Update on 2004 Background Paper

Background Paper 6.22
Pneumonia

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# Abbreviations

<table>
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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ARTI</td>
<td>Acute Respiratory Tract Infection</td>
</tr>
<tr>
<td>ALRTI</td>
<td>Acute Lower Respiratory Tract Infection</td>
</tr>
<tr>
<td>AMC</td>
<td>Advance Market Commitments for Vaccines</td>
</tr>
<tr>
<td>CAP</td>
<td>Community-Acquired Pneumonia</td>
</tr>
<tr>
<td>DALY</td>
<td>Disability-adjusted life-year</td>
</tr>
<tr>
<td>DHS</td>
<td>Demographic and Health Surveys</td>
</tr>
<tr>
<td>ECDC</td>
<td>European Centre for Disease Prevention and Control</td>
</tr>
<tr>
<td>EEA</td>
<td>European Economic Area</td>
</tr>
<tr>
<td>EFTA</td>
<td>European Free Trade Association</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>GAPP</td>
<td>Global Action Plan for Prevention and Control of Pneumonia</td>
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<td>GAVI</td>
<td>Global Alliance for Vaccine Immunization</td>
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<tr>
<td>GBD</td>
<td>Global Burden of Disease</td>
</tr>
<tr>
<td>GSK</td>
<td>Glaxo-Smith Kline</td>
</tr>
<tr>
<td>Hib</td>
<td><em>Haemophilus influenza</em> type b</td>
</tr>
<tr>
<td>IMCI</td>
<td>Integrated Management for Childhood Illness</td>
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<tr>
<td>IPD</td>
<td>Invasive Pneumococcal Disease</td>
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<tr>
<td>LRTI</td>
<td>Lower Respiratory Tract Infection</td>
</tr>
<tr>
<td>MDG</td>
<td>Millennium Development Goal</td>
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<tr>
<td>MICS</td>
<td>Multiple Indicator Cluster Surveys</td>
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<tr>
<td>PATH</td>
<td>Program for Appropriate Technology in Health</td>
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<tr>
<td>PCR</td>
<td>Polymerase Chain Reaction</td>
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<tr>
<td>PCV</td>
<td>Pneumococcal conjugate vaccine</td>
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<tr>
<td>PERCH</td>
<td>Pneumonia Etiology Research for Child Health</td>
</tr>
<tr>
<td>PPV</td>
<td>Pneumococcal Polysaccharide Vaccine</td>
</tr>
<tr>
<td>RSV</td>
<td>Respiratory Syncytial Virus</td>
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<tr>
<td>UNICEF</td>
<td>United Nations Children’s Fund</td>
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<tr>
<td>VE</td>
<td>Vaccine efficacy</td>
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<tr>
<td>VT-IPD</td>
<td>Vaccine-Serotypes Invasive Pneumococcal Disease</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>YLD</td>
<td>Years Lost due to Disability</td>
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<tr>
<td>YLL</td>
<td>Years of Life Lost</td>
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Executive Summary

The 2004 Priority Medicines for Europe and the World Report had 17 chronic and acute priority diseases whose inclusion were based on data from the World Health Organization (WHO) Global Burden of Disease and Database. This updated 2013 Report revised its methods and found reason for the inclusion of five new priority diseases using both the WHO Global Burden of Disease Database 2008 and the Lancet Global Burden of Disease Study 2010. In addition to previous conditions on the list, the five new priority diseases or risk factors are: obesity, low back pain, neonatal conditions, pneumonia, and hearing loss. This background paper focuses on pneumonia in two high-risk populations: children under five and the elderly. Worldwide, children under five are primarily affected by this disease, followed by adults 65 years and older, together making up the majority of pneumonia deaths especially in Europe.

Poor maternal and child health remains a significant problem in developing countries. Although the under-five mortality rate has dropped 35% since 1990, with every developing region seeing a 30% reduction, progress at the global level to reduce under-five mortality is behind schedule for 2015. Pneumonia remains a major killer of children under five years of age, and the highest under-five mortality rates are in low- and middle-income countries (LMIC), namely in sub-Saharan Africa and in Southern Asia. Children in low-income countries are nearly 18 times more likely to die before the age of five than children in high-income countries due to pneumonia and other acute infections.

As a result, there is a considerable need for effective interventions in all parts of the world in order to bring down mortality and morbidity rates due to pneumonia. Reducing child mortality is one of the eight Millennium Development Goals (MDGs), and one way to reach this target is to reduce pneumonia-related mortality by providing effective treatment promptly. Effective interventions to reduce pneumonia deaths are available through vaccinations and antibiotics. However, access to and information on antibiotic use is limited. In addition, only one in five caregivers know to seek appropriate medical care immediately for children with signs of pneumonia. Currently, rapid diagnostic devices that can be used at point of care are not available.

Rapid diagnostics for distinguishing between viral and bacterial pneumonia is not yet well developed. Existing laboratory tests for certain biochemical markers (e.g. procalcitonin, C-reactive protein, white blood cells, etc) only detect the likelihood of bacterial pneumonia. In addition, clinical signs (e.g. fever, shortness of breath, wheezing, crepitation, etc) and radiographic tests (e.g. consolidation or infiltration in the lung) can confirm or disprove diagnosis of pneumonia. However, it is difficult to differentiate between viral and bacterial pneumonia in resource-poor settings lacking in technology and laboratory equipment. Attention should focus on continued updates on existing pneumococcal vaccines to help match the pattern of disease. More effective and rapid diagnostics would also help play a substantial role in detecting cases of pneumonia in order to treat patients at the earliest onset of the disease. Furthermore, scaling up treatment coverage at a relatively low cost would aid in the reduction of childhood pneumonia mortality. While there are current care management for pneumonia, including interventions involving integration of vaccines into national immunization programs, targeted antibiotic treatments for both severe and non-severe pneumonia, and more accurate and rapid diagnostics will help to reduce the global
mortality rates in children under five and the elderly. Preventing children from developing or dying from pneumonia is critical to reducing mortality and working towards achieving the MDG4 in reducing the under-five mortality rate by two thirds by 2015.
1. Introduction

1.1 Background

Pneumonia is the single leading cause of mortality in children under five and is a major cause of child mortality in every region of the world, with most deaths occurring in sub-Saharan Africa and South Asia. Pneumonia kills more children under five than AIDS, malaria, and measles combined, yet increased attention in recent years have been on the latter diseases.\(^3\)

Pneumonia is a form of acute respiratory tract infection (ARTI) that affects the lungs. When an individual has pneumonia, the alveoli in the lungs are filled with pus and fluid, which makes breathing painful and limits oxygen intake. Pneumonia has many possible causes, but the most common are bacteria and viruses. The most common pathogens are \textit{Streptococcus pneumoniae}, \textit{Haemophilus influenzae} type b (Hib), and respiratory syncytial virus (RSV). \textit{S. pneumoniae} is the most common cause of bacterial pneumonia in children under five years in the developing world.\(^4\) The second most common cause of bacterial pneumonia in children is Hib, followed by RSV - the most common cause of viral pneumonia in children under two years. The populations most at risk for pneumonia are children under five years, people aged 65 or over, and people with pre-existing health problems.

\textit{Streptococcus pneumoniae} frequently colonizes the upper respiratory tract. The human nasopharynx is the only natural reservoir for \textit{S. pneumoniae} and these bacteria along with viruses are commonly found in a child’s nose or throat; these pathogens are then aspirated into the lungs, causing disease. Pneumonia can be spread in a number of ways. The pathogen is transmitted through direct contact with respiratory secretions, colonizes the nasopharynx and may then cause blood-borne diseases.\(^5\) \textit{S. pneumoniae} can cause both non-invasive and invasive disease in all age groups, particularly in children younger than five years and adults 65 years or older.\(^2,3\) In addition, people with certain medical conditions, such as chronic heart, lung, or liver diseases, or sickle cell anemia are also at increased risk for pneumococcal diseases. People living with HIV/AIDS or people who have had organ transplants and are taking medications that decrease their immunity to infection are also at high risk of getting this disease.\(^3\)

A healthy child has many natural defenses that protect its lungs from pneumonia. Undernourished children, especially those who are not exclusively breastfed or with inadequate zinc intake, are at a higher risk of developing pneumonia.\(^4\) Immunosuppression due to other coinfections are important risk factors in pneumonia-related mortality; infants, children, or the elderly suffering from illnesses, such as AIDS, measles, or malaria are also more likely to develop pneumonia. Additionally, environmental factors, such as crowded living conditions and exposure to indoor air pollution may contribute to increasing children’s susceptibility to pneumonia.

The Lancet Global Burden of Disease (GBD) Study 2010 has a category for lower respiratory tract infections (LRTI), which includes influenza, \textit{Streptococcus pneumoniae} (pneumococcal pneumonia), \textit{Haemophilus influenzae} type b (Hib), respiratory syncytial virus (RSV), and “other lower respiratory infections”. For the purposes of this report, pneumococcal
pneumonia, Hib, and RSV were chosen as the focus to assess the disease burden in further details.6

1.2 Size and nature of the disease burden

1.2.1 Europe

In Europe, mortality rates for pneumonia are substantially higher in children up to the age of 4 and in adults aged 75 and over than in most other age groups. Most strikingly, in Western Europe the highest mortality rates for pneumonia are in the elderly aged 80 and over (279 deaths per 100 000 people), while in Eastern Europe similar mortality rates for pneumonia exist in infants aged 0-6 days (278 deaths per 100 000). See Figure 6.22.2.

