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Epidemiology of Lower Respiratory Tract Infections in Children

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ABSTRACT

Context: Respiratory tract infections are the main cause of children's morbidity and mortality both in the developing and the developed countries. An accurate understanding of the epidemiology of these diseases, identification of risk factors, etiology and seasonality are critical for successful treatment and/or prevention program.
Evidence Acquisition: This article aims at offering clinicians a brief update on the recent epidemiology of respiratory infections in pediatrics. It also underlines the fact that any evidence-based recommendation needs more research in different areas.
Results: Almost 150 million new episodes of pneumonia are identified per year worldwide more than 90% of which occur in developing countries. Nearly 30% of total annual deaths occur in children younger than 5 years old. Viruses remain the most common cause of RTIs. S. pneumonia and HIB are the main causes of bacterial pneumonia in the world; however, infections due to many of these pathogens can be prevented.
Conclusions: Widespread immunization against influenza, measles, bacilli calmette-guerin (BCG) and now pneumococcus have been related to the decline of the LRTIs in children.

Keywords: Epidemiology; Respiratory Tract Infection; Children; Etiology

1. Context

1.1. Lower Respiratory Tract Infections

The most common LRIs in children are bronchiolitis and pneumonia. The most frequent symptoms and signs in these children are coughs and an increased respiratory rate. The occurrence of lower chest wall indrawing is indicative of a more severe disease. The most common causes of LRIs are viruses and RSV, a major cause among other viruses (1, 2).

Pneumonia: Pneumonia has both viral and bacterial roots. Bacterial pneumonia is usually the result of Streptococcus pneumonia (pneumococcus) or Haemophilus influenza, especially type b (Hib), and rarely Staphylococcus aureus or other streptococci. Chlamydia pneumonia and Mycoplasma pneumonia cause atypical pneumonias (3).

In young children, the pathogenesis of bacterial pneu-

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Implication for health policy/practice/research/medical education:
This article offers clinicians a brief update on the recent epidemiology of respiratory infections in pediatrics.

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monia has been recognized due to upper respiratory tract colonization by organisms and aspiration of the contaminated excretions. Viruses account for 40 to 50 percent of pneumonia hospitalizations for children in developing countries. RSV, parainfluenza viruses, adenoviruses and influenza type A virus are the most significant causes of viral pneumonia (3-5).

Bronchiolitis: Bronchiolitis mainly occurs in children less than one year and it shows decline during the second and third years of life. The clinical features are fever, rapid breathing, lower chest wall indrawing and wheezing (6).Hyperinflation and the collapse of lung segments occur because of the inflammatory obstruction of small airways. Differentiation between bronchiolitis and pneumonia is difficult for health workers for the fact that symptoms and signs are very similar. The seasonality of RSV in the area and the expertise to identify wheezing may help in diagnosis. RSV is the highest cause of bronchiolitis universally and can account for up to 70 or 80 percent of LRIs through high season. Parainfluenza virus type 3 and the influenza virus are the other causes for bronchiolitis (7, 8).

2. Evidence Acquisition

Acute respiratory tract infection (ARI) is the leading cause of morbidity and mortality in both developing and developed countries (9). WHO recognized respiratory diseases as the second important cause of death for children under five years in 2010 (10). WHO states that pneumonia is one of the main three causes for newborn infant deaths (11). Pneumonia was diagnosed in approximately 156 million children in 2008 (151 million in developing countries and 5 million in developed countries) and led to 1.4 million deaths (28-34% of all deaths in those younger than five years of age). More than 20 million patients with severe disease out of 156 million new cases of pneumonia need hospital admission yearly (9, 12). WHO reports in developing countries (e.g. Nigeria, Gambia, Senegal, Chad, Cameroon, Burkinofaso and Mali) demonstrate ARI incidence rate of 15-21% in children younger than five years old (13). In developing countries, respiratory tract infection accounts for more than 2 million deaths yearly. Pneumonia is the major cause of children's death in these countries (14). In developed countries, the yearly incidence of pneumonia is estimated to be 33 per 10000 in children < 5 years and 14/5 per 10000 in children 0 to 16 years old (15). Hospitalization rates of pneumonia (all causes) among children younger than two years in the United States have decreased (from 12 to 14 per 1000 population to 8 to 10 per 1000 population) after considering the pneumococcal conjugate vaccine as the routine childhood immunization plan since twelve years ago (16). A recent Meta-analysis study reveals that 1.9 million children died from ARI in 2000 all over the world, two third of them in Southeast Asia and Africa (17). Approximately one in five child deaths (18 percent) worldwide occurred during the neonatal period (the first four weeks of life) (9). The mortality rate in developed countries is at the lowest level (< per 1000) (16).

