Etiology of Childhood Community Acquired Pneumonia and Its Implications for Vaccination

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Pneumonia is an important cause of morbidity and mortality among children throughout the world. Vaccines are available for some organisms, but they are underutilized and/or still in development. To evaluate the potential impact of vaccines, we review studies in which the etiology of childhood community-acquired pneumonia was recorded. In North America and Europe (9 studies), the etiology of pneumonia was established in 62% of studied children (range 43%-88%) by use of noninvasive specific methods for microbiologic diagnosis. The most often identified agents were *S. pneumoniae* (22%), respiratory syncytial virus (RSV) (20%), *Haemophilus influenzae* (7%), and *Mycoplasma pneumoniae* (15%). In Africa and South America (8 studies), bacteria were recovered from 56% (range 32%-68%) of severely ill children studied by lung aspirate. The most often isolated bacteria were *Streptococcus pneumoniae* (33%) and *Haemophilus influenzae* (21%). A high percentage of *H. influenzae* strains were not serotype b. Throughout the world, children requiring hospitalization were most likely to have infection caused by pneumococcus *H. influenzae* or RSV. Out patients also had *Mycoplasma pneumoniae*. Countries in Africa and Asia recorded 2 to 10 times more children with pneumonia (7 to 40/100 annually) than in the USA. Widespread use of pneumococcal and *H. influenzae* type b conjugate vaccines could reduce the frequency of childhood pneumonia by one-third. Further reduction will require development of non-type b *H. influenzae*, RSV and *M. pneumoniae* vaccines. This could result in a > 50% reduction of pneumonia in children. This goal should be sought and achieved as soon as possible.

Key words: community-acquired pneumonia, children, etiology, vaccine, *S. pneumoniae*, respiratory syncytial virus.

Acute lower respiratory tract infections (ALRTI) are a common cause of morbidity among children [1]. Among these infections, pneumonia is the most serious illness with an incidence of 36 to 40 episodes/1,000 children/year in those < 5 years of age, and 11 to 16 episodes in children 5 to 14 years of age in the USA and in Finland [2, 3]. In poor areas of the world, the incidence of pneumonia is up to 10 times higher than that recorded above [4]. This data is summarized in Table 1 in which incidence data from the USA is compared to that of 6 countries in Africa and Asia. In these areas, pneumonia is one of the leading causes of hospitalization and death [5-7]. At present, the epidemiologic pattern of pneumonia is being altered by changes in patient characteristics, such as increased immunosuppression, and by changes in medical practice [8]. Many bacteria and viruses can cause pneumonia and many of them can be detected by methods available only in research laboratories [9]. Control of pneumonia depends upon an understanding of the relative importance of etiologic agents for recommendations regarding treatment and for the development of vaccines [10].

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In this report, we reviewed the literature to identify studies of childhood community-acquired pneumonia in which the etiology was assessed by either lung aspiration or noninvasive, but specific, methods to study viruses and bacteria. This information has been summarized in order to assess the potential for an impact by vaccine prevention.

Defining the etiology

The difficulties in establishing a firm etiology for patients with pneumonia are well known. Culture of sputum is of uncertain value and samples of sputum are difficult to obtain from children [11]; the degree of concordance between pharyngeal secretion cultures and lung aspirate cultures was poor [12]; blood cultures yield a positive result in 1% to 27% of patients [9, 10, 13-15], and its isolation rate is highly dependent on when during health care it is done [16], and on which patients are recruited. It was shown that identification of nonbacteremic pneumococcal infections in children is difficult and confusing because different assays give different results [9, 17-19]. For optimal yield, several techniques should be used even for the detection of 1 microbe [9]. As yet, there are no sensitive and simple tests for the detection of the etiologic agents in biological fluids from patients with pneumonia. Consequently, there is a great shortage of data necessary for implementing potentially effective intervention measures [20]. Ideally, the determination of etiology should be based on isolation of the organism from infected lung tissue, as any growth from a needle aspirate of the lungs appears to be significant [21].

