
Editorial

Acute Respiratory Infections in Developing Countries: Current Status and Future Directions

Acute respiratory infections (ARI) continue to be a major killer of children in developing countries. It is estimated that 3.9 million children die each year from ARI, most of them in developing countries (1). In contrast the number dying each year from diarrheal disease, the other major killer, is 2.5 million (1). This large mortality, which virtually goes unnoticed, has been described as being equivalent to a jumbo jet carrying 400 children crashing every hour, day after day (2). After a gap of 13 years, experts from around the globe met at the International Conference on ARI at Canberra, Australia in July 1997. They concluded that the fact that children continue to die from ARI in such large numbers is an international disgrace, because we have the means to prevent these deaths through appropriate case management, immunization and health education(2). The situation in India is very much the same as in most other developing countries. Therefore, it is appropriate that we review the progress that has been made and to plan strategies to reduce this high mortality.

Standard Case Management

Standard case management has been the primary strategy suggested by the World Health Organization (WHO) for reduction of pneumonia mortality (3). Since most cases of fatal pneumonia are caused by *S. pneumoniae* or *H. influenzae(A)* and since primary health care workers can be taught to reliably diagnose pneumonia using simple clinical signs(5), mortality can

be prevented by the early detection and treatment of pneumonia with inexpensive antibiotics. The simple guidelines developed by the WHO for early detection and treatment of pneumonia have been tested in several field trials in a number of developing countries and have been found to reduce acute lower respiratory infection (ALRI) mortality by 39% (95% CI 6-60%) and mortality from all causes by 29% (95% CI 17-46%) in children under the age of 5 years (6). Despite the proven benefit of this strategy, there have been many problems with its use.

Parents of children with pneumonia often do not seek the help of the trained health workers either because they fail to recognize signs and symptoms of the disease or because treatment of ARI by a trained health care worker is not an acceptable practice. In many rural communities in India, private practitioners (qualified or otherwise) are a major source of medical care. Such practitioners are seldom, or never, trained in standard case management strategies. Unless the case management is supplemented with health education to enable parents to recognize respiratory disease and seek appropriate care and all those who are involved in providing primary care in the community are active participants in the program, it is unlikely to succeed.

The personnel trained in identifying and treating cases are often not available in the village subcenters and there are difficulties in ensuring that antibiotics are available for use in children at all times and are not misused for other purposes [Bhattacharji S, personal communication]. Thus, in practice standard treatment is

often not available to children in the community even though the program may exist on paper.

There has been concern about the emergence of antibiotic resistant bacteria with the widespread use of antibiotics in the WHO ARI control program. There are a number of studies which have linked the emergence of resistance to the magnitude of antibiotic use in a community (7-9). However, the WHO case management program does not recommend antibiotics in mild infections, which constitute the majority of ARI; strict adherence to the management protocol will actually reduce the total amount of antibiotic use in most developing countries.

In many countries, including India, there has been an increase in the rates of resistance of *S. pneumoniae* and *H. influenzae* to cotrimoxazole, which is the antibiotic recommended for use in the outpatient treatment of pneumonia in the standard case management protocol and there has been considerable debate about the continued use of this antibiotic in the case management protocol. Use of alternative antibiotics such as amoxicillin would substantially increase the cost of therapy. Rates of resistance of pneumococci to cotrimoxazole from various centers in India have been in the range of 30-80% (Thomas K, personal communication). However, *in vitro* resistance may not necessarily mean that the antibiotic is not efficacious. Data from Pakistan have shown that 80% of community acquired non-severe pneumonia responded to cotrimoxazole even though 40-45% of nasopharyngeal isolates showed *in vitro* resistance to this antibiotic; children with radiologic evidence of pneumonia had higher failure rates (10). Thus, for the present cotrimoxazole use may be continued for non-severe community acquired pneumonia and more expensive antibiotics

reserved for those with radiologic evidence of pneumonia or the 20% of non-severe pneumonia which do not respond to cotrimoxazole.

