Chapter **25**

Acute Respiratory Infections in Children

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Acute respiratory infections (ARIs) are classified as upper respiratory tract infections (URIs) or lower respiratory tract infections (LRIs). The upper respiratory tract consists of the airways from the nostrils to the vocal cords in the larynx, including the paranasal sinuses and the middle ear. The lower respiratory tract covers the continuation of the airways from the trachea and bronchi to the bronchioles and the alveoli. ARIs are not confined to the respiratory tract and have systemic effects because of possible extension of infection or microbial toxins, inflammation, and reduced lung function. Diphtheria, pertussis (whooping cough), and measles are vaccine-preventable diseases that may have a respiratory tract component but also affect other systems; they are discussed in chapter 20.

Except during the neonatal period, ARIs are the most common causes of both illness and mortality in children under five, who average three to six episodes of ARIs annually regardless of where they live or what their economic situation is (Kamath and others 1969; Monto and Ullman 1974). However, the proportion of mild to severe disease varies between high- and low-income countries, and because of differences in specific etiologies and risk factors, the severity of LRIs in children under five is worse in developing countries, resulting in a higher case-fatality rate. Although medical care can to some extent mitigate both severity and fatality, many severe LRIs do not respond to therapy, largely because of the lack of highly effective antiviral drugs. Some 10.8 million children die each year (Black, Morris, and Bryce 2003). Estimates indicate that in 2000, 1.9 million of them died because of ARIs, 70 percent of them in Africa and Southeast Asia (Williams and others 2002). The World Health Organization (WHO) estimates that 2 million children under five die of pneumonia each year (Bryce and others 2005).

CAUSES OF ARIs AND THE BURDEN OF DISEASE

ARIs in children take a heavy toll on life, especially where medical care is not available or is not sought.

Upper Respiratory Tract Infections

URIs are the most common infectious diseases. They include rhinitis (common cold), sinusitis, ear infections, acute pharyngitis or tonsillopharyngitis, epiglottitis, and laryngitis—of which ear infections and pharyngitis cause the more severe complications (deafness and acute rheumatic fever, respectively). The vast majority of URIs have a viral etiology. Rhinoviruses account for 25 to 30 percent of URIs; respiratory syncytial viruses (RSVs), parainfluenza and influenza viruses, human metapneumovirus, and adenoviruses for 25 to 35 percent; corona viruses for 10 percent; and unidentified viruses for the remainder (Denny 1995). Because most URIs are self-limiting, their complications are more important than the infections. Acute viral infections predispose children to bacterial infections of the sinuses and middle ear (Berman 1995a), and aspiration of infected secretions and cells can result in LRIs.

Acute Pharyngitis. Acute pharyngitis is caused by viruses in more than 70 percent of cases in young children. Mild pharyngeal redness and swelling and tonsil enlargement are typical. Streptococcal infection is rare in children under five and more common in older children. In countries with crowded living conditions and populations that may have a genetic predisposition, poststreptococcal sequelae such as acute rheumatic fever and carditis are common in school-age children but may also

occur in those under five. Acute pharyngitis in conjunction with the development of a membrane on the throat is nearly always caused by *Corynebacterium diphtheriae* in developing countries. However, with the almost universal vaccination of infants with the DTP (diphtheria-tetanus-pertussis) vaccine, diphtheria is rare.

Acute Ear Infection. Acute ear infection occurs with up to 30 percent of URIs. In developing countries with inadequate medical care, it may lead to perforated eardrums and chronic ear discharge in later childhood and ultimately to hearing impairment or deafness (Berman 1995b). Chronic ear infection following repeated episodes of acute ear infection is common in developing countries, affecting 2 to 6 percent of school-age children. The associated hearing loss may be disabling and may affect learning. Repeated ear infections may lead to mastoiditis, which in turn may spread infection to the meninges. Mastoiditis and other complications of URIs account for nearly 5 percent of all ARI deaths worldwide (Williams and others 2002).

Lower Respiratory Tract Infections

The common LRIs in children are pneumonia and bronchiolitis. The respiratory rate is a valuable clinical sign for diagnosing acute LRI in children who are coughing and breathing rapidly. The presence of lower chest wall indrawing identifies more severe disease (E. Mulholland and others 1992; Shann, Hart, and Thomas 1984).

Currently, the most common causes of viral LRIs are RSVs. They tend to be highly seasonal, unlike parainfluenza viruses, the next most common cause of viral LRIs. The epidemiology of influenza viruses in children in developing countries deserves urgent investigation because safe and effective vaccines are available. Before the effective use of measles vaccine, the measles virus was the most important viral cause of respiratory tract–related morbidity and mortality in children in developing countries.

Pneumonia. Both bacteria and viruses can cause pneumonia. Bacterial pneumonia is often caused by *Streptococcus pneumoniae* (pneumococcus) or *Haemophilus influenzae,* mostly type b (Hib), and occasionally by *Staphylococcus aureus* or other streptococci. Just 8 to 12 of the many types of pneumococcus cause most cases of bacterial pneumonia, although the specific types may vary between adults and children and between geographic locations. Other pathogens, such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae,* cause atypical pneumonias. Their role as a cause of severe disease in children under five in developing countries is unclear.

The burden of LRIs caused by Hib or *S. pneumoniae* is difficult to determine because current techniques to establish bacterial etiology lack sensitivity and specificity. The results of pharyngeal cultures do not always reveal the pathogen that is the cause of the LRI. Bacterial cultures of lung aspirate specimens are often considered the gold standard, but they are not practical for field application. Vuori-Holopainen and Peltola's (2001) review of several studies indicates that *S. pneumoniae* and Hib account for 13 to 34 percent and 1.4 to 42.0 percent of bacterial pneumonia, respectively, whereas studies by Adegbola and others (1994), Shann, Gratten, and others (1984), and Wall and others (1986) suggest that Hib accounts for 5 to 11 percent of pneumonia cases.

Reduced levels of clinical or radiological pneumonia in clinical trials of a nine-valent pneumococcal conjugate vaccine provide an estimate of the vaccine-preventable disease burden (*valency* indicates the number of serotypes against which the vaccine provides protection; *conjugate* refers to conjugation of polysaccharides to a protein backbone). In a study in The Gambia, 37 percent of radiological pneumonia was prevented, reflecting the amount of disease caused by *S. pneumoniae,* and mortality was reduced by 16 percent (Cutts and others 2005).

