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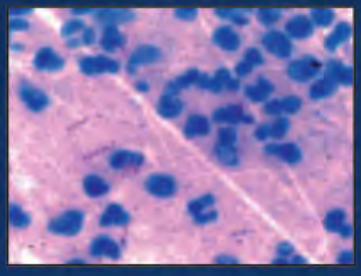

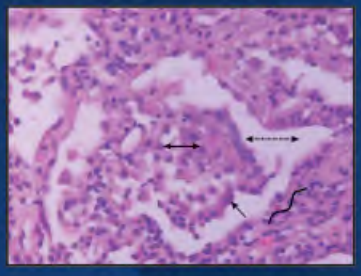

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Epidemiology and Risk Factors of Pneumonia

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ABSTRACT

Pneumonia is a common disorder, which affects all age groups. It is a leading cause of mortality among children. Epidemiology of pneumonia differs among children and adults, and understanding the epidemiology and risk factors of pneumonia is essential for proper diagnosis and management. Pneumonia is classified according to where it is acquired, which correlates with the etiology, severity, and final outcome. Causative organisms differ according to the age of onset as well. Prevalence and incidence of pneumonia vary according to the geographical distribution and seasonal pattern. Several known and unknown risk factors for pneumonia exist, which are important in the overall management and prevention of the disease. Morbidity and mortality of pneumonia is high and is a leading cause of disability-adjusted life years worldwide.

INTRODUCTION

The first recorded description of the symptoms of pneumonia was by Hippocrates, the "Father of Medicine", 2,500 years ago.[1] The burden of pneumonia is well illustrated by the quote of William Osler, who referred the disease as the "captain of the men of death".[2]

An understanding of the epidemiology and risk factors is important for the diagnosis, management, and control of pneumonia. Infective pneumonia, defined as inflammation of one or both lung parenchyma with consolidation due to infective organisms, will be discussed in this chapter. The term lower respiratory tract infection, which is a commonly used term, is not always synonymous with pneumonia and, therefore, not used here.

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The global burden of pneumonia with special reference to South Asia is the main focus of this chapter. The epidemiology of pneumonia in the immunosuppressed, hospital- and ventilator-associated pneumonia (HAP/VAP) and pneumonia in children are discussed briefly under risk factors.

EPIDEMIOLOGY

The etiology, severity, and prognosis of pneumonia depend to a great degree on where it is acquired (Table 1).[3]

Community-acquired pneumonia (CAP) is a leading cause of hospital admission. The microorganisms giving rise to CAP may show geographical variation; however, in general both bacteria and viruses are responsible (Table 2).

Classification based on the site of acquisition is important as the responsible organism varies according to where it was acquired. Results from a large database of culture-positive pneumonia from USA revealed a marked variability of the causative organisms (Figure 1) depending on the type of pneumonia.[4] It is noteworthy that, in this particular study, *Staphylococcus aureus* was the most common organism responsible in each category of pneumonia.

The etiological agent of CAP is an important factor for predicting the disease severity and the level of care warranted (Figure 2).[5] *Pneumococcus (S. pneumoniae)* and multiorganism infection are the most common causes warranting treatment in an intensive care unit (ICU) in CAP.

Table 1: Epidemiological Classification of Pneumonia[3]

Pneumonia category	Definition
Ventilator-associated pneumonia	Pneumonia that arises more than 48–72 hours after endotracheal intubation
Nosocomial pneumonia or hospital-acquired pneumonia	Hospital acquired pneumonia is defined as pneumonia that occurs 48 hours or more after admission, which was not incubating at the time of admission
Healthcare-associated pneumonia	Includes any patient who was hospitalized in an acute care hospital for 2 or more days within the past 90 days of infection; resided in a nursing home or long-term care facility; received recent intravenous antibiotic therapy, chemotherapy, or wound care within the past 30 days of the current infection; or attended a hospital or hemodialysis clinic
Community-acquired pneumonia	An acute infection of the pulmonary parenchyma in a patient who has acquired the infection in the community