S. pneumoniae which is the cause for the majority of pneumonia is rapidly becoming resistant to penicillin. While penicillin resistant pneumococci are currently not a major problem in India, resistant isolates are being frequently encountered in other Asian countries. In four Asian countries, including Korea, Japan, Thailand and Vietnam, more than 50% isolates of pneumococcus are penicillin resistant. Other Asian countries are reporting an increasing tendency for penicillin resistance with rates of resistance ranging from 20-30%. This is an alarming trend, especially in countries which cannot afford the use of more expensive newer antibiotics. While there is no doubt that penicillin resistance correlates with treatment failure in cases of meningitis, its relevance in the treatment of pneumonia is not clear. There is data to show that treatment with parenteral penicillin or ampicillin is as effective as alternate drugs in the treatment of non-invasive disease with penicillin resistant pneumococci (11). However, there is no data on the efficacy of oral preparations in such situations and trials to examine this aspect are urgently required.

The realization that there is considerable overlap between the signs and symptoms of pneumonia and other common illnesses in developing countries has led to the formulation of the Integrated Management of Childhood Illnesses (IMCI) by the WHO. This program has already been implemented in selected districts in 14 countries. The program includes identification and early treatment of pneumonia as well as other common childhood illnesses. As this new program replaces the ARI Control Program, it is important to consider factors

that would have impact on its effectiveness. These include care-seeking behavior and expectation of parents (specifically their demand for antibiotics), education of private practitioners and other indigenous practitioners who provide primary care to children in the use of standard treatment and provision of services at the home level by village health workers, especially in rural and remote areas where there are no doctors. Constant monitoring for resistance to the antibiotics used in standard treatment of pneumonia needs to be maintained and the effect of *in vitro* resistance on clinical efficacy of the antibiotic has to be examined further. Consideration must also be given to field trials to evaluate the efficacy of shorter courses amoxicillin and to see its effect on the emergence of antimicrobial resistance. At the same time efforts need to be made to restrict the use of antibiotics. In particular, over the counter sale of antibiotics need to be prohibited in developing countries where this is a common practice.

Vaccines for ARI

While standardized case management of pneumonia has the potential to achieve significant reductions in mortality from pneumonia, its impact will be limited because of difficulties listed above and by increasing antibiotic resistance among the pathogens causing pneumonia. Moreover, this strategy only reduces mortality without having a significant impact on morbidity. Immunization against the common pathogens would, therefore, have an important role in control of ARI.

Among the vaccines currently administered in the EPI in developing countries, pertussis and measles are expected to have an impact on ARI mortality. However, since mortality due to these infections contributes to only a small proportion of total ARI mortality, their impact is limited. Of

the other currently licensed vaccines, the efficacy of *Haemophilus influenzae* type b (Hib) conjugated vaccine and the pneumococcal polysaccharide vaccine on pneumonia mortality have been evaluated in field trials(12,13).

Hib Vaccine

Hib conjugate vaccines have been remarkably effective in nearly eliminating invasive Hib disease from many developed countries. In developing countries, the impact of this vaccine on pneumonia is likely to be greater (14). It is estimated that in developing countries, 30% of serious ARI is caused by *Haemophilus influenzae* (15). Studies from the Gambia and Pakistan show that 56% and 64%, respectively, of these infections are caused by Hib (3). The estimates of the yearly death toll from Hib ARI is estimated to be 340,000-600,000. In a field trial in Gambia the use of Hib conjugate vaccine had 100% efficacy in preventing proven Hib pneumonia and 21% efficacy in preventing any radiological pneumonia (12). In this study bacterial pneumonia was far more common than meningitis. In the fully vaccinated cohort, 11 cases of meningitis and 38 cases of pneumonia were prevented, which suggests that the overall effect on pneumonia and meningitis is 4.5-fold greater than the effect on meningitis alone. This unexpected bonus in developing countries with high rates of bacterial pneumonia is a case for not delaying the introduction of Hib vaccine. However, the high cost of this vaccine prevents its widespread use in developing countries. The Children's Vaccine Initiative (CVI) and the WHO are considering ways and means to make this vaccine available in developing countries(15).