Upper respiratory tract colonization with potentially pathogenic organisms and aspiration of the contaminated secretions have been implicated in the pathogenesis of bacterial pneumonia in young children. Infection of the upper respiratory tract with influenza virus or RSVs has been shown to increase the binding of both *H. influenzae* (Jiang and others 1999) and *S. pneumoniae* (Hament and others 2004; McCullers and Bartmess 2003) to lining cells in the nasopharynx. This finding may explain why increased rates of pneumococcal pneumonia parallel influenza and RSV epidemics. A study in South Africa showed that vaccination with a nine-valent pneumococcal conjugate vaccine reduced the incidence of virus-associated pneumonia causing hospitalization by 31 percent, suggesting that pneumococcus plays an important role in the pathogenesis of virus-associated pneumonia (Madhi, Petersen, Madhi, Wasas, and others 2000).

Entry of bacteria from the gut with spread through the bloodstream to the lungs has also been proposed for the pathogenesis of Gram-negative organisms (Fiddian-Green and Baker 1991), but such bacteria are uncommon etiological agents of pneumonia in immune-competent children. However, in neonates and young infants, Gram-negative pneumonia is not uncommon (Quiambao forthcoming).

Viruses are responsible for 40 to 50 percent of infection in infants and children hospitalized for pneumonia in developing countries (Hortal and others 1990; John and others 1991; Tupasi and others 1990). Measles virus, RSVs, parainfluenza viruses, influenza type A virus, and adenoviruses are the most important causes of viral pneumonia. Differentiating between viral and bacterial pneumonias radiographically is difficult, partly because the lesions look similar and partly because bacterial superinfection occurs with influenza, measles, and RSV infections (Ghafoor and others 1990).

In developing countries, the case-fatality rate in children with viral pneumonia ranges from 1.0 to 7.3 percent (John and others 1991; Stensballe, Devasundaram, and Simoes 2003), with bacterial pneumonia from 10 to 14 percent and with mixed viral and bacterial infections from 16 to 18 percent (Ghafoor and others 1990; Shann 1986).

Bronchiolitis. Bronchiolitis occurs predominantly in the first year of life and with decreasing frequency in the second and third years. The clinical features are rapid breathing and lower chest wall indrawing, fever in one-third of cases, and wheezing (Cherian and others 1990). Inflammatory obstruction of the small airways, which leads to hyperinflation of the lungs, and collapse of segments of the lung occur. Because the signs and symptoms are also characteristic of pneumonia, health workers may find differentiating between bronchiolitis and pneumonia difficult. Two features that may help are a definition of the seasonality of RSVs in the locality and the skill to detect wheezing. RSVs are the main cause of bronchiolitis worldwide and can cause up to 70 or 80 percent of LRIs during high season (Simoes 1999; Stensballe, Devasundaram, and Simoes 2003). The recently discovered human metapneumovirus also causes bronchiolitis (Van den Hoogen and others 2001) that is indistinguishable from RSV disease. Other viruses that cause bronchiolitis include parainfluenza virus type 3 and influenza viruses.

Influenza. Even though influenza viruses usually cause URIs in adults, they are increasingly being recognized as an important cause of LRIs in children and perhaps the second most important cause after RSVs of hospitalization of children with an ARI (Neuzil and others 2002). Although influenza is considered infrequent in developing countries, its epidemiology remains to be investigated thoroughly. The potential burden of influenza as a cause of death in children is unknown. Influenza virus type A may cause seasonal outbreaks, and type B may cause sporadic infection. Recently, avian influenza virus has caused infection, disease, and death in small numbers of individuals, including children, in a few Asian countries. Its potential for emergence in human outbreaks or a pandemic is unknown, but it could have devastating consequences in developing countries (Peiris and others 2004) and could pose a threat to health worldwide. New strains of type A viruses will almost certainly arise through mutation, as occurred in the case of the Asian and Hong Kong pandemics in the 1950s and 1960s.

HIV Infection and Pediatric LRIs

Worldwide, 3.2 million children are living with HIV/AIDS, 85 percent of them in Sub-Saharan Africa (UNAIDS 2002). In southern Africa, HIV-related LRIs account for 30 to 40 percent of pediatric admissions and have a case-fatality rate of 15 to 34 percent, much higher than the 5 to 10 percent for children not infected with HIV (Bobat and others 1999; Madhi, Petersen, Madhi, Khoosal, and others 2000; Nathoo and others 1993; Zwi, Pettifior, and Soderlund 1999). *Pneumocystis jiroveci* and cytomegalovirus are important opportunistic infections in more than 50 percent of HIV-infected infants (Jeena, Coovadia, and Chrystal 1996; Lucas and others 1996). Gram-negative bacteria are also important in more than 70 percent of HIV-infected malnourished children (Ikeogu, Wolf, and Mathe 1997). Patient studies have confirmed the frequent association of these bacteria but added *S. pneumoniae* and *S. aureus* as important pathogens (Gilks 1993; Goel and others 1999). The first South African report on the overall burden of invasive pneumococcal disease reported a 41.7-fold increase in HIV-infected children compared with uninfected children (Farley and others 1994).

INTERVENTIONS

Interventions to control ARIs can be divided into four basic categories: immunization against specific pathogens, early diagnosis and treatment of disease, improvements in nutrition, and safer environments (John 1994). The first two fall within the purview of the health system, whereas the last two fall under public health and require multisectoral involvement.

Vaccinations

Widespread use of vaccines against measles, diphtheria, pertussis, Hib, pneumococcus, and influenza has the potential to substantially reduce the incidence of ARIs in children in developing countries. The effects of measles, diphtheria, and pertussis vaccines are discussed in chapter 20. The limited data on influenza in developing countries do not permit detailed analysis of the potential benefits of that vaccine. This chapter, therefore, focuses on the potential effects of Hib and pneumococcal vaccines on LRIs.

Hib Vaccine. Currently three Hib conjugate vaccines are available for use in infants and young children. The efficacy of Hib vaccine in preventing invasive disease (mainly meningitis, but also pneumonia), has been well documented in several studies in industrialized countries (Black and others 1992; Booy and others 1994; Eskola and others 1990; Fritzell and Plotkin 1992; Heath 1998; Lagos and others 1996; Santosham and others 1991) and in one study in The Gambia (K. Mulholland and others 1997). All studies showed protective efficacy greater than 90 percent against laboratory-confirmed invasive disease, irrespective of the choice of vaccine. Consequently, all industrialized countries include Hib vaccine in their national immunization programs, resulting in the virtual elimination of

invasive Hib disease because of immunity in those vaccinated and a herd effect in those not vaccinated. Available data from a few developing countries show a similar herd effect (Adegbola and others 1999; Wenger and others 1999).

