

The Impact of Pneumonia on Development of Chronic Respiratory Illness in Childhood

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Pneumonia is the leading cause of mortality in children under 5 years of age in low- and middle-income countries. As most deaths are preventable, the primary focus has been on mortality reduction, with relative neglect of the potential long-term morbidity, particularly the development of chronic respiratory illness. Nevertheless, chronic respiratory illness is common among children in low- and middle-income countries and causes substantial morbidity. The aim of this article was to review the evidence for an association between pneumonia and the development of chronic respiratory illness, specifically bronchiectasis, chronic bronchitis, and bronchiolitis obliterans. In addition, the effects of modifying factors known to be associated with respiratory illness in children, including exposure to biomass fuel smoke, malnutrition, lack of access to healthcare, and poverty, were considered. Medline search using pneumonia and each of the chronic respiratory illness terms, limited to children, was conducted. Article abstracts were extracted and reviewed, and full articles retrieved where they met the search definitions. Studies reported an association between severe pneumonia and the development of chronic respiratory illness in a substantial proportion of children; few studies have been done in low- and middle-income countries and many have methodological limitations. Pneumonia has been most closely associated with the development of bronchiectasis, especially among certain high-risk children. Persistent bacterial bronchitis is a poorly defined clinical entity that may be a precursor for bronchiectasis. Postinfectious bronchiolitis obliterans has been well described, especially following adenovirus pneumonia. Limited evidence suggests an association between severe pneumonia and development of chronic respiratory illness. However, further research, especially after the introduction of new conjugate vaccines in low- and middle-income countries, is needed.

Background

PNEUMONIA IS A LEADING cause of death and hospitalization in children under 5 years of age in low- and middle-income countries.¹ The estimated incidence of childhood pneumonia is 0.29 events per child year in developing and 0.05 per child year in developed countries.² Seven percent to 13% of all cases are severe enough to require hospitalization.² There are ~2 million deaths from pneumonia in children annually, 90% of which occur in low- and middle-income countries.¹ Owing to the huge burden of pneumonia cases in this context, the morbidity resulting from pneumonia has been overshadowed by the drive to prevent mortality.

Severe pneumonia is usually caused by bacterial pathogens such as *Streptococcus pneumoniae*, *Haemophilus influenzae*,

and *Staphylococcus aureus*.³ *Mycobacterium tuberculosis* has increasingly been identified as a cause of acute pneumonia in high tuberculosis (TB) prevalence areas.^{4–7} Respiratory viral infections such as adenovirus, influenza, or respiratory syncytial virus can produce severe pneumonia especially in human immunodeficiency virus (HIV)-infected children. Polymicrobial infections are increasingly recognized and are associated with a higher mortality than single-organism infections.⁸ More widespread availability of conjugate vaccines [*H. influenzae type b* (HiB) and pneumococcal conjugate vaccine] in low- and middle-income countries can be expected to change the epidemiology and etiology of childhood pneumonia in the future.

There is increasing recognition of the potential role of childhood pneumonia in the subsequent development of

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childhood chronic respiratory illness. Chronic respiratory illness in childhood encompasses a spectrum of clinical entities ranging from obstructive disease (asthma/wheezing illness) to restrictive or suppurative lung disease.^{9,10} A number of birth cohort studies have suggested an association of early viral lower respiratory tract infection with subsequent wheezing illness/asthma.^{9,11–13} In addition, there is evidence to suggest that adult chronic obstructive pulmonary disease has its origins in childhood.¹⁴ In contrast, there is relatively little evidence linking pneumonia to the development of restrictive or suppurative chronic respiratory illness.

Chronic suppurative lung disease in childhood encompasses a spectrum of diseases, including chronic bronchitis and bronchiectasis. There is no clear international consensus on the classification of chronic suppurative lung disease in childhood.¹⁵ Proposed definitions for chronic bronchitis in childhood include persistent bronchitis, protracted bacterial bronchitis (PBB), or persistent endobronchial infection.^{10,15} Some regard chronic bronchitis as a “pre-bronchiectasis” condition.¹⁰ Quantitative estimates of the worldwide prevalence and evolution of chronic suppurative lung disease in children are lacking, and epidemiologic studies are required.¹⁶ Similarly, there is little information on the global epidemiology of bronchiolitis obliterans (BO) or on optimal management strategies.

