EDITORIAL

EMERGING ISSUES IN MEASLES

Measles, an extremely virulent infectious disease remains one of the top ten killers of children worldwide. Widespread use of measles vaccine over the past three decades has resulted in a reduction of measles morbidity and mortality by 74% and 85%, respectively, compared to the prevaccine era(1). In 1998, an estimated thirty million cases of measles occurred worldwide, with 888,000 measles-related deaths, 85% of which occurred in Africa and Southeast Asia(2).

The World Summit for Children in 1990 set a goal of vaccinating 90% of the world's children against measles by the year 2000(3). In 1989, the World Health Assembly set a goal to reduce measles morbidity and mortality by 90% and 95% respectively compared to the prevaccine era by 1995(4). No continent has yet achieved these goals. Global reported coverage with one dose of measles vaccine actually declined throughout the nineties. Between 1997 and 1998 alone, measles vaccine coverage declined from 79% to 72%, with 14 countries (ten in Africa) reporting coverage below 50% in 1998(2).

The World Health Organisation (WHO) has embarked on a measles elimination initiative that comprises a three-part vaccination strategy ('catch-up', 'keep-up' and 'follow-up') and enhanced surveillance. 'Catch-up' involves mass supplemental vaccination campaigns of all children aged nine months to 14 years, 'keep-up' involves strengthening existing routine measles immunisation, and 'follow-up' involves mass supplemental vaccination targeting all children born since the previous catch-up campaign(1,2,5). Three major regions of the world are working towards regional elimination of measles: the Americas (by 2000), Europe (by 2007) and the Eastern Mediterranean region (by 2010)(1). They have or are carrying out mass measles immunisation of all children aged one through 15 years, regardless of previous immunisation status, and maintaining a high routine childhood immunisation coverage against measles. By 1998 the American region had achieved a reported coverage rate of 86%, the Eastern Mediterranean region 78% and Europe 71%*(2).

Six southern African countries (Botswana, Malawi, Namibia, South Africa, Swaziland and Zimbabwe) have also adopted national measles elimination goals(1). A sero-epidemiologic survey carried out in Malawi showed measles antibody positivity increased from 17.4% in children aged eight to twelve months to 90% in four-year old children, and measles antibody titres waned with increasing age. At the time the serological samples were collected, the children aged nine months to 14 years were immunised against measles in a 'catch-up' immunisation campaign. The campaign was highly successful, with 100% of previously sero-negative children sero-converting by eight weeks after vaccination, and antibody titres in previously sero-positive children increasing significantly after vaccination(6).

Other regions of the world are putting into place "accelerated measles control programmes" working towards achieving the World Summit for Children and World Health Assembly goals(3,4). These countries are carrying out mass catch-up immunisation campaigns or implementing routine two-dose immunisation schedules, or strengthening the implementation of existing routine one-dose schedules below the age of one year. Among these regions, the Western Pacific Region reports the highest measles immunisation coverage (93%), whilst Southeast Asia and Africa report the lowest (67% and 49% respectively). The latter two regions reported the greatest decrease in coverage during 1997-1998(2).

In Kenya, national measles immunisation coverage rose under Kenya Expanded Programme of Immunisation (KEPI) from below 30% in the seventies to a peak of 79% in 1993, but declined to 65% in 1998(7,8). KEPI is putting into place a five-year action plan towards achieving the World Summit for Children goal by the year 2005. The first 'catch-up' campaign is scheduled for late 2001 and early 2002, whereby 13.9 million children aged nine months to 14 years are targeted for measles immunisation and vitamin A supplementation. KEPI is also planning to strengthen routine primary vaccination services to ensure 'keep-up' immunisation of each birth cohort of every subsequent year. A follow-up campaign is planned for late 2004 and early 2005, whereby 5.7 million children aged nine through 59 months are targeted for measles immunisation and vitamin A supplementation(9).

One factor hindering successful widespread measles immunisation especially in resource-poor countries is the nature of the present vaccine. It must be stored at temperatures below 8°C, and must be given by injection, necessitating cold storage facilities and trained medical personnel for administration. Researchers are working towards developing vaccines that are simpler to store and deliver, and more effective than present vaccines. Various non-percutaneous routes of administration have been explored - aerosol, intranasal, conjunctival, oral and intradermal(10).

Various methods of aerosol administration have been studied involving delivery of aerosolised or nebulised vaccine via facial mask, or directly into the mouth, or by aerosolising vaccine for 30 minutes into a room in which children were playing. Generally, good results have been obtained from all methods. Most promising results have been found with aerosol administration of measles vaccine

* Twenty one of 51 European countries did not report coverage data to the WHO

to previously seronegative children over nine months of age, in whom 90-100% sero-response was obtained regardless of vaccine strain. When administered to seropositive children, the boosting response was higher after aerosol than after percutaneous vaccine, and higher with Edmonston-Zagreb vaccine than Schwartz vaccine. Aerosol administration to younger infants (less than nine months) was difficult and produced lower seroresponse (80%) than that obtained from percutaneous vaccination. A greater reduction in post-vaccination attack rates for measles was noted in children vaccinated via aerosol compared with subcutaneous vaccinees and unvaccinated children(10).