The initial promise and consequent general perception was that Hib vaccine was to protect against meningitis, but in developing countries the vaccine is likely to have a greater effect on preventing LRIs. The easily measured effect is on invasive disease, including bacteraemic pneumonia. The vaccine probably has an effect on nonbacteremic pneumonia, but this effect is difficult to quantify because of the lack of an adequate method for establishing bacterial etiology. In Bangladesh, Brazil, Chile, and The Gambia, Hib vaccine has been associated with a reduction of 20 to 30 percent in those hospitalized with radiographically confirmed pneumonia (de Andrade and others 2004; Levine and others 1999; K. Mulholland and others 1997; WHO 2004a). However, results of a large study in Lombok, Indonesia, were inconclusive with regard to the effect of Hib vaccine on pneumonia (Gessner and others 2005).

Pneumococcal Vaccines. Two kinds of vaccines are currently available against pneumococci: a 23-valent polysaccharide vaccine (23-PSV), which is more appropriate for adults than children, and a 7-valent protein-conjugated polysaccharide vaccine (7-PCV). A 9-valent vaccine (9-PCV) has undergone clinical trials in The Gambia and South Africa, and an 11-valent vaccine (11-PCV) is being tried in the Philippines.

Studies of the efficacy of the polysaccharide vaccine in preventing ARIs or ear infection in children in industrialized countries have shown conflicting results. Whereas some studies of this vaccine show no significant efficacy (Douglas and Miles 1984; Sloyer, Ploussard, and Howie 1981), studies from Finland show a generally protective effect against the serotypes contained in a 14-PSV (Douglas and Miles 1984; Karma and others 1980; Makela and others 1980). The efficacy was more marked in children over two years of age than in younger children. The only studies evaluating the effect of the polysaccharide vaccine in children in developing countries are a series of three trials conducted in Papua New Guinea (Douglas and Miles 1984; Lehmann and others 1991; Riley and others 1981; Riley, Lehmann, and Alpers 1991). The analysis of the pooled data from these trials showed a 59 percent reduction in LRI mortality in children under five at the time of the vaccination and a 50 percent reduction in children under two. On the basis of these and other studies, the investigators concluded that the vaccine had an effect on severe pneumonia. The greater-than-expected efficacy in these trials was attributed to the greater contribution of the more immunogenic adult serotypes in pneumonia in Papua New Guinea (Douglas and Miles 1984; Riley, Lehmann, and Alpers 1991). On account of the poor immunogenicity of the antigens in the 23-PSV against prevalent pediatric serotypes, attention is now directed at more immunogenic conjugate vaccines (Mulholland 1998; Obaro 1998; Temple 1991).

The 7-PCV and 9-PCV have been evaluated for efficacy against invasive pneumococcal disease in four trials, which demonstrated a vaccine efficiency ranging from 71.0 to 97.4 percent (58 to 65 percent for HIV-positive children, among whom rates of pneumococcal disease are 40 times higher than in HIV-negative children) (Black and others 2000; Cutts and others 2005; Klugman and others 2003; O'Brien and others 2003).

In the United States, the 7-PCV was included in routine vaccinations of infants and children under two in 2000. By 2001 the incidence of all invasive pneumococcal disease in this age group had declined by 69 percent and disease caused by the serotypes included in the vaccine and related serotypes had declined by 78 percent (Whitney and others 2003). Similar reductions were confirmed in a study in northern California (Black and others 2001). A slight increase in rates of invasive disease caused by serotypes of pneumococcus not included in the vaccine was observed, but it was not large enough to offset the substantial reduction in disease brought about by the vaccine. The studies also found a significant reduction in invasive pneumococcal disease in unvaccinated older age groups, especially adults age 20 to 39 and age 65 and older, suggesting that giving the vaccine to young children exerted a considerable herd effect in the community. Such an advantage is likely to occur even where the prevalence of adult HIV disease is high and pneumococcal disease may be recurrent and life threatening.

The effect of the vaccine on pneumococcal pneumonia as such is difficult to define given the problems of establishing the bacterial etiology of pneumonia. Three studies have evaluated the effect of the vaccine on radiographic pneumonia (irrespective of the etiological agent) and have shown a 20.5 to 37.0 percent reduction in radiographically confirmed pneumonia (9.0 percent for HIV-positive individuals) (Black and others 2000; Cutts and others 2005; Klugman and others 2003).

Several field trials have evaluated the efficacy of PCV against ear infection. Even though the vaccine resulted in a significant reduction in culture-confirmed pneumococcal otitis, no net reduction of ear infection was apparent among vaccinated children, probably because of an increase in the rates of otitis caused by types of pneumococci not covered by the vaccine, *H. influenzae* and *Moraxella catarrhalis* (Eskola and others 2001; Kilpi and others 2003). However, a trial in northern California showed that the vaccine had a protective effect against frequent ear infection and reduced the need for tympanostomy tube placement (Fireman and others 2003). Thus, a vaccine for ear infection may be beneficial in developing countries with high rates of chronic otitis and conductive hearing loss and should be evaluated by means of clinical trials.

The most striking public health benefit of a vaccine in developing countries would be a demonstrable reduction in mortality. Although the primary outcome in The Gambia trial

was initially child mortality, it was changed to radiological pneumonia. Nevertheless, the trial showed a 16 percent (95 percent confidence level, 3 to 38) reduction in mortality. This trial was conducted in a rural area in eastern Gambia where access to round-the-clock curative care, including case management, is difficult to provide. This trial demonstrates that immunization delivered through outreach programs will have substantial health and economic benefits in such populations. One additional study evaluating the effect of an 11-PCV on radiological pneumonia is ongoing in the Philippines; results are expected in the second half of 2005.

Case Management

The simplification and systematization of case management for early diagnosis and treatment of ARIs have enabled significant reductions in mortality in developing countries, where access to pediatricians is limited. WHO clinical guidelines for ARI case management (WHO 1991) use two key clinical signs: *respiratory rate*, to distinguish children with pneumonia from those without, and *lower chest wall indrawing,* to identify severe pneumonia requiring referral and hospital admission. Children with audible stridor when calm and at rest or such danger signs of severe disease as inability to feed also require referral. Children without these signs are classified as having an ARI but not pneumonia. Children showing only rapid breathing are treated for pneumonia with outpatient antibiotic therapy. Children who have a cough for more than 30 days are referred for further assessment of tuberculosis and other chronic infections.

