# Epidemiology and etiology of childhood pneumonia

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**Abstract** Childhood pneumonia is the leading single cause of mortality in children aged less than 5 years. The incidence in this age group is estimated to be 0.29 episodes per child-year in developing and 0.05 episodes per child-year in developed countries. This translates into about 156 million new episodes each year worldwide, of which 151 million episodes are in the developing world. Most cases occur in India (43 million), China (21 million) and Pakistan (10 million), with additional high numbers in Bangladesh, Indonesia and Nigeria (6 million each). Of all community cases, 7–13% are severe enough to be life-threatening and require hospitalization. Substantial evidence revealed that the leading risk factors contributing to pneumonia incidence are lack of exclusive breastfeeding, undernutrition, indoor air pollution, low birth weight, crowding and lack of measles immunization. Pneumonia is responsible for about 19% of all deaths in children aged less than 5 years, of which more than 70% take place in sub-Saharan Africa and south-east Asia. Although based on limited available evidence, recent studies have identified *Streptococcus pneumoniae*, *Haemophilus influenzae* and respiratory syncytial virus as the main pathogens associated with childhood pneumonia.

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*Une traduction en français de ce résumé figure à la fin de l'article.* *Al final del artículo se facilita una traducción al español.* الترجمة العربية لهذه الخلاصة في نهاية النص الكامل لهذه المقالة.

## Introduction

In the early 1970s Cockburn & Assaad[1] generated one of the earliest estimates of the worldwide burden of communicable diseases. In a subsequent review, Bulla & Hitze[2] described the substantial burden of acute respiratory infections and, in the following decade, with data from 39 countries, Leowski[3] estimated that acute respiratory infections caused 4 million child deaths each year – 2.6 million in infants (0–1 years) and 1.4 million in children aged 1–4 years. In the 1990s, also making use of available international data, Garenne et al.[4] further refined these estimates by modelling the association between all-cause mortality in children aged less than 5 years and the proportion of deaths attributable to acute respiratory infection. Results revealed that between one-fifth and one-third of deaths in preschool children were due to or associated with acute respiratory infection. The 1993 World Development Report[5] produced figures showing that acute respiratory infection caused 30% of all childhood deaths.

The increasing focus on the reduction of child mortality arising from the Millennium Declaration and from the Millennium Development Goal (MDG) 4 of "reducing by two-thirds, between 1990 and 2015, the under-five mortality rate",[6] has generated renewed interest in the development of more accurate assessments of the number of deaths in children aged less than 5 years by cause. Moreover, the monitoring of the coverage of interventions to control these deaths has become crucial if MDG 4 is to be achieved; thus a more accurate establishment of the causes of deaths in children aged less than 5 years becomes crucial. In 2001, WHO established the Child Health Epidemiology Reference Group (CHERG) – a group of independent technical experts, to systematically review and improve data collection, methods and assumptions underlying the estimates of the distribution of the main causes of death for the year 2000. In this paper, we summarize the findings of this group on the morbidity and mortality burden of childhood pneumonia. We also provide new regional and country pneumonia morbidity estimates for the year 2000, and review the current understanding of the distribution of the main etiological agents of pneumonia among children aged less than 5 years.

## Search strategy and selection criteria

Most of the morbidity and mortality estimates in this paper are based on work published by CHERG's pneumonia working group.[7,8] As a first step, the group reviewed publications on childhood pneumonia and created a database including more than 2200 sources of information. Further details on the literature search strategies, inclusion criteria, methods and models used for estimating pneumonia burden were published elsewhere.[7–9] However, the results of the distribution of global pneumonia episodes by regions and countries with the prevalence of exposure to main risk factors have not yet been published. Thus, we present the details on methods and models used for estimating these disaggregated figures in Appendix A (available at: http://www.who.int/bulletin/volumes/86/5/07-048769/en/index.html).[10–27]

### Incidence of clinical pneumonia

Rudan et al.[8] calculated and published the first global estimate of the incidence of clinical pneumonia in children aged

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less than 5 years for the year 2000. This estimate was based on the analysis of data from selected 28 community-based longitudinal studies done in developing countries that were published between 1969 and 1999. These studies were the only sources meeting the predefined set of minimum-quality criteria for inclusion in the analysis.[8] The estimated median incidence for developing countries was 0.28 episodes per child-year, with an interquartile range 0.21–0.71 episodes per child-year.[8] The variation in incidence between the selected studies was very large, most probably due to the distinct study designs and real differences in the prevalence of risk factors in the various study settings. Given the substantial uncertainty over the point estimate, we used a triangular approach to check for plausibility of our assessment of pneumonia incidence. The ranges obtained by the main appraisal and two ancillary assessments overlapped between the values of 148 and 161 million new episodes per year. Giving most weight to the estimate obtained through the main approach, the analyses suggested that the incidence of clinical pneumonia in children aged less than 5 years in developing countries worldwide (WHO regions B, D and E; see Annex A) is close to 0.29 episodes per child-year. This equates to 151.8 million new cases every year, 13.1 million (interquartile range: 10.6–19.6 million) or 8.7% (7–13%) of which are severe enough to require hospitalization.[8] In addition, a further 4 million cases occur in developed countries worldwide (all WHO regions A and Europe regions B and C). The regions and their populations are defined by WHO region and child and adult mortality stratum (Table 1 and the statistical annex of *World Health Report 2000*, available: at http://www.who.int/whr2001/2001/archives/2000/en/pdf/Statistical_Annex.pdf).[22]

It is of major public health interest to assess the distribution of these estimated 156 million episodes by regions and countries to assist planning for preventive interventions and case management at community and facility levels, including vaccine and antibiotic needs and delivery. Therefore, we calculated these figures with the model described in Appendix A. Table 2 shows the 15 countries with the highest predicted number of new pneumonia episodes and their respective incidence. These 15 countries account for 74% (115.3 million episodes) of the estimated 156 million global episodes. More than half of the world's annual new pneumonia cases are concentrated in just five countries where 44% of the world's children aged less than 5 years live: India (43 million), China (21 million) and Pakistan (10 million) and in Bangladesh, Indonesia and Nigeria (6 million each). Differences in incidence of childhood clinical pneumonia in the world at the country level are shown in Fig. 1.