Very young children and the elderly are most at risk for invasive pneumococcal disease (IPD), which is a form of pneumonia where the bacterium S. pneumoniae enters the blood, cerebrospinal fluid, pleural fluid, joint fluid, or pericardial fluid and can lead to other complications and infections such as pneumococcal sepsis.7 In contrast, non-invasive pneumococcal disease, spread through aerosolization of bacteria from the nasopharynx to the alveoli– can cause otitis media, sinusitis, and bronchitis. Comparing the two, IPD is the leading cause of mortality and morbidity in children and adults compared to non-invasive pneumococcal disease.8 Although pneumococcal conjugate and Hib vaccines have been introduced into the childhood vaccination schedule in a number of European Union (EU), European Economic Area (EEA), and European Free Trade Association (EFTA) countries, the average number of confirmed cases for IPD in 2009 was 4.3 cases per 100 000 population (see Figure 6.22.1 below).8 In 2009, the European Center for Disease Prevention and Control (ECDC) detected 14 272 cases of confirmed IPD. In 2008 the number of confirmed cases of IPD has decreased since the previous year (14 759 cases in 2008); however, the 2009 total cases was still higher than the number of confirmed cases in 2006 (14 272 versus 13 235 cases, respectively).8 The rates for IPD cases in children 0-4 years and in adults 65 years and older are higher than most other age groups (see Figure 6.22.1).

Figure 6.22.1: Rates of reported cases of confirmed invasive pneumococcal disease, by age and gender, in EU and EEA/EFTA countries, 2009

Source: European Centre for Disease Prevention and Control 2011
Data for combined non-invasive and invasive pneumonia mortality rates are listed in Figure 6.22.2 below; the graph shows that pneumonia mortality rates are highest among children under five and the elderly over 75 years of age with well over 300 deaths per 100,000 in the relative age categories for all of Central, Eastern, and Western Europe. Most notable are the high mortality rates due to pneumonia in Eastern Europe among children under five and in Western Europe among the elderly. For clarification, this report refers to *S. pneumoniae* (pneumococcal pneumonia), Hib, and RSV as the three major pathogens contributing to pneumonia incidence and mortality. Despite good access to antibiotics and immunization programs, pneumonia is still a substantial cause of illness and death in the EU and EEA/EFTA countries especially among the elderly.

**Figure 6.22.2: Death rates caused by pneumonia by European region and age group, 2010**

![Graph showing death rates caused by pneumonia by European region and age group, 2010](source)

Source: Institute of Health Metrics and Evaluation 2010

**Europe: Children Under Five**

According to the ECDC, rates of reported IPD cases for children under the age of five in Europe are lower than rates for people aged 65 and older (see Figure 6.22.1). Nonetheless, this number still constitutes a majority of reported cases. Central, Eastern, and Western regions of Europe show similar trends in mortality rates for each pneumonia-causing organism (*S. pneumoniae*, Hib, and RSV); Eastern Europe has the highest mortality rates for all three pneumococcal diseases, followed by Central Europe, then Western Europe (see
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Figure 6.22.2). Respiratory syncytial virus has the highest mortality rates in all three European regions among children under five, of about 105 deaths per 100 000 –nearly double the highest RSV mortality rate for Central Europe of roughly 48 deaths per 100 000 (see Figure 6.22.3). Out of the three pneumonia-causing organisms, RSV mainly affects infants and children 0-364 days, but children 1-4 years show a higher mortality rate due to pneumococcal pneumonia than Hib or RSV. The disability-adjusted life-year (DALY) burden for children aged 0-364 days is highest compared to other age groups, with over 24 000 DALYs per 100 000 in Eastern Europe (see Figure 6.22.4). Therefore, pneumonia interventions would yield the highest health benefits and DALYs averted in children less than one year of age, especially in Eastern and Central Europe.

Figure 6.22.3: Under-five death rates by region in Europe and causes of pneumonia, 2010

Source: Institute of Health Metrics and Evaluation 2010

Europe: The Elderly

Another at-risk population is the elderly, who often suffer from flu-like symptoms caused by RSV and *S. pneumoniae*. Due to an increasing ageing population in developed countries, nursing homes are often overcrowded, which provides for opportunistic infections. Moreover, the incidence of infectious diseases, such as pneumonia is common in the elderly because of their impaired immunity. The rate of intermittent pneumonia among nursing
home residents is almost 14 times as high as that among elderly people living in the community.9

In 2009 the ECDC showed that reported cases of IPD are the highest among people over the age of 65 (see Figure 6.22.1). Within the 65 and older age group, there is a gender discrepancy of more cases in males than females. Similarly, data from the Lancet Global Burden of Disease (GBD) Study 2010 also showed that people aged 80 and older have the highest mortality rates due to pneumonia (from S. pneumoniae, Hib, and RSV) with 279 deaths per 100 000 in Western Europe, comparable to the 278 deaths per 100 000 for infants 0-6 days in Eastern Europe (see Figure 6.22.2). People 80 years and older in Central Europe have the third highest mortality rate among all age groups with 157 deaths per 100 000. However, the DALY burden for people 65 years and older is relatively low (355–1709 DALYs per 100 000) compared to the under-five age groups (399–23 972 DALYs per 100 000) (see Figure 6.22.4 below).

Figure 6.22.4: DALY rates caused by pneumonia by European region and age group, 2010

Source: Institute of Health Metrics and Evaluation 2010
1.2.2 Worldwide

Globally, the four major killers of children under five years old are pneumonia, diarrhoeal diseases, preterm birth complications, and birth asphyxia. Pneumonia remains the leading cause of mortality in children under five worldwide. Of the estimated 6.9 million child deaths each year, pneumonia accounts for anywhere from 1.3 to 1.6 million deaths a year in this age group, roughly 18% of deaths among children under age five (see Figure 6.22.5).

Figure 6.22.5: Global distribution of deaths among children under age five by cause, 2009

Note: Undernutrition contributes to more than a third of deaths among children age five. Values may not sum to 100% because of rounding.

The trend in global mortality due to pneumonia and pneumonia-related deaths has decreased between 1990 and 2010, along with deaths under five due to pneumonia (see Annex 6.22.1). However, mortality for children under five due to pneumonia constitutes over 20% of the total global mortality for pneumonia for 1990, 2005, and 2010 (33%, 23%, and 20%, respectively, see Annex 6.22.1). More than 99% of all pneumonia mortalities occur in low- and middle-income countries (LMIC). South Asia and sub-Saharan Africa bear the
burden of more than half of the total number of cases of suspected pneumonia among children under five worldwide (see Figure 6.22.6 below, also see Annex 6.22.2). Children in low-income countries are nearly 18 times more likely to die before the age of five than children in high-income countries, due mainly to pneumonia and other acute infections. In 2010, 70% of the world’s under-five mortalities occurred in only 15 countries, and about half in only five countries (India, Nigeria, Democratic Republic of Congo, Pakistan, and China). These numbers looked only at the three leading pneumonia-causing organisms: S. pneumoniae, Hib, and RSV. For both European Regions and the world, the disease burden for pneumonia (caused by pneumococcus, Hib, and RSV) is highest in children under one year of age. Roughly 434 779 pneumonia deaths occur in this age group and this is over 74% of pneumonia deaths in the under-five age group.

**Figure 6.22.6: Under-five deaths due to pneumococcal pneumonia, Hib, and RSV by regions, 2010**

<table>
<thead>
<tr>
<th>Region</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td>3,154</td>
</tr>
<tr>
<td>South Asia</td>
<td>220,287</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>252,970</td>
</tr>
<tr>
<td>World</td>
<td>585,125</td>
</tr>
</tbody>
</table>

Source: Institute of Health Metrics and Evaluation 2010

Of the 7.6 million children who died in the first five years of life in 2010, 4.9 million (64%) died of infectious conditions. Of all infectious diseases, pneumonia, diarrhoea, and malaria were the leading causes of death in children under five worldwide. Pneumonia caused 1.4 million deaths (18.3%) of all mortalities in children under five, and 4% of that 18.3% of pneumonia mortalities are in the neonatal period. Overall, numbers in under five mortality for pneumonia is less in children aged 1-59 months than they are in neonates (for neonatal conditions, see Background Paper Chapter 6.23).

Globally, respiratory syncytial virus (RSV) causes 253 537 worldwide mortalities each year (see Annex 6.22.3) and it is the most common cause of serious lower respiratory tract infections in infants and young children aged 0-364 days worldwide (see Figure 6.22.7). While all children are at risk of RSV disease, the incidence of severe disease is highest in children with cardiopulmonary disease and those born prematurely. The highest mortality
rates due to RSV complications occur in all regions of sub-Saharan Africa and South Asia in infants aged 0-6 days. A substantial proportion of RSV-associated morbidity occurs in the first year of life, with incidence in infants that is two or three times greater than is reported for children younger than five years of age overall. Also important to consider is the etiologic diagnosis of pneumonia causing organisms where coinfections from both viruses and bacteria can make it difficult to distinguish which organism is the major contributor to the disease outcome. Viruses are thought to cause most of LRTIs, but identification of the viral pathogen is not always successful. In other cases, bacteria *S. pneumoniae* are isolated in the sputum of 50% of patients with bronchitis, but such colonization of the bacteria presents little clinical relevance. Therefore, reported pneumonia mortalities from a specific organism may have some uncertainty because no sensitivity and specific tests for the diagnosis of Hib, RSV, or pneumococcal pneumonia are available. Nonetheless, impact of pneumonia interventions looking at population costs and health effects of the intervention of different country profiles show low-cost outcomes between US$ 10 and US$ 60 per DALY averted for interventions in the WHO Africa D and E subregions, and in the WHO Eastern Mediterranean D subregion.

