Pneumococcal vaccination and childhood pneumonia in South Africa

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For the past 30 years the dominant role of acute respiratory infections, especially pneumonia, as a cause of illness and death in children in the developing world has been appreciated. The strategy employed throughout the developing world to address the problem was based on the early detection and treatment of likely pneumonia cases at the community level by primary healthcare workers using a strategy developed in Papua New Guinea in the 1970s.[1] The strategy relied on two physical signs—fast breathing (to identify possible pneumonia cases in need of antibiotics) and lower chest wall indrawing (to identify more severe cases in need of admission). Originally a programme, solely for the management of acute respiratory infection cases, this was integrated, in 1991, into a broader case management strategy for young children, Integrated Management of Childhood Illness (IMCI).[2] IMCI has since formed the basis of child survival strategies throughout the developing world. The effectiveness of this approach is uncertain, although it is clear that child mortality has since fallen throughout most of the developing world. Studies of the aetiology of severe pneumonia have repeatedly shown the dominant bacterial causes to be *Streptococcus pneumoniae* (pneumococcus) and *Haemophilus influenzae* (usually type b or Hib), and these are generally assumed to be responsible for most deaths.

In a global public health effort that is unprecedented since the UNICEF-WHO led Universal Childhood Immunisation campaign of the 1980s, the international community is in the process of rolling out new expensive vaccines, including Hib and pneumococcal conjugate vaccines (PCVs) into the poorest countries of the world (http://www.gavi.org/support/nvs/pneumococcal/).[3] This is not just the latest in a series of new vaccines to be added to national programmes. Hib and PCV introduction represent a direct attack on the leading cause of child illness and death in the world today, pneumonia. Yet curiously the true burden of pneumonia, at national and global levels, remains unclear. This is in part because we lack clear definitions. As most deaths from pneumonia occur outside the health system in settings that lack appropriate healthcare, pneumonia mortality estimates are based on verbal autopsy studies, in which the families of deceased children are visited some months after the death and their recollection of the course of the child's final illness is recorded and interpreted by a panel of doctors to identify the most likely cause. This is of course very crude, as are the models that are derived from such studies combined with vital registration data. The result is a very wide range of possible estimates for pneumonia mortality.[4] In recent years there have been a series of global and regional estimates of pneumonia mortality by specific aetiology, also using models that are based on very sparse data. In fact the only valid approach to understanding pneumonia burden by aetiology comes from vaccine trials designed to measure the impact of Hib and pneumococcal vaccines.[5] These trials used the WHO standard of radiographic pneumonia, and all found that the radiological definition was the pneumonia definition that produced the clearest difference between vaccinated and unvaccinated children.[6] By implication this was the pneumonia definition that was most enriched for bacterial pneumonia. This has been used to provide an estimate of the fraction of radiological pneumonia cases due to the immunisation target (Hib or pneumococcus), and this is used, in turn to estimate the distribution of pneumonia deaths by bacterial aetiology.[7 8]

When it comes to understanding the morbidity burden of pneumonia we are not in much better shape. There have been brave efforts to develop global conclusions based on meta-analysis of many studies that used a variety of surveillance methods and definitions. These have attempted to apply WHO IMCI definitions to the various studies, and concluded that, in developing countries, the overall incidences of pneumonia and severe pneumonia are 290 and 19.7 per 1000 child-years, respectively, for children under 5 years of age.[9 10] In fact, prospective studies of the burden of pneumonia are rare, and again the best data available come from trials of Hib or pneumococcal vaccines. In rural Gambia the incidences of pneumonia and severe pneumonia in children 6 weeks–2 years were 249 and 15 per 1000 child-years, respectively, in a pneumococcal vaccine trial.[5] Two recent studies from South Africa address the childhood pneumonia burden from two perspectives. Madhi *et al*, writing in this journal, present a case control study of the impact of PCV introduction on pneumonia in South Africa, while in another publication, le Roux *et al*[11] present a fascinating look at pneumonia in two rather different communities after the introduction of PCVs in South Africa.