Table 1. **Estimates of incidence and number of new cases per year of clinical pneumonia in children aged less than 5 years, by WHO region**[a]

| WHO region | Total population aged 0–4 years (millions) | Estimated incidence (e/cy) | Estimated no. of new cases per year (millions) |
|---|---|---|---|
| African | 105.62 | 0.33 | 35.13 |
| Americas | 75.78 | 0.10 | 7.84 |
| Eastern Mediterranean | 69.77 | 0.28 | 19.67 |
| European | 51.96 | 0.06 | 3.03 |
| South-East Asia | 168.74 | 0.36 | 60.95 |
| Western Pacific | 133.05 | 0.22 | 29.07 |
| Total (developing countries) | 523.31 | 0.29 | 151.76 |
| Total (developed countries) | 81.61 | 0.05 | 4.08 |
| Total | 604.93 | 0.26 | 155.84 |

e/cy, episodes per child-year.
[a] Up to 10% of all new cases may progress to severe episodes and require hospitalization.

Country estimates of the number of clinical pneumonia cases among children aged less than 5 years were assembled into six WHO regions (African Region, Region of the Americas, South-East Asia Region, European Region, Eastern Mediterranean Region and Western Pacific Region) as well as into developing and developed regions. These aggregated results together with estimates of new episodes per child-year and the number of severe episodes are shown in Table 1. Estimates of clinical pneumonia incidence are highest in South-East Asia (0.36 episodes per child-year), closely followed by Africa (0.33 episodes per child-year) and by the Eastern Mediterranean (0.28 episodes per child-year), and lowest in the Western Pacific (0.22 episodes per child-year), the Americas (0.10 episodes per child-year) and European Regions (0.06 episodes per child-year).

We explored the plausibility of the model estimates by computing incidence for more extreme values of risk-factor prevalence. When prevalence of exposure was set to 1% (an idealized scenario roughly similar to that in the most developed countries of the world), the incidence computed by the model was less than 0.05 episodes per child-year. This estimate is lower than those reported in two classic reports of clinical pneumonia incidence among children in the United States of America and in the United Kingdom in the 1970s and 1980s, respectively, and is close to our current estimate for the year 2000 for the European Region.[28,29] When the prevalence of exposure was set to 99% (an unrealistic scenario at the country level, even for the poorest countries of the world) the incidence computed by the model was about 0.77 episodes per child-year. This estimate is slightly above the upper limit of individually reported pneumonia incidence from the 28 community-based studies from the developing world (75% interquartile range estimate of 0.71 episodes per child-year). The model yields plausible estimates over a wide range of values of risk-factor prevalence, supporting its use for calculating the distribution of clinical pneumonia episodes.

## Under-five mortality

Several attempts to understand worldwide child pneumonia mortality have been made over the past 30 years.[3–5,7,30] Despite the difficulties of producing estimates with available evidence, pneumonia has consistently been estimated as the leading single cause of childhood mortality. Some of the complexities for developing these estimates include large differences in case definition of pneumonia between studies, low specificity

of verbal autopsies in community-based studies, the fact that similar symptoms from both pneumonia and malaria lead to death, difficulties in distinguishing pneumonia from sepsis in neonates and the synergy between several disorders leading to a single death.[31]

Two recent estimates of the total number of deaths due to clinical pneumonia have been made by CHERG. A single-cause model derived from 40 studies published between 1961 and 2000 and based on the relationship between the proportional mortality due to respiratory infections and the overall mortality in children aged less than 5 years, estimated the number of deaths attributable to childhood pneumonia to be 1.9 million in 2000.[7] However, the data sources used to model the relationship between pneumonia proportional mortality and all-cause mortality were not representative of the whole world as most of the studies were from Latin America and only a few data points were from countries with very high all-cause mortality. Moreover, many of them had been done more than three decades ago, in the 1960s and 1970s. A multiple-cause model that analysed 38 more recent studies (average midstudy surveillance year of 1990) from sub-Saharan Africa and south Asia, in countries with mortality rates for children aged less than 5 years of at least 26 per 1000 live births, predicted a similar number of deaths attributable to pneumonia (i.e. approximately 1.8 million under-5 pneumonia deaths in these two regions in the year 2000).[32]

Some evidence suggests, however, that both models underestimate the number of deaths attributable to clinical pneumonia in children aged less than 5 years. Many neonatal deaths have been attributed to severe infections[33] that have not been taken into account in these models (Fig. 2). The exact proportion of pneumonia among these infections has not been clearly established because of the difficulties in distinguishing causes among severe infections in newborns. However, at least another 300 000 deaths caused by pneumonia are likely to occur worldwide during the neonatal period (Lawn J, personal communication).

The interquartile range for available case-fatality ratios was 1.3–2.6%, leading to an estimated 1.96–3.92 million expected deaths from pneumonia per year based on the basis of observed incidence.[8] Therefore, two lines of evidence both indicate that there are more than 2 million deaths due to pneumonia each year in children aged less than 5 years.

Table 2. **The 15 countries with the highest estimated absolute number of new cases of clinical pneumonia**

| Country | Predicted no. of new cases (millions) | Estimated incidence (e/cy) |
|---|---|---|
| India | 43.0 | 0.37 |
| China | 21.1 | 0.22 |
| Pakistan | 9.8 | 0.41 |
| Bangladesh | 6.4 | 0.41 |
| Nigeria | 6.1 | 0.34 |
| Indonesia | 6.0 | 0.28 |
| Ethiopia | 3.9 | 0.35 |
| Democratic Republic of the Congo | 3.9 | 0.39 |
| Viet Nam | 2.9 | 0.35 |
| Philippines | 2.7 | 0.27 |
| Sudan | 2.0 | 0.48 |
| Afghanistan | 2.0 | 0.45 |
| United Republic of Tanzania | 1.9 | 0.33 |
| Myanmar | 1.8 | 0.43 |
| Brazil | 1.8 | 0.11 |

e/cy, episodes per child-year.