The information gained from 8 studies in which lung aspiration for culture was done are shown in Table 2. Since only culture was used, there is no information on virologic causes of childhood pneumonia. Criteria to be included was no history of recent antibiotic use in the studies from Africa, South America and Asia. Bacteria were recovered from 273 of 490 (56%) critically ill children studied [11, 12, 21-26]. The bacteria most often isolated were *Streptococcus pneumoniae* and *Haemophilus influenzae*, including both organisms several times. 19% of the *H. influenzae* strains typed were type b and the majority were other serotypes (25%) or nonserotypable types (NST) (56%) [11, 25]. The sensitivity of biopsy or needle aspiration of lung tissue was less than 100% [27]. Aspiration of lung tissue is a very invasive procedure, and was restricted to critically ill children. It is rarely done at the present time. However, in many countries of the world, this approach has yielded the only firm data on the frequency of various etiologic causes of pneumonia.

Noninvasive techniques can be used to seek evidence of viral and bacterial pulmonary infection, making it possible to study children with mild disease who could not ethically be studied for bacterial infection using lung aspiration [28]. Table 3 shows the summary of specific noninvasive methods for microbiologic diagnosis of the etiology of pneumonia, performed in several studies (see results in Tables 4 and 5) which results are shown in Tables 4 and 5 [9, 10, 13, 14, 18, 29-32]. In addition to the pathogens listed in Tables 4 and 5, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Chlamydia pneumoniae*, *Chlamydia trachomatis*, *Legionella pneumophila*, herpes virus, enterovirus, rotavirus, coronavirus, Epstein-Barr virus and varicella-zoster were also identified in several of those studies. Those studies were conducted in the USA, Finland, Spain, and Sweden. The etiology was established in 62% of the children studied (including both out patients and hospitalized children) and *S. pneumoniae* was identified as an important cause of pneumonia in all age groups. Respiratory syncytial virus (RSV) and *Mycoplasma pneumoniae* were the other most frequently identified agents. The classic view is that viruses probably do have a role in the initiation of bacterial invasion in pneumonia [33]. In this review, it is noted that respiratory viruses were present in 36% of the patients and mixed viral-bacterial infection was detected in 13% of the pneumonia cases.

RSV has long been recognized as the major viral pathogen of the lower respiratory tract of infants [34]. In Pakistan, RSV was identified in 33% of children with ALRTI.[35] In 148 Filipino children with ALRTI, evidence for viral infection was found for RSV (44.6%), adenovirus (18.2%), parainfluenza 3 (11.5%), influenza A (7.4%), influenza B (6.8%), parainfluenza 1 (6.1%) and parainfluenza 2 (5.4%) [36]. In South Africa, acute

Table 1. Examples of annual incidence of pneumonia in USA Compared to 5 Countries in Africa/Asia (Pechere J.C., 1995)

Location	Age (yr)	Annual incidence per 100 children
United States of America		
Chapel Hill, NC	<5	3.6
Seattle, WA	<5	3.0
Africa		
Maragna, Kenya	<5	18.0
Asia		
Bangkok, Thailand	<5	7.0
Gadchiorli, India	<5	13.0
Gilgit, Pakistan	<5	30.0
Haryana, India	<1*	40.0
	<1†	30.0
Papua New Guinea	<1	25.6

*Low birth weight; †Normal birth weight.

respiratory tract infections caused approximately 8% of all deaths in the under-5 age group; the published hospital-based incidence of RSV infection varied from 3% to 18%, and mortality rates were between 12% and 43% [37]. Currently available information from laboratory records and published South African literature is not sufficient to assess the impact of RSV infection [37]. In Hong Kong, the estimated annual incidence of RSV infection requiring hospitalization was 2.5/1000 children < 5 years old with a mortality of 0.15% among hospitalized cases and a mean hospital stay of 5 days. RSV vaccine is considered a priority by several experts [38]. RSV frequency has ranged from 15.8%-28% in several other studies conducted in Argentina, Ethiopia, Japan and Mexico, studying children with ALRTI [39-42]. Despite its important frequency, distinguishing RSV from other ALRTIs is difficult because of the similarities in clinical presentation [43]; RSV has also been associated with recurrent episodes of wheezing in children [44].

