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Serotypes and pathogens in paediatric pneumonia

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ABSTRACT

Multiple pathogens may cause pneumonia. Three vaccines with demonstrated or potentially major impact on paediatric pneumonia caused by pneumococcus and/or non-typable *Haemophilus influenzae* (NTHi) are projected to soon become globally available. Estimating the magnitude of this impact requires precise knowledge of the etiology of pneumonia. We reviewed studies to evaluate the relative importance of specific pneumococcal serotypes and NTHi as pneumonia pathogens. While emerging conjugate vaccines, especially those containing serotype 1, appear to have great potential toward the prevention of childhood pneumonia based on expanded serotype coverage, the importance of NTHi in childhood pneumonia has yet to be elucidated.

1. Introduction

Clinicians usually treat paediatric pneumonia without determining a precise etiologic diagnosis, due to the insensitivity and/or lack of specificity of current diagnostic tools. Sputum, urine samples, and nasopharyngeal swabs are minimally invasive and relatively easy to collect; however, they have limited ability to determine pneumonia etiology in young children, likely due to the high prevalence of asymptomatic nasopharyngeal colonization with both *Streptococcus pneumoniae* and *Haemophilus influenzae*, making them inappropriate techniques for research or clinical settings [1–3].

However, to assess the value of new conjugate vaccines targeted at a broad range of pneumococcal serotypes or non-typable *H. influenzae* [3], it is important to identify the pathogens responsible for disease. *S. pneumoniae* is generally considered the major cause of pneumonia, but this pathogen alone has multiple disease-causing serotypes, and the individual importance of each serotype is only partially known. The role of non-pneumococcal bacteria, such as *H. influenzae*, in pneumonia is believed to be significant, but the precise proportion due to non-typable *H. influenzae* (NTHi) – considered "non-typable" because it lacks a polysaccharide capsule – remains unclear. The involvement of NTHi in paediatric respiratory disease has been suspected because NTHi is a common colonizer of the nasopharynx in young children and because, along with pneumococcus, it represents one of the two major causes of another mucosal disease, bacterial acute otitis media [4]. In addition, the lack of the polysaccharide capsule, widely presumed to be an important (though not absolute) impediment towards efficient survival in the blood stream [5], might not be a major barrier to causing pulmonary infection.

Notwithstanding the dearth of etiological data for most pneumonias, some information may be gleaned from microbiologic and vaccine studies of certain pneumonia subsets and related conditions where more definitive diagnoses are available. These include studies utilizing the lung tap methodology, analyses of bacteremic pneumonias, and culture- and molecular-based diagnoses of parapneumonic effusions and empyemas. In addition, some estimates of pneumococcal serotype distribution can be deduced from clinical efficacy studies with pneumococcal conjugate vaccines.

2. Assessing pathogens in pneumonia: potential role of the lung tap

Transthoracic needle aspiration, or lung tap, provides samples from areas of consolidation within the lung and is thus, in principle, one of the most definitive ways to assess pneumonia. Due to concerns about safety of the procedure, studies of this technique have generally been limited to those severe cases where a radiologically identifiable lobar consolidation can be targeted, and use of this procedure has been limited in the most recent years. Vuori-Holopainen and Peltola [6] performed a review of 59 studies which evaluated lung tap results between 1909 and 1997, all before the era of *H. influenzae* type b vaccine. Table 1 summarizes their results. Not surprisingly, the last studies reported from Europe and North America were from 1956 and 1967, respectively. Many patients had

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Table 1
Summary of lung tap studies

Years	Continent	Number of studies	Number of patients	Cases of *S. pneumoniae* identified (%)	Cases of *H. influenzae* identified (%)	Proportion NTHi of all cases of *H. influenzae* (%)
1909–1956	Europe	7	168	81 (40)	42 (21)[a]	ND
1917–1975	North America	10	204	63 (31)	4 (2)	0/1 (0)
1966–1980	South America	7	885	85 (10)	52 (6)	0/2 (0)
1933–1997	Africa	18	659	164 (17)	112 (12)	3/8 (38)
1966–1996	Asia	12	674	67 (10)	30 (5)	ND
1983–1991	PPNG	2	101	34 (34)	42 (2)	26/31 (84)

NTHi = non-typable *Haemophilus influenzae*, ND = not done, PPNG = Papua New Guinea. Source: Ref. [6].
[a] ≥81% of all *H. influenzae* during a measles epidemic.

lung taps, and in many of these cases culture of the taps revealed infection due to *S. pneumoniae*. Specifically, the lung taps identified *S. pneumoniae* in 10–40% of these cases and *H. influenzae* in 2–21% of these cases.