The aim of this article was to review the evidence for an association between pneumonia and the development of chronic respiratory illness, specifically bronchiectasis, chronic bronchitis, or BO in low- and middle-income countries. The role of modifying factors (known to be associated with respiratory illness in children) that may be highly prevalent in resource poor settings such as exposure to biomass fuel smoke,¹⁷ malnutrition,¹⁸ HIV,¹⁹ lack of access to healthcare, or poverty²⁰ was also reviewed.

Methods

A Medline search using each of the chronic respiratory illness terms (bronchiectasis, chronic bronchitis, and BO) and the term “pneumonia” was conducted. Due to the lack of standard nomenclature for chronic respiratory illness in children, multiple searches were performed. For chronic bronchitis additional searches with other accepted terms, “persistent bacterial bronchitis,” “persistent endobronchial infection,” and “protracted bronchitis” were also performed. Cross checks were done using the MeSH database, with the following terms used: pneumonia and chronic bronchitis, bronchiectasis, or BO. All results were limited to clinical studies in children from 0 to 18 years of age. Article abstracts were obtained and reviewed. Excluded sources were those published before 1990, laboratory-based research without clinical measures, multiple publications from the same study, and abstracts containing children with underlying chronic illnesses such as cystic fibrosis or postlung transplantation. Conference abstracts and unpublished reports were excluded. The remaining articles were retrieved and reviewed in full text. Reference lists of all full-text articles were reviewed and screened for other possible articles. The review analyzed articles relating to the general epidemiological association between chronic respiratory illness and pneumonia ($n = 4$), to pneumonia and bronchiectasis ($n = 13$), chronic bronchitis ($n = 2$), and BO ($n = 4$).

Epidemiologic Evidence

Pneumonia and unclassified chronic respiratory illness

The association between pneumonia in early childhood and subsequent unclassified chronic respiratory illness has been investigated in a variety of settings (Table 1).^{21–24} All studies were done before the widespread availability of pneumococcal conjugate vaccine and some before the use of HiB.

An early study from South Africa prospectively followed 62 children for 1–7 years after hospitalization for pneumonia.²¹ Recurrence of cough or wheeze for >6 months occurred in 85% of the cohort, and abnormal radiographic features, consisting of peribronchial and or parenchymal lesions, persisted in 53% of children. In addition, approximately a third of children had abnormal lung function at follow-up. The study highlighted that long-term sequelae are common after hospitalization for pneumonia, and produce considerable morbidity, with a number of children requiring subsequent management of symptoms.²¹

More recently, an observational cohort study from The Gambia traced children who had been hospitalized with severe pneumonia 12–14 years later and compared them to neighborhood-matched controls.²² Thirteen percent of cases compared to 4% of controls had evidence of lung disease clinically or on spirometry. The risk of lung disease was 2.93 [95% confidence interval (CI) 0.69–12.48] in cases compared to controls. Although the study is limited due to the poor measurement of chronic respiratory illness, it does suggest a link between early severe childhood pneumonia and development of chronic respiratory illness in a low- and middle-income country. Similarly, Kyler et al. investigated 55 Polish children hospitalized with severe pneumonia, following them for 2–10 years; 44% of children had a repeated bronchitis and 9% had recurrent pneumonia.²³ Forty children underwent pulmonary function tests; 35% had restrictive disease, whereas 17% had an obstructive pattern after pneumonia. Although the outcome definitions were unclear, this study also suggests long-term sequelae following severe pneumonia in childhood. In the United Kingdom, Eastham et al. conducted a controlled follow-up study of 103 children with radiologically confirmed community acquired pneumonia and matched randomly selected class controls for a median of 5.6 years (range 4.4–7.4) after hospitalization.²⁴ They found that cases had a 2.9 (95% CI 1.5–5.7) times higher risk of persistent cough and were 5.5 (95% CI 1.7–18.3) times more likely to have an abnormal chest shape than controls.²⁰

These studies, although similar in design (predominantly case-based studies of children hospitalized for pneumonia), are not comparable in their outcome or exposure measures. Nevertheless, the combined evidence suggests a possible association between pneumonia and the development of chronic respiratory illness. A larger body of research has focused on the role of pneumonia in the pathogenesis of specific chronic respiratory illnesses, below.