2.1. Risk Factors

Environment-related risk factors have an important role in the incidence of respiratory tract infections in children. The most significant risk factors are malnutrition, low birth weight, nonexclusive breast feeding (especially in the course of the first 4 months after birth) air pollution, indoor crowding and lack of measles immunization in the children under one year of age. The most important risk factors with identified effects are parental smoking, zinc deficiency, mother's experience as a caregiver and concomitant diseases (e.g. asthma, diarrhea, heart disease, etc.). Finally, the possible risk factors may include mother's education, day care attendance, humidity and cold weather, vitamin A deficiency and outdoor air pollution (9).

2.2. Etiology

Respiratory tract infection is caused by both viral and bacterial organisms. It has been known that viral infections are the main causes of mild to moderate pneumonia (especially in the first years of life) while bacterial infections are the leading cause of severe pneumonia (9, 18-20).

2.2.1. Viruses

Viruses have already been recognized as the most common cause of acute respiratory tract infections in young children. According to WHO reports, viruses account for 30 to 67% of pneumonia mostly occurring in children < 1 year (11). A study carried out in Iran in 1960 on children under 5 years old with acute respiratory tract infection found that the contribution of viral agents in acute respiratory tract infection was 54% (less than 10% of which were dual-cause infection). The prevalence of viruses detected in this study were PI3 (15.8%), RSV (12.9%), Inf A (7.4%), PI1 (6.4%), PI2 (6.4%), adenovirus (5.9%) and Inf B (3.5%) (21).

Respiratory Syncytial Virus (RSV): RSV is the principal viral cause of ARI detected in 15-40% of children admitted for bronchiolitis and pneumonia in developing countries (22). RSV is the most significant cause among all causes of lower respiratory infection in infants and children globally (23). Although a new vaccine is recognized, RSV still remains a very important fatal pathogen that in combination with other bacterial pathogens or solely leads to pneumonia in children. The most severe form of the disease happens in infants in their 3rd weeks to 3rd months of age (23). In the United States, 85000-144000 infants were hospitalized and admitted for respiratory infection resulting from RSV (23). Seventy percent of hospitalized infants suffered bronchiolitis and 20-25% of them were diagnosed with pneumonia (24). In North America and

Europe, RSV infection happens in winter and spring. Studies in the developing countries with a temperate climate such as Argentina have shown a similar seasonal pattern. Studies in the tropical countries have shown an increase in the rainy season (17). Milani et al demonstrated that RSV's clinical spectrum in Iran is similar to other countries. His research showed an incidence of 19.18 % in the children under 5 years old in Tehran (prevalence was higher in crowded living conditions). According to the study RSV is a significant cause of hospitalization in winter mostly occurring in infants >6 months of age. Nearly all of the infected children were up to 2 years old and less than 50% of the cases appeared in infants >1 years of age (25).

Parainfluenza: After RSV, Parainfluenza viruses - type 1, 2, and 3 (PIV-1, PIV-2 and PIV-3) - are the second leading cause of viral respiratory infections in young children (26). PIV-1 and PIV-2 are the principal cause of croup, which is mostly seen in children between 6 months and 4 years old. PIV-3 causes bronchiolitis and pneumonia, mostly in children younger than 12 months. Annual hospitalization rates of PIV-1, PIV-2 and PIV-3 in the USA are estimated to be 5800 to 28900, 1800 to 15600 and 8700 to 52000 respectively. PIV1 causes a high incidence of croup in the autumn. PIV2 infection is usually followed by PIV1 outbreak. The seasonality of PIV3 infection is in spring and summer (17).

Influenza: The seasonal epidemics of influenza are the consequence of antigenic changing of influenza viruses. Hospitalization rate due to severe disease is 3 per 1000 in children aged 6 to 23 months and 9 per 1000 in children less than 6 months (27). A recent multicenter study in Japan, Russia and Michigan (USA) suggests that vaccination of children in school ages lowers the incidence of respiratory diseases. A recent surge in the new influenza virus (H1N1) has obviously revealed that viral infection can result in pneumonia with a poor outcome in all age groups of children (28-30). The seasonality pattern of influenza is different around the world. Seasonal epidemic peaks occur in mid-winter in temperate climates. The seasonal patterns of tropical regions can include a whole year (31).