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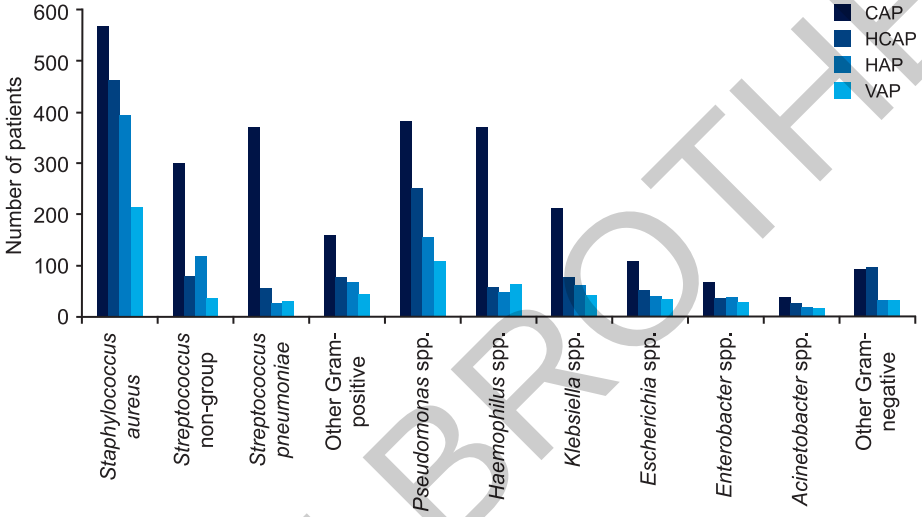
Table 2: Common Causes of Community-acquired Pneumonia in Adults

- *Streptococcus pneumoniae* (*Pneumococcus*)
- *Mycoplasma pneumoniae*
- Other bacteria: *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Legionella pneumophila*, *and S. aureus*
- *Chlamydophila pneumoniae*
- Viruses: influenza, rhinovirus, parainfluenza, and adenovirus



CAP, community-acquired pneumonia; HCAP, healthcare-associated pneumonia; HAP, hospital associated pneumonia; VAP, ventilator acquired pneumonia.

Figure 1: Frequency of occurrence of bacterial pathogens associated with CAP, HCAP, HAP, and VAP.[4]

A multicenter study conducted in Asia had identified common organisms responsible for HAP and VAP (Figure 3), where *Acinetobacter*, *Pseudomonas*, and *Staphylococcus* are the major causative organisms.[6]

Global Burden of Pneumonia

The WHO estimated CAP incidence of 69 per 1,000 among the adult population each for the year 2004, although the exact global incidence is not known. The annual incidence of CAP in adults is between 3 and 13 per 1,000 according to population-based studies.[7] The disease commonly presents acutely, although chronic forms are known.

Pneumonia is common in children aged less than 5 years and becomes progressively more common from 40 years onwards with a peak incidence in the