Pneumonia and bronchiectasis

Pediatric noncystic fibrosis bronchiectasis has been neglected and regarded as an “orphan disease” among children in the developed world.²⁵ Immunization strategies, effective antibiotic treatment for pneumonia, and improved living conditions have accompanied the virtual disappearance of

TABLE 1. STUDIES OF PNEUMONIA AND ASSOCIATION WITH UNCLASSIFIED CHRONIC RESPIRATORY ILLNESS

Study	Type	Number of study subjects	Comparison group	Location	Causes of pneumonia	Sequelae	Additional information
Wesley ²¹	Prospective follow-up	62 hospitalized with pneumonia (6 months–12 years) Median age of pneumonia: 17 months Follow-up: 1–7 years		South Africa	Measles 39%; measles and other infection 18%; adenovirus 12.5%; <i>Mycoplasma pneumoniae</i> 4.6%; RSV 4.6%; influenza A 3%; parainfluenza 1.5%	Persistent cough or wheeze 40% Chest X-ray: normal 47%; thickened bronchi 18%; parenchymal pathology 35% Lung function: abnormal 34%; exercise induced bronchospasm 8%	Persistent symptoms and abnormal lung function more common postmeasles or other viral infection. Clinical abnormalities improved with longer follow-up, resolution of radiographic changes was less marked, and abnormalities of lung function consistently present
Kyler et al. ²³	Prospective follow-up	55 hospitalized with pneumonia Follow-up: 2–10 years		Poland	No pathogens reported	43.6% bronchitis; 9.1% recurrent pneumonia; 34.5% limited physical activity; 40/55 had spirometry-35% restrictive, 17% obstructive disease	Article in Polish, only abstract available
Eastham et al. ²⁴	Controlled prospective follow-up study	103 cases radiologically confirmed pneumonia (5–16 years) Median follow-up 5.6 years (4.4–7.4 years)	248 matched controls	United Kingdom	No pathogens reported	OR of persistent cough for cases 2.9 (95% CI 1.45–5.71); OR for abnormal chest shape 5.5 (95% CI 1.65–18.28)	Cases of a nonatopic parent had increased risk of subsequent asthma (OR 4.8, 95% CI 1.43–16.34) but not of deficit in lung function
Puchalski Ritchie et al. ²²	Controlled, prospective follow-up study	68 cases hospitalized pneumonia (<5 years) Follow up: 12–14 years	67 matched controls	The Gambia	No pathogens reported	OR of CRI in cases 2.93 (95% CI 0.69–12.48)	CRI diagnosed on symptoms and clinical examination

CI, confidence interval; CRI, chronic respiratory illness; OR, odds ratio; RSV, respiratory syncytial virus.

TABLE 2. STUDIES OF PNEUMONIA AND ASSOCIATION WITH BRONCHIECTASIS

Study	Type	Number of children	Location	Clinical features and diagnosis of bronchiectasis	Etiology	Additional information
Nikolaizik and Warner ³²	Retrospective case review	41	United Kingdom	Diagnosis bronchography, HRCT, histology, or persistent CXR abnormalities Clinical features not reported	Congenital malformation, 15%; PCD, 17%; immunologic abnormality, 27%; aspiration, 5%; idiopathic, 37%	
Singleton et al. ²⁹	Retrospective case review	46	Alaska	Diagnosis 61% "definite" bronchogram/HRCT; 39% "probable" clinical and CXR; Median age: first LRTI 4.8 months (0–57 months); diagnosis 4.8 years (1–15 years) Clinical features not reported HRCT diagnosis Clinical features not reported	Recurrent pneumonia 85%; TB 4%; foreign body 2%; aspiration pneumonia 2%; interstitial pneumonia 2%; neonatal pneumonia 4%	Association between lobes affected by pneumonia and subsequent bronchiectasis Left lower lobe most frequently involved
Karakoc et al. ³⁰	Retrospective case review	23 Mean age 8.45 ± 4.02 years	Turkey		Post-TB 17%; pneumonia 17% (<i>Staph aureus</i> , <i>Strep pneumoniae</i>); immunodeficiency 17.4%; PCD 13%; CF 17.4%; asthma, 17.4%	Bronchiectasis lesions in left-lower lobe, 30%; multilobar, 57%
Tsao and Lin ³⁴	Retrospective case review	21	Taiwan	Recurrent cough 86%; fetid sputum 71.4%; haemoptysis 52.3%; digital clubbing 4.7%; wheezing 19%	Infection 48%: Pneumonia 24%, TB 24%; Immunodeficiency syndromes 14.3%, PCD 9.5%, Asthma 9.5%, Aspiration pneumonia 4.7%	Emphasized early diagnosis and treatment
Edwards et al. ³⁵	Retrospective case review	60 Median age 10 years (1–17 years)	New Zealand	HRCT diagnosis Digital clubbing 52%; chest deformity 60%	Unknown 50%; Significant Pneumonia 25%; <i>Staphylococcus aureus</i> 2%, <i>Streptococcus pneumoniae</i> 1%, adenovirus 5%, pertussis 3%, RSV 1%, aspergillosis 1%, mycoplasma 1%, tuberculosis 1%; immunodeficiency 12%; aspiration 0%, other 3%	Increase prevalence: Pacific Island and Maori Association with low socioeconomic status Lower lobes worst affected, 93% had bilateral disease

