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Policy Forum

What Are the Implications for Childhood Pneumonia of Successfully Introducing Hib and Pneumococcal Vaccines in Developing Countries?

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Pneumonia is the single commonest cause of death in children under five years old, accounting for 2 million out of 10 million childhood deaths worldwide [1]. Severe pneumonia is an important diagnostic syndrome within the World Health Organization (WHO)/UNICEF system for triage and clinical management in developing countries, the Integrated Management of Childhood Illness (IMCI). The objective of IMCI is early recognition of disease and timely access to effective therapy; for severe pneumonia, this means referral to hospital and treatment with life-saving antibiotics directed against the principal etiological agents, *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) [2].

The Global Alliance on Vaccines and Immunization (GAVI) is now supporting introduction of conjugate Hib vaccine into routine childhood immunization programs in 24 developing countries [3], and introduction of 7-valent pneumococcal conjugate vaccine (PCV) will begin in three countries in 2008 [4]. As global coverage of these vaccines expands, the principal etiological causes of severe pneumonia will largely be controlled by immunization. The incidence of severe pneumonia and its attendant mortality may be reduced by 50% or more. If so, this will become a historic public health achievement and a pattern to emulate in other significant infectious diseases of poverty. However, even if these highly effective vaccines reduce pneumonia mortality by half, residual deaths from pneumonia in childhood will still outnumber deaths from malaria [5]. A tremendous global health problem will remain.

Furthermore, as much of our thinking about pneumonia is dominated by the two vaccine-preventable pathogens, we will be poorly positioned to diagnose and manage these residual cases. In this policy discussion paper, we look to the future and imagine the implications of a successful vaccination campaign against *H. influenzae* type b and pneumococcus. Our assumption in doing so is that the burden of childhood pneumonia due to these infections will be dramatically reduced, and we discuss how such a reduction will influence the clinical diagnosis, classification, management, and control of pneumonia. Although significant global coverage of 10- or 13-valent pneumococcal vaccines may be 10–15 years ahead, the slow translation of ideas to research, policy, and then practice in developing countries suggests that we need to anticipate this scenario now.

Summary Points

- In developing countries, pneumococcus and *H. influenzae* type b are the dominant causes of severe pneumonia in children, and introduction of conjugate vaccines against these diseases could reduce the global burden of severe pneumonia by about half.
- Present classification and management guidelines for childhood pneumonia are founded on the dominance of these two organisms and will rapidly become obsolete as these vaccines are introduced.
- The residual cases of pneumonia will have a wide variety of etiological causes and will include many cases of tuberculosis and noninfectious respiratory disease.
- This broad etiological diversity will make the diagnosis, classification, and management of pneumonia much more complex and expensive in future.
- To be relevant to future policy, research in the areas of pneumonia diagnosis, classification, prevention, or management should begin to anticipate this scenario now.

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Abbreviations: GAVI, Global Alliance on Vaccines and Immunization; Hib, *Haemophilus influenzae* type b; IMCI, Integrated Management of Childhood Illness; PCP, *Pneumocystis jiroveci* pneumonia; PCV, pneumococcal conjugate vaccine; RSV, respiratory syncytial virus; WHO, World Health Organization

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1. Present Classifications of Pneumonia Will Become Obsolete

The World Health Organization pneumonia classification system was designed to be used at first point of contact, where a few reproducible signs could be elicited by health workers with only basic training. Bacteria account for the majority of fatal cases of pneumonia and, as treatment with antibiotics may be life-saving and the adverse consequences of overtreatment are not significant, the case definition emphasizes sensitivity over specificity. Thus, pneumonia is diagnosed simply by counting breaths per minute with different rate thresholds at different ages in children with a history of cough or difficulty breathing. Severe pneumonia is classified by the presence of lower chest wall indrawing and very severe pneumonia by signs of hypoxia or mental changes [6].

Pneumonia may also be classified by radiological patterns. Here again WHO has set standards in the interpretation of chest radiographs to minimize inter-observer variation in detecting alveolar consolidation or pleural effusion, both of which are strongly associated with bacterial etiology [7,8]. Hib vaccine was shown to reduce radiologically confirmed pneumonia by approximately 20% among children in trials in The Gambia and Chile [9,10]. A 9-valent PCV prevented 37% of cases of radiologically confirmed pneumonia among children in The Gambia who were already receiving Hib vaccine [11]. Combining these two protective effects from The Gambia suggests that radiologically confirmed pneumonia would be reduced by 50% following introduction of both vaccines. The effectiveness of each vaccine may be augmented further, in operational use, by herd protection [12,13], and the breadth of protection of PCV may also increase when 10- and 13-valent vaccines become available over the next two to four years. The radiological classification was designed primarily to evaluate vaccines against Hib and pneumococcal pneumonia and is not particularly sensitive to other etiologies. For example, in the Gambian trial of 9-valent PCV, only one third of placebo recipients with severe clinical pneumonia had radiographic appearances that satisfied the WHO criteria [11].