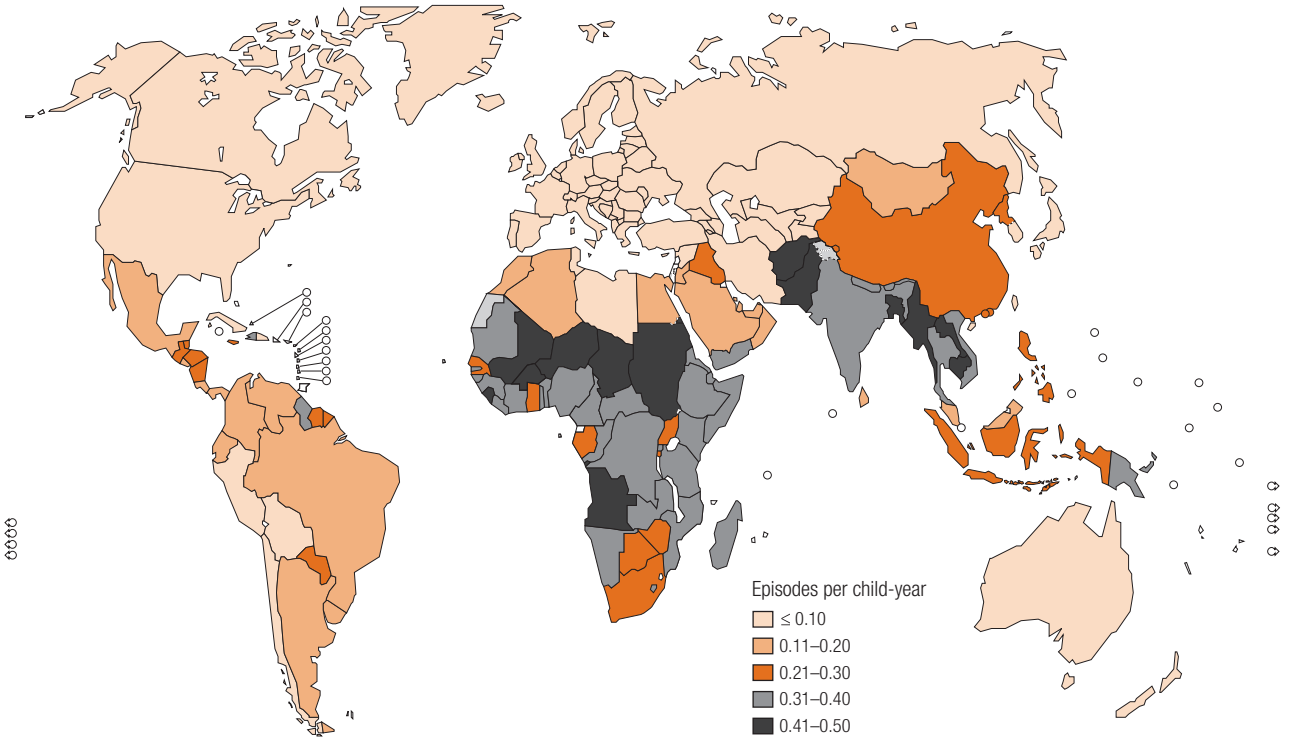
The relative importance of the different causes of death in children aged less than 5 years varies across regions of the world, although the major causes, such as pneumonia, remain the same (Fig. 2). As with the incidence of pneumonia, mortality is unequally distributed.[6] The proportion of pneumonia-attributed deaths varies widely between WHO regions and significantly increases in relative importance in regions that have inefficient health systems (Fig. 2).

The African Region has, in general, the highest burden of global child mortality (Fig. 2). Although it comprises about 20% of the world's population of children aged less than 5 years,[22] it has about 45% of global under-5 deaths and 50% of worldwide deaths from pneumonia in this age group.[34] By contrast, less than 2% of these deaths take place in the European Region and less than 3% in the Region of the Americas. More than 90% of all deaths due to pneumonia in children aged less than 5 years take place in 40 countries. Even more striking is the fact that, according to the official estimates from WHO for the year 2000, two-thirds of all these deaths are concentrated in just 10 countries[34]: India (408 000 deaths), Nigeria (204 000), the Democratic Republic of the Congo (126 000), Ethiopia (112 000), Pakistan (91 000), Afghanistan (87 000), China (74 000), Bangladesh (50 000), Angola (47 000) and Niger (46 000; Table 3).

Although the absolute number of deaths provides important information regarding the global magnitude of the problem, it does not take into account the size of the population at risk and hence does not reflect the risk of death. For instance, while China has the seventh highest absolute number of pneumonia deaths in children aged less than 5 years, the mortality is about 8.6 per 10 000, whereas several countries have rates above 100 per 10 000.