Chang et al. ³⁶	Prospective, observational study	65	Central Australia	HRCT diagnosis Clinical features not reported	Previous hospitalization for pneumonia and repeated admissions were common	Left lower lobe most frequent site of previous pneumonia and bronchiectasis Prevalence of CSLD 14.7/1,000 aboriginal children ≤15 years Agreement between CXR and HRCT in 5% of cases Concept of “prebronchiectasis” as repeat CT scan with resolution in 6/18
Eastham ¹⁶	Retrospective case review	93	United Kingdom	HRCT diagnosis Mean age 7.2 years (1.6–18.8 years); mean age of symptom onset 1.1 years (0–16 years) median time from symptom onset to HRCT diagnosis 3 years (0.1–4.5)	Previous pneumonia 30%; immunocompromise 21%; obliterative bronchiolitis 9%; congenital lung abnormality 5%; chronic aspiration 3%; PCD 1%; RML syndrome 1%; idiopathic 18% OR of hospitalized pneumonia in cases 15.3 (95% CI 4.4–52.7). Strong association with recurrent hospitalized pneumonia, severe pneumonia (<i>P</i> value <0.05 for trend)	
Valery et al. ³⁸	Case-control (medical record-based)	61 cases 183 matched controls	Central Australia	HRCT diagnosis and medical work up		Malnutrition prematurity, small for gestational age were common among cases. OR of breast-feeding in cases 0.2 (95% CI 0.1–0.7)
Li et al. ²⁸	Retrospective case review	136 Median age 12.1 years (3–18 years)	United Kingdom	HRCT diagnosis; chronic cough 34.6%; recurrent wheeze 10.3%; rhinitis 5.1%; recurrent otitis media 5.1%; GORD 8.1%; failure to thrive 4.4%; exercise intolerance 1.5%; recurrent chest infection 77.2%	Immunodeficiency, 33.8%; aspiration, 18.4%; PCD, 14.7%; idiopathic, 25.7%; childhood pneumonia, 4%; measles 1%, pertussis 1%, adenovirus 1%, tuberculosis 1%; congenital structural malformation, 3.7% Postinfectious 29.7%; severe pneumonia 17.1%, measles 8.1%, varicella 2.7%, TB 1.8%; idiopathic 37.8%; immunodeficiency 15.3% (9% IgG deficiency 4.5% IgG subclass deficiency); PCD 6.3%; foreign body aspiration 3.6%	Immunodeficiency and other intrinsic abnormalities account for the majority of non-CF bronchiectasis in this series. In 77%, identifying a cause led to change in management.
Karadag et al. ³¹	Retrospective case review	111	Turkey	HRCT diagnosis Children symptomatic for 4.9 years (1–14.9). Cough, 96.9%; sputum, 80.6%; dyspnoea, 49%; wheeze, 46.9%; haemoptysis, 10%; finger clubbing, 40.9%		Left lower lobe most commonly affected
Doğru et al. ³³	Retrospective case review	204 mean age 7.16 ± 3.72 years	Turkey	Diagnosis CXR, HRCT, bronchography, or histology Cough 84%, sputum production 22.5%, dyspnoea 8.8%	Infection 16.1%, asthma 11.8%, PCD 11.8%, congenital immune deficiency 5.4%, FB aspiration 2.4%, unknown 49%	Emphasized early diagnosis and treatment

(continued)

TABLE 2. (CONTINUED)