At present the WHO radiological definition beautifully illustrates the efficacy of Hib and pneumococcal vaccines in trials, and the WHO clinical case definition sensitively captures patients with Hib and pneumococcal pneumonia for timely and effective antibiotic treatment. When these two diseases are controlled by vaccination, the rationale supporting both definitions will disappear. Little attention has been given to classifying the other etiologies of pneumonia, and in 10–15 years "other etiologies" will comprise almost all cases of pneumonia.

2. Present Case Management Strategies Will Become Outmoded

The WHO case management strategy, formulated in 1991, is rational and evidence-based [14]. A review of all etiology studies in developing countries using blood and lung aspirate cultures concluded that 55% of cases of hospitalized pneumonia were caused by bacteria, and approximately 70% of these cases were attributable to just two organisms, *S. pneumoniae* and *H. influenzae* type b [14]. Given the insensitivity of culture techniques [15], it is reasonable to assume that more than half of all cases are attributable to just two agents, and empiric treatment guidelines were designed to target these pathogens specifically. WHO supported a series of community-based controlled trials of this case management strategy, and in a meta-analysis of seven of these trials the estimated reduction in pneumonia mortality attributable to the intervention was 24% [16]. As WHO extended its empiric management guidelines to all the major syndromes of childhood, the pneumonia case management strategy became formalized within IMCI [2]. The two pathogens upon which the strategy is founded are precisely those whose decline we now anticipate.

3. Causes of Pneumonia Will Become More Diverse

Beyond Hib and pneumococcus, the limited evidence we have from children 2–59 months old suggests that the remaining pathogens are more equally distributed [17–23]. These include the bacteria *Staphylococcus aureus*, *Moraxella catarrhalis*, viridans group streptococci, *Klebsiella pneumoniae*, *Escherichia coli*, Acinetobacter species, non-typhi Salmonellae, *Bordetella pertussis*, non-typeable *H. influenzae*, and *Mycobacterium tuberculosis*; the viruses RSV (respiratory syncytial virus), influenza A, influenza B, parainfluenza, adenovirus, human metapneumovirus, and rhinovirus; and the atypical organisms *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Chlamydia trachomatis*. *Pneumocystis jiroveci* pneumonia (PCP) occurs primarily in immunosuppressed infants and children [23–25]. With a broad and even diversity of pathogens, the old strategy for empiric therapy of "picking the winners" may not have a significant clinical impact.

This diversity also reveals the impracticability of vaccination as the mode of further pneumonia control, except perhaps for RSV pneumonia. The benefits of vaccination against *H. influenzae* type b and pneumococcus have been efficient because of the simplicity of immunization and the dominance of the two pathogens; for the myriad of remaining causes of severe pneumonia, which cannot all be prevented by vaccination, devising effective diagnostic and case management strategies will be considerably more difficult. By contrast, preventive strategies that act across a range of different etiologies, such as improving indoor air quality or preventing micronutrient deficiency, will appear relatively more efficient in future.

4. Noninfectious Respiratory Disease Will Become More Prominent

The sensitive WHO clinical definitions of pneumonia encompass a wide variety of lung diseases, not all of which have the typical lung consolidation of pneumonia. Furthermore, etiology studies tend to overemphasize infectious causes of respiratory disease, and it is not until the lung is examined at post-mortem that the full breadth of noninfectious causes becomes apparent. Among 84 HIV-negative children who died of respiratory disease in Zambia, half had acute pyogenic pneumonia at necropsy and 7% had PCP, while 18% had interstitial pneumonitis and 11% had pulmonary edema [24]. Anemia, malaria, congenital heart disease, acute interstitial pneumonitis, eosinophilic pneumonia (secondary to helminthiasis or schistosomiasis), and poisoning,

especially with kerosene [26], may all present with difficulty breathing or cough and a raised respiratory rate.