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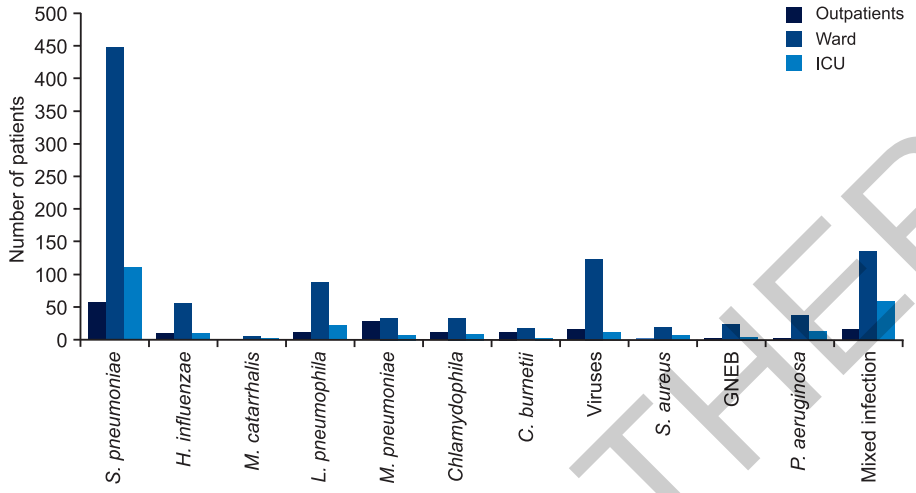
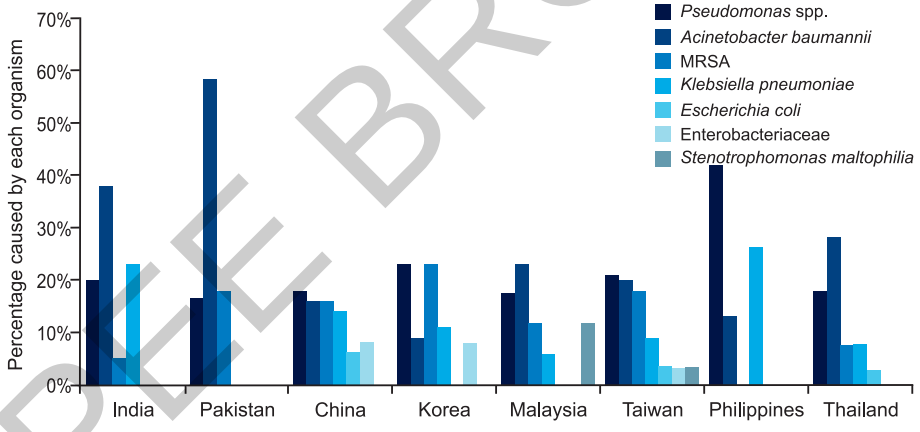


ICU, intensive care unit; GNEB, Gram-negative enterobacteria.

Figure 2: Organisms causing community-acquired pneumonia with percentages.[5]



MRSA, methicillin-resistant *Staphylococcus aureus.*

Figure 3: Common organisms causing hospital-associated pneumonia and ventilator-associated pneumonia in Asia.[6]

very elderly. Pneumonia can affect previously healthy individuals, but susceptibility is greatly increased by a variety of risk factors. The incidence of pneumonia varies around the globe (Figure 4).[8]

This distribution is the result of a complex interrelationship between environment, host, and socioeconomic factors. Poverty, HIV, and drug resistance are major contributors to resurgence of pneumonia.

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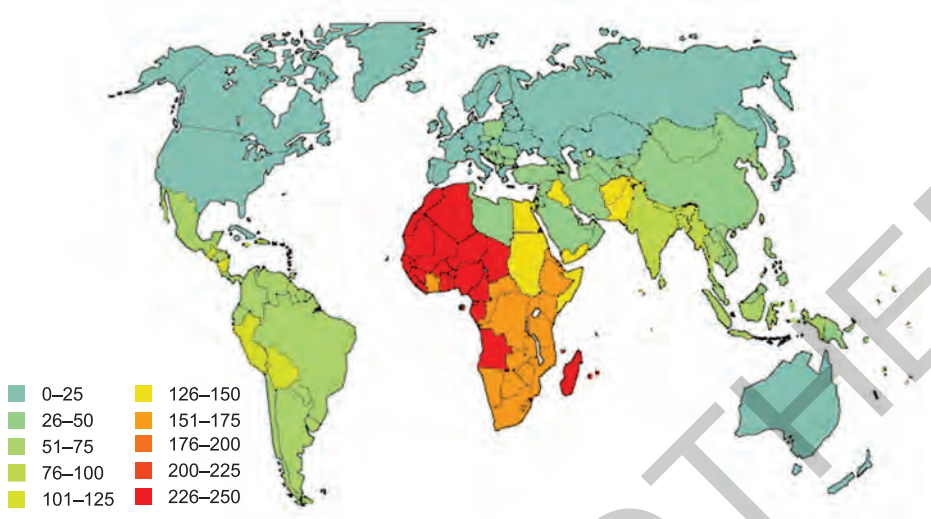

Figure 4: Incidence of pneumonia per 1000 population according to WHO subregions.[8]

The highest incidence of pneumonia in 2004 was is in West Africa with 233 per 1,000 population and the lowest is in Western Europe with 10 per 1,000 population. Approximately 98% of pneumonia cases occur in low income countries. This reflects the higher incidence in lower socioeconomic groups as well, as the fact that 85% of the world population were residing in lower income countries.[8]

Pneumonia in tropical countries occurs throughout the year; however, there is an increase in incidence with rainfall, especially for influenza and melioidosis. In the temperate countries, the peak incidence of pneumonia is in winter months. However, *Legionella* pneumonia tends to occur more frequently when the temperatures are warmer. The prevalence of malnutrition and micronutrient deficiency, such as zinc also contributes to geographic variation. The rates of pneumonia are higher in men than in women and in Blacks compared with Caucasians.