<i>Study</i>	<i>Type</i>	<i>Number of children</i>	<i>Location</i>	<i>Clinical features and diagnosis of bronchiectasis</i>	<i>Etiology</i>	<i>Additional information</i>
Santamaria et al. ³⁷	Retrospective case review	105	Italy	HRCT diagnosis median 7 years after chronic symptoms; 5.7 years after initial pneumonia	PCD 24%, primary immunodeficiency 10%, aspiration 4%, postpneumonia 7%; pertussis 4%, measles 3%; unknown 55%	First pneumonia <2 years of age associated with extensive disease Cohort higher prevalence of asthma
Zaid et al. ³⁹	Retrospective case review	92	Ireland	HRCT diagnosis. Median age 6.4 years. Symptoms for 3 years before diagnosis. Symptoms chronic wet cough, wheeze, and recurrent respiratory tract infection	Idiopathic 32%; postpneumonia 17%, immune deficiency 16%; recurrent aspiration 16%; primary ciliary dyskinesia 9%; chronic aspiration with immune deficiency 5%; postforeign body inhalation 2%; tracheomalacia 1%; obliterative bronchiolitis 1%. Concurrent bronchial asthma 20% GORD 11%	Left lower lobe commonly involved

CF, cystic fibrosis; CSLA, chronic suppurative lung disease; CXR, chest X-ray; FB, foreign body; GORD, gastro-oesophageal reflux disease; HRCT, high-resolution computerized tomography; LRTI, lower respiratory tract infection; PCD, primary ciliary dyskinesia; RML, right middle lobe; TB, tuberculosis.

TABLE 3. STUDIES OF PROTRACTED BACTERIAL BRONCHITIS

Study	Type	Number of children	Location	Diagnosis of PBB and clinical features	Main findings	Additional findings
Marchant et al. ⁴⁰	Prospective cohort study	108 investigated for chronic cough; median age 2.6 years	Australia	Adult-based algorithm for chronic cough followed until a diagnosis. Wet cough 89% and BAL led to a diagnosis in 45.4%.	PBB commonest final diagnosis; definite PBB 22.2%; probable PBB 17.6%	Asthma, GORD, and upper airway cough syndrome in <10% of the cohort
Donnelly et al. ¹⁵	Retrospective case review	81 with PBB. Median age 3 years 9 months (5 months–14 years 9 months)	United Kingdom	Clinical diagnosis. Persistent wet cough 95%; wheeze 48% and dyspnoea 43%.	<i>Haemophilus influenzae</i> 81%; <i>S. pneumoniae</i> 37%; both 30% from cough swab.	>50% cases symptom free after 2 courses of antibiotics. Thirteen percent required ≥ 6 courses. Treatment may prevent progression to bronchiectasis

BAL, broncho alveolar lavage; PBB, protracted bacterial bronchitis.

this clinical entity in industrialized nations. However, bronchiectasis remains a persistent problem among children in low- and middle-income countries as well as in certain indigenous populations, such as Alaskan natives in the United States, Aboriginal children in Australia, and Maori and Pacific Islanders in New Zealand, affecting predominantly children in lower socioeconomic classes.²⁶ Affected children have shorter life expectancy and place a considerable burden on the family as well as healthcare system.¹⁰

The pathophysiology of bronchiectasis includes airway inflammation, mucus production, and regional airway obstruction, yet the reasons why some children develop bronchiectasis and others do not are unclear.²⁵ In low- and middle-income countries, infections are the most common etiology of bronchiectasis.²⁶ Key infections implicated in the development of bronchiectasis are measles, tuberculosis, pertussis, and severe bacterial pneumonia.²⁷ Recent literature supports the hypothesis that bronchial infection and inflammation are key factors in the development of bronchial wall destruction and resultant bronchiectasis.²⁶

Studies of noncystic fibrosis bronchiectasis have consistently reported that infection remains a major cause of bronchiectasis, particularly in high-risk groups of low socioeconomic status (Table 2).^{16,28–39} The only case-control study, conducted in indigenous children in central Australia, showed a strong association between bronchiectasis and a history of hospitalization for pneumonia [odds ratio (OR) 15.2, 95% CI 4.4–52.7].³⁸ Delay in diagnosis of bronchiectasis was common, with the median duration of symptoms before diagnosis ranging from 17 months to 4.8 years across the reports. With improved immunization programs and aggressive antibiotic treatment of pneumonia, the incidence of bronchiectasis may diminish.

Despite the growing body of literature on bronchiectasis, there are still few data from low- and middle-income countries, especially those areas with high HIV or tuberculosis (TB) prevalence rates. Further research is needed to identify specific

infections or factors associated with development of bronchiectasis, in areas where pneumococcal conjugate vaccine has been introduced so as to improve prevention and management.