M. pneumoniae has been found in 27% to 38% of children with pneumonia studied in India, Japan and Poland [45-47]. Two other prospective studies reported evidence of infection with *M. pneumoniae* in 27% to 29.5%, and with *Chlamydia pneumoniae* in 15% to 28% of children with community-acquired pneumonia in the USA [48, 49].

The data presented here support the view that the most serious forms of pneumonia in children of all ages are pneumococcus, *H. influenzae* and respiratory syncitial virus. These are the agents against which vaccines are most needed, and, indeed, are most likely soon to be available. These are the agents that are also most likely to be the cause of pneumonia in children under 5 years of age. *Mycoplasma pneumoniae* and chlamydial pneumonia occur in older children and are less likely to require hospitalization. Viral pneumonia occurs most commonly in the very young, under age 5 years but, other than RSV, they are not as common a cause of hospitalization as are bacterial pneumonias. From this data, it can be concluded that the most important causes of morbidity and mortality in childhood pneumonia can be prevented by vaccines that are either now, or soon to be available.

Table 2. Bacteriologic findings in studies from Africa, Asia and South America evaluated using lung aspirates

Study	Country	Age (years)	Nº of positive bacteria isolated				
			Culture/total	*S. pneumoniae*	*H. influenzae*	*S. aureus*	Others
Schuster et al., 1966	Chile	≤ 10	67/125 (54%)	26/125 (21%)	19/125 (15%)	15/125 (12%)	13/125 (10%)
Rozov et al., 1974	Brazil	≤ 7	20/37 (54%)	15/37 (41%)	3/37 (8%)	1/37 (3%)	1/37 (3%)
Silverman et al., 1977	Nigeria	≤ 8	54/88 (61%)	31/88 (35%)	9/88 (10%)	8/88 (9%)	20/88 (23%)
Ferreira et al., 1978	Brazil	≤ 4	34/60 (57%)	25/60 (42%)	13/60 (22%)	0	0
Riley et al., 1983	Papua New Guinea	≤ 9	8/18 (44%)	7/18 (39%)	1/18 (6%)	0	0
Shann et al., 1984	Papua New Guinea	≤ 5	48/71 (68%)	27/71 (38%)	41/71 (58%)	1/71 (1%)	23/71 (32%)
Wall et al., 1986	The Gambia	≤ 9	29/51 (57%)	26/51 (51%)	12/51 (24%)	1/51 (2%)	2/51 (4%)
Ikeogu et al., 1988	Zimbabwe	≤ 11	13/40 (32%)	7/40 (18%)	3/40 (8%)	4/40 (10%)	1/40 (2%)
Total			273/490 (56%)	164/490 (33%)	101/490(21%)	30/490(6%)	60/490(12%)
Microbe Cause/ Detected				164/273 (60%)	101/273 (37%)	30/273 (11%)	60/273 (22%)

Table 3. Summary of noninvasive specific methods for microbiologic diagnosis of pneumonia*