The economic burden of pneumonia is colossal, and, in USA, the total medical and indirect costs, including lost work and productivity due to pneumonia added up to more than $40 billion in 2005.[9] The global disability due to pneumonia as illustrated by disability-adjusted life years is shown in figure 5.

Pneumonia caused 4.2 million deaths throughout the world in 2004 and was the cause for 7.1% of all deaths and was the third most common cause of mortality after cardiovascular and cerebrovascular disease. Mortality of pneumonia varies according to the place of acquisition (Figure 6).[4]

Even in the Asian countries, VAP and HAP present a significant health burden with high mortality rates due to HAP and even higher mortality rates for VAP.

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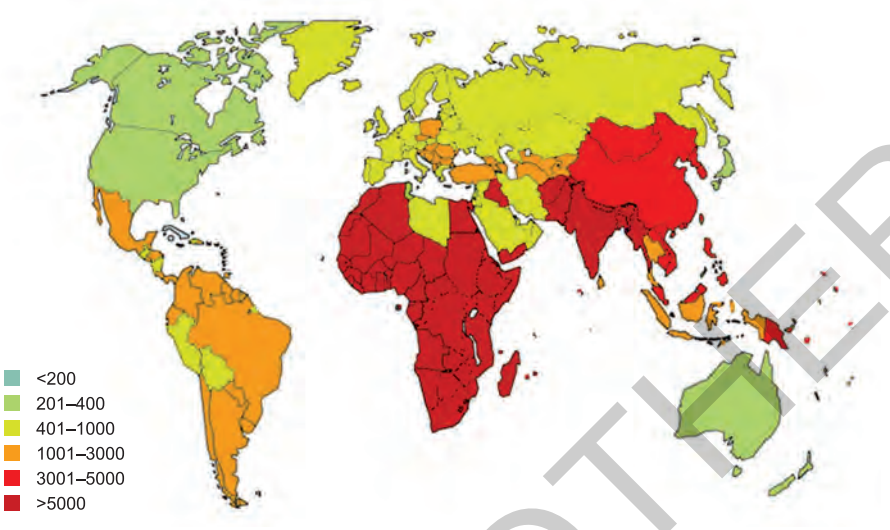

Figure 5: Pneumonia disability-adjusted life years rate (DALYs per 1,000) according to WHO subregions, 2004.[8]