Figure 6.22.7: Under five death rates by regions in sub-Saharan Africa and South Asia according to the causes of pneumonia, 2010

Source: Institute of Health Metrics and Evaluation 2010
2. **Control Strategy**

Pneumonia is caused by a combination of a variety of factors, including pathogens, the environment, health systems, and health-seeking behaviours. Therefore, no single intervention can effectively prevent, treat, or control pneumonia. As such, a confluence of key interventions to control pneumonia would include immunization against specific pathogens, early diagnosis and treatment of the disease, and improvements in nutrition and environmental living conditions (e.g. safe drinking water, sanitation, hygiene, low household air pollution). Children under five, especially infants aged 0-5 months, not exclusively breastfed are 15 times more likely to die due to pneumonia than children who are exclusively breastfed (see Figure 6.22.8); interventions for increased breastfeeding practices will help decrease childhood mortality due to pneumonia as well as diarrhoea (also see Background Paper Chapter 6.20 on diarrhoeal disease). The potential for saving lives by scaling up the proper interventions is large. Modeled estimates suggest that by 2015 child mortality, due to pneumonia, could fall 30% across the 75 countries with the highest mortality burden if national coverage of key pneumonia interventions were raised to the level in the richest 20% of households in each country.4

Figure 6.22.8: Relative risk among young infants who are not/partially breastfed compared to those exclusively breastfed for pneumonia and diarrhoea incidence and mortality

Source: UNICEF. *Pneumonia and diarrhoea: Tackling the deadliest diseases for the world’s poorest children*, 2012
2.1 Care-seeking behavior

The Multiple Indicator Cluster Surveys (MICS) and Demographic Household Survey (DHS) provide information on caregivers’ knowledge of symptom of pneumonia and on the extent to which caregivers seek appropriate provider for their children with suspected pneumonia. According to these two surveys from 1998 to 2004, the majority of caregivers did not recognize the common symptoms of pneumonia and only 54% of children under five in the developing world were taken to an appropriate provider. However, recent data from MICS and DHS between 2000 to 2010 showed that care-seeking for children with symptoms of pneumonia has increased slightly in developing countries, from 54% in 2000 to 60% in 2010 (see Figure 6.22.9).

Figure 6.22.9: Every region has shown progress in appropriate care seeking for suspected childhood pneumonia over the past decade.

In addition, feeding infants only breast milk in the first six months of life is a key protective intervention highlighted in the Global Action Plan for Prevention and Control of Pneumonia (GAPP) report. Exclusive breastfeeding has multiple positive effects such as nutritional benefits and allows the mother to pass on key components of her immune system to her child to strengthen the infant’s immunity, thereby protecting infants from pneumonia, diarrhoea, and other infections (see Figure 6.22.8).
2.2 Diagnosis

Pneumonia can be diagnosed in a number of different ways. Healthcare providers can diagnose pneumonia by the symptoms, a physical examination, or by ordering diagnostics. Laboratory tests can include chest X-rays and cell cultures (followed by PCR antigen testing of blood or antigen testing of urine.) to look for pathogenic bacteria in the infected part of the body. Usually there should be a combination of clinical, radiological, and laboratory findings to increase the likelihood of correct diagnosis. Chest X-rays and laboratory tests can help confirm the diagnosis of pneumonia by presence of specific findings, such as consolidation or infiltration in the lung, which still would need qualified assessment in conjuction with clinical picture. Localization of infiltrates is important for differential diagnosis (e.g. primary tuberculosis with other pathogens, and in the case of upper lob infiltrate, diffusive infiltration can be seen in pneumocystic pneumonia and sometimes in disease caused by virus or Chlamydia), but should not be used as a unique criteria. In the developing world, children with suspected pneumonia are diagnosed based on their clinical symptoms, given that access to laboratory technologies is often unavailable in resource-poor settings. Healthcare providers can diagnose many cases by using a stethoscope and/or observe a child’s respiratory rate and any breathing problems. Children and infants are presumed to have pneumonia if they exhibit a cough and fast or difficult breathing. The WHO and UNICEF Integrated Management of Childhood Illness (IMCI) guidelines help inform healthcare providers and personnel on standard clinical symptoms and effective treatment for pneumonia.

Respiratory syncytial virus (RSV) is an important cause of viral pneumonia in children under five. However, differentiating between viral and bacterial pneumonia is difficult because X-ray detected lesions can look similar for various viruses and coinfections can occur between various pathogens. Studies looking at RSV incidence and mortality in developing countries identified RSV by enzyme-linked immunosorbent assay (ELISA) or immunofluorescence assays, which have 12% to 50% lower sensitivity than does polymerase chain reaction (PCR). The need for low-cost, key interventions like accurate and point-of-care diagnostic tools for pneumonia would significantly contribute to the prevention of childhood mortality related to pneumonia.

2.3 Antibiotic treatments

Around 85% to 90% of antibiotic consumption occurs in the community, with 80% of this consumption going towards treating respiratory tract infections. Once a child develops pneumonia, death is avoidable through cost-effective and life-saving treatment from antibiotics for bacterial pneumonia. When children suffering from pneumonia are treated promptly and effectively with antibiotics their chances of survival increases significantly. The most common antibiotics currently recommended for children younger than five years are cotrimoxazole and amoxicillin. Children aged 2-59 months with non-severe pneumonia can be treated with oral amoxicillin (40 mg/kg/dose) for three days and five days for severe pneumonia (see Table 6.22.10). For very severe pneumonia, parenteral ampicillin (or penicillin) and gentamicin are recommended as a first line treatment; ceftriaxone should be used as a second line treatment when the first line treatment fails.
While there is a variety of therapeutics for children under five with suspected pneumonia, healthcare providers must be able to identify pneumonia among children with different types of “wheezes” with or without lower chest indrawing, fast breathing, and fever. Accurately diagnosing the type of pneumonia (severe, non-severe, bacterial, viral) will help with rationalizing appropriate treatment while reducing risk for antimicrobial resistance from judicious use of antibiotics (see Background Paper Chapter 6.1 on antimicrobial resistance). Although preventive measures such as vaccination against common pathogens can help to reduce the overall number of pneumonia cases, these interventions will not eliminate pneumonia completely, thus the need for access to safe and effective antibiotic treatments will remain.

### 2.4 Vaccination

Vaccination is a safe, effective, and cost-effective tool for preventing pneumonia. There are vaccines against major infectious diseases that can cause pneumonia – the flu (influenza virus), measles, pertussis, Hib, and pneumococcus. The WHO recommends that all routine childhood immunization programs include vaccines that protect against these diseases.

New vaccines against Hib and pneumococcus are available; many low-income countries have already introduced the Hib vaccine, and pneumococcal conjugate vaccines (PCVs) are increasingly becoming available in developing countries as well. The 7- and 13-valent conjugate vaccines (PCV7, PCV13) have demonstrated effectiveness in reducing incidence and severity of pneumonia and other lower respiratory infections in children. Immunizations help reduce childhood pneumonia in two ways. First, vaccinations help prevent children from developing infections that directly cause pneumonia, such as Hib and S. pneumoniae. Second, immunizations may prevent infections that can lead to pneumonia as a complication, such as influenza, measles, and pertussis. Pneumococcal conjugate vaccines are highly effective in preventing pneumococcal disease. Currently, there are three vaccines on the children’s routine immunization schedule that have the potential to significantly reduce childhood mortality from and related to pneumonia: measles, Hib, and pneumococcal conjugate vaccines. In 2007, the WHO recommended introducing pneumococcal conjugate vaccine (PCV) into all national immunization programs, particularly in countries with high mortality. Since that time, progress has been made in introducing PCV globally with increasing usage in low-income countries.

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**Table 6.22.10: Treatments for pneumonia and their dosage forms**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage</th>
<th>Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxycillin</td>
<td>250 mg, 500 mg</td>
<td>Tablets</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>500 mg, 1 g</td>
<td>Powder for injection</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>250 mg, 1 g</td>
<td>Powder for injection</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>20 mg/ml, 40 mg/ml</td>
<td>Injection</td>
</tr>
<tr>
<td>Procaine benzylpenicillin</td>
<td>1 g, 3 g</td>
<td>Powder for injection</td>
</tr>
<tr>
<td>Oxygen</td>
<td>-</td>
<td>Medicinal gas</td>
</tr>
</tbody>
</table>

2.4.1 Hib vaccine

*Haemophilus influenzae* type b (Hib) is the second leading cause of bacterial pneumonia in children, but it is preventable with the highly effective Hib vaccine. The Hib vaccine has been shown to have protective efficacy greater than 90% against both laboratory-confirmed invasive meningitis and bacteraemic and non-invasive pneumonia.\(^{20,25,26}\) By the end of the 1990s, two-thirds of high-income countries had added Hib vaccine to their immunization schedule, but lower-income countries were slower to implement routine vaccination into their national programmes.\(^{27}\) In 2006, the WHO recommended the introduction of the Hib vaccine into all national routine immunization programmes. By 2010, 169 countries (88% of all WHO Member States) have adopted this plan.\(^{7}\) Since then the gap in vaccination introduction between low- and high-income countries has significantly decreased (Figure 6.22.11).\(^{4}\) Hib conjugate vaccines are some of the safest and efficacious (over 90% efficacious against invasive Hib disease) vaccines available.\(^{28,25,26}\) High coverage of Hib vaccine immunization in children under five could reduce childhood pneumonia and decrease incidence of severe pneumonia.

Figure 6.22.11: Closing the ‘rich-poor’ gap in the introduction of Hib vaccine in recent years

![Graph showing the introduction of Hib vaccine in different income groups](image)

Note: Income groups are based on the World Bank July 2011 classification and are applied for the entire time series (see http://data.worldbank.org/about/country-classifications/country-and-herding-groups#Low_income). Source: WHO Department of Immunization, Vaccines and Biologicals 2011.

