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PNEUMOCOCCAL ETIOLOGY OF PNEUMONIA IN CHILDREN

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✓ **Annotation**
Following the widespread introduction of childhood pneumococcal conjugate vaccines (PCVs), a significant impact on pneumonia mortality in children under five years of age has been reported. It is still unknown whether PCVs are expected to reduce pneumonia burden in younger children, particularly ≤2 months of age, as current evidence on the role of S. pneumoniae in pneumonia etiology in this age group is scarce.
Keywords: Mycoplasma pneumoniae, Systematic Review, pneumonia etiology, bacterial pneumonia, children

Introduction

Globally, pneumococcal infections, caused by Streptococcus pneumoniae (Pneumococcus), are one of the leading causes of morbidity and mortality in children <5 years of age [1-3]. A variety of clinical syndromes of varying severity are associated with pneumococcus, including pneumonia, meningitis, bacteremia, otitis media and sinusitis. It has been estimated that prior to the introduction of pneumococcal conjugate vaccines (PCVs), diseases caused by pneumococcus were responsible for approximately 600,000 deaths per year globally in children 1-59 months of age [4-7].

Pneumonia is among the leading causes of mortality in children under 5 years of age [8-11]. The main causative pathogens attributable to pneumonia include Streptococcus pneumoniae, *Haemophilus influenzae* type B, all of which have vaccine-preventable bacterial causes, and respiratory syncytial virus. Infants and young children are at highest risk for serious disease, with children younger than 4 months being more likely to die. In addition to pneumococcus, a variety of other infectious agents are related to pneumonia in children [12-16].

In the last two decades, more than 140 countries globally have introduced PCVs into national routine immunization schedules. Several studies have demonstrated the impact of PCVs on reducing invasive pneumococcal diseases and hospitalizations due to pneumonias[17-21]. However, pneumonia mortality is the greatest concern for policymakers and donors, and there is limited evidence on the impact of PCVs on pneumonia deaths in children.

Recent evidence from countries in Latin American using secondary mortality data demonstrated the impact of PCVs on pneumonia mortality in children under 5 years of age. Most studies did not include children <3 months of age assuming that perinatal causes of mortality and other etiologic agents and not pneumococcal disease are responsible for the pneumonia mortality in this age group [18-21]. Nonetheless, this assumption is not fully backed up by the very little available evidence in the literature on the etiology of pneumonia in this age group. Although selected studies have indicated that respiratory viruses are the most common pathogens of pneumonia in infants and toddlers, some investigators have implicated pneumococcus and *Haemophilus* in 4–20% of cases. These findings vary significantly in

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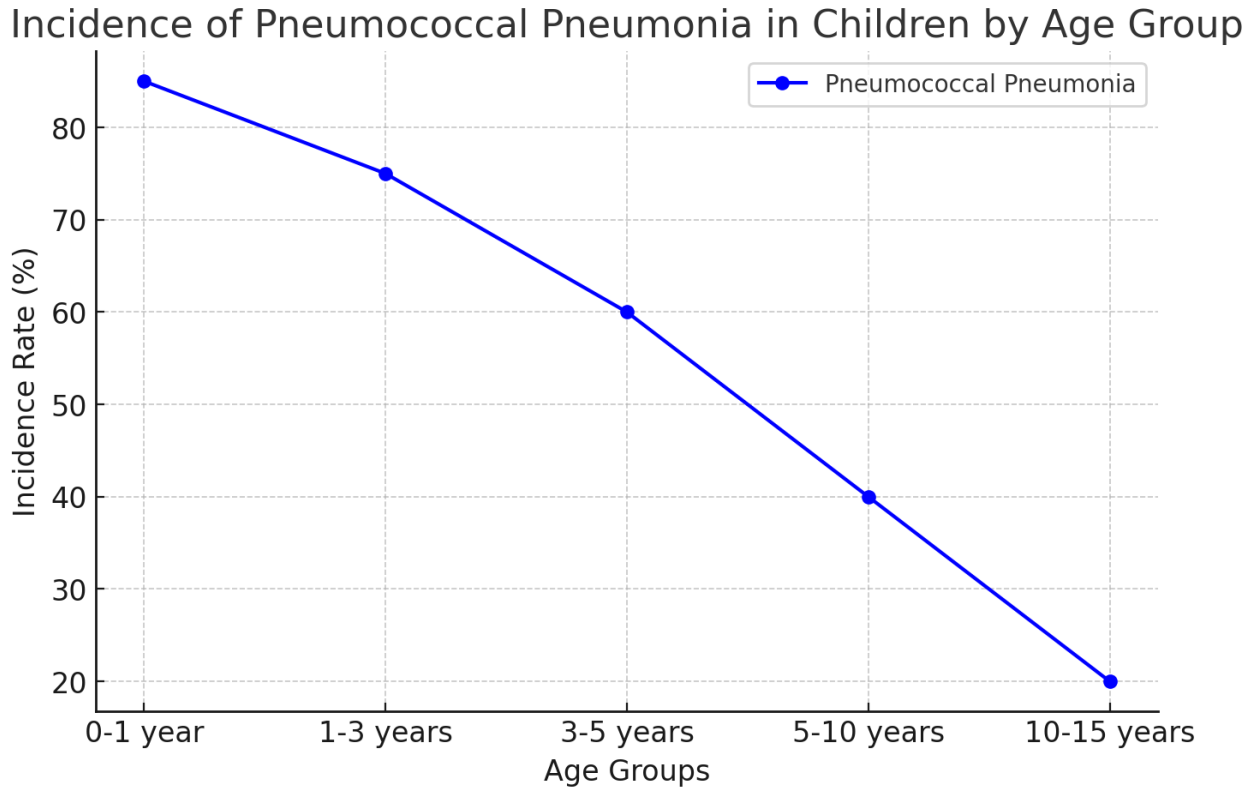
developing versus industrialized countries, over time, and depending on laboratory methods used to assess etiologies.