In their review of the 59 lung tap studies, Vuori-Holopainen and Peltola [6] identified 558 cases in which both blood cultures and lung taps were performed. Of these cases, a causative agent was identified in 45% (252 cases) of the lung aspirates, in comparison to 25% (137 cases) of blood cultures. In this review, Vuori-Holopainen and Peltola examined 570 cases that evaluated findings from lung taps in patients with chest radiographs that demonstrated lobar pneumonia. Of these cases, 50% (284 cases) had lung taps that identified an etiologic agent, 78% of which were due to *S. pneumoniae* and 7% were due to *H. influenzae.*

The literature review also examined the safety of this procedure. While the lung tap is an invasive procedure, it was noted that the procedure was safer than is generally considered. The overall complication rate was 4.8%. Pneumothorax, the most common complication, was usually asymptomatic and resolved spontaneously.

Vuori-Holopainen et al. [7] also conducted a recent prospective study in Finland evaluating lung tap. In this study, 34 children were enrolled following hospital admission for pneumonia, defined as respiratory symptoms and signs in combination with a history of fever and chest radiograph demonstrating consolidation. Lung aspirates were obtained from all of the children, and 26 of these samples were considered representative samples, meaning the sample showed leukocytes on microscopic examination. Using culture and PCR detection techniques, a bacterial etiology was determined in 59% of all patients enrolled and 69% of patients with a representative sample. Pneumococcus was identified in 18 of the 20 cases with representative samples. No *H. influenzae* was identified in these 20 samples. In comparing the result of lung tap to blood cultures, they found that lung tap identified an etiologic agent in 16 cases where blood culture did not identify an organism.

3. Pneumococcal serotypes in pneumonia

While a diagnosis of pneumococcal pneumonia provides a disease etiology, without serotype information this etiology remains nonspecific when attempting to develop or evaluate a pneumonia vaccine. Pneumococcus has at least 91 immunologically distinct serotypes. Multiple serotypes may cause disease and the predominant serotypes may vary over time and geography. Furthermore, serotypes have varied virulence and immunogenicity. The licensed heptavalent pneumococcal conjugate vaccine (PCV7) contains serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. An experimental nonavalent vaccine (PCV9) produced by the same manufacturer includes the additional serotypes 1 and 5 and was tested in clinical efficacy studies in The Gambia and South Africa. However, PCV9 apparently will not be commercialized in favor of a 13-valent pneumococcal conjugate vaccine (PCV13), containing those serotypes plus 3, 6A, 7F and 19A. Finally, serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F are also contained within the 10-valent Pneumococcal *H. influenzae* protein D conjugate vaccine (PHiD-CV), and a similar vaccine using the protein D carrier protein has previously demonstrated some clinical efficacy against non-typable *H. influenzae* acute otitis media [8]. Therefore serotype (and pathogen) identification is critical to understanding the potential value of each of these formulations.

3.1. What can be deduced from vaccine probe studies?

The impact of PCV9 on all consolidated pneumonias in young children (as determined by standardized radiological criteria developed under the auspices of the World Health Organization) was assessed in large efficacy studies in South Africa [9] and the Gambia [10]. While the results of these studies do not reveal the serotype-specific contribution to these pneumonias, using a few reasonable assumptions one can calculate the minimal proportion of consolidated pneumonias that must be due to one of the nine serotypes contained in the vaccine, as indicated by the formula in Fig. 1a. Rearranging the equation, one can then "solve" the equation for the proportion of all pneumococcus due to those types (Fig. 1b). The numerator (proportion prevented) is a known quantity, as it was measured in the two studies, and is the average of 37% (The Gambia) and 20% (South Africa), or 28.5% (Fig. 1c).

To obtain the minimum proportion of consolidated pneumonia-causing pneumococcus that must be vaccine types, one needs to maximize the denominator (proportion of pneumonia caused by pneumococcus multiplied by vaccine efficacy against vaccine types). The proportion of all pneumonias caused by pneumococcus cannot be more than 100%. It is extremely unlikely that the true vaccine efficacy against pneumonia is higher than that measured in those trials against invasive pneumococcal disease (IPD), and that is 80%, the average of 77% in The Gambia and 83% in South Africa. With these values, one can calculate that least 35.6% of the pneumococcus causing consolidated pneumonias must be vaccine-preventable types (Fig. 1d).

It may be more plausible to (arbitrarily) assume than no more than 80% of all consolidated pneumonias are due to pneumococcus, and that true vaccine efficacy against pneumonia is actually 57%, which was what was seen with PCV7 against another mucosal infection, acute otitis media (AOM) [11]. In that case the proportion of pneumococcus due to the nine-valent vaccine types would be calculated to be equal to 62.5% (Fig. 1e). Vaccine efficacy most likely falls between 57 and 80%, thus the proportion of nine-valent vaccine type pneumococcus in alveolar pneumonia is somewhere between 35.6 and 62.5%.

3.2. Pneumococcal serotypes in bacteremic pneumonia

Blood samples allow a highly specific, culture-confirmed identification of pathogens, with two limitations. First, they have an unknown sensitivity, and secondly, by definition they only pro-