Source: UNICEF. *Pneumonia and diarrhoea: Tackling the deadliest diseases for the world’s poorest children*, 2012
2.4.2 Pneumococcal vaccines

The two vaccines that protect against pneumococcal disease are the 23-valent polysaccharide vaccine (PPV23) and the 13-valent protein-conjugated polysaccharide vaccine (PCV13), which replaced the 7-valent conjugate vaccine (PCV7) in 2010 in the United States. The polysaccharide vaccine (PPV) is T cell-independent and does not produce an anamnestic reaction; this means it does not enhance the reaction of the body’s immunologic memory and immunity may not be long-lasting. Therefore, PPV is not effective in children younger than two years old, but it is approved for individuals aged two and older at risk for developing pneumonia and the vaccine is deemed more appropriate for adults (mostly those aged 50 years and older). On the other hand, conjugate vaccines (PCV) elicits a T cell-dependent response and produce an anamnestic reaction that makes the vaccine more effective in infants and children younger than two years of age. There are three PCVs available globally:

- **PCV7** (the 7-valent CRM197 conjugated vaccine)
- **PCV10** (has the same serotypes as PCV7 plus serotypes 1, 5, and 7F, but different carrier proteins: protein D, diphtheria toxoid and tetanus toxoid)
- **PCV13** (has the same serotypes as PCV7 plus serotypes 1, 3, 5, 6A, 7F, and 19A each conjugated to CRM197)

As the first licensed conjugate vaccine, PCV7 demonstrated effectiveness against invasive (meningitis, bacteraemia, and bacteraemic pneumonia) and non-invasive (pneumonia and otitis media) pneumococcal disease. The subsequent vaccines, PCV10 and PCV13, were licensed against invasive disease based on demonstrating in clinical trials comparable immunogenicity to the PCV7. PCV7 and PCV10 are indicated for use in children from six weeks to five years old. PCV13 is available to children six weeks to 17 years old and for adults 50 years and older. The PCV7 was first introduced in the United States in 2000, followed by many other countries in the subsequent years, both in industrialized countries and in the developing world. This conjugate vaccine protected against seven serotypes of the bacterium responsible for 65% to 80% of cases of severe pneumonia in young children living in industrialized countries. By 2008, the 7-valent pneumococcal conjugate vaccine (PCV7) was used in more than 60 countries. By 2010, PCVs had been introduced into the national immunization program of 55 countries. However, this 7-valent vaccine did not contain all the other important serotypes that are more prevalent in developing countries. Most countries in the European Union have recommended national vaccination with PCV in children.

Newer pneumococcal vaccines with more serotypes (PCV10, PCV13) are currently on the market and have been prequalified by the WHO for use in developing countries, which will provide increased coverage of the serotypes most commonly found in those areas (Table 6.22.12). The WHO recommends that use of PCV in routine childhood immunization programs in all countries and particularly in countries where all-cause mortality among children under five is greater than 50 per 1000 live births, or where there are more than 50 000 children dying annually in countries with a high prevalence of HIV infection.
Table 6.22.12: Current pneumococcal conjugate vaccines

<table>
<thead>
<tr>
<th>Pneumococcal vaccine</th>
<th>Serotypes included</th>
<th>Conjugate protein</th>
<th>Trade name (manufacturer)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCV7</td>
<td>4, 6B, 9V, 14, 18C, 19F, 23F</td>
<td>Mutant diptheria toxoid (CRM 197 protein)</td>
<td>Prev(e)nar ® (Pfizer)</td>
</tr>
<tr>
<td>PCV10</td>
<td>4, 6B, 9V, 14, 18C, 19F, 23F, 1, 5, 7F</td>
<td>Protein D from non-typeable Haemophilus influenzae, tetanus toxoid and diphtheria toxoid</td>
<td>Synflorix ® (GlaxoSmithKline)</td>
</tr>
<tr>
<td>PCV13</td>
<td>4, 6B, 9V, 14, 18C, 19F, 23F, 1, 5, 7F, 3, 6A, 19A</td>
<td>CRM 197 protein</td>
<td>Prev(e)nar-13 ® (Pfizer)</td>
</tr>
</tbody>
</table>

Source: Measuring impact of Streptococcus pneumonia and Haemophilus influenza type b conjugate vaccination. WHO Department of Immunization, Vaccines and Biologicals, 2012.

3. Why Does the Disease Burden Persist?

Children of low socioeconomic class or caste (social stratification in India), minority ethnic groups, or living in isolated geographic areas suffer more from inequity than their counterparts. These children are at a disadvantage in access to appropriate and adequate health services. The extent to which caregivers are aware of the basic symptoms for pneumonia and seek appropriate care for their children with is often low. A child’s condition may worsen if he or she is not brought into be seen by a health care worker and given treatment immediately, and the chances of dying from pneumonia or co-infections increases. As a result, less than 50% of the children from families of the poorest quintile receive the necessary care for pneumonia compared to the richest quintile whose coverage in care seeking for pneumonia is well over 60%. Also important to note is that antibiotic treatments are usually empirical, as in most cases of bacterial pneumonia, where isolation of the organism is an exception rather than the rule. Health-care providers prescribing or care givers administering oral antibiotics to children with suspected pneumonia without ascertaining the actual pathogenic cause of pneumonia are taking the risk of treating an organism that may or may not respond to antibiotics.

Furthermore, lack of rapid diagnostic testing plays a major role in the continual presence of pneumococcal disease incidence in developing countries. Community health care workers in less developed countries rely on 1) observation of clinical symptoms of pneumonia to determine the severity of the illness, and 2) empirical antibiotic treatments. This form of care management may not always result in accurate diagnosis of pneumococcal diseases as other coinfections can occur. Chest indrawing, wheezing and/or a temperature greater than 39 degrees Celsius are indications of pneumonia. However, the presence of either or both can be misleading to caregivers (and untrained health care workers) in assessing whether the condition is bacterial or viral. More often than not, antibiotic treatments are prescribed for cases of suspected pneumonia. The use of antibiotics to treat pneumonia is ineffective when the child has viral pneumonia, which can be difficult to determine without proper diagnostics or health care provider knowledge of clinical symptoms.
Globally, respiratory syncytial virus (RSV) is the most common cause of childhood acute lower respiratory tract infections (ALRTI) and a major cause of admission to hospitals as a result of severe ALRTI. Unlike pneumococcal pneumonia or Hib, there is no current effective vaccine for the prevention of RSV. While there is immunoprophylaxis with monoclonal antibodies therapy for RSV the high cost of treatment is not affordable in developing countries.\textsuperscript{14}

In developing countries with weak health systems and lack of laboratory diagnostic tools, the management of childhood illnesses is presumptive and symptom-based and health-care providers rely on the WHO/UNICEF Integrated Management of Childhood Illnesses (IMCI) algorithm. In these guidelines, pneumonia includes history of a fever, cough, or difficulty in breathing in the presence of increased respiratory rate according to age-related symptoms (e.g. fever and coughing, etc) that may also indicate malaria. Children who are brought into these health centers with malaria, with overlapping pneumonia symptoms, are given both antimalarials and antibiotics.\textsuperscript{31} This dual treatment results in unnecessary overprescription of either or both medicines, which in turn could lead to antimicrobial resistance down the road (see Background paper 6.1 on antibacterial drug resistance).

4. Lessons From Research Into Pharmaceutical Interventions For Pneumonia

4.1 Antibiotics

4.1.1 Treatment for children

There are multiple antibiotics indicated and effective in the treatment of pneumonia. Administration of the most appropriate antibiotic as a first-line medicine may improve the outcome of pneumonia. In order to effectively treat the disease while minimizing antimicrobial resistance and virulence, it is important to know which antibiotics work best for children depending on the severity of the illness. The four types of antibiotics suggested for treatment of pneumonia are cotrimoxazole, amoxicillin, cephalosporins, and macrolides. Current recommendations to treat non-severe pneumonia in children includes oral amoxicillin and for very severe pneumonia ampicillin and gentamicin.\textsuperscript{23} The WHO recommends amoxicillin provided twice daily for three days (in settings with low HIV prevalence) or five days (in settings with high HIV prevalence) as the most effective antibiotic treatment for childhood pneumonia.\textsuperscript{4}
Figure 6.22.13a: Comparative effectiveness of antibiotics on clinical cures for community-acquired pneumonia in children under 18 years of age

**Comparative effectiveness of antibiotics on clinical cures for community-acquired pneumonia in children under 18 years of age**

![Graph](image)

**Results from various randomized controlled studies from the Cochrane Database of Systematic Reviews (see Figure 6.22.13a above, and respective studies indicated in brackets e.g. [1]) show a multitude of available treatments for pneumonia in children. Only three of the 17 antibiotic comparisons proved to be statistically significant difference in its outcome to clinically cure community-acquired pneumonia (CAP) in children; cefpodoxime was more effective than amoxycillin [3] and amoxycillin was more effective than chloramphenicol [4]. The comparison between co-amoxycavulanic acid and amoxycillin [13] was also statistically different in its outcome; however, the confidence interval range was very large and the sample size of 100 children was small, which cannot be generalizable data for the population of children under five. The rest of the comparisons showed no statistically significant differences in favoring one treatment over the other. The implications for practice based on these studies is that for the treatment of ambulatory patients with CAP, amoxycillin is an alternative to co-trimoxazole [14] with little difference in outcome of clinical cure of CAP of one treatment over the other (OR=1.12, CI 0.61-2.03). There are no apparent differences between azithromycin and erythromycin [6], azithromycin and co-amoxycavulanic acid [7], or cefpodoxime and co-amoxycavulanic acid [9]. Co-amoxycavulanic acid and cefpodoxime may be alternative second-line drugs. For children hospitalized with severe and very severe CAP, penicillin/ampicillin plus gentamycin is superior to chloramphenicol (see Annex 6.22.4 [3]).**

6.22-23
While there are many antimicrobials available for the management of non-severe and severe community-acquired pneumonia (CAP), there is also a need for more studies and higher quality trials with large numbers of patients, for example, to compare amoxyccillin with co-amoxyclavulanic acid, macrolides with amoxyccillin and amoxyccillin with oral cephalosporins.\textsuperscript{32} Data from these studies comparing the different types of antibiotics were mainly from least-developed countries and included children with varying severity of illness and geographic locations. Therefore, attempts to isolate specific etiological agents of pneumonia in order to targetly treat the pathogen may not be as cost-effective as empirical treatment.\textsuperscript{32} Results from these studies may be more applicable to the management of pneumonia in developing countries, but the comparisons can also help guide antibiotic therapy in industrialized countries.