It is still not clear whether pneumococcus is a significant cause of pneumonia in younger children, particularly neonates and children <3 months of age. Whether or not to include children in this age group in impact assessment studies will depend on evidence suggesting whether pneumococcus is a significant etiology of pneumonia and thus an important burden in children under 3 months of age [22-26].



This systematic review aims at summarizing the evidence of the bacterial etiology of respiratory infections in children under 3 months of age, in particular the role of pneumococcus as a significant etiology in this age group.

The aim of the work: to develop an algorithm for timely diagnosis in bacterial etiology of pneumonia in children based on the study of clinical diagnostic markers and serum predictors.

Materials and methods

PCR is considered the new "gold standard" with the higher sensitivity, most assays can detect <100 CFU/mL; The specificity is strong and there is no cross-reactivity when appropriate target selection and amplification conditions are validated. Nucleic acid amplification techniques used to detect MP DNA or RNA differ in the selection of target genes used (e.g. P1 gene, 16S rDNA, 16S rRNA, ATPase operon gene, etc.) (PCR versus isothermal amplification techniques) and the form of detection (conventional versus real-time, single versus multiple) [27-29]. The most problematic issue with PCR is colonization or asymptomatic carriage.

It is extremely rare to compare the performance of PCR methods with different Mycoplasma pneumoniae target areas and primers. P1 adhesin gene primers were

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found to be more sensitive than 16S rRNA primers, which may be due to the presence of multiple copies of the P1 cell adhesion gene. Studies have compared three different PCR detection methods: the detection method initially described by Bernet, with and without additional hybridization steps for amplicon detection, and the newly developed nested PCR [35-39]. All three PCR methods are reliable in detecting MP in respiratory specimens, but nested PCR is the most sensitive [30-34]. Due to the differences in sample collection, transportation and extraction procedures, input sample size, target genes, primers, cycle parameters, and detection systems, the comparison of sensitivity data for different PCRs becomes complicated.

Clinical treatments

When MP infection is clearly defined, the main treatment method is drug treatment. Rational and standardized use of antibiotics can reduce symptoms and shorten the course of disease.

Mild MPP is more common in school-age children over 5 years old, with a course of 7–10 days, most patients have a good prognosis. The main clinical manifestations are fever and cough, wheezing and dyspnea can be detected in a small number of infants and young children. Imaging findings are bronchitis and bronchopneumonia; only a few patients can develop into severe. Severe MPP refers to the severe condition of MPP, which conforms to any of the following manifestations: high fever ≥ 5 days or fever ≥ 7 days, or wheezing, shortness of breath, dyspnea, chest pain, hemoptysis and other symptoms. These manifestations are related to severe lesions, combined with plastic bronchitis, asthma attacks, pleural effusion and pulmonary embolism; extrapulmonary complications occurred, but did not meet the criteria for critical illness; finger pulse oxygen saturation ≤ 93% when breathing air at rest. The imaging findings were one of the following: large area of pulmonary consolidation; single lung diffuse or double lung multi-leaf segmental bronchiolitis showed. Critically MPP refers to severe MPP with rapid progression, respiratory failure or life-threatening extrapulmonary complications that require life-support treatment.

Conclusion

This review demonstrates that available evidence on etiology of pneumonia in young children, particularly children younger than 3 months of age is based on a variety of studies with non-standardized methodology. Syndromes and case definitions as well as age subgroups included (younger than 7 days and younger than 28 days) vary significantly among studies. Samples collected and tests performed also vary significantly, and also over time, with molecular methods available in more recent studies. Studies also vary in terms of sample size, and time and locality in which it has been conducted. All of these are known factors which may influence the reported etiology and also the ability to identify selected agents. Adequate specimens and testing methods should be used for studies evaluating etiology of pneumonia in children, in particular molecular techniques with higher sensitivity.

Despite the above limitations and challenges, this review reinforces that Gram-positive organisms, in particular *S. pneumoniae*, are still important etiologic agents of pneumonia in children under 3 months of age and should thus be considered when assessing impact of PCV in the children. In addition, viral etiologies are also important, responding for a significant proportion of pneumonia in children younger than 3 months of age.

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