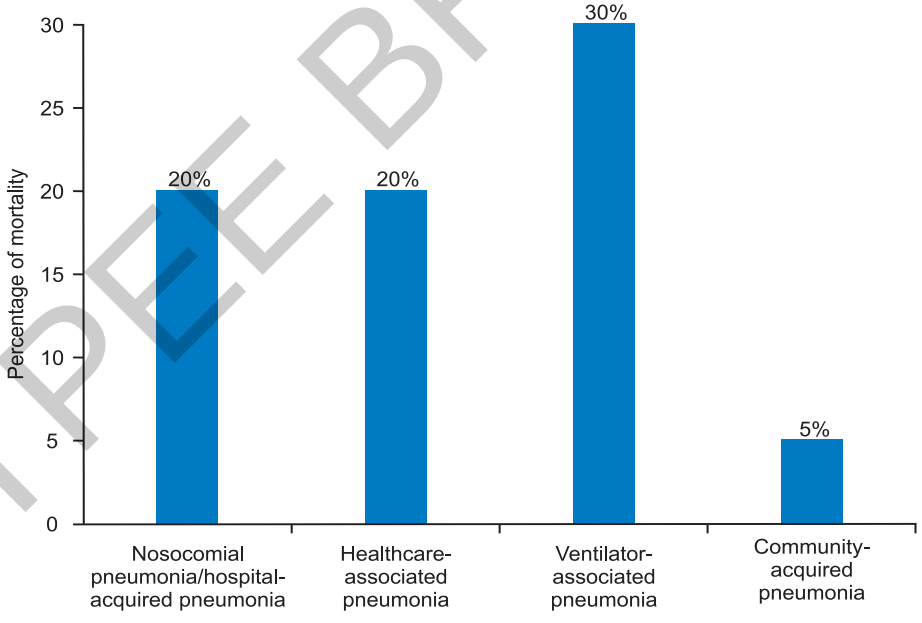

Figure 6: Mortality of pneumonia in different category.[4]

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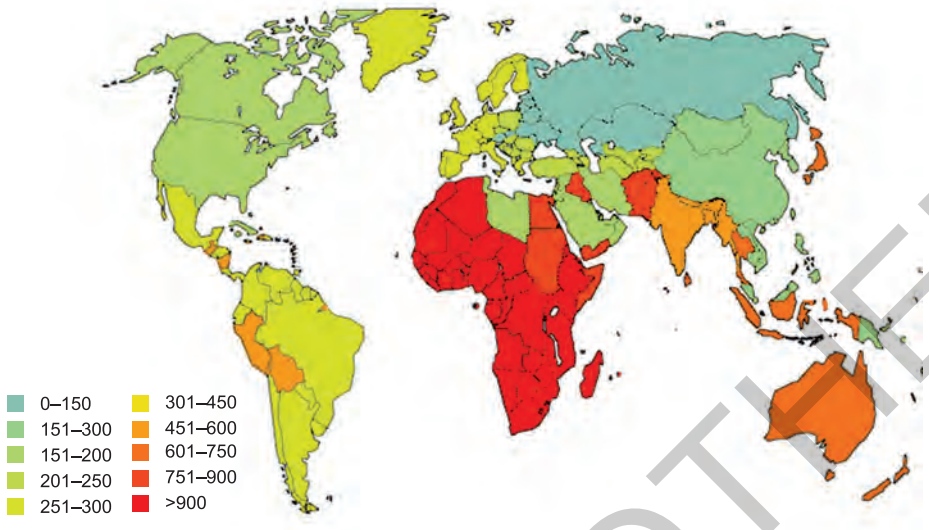

Figure 7: Deaths of pneumonia for all ages, in thousands, in 2008.[8]

Mortality rates of pneumonia shows geographic variation (Figure 7) which depends on many factors including health standards, patient factors, and etiological agents. It can be seen that certain central African countries, India, and China have the highest mortality rates. There is an increased death rate due to pneumonia among males, even after adjusting for age.[8]

Situation in South East Asia

South East Asian WHO region consist of Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand, and Timor-Leste.

South East Asian subregion D, which consists of Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Maldives, Myanmar, Nepal, and Timor-Leste has the 5th highest incidence of pneumonia at 93 per 1,000 out of the 14 WHO subregions in 2004.[8]

South East Asian WHO region has a death rate of 8 per 10,000 due to pneumonia. There is a male dominance in the deaths due to pneumonia and the highest incidence is at extremes of age as can be seen in figure 8.[8]

Global Epidemics of Pneumonia

Infective pneumonia in which the causative agent is airborne has been known to cause epidemics and pandemics. A famous example is the Spanish flu epidemic which occurred just after the First World War, which killed 50 million people,