Pneumonia Diagnosis Based on Rapid Breathing. The initial guidelines for detecting pneumonia based on rapid breathing were developed in Papua New Guinea during the 1970s. In a study of 200 consecutive pediatric outpatients and 50 consecutive admissions (Shann, Hart, and Thomas 1984), 72 percent of children with audible crackles in the lungs had a respiratory rate of 50 or more breaths per minute, whereas only 19 percent of children without crackles breathed at such a rapid rate. Therefore, the initial WHO guidelines used a threshold of 50 breaths per minute, at or above which a child with a cough was regarded as having pneumonia.

The major concern was the relatively low sensitivity of this approach, which could miss 25 to 40 percent of cases of pneumonia. A study in Vellore, India, found that sensitivity could be improved by lowering the threshold to 40 for children age 1 to 4, while keeping the 50 breaths per minute cutoff for infants age 2 months through 11 months (Cherian and others 1988). Subsequent studies showed that when these thresholds were used, sensitivity improved from 62 to 79 percent in the Philippines and from 65 to 77 percent in Swaziland, but at the same time, the specificity fell from 92 to 77 percent in the Philippines and 92 to 80 percent in Swaziland (Mulholland and others 1992). On the basis of these and other data (Campbell, Byass, and others 1989; Kolstad and others 1997; Perkins and others 1997; Redd 1994; Simoes and others 1997; Weber and others 1997), WHO recommends a respiratory rate cutoff of 50 breaths per minute for infants age 2 through 11 months and 40 breaths per minute for children age 12 months to 5 years.

Rapid breathing, as defined by WHO, detects about 85 percent of children with pneumonia, and more than 80 percent of children with potentially fatal pneumonia are probably successfully identified and treated using the WHO diagnostic criteria. Antibiotic treatment of children with rapid breathing has been shown to reduce mortality (Sazawal and Black 2003). The problem of the low specificity of the rapid breathing criterion is that some 70 to 80 percent of children who may not need antibiotics will receive them. Nevertheless, for primary care workers for whom diagnostic simplicity is essential, rapid breathing is clearly the most useful clinical sign.

Pneumonia Diagnosis Based on Chest Wall Indrawing. Children are admitted to hospital with severe pneumonia when health workers believe that oxygen or parenteral antibiotics (antibiotics administered by other than oral means) are needed or when they lack confidence in mothers' ability to cope. The rationale of parenteral antibiotics is to achieve higher levels of antibiotics and to overcome concerns about the absorption of oral drugs in ill children.

The Papua New Guinea study (Shann, Hart, and Thomas 1984) used chest wall indrawing as the main indicator of severity, but studies from different parts of the world show large differences in the rates of indrawing because of variable definitions. Restriction of the term to lower chest wall indrawing, defined as inward movement of the bony structures of the chest wall with inspiration, has provided a better indicator of the severity of pneumonia and one that can be taught to health workers. It is more specific than intercostal indrawing, which frequently occurs in bronchiolitis.

In a study in The Gambia (Campbell, Byass, and others 1989), a cohort of 500 children from birth to four years old was visited at home weekly for one year. During this time, 222 episodes of LRI (rapid breathing, any chest wall indrawing, nasal flaring, wheezing, stridor, or danger signs) were referred to the clinic. Chest indrawing was present in 62 percent of these cases, many with intercostal indrawing. If all children with any chest indrawing were hospitalized, the numbers would overwhelm pediatric inpatient facilities.

Studies in the Philippines and Swaziland (E. Mulholland and others 1992) found that lower chest wall indrawing was more specific than intercostal indrawing for a diagnosis of severe pneumonia requiring hospital admission. In the Vellore study (Cherian and others 1988), lower chest wall indrawing correctly predicted 79 percent of children with an LRI who were hospitalized by a pediatrician.

Antimicrobial Options for Oral Treatment of Pneumonia. The choice of an antimicrobial drug for treatment is based on the well-established finding that most childhood bacterial pneumonias are caused by *S. pneumoniae* or *H. influenzae*. A single injection of benzathine penicillin, although long lasting, does not provide adequate penicillin levels to eliminate *H. influenzae*. WHO has technical documents to help assess the relevant factors in selecting first- and second-line antimicrobials and comparisons of different antimicrobials in relation to their antibacterial activity, treatment efficacy, and toxicity (WHO 1990).

The emergence of antimicrobial resistance in *S. pneumoniae* and *H. influenzae* is a serious concern. In some settings, in vitro tests show that more than 50 percent of respiratory isolates of both bacteria are resistant to co-trimoxazole, and penicillin resistance to *S. pneumoniae* is gradually becoming a problem worldwide.

In pneumonia, unlike in meningitis, in vitro resistance of the pathogen does not always translate into treatment failure. Reports from Spain and South Africa suggest that pneumonia caused by penicillin-resistant *S. pneumoniae* can be successfully treated with sufficiently high doses of penicillin. Amoxicillin is concentrated in tissues and in macrophages, and drug levels are directly correlated with oral dosages. Therefore, higher doses than in the past—given twice a day—are now being used to successfully treat ear infections caused by penicillin-resistant *S. pneumoniae*. Amoxicillin is clearly better than penicillin for such infections. The situation with co-trimoxazole is less clear (Strauss and others 1998), and in the face of high rates of co-trimoxazole resistance, amoxicillin may be superior for children with severe pneumonia.

Intramuscular Antibiotics for Treatment of Severe Pneumonia. Even though chloramphenicol is active against both *S. pneumoniae* and *H. influenzae,* its oral absorption is erratic in extremely sick children. Thus, the WHO guidelines recommend giving intramuscular chloramphenicol at half the daily dose before urgent referral of severe pneumonia cases. An additional rationale is that extremely sick children may have sepsis or meningitis that are difficult to rule out and must be treated immediately. Although intravenous chloramphenicol is superior to intramuscular chloramphenicol, the procedure can delay urgently needed treatment and adds to its cost.