Beyond inter-country inequities, further critical inequities are present within countries, where children from the poorest families, living in rural areas and whose mothers are less educated, are those more likely to die from pneumonia. Data on the distribution of causes of death within countries from the demographic and health surveys done in Bangladesh in 2004 show differentials in mortality due to acute respiratory infections by divisions, place of residence (rural/urban) and mother's education. Deaths due to acute respiratory infections were proportionately more common in the Sylhet division and least common in Rajshahi, with a 1.4-fold difference between the two. These infections were also a more common cause of death in rural (22.3%)

Fig. 1. **Incidence of childhood clinical pneumonia at the country level**




than in urban (16.8%) areas. Furthermore, acute respiratory infection was associated with a large proportion of deaths among children of mothers with no education.[35]

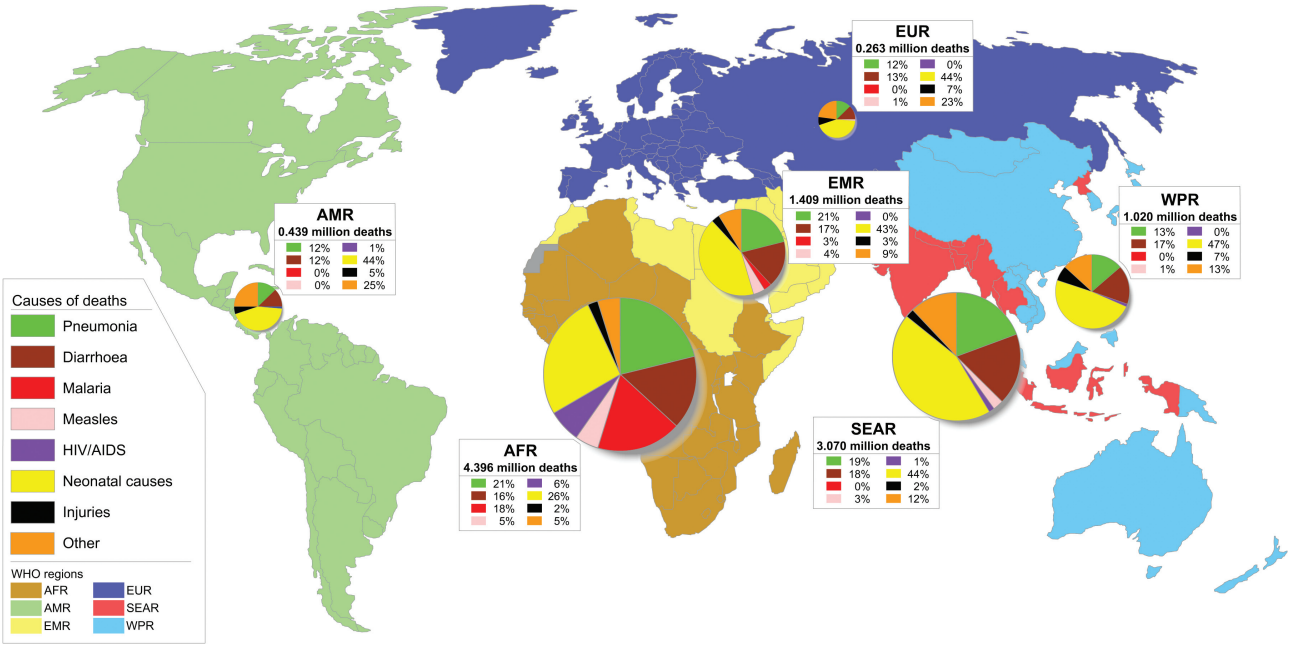
## Causes of pneumonia in children

Childhood clinical pneumonia is caused by a combination of exposure to risk factors related to the host, the environment and infection. To identify the former two categories of causal factors for development of pneumonia at the community level, we used the methods described in steps 2–4 of Appendix A. We then established the following categories of risk factors for childhood pneumonia: definite (most evidence consistently pointing to the role of the risk factor); likely (most evidence consistently pointing to the role, but with some opposing findings; or scarce but consistent evidence of the role); and possible (with sporadic and inconsistent reports of the role in some contexts). These risk factors for development of pneumonia, related to the host or the environment, are listed in Box 1. In the remainder of this paper, we discuss etiological agents associated with childhood pneumonia.

Before vaccines were available, the cause of childhood pneumonia was a matter of great interest as specific therapy was available for pneumococcal pneumonia of certain serotypes, requiring not only an etiological diagnosis for effective therapy, but also pneumococcal serotyping. Studies from that era identified *Streptococcus pneumoniae* (pneumococcus) and *Haemophilus influenzae* as the main bacterial causes of pneumonia, with some severe cases caused by *Staphylococcus aureus* and *Klebsiella pneumoniae*.[36] In the modern era, our understanding of the causes of pneumonia in developing countries is based on two types of study. The first type consists of prospective hospital-based studies that have relied on blood cultures and, in some studies, of percutaneous lung aspiration.[37] Some other studies also examined nasopharyngeal specimens for virus identification.[38] This approach lacks sensitivity for the identification of bacterial cause. Attempts to augment culture-based methods with various indirect markers of bacterial cause have been largely unsuccessful as the tests employed have been unable to distinguish between carriage of pneumococcus and *H. influenzae*, which is usual for children in developing countries, and invasive disease.[39] The second type of study is the vaccine trial, in which the burden of pneumonia prevented by a specific vaccine is presumed to be a minimum estimate of the burden of pneumonia due to the organism against which the vaccine is directed.[40]

In prospective, microbiology-based studies, the leading bacterial cause is pneumococcus, being identified in 30–50% of pneumonia cases.[36,37,41–45] The second most common organism isolated in most studies is *H. influenzae* type b (Hib; 10–30% of cases), followed by *S. aureus* and *K. pneumoniae*. In addition, lung aspirate studies have identified a significant fraction of acute pneumonia cases to be due to *Mycobacterium tuberculosis*, which is notoriously difficult to identify in children.[45] Controversy surrounds the role of three important organisms, non-typable *H. influenzae* (NTHI), *S. aureus* and non-typhoid *Salmonella* spp. NTHI was found to be an important pathogen in a lung aspirate study from Papua New Guinea,[43] whereas in a series of lung aspirate studies from the Gambia, and in most blood culture-based studies, Hib was the main type of *H. influenzae* identified.[37] Studies from Pakistan found NTHI to be a common blood culture isolate,[46,47] but this has not been replicated elsewhere. The first major study of the modern era that used

Fig. 2. **Distribution of deaths from pneumonia and other causes in children aged less than 5 years, by WHO region**