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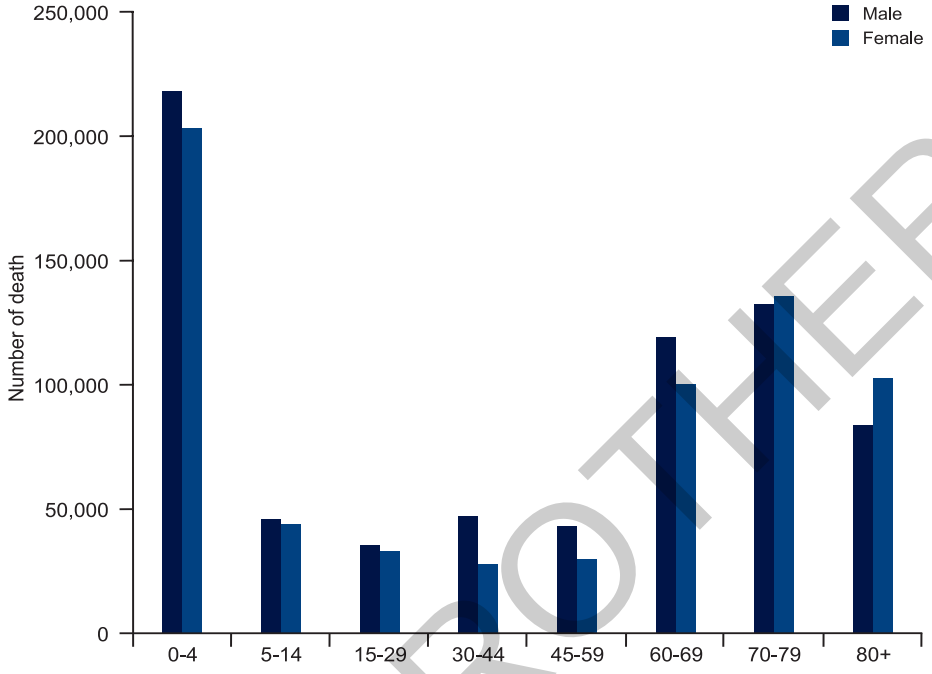

Figure 8: Deaths due to pneumonia by gender and age in the South East Asian WHO region.[8]

Table 3: Influenza Pandemics[10]

Name of pandemic	Years	Deaths	Subtype involved
Asiatic (Russian) flu	1889–1890	1 million	Possibly H2N2
Spanish flu	1918–1920	50 million	H1N1
Asian flu	1957–1958	1.5–2 million	H2N2
Hong Kong flu	1968–1969	1 million	H3N2
Swine flu	2009–2010	Over 18,209	Novel H1N1

much more than the 15 million deaths due to the war itself. Since then, there have been several pandemics of influenza (Table 3).[10] The cyclical nature of the pandemics is due to the phenomenon of antigenic shift creating new organisms to which the population lacks immunity. Increased travel and immigration of individuals from countries with epidemics are certain to bring new challenges to pneumonia control.

Epidemiology of Childhood Pneumonia

Pneumonia in childhood is a major cause of disease morbidity and deaths, especially in developing nations. The epidemiology of pneumonia in children

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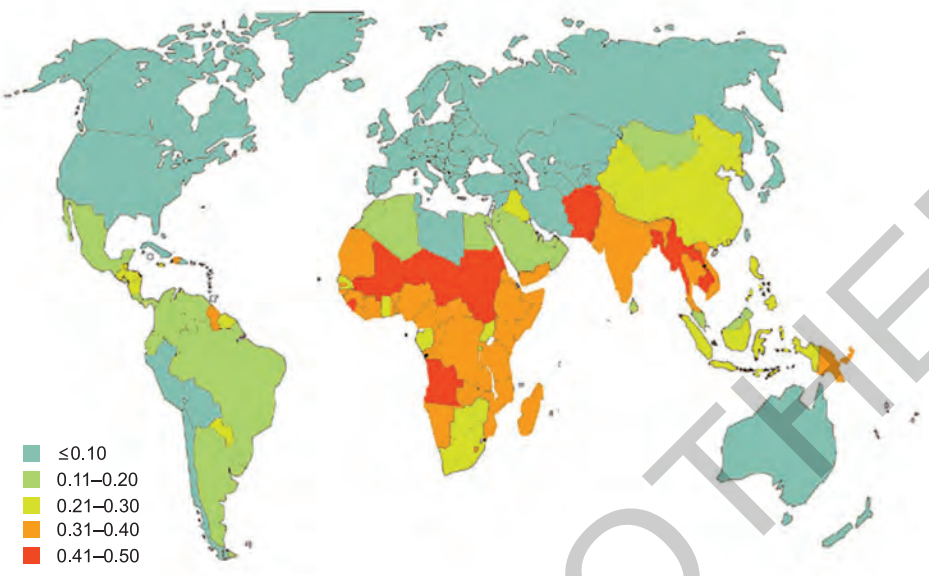