Unless the visual pattern of breathing is examined critically or an audible wheeze is sought in the breath sounds, asthma is easily misclassified as WHO-defined pneumonia [27]. As bacterial pneumonia declines in incidence, asthma will become relatively more prominent in the differential diagnosis of respiratory disease. Simultaneously with the increase in industrialization and urbanization in the developing world, the prevalence of asthma, bronchospasm, and atopy are also increasing in absolute terms [28,29]. The implications for health services are substantial: to distinguish asthma from pneumonia and provide appropriate therapy requires clinical training at a level much higher than is presently required for community- or primary care–level IMCI.

5. Tuberculosis Will Cause a Significant Proportion of Severe Pneumonia

Among children with HIV infection, tuberculosis is a common cause of respiratory disease. For example, among 242 children admitted to hospital in Durban with WHO-defined severe pneumonia, 38 (16%) had culture-proven tuberculosis and 85% of these had a history of illness lasting less than two weeks [23]. In the necropsy study in Zambia, tuberculosis was diagnosed in 32 (18%) of 180 HIV-infected children dying with respiratory disease [24]. In both these studies the prevalence of tuberculosis was equally high in HIV-uninfected children. If half of all present cases of severe pneumonia were prevented by antibacterial vaccines, tuberculosis would account for one third of future pneumonia cases in areas like these with a high prevalence of HIV. The insensitivity of diagnostic tests makes it difficult to estimate the role and prominence of *M. tuberculosis* in childhood pneumonia, and a "trial of treatment" in patients who are unresponsive to penicillin or chloramphenicol is a blunt diagnostic tool with significant toxic potential.

6. Antibiotic Therapy Will Become More Expensive

The decline of pneumococcus and Hib will raise two therapeutic problems. Firstly, if an antibiotic is required at all it will have to cover a significant proportion of the bacteria listed above in section 3, which, in practice, suggests a third-generation cephalosporin, a macrolide, or a quinolone. These drug classes are substantially more expensive than the present developing world pharmacopoeia of benzyl penicillin, amoxicillin, gentamicin, and chloramphenicol. Although newer drugs are widely available in Asia, their cost is likely to create inequities in health care on a local scale and also between continents as they are less accessible in Africa. Furthermore, the potentially massive scale of their use in childhood pneumonia may lead to widespread antibiotic resistance, compromising the treatment of other important infectious diseases such as typhoid, bacterial meningitis, nosocomial infections, and tuberculosis.

Secondly, there is little existing clinical evidence from developing countries to support the use of alternative antibiotics. For some of the causes listed, such as *C. trachomatis*, what evidence there is suggests that most patients recover without requiring antibiotics [30]. Antibiotic treatment is also superfluous for uncomplicated viral pneumonia. In a context where antibiotics are expensive and are actually required in only a minority of cases, a management algorithm that can focus this expensive resource on those who are likely to need it becomes an urgent priority. This will require a higher standard of clinical assessment than is presently available under IMCI and the implementation of follow-up appointments in health systems, especially for those not receiving an antibiotic.

7. There Will Be Too Much Etiological Data, Not Too Little

In the past, microbiological studies have rarely defined the etiology of more than two-thirds of all cases of pneumonia [17–20,22]. It is assumed that the undiagnosed fraction has roughly the same distribution of causes as the diagnosed fraction and that the division is accounted for by the poor sensitivity of the diagnostic assays used, such as blood cultures and complement fixation tests. Molecular diagnostics, using multiplex PCR assays, MassTag PCR, and microarrays, will provide a wealth of data to re-evaluate this undiagnosed group [31–33]. However, existing studies, using traditional insensitive techniques, have frequently found evidence of two or more pathogenic agents within the same patient with pneumonia [17,23]. Highly sensitive molecular techniques are likely to lead to an explosion of "multiple etiologies." Although the interaction between different agents in pneumonia pathogenesis is an interesting and convincing biological phenomenon, the likelihood is that the majority of agents identified in these patients will be either false laboratory positives or, more likely, false etiological positives—meaning that they are truly present but not involved critically in the development of disease. This tends to occur especially when the material under assay comes from the upper respiratory tract.