Agents and assays	Assay	Diagnostic finding
Streptococcus pneumoniae		
Antibodies		
To capsular polysaccharides	EIA	3-fold rise
To C-polysaccharide	EIA	3-fold rise
To pneumolysin	EIA	2-fold rise
Immune complexes specific		
To capsular polysaccharides	EIA	GM + SD
To C-polysaccharide	EIA	GM + SD
To pneumolysin	EIA	GM + SD
Antigens	CIE, LA, CoA	
H. influenzae		
Antibodies(noncapsulated *H. i.*)	EIA	3-fold rise
Antigens	CIE, LA	
Moraxella catarrahalis		
Antibodies	EIA	3-fold rise
Chlamydiae		
Antibodies		
To re-lipopolysaccharide	EIA	3-fold rise
To common group antigen	CF	3-fold rise
Chlamydia pneumoniae	MIF	4-fold rise or IgM>1/16
Chlamydia psittaci	Culture, PCR	
Chlamydia trachomatis	MIF	4-fold rise or IgM>1/16
Mycoplasma pneumoniae	CF, EIA	3-fold rise
	IgM-EIA	
	Culture, PCR	
Legionella	IFA	
Respiratory viruses	Culture	
Antibodies	CF	4-fold rise
	EIA*, MIF, DFA, MNA	*3-fold rise
Antigens	Reverse-transcriptase PCR, FIA	
	Solid phase EIA	

*Modified from Heiskanen-Kosma et al. [31]; EIA: enzyme immunoassay; GM+SD: geometric mean + 2SD; CIE: counterimmunoelectrophoresis; LA: latex agglutination; CoA: coagglutination; CF: complement-fixation; MIF: microimmunofluorescence; MNA: microtiter neutralization assay; IFA: indirect immunofluorescent antibody *H.i.: H. influenzae*; DFA: viral direct fluorescent antibody; FIA:time-resolved fluoroimmunoasay with monoclonal antibodies.

Table 4. Etiology of childhood community-acquired pneumonia in Europe using non-invasive diagnostic techniques - hospitalized patients

Study	N	Country	Age	Etiology detected (total)	Total bacteria	*S. pneumoniae*	*H. influenzae*	*M. pneumoniae*	*M. catarrhalis*	Total viruses	Respiratory syncytial virus	Adenovirus	Rhinovirus	Influenza A or B	Parainfluenza 1,2,3	Mixed viral bacterial
Claesson et al., 1989	167	Sweden	Median 1 yr	71/167 (43%)	32/167 (19%)	27/167 (16%)*	1/167 tybe b (0.6%)	6/167 (4%)	NS	45/167 (27%)	33/167 (20%)	11/167 (7%)	NS	3/167 (2%)	5/167 (3%)	6/167 (4%)
Nohynek et al., 1991	121	Finland	Median 1.8 yr	84/121 (69%)	54/121 (45%)	19/121 (16%)*	21/121 (17%)	11/121 (9%)	9/121 (7%)	54/121 (45%)	34/121 (28%)	16/121 (13%)	NS	4/121 (3%)	8/121 (7%)	24/121 (20%)
Ruuskanen et al., 1992	50	Finland	Mean 4.4 yr	44/50 (88%)	31/50 (62%)	19/50 (38%)	6/50 (12%)	10/50 (20%)	5/50 (10%)	30/50 (60%)	15/50 (30%)	5/50 (10%)	5/50 (10%)	1/50 (2%)	4/50 (8%)	17/50 (34%)
Juvén et al., 2000	254	Finland	Mean 3.8 yr	215/254 (85%)	134/254 (53%)	93/254 (37%)	22/254 (9%)	17/254 (7%)	10/254 (4%)	158/254 (62%)	73/254 (29%)	19/254 (7%)	58/238 (24%)	10/254 (4%)	25/254 (10%)	77/254 (30%)
Total	592			414/592 (70%)	251/592 (42%)	158/592 (27%)	49/425** (12%)	44/592 (7%)	24/425** ** (6%)	287/592 (48%)	155/592 (26%)	51/592 (9%)	63/288 *** (22%)	18/592 (3%)	42/592 (7%)	124/592 (21%)
Microbe Cause/ Detected	X 414				251/414 (61%)	158/414 (38%)	49/343 ** (14%)	44/414 (11%)	24/343 ** (7%)	287/414 (69%)	155/414 (37%)	51/414 (12%)	63/259 *** (24%)	18/414 (4%)	42/414 (10%)	124/414 (30%)

NS = not studied; * low percentage in very young infants believed by the authors due to poor immune response. Organism was present in nasopharynx (25%).
**Claesson study excluded because only type b *H. infuenzae* was tested and *M. catarrhalis* was not tested.
***rhinovirus not tested in 2 studies.

