Nontypeable *Haemophilus influenzae* and childhood pneumonia

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**SUMMARY**

Nontypeable *Haemophilus influenzae* (NTHi) is a common microbe frequently isolated from the nasopharynx of children. Bacterial pneumonia is a major cause of morbidity and mortality in children less than 5 years of age, with the burden of disease being greatest in developing countries. Determination of the bacterial aetiology of pneumonia is difficult due to sampling constraints. However, with a combination of sampling approaches, trans-thoracic fine-needle aspiration, blood culture and screened sputum, the evidence strongly suggests that NTHi is a significant causative pathogen of pneumonia in young children. However, further studies are required. The development of a new pneumococcal conjugate vaccine containing *H. influenzae* protein D has the potential to be beneficial against disease caused by NTHi, including pneumonia. With the implementation of this vaccine in many regions of the world where NTHi disease is endemic, it will be critical to introduce surveillance programs wherever it is used.

**Introduction**

Nontypeable *Haemophilus influenzae* (NTHi) is a common microbe isolated from the upper respiratory tract of both children and adults. Despite its commensal colonization profile NTHi has been identified as the causative agent of a number of diseases with significant socioeconomic impacts. The disease spectrum of NTHi includes serious diseases such as pneumonia, otitis media and invasive diseases, particularly bacteraemia and meningitis. In addition, NTHi is renowned for causing disease primarily associated with mucosal surfaces such as sinusitis, conjunctivitis and exacerbations of chronic bronchitis.

**Carriage**

In developed countries, NTHi is carried in the nasopharynx of up to 40% of children (1-3). However, children in many developing countries such as Papua New Guinea (PNG) and in indigenous nations within developed countries are heavily colonized in the nasopharynx by NTHi, as well as *Streptococcus pneumoniae* and *Moraxella catarrhalis* within weeks of birth (4,5). Whilst it has been suggested that this very early and heavy colonization of the upper airways may downregulate mucosal immune responses (6), further studies are required to confirm this observation and to assess the clinical relevance of carriage-induced hyporesponsiveness.

**Burden of respiratory disease**

Respiratory infections account for greater than 50% of paediatric disease globally with greater proportions being reported in Africa and Asia (7). Pneumonia represents the greatest burden of disease, accounting for more than a third of all respiratory diseases and approximately 1.5 million deaths in children less than 5 years of age annually (8).

NTHi as a causative agent of pneumonia

Determination of the bacterial aetiology of pneumonia is difficult, with trans-thoracic fine-needle aspiration being the most reliable sample to culture. However, because of the potential risks associated with needle aspiration it is not used as a routine source of culture material (9). Furthermore, needle aspiration is only performed in the presence
of consolidation. Hence the identified pathogens represent those associated with severe disease. Blood cultures are routinely conducted in laboratories but are only of value in cases of bacteraemic pneumonia. There are also issues of poor sensitivity of blood culture as well as the possibility that bacteria, which do cross from the lung into the blood stream may not be reflective of the bacteria present in the infected lung. Blood culture favours capsular organisms and is therefore likely to underestimate the presence of NTHi in the lung. A number of studies have collected sputum from patients with pneumonia. As NTHi is often found in the upper respiratory tract of healthy subjects, sputum samples can be technically criticized on the basis that contamination from the upper respiratory tract could occur. If sputum samples are to be considered it is important that they be screened for upper airway contamination by assessing the number of squamous epithelial cells (10-12). Studies comparing paired sputum and trans-tracheal aspirates (13) and sputum culture for Haemophilus species (14) have demonstrated that if sputum samples are selected on the basis of containing less than 25 squamous epithelial cells per low-power field and 2 or more alveolar macrophages then these sputum samples are valuable in determining the aetiology of bacterial pneumonia (13), particularly that caused by Haemophilus species (14). Nevertheless the collection of quality sputum samples from young children is difficult. More recently, bronchoalveolar lavage has been helpful in determining the bacterial aetiology of pneumonia, particularly as this sampling method has less risk of contamination from the upper airway secretions.