Investigators have questioned the adequacy and safety of intramuscular chloramphenicol. Although early studies suggested that adult blood levels after intramuscular administration were significantly less than those achieved after intravenous administration, the intramuscular route gained wide acceptance following clinical reports that confirmed its efficacy. Local complications of intramuscular chloramphenicol succinate are rare, unlike the earlier intramuscular preparations. Although concerns about aplastic anemia following chloramphenicol are common, this complication is extremely rare in young children. There is no evidence that intramuscular chloramphenicol succinate is more likely to produce side effects than other forms and routes of chloramphenicol.

Hypoxemia Diagnosis Based on WHO Criteria. The ARI case-management and integrated management of infant and childhood illness (IMCI) strategies depend on accurate referral of sick children to a hospital and correct inpatient management of LRI with oxygen or antibiotics. Hypoxemia (deficiency of oxygen in the blood) in children with LRI is a good predictor of mortality, the case-fatality rate being 1.2 to 4.6 times higher in hypoxemic LRI than nonhypoxemic LRI (Duke, Mgone, and Frank 2001; Onyango and others 1993), and oxygen reduces mortality. Thus, it is important to detect hypoxemia as early as possible in children with LRI to avert death. Although diagnoses of acute LRIs are achieved very easily by recognizing tachypnoea, and although severe LRI is associated with chest wall indrawing, the clinical recognition of hypoxemia is more problematic. Different sets of clinical rules have been studied to predict the presence of hypoxemia in children with LRI (Cherian and others 1988; Onyango and others 1993; Usen and others 1999). Although some clinical tools have a high sensitivity for detecting hypoxemia, a good number of hypoxemic children would still be missed using these criteria. Pulse oximetry is the best tool to quickly detect hypoxemia in sick children. However, pulse oximeters are expensive and have recurring costs for replacing probes, for which reasons they are not available in most district or even referral hospitals in developing countries.

Treatment Guidelines. Current recommendations are for co-trimoxazole twice a day for five days for pneumonia and intramuscular penicillin or chloramphenicol for children with severe pneumonia. The problems of increasing resistance to co-trimoxazole and unnecessary referrals of children with any chest wall indrawing have led to studies exploring alternatives to the antibiotics currently used in ARI case management. One study indicated that amoxicillin and co-trimoxazole are equally effective for nonsevere pneumonia (Catchup Study Group 2002), though amoxicillin costs twice as much as co-trimoxazole. With respect to the duration of antibiotic treatment, studies in Bangladesh, India, and Indonesia indicate that three days of oral co-trimoxazole or amoxicillin are as effective as five days of either drug in children with nonsevere pneumonia (Agarwal and others 2004; Kartasasmita 2003). In a multicenter study of intramuscular penicillin versus oral amoxicillin in children with severe pneumonia, Addo-Yobo and others (2004) find similar cure rates. Because patients were treated with oxygen when needed for hypoxemia and were switched to other antibiotics if the treatment failed, this regimen is not appropriate for treating severe pneumonia in an outpatient setting.

WHO recommends administering oxygen, if there is ample supply, to children with signs and symptoms of severe pneumonia and, where supply is limited, to children with any of the following signs: inability to feed and drink, cyanosis, respiratory rate greater than or equal to 70 breaths per minute, or severe chest wall retractions (WHO 1993). Oxygen should be administered at a rate of 0.5 liter per minute for children younger than 2 months and 1 liter per minute for older children. Because oxygen is expensive and supply is scarce, especially in remote rural areas in developing countries, WHO recommends simple clinical signs to detect and treat hypoxemia. Despite those recommendations, a study of 21 first-level facilities and district hospitals in seven developing countries found that more than 50 percent of hospitalized children with LRI were inappropriately treated with antibiotics or oxygen (Nolan and others 2001)—and in several, oxygen was in short supply. Clearly, providing oxygen to hypoxemic babies is lifesaving, though no randomized trials have been done to prove it.

Prevention and Treatment of Pneumonia in HIV-Positive Children. Current recommendations of a WHO panel for managing pneumonia in HIV-positive children and for prophylaxis of *Pneumocystis jiroveci* are as follows (WHO 2003):

- *Nonsevere pneumonia up to age 5 years.* Oral co-trimoxazole should remain the first-line antibiotic, but oral amoxicillin should be used if it is affordable or if the child has been on co-trimoxazole prophylaxis.
- *Severe or very severe pneumonia.* Normal WHO case-management guidelines should be used for children up to 2 months old. For children from 2 to 11 months, injectable antibiotics and therapy for *Pneumocystis jiroveci* pneumonia are recommended, as is starting *Pneumocystis jiroveci* pneumonia prophylaxis on recovery. For children age 12 to 59 months, the treatment consists of injectable antibiotics and therapy for *Pneumocystis jiroveci* pneumonia. *Pneumocystis jiroveci* pneumonia prophylaxis should be given for 15 months to children born to HIV-infected mothers; however, this recommendation has seldom been implemented.

COST-EFFECTIVENESS OF INTERVENTIONS

Pneumonia is responsible for about a fifth of the estimated 10.6 million deaths per year of children under five. Where primary health care is weak, reducing mortality through public health measures is a high priority. As noted earlier, the available interventions are primary prevention by vaccination and secondary prevention by early case detection and management.

The cost-effectiveness of Hib vaccines is discussed in chapter 20. We did not attempt an analysis of the cost-effectiveness of pneumococcal vaccines, because global and regional estimates of the pneumococcal pneumonia burden are currently being developed and will not be available until later in 2005. In addition, current vaccine prices are relatively stable in developed countries, but the prices for low- and middle-income countries are expected to be substantially lower when vaccines are purchased through a global tender.

We evaluate case-management intervention strategies for LRIs in children under five. Health workers who implement case management diagnose LRIs on the basis of fast breathing, lower chest wall indrawing, or selected danger signs in children with respiratory symptoms. Because this method does not distinguish between pneumonia and bronchiolitis, nor between bacterial and viral pneumonia, we group these conditions into the general category of "clinical pneumonia" (Rudan and others 2004). This approach assumes that a high proportion of clinical pneumonia is of bacterial origin and that health workers can considerably reduce case fatality through breathing rate diagnosis and timely administration of antibiotics (Sazawal and Black 2003). We calculated treatment costs by World Bank region using standardized input costs provided by the volume editors and costs published in the *International Drug Price Indicator Guide* (Management Sciences for Health 2005) and other literature (table 25.1). The analysis addresses four categories of case management, which are distinguished by the severity of the infection and the point of treatment:

- nonsevere pneumonia treated by a community health worker
- nonsevere pneumonia treated at a health facility
- severe pneumonia treated at a hospital
- very severe pneumonia treated at a hospital.