AFR, African Region; AMR, Americas Region; EMR, Eastern Mediterranean Region; EUR, European Region; SEAR, South-East Asia Region; WPR, Western Pacific Region.

lung aspiration on over 500 children in Chile, including normal controls, found *S. aureus* to be the main pathogen.[48] This finding has not been replicated in more recent studies, although a recently completed WHO study of very severe (hypoxaemic) pneumonia in seven countries found *S. aureus* in 47 of the 112 cases (42% of cases) in which a bacterium was identified, making it the second largest cause.[49] The role of non-typhoid *Salmonella* spp. is also unclear. Studies from Africa have shown bacteraemia caused by non-typhoid *Salmonella* spp. to be common[50,51] and often associated with malaria. Although the work of Graham et al.[52] in Malawi has implicated non-typhoid *Salmonella* spp. in radiological pneumonia cases, the role of these organisms in pneumonia is still unclear, as blood-culture studies have focused on children with fever and fast breathing and, therefore, may have identified children with bacteraemia only.[53]

The two causes of bacterial pneumonia that are vaccine-preventable are Hib and pneumococcus.[54–60] In both cases, the vaccines will prevent most pneumonia due to each pathogen, and microbiological methods will detect only a few cases. Thus, the vaccine probe concept has emerged to describe studies that are designed to determine the burden of pneumonia that can be prevented by the vaccine, and is therefore attributable to the organism. These studies have used the WHO definition of radiological pneumonia as the main outcome. For Hib, two randomized controlled trials,[54,55] one open trial,[56] a case–control study with random allocation of vaccine[57] and several other case–control studies have led to the conclusion that, in developing countries with a high burden of pneumonia, 15–30% of radiological pneumonia cases, and probably the same proportion of pneumonia deaths, are due to Hib. For pneumococcus, three randomized controlled trials in developing countries have shown that the nine-valent pneumococcal conjugate vaccine can prevent 20–35% of radiological pneumonia cases and probably a similar proportion of pneumonia deaths.[58–60] The newer pneumococcal vaccines covering 10–13 serotypes will likely extend this protection considerably. In addition, one of the vaccines contains elements that may prevent non-typable *H. influenzae* pneumonia as well. Thus, future pneumococcal vaccines may prevent 30–50% of radiological and fatal pneumonia. WHO has recently established modelled estimates of the number of pneumonia cases and deaths that are attributable to these organisms on a country-by-country basis. These estimates will be available soon (Kate O'Brien, Thomas Cherian and Maria D Knoll, personal communications).

Pneumonia etiology studies that incorporate viral studies show that respiratory syncytial virus is the leading viral cause, being identified in 15–40% of pneumonia or bronchiolitis cases admitted to hospital in children in developing countries, followed by influenza A and B, parainfluenza, human metapneumovirus and adenovirus.[38,61,62] In the prospective microbiology-based studies, viral causes of pneumonia are identified by rapid diagnostic tests (such as indirect immunofluorescence, enzyme-linked immunosorbent assay, polymerase chain reaction, viral culture on upper respiratory secretions – such as in nasopharyngeal aspirates – or by viral serology in paired samples).[38,61] It will be some time before any of these causes are preventable by routine immunization.

Weber et al.[38] made the most informative overview of respiratory syncytial virus. Because this virus is fragile, it is difficult to detect and its importance is probably underestimated. It was found in substantial frequency in all climatic and geographical areas, with sharp peaks of activity over a period of 2–4 months, but its seasonality varies considerably between regions. The peaks typically occur in the cold season in temperate climates and in the rainy season

in tropical climates. Disease burden estimates from vaccine-probe studies are not yet available as for Hib and pneumococcus, but such data may become available from monoclonal antibody trials, which show high efficacy against severe disease caused by respiratory syncytial virus. Primary respiratory infection by this virus increases the risk of secondary bacterial pneumonia and viral or bacterial coinfection is a common finding in young children with pneumonia in developing countries (approximately 20–30% of episodes).[41,46] Furthermore, episodes of wheezing due to reactive airways are more common after such episodes. Some two-thirds of the episodes are seen in the first year of life, with 1.5–1.8 times greater frequency in boys than in girls. This implies that any vaccination efforts would need to be made early in life. The risk of pneumonia or bronchiolitis caused by respiratory syncytial virus is highest among children aged less than 2 years with the most severe disease occurring in infants aged 3 weeks to 3 months.[63,64] A recent postmortem study of lung tissue samples from 98 Mexican children aged less than 2 years who died of pneumonia, which used nested polymerase chain reactions, showed that 30% were positive for respiratory syncytial virus: 62% of those with histopathological diagnosis of viral pneumonia and 25% with diagnosis of bacterial pneumonia.[65] This study reaffirmed the role of respiratory syncytial virus as a very significant and potentially deadly pathogen that causes childhood pneumonia, both alone and through mixed infections with bacterial causes.

Table 3. **The 15 countries with the highest estimated number of deaths due to clinical pneumonia**

| Country | Predicted no. of deaths (thousands) | Estimated mortality rates (per 10 000 under-five population) |
|---|---|---|
| India | 408 | 32.2 |
| Nigeria | 204 | 84.7 |
| Democratic Republic of the Congo | 126 | 110.1 |
| Ethiopia | 112 | 84.6 |
| Pakistan | 91 | 48.1 |
| Afghanistan | 87 | 185.9 |
| China | 74 | 8.6 |
| Bangladesh | 50 | 26.6 |
| Angola | 47 | 157.1 |
| Niger | 46 | 173.9 |
| Uganda | 38 | 67.6 |
| United Republic of Tanzania | 36 | 52.6 |
| Mali | 32 | 147.8 |
| Kenya | 30 | 50.3 |
| Burkina Faso | 25 | 99.4 |