Furthermore, there is a need for reformulation of existing, recommended antibiotic treatments for children. The WHO ‘Priority life-saving medicines for women and children 2012’ listed two recommended dosages of gentamicin: 40 mg/ml and 20 mg/ml. The 40mg/ml is an adult formulation, adaptable to older children but unsuitable for neonates, and the 20 mg/ml formulation is ideal for neonates and children. However, 20 mg/ml of gentamicin is not currently manufactured; as a result, dilutions of the 40 mg/ml formulation will need to be made until that time when the 20 mg/ml formulation is available.\textsuperscript{33} Lastly, the worldwide estimate is that 30\% of isolates from those with pneumonia are resistant to macrolides, including erythromycin, azithromycin, and clarithromycin. Similarly, 30\% of \textit{S. pneumoniae} is now multidrug resistant.\textsuperscript{34} The continual rise in antibiotic resistance is a major public health concern that requires keen observation of respiratory illness in children to assess proper treatment options.

4.1.2 Treatment for the elderly

Studies on comparative effectiveness of antibiotics in community-acquired pneumonia (CAP) in adults reviewed by the Cochrane Database of Systematic Reviews indicated that \textit{S. pneumoniae} was the main causative organism, showing 56\% of positive cultures.\textsuperscript{35} In each of the comparisons across antibiotic groups, a macrolide and a quinolone were compared. Overall, success rates (based on clinical, bacteriological, or radiological examination) were very high, ranging from 87\% to 96\% (see Figure 6.22.13b below).\textsuperscript{35} However, individual study results did not reveal significant differences in efficacy between various antibiotics and antibiotic groups. Given the limited studies reviewed, it is not possible to make strong evidence-based recommendations for the choice of antibiotics to be used for the treatment of CAP in ambulatory adult patients.
4.2 Vaccines

4.2.1 Prevention for children

Streptococcus pneumoniae is a transformable bacterial pathogen that has been showing rapid evolution in response to antibiotic therapies. Since the introduction of the 7-valent pneumococcal conjugate vaccine (PCV7) in 2000 for immunization in children, the incidence of invasive pneumococcal disease (IPD) has declined in both children and adult population. This reduction is driven by the decrease in incidence of IPD caused by vaccine-serotypes (VT-IPD) targeted by the PCV7. Randomized controlled trials conducted in Africa, the USA, the Philippines, and Finland on PCV effectiveness in children provided evidence that the conjugate vaccine was able to prevent pneumococcal infections. In these studies, the tested conjugate vaccines included 7-, 9-, and 11-valent serotypes and not the 10- or 13-valent serotypes. In a study in Gambia conducted by Cutts et. al in 2005, PCV9 (9-valent CRM197 conjugated vaccine) had a vaccine efficacy of 35% in preventing radiological (X-ray) pneumonia caused by S. pneumoniae (see Figure 6.22.14 below) and mortality was reduced by 16%. 

Figure 6.22.13b: Comparative effectiveness of antibiotics on success rates for CAP in adults aged 65 years and older

Comparative effectiveness of antibiotics on success rates for community acquired pneumonia in adult patients

- Erythromycin vs. clarithromycin [1]
- Azithromycin microspheres vs. levofloxacin [2]
- Azithromycin microspheres vs. clarithromycin [3]
- Telithromycin vs. clarithromycin [4]
- Telithromycin vs. levofloxacin [5]

Outcome: Success rates defined as cure or improvement in clinical, bacteriological, or radiological, as assessed at a predefined follow-up visit.
Outcome measure: odds ratio. A favors first treatment, B favors the other treatment

- Outcome: Success rates defined as cure or improvement in clinical, bacteriological, or radiological, as assessed at a predefined follow-up visit.
- Outcome measure: odds ratio. A favors first treatment, B favors the other treatment
Children in developing countries may develop pneumococcal diseases caused by a broader range of serotypes of the pneumococcal bacteria than children in industrialized countries. A review of studies done on pneumococcal conjugate vaccines looked at 9-valent PCV and 11-valent PCV (neither of these PCVs have been registered) in Africa and the Philippines to determine the vaccines' efficacy on IPD among children under two years of age. The studies showed that PCV9 and PCV11 were effective in preventing X-ray defined pneumonia in children under two, with a pooled vaccine efficacy of 27% (see Figure 6.22.14). For children in industrialized countries, PCV7, PCV10, and PCV13 are readily available and part of the national immunization programs; however, the WHO is now recommending using higher valent conjugate vaccines (higher than PCV7) to cover more serotypes in developing countries.

Pneumococcal conjugate vaccine impact assessment from the WHO and the GAVI Alliance deemed PCV7, PCV10, and PCV13 appropriate for introduction into immunization programs in countries around the world. Serotypes not covered by the existing 7-, 10-, and 13-valent pneumococcal conjugate vaccines may still contribute to pneumonia incidence in children; such a situation requires surveillance for evolving pneumococcal isolates and attention to research newer vaccine serotypes.
4.2.2 Prevention for the elderly

Unlike the conjugate type vaccine recommended for children, the 23-valent pneumococcal polysaccharide vaccine (PPV23) has been utilized internationally in high- and low-income countries to varying extents, but mainly limited to older adults and adults with risk factors for IPD.\textsuperscript{37} Meta-analysis provides evidence supporting the recommendation for PPV to prevent IPD in adults. Figure 6.22.15 shows a selective number of trials designed for adults 65 years and older. Of the seven trials conducted, three showed that the PPV was efficacious in preventing pneumococcal infections in the elderly. Vaccine efficacy (VE) among the three statistically significant trials ranged from 45\% to 70\% efficacy; however, the upper limit of the vaccine’s efficacy is still lower than the desired 80\% to 90\% protection. The available evidence does not demonstrate that PPVs prevent all causes of pneumonia or mortality in adults. The studies that were not randomized-controlled studies may be more susceptible to confounding with smoking status and influenza vaccination status.\textsuperscript{37} Moreover, these results were based on limited studies looking at a specific population group (the elderly) that are often excluded from drug clinical trials (see Chapter 7.3 on Priority Medicines for the Elderly). However, another study done by Maruyuma et al. looking at PPV in nursing home showed that the vaccine prevented pneumococcal pneumonia in nursing home residents. Although the vaccination rate in nursing homes is only 5\%, the possibility of a protective effect for residents is attainable through increased coverage.\textsuperscript{37}

In late 2011, a supplement was issued to the U.S. Food and Drug Administration (FDA) license for expanded use of PCV13 in adults. Thus, the 13-valent conjugate vaccine (PCV13) is now registered to use in adults 50 years and older and not just in children aged 2-59 months as before.\textsuperscript{38} While PCV13 has demonstrated equal or greater immunogenicity than PPV23, an immune response comparable with the establishment of immune memory could only be shown for the PCV13.

In addition to PPV23 and now PCV13 as the recommended vaccines in adults, newer PCVs have been shown to reduce the number of healthy carriers of the pathogen in a community, which is known as “herd immunity” where unvaccinated people are protected from the pathogen. An example of this herd immunity took place in the United States where one year after the introduction of PCVs, the incidence of IPD fell by 69\% among vaccinated children under two years. Incidence of IPD also declined by 32\% in adults aged 20-39 and by 18\% in people 65 years and older, none of whom were vaccinated.\textsuperscript{5}
Update on 2004 Background Paper, BP 6.22 Pneumonia

Figure 6.22.15: Efficacy of PPV in preventing pneumococcal infections in the elderly aged 65 years and older

4.3 Diagnostics

It is important to determine the cause of community acquired pneumonia (CAP) (e.g. bacterial, viral, fungal, or mixed) because of differences in treatment approaches. In children under five, the bacterium *S. pneumoniae*, which is a bacterium, is the most common cause of pneumonia, another cause of the disease is RSV. Although symptoms may differ, they often overlap, which can make it difficult to identify the organism by symptoms alone.

In resource-rich settings where inpatient care can be monitored, health-care providers can request laboratory tests such as bacteriological and/or PCR tests of blood, induced sputum, urine, or chest X-rays. However, health facilities (i.e. hospitals where patients can have co-infections, present diagnostic difficulties in that sputum or blood tests) often detect bacteria or other organisms, but such agents do not necessarily indicate pneumonia. Finding bacteria or viruses in sputum or nasopharyngeal swab does not confirm their etiological potential in causing pneumonia. Polymerase chain reaction (PCR) and latex agglutination are two methods that would ensure a high degree of specificity and sensitivity using DNA sequencing and organism-specific antibodies-antigen for detection. Current tests for identifying the respiratory syncytial virus include (but are not limited to) six different laboratory diagnostic methods (see Table 6.22.16). Most of these tests require utilization of health facilities and serves patients who are admitted to hospitals. Ultimately, the cost of these diagnostic tools present a barrier in resource-poor settings and health care workers must rely on observations of symptoms based clinical IMCI guidelines.
Table 6.22.16: Laboratory diagnostic tests for detection of respiratory syncytial virus, 2010

<table>
<thead>
<tr>
<th>Diagnostic tests</th>
<th>Full name</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFA</td>
<td>Direct fluorescent antibody test</td>
</tr>
<tr>
<td>ELISA</td>
<td>Enzyme-linked immunosorbent assay</td>
</tr>
<tr>
<td>IF</td>
<td>Immunofluorescence</td>
</tr>
<tr>
<td>IFA</td>
<td>Indirect immunofluorescent antibody test</td>
</tr>
<tr>
<td>MPCR</td>
<td>Multiplex reverse transcription polymerase chain reaction</td>
</tr>
<tr>
<td>RT-PCR</td>
<td>Reverse transcriptase polymerase chain reaction</td>
</tr>
</tbody>
</table>

**Source:** Nair et al. Lancet, 2010.

The Pneumonia Etiology Research for Child Health (PERCH) study has looked at diagnosing the microbiological etiology of pneumonia using various specimens to formulate a rational approach to the appropriate types of specimens collected. Of the eight possible specimens (lung aspirates, lower respiratory tract secretions, pleural fluid, upper respiratory tract, blood, urine, postmortem lung tissues, and exhaled breath), lung aspirates and pleural effusion provided high specificity. Even though there are a variety of preventive medicines and treatments available in the form of pneumococcal vaccines and different types of antibiotics, some children are not benefiting from these interventions because the pneumonia-causing organism may be viral rather than bacterial. There are currently no available rapid point-of-care diagnostics to differentiate between bacterial and viral pneumonia; this is a key gap in monitoring the spread of both bacteria and viruses contributing to pneumococcal disease and in providing proper treatment.