Pneumococcal Vaccine

S. pneumoniae is the commonest cause of ALRI in children in developing countries.

Though pneumococcal polysaccharide vaccines are not immunogenic in infants and young children, studies using the 14-valent and 23-valent pneumococcal polysaccharide vaccines in children 6 months and older in Papua New Guinea (PNG) showed a vaccine efficacy against ALRI as the sole cause of death of 59% among children vaccinated when they were <5 years of age and an efficacy of 50% amongst those vaccinated when they were vaccinated <2 years of age(13). One of the reasons postulated for the greater than expected efficacy of pneumococcal polysaccharide vaccines in PNG is that a high proportion of invasive pneumococcal serotypes from children were "adult" serotypes. In Goroka, PNG 47% of proven invasive pneumococcal strains were "adult" serotypes and 20% were "pediatric"(16). Similarly, in Nigeria all invasive pneumococcal isolates were "adult" serotypes(17). Children respond to "adult" serotypes but not to "pediatric" serotypes at a younger age. However, in South Asia the proportion of invasive disease in children caused by "adult" serotypes is not as high. In Pakistan, only 11% of pneumococcal strains from invasive disease in children were "adult" serotypes(18). In Vellore, 27% of pneumococcal strains causing invasive disease in children under 6 years of age were "adult" serotypes whereas 41% were "pediatric" serotypes (Lalitha MK, personal communication). Therefore, the vaccine efficacy of the polysaccharide vaccines in Asian countries may not be as high as observed in PNG and the use of these vaccines need to be evaluated further in these countries.

Following the success of the protein-conjugated Hib vaccines, a new generation of protein conjugated pneumococcal vaccines have been developed using similar linking technology and carrier proteins as

the Hib vaccines(19). Early studies show that the vaccines are immunogenic in infants though less so than the Hib vaccines (20). Also, unlike the Hib conjugate vaccines, the protective mechanism of the pneumococcal vaccine is opsonization and not bactericidal. However, the vaccine does prime for a booster response and appears to reduce nasopharyngeal carriage. Because the currently available vaccines contain a limited number of serotypes, strict surveillance needs to be maintained to detect shifts in serotype distribution. Efficacy trials of this vaccine are underway. As with the Hib vaccine, cost will be a major limitation to the widespread use of this vaccine in developing countries. Future developments of the conjugate vaccine include the use of "common" pneumococcal proteins as carrier protein.

Respiratory Syncytial Virus (RSV) Vaccine

Even in developing countries viral infections account for 30-40% of ALRI (3). RSV is the commonest viral pathogen in childhood ALRI. In India, 32% of all ALRI and 58% of bronchiolitis was caused by RSV (21,22). Unlike in developed countries, studies from developing countries show that in a substantial proportion of children with RSV infection there is evidence of concomitant bacterial infection (18,23). It is estimated that among children who die from pneumonia, 21% have a viral infection and 31% have a mixed viral and bacterial infection. Therefore, vaccines against viral pathogens, especially RSV, will have an important role in reduction of ARI mortality.

Passive immunization against RSV has been shown to protect high risk infants against RSV ALRI. However, its usefulness is limited and a vaccine against RSV is clearly needed. Because of enhanced disease seen in RSV naive infants vaccinated with formalin inactivated vaccine in the

1960s, progress with a RSV vaccine has been cautious. The purified F-protein vaccine has been shown to be immunogenic but offers only modest protection. However, if used as a maternal immunogen during pregnancy, it may be useful in protecting young infants. Several candidates live attenuated vaccines including temperature sensitive mutant viruses are currently undergoing trials. The most exciting developments, however, are the use of reverse genetics to produce infectious RSV from cDNA. The possibility of immune modulation using the insertion of foreign genes (such as cytokines) into the cDNA may give us the tools to make RSV vaccines that may be more immunogenic than the wild virus(24).