Information about these categories of case management and their outcomes is drawn from a report on the methodology and assumptions used to estimate the costs of scaling up selected health interventions aimed at children (WHO and Child Adolescent Health forthcoming). We assumed a total of three follow-up visits for each patient treated by a community health worker rather than the twice-daily follow-ups for 10 days recommended by the report. We also assumed that all severe pneumonia patients receive an x-ray examination, rather than just 20 percent as suggested by the report. Moreover, we assumed a five-hour workday for a community health worker, the minimum workday required for community health workers under the Child Health and Survival initiative of the U.S. Agency for International Development (Bhattacharyya and others 2001).

Table 25.2 presents region-specific estimates of average treatment costs per episode for the four case-management strategies. Because we considered the prices of tradable commodities such as drugs and oxygen to be constant across

Table 25.1 Inputs for Case Management of Pneumonia in Low- and Middle-Income Countries

Condition and intervention	Cost per unit (2001 US$)	Quantity	Percentage of patients
Nonsevere pneumonia at the community level			
Oral amoxicillin (15 mg/kg)	0.03/dose	3 doses/day for 3 days	100
Acetaminophen (100-mg tablet)	0.001/dose	6 doses	100
Community health worker hour[a]	1.83/hour	1 initial 1-hour visit and 3 follow-up visits	100
Nonsevere pneumonia at the facility level			
Oral amoxicillin (15 mg/kg)	0.03/dose	3 doses/day for 3 days	100
Acetaminophen (100-mg tablet)	0.001/dose	6 doses	100
Oral salbutamol (2-mg tablet)	0.003/dose	3 doses/day for 4 days	10
Outpatient health facility visit[a]	1.72/visit	1 visit	100
Severe pneumonia at the hospital level			
Oral amoxicillin (15 mg/kg)	0.03/dose	3 doses/day for 5 days	100
Nebulized salbutamol (2.5 mg)	0.13/dose	6 doses/day for 4 days	50
Injectable ampicillin (50 mg/kg)	0.21/dose	4 doses/day for 3 days	100
X-ray[a]	9.21/test	1 test	100
Oxygen (1 liter/minute)[b]	20/day	3.5 days	50
Inpatient hospital care[a]	10.8/day	3 days	100
Very severe pneumonia at the hospital level			
Oral amoxicillin (15 mg/kg)	0.03/dose	3 doses/day for 5 days	100
Nebulized salbutamol (2.5 mg)	0.13/dose	6 doses/day for 4 days	50
Injectable ampicillin (50 mg/kg)	0.21/dose	4 doses/day for 5 days	100
Injectable gentamicin (2.5 mg/kg)	0.14/dose	1 dose/day for 10 days	100
Oral prednisolone (1 mg/kg)	0.02/dose	1 dose/day for 3 days	5
X-ray[a]	9.21/test	1 test	100
Oxygen (1 liter/minute)[b]	20/day	5 days	100
Inpatient hospital care[a]	10.8/day	5 days	100

Source: Management Sciences for Health 2005.
Note: We assumed that the average patient weighs 12.5 kilograms.
a. Provided by the volume editors. Input costs vary by region.
b. Median costs obtained from Dobson 1991; Pederson and Nyrop 1991; Schneider 2001; WHO 1993.

Table 25.2 Average per Episode Treatment Costs of Case-Management Interventions for Acute Lower Respiratory Infection *(2001 US$)*

Region	Nonsevere, community level	Nonsevere, facility level	Severe, hospital level	Very severe, hospital level
Low- and middle-income countries	8	2	82	172
East Asia and the Pacific	6	2	75	160
Latin America and the Caribbean	13	4	134	256
Middle East and North Africa	22	3	113	223
South Asia	5	2	66	148
Sub-Saharan Africa	7	2	64	145

Source: Authors' calculations.

regions, regional variations were due to differences in hospital and health worker costs. Latin America and the Caribbean and the Middle East and North Africa had the highest treatment costs.

We calculated region-specific cost-effectiveness ratios (CERs) for a model population of 1 million in each region, following the standardized guidelines for economic analyses (see chapter 15 for details). Input variables included the treatment

costs detailed in tables 25.1 and 25.2, region-specific LRI morbidity rates, adapted from Rudan and others (2004), region-specific mortality rates and age structures provided by the volume editors, and region-specific urban to rural population ratios (World Bank 2002). The Europe and Central Asia region was excluded from this analysis because of a lack of incidence information. In the absence of region-specific information, we assumed uniform intervention effectiveness rates.

Disability-adjusted life years are averted through reduced duration of illness and decreased mortality with treatment. We assumed an average illness duration of 8.5 days for those not treated and of 6.0 days for those treated. We used a case-fatality reduction of 36.0 percent on account of treatment (Sazawal and Black 2003) and a diagnosis specificity of 78.5 percent for patients diagnosed based on breath rate alone. The disability weight cotemporaneous with infection was 0.28. We did not consider disabilities caused by chronic sequelae of LRIs because it is unclear whether childhood LRI causes long-term impaired lung function or whether children who develop impaired lung function are more prone to infection (von Mutius 2001).

Because a single year of these interventions yields only cotemporaneous benefits—because effectively treated individuals do not necessarily live to life expectancy given that they are likely to be infected again the following year—we calculated the cost-effectiveness of a five-year intervention. This time period enabled us to consider the case in which an entire cohort of newborns to four-year-olds avoids early childhood clinical pneumonia mortality because of the intervention and receives the benefit of living to life expectancy. Finally, this analysis considered only long-run marginal costs, which vary with the number of individuals treated, and did not include the fixed costs of initiating a program where none currently exists.

Table 25.3 presents the region-specific CERs of the four case-management categories as well as the CER for providing all four categories to a population of 1 million people. Among all low- and middle-income countries, treatment of nonsevere clinical pneumonia was more cost-effective at the facility level than at the community level, and of all four case-management categories, treatment of very severe clinical pneumonia at the hospital level was the least cost-effective. Treatment of nonsevere clinical pneumonia at the facility level was more cost-effective than treatment by a community health worker because of the lower cost of a single visit to a health facility than of multiple visits by a health worker. The CER of providing all levels of treatment to all low- and middle-income countries was estimated at US$398 per disability-adjusted life year.