Table 5. Etiology of chilhood pneumonia in North America and Europe diagnosied by non-invasive techniques - primarily out-patient children

Study	N	Country	Age	Etiology detected (total)	Total bacteria	*S. pneumo-niae*	*H. influ-enzae*	*M. pneumo-niae*	*M. catar-rhalis*	Total viruses	Respir-atory syncytial virus	Adeno-virus	Rhino-virus	Influ-enza A or B	Para-influ-enza 1,2,3	Mixed viral bacterial
Ramsey et al., 1986*	162	USA	Median 21 mo	77/162 (48%)	47/162 (29%)	29/162 (18%)	12/162 (7%)	13/162 (8%)	NS	50/162 (31%)	15/162 (9%)	6/162 (4%)	6/162 (4%)	10/162 (6%)	10/162 (6%)	13/162 (8%)
Turner et al., 1987*	98	USA	Median <2 yr	47/98 (48%)	19/98 (19%)	17/98 (17%)	2/98 (2%)	0	NS	39/98 (39%)	27/98 (28%)	1/98 (1%)	2/98 (2%)	2/98 (2%)	5/98 (5%)	10/98 (1%)
Ausina et al., 1988*	198	Spain	Median 5 yr	157/198 (79%)	115/198 (58%)	29/198 (15%)	3/198 (2%)	79/198 (40%)	NS	53/198 (27%)	29/198 (15%)	5/198 (3%)	NS	8/198 (4%)	10/198 (5%)	NS
Heiska-nen-Kosma et al.,1998**	201	Finland 5.6 yr	Mean (66%)	133/201 (51%)	102/201 (28%)	57/201 (6%)	12/201 (22%)	44/201 (3%)	6/201 (25%)	51/201 (21%)	43/201 (2%)	4/201	NS	0 (3%)	6/201 (10%)	20/201
Wubbel et al., 1999	168	USA	Median 3 yr	73/168 (43%)	47/168 (28%)	35/129 (27%)	NS	12/168 (7%)	NS	31/157 (20%)	13/157 (8%)	3/157 (2%)	NS	5/157 (3%)	7/157 (4%)	5/168 (3%)
Claesson et al., 1989	169	Sweden	Median 5 yr	89/169 (53%)	45/169 (27%)	17/169 (10%)	2/169 type b (1%)	27/169 (15%)	NS	52/169 (31%)	34/169 (20%)	7/169 (4%)	NS	7/169 (4%)	6/169 (4%)	8/169 (7%)
Total Microbe X/	996			576/996 (58%)	375/996 (38%)	184/957 (19%)	29/659 (4%)	175/898 (19%)	6/201 (3%)	275/985 (28%)	161/985 (16%)	26/985 (3%)	8/260 (3%)	32/784 (4%)	44/985 (4%)	56/798 (7%)
Cause/ Detected	576				375/576 (65%)	184/576 (32%)	29/414 (7%)	175/529 (33%)	6/133 (5%)	275/576 (48%)	161/576 (28%)	26/576 (5%)	8/124 (6%)	32/443 (7%)	44/576 (8%)	56/419 (13%)

* 19% to 21% of patients required hospitalization. ** 32% of patients required hospitalization.