Figure 9: Incidence of childhood pneumonia at country level (per child-year).[14]

below 5 years of age has been extensively studied and reports have shown that between 20 and 33% of deaths in 1990s among preschool children were related to acute chest infection.[11] This leads to about 1.5 million deaths annually, second highest number after neonatal causes.[12]

Calculated median incidence of childhood pneumonia for developing countries for the year 2000 was 0.28 per child-year.[13] A reanalysis had shown that this accounts for 151.8 million new annual cases in developing regions. Of them, 13.1 million (8.7%) cases need hospital admission.[14]

Incidence of childhood clinical pneumonia under age 5 years at country level revealed that more than 50% of the new cases come from India, China, Pakistan, Bangladesh, Indonesia, and Nigeria (Figure 9).[14]

Prompt and effective antibiotic therapy is essential in managing pneumonia and thereby reducing deaths. Yet, in the developing world (excluding China), only less than two-thirds are given appropriate care, while in Sub-Saharan Africa, this amounts to below 50%.[12] It is equally important to note that, despite the huge disease burden, the public attention and the funds allocated for management of pneumonia are grossly inadequate in many parts of the world.

Knowledge of the etiology of childhood pneumonia with geographical variants is essential for the rational treatment (Table 4). In the developing world, bacteria, especially *S. pneumoniae, H. influenzae*, and *S. aureus* are the leading causes of life-threatening lobar pneumonia. Bacteria are also responsible for severe childhood pneumonia in developed nations, although *H. influenza* type B infection is much

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Table 4: Causative Organism for Community-acquired Pneumonia in Children

Common causes

- Viruses: influenza, parainfluenza, RSV, adenovirus, and rhinovirus
- *Mycoplasma* infection
- Bacteria: *S. pneumoniae*, *M. tuberculosis*, *S. aureus*, and *H. influenzae*
- *Chlamydia* infection: *C. pneumonia and C. trachomatis*

Uncommon causes

- Viruses: VZV, EBV, CMV, HSV, coronaviruses, enteroviruses, and huntavirus
- Bacteria: *S. pyogenes, S. milleri, S. peptostreptococcus, Meningococcus, E. coli, Listeria, and* other groups of *Haemophilus, P. pseudomallei, and Brucella*
- *Coxiella burnetii*
- *Chlamydia psittaci*
- Fungi: histoplasmosis, blastomycosis, and coccidioidomycosis

RSV, respiratory syncytial virus; VZV, varicella zoster virus; EBV, Epstein-Barr virus; CMV, cytomegalovirus; HSV, herpes simplex virus.

less common in USA, following mass immunization.[15] Furthermore, respiratory viruses: *Chlamydia* and *Mycoplasma* are common causes of respiratory disease in this age group.

Although clinically useful in adolescents and adults, the differentiation between typical and atypical pneumonia (i.e., bacterial versus viral/mycoplasma) may be difficult in infants and children. In one series from the USA, mixed bacterial/viral infections were identified among one-fourth of children admitted with CAP. These mixed infections were not distinguishable from single infections on clinical, biochemical, or imaging features. Out of all cases, majority were of bacterial origin (single or mixed), which was strongly favored by the presence of high fever within first 3 days and pleural effusion. Therefore, empirical antibiotics targeting usual bacterial pathogens are recommended, at least during first few days, for children admitted with pneumonia to overcome the disease morbidity and mortality.[16]

Epidemiology of *Pneumocystis* Pneumonia

Pneumonia due to *Pneumocystis* (*carinii*) *jirovecii* pneumoniae (PCP) needs special consideration due to its growing incidence among immunocompromised populations, especially in HIV-infected. This remains the most common AIDS defining condition even today, despite the significant reduction of the prevalence among AIDS population, following the introduction of highly active antiretroviral therapy. Furthermore, the rate of *Pneumocystis* colonization among HIV-infected population can be significantly high (69%). However, PCP is commonly under-reported in many parts of the world due to diagnostic limitations.[17]

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RISK FACTORS

Causative organisms from the upper airways or, less commonly, from hematogenous spread or direct spread from a contiguous focus, find their way to the lung parenchyma. Conditions, such as altered mental status, stroke, and other neurological diseases may result in loss of protective upper airway reflexes and facilitate aspiration of contents from the upper airways into the lungs. The development of pneumonia depends on numerous extrinsic and intrinsic factors, including virulence of the organism, local defenses, and overall health of the patient. In this section, risk factors for development of pneumonia will be discussed in general, while specific risk factors in special circumstances, such as in VAP, will be discussed in the article "Nosocomial and Healthcare-associated Pneumonias".