Because we assumed that effectiveness rates were constant, regional variations in the CER for each case-management category were due only to variations in the intervention costs, and the relative cost-effectiveness rankings for the strategies was the same for all the regions. Variation in the CERs for providing all categories of care was also due to region-specific urban to rural population ratios. We assumed that all patients in urban areas seek treatment at the facility level or higher, whereas 80 percent of nonseverely ill patients in rural areas receive treatment at the community level and the remainder seek treatment at the facility level.

IMPLEMENTATION OF ARI CONTROL STRATEGIES: LESSONS OF EXPERIENCE

The lessons of ARI prevention and control strategies that have been implemented by national programs include the vaccination and case-management strategies discussed below.

Vaccine Strategies

Hib vaccine was introduced into the routine infant immunization schedule in North America and Western Europe in the early 1990s. With the establishment of the Global Alliance for Vaccines and Immunization (GAVI) and the Vaccine Fund, progress is being made in introducing it in developing countries, although major hurdles remain. By 2002, only 84 of the 193 WHO member nations had introduced Hib vaccine. Five

Table 25.3 CERs of Case-Management Interventions for Pneumonia
(2001US$/disability-adjusted life year)

Region	Nonsevere, community level	Nonsevere, facility level	Severe, hospital level	Very severe, hospital level	Provision of all four interventions
Low- and middle-income countries	208	50	2,916	6,144	398
East Asia and the Pacific	439	91	6,511	13,945	900
Latin America and the Caribbean	547	424	14,719	28,106	1,941
Middle East and North Africa	733	180	6,810	13,438	1,060
South Asia	140	28	1,931	4,318	264
Sub-Saharan Africa	139	24	1,486	3,376	218

Source: Authors' calculations.

countries have since been approved for support from GAVI for Hib vaccine introduction in 2004–5.

The United States added 7-PCV to the infant immunization program in 2000. Several other industrialized countries have plans to introduce the vaccine into their national immunization programs in 2005, whereas others recommend the use of the vaccine only in selected high-risk groups. In some of these last countries, the definition of *high risk* is quite broad and includes a sizable proportion of all infants. The currently licensed 7-PCV lacks certain serotypes important in developing countries, but the 9-PCV and 11-PCV would cover almost 80 percent of serotypes that cause serious disease worldwide.

Despite the success of Hib vaccine in industrial countries and the generally appreciated importance of LRIs as a cause of childhood mortality, as a result of a number of interlinked factors, uptake in developing countries has been slow. Sustained use of the vaccine is threatened in a few of the countries that have introduced the vaccine. First, the magnitude of disease and death caused by Hib is not recognized in these countries, partly because of their underuse of bacteriological diagnosis (a result of the lack of facilities and resources). Second, because the coverage achieved with traditional Expanded Program on Immunization vaccines remains low in many countries, adding more vaccines has not been identified as a priority. Third, developing countries did not initiate efforts to establish the utility of the vaccine until after the vaccine had been licensed and used routinely for several years in industrialized countries. Consequently, Hib vaccination has been perceived as an intervention for rich countries. As a result of all these factors, actual demand for the vaccine has remained low, even when support has been available through GAVI and the Vaccine Fund.

In 2004, the GAVI board commissioned a Hib task force to explore how best to support national efforts to make evidence-based decisions about introducing the Hib vaccine. On the basis of the task force's recommendations, the GAVI board approved establishment of the Hib Initiative to support those countries wishing either to sustain established Hib vaccination or to explore whether introducing Hib vaccine should be a priority for their health systems. A consortium consisting of the Johns Hopkins Bloomberg School of Public Health, the London School of Hygiene and Tropical Medicine, the Centers for Disease Control and Prevention, and the WHO has been selected to lead this effort.

Case-Management Strategies

Sazawal and Black's (2003) meta-analysis of community-based trials of the ARI case-management strategy includes 10 studies that assessed its effects on mortality, 7 with a concurrent control group. The meta-analysis found an all-cause mortality reduction of 27 percent among neonates, 20 percent among infants, and 24 percent among children age one to four. LRI-specific mortality was reduced by 42, 36, and 36 percent, respectively. These data clearly show that relatively simplified, but standardized, ARI case management can have a significant effect on mortality, not only from pneumonia, but also from other causes in children from birth to age four. Currently, the ARI case-management strategy has been incorporated into the IMCI strategy, which is now implemented in more than 80 countries (see chapter 63).

Despite the huge loss of life to pneumonia each year, the promise inherent in simplified case management has not been successfully realized globally. One main reason is the underuse of health facilities in countries or communities in which many children die from ARIs. In Bangladesh, for example, 92 percent of sick children are not taken to appropriate health facilities (WHO 2002). In Bolivia, 62 percent of children who died had not been taken to a health care provider when ill (Aguilar and others 1998). In Guinea, 61 percent of sick children who died had not been taken to a health care provider (Schumacher and others 2002). Schellenberg and others' (2003) study in Tanzania shows that children of poorer families are less likely to receive antibiotics for pneumonia than children of better-off families and that only 41 percent of sick children are taken to a health facility. Thus, studies consistently confirm that sick children, especially from poor families, do not attend health facilities.

A number of countries have established large-scale, sustainable programs for treatment at the community level:

- The Gambia has a national program for community-level management of pneumonia (WHO 2004b).
- In the Siaya district of Kenya, a nongovernmental organization efficiently provides treatment by community health workers for pneumonia and other childhood diseases (WHO 2004b).
- In Honduras, ARI management has been incorporated in the National Integrated Community Child Care Program, whereby community volunteers conduct growth monitoring, provide health education, and treat pneumonia and diarrhea in more than 1,800 communities (WHO 2004b).
- In Bangladesh, the Bangladesh Rural Advancement Committee and the government introduced an ARI control program covering 10 subdistricts, using volunteer community health workers. Each worker is responsible for treating childhood pneumonia in some 100 to 120 households after a three-day training program.
- In Nepal during 1986–89, a community-based program for management of ARIs and diarrheal disease was tested in two districts and showed substantial reductions in LRI mortality (Pandey and others 1989, 1991). As a result, the program was integrated into Nepal's health services and is being implemented in 17 of the country's 75 districts by female community health volunteers trained to detect and treat pneumonia.

- In Pakistan, the Lady Health Worker Program employs approximately 70,000 women, who work in communities providing education and management of childhood pneumonia to more than 30 million people (WHO 2004b).