The new diagnostic tests will pose a considerable challenge to scientists working on pneumonia to evaluate causation through convincing observational and experimental designs. Identification of the pathogen within lung tissue is more convincing than identification in the nasopharynx. The absence of the pathogen in healthy controls or in subjects whose illness is confined to the upper respiratory tract would add yet more conviction to the claim of causality. However, the most convincing evidence would come from focused intervention studies. Reduction of pneumonia in vaccine probe studies using influenza or RSV vaccines would permit an assessment of primary viral pneumonia and the role of viruses in secondary bacterial pneumonia. Alternatively, the additional effectiveness of broad spectrum antibiotics over present treatment standards in "undiagnosed" pneumonia would argue for a bacterial etiology.

8. Management of Pneumonia Will Be Determined by Risk Groups

Inevitably, without one or two dominant causes common to all types of patients, we will use the matrix of etiologies against patient and geographical risk factors to focus treatments to best effect. The single convenient and globally applicable treatment algorithm for "pneumonia" will be replaced by a complex branched algorithm. The full matrix will only

become apparent through further etiological studies, but some divisions are well established, and WHO has already differentiated its guidelines on treatment of HIV-positive and malnourished children. Pneumonia is more likely to be bacterial in young infants than it is in older children, and the causative bacteria are different; "adult" pneumococcal serotypes, which are not covered by present vaccines, group A streptococcus, group B streptococcus, and *E. coli* all occur with relatively greater frequency in the first two months of life [34–36]. Gram-negative bacteria are considerably more common among malnourished children than well-nourished children [19]. PCP, salmonellosis, and lymphoid interstitial pneumonitis are all more frequent among children with HIV [37]. In all children, contact with a case of tuberculosis may be a risk factor well worth determining. Nosocomial infections represent a large potential risk that has been little studied in developing world settings. Geography too may play a significant part in the distribution of likely causes, separating for example Asia from Africa but also differentiating at country level. The prior probabilities of several etiologies, such as RSV, also vary considerably with season [38].

9. Ideal Point-of-Care Diagnostics Will Define Risk Factor Classification

One solution to the changing epidemiology of pneumonia is the development of a new bedside diagnostic test using modern molecular technology. However, given the scenario envisaged above, the point-of-care diagnostics that will be most useful in the specific management of pneumonia will be an HIV test with CD4 lymphocyte count, a generic marker of invasive bacterial disease, and a sensitive and rapid test for tuberculosis. Indications for supportive therapy are unlikely to change in the post-vaccine era and will rely heavily on the availability of oximetry to guide oxygen therapy. Radiographic classification of respiratory disease has evolved little in the developing world, though many district hospitals that lack relatively basic tools are equipped with X-ray machines. There may be considerable additional gains in extending the WHO radiological classification of pneumonia to define simple reproducible signs for lung disease caused by other etiologies.

Conclusion

It may seem rash even to contemplate the decline of *S. pneumoniae*, which has evolved as a varied, adaptable, and enduring human parasite. However, the operational success of PCV immunization in America does prompt this very consideration. If the initiative of the GAVI Alliance to introduce effective vaccines against Hib and pneumococcus throughout the developing world succeeds in reducing these diseases significantly, our present approach to the management of pneumonia will abruptly become irrelevant.

To prepare against this possibility, we need to re-examine thoroughly the broad clinical problem that is currently labeled "pneumonia"; that is, (i) to define and measure the causes of this collection of respiratory diseases; (ii) to determine the clinical, radiological, and laboratory features, or risk factors, that will differentiate these causes; (iii) to develop and validate appropriate tests to make this differentiation at first and second referral level; (iv) to invest in community health systems and train health workers to recognize these more complex clinical patterns and use these new tests; (v) to estimate the effectiveness of treatments against the various causes through clinical trials which, by virtue of their focus on a subset of all cases of pneumonia, are likely to involve multiple sites; and (vi) to combine all these steps into a rational and appropriate management strategy within developing countries that also integrates attempts to reduce risk factors such as HIV infection, indoor air pollution, and poor nutrition. This represents at least a decade's work, yet the situation we anticipate will arrive in many developing countries before a decade is out. "Early adopter" countries that introduce both vaccines into routine immunization in the next few years will provide useful settings in which to test research ideas.

Despite dominating the childhood mortality tables throughout the developing world, severe pneumonia has received little scientific or public health attention for decades. The formation of a Global Action Plan for Pneumonia at WHO and the interest of public health foundations in supporting pneumonia research in developing countries are both welcome reversals of this longstanding neglect [39]. In the context of this renewal of interest, we argue that it is critically important to recognize the rapidity with which the target disease will change across the developing world and to anticipate in the research we propose today the very different clinical and epidemiological spectrum of pneumonia in the future. ■

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