Adenovirus: Adenoviruses fall into four recognized genera; Aviadenovirus, Atadenovirus, Mastadenovirus and Siadenovirus. Studies have reported 51 antigenic types of human adenoviruses.

According to physical, chemical and biological basis, adenoviruses have been classified into six groups (A–F). The correct outbreak statistics of adenoviral infections is unidentified because nearly all cases are visited by general practitioners. Adenovirus is a very frequent infection, it consists 2%-5% of all respiratory infections (32).

In several studies on the children under 5 years old in Germany, Brazil, India and Jordan of all children who had been examined (12.9%), (6%), (1.5%) and (37%) respectively were reported to suffer from adenoviruses. Incidence of this pathogen in Jordanian children was significantly higher than other countries (33-36). Incidences of adenovirus-associated respiratory infections have risen in late winter, spring, and near the beginning summer; but adenovirus infections can be happened all over the year (32).Human Rhinoviruses (HRV): Rhinoviruses are well known causes of upper respiratory tract infections. In an Australian study it was reported that nearly half of the patients suffered lower respiratory tract infections. Several studies in Australia, Korea, and Jordan report the prevalence of HRV in children as (44%), (5.8%) and (11%) respectively (36-38). Rhinovirus was not associated with any specific season. It was the most common diagnosis in Indian children, both in dry and rainy seasons (39). A study in the United States reported that rhinovirus infections occurred year-round; however, 40% of all cases were detected in spring. This supports the previous interpretation that rhinovirus has the largest number in spring (40-42).

Measles: Pneumonia is the most serious complication associated with measles. Pneumonia due to measles occurs in 16–77% of hospitalized children and 2–27% of the children in community-based studies. In addition, pneumonia is recognized in 56–86% of all deaths due to measles (43). There were more than 2.5 million deaths due to measles in 1980, before the general utilization of measles vaccine in developing countries. In 1999 the incidence of measles declined to about 873000 deaths (44). Measles mortality reduction strategy was carried out in 47 countries with the highest disease burden in 2001. The strategy consisted of expanding the routine measles vaccination coverage of the first dose, provision of an additional opportunity through complementary immunization activities, suitable case management and improved observation. The widespread application of this strategy, particularly in countries such as Africa, led to a 60% decrease in the measles deaths from 873000 to 345000 between 1999 to 2005 (45).

New viruses: Human metapneumovirus (hMPV) has been known as a respiratory tract pathogen that caused a major outbreak of both upper and lower respiratory tract infections affecting infants and children in 2001 (46). Human bocavirus (HBoV) has been identified as a cause of respiratory tract diseases since 2004 and it belongs to the family of Parvoviridae (47). The newly-recognized viruses such as human metapneumovirus (hMPV) and human bocavirus have been recognized in 8-12% and 5% of pneumonia cases in children, respectively. RSV, hMPV and HRV have been identified as the leading causes of children's pneumonia in developed countries (48-50).

Other viruses: Varicella zoster, Herpes simplex virus, Cytomegalovirus, measles and Enteroviruses are the other causes of RTIs (22).

2.2.2. Bacteria

Streptococcus pneumonia: S. pneumonia is a frequent cause of morbidity and mortality among children all over the world, especially in the developing countries (51-53). The peak age of this infection is in children under 5 years old. Centers for Disease control and Prevention

(CDC) have analyzed the invasive pneumococcal disease (IPD) in USA since 1994. CDC data indicates that children less than 2 years of age have the most prevalence of the invasive disease (54) (*Table 1*).

Table 1. Incidence of Pneumococcal Infection in the United States

Age, y	Disease Incidence,Cases/100000	Cases, No.	Death Rate,Deaths/100000	Death, No.
<1	31.4	142	0.22, 1	1
1	24.6	112	0.22, 1	1
4-2	12.6	171	0.15, 2	1
5-17	2.2	111	0.02, 1	1
Total	70.8	536	0.61	4

