrobok V, Kriz P, Novakova E, Kaliskova E, et al. Pneumococcal capsular polysaccharides conjugated to protein D for prevention of acute otitis media caused by both *Streptococcus pneumoniae* and non-typable *Haemophilus influenzae*: a randomised double-blind efficacy study. Lancet. 2006 Mar 4;367(9512):740–8.
86. Shann F. Heterologous immunity and the nonspecific effects of vaccines: a major medical advance? Pediatr Infect Dis J. 2004 Jun;23(6):555–8.
87. Veirum JE, Sodemann M, Biai S, Jakobsen M, Garly M, Hedegaard K, et al. Routine vaccinations associated with divergent effects on female and male mortality at the paediatric ward in Bissau, Guinea-Bissau. Vaccine. 2005 Jan 19;23(9):1197–204.