RESEARCH AND DEVELOPMENT AGENDA

The research and development agenda outlined below summarizes the priorities that have been established by advisory groups to the Initiative for Vaccine Research (vaccine intervention strategies) and the WHO Division of the Child and Adolescent Health (case-management strategies).

Vaccine Intervention Strategies

The GAVI task force on Hib immunization made a number of recommendations that vary depending on the country. Countries that have introduced Hib vaccine should focus on documenting its effect and should use the data to inform national authorities, development partners, and other agencies involved in public health to ensure sustained support to such vaccination programs. Countries eligible for GAVI support that have not yet introduced Hib vaccines are often hindered by a lack of local data and a lack of awareness of regional data. They can address these issues through subregional meetings at which country experts can pool data and review information from other countries. In addition, most of the countries need to carry out economic analyses that are based on a standardized instrument. Finally, all countries that face a high Hib disease burden need to develop laboratory facilities so that they can establish the incidence of Hib meningitis at selected sites. Countries in which the disease burden remains unclear may have limited capacity to document the occurrence of Hib disease using protocols that are based on surveillance for meningitis invasive disease. They will need to explore the possibilities of using alternative methods for measuring disease burden, including the use of vaccine-probe studies.

On the basis of experience with introducing Hib and hepatitis B vaccines, GAVI took a proactive approach and in 2003 established an initiative based at the Johns Hopkins School of Public Health in Baltimore to implement an accelerated development and introduction program for pneumococcal vaccines (the PneumoADIP; see http://www.preventpneumonia.org). The program's intent is to establish and communicate the value of pneumococcal vaccines and to support their delivery. Establishing the value of the vaccine involves developing local evidence about the burden of disease and the vaccines' potential effect on public health. This effort can be accomplished through enhanced disease surveillance and relevant clinical trials in a selected number of lead countries. Once established, the evidence base will be communicated to decision makers and key opinion leaders to ensure that data-driven decisions are made. Once the cost-effectiveness of routine vaccination is established, delivery systems will have to be established, and countries will need financial support so that the vaccines can be introduced into their immunization programs. These activities are being initiated before the launch of vaccine formulations designed for use in developing countries, so as to inform capacity planning, product availability, and pricing.

Case-Management Strategies

In 2003, WHO's Division of Child and Adolescent Health convened a meeting to review data and evidence from recent ARI case-management studies and to suggest the following revisions to case-management guidelines and future research priorities:

- Nonsevere pneumonia:
  - Improve the specificity of clinical diagnostic criteria.
  - Reassess WHO's current recommended criteria for detecting and managing treatment failure, given the high rates of therapy failure.
  - Reanalyze data from short-course therapy studies to better identify determinants of treatment failure.
  - Carry out placebo-controlled trials among children presenting with wheezing and pneumonia in selected settings that have a high prevalence of wheezing to determine whether such children need antibiotics.
- Severe pneumonia: In a randomized clinical trial in a controlled environment, Addo-Yobo and others (2004) showed that oral amoxicillin is as effective as parenteral penicillin or ampicillin; however, the following actions need to be undertaken before it can be recommended on a general basis:
  - Analyze data on exclusions from the trial.
  - Identify predictors that may help distinguish children who require hospitalization and who subsequently deteriorate.
  - Reassess WHO's current recommended treatment failure criteria for severe pneumonia, given the overall high rates of therapy failure.
  - Conduct descriptive studies in a public health setting in several centers worldwide, to evaluate the clinical outcomes of oral amoxicillin in children age 2 to 59 months who present with lower chest wall indrawing.
  - Document the effectiveness of WHO's treatment guidelines for managing children with pneumonia and HIV infection.
- LRI deaths:
  - To help develop more effective interventions to reduce LRI mortality, study the epidemiology of LRI deaths in various regions in detail, using routine and advanced laboratory techniques.
- Oxygen therapy:
  - Carry out studies to show the effectiveness of oxygen for managing severe respiratory infections.

- Collect baseline information about the availability and delivery of oxygen and its use in hospital settings in low-income countries.
- Explore the utility of pulse oximetry for optimizing oxygen therapy in various clinical settings.
- Undertake studies to improve the specificity of clinical signs in the overlapping signs and symptoms of malaria and pneumonia.
- Study rapid diagnostic tests for malaria to assess their effectiveness in differentiating between malaria and pneumonia.
- Examine the effect of widespread use of co-trimoxazole on sulfadoxine-pyrimethamine resistance to *Plasmodium falciparum*.

• Etiology: Data on the etiology of pneumonia in children are somewhat out of date, and new etiological studies are needed that use modern technology to identify pathogens.

CONCLUSIONS: PROMISES AND PITFALLS

The evidence clearly shows that the WHO case-management approach and the wider use of available vaccines will reduce ARI mortality among young children by half to two-thirds. The systematic application of simplified case management alone, the cost of which is low enough to be affordable by almost any developing country, will reduce ARI mortality by at least one-third. The urgent need is to translate this information into actual implementation.

The case-management strategy has to be applied and prospectively evaluated so that emerging problems of antimicrobial resistance, reduced efficacy of current treatment with the recommended antimicrobials, or emergence of unexpected pathogens can be detected early and remedial steps can be taken rapidly. If community-level action by health workers is supplemented by the introduction of the IMCI strategy at all levels of primary care, then both applying and evaluating this strategy will be easier. Such synergy may also help in gathering information that will help further fine-tune clinical signs, so that even village health workers can better distinguish bronchiolitis and wheezing from bacterial pneumonia. The criticism that the case-management steps may result in overuse of antimicrobials should be countered by documenting their current overuse and incorrect use by doctors and other health workers. Although there is a resurgent interest in basing interventions at the community level, our analysis suggests that doing so may not be cost-effective. Indeed, ARI case management at the first-level facility may still be the most cost-effective when coupled with better care-seeking behavior interventions.

The international medical community is only beginning to appreciate the potential benefits of Hib and pneumococcal vaccines. They are currently expensive compared with Expanded Program on Immunization vaccines, but the price of Hib vaccine may fall with the entry of more manufacturers into the market in the next few years. Nevertheless, convincing evidence of the vaccines' cost-effectiveness is required to facilitate national decisions on introducing the vaccine and using it sustainedly. In low-income countries, positive cost-benefit and cost-effectiveness ratios alone appear to be insufficient to enable the introduction of these vaccines into national immunization programs.

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