Pneumonia and chronic bronchitis

Chronic bronchitis or PBB is a chronic productive cough occurring for >3 weeks that resolves with appropriate antibiotic treatment.^{15,40} The definition of this condition has not been standardized and even its existence has been questioned.⁴¹ Landmark work conducted by Marchant et al. demonstrated that among children investigated for chronic cough with a modified adult protocol, the commonest diagnosis was PBB (accounting for 40% of all diagnoses; Table 3).^{15,40} In a retrospective review of clinically diagnosed PBB cases, *H. influenzae* and *S. pneumoniae* were the most commonly isolated organisms.¹⁵ Importantly, these studies were conducted before pneumococcal conjugate vaccine inclusion in the national immunization programs.

This research has been criticized for the definition of PBB used. Chronic cough of 1-month duration could be normal postinfectious cough and therefore a period of symptoms for >8 weeks has been suggested as more appropriate for defining PBB.⁴¹ Further diagnosis based on response to a 2-week course of antibiotics is limited, as this has not been compared to placebo. There are no well-established criteria for diagnosis of PBB and therefore no estimates of the burden of PBB in low- and middle-income countries. Agreeing on a universally accepted classification and diagnostic criteria will enhance the understanding of chronic bronchitis in childhood.

Pneumonia and BO

BO is a pathological process triggered by severe insults to the lower respiratory tract with subsequent narrowing and complete obliteration of the small airways.^{42,43} In children, BO most commonly occurs following severe pneumonia caused by adenovirus. Other common preceding infections

TABLE 4. STUDIES OF PNEUMONIA AND ASSOCIATION WITH BRONCHIOLITIS OBLITERANS

Study	Type	Number of patients	Location	Diagnosis of BO and clinical features	Outcomes	Additional findings
Zhang et al. ⁴⁹	Prospective, observational study	31 postinfectious BO Mean follow-up 3.5 years	Brazil	Clinical diagnosis, CXR, spirometry	Clinical remission 22.6%; persistence of symptoms and signs 67.7%, death 9.7%	Poor prognosis: older age at onset of illness and presence of atopy (elevated serum IgE)
Colom et al. ⁴⁴	Case-control	109 cases BO 99 controls without subsequent BO	Argentina	Diagnosis clinical and HRCT. Tachypnoea; rigid thorax 70%; wheeze 74%; persistent productive cough 89%; low SpO ₂ CXR: air trapping 96%; atelectasis 75%; incr interstitial pattern 55%; honeycombing 34% HRCT scans: mosaic perfusion 60%; bronchiectasis 58%; atelectasis 44%	Postinfectious BO- Ad 72%, RSV 10%, parainfluenza 4%, influenza 1%. Control patients, RSV most frequently identified 58%	OR of Ad infection in cases 83 (95% CI 22-441); need for mechanical ventilation (OR 12, 95% CI 5-34)
Castro-Rodriguez et al. ⁴⁶	Prospective, observational study	45 cases hospitalized Ad pneumonia Follow-up: 5 years	Chile	Diagnosis HRCT and impulse oscillometry technique: BO 47.4%	All cases had previous Adenovirus pneumonia	BO: nosocomial Ad; more severe infection. No cases had clinical deterioration during follow-up.
Murtagh et al. ⁴⁸	Retrospective, observational study	415 cases hospitalized Ad ALRI Mean age 10.7 months	Argentina	Diagnosis of BO HRCT Adenovirus ALRI bronchiolitis 45%, multifocal pneumonia 42%, unifocal pneumonia 13%. Eighty percent healthy before ALRI	Sequelae in 150; BO 78%, bronchiectasis and chronic atelectasis 22%.	9% of Ad serotyped: Ad7h 76.3%. Risks for BO: >30 days of hospitalization (OR 27.2, 95% CI 14.6-50.9), multifocal pneumonia (OR 26.6, 95% CI 5.3-132), and hypercapnia (OR 5.6, 95% CI 3.5-9)

Ad, adenovirus; ALRI, acute lower respiratory tract infection; BO, bronchiolitis obliterans.