In recent years, the HIV epidemic has also contributed substantially to increases in incidence and mortality from childhood pneumonia. In children with HIV, bacterial infection remains a major cause of pneumonia mortality, but additional pathogens (e.g. *Pneumocystis jiroveci*) are also found in HIV-infected children,[66,67] while *M. tuberculosis* remains an important cause of pneumonia in children with HIV and uninfected children.[63] Available vaccines have lower efficacy in children infected with HIV, but still protect a significant proportion against disease.[67] Antiretroviral programmes can reduce the incidence and severity of HIV-associated pneumonia in children through the prevention of HIV infection, use of co-trimoxazole prophylaxis and treatment with antiretrovirals.[67]

Other organisms, such as *Mycoplasma pneumoniae*, *Chlamydia* spp., *Pseudomonas* spp., *Escherichia coli*, and measles, varicella, influenza, histoplasmosis and toxoplasmosis, also cause pneumonia. Most of them are not preventable, but immunization against measles, influenza and possibly use of bacille Calmette–Guérin (BCG) have probably contributed substantially to decreasing the pneumonia burden. There are few data on the causes of neonatal pneumonia in developing countries, but studies of neonatal sepsis suggest that these include Gram-negative enteric organisms, particularly *Klebsiella* spp, and Gram-positive organisms, mainly pneumococcus, group b *Streptococcus* and *S. aureus*.[68]

Box 1. **Risk factors related to the host and the environment that affect incidence of childhood clinical pneumonia in the community in developing countries**

**Definite risk factors**

Malnutrition (weight-for-age *z*-score < −2)
Low birth weight (≤ 2500 g)
Non-exclusive breastfeeding (during the first 4 months of life)
Lack of measles immunization (within the first 12 months of life)
Indoor air pollution
Crowding

**Likely risk factors**

Parental smoking
Zinc deficiency
Mother's experience as a caregiver
Concomitant diseases (e.g. diarrhoea, heart disease, asthma)

**Possible risk factors**

Mother's education
Day-care attendance
Rainfall (humidity)
High altitude (cold air)
Vitamin A deficiency
Birth order
Outdoor air pollution

## Conclusions

About 156 million new episodes of childhood clinical pneumonia occurred globally in 2000, more than 95% of them in developing countries. Of all the pneumonia cases occurring in those countries, 8.7% are severe enough to be life-threatening and require hospital admission. About 2 million pneumonia deaths occur each year in children aged less than 5 years, mainly in the African and South-East Asia Regions. The main bacterial causes of clinical pneumonia in developing countries are *S. pneumoniae* and Hib, and the main viral cause is respiratory syncytial virus, but estimates of their relative importance vary in different settings. The only vaccines for the prevention of bacterial pneumonia (excluding pertussis) are Hib and pneumococcal vaccines. Future studies, with new molecular techniques to better detect infections due to the wide range of pathogens, will broaden our understanding of the cause of pneumonia and may highlight which pathogens should be the targets for new vaccines. Despite the lack of data, mainly for the developing regions of the world, morbidity and mortality estimates and the main risk factors presented in this review could contribute to an understanding of the burden of acute lower respiratory infections in children aged less than 5 years in developing countries and to informed care and vaccine policy. ■

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## Résumé

### Epidémiologie et étiologie de la pneumonie chez l'enfant

La pneumonie est la principale cause simple de mortalité chez les enfants de moins de 5 ans. L'incidence dans cette tranche d'âge est estimée à 0,29 épisode/enfant/an dans les pays en développement et à 0,05 épisode/enfant/an dans les pays développés. Il en résulte environ 156 millions de nouveaux épisodes de pneumonie chaque année dans le monde, dont 151 millions dans les pays en développement. La plupart des cas se produisent en Inde (43 millions), en Chine (21 millions), au Pakistan (10 millions) et également en grands nombres au Bengladesh, en Indonésie et au Nigéria (6 million pour chacun de ces pays). Parmi l'ensemble des cas communautaires, 7 à 13 % sont assez graves pour menacer le pronostic vital et nécessiter une hospitalisation. De nombreux éléments ont fait apparaître comme facteurs de risque principaux pour l'incidence de la pneumonie l'absence d'allaitement au sein exclusif, la dénutrition, la pollution de l'air intérieur, le petit poids à la naissance, le surpeuplement et le manque de couverture par la vaccination antirougeoleuse. La pneumonie est responsable d'environ 19 % des décès d'enfants de moins de 5 ans, dont plus de 70 % se produisent en Afrique sub-saharienne et en Asie du Sud-est. Bien que reposant sur les données disponibles limitées, les études récentes ont identifié *Streptococcus pneumonia*, *Haemophilus influenzae* et le virus respiratoire syncytial comme les principaux agents pathogènes associés à la pneumonie de l'enfant.

## Resumen

### Epidemiología y etiología de la neumonía en la niñez

La neumonía es la principal causa única de mortalidad entre los menores de cinco años. Se estima que la incidencia en ese grupo de edad es de 0,29 episodios por niño y año en los países en desarrollo y de 0,05 episodios por niño y año en los países desarrollados. Ello se traduce en unos 156 millones de episodios nuevos cada año en todo el mundo, de los cuales 151 millones se registran en el mundo en desarrollo. La mayoría de los casos se dan en la India (43 millones), China (21 millones), el Pakistán (10 millones), y también presentan cifras altas Bangladesh, Indonesia y Nigeria (6 millones cada uno). De todos los casos comunitarios, un 7%-13% son lo bastante graves para poner en peligro la vida y requerir hospitalización. Numerosos datos demuestran que los principales factores de riesgo de la incidencia de neumonía son la falta de lactancia materna exclusiva, la desnutrición, la contaminación del aire en locales cerrados, el bajo peso al nacer, el hacinamiento y la falta de inmunización contra el sarampión. La neumonía provoca aproximadamente un 19% de todas las defunciones entre los niños menores de cinco años, y más del 70% de esas muertes se producen en el África subsahariana y en Asia sudoriental. Aunque la evidencia disponible es aún limitada, estudios recientes señalan a *Streptococcus pneumoniae*, *Haemophilus influenzae* y el virus sincitial respiratorio como los principales agentes patógenos asociados a la neumonía en la niñez.