Maternal Immunization

In developing countries, it is estimated that 42% of pneumonia deaths occur in children under the age of 6 months. These infants may not be benefited by immunization in infancy, since protection from such immunization will result only around 5-6 months of age. Maternal immunization has the potential to enhance passive immunity of infants against agents that produce life-threatening illness in early infancy. The best example of the effective use of this method of prophylaxis is the administration of tetanus toxoid to pregnant women. Since administration of tetanus toxoid during pregnancy is part of the EPI program in most developing countries, maternal immunization with other vaccines should be easy to implement. Immunization of mothers with Hib and pneumococcal vaccines have been shown to result in significantly higher antibody in infants(25,26). These infants will most likely have protective antibody till about 5 months of age. It is not known whether and to what extent the high levels of maternal antibody will interfere with active immune response to vacci-

nation. Further studies are required to examine this and to evaluate the efficacy of this strategy in reducing pneumonia deaths.

Maternal immunization with vaccines against Hib, *S. pneumoniae*, *B. pertussis*, RSV and parainflueza virus type 3 are likely to have a significant impact on ARI mortality during early infancy.

Micronutrient Supplementation

Vitamin A

Histopathological changes in the epithelial tissues suggest that vitamin A deficiency may predispose to respiratory infections. In addition, abnormalities in systemic immunity occur with vitamin A deficiency. Therefore, the results of longitudinal field observation studies which showed that children with vitamin A deficiency have increased risk of ARI (27,28) did not come as a surprise. However, the results of field trials which evaluated the effect of vitamin A supplementation on pneumonia incidence and mortality were conflicting. A recent meta-analysis of 12 large scale field trial done in 7 developing countries, including 3 in India, showed that summary estimate of the relative risk for pneumonia incidence and pneumonia mortality was 0.95 (95% CI 0.89-1.01) and 0.98 (95% CI 0.75-1.2), respectively. However, there was an impact of vitamin A supplementation on mortality from all causes (RR=0.77, 95% CI = 0.71, 0.8) (29). Thus, vitamin A supplementation is unlikely to cause significant reduction in ARI mortality.

Zinc

The preliminary results from a series of community-based trials of the impact of zinc supplementation in preschool children showed a 6%-56% reduction in ALRI among supplemented children. This effect was more marked in children with low baseline serum zinc levels and those who

were severely malnourished. Further research is needed to examine the impact of zinc supplementation in preventing ARI using more rigorous methods for case detection. Also, studies are required to examine the role of zinc as an adjunct in the treatment of childhood pneumonia, especially in populations with suboptimal nutritional status (30).

Conclusion

Obviously there is a need for more data in a number of areas. These include more ethnographic studies to determine factors that influence the acceptance of the standard case management by the community. Better guidelines are required for the use of oxygen and on importance and means of fluid management of ALRI in areas with limited resources. Ongoing surveillance for antibiotic resistance needs to be continued, and research to identify genetic mechanisms for antibiotic resistance may be important to formulate strategies to prevent antibiotic resistance. Several new vaccines are available or will soon be available and studies to determine their efficacy and to decide on their optimal use, including the use of maternal immunization, are required. If the vaccines prove to be efficacious, efforts have to be made to make these vaccines available in developing countries at prices these countries can afford. The role of micronutrient supplementation also warrants further examination. While there is much scope for further research it is also imperative that all efforts be made to effectively implement strategies which have been shown to have a definite impact on ALRI mortality in order to reduce the unacceptably high mortality rates in developing countries. The responsibility for this does not lie with the government agencies alone but requires the concerted and sincere effort of all those involved in health care.

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