Prevention

The etiology of childhood community-acquired pneumonia is varied and establishing its etiology is complex. Nonetheless, from both groups of studies listed (Tables 2, 4 and 5), *S. pneumoniae* was the most frequently identified agent. *S. pneumoniae* was also found to be associated with death in children with pneumonia [28]. Pneumococcal polysaccharide vaccines have been recommended since 1985, for children older than 2 years who are at high risk of invasive disease (for example asplenic children). These vaccines have not been recommended for younger children and infants because of poor antibody response before 2 years of age [50]. In contrast, pneumococcal conjugate vaccine (Prevnar) induces protective antibody responses in > 90% of infants after 3 doses are given at 2, 4, and 6 months of age [51]. In efficacy trials, infant immunization with Prevnar decreased pneumonia by 73% [52]. The Food and Drug Administration (FDA) and the Committee on Infectious Diseases of the American Academy of Pediatrics have recently approved the use of Prevnar in children younger than 24 months in the USA [52]. However, it is clear that the efficacy of Prevnar, or any other conjugate pneumococcal vaccine, will depend on the serotype distribution of *S. pneumoniae* in the region where the vaccine is to be used [53, 54]. For example, by comparing Prevnar serotypes with the prevalence of serotypes among 360 pneumococcus strains isolated from children with invasive disease in three cities of Brazil, Prevnar would prevent 55% of pneumococcal invasive disease [55]. Since the licensure of conjugate *H. influenzae* type b (Hib) vaccines in late 1990, there has been a > 98% elimination of Hib disease in the USA [56]. Hib is a very important cause of primarily invasive diseases like meningitis and bacteremia [57].

Pneumonia can also be an invasive disease but secondarily because the initial contamination route is the respiratory airway [58]. Serotype b is more likely to invade the bloodstream from the lung than NST strains [56]. It is believed that *H. influenzae* pneumonia is usually due to serotype b because of results from blood cultures [59]. However, Ghafoor et al., reported that nonencapsulated *H. influenzae* accounted for 32% of the *Haemophilus* isolated from the blood of children with acute lower respiratory tract infections in Pakistan [35]. It has been shown that Hib was found in just 19% of pneumonia caused by *H. influenzae* in lung aspirate investigations [11, 25]. Because the conjugate *H. influenzae* vaccine is restricted to serotype b, we can expect that the wide use of the conjugate Hib vaccines would reduce about 20% to 30% of pneumonia caused by *H. influenzae.* A RSV effective vaccine is not currently available.

New approaches to the development of a vaccine are promising [60]. However, phase III efficacy trials in infants and young children are still required before final approval [61]. The current trend has been to identify subunit vaccines [62], or a live RSV intranasally administered vaccine. Both of these vaccines are immunogenic and safe in children and adults, and the latter also protects against RSV-induced airway hyperresponsiveness in the setting of allergic sensitization [63]. Recent advances in RSV vaccines have made RSV a more important topic for epidemiological research and surveillance. Basic research required before vaccine programs can be developed includes quantifying the burden of disease attributable to RSV, and defining the best surveillance methods with which to evaluate different vaccination strategies [64]. *M. pneumoniae* oral vaccination offers a promising route for stimulating protective immunity while minimizing undesirable recall immune events, but those studies are still restricted to animal models [65].

Conclusion

The etiology of childhood community-acquired pneumonia is only partly known. Up to this moment, many pathogens may have a role in establishing the infection but *S. pneumoniae, H. influenzae,* RSV and *M. pneumoniae* are responsible for more than half of the cases. Non-type b *H. influenzae* is an important cause of pneumonia, as are numerous serotypes of pneumococcus. The immunogenicity of the conjugate vaccines for *S. pneumoniae* and *H. influenzae* is type-specific. It can be calculated that by widespread use

of currently available pneumococcal and *H. influenzae* type b conjugate vaccines, 30% of pediatric pneumonia cases could be prevented, depending on the serotype distribution of each of those pathogens in the region where vaccines are to be used. From the foregoing data, it is clear that, in addition to pneumococcal and Hib conjugate vaccines, an efficacious RSV vaccine is highly desirable, as well as non-type b *H. influenzae* and *M. pneumoniae* vaccines, in order to reduce the pneumonia burden by at least 50% of present levels. This would be an important advance in medical care, particularly in regions of the world where childhood pneumonia is so common.

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