include measles, respiratory syncytial virus, pertussis, *Mycoplasma pneumoniae*, influenza, or parainfluenza virus.^{42,43} There is little epidemiologic data available on the incidence of BO in children other than samples of patients who have undergone lung or bone marrow transplantation. Several investigators have suggested that postinfectious BO is more common in the Southern Hemisphere, particularly Argentina, Brazil, Chile, Australia, and New Zealand,^{43,44} and the possibility of a genetic predisposition has been proposed among Argentine Amerindians.⁴⁵

In a recent case-control study from Buenos Aires, Colom et al. showed that adenovirus was the factor most commonly associated with BO.⁴⁴ Both adenovirus infection (OR 49, 95% CI 12–199) and the need for mechanical ventilation (OR 11, 95% CI 2.6–45) were strongly and independently associated with an increased risk of developing BO. It is unclear whether mechanical ventilation contributes to BO by causing lung injury or whether it is an indicator of pneumonia severity. Castro-Rodriguez et al.⁴⁶ found similar associations between adenovirus and BO in a prospective study in Chilean children hospitalized with adenovirus pneumonia during an outbreak from June to August 1998, who were followed for 5 years. Of 45 children found to have adenovirus pneumonia, 38 survived the acute infection and almost half (47%) subsequently developed BO. Children who developed BO had more severe initial illness (intensive care unit admission, need for mechanical ventilation, and oxygen therapy) than children who did not develop BO. Adenovirus serotype may also play a role in the development of BO, with serotypes 3, 5, 7, and 21 implicated in pneumonia severity.⁴⁷ Only one of the observational studies (Table 4^{44,46,48,49}) reported on viral serotypes for 9% of their cohort and found that Ad7h was most commonly isolated.

More recently, Murtagh et al.⁴⁸ published findings from a case review of 415 children who were hospitalized with adenovirus pneumonia between 1988 and 2005 in Argentina. Independent risk factors for BO were >30 days of hospitalization (OR 27.2, 95% CI 14.6–50.9), multifocal pneumonia (OR 26.6, 95% CI 5.3–132), and hypercapnia (OR 5.6, 95% CI 3.5–9). Mechanical ventilation was an independent risk factor for death (OR 121, 95% CI 18.2–814) during the acute stage of illness but not for the development of BO.

Several studies have followed children with a diagnosis of postinfectious BO to investigate the long-term outcome of disease (Table 4). No deterioration in symptoms or pulmonary function occurred in the Chilean study⁴⁶ after BO diagnosis. Similarly, Zhang et al.,⁴⁹ in a prospective study, also found that postinfectious BO appears nonprogressive. In this study, children with an older age at onset of pneumonia or those with an elevated serum IgE (during diagnostic work up) had a worse prognosis. Although the prognosis of postinfectious BO is more favorable compared to BO postlung transplantation, there is still considerable morbidity in the form of increased use of home oxygen, recurrent pneumonia, and severe wheezing episodes. Relatively little literature on BO in low- and middle-income countries is available, perhaps largely due to lack of detection and diagnosis.

Associated Factors

There are a number of environmental or host factors that are prevalent in low- and middle-income countries that may impact on the susceptibility to developing severe pneumonia

in childhood and to chronic respiratory illness. These include exposure to biomass fuel smoke, malnutrition, poverty, and HIV.

Biomass fuel smoke exposure

Several studies have shown an association between respiratory illness and indoor air pollution.^{50–55} A recent World Health Organization meta-analysis reported that exposure to smoke from unprocessed solid fuels increased the risk of developing pneumonia in young children by 80% (OR 1.78, 95% CI 1.45–2.18).¹⁷ The contribution of indoor air pollution to chronic respiratory illness in childhood remains an important question and there is an accumulating body of scientific evidence to support such an association. A study conducted in an indigenous Guatemalan population demonstrated that the prevalence of asthma symptoms was higher in children from households using open fires compared to stoves with chimneys.⁵⁵ Further, studies have consistently demonstrated decreased pulmonary function among children exposed to indoor air pollution from biomass smoke.^{53,54,56,57} As yet, there are no longitudinal data on exposure to biomass fuel smoke and lung function in children or on its influence on the severity of respiratory disease or incidence of chronic suppurative lung disease.⁵²

Passive smoke exposure has been shown to affect lung growth *in utero*,^{58,59} and increase the risk for postnatal pneumonia and wheezing.^{60,61} The effect of passive smoke exposure on chronic respiratory illness may be mediated by predisposing to asthma, pneumonia, or bronchitis in children.⁶² Passive smoking represents an important preventable hazardous exposure in children.