The Madhi study uses a case control methodology to evaluate the impact of PCVs on pneumonia in South Africa. To define pneumonia they used the WHO radiological definition, but added a softer group with non-specific X-ray changes and an elevated C-reactive protein (CRP). This probably did not affect the results as only 22% fitted into this category. The use of case control methodology to evaluate vaccine effectiveness is based on the comparison of vaccination rates among cases and controls of the same age. A relatively simple formula is used to calculate vaccine effectiveness from ORs. However the approach has some problems that are evident in this study. The first is the choice of controls. The control group is used as a measure of the vaccine coverage in the community, against which the vaccination statuses of cases are compared. In short, a lower rate of vaccination among cases can be translated into a measure of vaccine effectiveness. Identifying and sampling the community from which the cases are drawn is not easy, especially in settings where access to care varies within a community. The choice is between controls recruited from hospitalised patients potentially matched for known confounders, and community controls, recruited from neighbouring households, or (better) selected randomly from a community database, as was done in the Madhi study. Whether hospital or community controls are used there is always a problem with refusals. Potential controls who refuse are less likely to be vaccinated, so the more refusals there are the greater the estimate of vaccine coverage in the community, and the greater the measured

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effectiveness. In this study we are not given information about refusals. Hospital-based controls on the other hand, are ill and may not be representative of the population from which the cases have been drawn. It is also possible that their hospitalisation is associated with risk factors of interest, which may lead to biased estimates of vaccine effectiveness. In the Madhi study, the authors address the challenges of selecting suitable controls by recruiting two different control groups; age-matched hospital controls were recruited for all sites, and for Soweto community controls were also recruited. The results are presented as crude estimates (taking no account for confounding factors) and adjusted estimates (controlled for potential confounding variables). In the case of rare diseases, such as meningitis, where the dominant risk factors can be seen as lack of immunisation and bad luck, this can be expected to produce reliable results. This may not be the case with pneumonia, as risk of pneumonia is largely due to factors such as malnutrition, poverty and crowding, and it can be expected that higher-risk children may be less likely to be immunised, leading to an elevation in measured effectiveness.

In fact what we see with this study is a wide range of estimates with effectiveness estimates derived from use of community controls declining when risk factors are adjusted for, as we might expect, but with the analysis of hospital controls the opposite trend occurs, which is hard to understand. From these results we can conclude that PCV introduction seems to be associated with a reduction in radiological pneumonia incidence among HIV-negative South African children, but we cannot quantify the effect.

Our understanding of the burden and trends of childhood pneumonia has been greatly limited by unclear definitions, and a startling lack of research. The situation has been complicated by the recent decision by WHO to alter the definition of 'severe pneumonia requiring admission'. Until 2013, the definition was based on the presence of lower chest wall indrawing or danger signs. Since 2013 lower chest wall indrawing has been dropped from the definition, while other signs such as respiratory distress have been added.

The changes in the WHO definitions of severe pneumonia span the enrolment period for the recent prospective study of pneumonia epidemiology by le Roux *et al* (May 2012–May 2014).[11] It is important to note that the study was conducted after the introduction of the 13-valent PCV in South Africa in 2011. The analysis of the study incorporates the new WHO definition. The incidence rates of pneumonia and severe pneumonia in the study were 270 and 60 per 100 000 child-years, respectively. The high rate of severe pneumonia is based on only 32 cases and may reflect some uncertainty with the changing definitions. The continuing high rate of clinical pneumonia may appear to indicate that the vaccine has had little impact, but this may also reflect the fairly intense monitoring of the cohort.