Predisposing Host Conditions

Loss of Upper Airway Reflexes

The upper airway reflexes consist of many different types of reflex responses, including sneezing, laryngeal closure, coughing, expiration reflex, and negative pressure reflex, which play an important role in preventing both microaspiration and macroaspiration of upper airway contents into lungs. These reflexes are carried out via many neural and chemical mediators and can be depressed in certain disease conditions and situations (Table 5).[18-21]

Impairment of Local Defenses

The human lung has a complex local defense mechanism against infections. Many physical, chemical, and biological components act synergistically to combat invading organisms (Table 6). These factors are effective in maintaining normal sterility of the lower respiratory tract in the healthy host.[22]

Mucus prevents attachment of organisms to the respiratory epithelium, and the mucociliary escalator removes the particles away from lung parenchyma. Excessive mucus secretion or ciliary dysfunction may result in failure to clear mucus, which results in formation of mucus plaques and plugs, which can serve

Table 5: Conditions Leading to Depressed Upper Airway Reflexes[18-21]

- Increasing age
- Sleep
- General anesthesia
- Alterations in the level of consciousness (stroke, seizures, drug intoxication, alcohol abuse, and head injury)

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Table 6: Components of Local Lung Defenses

- Mucus and mucociliary escalator
- Alveolar epithelial barrier
- Epithelial response and repair mechanisms
- Chemical mediators and innate defense molecules (antimicrobial peptides, lysozymes, lactoferrins, and defensins)
- Pulmonary phagocytes (alveolar macrophages, polymorphonuclear granulocytes, and monocytes)
- Humoral factors (inflammatory mediators, cytokines, acute-phase reactants, secretory IgA, IgG, and opsonins)
- Fluid homeostasis

IgA, immunoglobulin A; IgG, immunoglobulin G

Table 7: Conditions Leading to Impaired Mucociliary Clearance

Excessive mucus production

- Congenital—cystic fibrosis
- Acquired—asthma, chronic obstructive pulmonary disease, and allergic bronchopulmonary aspergillosis

Ciliary dysfunction

- Primary ciliary dyskinesia and variants—Kartagener's/Young's syndrome
- Acquired—smoking

as a focus for infection by opportunistic pathogens (Table 7). In cystic fibrosis, large volumes of mucin are produced due to ion transfer defect through epithelial membrane, while goblet cell hyperplasia is seen in some other airway diseases. Kartagener's syndrome has a limited variant of primary ciliary dyskinesia (immotile cilia syndrome) characterized by chronic sinusitis, bronchiectasis, and dextrocardia, while azoospermia, sinusitis, and recurrent pneumonia are seen in Young's syndrome.[23]

Epithelial cells form an effective mechanical barrier for invading organisms and also mediate a major role in local inflammatory response. They secrete chemokines, including interleukins and chemotactic proteins, in response to noxious stimuli and upregulate cell adhesion molecules, thereby, playing an active role in attraction and adhesion of neutrophils and monocytes.[24] Certain factors may depress alveolar epithelial function by causing damage to alveolar epithelium or by increasing its permeability (Table 8).

The pulmonary phagocytic system, consisting of alveolar macrophages, monocytes, granulocytes, and dendritic cells use oxidative and nonoxidative microbicidal mechanisms, which are lethal for most ordinary microbes.[25] However, pulmonary phagocytosis may be limited in many conditions (Table 9). Congenital deficiencies in macrophage-mediated phagocytosis are rarely seen beyond the very early stages of life, as most of these syndromes are usually fatal.

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