Malnutrition

Promotion of exclusive breastfeeding is protective against pneumonia.^{63,64} Malnourished children are more susceptible to infection and have a higher risk of pneumonia and of developing more severe disease.¹⁸ Increased susceptibility to infection, multiple infections, and more severe pneumonia may predispose to the development of chronic respiratory illness. Micronutrient deficiencies such as vitamin A or zinc deficiency have also been linked to an increased risk of pneumonia or severe pneumonia,^{63,65} and may consequently influence the development of chronic respiratory illness.

Socioeconomic status

Lower socioeconomic status predisposes to more severe pneumonia and chronic respiratory illness.²⁰ There are many potential mechanisms that may be involved, including concomitant malnutrition, crowding, biomass fuel exposure, and poorer access to healthcare. Timely access to healthcare is essential for appropriate management of pneumonia and reducing mortality and severity of illness. Bronchiectasis and chronic bronchitis have consistently been shown to be associated with poor socioeconomic status and their diagnosis is often delayed in these environments leading to further morbidity.³⁵

Human immunodeficiency virus

Pneumonia is the leading cause of death and hospitalization in HIV-infected children, with most developing a lower respiratory tract infection during the course of their

HIV disease.¹⁹ Both infected or exposed but HIV-negative children with pneumonia have poorer outcomes than unexposed children.⁴ HIV has also altered the spectrum of etiological pathogens with a higher incidence of opportunistic infections such as *pneumocystis jirovecii* pneumonia or cytomegalovirus, gram-negative bacterial and mycobacterial infections, and more severe respiratory disease.⁵ Additionally, there is a higher rate of polymicrobial infection together with increased antimicrobial resistance with HIV infection.⁸ HIV-infected children are also at risk of chronic respiratory illness as a consequence of HIV progression, recurrent pneumonia, or severe pneumonia.⁶⁶ In the absence of highly active antiretroviral therapy, more than a third of HIV-infected children will develop some form of chronic respiratory illness by 4 years of age.⁶⁷ The development of bronchiectasis in HIV-infected children is strongly associated with low CD4 counts and severe immune suppression. Widespread use of highly active antiretroviral therapy and trimethoprim-sulfamethoxazole prophylaxis coupled with other preventive interventions, case management guidelines, and immunization can reduce the morbidity and mortality from pneumonia in HIV-infected children with possible impact on the risk for developing chronic respiratory illness.⁶⁸

Research Priorities

Based on this review, several critical gaps are apparent in existing understandings of chronic respiratory illness in children especially in low- and middle-income countries. In particular, the potential relationship of chronic respiratory illness with early childhood pneumonia and interaction of pneumonia with potential modifying factors has not been well studied. Future research priorities should include

- Standardized definitions of chronic respiratory illness, and the spectrum of chronic suppurative lung diseases in childhood for appropriate diagnosis, management, and comparison of research across a variety of settings. A recent position statement by Chang et al. proposes standard definitions to be used for chronic suppurative lung disease and bronchiectasis in children in Australia and New Zealand.⁶⁹ Comparison of these definitions and treatment recommendations across a variety of settings is needed.
- Study of the epidemiology of chronic respiratory illness across a range of low- and middle-income settings around the globe, particularly chronic suppurative lung disease in childhood following pneumococcal conjugate vaccine introduction
- Investigating the determinants of chronic respiratory illness in low- and middle-income countries to identify preventative interventions
- Longitudinal studies assessing the role of pneumonia and risk factors in the development of chronic respiratory illness in the context of pneumococcal conjugate vaccine and Hib immunization
- Gene-environmental interactions that may predispose to development of chronic respiratory illness in children

Conclusion

Chronic respiratory illness in childhood constitutes a spectrum of disease with varying natural history and considerable associated morbidity. There is broad epidemiological evidence to suggest an association between early pneumonia

and subsequent chronic respiratory illness; however, the quality of evidence varies considerably by each chronic disease. Although the pathogenesis of childhood chronic respiratory illness is likely multifactorial, prior pneumonia appears to play an important role. Preventing pneumonia through the use of vaccines and other public health strategies is likely to reduce mortality and morbidity from childhood respiratory illness. Chronic respiratory illness in children in low- and middle-income countries has been poorly studied; further research in this area is urgently needed.

Author Disclosure Statement

No competing financial interests exist.

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Received for publication November 17, 2010; accepted after revision December 13, 2010.