### 5. Current “Pipeline” of Products That Are to Be Used For Pneumonia

There are several protein vaccine studies currently underway. One such progress in pneumococcal disease research is undertaken by PATH and Intercell AG to launch the first-in-human clinical trial for a “common protein” pneumococcal vaccine candidate. Phase I clinical trials, currently taking place in Germany, will test the safety and immunogenicity of IC₄₇ recombinant subunit vaccine consisting of three conserved surface proteins from the pneumococcus bacteria. Vaccines containing proteins common to all pneumococcus serotypes are promising because they could provide broad protection to children worldwide. Another study looking at innovative protein-plus-conjugate vaccines that could lead to broad coverage across numerous pneumococcal serotypes is currently in Phase II in Gambia with collaborators such as GSK, PATH, the Medical Research Council in Gambia, and the London School of Hygiene and Tropical Medicine.

The Pneumococcal vaccines Accelerated Development and Introduction Plan (PneumoADIP) is another collaborating centre currently conducting various research and surveillance
studies looking at novel diagnostic tools for pneumonia. There is the Binax study that evaluates the utility of Binax Now®, which is an antigen test for *S. pneumoniae* as an adjunct to culture for the diagnosis of pneumococcal meningitis in a variety of settings.

In addition to radiography and laboratory culture specimen testing, more accurate, robust, and straightforward techniques to count the breathing rate of sick children can help improve specificity for pneumonia. One such example is pulse oximetry, which is a non-invasive method allowing the monitoring of the oxygen saturation of a patient’s hemoglobin. The pulse oximeter sensor is placed on a thin part of the body, usually a fingertip or earlobe, or in the case of an infant, across the foot. The device monitors blood oxygen saturation levels and pulse rate. In emergency situations, the simplicity of this medical device can help to detect the severity of a child’s respiratory condition in order to determine the severity of wheezing in suspected pneumonia. Although the utility of pulse oximetry may not be for diagnosing pneumonia, it can help to monitor a patient’s intake of oxygen that may be indicative of severe pneumonia. This has the potential to improve the diagnosis and appropriate treatment of pneumonia.

Clinical trials looking at RSV prevention in children included studies for humanized monoclonal antibody produced by recombinant DNA technology, such as Motavizumab (MEDI-524), MEDI-534, and palivizumab (see Table 6.22.17). These biologics have been investigated by MedImmune, Abbott Laboratories, and other major pharmaceuticals as prophylaxis for the prevention of RSV infection in high-risk infants in hopes of decreasing the need for hospitalization. There has been a study looking at a live, attenuated RSV vaccine candidate, called MEDI-559, which completed in August 2012. These studies have been completed (from 2008 to the latest in 2012), but no study results have been published as to date.

### Table 6.22.17: Clinical trials on pneumonia in children and the elderly as of 2013

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Topic</th>
<th>Group</th>
<th>No. of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. pneumoniae</em>:</td>
<td>Safety and immunogenicity of pneumococcal vaccines.</td>
<td>Elderly</td>
<td>19</td>
</tr>
<tr>
<td>RSV</td>
<td>Evaluation of prophylaxis treatments and vaccines: MEDI-524, MEDI-534, palivizumab, MEDI-559.</td>
<td>Children</td>
<td>74</td>
</tr>
</tbody>
</table>

Source: [www.clinicaltrials.gov](http://www.clinicaltrials.gov)
5.1 Research and development funding

Funding for research, prevention, and treatment for pneumonia is by a few large organizations: the Bill and Melinda Gates Foundation for investing in the creation and delivery of diagnostics and treatment for pneumonia; Program for Appropriate Technology in Health (PATH) for the research and development of new serotypes in pneumococcal conjugate vaccines; GAVI Alliance for the introduction of new vaccines into developing nations’ immunization programs; and AMC for Vaccines for the procurement of pneumococcal vaccines (see Table 6.22.18 below).

Table 6.22.18: Funding from donors for prevention, treatment, and/or research for pneumonia in 2011

<table>
<thead>
<tr>
<th>Funder</th>
<th>Intervention</th>
<th>Funding amount US$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gates Foundation</td>
<td>Grants for Global Health program area in pneumonia</td>
<td>88.9 million</td>
</tr>
<tr>
<td>GAVI Alliance</td>
<td>To UNICEF for purchase of pneumococcal vaccines</td>
<td>380.7 million</td>
</tr>
<tr>
<td>PATH</td>
<td>Research for development of new pneumococcal vaccines</td>
<td>96.5 million</td>
</tr>
<tr>
<td>AMC for Vaccines</td>
<td>Procurement of pneumococcal vaccines from manufacturers</td>
<td>270.0 million</td>
</tr>
<tr>
<td></td>
<td>Purchase of pneumococcal vaccines (Funds for GAVI to fund UNICEF’s purchase)</td>
<td>168.6 million</td>
</tr>
</tbody>
</table>


According to the Global Action Plan for Prevention and Control of Pneumonia (GAPP), commodities like medicines, injection materials, and diagnostics for pneumonia management account for only 0.4% of total costs of 68 countries that makes up about 98% of global pneumonia mortalities in children under five. Bacterial pneumonia is considered a ‘second tier’ disease in the realm of global investment into research and development (R&D) compared to the ‘top tier’ diseases like HIV/AIDS, malaria, and tuberculosis. Nonetheless, bacterial pneumonia has seen an increase in funding (up US$ 10.7 million) from 2010 to 2011. The total funding for neglected disease R&D in 2011 was US$ 3.045 million, of which bacterial pneumonia received about 13.1% of global neglected disease R&D funding.

The Advance Market Commitments for Vaccines (AMC) scheme ensures that partners like GAVI Alliance, contracts with major manufacturers like Pfizer and Glaxo-Smith Kline to allocate AMC funds in the procurement of pneumococcal vaccines at a set amount of supply of doses and price over an agreed upon period of time. Both suppliers have agreed to supply 18 million doses annually from 2014 for a period of 10 years up to a maximum of 180 million doses, with each dose priced at US$ 3.50, and an increase of supply should there be a demand. The price of US$ 3.50 is specifically priced for developing countries while the
current existing pneumococcal vaccine is more than US$ 70 per dose in industrialized countries.\textsuperscript{27}

Globally, funding for pneumonia research and development, specifically for bacterial \textit{S. pneumoniae} is approximately US$ 200 million. Over 90\% of this amount went towards vaccines research and development while diagnostics only received 5\% of the total funding (see Table 6.22.19). Finally, there have been three projects commissioned by the European Commission, under the Seventh Framework Programme (FP7), towards methods for identification of various organisms contributing to pneumonia (see Table 6.22.20).\textsuperscript{44} The aims of these projects are to gain understanding of the host-pathogen interaction and to fill the gap between genomic data and development of novel vaccines and diagnostic tools.

**Table 6.22.19: Funding for pneumonia R&D (thousand US$), by pathogen, 2008-2011**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Vaccines</th>
<th>Diagnostics</th>
<th>Unspecifed</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial pneumonia \textit{(Streptococcus pneumoniae)}</td>
<td>185 715 751</td>
<td>10 116 222</td>
<td>4 180 877</td>
<td>200 011 851</td>
</tr>
</tbody>
</table>

**Source:** G-FINDER Global Funding of Innovation for Neglected Diseases. 2008-2011 funding data has been adjusted for inflation and is reported in 2007 US dollars (US$). [http://g-finder.policycures.org/gfinder_report/search.jsp](http://g-finder.policycures.org/gfinder_report/search.jsp)

**Table 6.22.20: European Commission projects for vaccines and diagnostic research and development**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Project Title</th>
<th>Start Date</th>
<th>EC contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>MICROBEARRAY</td>
<td>Genome scale analysis of the immune response against pathogenic micro-organisms leading to diagnostic and vaccine candidates and development of an integrated micro array platform for clinical use.</td>
<td>21 June 2004</td>
<td>€1 401 002</td>
</tr>
<tr>
<td>OMVAC</td>
<td>Novel prevention and treatment possibilities for otitis media through the comprehensive identification of antigenic proteins.</td>
<td>1 October 2006</td>
<td>€2 320 000</td>
</tr>
<tr>
<td>SAVINMUCOPATH</td>
<td>Novel therapeutic and prophylactic strategies to control mucosal infections by South American bacterial strains.</td>
<td>1 October 2006</td>
<td>€1 699 908</td>
</tr>
</tbody>
</table>

**Source:** European Commission. Seventh Framework Programme. Vaccines for Humans: Project Synopses; 2008
6. Opportunities for Research and Challenges

To date, only live attenuated vaccine candidates have been tested in young infants – the group most at risk for severe RSV disease. A recombinant RSV vaccine with multiple mutations can be well tolerated and can likely be protective in this age group. Clinical testing of the vaccine candidates was conducted by a consortium of investigators as part of a cooperative agreement between industry (Wyeth Vaccines Research) and the United States government laboratories (National Institute of Allergy and Infectious Diseases and the National Institute of Health). New approaches to the genetic manipulation of vaccine candidates can now be considered, including the use of gene rearrangement or genetic recombination of several candidate viral genes.