The outbreak of invasive pneumococcal disease in children < 5years old declined from 77 to 22 new cases per 100000 (74%) from 1997 to 2008 which is better than target of 46 cases per 100000 population in 2010. The outbreak of penicillin resistant pneumococcal infections in children less than 5 years old decreased from 16 to 7 new cases per 100000 while 2010 target was 6 cases per 100000 (55). Target goals in 2020 for children less than 5 years are 12 invasive pneumococcal disease cases per 100000 population; also penicillin-resistant pneumococcal infections decline in children under 5 years to 3 cases per 100000 population (56). The incidence of pneumococcal disease in Europe is lower than USA but the disease rate varies from 14 cases per 100000 in Netherlands and Germany to more than 90 per 100000 in Spain (57). The outbreak of invasive pneumococcal infection in the Gambia reaches 500 per 100000 in the first year of life and 250 per 100000 in the children under 5 years of age (58). The study in Kenya reported that prevalence of pneumococcal bacteremia in children less than 5 years old was 597 per 100000 (59). The seasonal pattern of pneumococcal infection points to winter and the peak months are December and January (3-5 times more than August) (60). Senstad *et al* in Norway also reported a peak in January and a small outbreak of hospital pneumonia in summer (61). Pneumococcal infection peak is winter in temperate climates. The seasonality is due to several factors such as indoor crowding, low humidity, associated viral infections, cold weather and air pollution (62).

Haemophilus influenzae: Haemophilus influenzae type B (HIB) remains the second important bacterial pathogen of pneumonia (22). Almost one in 200 children less than 5 years old developed invasive HIB disease and nearly two-third of HIB infections occurred in children under 18 months. In 2009, a study on children less than 5 years old in the United States showed 32 cases of invasive HIB disease. In addition, they detected *H. influenzae* serotypes in 178 cases. Most cases were found in unvaccinated or incompletely vaccinated children. Outbreaks of HIB have fallen by 99% after vaccination (63). HIB vaccination has been available from 1990 and is recommended for children younger than five years (64). In 2010 and 2011 HIB caused just 12% of *H. influenzae* cases. From 2010 to 2011 the outbreak of invasive non-HIB influenza was 0.60 cases per 100000. Highest incidence was seen in under one year old children (3.14) and then in children between the ages one to four years old (1.50) (65).

Staphylococcus aureus: Staphylococcus aureus, after *S. pneumonia* and *H. influenzae*, is the third important bacterial organism in pneumonia (22). In the United States, *S. aureus* has augmented in the past decade and many of them are methicillin-resistant *S. aureus* (MRSA). Viral coinfection causes respiratory failure in nearly 15% of cases. A study in Texas from August 2001 to April 2009 on hospitalized children identified *S. aureus* in the cultures of 117 patients with pneumonia. The rate of *S.A pneumonia* per 10000 increased from 4.81 to 9.75 hospitalizations in the period of 2001 to 2009while the infections due to MRSA and methicillin-susceptible SA (MSSA) were 74% and 26% respectively .USA300 is a genotype that is known in this study and is represented in 14.28 (50%) of MSSA and 75.82 (92%) of MRSA (66). The outbreak of staph infection among children in UK has risen in the past decade (67-69). There are limited data about MRSA infection in children in developing countries (22).

Mycoplasma pneumonia: Mycoplasma pneumonia (MP), categorized as an atypical pathogen, is one of the most important causes of lower respiratory tract infections (LRTIs) worldwide. The epidemiological and clinical features of *Mycoplasma pneumonia*, including the cyclic epidemic and lymphopenia, are similar to other viral infections such as influenza. Although MP is identified to be the main cause of pneumonia in school-aged children the highest prevalence is seen in the group of children between the ages of 4 and 6 year according to a study in Korea. MP infection is endemic in many countries of the world but epidemics occasionally occur every 3 to 7 years. In Korea, epidemic periods lasting 12 to 18 months and 3 to 4-year cycles of MP pneumonia have been recognized from 1980 to now (69). One study in India conducted on 75 children infected by LRTIs reported 30.7% prevalence of *M. pneuminiae* (70). In England epidemics last approximately 18 months with 4-yearly intervals. The seasonal peaks of infection occur from December to February (71, 72). One study in Iran investigated one hundred patients with acute LRTIs and found 10 positive PCR for *M. pneumoniae* with the prevalence of 10% including 6 of 62 hospitalized patients and 4 of 38 outpatients (73).

Others bacteria: *Histoplasmosis, Chlamydia, Mycobacterium tuberculosis*, Pseudomonase, Salmonella and Toxoplasmosis are other bacterial causes of RTIs in children (22).

3. Results

Almost 150 million new episodes of pneumonia are identified per year worldwide more than 90% of which occur in developing countries. Nearly 30% of total annual deaths occur in children younger than 5 years old. Viruses remain the most common cause of RTIs. *S. pneumonia* and HIB are the main causes of bacterial pneumonia in the world; however, infections due to many of these pathogens can be prevented.

4. Conclusions

Widespread immunization against influenza, measles, bacilli calmette-guerin (BCG) and now pneumococcus have been related to the decline of the LRTIs in children.

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Authors' Contribution

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