## ملخص

### وبائيات ومسببات الالتهاب الرئوي الطفولي

يعدُّ الالتهاب الرئوي الطفولي في طليعة المسببات التي يمكن أن تؤدي لوحدها إلى وفيات الأطفال دون سن الخامسة. وتقدَّر وقوعات هذا المرض في هذه الفئة العمرية بـ 0.29 نوبة لكل طفل – سنة في البلدان النامية، و0.05 نوبة لكل طفل – سنة في البلدان المتقدمة. وهذا يعني وقوع 156 مليون نوبة جديدة كل عام على مستوى العالم، منها 151 مليوناً في العالم النامي. وتقع معظم النوبات في الهند (43 مليونا)، والصين (21 مليونا)، وباكستان (10 ملايين)، مع وقوع أعداد أخرى كبيرة منها في بنغلاديش، وإندونيسيا، ونيجيريا (6 ملايين في كل منها). ويكون 7 – 13% من النوبات التي تقع في المجتمع من الوخامة بما يهدد حياة الطفل المصاب ويتطلب إدخاله المستشفى. وقد أظهرت بينات مؤكدة أن عدم الاقتصار على الإرضاع من الثدي ، ونقص التغذية، وتلوث الهواء داخل المنزل، وانخفاض الوزن عند الولادة ، وازدحام المساكن، ونقص التمنيع ضد الحصبة،كل هذه تمثل عوامل الاختطار الرئيسية التي تسهم في الإصابة بالالتهاب الرئوي. وهذا المرض مسؤول عن نحو 19% من جميع الوفيات بين الأطفال الذين تقل أعمارهم عن خمس سنوات،والتي يقع أكثر من 70% منها في البلدان الأفريقية جنوب الصحراء، وبلدان جنوب شرق آسيا. ولقد أشارت الدراسات الحديثة إلى أن العقدية الرئوية، والمستدمية النزفية، والفيروس المخلوي التنفسي، هي المسببات المرضية الرئيسية المرتبطة بالالتهاب الرئوي الطفولي، رغم محدودية البينات المتوفرة التي ترتكز عليها هذه الدراسات.

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**Corrigendum**

In Volume 86, Number 4, April 2008:

pages 244 and 245, Dr Alejandro Almaguer is the director of the Alternative Medicine Department at Mexico's health ministry, and Dr Hernán Jose García Ramirez is the deputy director. Also, the name of the co-founder of CASA is Nadine Goodman.

Appendix A. **Methods and models used to distribute the estimated total annual number of pneumonia episodes by country and WHO region**[7–27]

| Step | Methods and models |
|---|---|
| Step 1 | The Child Health Epidemiology Reference Group (CHERG) working group on pneumonia did an extensive review of the research on childhood pneumonia that was subsequently synthesized in a database including more than 2200 sources of information. Further details on search strategies, inclusion criteria and methods are published elsewhere.[7–9] |
| Step 2 | A review of the database with 2200 CHERG studies identified risk factors for pneumonia at the community level. Only studies that investigated the role of several risk factors at the same time at the community level using a multivariate design and that included more than 500 children were initially used to establish definite, likely and possible risk factors. This step was needed to avoid confounding issues and publication bias typical of studies that use univariate design, study a single risk factor or are simply based on a too-small sample and lack power. |
| Step 3 | Four studies were identified[10–13] and several other methodologically sound studies were used as supporting evidence.[14–21]<br>On the basis of those studies, we established three categories of risk factors for development of childhood clinical pneumonia in the community. The risk factors were then defined as:<br>(i) definite (the large majority of evidence consistently pointing to the role of the risk factor):<br>malnutrition (weight-for-age *z*-score $< -2$)<br>low birth weight ($\leq$ 2500 g)<br>non-exclusive breastfeeding (during the first 4 months of life)<br>lack of measles immunization within the first 12 months of life<br>indoor air pollution<br>crowding<br>(ii) likely (most evidence consistently pointing to the role, but with some opposing findings; or scarce but consistent evidence of the role):<br>parental smoking<br>zinc deficiency<br>mother's experience as a carer<br>concomitant diseases (e.g. diarrhoea, heart disease, asthma)<br>(iii) possible (with sporadic and inconsistent reports of the role in some contexts):<br>mother's education<br>day-care attendance<br>rainfall (humidity)<br>high altitude (cold air)<br>vitamin-A deficiency<br>birth order<br>outdoor air pollution. |
| Step 4 | We decided to use only the prevalence of exposure to definite risk factors for distributing global number of pneumonia cases by individual countries. However, we decided to exclude measles immunization coverage on two grounds: because the coverage has approached high levels in recent years (while the studies that identified it as an important risk factor were done mainly in the 1980s and 1990s), so this factor is less discriminative than in was several years ago; and because there is no theoretical justification for including it apart from historically serving as a proxy for health system functioning (but this cannot justify its inclusion). |
| Step 5 | After defining five risk factors that will be used to distribute all cases of childhood pneumonia that occur in 1 year globally, this total number was computed. It was derived by:<br>(i) multiplying the number of all children aged less than 5 years living in developing countries (this includes WHO regions AFR D, AFR E, AMR B, AMR D, EMR B, EMR D, SEAR B, SEAR D and WPR B)[a] in the year 2003 with incidence of 0.28 episodes per child-year, as estimated by Rudan et al.;[8]<br>(ii) multiplying the number of all children aged less than 5 years living in the most developed regions of the world (this includes WHO A regions AMR A, EUR A and WPR A) in the year 2003 with incidence of 0.03 episodes per child-year, as estimated by Rudan et al.[8]; the children in EUR B by 0.07 and in EUR C by 0.09;[8] and<br>(iii) adding up all the cases predicted from the first two calculations.<br>National under-5 population information was obtained from the United Nations Population Division.[22] |
| Step 6 | Three parameters were then used to distribute the global number of episodes into regional and national estimates:<br>(i) national under-5 population;[22]<br>(ii) prevalence of five of the definite pneumonia risk factors (underweight, low birth weight, non-exclusive breastfeeding during the first 4 months of life, indoor air pollution, and crowding); and<br>(iii) estimates of relative risks for each of these five risk factors. |