Academic researchers have been hesitant to pursue RSV vaccine development and testing. Respiratory syncytial virus vaccine development by manufacturers has been affected by the financial risk involved, the high level of investment required, and the low return the investment provides. Therefore, clinical development of RSV vaccine candidates remains extremely limited.

Rapid diagnostic tests (RDTs) currently exist for malaria, which allow for a definitive diagnosis to be made even in health settings lacking any laboratory facility. While RDTs help to differentiate between malaria and pneumonia, it does not differentiate between viral and bacterial infections in the case of pneumonia. The availability of a RDT for malaria to target the use of artemisinin based combination therapy (ACT) should also call for a RDT for pneumonia to target the use of antibiotics.

The Advanced Market Commitment (AMC) has ensured the rollout of the pneumococcal vaccine in 2006 with US$ 1.5 billion funding from Italy, Norway, the United Kingdom, Canada, Russia, and the Bill & Melinda Gates Foundation. The commitment established a set price for any vaccine, guaranteeing a future market for vaccine producers and lowering the risk of product development. For developing countries, AMC allows organizations like GAVI Alliance to subsidize the price of vaccines, with each dose priced at US$ 3.50 (subsidy can lower price to US$ 0.15 per dose). This effective approach to ensuring an advanced market commitment for conjugate vaccines could be tried for a product other than a vaccine; a promising area would be towards the development for rapid point-of-care diagnostic test to differentiate between viral and bacterial pneumonia. A possible challenge for such an invention would be an issue of effective usage of the technology. For example, results from malaria studies conducted in Tanzania showed that although point-of-care tests for malaria are more accurate than diagnosis using microscopy, clinicians often ignored both negative results and those patients were still being treated with antimalarial drugs.

Pneumonia often coincides with other infections, especially in preterm infants as well as in the elderly. If pneumonia is combined with hypoxaemia, as happens in 13% of cases, children are five time more likely to die than those with only pneumonia. Oxygen concentration should therefore be monitored and oxygen therapy should be made available. In addition to radiography and laboratory culture specimen testing, pulse oximetry can help improve specificity for pneumonia.

Even with the availability of novel pneumococcal vaccines, the decision to introduce at the country level is only the first step; storage, transport, education efforts, and health care
worker training must also be strong enough to successfully manage the increased human resource and infrastructure burdens of new vaccine introduction. Without sufficient and operational system capacity, health systems face a hurdle in supporting the introduction of PCVs into countries’ national immunization programs.

7. Pharmaceutical Gaps

Despite existing Hib and pneumococcal conjugate vaccines, disparities in access to these vaccines exist within countries, which reduce vaccines’ impact as cost-effective interventions against childhood pneumonia and impede efforts to close the ‘rich-poor’ gap in vaccine introduction. The ‘rich-poor’ gap still exists in national vaccination programs among countries with varying income levels (see Figure 6.22.21). Introducing a vaccine into the national program does not necessarily translate to equitable and high coverage even within countries, which further reduces the impact of vaccines. While there are currently three types of pneumococcal vaccines for children under five, none of the PCVs are available in a combined form with other vaccines within the same routine immunization schedule. The multiple shots vaccination to a child under five or to a toddler within multiple visits may create additional discomfort; this could create potential problems where mothers are less likely to get their child vaccinated due to skepticism of vaccine effectiveness and side effects.

Figure 6.22.21 Progress in introducing PCV globally, particularly in the poorest countries, but a ‘rich-poor’ gap remains

![Graph showing the progress of PCV introduction globally](image)

Note: Income groups are based on the World Bank July 2011 classification and are applied for the entire time series (see http://data.worldbank.org/about/country-classifications/country-and-lending-groups#Low_income). Source: WHO Department of Immunization, Vaccines and Biologicals 2011.

Source: UNICEF. Pneumonia and diarrhoea: Tackling the deadliest diseases for the world’s poorest children, 2012
Furthermore, new pneumococcal serotypes are continuously shifting. There is the possibility that serotypes not covered by PCV7, PCV10, or PCV13 could be replaced by new serotypes not in current vaccines, as already observed in some countries in the EU. Therefore, there is a need for constant monitoring of possible serotype replacement to guide research and development for next generation vaccines. Such research and development requires constant funding throughout multiple clinical trials in order to get the vaccine on the market and implemented into national immunization programs. There is a need for additional conjugate vaccines, as well as vaccines made of protein antigens that are conserved across pneumococcal serotypes so that an immune response can be generated against all pneumococcal pathogens regardless of their serotype. Research is needed towards the discovery of a pneumococcal vaccine which is immunogenic in all young children as well as the elderly. An ideal vaccine would also protect against pneumococci regardless of their capsular types. Another pneumonia-causing organism is the respiratory syncytial virus (RSV), which is the leading cause of bronchiolitis and pneumonia in infants and the elderly worldwide. Despite that, there is no licensed RSV vaccine and only limited therapeutics exist.

Further pharmaceutical gaps lie in the need for rapid diagnostic tools for pneumonia. While X-rays and cultures laboratory tests can confirm the presence of the organism, those diagnostic tools can be costly and time consuming, especially in lower-income and least-developed countries. These tests may have low specificity. Moreover, cases of suspected pneumonia cannot be categorized as a bacterial infection or a viral infection without performing the necessary lab cultures. The burden of lower respiratory tract infections caused by *S. pneumoniae*, Hib, or RSV is difficult to determine because current techniques to establish bacterial etiology lack sensitivity and specificity. Therefore, there is a need for rapid diagnostic tools to differentiate between a viral or bacterial infection. A quick and accurate point of care tool could aid health-care providers in providing children with proper treatment in a timely manner and help decide whether or not antibiotics are needed. More precise diagnosis would also help reduce antimicrobial resistance through rational and judical use of antibiotics in treating pneumonia.

Despite good access to antibiotics, *S. pneumoniae* is still a major cause of illness and mortality in EU and EEA/EFTA countries. The implication of this is associated with the increasing trend in antimicrobial resistance (AMR); thus, development of new antibiotics is imperative to addressing AMR and the decrease in effective antibiotics for pneumonia (See Background Paper Chapter 6.1 on antimicrobial resistance). The goal to reduce incidence and increase prevention lies with access to affordable vaccines and treatments. Meanwhile, there is also a need to balance access and affordability with research and development of new vaccines and antibiotics in order to stay on track with the disease’s evolving pathogenic strains and increased susceptibility to drug resistance.

### 7.1 Research priorities

**University and research institutions**

- Institutions in high-income countries should support the collaboration of public-private partnerships to share knowledge and skills and enable development of low-cost technologies benefiting the health of specific, at-risk population groups.
- More research should be done on the elderly population and PPV/PCV efficacy trials involving large number of participants from this age group.
Ministries of health

- Methods to implement or strengthen monitoring and evaluation of interventions.
- Evaluation of approaches to implementation or strengthening of immunization programmes in countries to ensure all child and elderly patients are vaccinated with the WHO recommendations for vaccinations and integrate the latest pneumococcal conjugate vaccine in all national immunization programme schedule.
- Develop robust effective prompt methods to strengthen regulation in pricing, sustainable procurement, and quality of pneumococcal vaccines and antibiotic supplies.
- Research into barriers affecting PPV vaccination in the elderly in nursing homes (see Chapter 7.3 on Priority Medicines for the Elderly).

Health care pharmaceutical technology companies and small and medium enterprises

- Develop low-cost pneumococcal vaccines with room for more production should there be an increase in market demand.
- Conduct more research into vaccine development to discover new targets for 1) novel serotypes in pneumococcal vaccines, and 2) antiviral drugs for viral pneumonia like RSV.
- Research and develop a high specificity rapid diagnostic test at point-of-care for bacterial versus viral pneumonia organisms.
- Reformulation of currently recommended antibiotics for treatment of pneumonia for better metabolic uptake in children and dosage of injectable products for neonates.

8. Conclusion

Over one million children will die before their fifth birthday, nearly all of which are preventable. The attainment of the Millenium Development Goal 4 (MDG4) is possible only if life-saving newborn and child health interventions for pneumonia are rapidly scaled up in high-burden regions and countries, as well as in special population groups in the next few years. Prevention by means of vaccination would be most crucial for reducing pneumonia mortality in children under five, while effective (uptake of) antibiotic therapy for the elderly would serve to decrease mortality due to pneumonia in Europe. Community-based management of severe disease could be an important complementary strategy to reduce pneumonia mortality in children under five as well as in the elderly. Pneumonia has a great burden of morbidity and mortality in developing countries, which results in economic and social pressures on families and the country as a whole. Therefore, pneumonia prevention is not only about saving the lives of children, but it is also about preventing illness, hospitalization, and related economic costs. An integrated care management system has proven to be effective in reducing pneumonia mortality by 17% with the available vaccines against Hib and S. pneumoniae; in addition to breastfeeding promotion and zinc supplementation, overall childhood mortality could be further reduced.17
Update on 2004 Background Paper, BP 6.22 Pneumonia

The high global burden of pneumonia warrants further investigation in technology innovation in the field of rapid diagnostic tests and in novel vaccines for viral pneumonia. Improved rapid diagnostics at point-of-care along with effective antibiotic treatments would aid in the reduction of pneumonia mortality, while wide-scale implementation of pneumococcal vaccines would help prevent incidences of pneumonia worldwide. Moving forward, research institutions, pharmaceuticals, and small and medium enterprises must work alongside government and funders to create initiatives for the development of novel medical devices and biologics. The constant and unpredictable nature of pneumococcal pathogens can outpace technological and drug development, thus it is crucial for researchers and innovators to continue to make progress in research and development of pharmaceuticals and non-pharmaceuticals interventions.