Studies in PNG in the early 1980s demonstrated that bacterial pneumonia was a major cause of child mortality (15,16). Whilst H. influenzae type b accounted for much of the Haemophilus isolated from the blood of children with bacteraemic pneumonia and the cerebrospinal fluid of children with meningitis, NTHi predominated in lung tissue of children with severe pneumonia. Furthermore, NTHi was often co-cultured in the lung tissue with S. pneumoniae or serotypeable H. influenzae (17). Outside PNG, lung aspirate studies to support an aetiological role for NTHi in childhood pneumonia have had mixed results, suggesting that there are possibly geographical as well as socioeconomic determinants of the bacterial aetiology of pneumonia. In South Africa, Nigeria and Zimbabwe lung aspirate samples were positive for NTHi on 15%-40% of occasions (18-20). In a very recent study in The Gambia 50 lung aspirate samples obtained from children under 5 years of age were analysed by both culture and molecular typing (21). As might be predicted molecular typing was found to be much more sensitive than routine culture. S. pneumoniae was found in 92% of the samples whilst H. influenzae was found in 20%. However, H. influenzae was always detected with S. pneumoniae. All the Haemophilus detected was non-type b with half being NTHi. In the early 1970s, 2 studies were reported from the USA (22,23). The first of these studies (23) reported the presence of H. influenzae in 5% of aspirates that produced positive cultures. Unfortunately, no serotyping of the cultured Haemophilus was conducted and the media was not ideal for the culture of Haemophilus. In the second study Haemophilus was not cultured from any of 27 lung aspirates taken from children with pneumonia aged 2 months to 16 years. S. pneumoniae was the predominant bacterium isolated (22). In a study from Chile NTHi was not cultured from 31 lung aspirate samples (24). Surprisingly, in the Chilean study NTHi was not present in cultures of the nasopharynx, suggesting a possible technical problem for the culture and identification of NTHi.

Despite the disadvantages of blood culture, NTHi has been detected in 2%-10% of samples from children with bacteraemic pneumonia (17,25-27).

In two studies of community-acquired pneumonia, sputum results are informative. A study conducted in Singapore of children aged 1 month to 16.3 years (median 4.2 years) demonstrated that NTHi predominated among the Haemophilus species detected (94%) and was present in 22% of samples in which bacteria were identified (28). The second study, conducted in Australia, isolated bacteria from approximately a third of sputum samples collected from children aged 4-15 years; in a third of these positive samples NTHi was isolated. However, NTHi was not detected in blood cultures, where S. pneumoniae predominated (29).

Bronchoalveolar lavage has recently been used to assess bacterial aetiology in children with community-acquired bronchopneumonia
(30). In this study H. influenzae was the predominant bacterium isolated with most strains being nontypeable.

Overall, the published literature suggests that NTHI can be a causative agent for bacterial pneumonia without any predisposing risk factors. However, there are some clear geographical differences and further studies are required not only to determine more accurately the distribution and burden of disease due to NTHI, but also to assess the impact of pneumococcal conjugate vaccines on NTHI disease.

The need for a vaccine

Of the bacterial pneumonias in children, NTHI pneumonia is clearly the most prevalent after that caused by S. pneumoniae, and in some regions NTHI may predominate or at the very least be a significant co-infecting organism. Whilst there are very poor surveillance data for NTHI pneumonia, it is not unreasonable to predict that following the introduction of pneumococcal conjugate vaccines containing a greater number of serotype valencies the prevalence of NTHI pneumonia will increase. This is most likely to occur in regions where there is high carriage load of NTHI in the upper airways. Therefore, there is a need to develop a vaccine against NTHI. When the total burden of NTHI disease (otitis media, exacerbation of chronic bronchitis and invasive disease) is considered, the case for an NTHI vaccine is even more compelling (31). The development of a vaccine by GSK (GSK Belgium), Synflorix™, where the pneumococcal polysaccharides are conjugated to an active carrier from NTHI, protein D, is an innovative step. However, it will be important to implement appropriate surveillance to monitor the impact of this vaccine on both pneumococcal and NTHI disease.

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