(Appendix A, cont.)

| Step | Methods and models |
|---|---|
| Step 7 | Data on the prevalence of children underweight (weight-for-age z-score < −2), low birth weight (≤ 2500 g), and non-exclusive breastfeeding (during the first 4 months of life) were obtained from the Demographic and Health Surveys (DHS) or from the Multiple Indicators Cluster Surveys (MICS).[23–25] Both DHS and MICS are nationally representative household surveys with large sample sizes, generally carried out every 3–5 years. Together they cover most developing countries and provide data on demographic and health indicators.<br>Data for the prevalence of indoor air pollution were collected from WHO's document: *Indoor air pollution (national burden of disease estimates)*[26] as "percentage of population using solid fuels".<br>Data on crowding prevalence (defined as ≥ 5 people per household) were obtained from national official governmental information retrieved country-by-country from the internet. For the countries where information could not be obtained, national data on the prevalence of exposure to specific risk factors were replaced with the mean value calculated for that particular region.<br>We aimed to collect the information on the prevalence of exposure to these five risk factors for the year 2001–2003.<br>The table below summarizes the availability of data on the prevalence of risk factors used in this analysis for the year 2003 and for developing countries, where more than 95% of pneumonia episodes occur. |

| Risk factors | No. countries with available population-based data on prevalence of exposure | Prevalence of exposure (%) | Estimated number of children aged 0–4 years exposed (million) |
|---|---|---|---|
| Malnutrition (weight-for-age *z*-score < −2) | 98 | 27 | 141 |
| Low birth weight (≤ 2500 g) | 107 | 16 | 83 |
| Non-exclusive breastfeeding (for first 4 months) | 98 | 64 | 337 |
| Indoor air pollution | 117 | 66 | 342 |
| Crowding (≥ 5 people per household) | 52 | 53 | 278 |

| | |
|---|---|
| Step 8 | Estimates of relative risks for each of the five definite risk factors for malnutrition, low birth weight, non-exclusive breastfeeding and crowding were obtained from available studies[10–21] and from Dherani et al. for indoor air pollution (personal communication; review is a part of this theme issue). Relative risk was set to the median of relative risks (or odds ratios) reported in these studies. We ensured that the definitions of risk factors were the same in the studies estimating relative risk as well as in the surveys that measured prevalence of exposure to these risk factors. Relative risks (RR) for the five definite risk factors were applied as follows:<br>- malnutrition (weight-for-age *z*-score < −2), RR = 1.8<br>- low birth weight (≤ 2500 g), RR = 1.4<br>- non-exclusive breastfeeding (during the first 4 months of life), RR = 1.9<br>- indoor air pollution, RR = 1.8<br>- crowding, RR = 1.4 |
| Step 9 | The global number of new episodes of clinical pneumonia was calculated for each developing country with a model based on the epidemiological concept of potential impact fraction[27] as follows:<br>$N_{e/cy} = (Pop_{<5yrs}) \times (Inc._{DevW}) \times \{1 + \Sigma_{(RF=1\rightarrow n)} [(Prev_{RFn} - Prev_{RFnDevW}) \times (RR_{RFn} - 1)]\}$,<br>where $N_{e/cy}$ is the number of new clinical pneumonia episodes per year in each developing country, $Pop_{<5yrs}$ is the population of children less than 5 years in each developing country, $Inc._{DevW}$ is the estimated incidence of clinical pneumonia in the developing world, $Prev_{RFn}$ is the prevalence of exposure to *n*-th risk factor among under-fives in the developing country of interest, $Prev_{RFnDevW}$ is the prevalence of exposure to *n*-th risk factor among under-fives in all developing countries and $RR_{RFn}$ is the relative risk for developing clinical pneumonia associated with the *n*-th risk factor. |
| Step 10 | Cautionary notes on limitations of this approach:<br>(i) In our calculations, we used the child population estimates for the year 2000 and the prevalence of exposures to risk factors relevant to the years 2001–2003; however, the global childhood pneumonia incidence estimate is based mostly on studies conducted in the 1980s and 1990s, and so are relative risks associated with different risk factors.<br>(ii) Prevalence of malnutrition, low birth weight and lack of exclusive breastfeeding mostly comes for MICS and DHS data that were made available in 2003–2004, but relevant to the years 2000–2001; indoor air pollution information comes from the World Bank's source and refers to 2002–2003, while the search of the information for crowding was also done during 2002; we decided that it is most appropriate to present national-level estimates for the year 2000, as these then ensure consistency and complement the papers on global incidence of childhood pneumonia[8] and global mortality from childhood pneumonia.[7]<br>(iii) Our model, described in step nine, does not necessarily assume that the five risk factors are independent, because we applied relative risks derived primarily from the studies of multivariate design; however, it does assume that the magnitude of the five chosen risk factors is constant over the whole range of countries, which may not be the case in different environments with different combinations of risk factor exposures. |

AFR, African Region; AMR, Americas Region; EMR, Eastern Mediterranean Region; EUR, European Region; SEAR, South-East Asia Region; WPR, Western Pacific Region.

[a] WHO regions are subdivided based on child and adult mortality strata: A, very low child and very low adult mortality; B, low child and low adult mortality; C, low child and high adult mortality; D, high child and high adult mortality; E, high child and very high adult mortality.