References


Recommendations for management of common childhood conditions: Newborn conditions, dysentery, pneumonia, oxygen use and delivery, common causes of fever, sev er acute malnutrition and supportive care. WHO, 2012.


Update on 2004 Background Paper, BP 6.22 Pneumonia


Annexes


Annex 6.22.3: Mortality for all ages due to pneumococcal disease by European regions and the world, 2010.

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Annex 6.22.6: Pneumococcal conjugate vaccine in preventing all-serotypes invasive pneumococcal disease in children <24 months

Annex 6.22.7: Pneumococcal conjugate vaccine in preventing clinical pneumonia in children <24 months

Annex 6.22.8: Comparative effectiveness of antibiotics on community-acquired pneumonia deaths in children under 18 years of age

Annex 6.22.9: Global mortality for all causes of death and pneumonia by age groups, 2010.

Annex 6.22.10: Death rates caused by pneumonia in the world by age group, 2010

Annex 6.22.11: DALY rates caused by pneumonia in the world by age group, 2010

Annex 6.22.12: Global mortality rates by age group and gender for pneumococcal pneumonia, 2010

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Annex 6.22.14: Death rates caused by pneumonia by gender, age group, and European region, 2010

Annex 6.22.15: DALY rates caused by pneumonia by gender, age group, and region, 2010

Annex 6.22.16: DALY rates caused by pneumonia by gender, age group, and European region, 2010

Annex 6.22.17: Death rates by pneumococcal pneumonia, Hib, and RSV, and region, 2010

<table>
<thead>
<tr>
<th>Year</th>
<th>Global mortality for all causes of death</th>
<th>Global mortality due to pneumonia</th>
<th>Deaths under five for all causes</th>
<th>Deaths under five due to pneumonia</th>
<th>Percentage total pneumonia deaths for children under five of the total global mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>93 022 392</td>
<td>4 000 312</td>
<td>11 559 494</td>
<td>1 348 153</td>
<td>33.7</td>
</tr>
<tr>
<td>2005</td>
<td>103 326 074</td>
<td>3 057 075</td>
<td>7 842 254</td>
<td>705 716</td>
<td>23.1</td>
</tr>
<tr>
<td>2010</td>
<td>105 539 348</td>
<td>2 921 420</td>
<td>6 841 199</td>
<td>585 125</td>
<td>20.0</td>
</tr>
</tbody>
</table>

Source: Institute of Health Metrics and Evaluation (IHME).


<table>
<thead>
<tr>
<th>Region</th>
<th>Under five deaths due to pneumonia</th>
<th>Percentage total pneumonia deaths for children under five of the total global mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global</td>
<td>585 125</td>
<td>-</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>252 970</td>
<td>43.2</td>
</tr>
<tr>
<td>South Asia</td>
<td>220 287</td>
<td>37.6</td>
</tr>
<tr>
<td>Europe</td>
<td>3 154</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Source: Institute of Health Metrics and Evaluation (IHME).
Annex 6.22.3: Mortality for all ages due to pneumococcal disease by European regions and the world, 2010.

<table>
<thead>
<tr>
<th>Region</th>
<th>Disease</th>
<th>Moralties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global</td>
<td>Pneumococcal pneumonia</td>
<td>827 316</td>
</tr>
<tr>
<td></td>
<td>Hib</td>
<td>379 857</td>
</tr>
<tr>
<td></td>
<td>RSV</td>
<td>253 537</td>
</tr>
<tr>
<td>Central Europe</td>
<td>Pneumococcal pneumonia</td>
<td>10 659</td>
</tr>
<tr>
<td></td>
<td>Hib</td>
<td>3 153</td>
</tr>
<tr>
<td></td>
<td>RSV</td>
<td>647</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>Pneumococcal pneumonia</td>
<td>13 755</td>
</tr>
<tr>
<td></td>
<td>Hib</td>
<td>6 454</td>
</tr>
<tr>
<td></td>
<td>RSV</td>
<td>969</td>
</tr>
<tr>
<td>Western Europe</td>
<td>Pneumococcal pneumonia</td>
<td>66 741</td>
</tr>
<tr>
<td></td>
<td>Hib</td>
<td>9,442</td>
</tr>
<tr>
<td></td>
<td>RSV</td>
<td>1,584</td>
</tr>
</tbody>
</table>

Source: Institute of Health Metrics and Evaluation (IHME).
Annex 6.22.4: Comparative effectiveness of antibiotics on community-acquired pneumonia death in children under 18 years of age.

### Comparative effectiveness of antibiotics on community-acquired pneumonia deaths in children under 18 years of age

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Odds Ratio</th>
<th>Study Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin vs. penicillin (1)</td>
<td>0.07</td>
<td>1965 children aged three months to 59 months</td>
</tr>
<tr>
<td>Amoxicillin with IV ampicillin (2)</td>
<td>0.25</td>
<td>2037 children between three to 59 months</td>
</tr>
<tr>
<td>Chloramphenicol vs. penicillin (3)</td>
<td>1.25</td>
<td>1116 children aged one month to five years</td>
</tr>
<tr>
<td>Chloramphenicol + gentamicin (4)</td>
<td>1.65</td>
<td>988 children between two to 59 months</td>
</tr>
<tr>
<td>Chloramphenicol + penicillin (5)</td>
<td>0.73</td>
<td>748 children</td>
</tr>
</tbody>
</table>

Odds Ratio >1 favors the intervention (less deaths due to pneumonia).

Clinical pneumonia: an infection that can occur in a child's lung.

Annex 6.22.5: Pneumococcal conjugate vaccine in preventing vaccine-serotypes invasive pneumococcal disease in children <24 months

![Graph showing the effectiveness of pneumococcal conjugate vaccine in preventing invasive pneumococcal disease in children <24 months.](Image)

Outcome: Vaccine-serotypes invasive pneumococcal disease (VT-PCV)
Risk Ratio: Relative risk less than 1 favors the intervention (less VT-PCV)
PCV7 serotypes include: 4, 6B, 9V, 14, 18C, 19F, 23F.
PCV13 serotypes include: 4, 6B, 9V, 14, 18C, 19F, 22F, 11A, 23F.
Source: Lucero et al. Cochrane Database of Systematic Reviews, 2009

Annex 6.22.6: Pneumococcal conjugate vaccine in preventing all-serotypes invasive pneumococcal disease in children <24 months

[Diagram showing relative risk and outcomes for different vaccine types and control groups, with references listed at the bottom of the diagram.]
Annex 6.22.7: Pneumococcal conjugate vaccine in preventing clinical pneumonia in children <24 months

Pneumococcal Conjugate Vaccine in preventing clinical pneumonia in children <24 months

Outcome: Clinical pneumonia
Risk Ratio or Relative Risk: less than 1 favors the intervention (less X-ray defined pneumonia)
Clinical pneumonia: an infection that can occur in a child’s lung
Annex 6.22.8: Comparative effectiveness of antibiotics on community-acquired pneumonia deaths in children under 18 years of age

**Comparative effectiveness of antibiotics on community-acquired pneumonia deaths in children under 18 years of age**

- Amoxicillin vs. penicillin [1]
- Aminopenicillin vs. amoxicillin [2]
- Chloramphenicol vs. ampicillin + gentamicin [3]
- Chloramphenicol vs. ampicillin + gentamicin [4]
- Chloramphenicol vs. chloramphenicol + penicillin [5]

Outcome: Deaths
Odds Ratio < 1 favors the intervention (less deaths due to pneumonia)
Clinical pneumonia: an infection that occurs in a child's lung


- [1] 1065 children aged three months to 59 months
- [2] 207 children between three to 59 months
- [3] 1116 children aged one month to five years
- [4] 958 children between two to 59 months
- [5] 744 children

6.22-47
Annex 6.22.9: Global mortality for all causes of death and pneumonia by age groups, 2010.

<table>
<thead>
<tr>
<th>All causes of mortality</th>
<th>All age groups</th>
<th>Under 5</th>
<th>5-9 years</th>
<th>Adolescents (10-19)</th>
<th>Adults (20-64)</th>
<th>65+</th>
</tr>
</thead>
<tbody>
<tr>
<td>All causes of mortality</td>
<td>52 769 679</td>
<td>13 682 307</td>
<td>453 051</td>
<td>1 075 214</td>
<td>17 750 910</td>
<td>26 649 295</td>
</tr>
<tr>
<td>Mortalities due to pneumonia</td>
<td>2 921 422</td>
<td>585 125</td>
<td>14 423</td>
<td>17 240</td>
<td>237 276</td>
<td>606 646</td>
</tr>
</tbody>
</table>

Source: Institute of Health Metrics and Evaluation (IHME).

Annex 6.22.10: Death rates caused by pneumonia in the world by age group, 2010

Source: Institute of Health Metrics and Evaluation 2010
Annex 6.22.11: DALY rates caused by pneumonia in the world by age group, 2010

Source: Institute of Health Metrics and Evaluation (IHME).
Annex 6.22.12: Global mortality rates by age group and gender for pneumococcal pneumonia, 2010

Source: Institute of Health Metrics and Evaluation 2010
Annex 6.22.13: Death rates caused by pneumonia by gender, age group, and region, 2010

Source: Institute of Health Metrics and Evaluation 2010
Annex 6.22.14: Death rates caused by pneumonia by gender, age group, and European region, 2010

Source: Institute of Health Metrics and Evaluation 2010
Annex 6.22.15: DALY rates caused by pneumonia by gender, age group, and region, 2010

Source: Institute of Health Metrics and Evaluation 2010
Annex 6.22.16: DALY rates caused by pneumonia by gender, age group, and European region, 2010

Source: Institute of Health Metrics and Evaluation 2010
Annex 6.22.17: Death rates by pneumococcal pneumonia, Hib, and RSV, and region, 2010

Source: Institute of Health Metrics and Evaluation 2010