One pharmaceutical company has developed an inhaler that can aerosolise powder vaccine and deliver a consistent dose to the lungs over a wide range of inspiratory flow rates. Use of powder vaccine overcomes the problem of decreasing stability of vaccine after re-constitution, and reduces the risk of microbial proliferation as would occur in aerosolisers and nebulisers(11).

Intradermal administration using needle and syringe was more difficult than subcutaneous administration, and produced lower sero-responses. Less than 50% of children seroconverted after oral administration in three small studies. Conjunctival administration was difficult in young children, and seroconversion was very variable(10).

Aerosol delivery of vaccine therefore appears to be the most promising method of vaccine administration for mass immunisation of children older than nine months. The challenge to determine optimal aerosolised dose and to develop technology for easy aerosol delivery remains. Directions for future research include development of aerosolisation equipment that includes microbiological air filters, a simple means to maintain vaccine below 8°C, and valves at the delivery end to prevent reflux of microbes from the mouth of the vaccinee(10).

Regarding safety of the measles vaccine, in recent years comprehensive review of world literature on the subject reveals that during 30 years of worldwide use, measles vaccination has proven to be one of the safest and most successful health interventions in the history of mankind. Severe adverse events are extremely rare, and risk of death or severe longterm sequelae from wild virus infection far exceeds risk of adverse events from the vaccine. Known severe adverse events associated with measles vaccination include post-infectious encephalomyelitis (vaccine risk 0.5 per 1000000, natural infection risk 1 per 1000), thrombocytopenia (vaccine risk 1 per 30000, natural infection risk unquantified), and anaphylaxis (vaccine risk 1 per 100000 - 1000000, natural infection risk 0)(12). Evidence is now suggesting that modified gelatin rather than egg proteins is responsible for most episodes of anaphylaxis following measles vaccination(12,13). New work weakens the possible links between measles vaccine and subacute sclerosing panencephalitis (vaccine risk 0, natural infection risk 1 per 100000) and Guillain-Barre syndrome(12,14). There have also been some suggestions of an association between measles vaccination and Crohn's disease and autism, but the evidence is unconvincing and has been refuted by a large volume of strong research(12,15).

Currently the diagnosis of measles is largely clinical, especially in resource-poor countries. Accurate diagnosis of measles is often difficult as other viral exanthems may present with similar symptoms and signs. There is need to develop simple accurate and affordable tests for rapid diagnosis of measles infection that can be used for surveillance and confirmation of measles diagnosis, and that may be carried out in a primary health care setting. Currently available tests include detection of measles-specific IgG or IgM antibodies in blood or saliva(1). Takechi *et al*(6) used a simple serological particle agglutination test in a serological field survey in Malawi and demonstrated that it was easy to perform and suitable for field conditions in developing countries. A global network of laboratories for measles surveillance has been proposed, with national level (or subnational for large countries) laboratories to have capacity for measles IgM antibody assays(1,2). At the international level, a strain bank is being established, and the genetic characteristics of the eight known groups of wild-type measles viruses are being described. Genotyping of viruses will assume increasing usefulness in detecting the origin of cases as measles transmission declines(16,17).

Human immunodeficiency virus (HIV) infected individuals with declining immunity have been found to have increased measles-associated morbidity and mortality, reduced serological response to vaccine, and waning measles immunity post-vaccination(1). A two-dose measles vaccination schedule at six and nine months has been recommended by WHO/UNICEF since 1987, but has never been evaluated. Research is needed to determine the immunogenicity and safety of such schedule, and to determine the duration of immunity in HIV-infected persons. One case of measles vaccine-induced pneumonia has been described so far(18).

Kenyan infants born to HIV sero-positive mothers were found to have a fourfold increased risk of measles before the age of nine months compared with infants born to HIV sero-negative mothers(19). The majority of affected infants suffered significant sequelae related to their measles infection. In the same study infants of HIV seropositve mothers were found to have relatively lower anti-measles antibody titres at birth compared with infants of HIV sero-negative mothers, a phenomenon that has been described elsewhere(20).

Measles, one of the most transmissible human diseases known in history, which prior to the vaccine era infected almost every human being, is now being brought under control after 30 years of vaccination, and can indeed be eliminated from the face of the earth. Researchers are working towards a more effective vaccine, easier forms of vaccine delivery, and simpler tests for accurate diagnosis of the infection. Various regions of the world are working towards controlling and eventually eradicating this disease.

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