The contrasting nature of the two communities involved in the study make the le Roux study a truly fascinating and important study. While in Mbekweni, the predominantly black African community is poorer and less likely to be living in formal housing, with a higher prevalence of maternal HIV infection, their children have a lower incidence of pneumonia than those of the predominantly mixed-race TC Newman community (220 vs 320 episodes per 1000 child-years). This appears to be related to three important risk factors:

1. Maternal smoking, which was much higher in the TC Newman community
2. Nutrition, which was substantially worse in the TC Newman community, and
3. Crowding, which was also worse in the TC Newman community, despite the factors mentioned above

The nutrition differences are of interest. While more Mbekweni children were never breastfed, possibly due to the HIV-positive mothers being advised not to breastfeed, birth weights were lower in the TC Newman community, presumably due to maternal smoking. Rates of exclusive breastfeeding were low and similar in both communities, but it seems possible that qualitative aspects of breastfeeding were superior in the Mbekweni community. Overall the study highlights the devastating impact of maternal smoking on the respiratory health of children, probably overwhelming all other risk factors.

This study was undertaken in a community with good vaccination coverage. Seventy per cent of children received the primary series of three doses of Hib and two doses of PCV, with most receiving the third dose of pneumococcal vaccine at or soon after 9 months. Those vaccines, and probably other trends associated with development and availability of antibiotics, are changing global patterns of pneumonia epidemiology while the international community continues not to monitor these effects in any systematic way. In the present study mortality was low; only one child actually died of pneumonia. Meanwhile the prevalence of wheezing was high, with over 60% of pneumonia cases having wheeze. This is becoming a common feature of pneumonia studies in some parts of the world, especially south Asia. This raises difficulties in interpretation, and is closely related to the WHO decision to change the definition of severe pneumonia. Lower chest wall indrawing has been a strong sign of severe pneumonia and a recent study of factors identified with a fatal outcome in pneumonia found indrawing to be an important sign.[12] It is also a common sign in wheezing children, especially infants in whom the likely diagnosis is bronchiolitis.[13] Growing dissatisfaction with this component of the WHO definitions is likely to be associated with an increasing proportion of children classified as severe pneumonia who actually have wheezing illness, with a much lower probability of a fatal outcome. This led to a series of studies of community management of severe pneumonia, which generally showed this approach to be safe and effective. Many children in those studies had wheezing and case fatality rates were extremely low, raising serious doubts about the applicability of the study results to high mortality settings where wheezing is not so common.[14]

Here again the international community is shamed by its lack of serious prospective studies of respiratory disease in children in a range of settings. With notable exceptions of internationally funded studies of particular communities, such as those in Mozambique, Gambia, Kenya, Vietnam and Bangladesh, there are few studies monitoring communities at a time when the epidemiology is changing, under the influence of specific measures such as new vaccines as well as rapid societal changes such as urbanisation. We must first recognise those studies that publish data that are partly or totally modelled. Then studies such as the study of le Roux *et al* must be supported and converted to long-term cohort studies.

Understanding the overall impact of vaccines on pneumonia is not a simple task. The case control methodology seems like the logical way to approach this, but the Madhi study shows just how difficult this approach is, and how uncertain the results may be. Of particular concern is the susceptibility to bias with this approach. A recently completed multicountry study of the aetiology of childhood pneumonia, the Pneumonia Etiology Research for Child Health (PERCH) study, has attempted to define

the aetiological causes of pneumonia in settings of new vaccine introduction. While the long awaited publication of PERCH data may provide some indication of how pneumonia aetiology has changed since the last such study, over 20 years ago, it seems likely that the variable prevalence of wheeze in the sites will limit that interpretation. What is needed now are more long-term prospective studies undertaken in settings where community development, healthcare and public health interventions are evolving. Such studies need to use common methodologies to address trends in the incidence of pneumonia, the prevalence of wheezing and pneumonia mortality rates. Only then can we begin to understand the changes in the patterns of respiratory diseases that fill the paediatric wards of developing countries, still kill many children, and lay the foundation for an unknown burden of chronic respiratory disease in tomorrow's adults.

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