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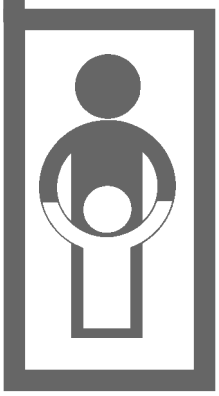
Report of a meeting on research related to measles control and elimination

Geneva, 27-29 March 2000



DEPARTMENT OF VACCINES AND BIOLOGICALS

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Contents

Glossary

ALRI	acute lower respiratory tract infection
CD4 and CD8	subpopulations of T lymphocytes
CDC	Centers for Diseases Control and Prevention (USA)
DNA	deoxyribonucleic acid
EIA	enzyme immunoassay
ELISA	enzyme-linked immunosorbent assay
EZae	aerosolized Edmonston-Zagreb measles vaccine
EZsc	subcutaneous Edmonston-Zagreb measles vaccine
F, H and/or N	proteins of measles virus
GMT	geometric mean titre
Hib	*Haemophilus influenzae type B*
HIV	human immunodeficiency virus
IFN-a/b	a/b-interferons
IgM, IgG, IgA	classes of immunoglobulins
IL-2, IL-4, IL-5, IL-12	types of cytokines (mediators of immune responses)
ISCOM	immune-stimulating complex
MMR	measles-mumps-rubella vaccine
MR	measles-rubella vaccine
MV	measles virus
MVA	modified vaccine virus Ankara
NFIs	needle-free injectors
PCR	polymerase chain reaction
PRN	plaque reduction neutralization
RT	reverse transcriptase
SIV	simian immunodeficiency virus
SWae	aerosolized Schwarz measles vaccine
SWsc	subcutaneous Schwarz measles vaccine
TRAIL	tumour necrosis factor-related apoptosis-inducing ligand
URI	upper respiratory tract infection
WHO	World Health Organization

Executive summary

A meeting was held in Geneva on 27-29 March 2000 with the specific objective of defining and prioritizing research that would lead to the best possible approach to measles control and elimination.[1] It is estimated that measles currently causes a million deaths annually, a decrease of 4.8 million in comparison with the pre-vaccination era. The annual number of measles cases has fallen from 30 million to 10 million, thanks to good control in substantial areas of the world and to the elimination of disease transmission in some countries. The Region of the Americas, the European Region and the Eastern Mediterranean Region have set targets for the elimination of measles by or before 2010. Many countries have held or are planning mass immunization campaigns. A clear understanding of the biology and epidemiology of measles is necessary if these efforts are to be directed successfully. The meeting included discussion of:

- the immunopathogenesis of measles;
- the consequences of measles infection in normal and immunocompromised individuals;
- alternative routes of administration of measles vaccine;
- vaccine strategies for measles control and elimination;
- optimal disease surveillance;
- the development of new products.

A key issue is the duration of vaccine efficacy in developing countries. The data presented indicate that immunity is shorter-lived in Africa and India than elsewhere. Subclinical measles may result in vaccinated individuals being able to transmit disease. The nature and molecular basis of the immunosuppression that accompanies measles is becoming better defined and the impact of late complications of measles is being re-explored. Of particular significance is the interaction of measles and HIV infection: there is concern about vaccine safety and efficacy in people with HIV and other immunosuppressed populations, and about the potential for measles to find a niche in immunocompromised individuals.

[1] Measles elimination is defined as the interruption of indigenous measles virus transmission (i.e. measles is no longer an endemic disease) in a large geographical area as a result of deliberate efforts. Continuing intervention is required.

The successes of mass immunization in the control of measles were discussed with reference to experience gained in the Americas. Attention was drawn to the need to sustain a high level of routine coverage as a component of measles control, and to the potential role of serosurveys and modelling in defining the age spectrum of susceptible individuals and thus influencing the design of mass campaigns. Data were presented on alternative approaches to measles control through routine second immunizations. The susceptibility of infants to vaccine virus and their immunological capacity to respond to vaccination were discussed in relation to whether, before the age of routine immunization, they could contribute to sustaining the circulation of measles. The continuing need for simpler diagnostic tests was discussed. There was enthusiasm for salivary antibody assays and other assays that did not require blood sampling. The role of molecular epidemiology in defining the origins of measles outbreaks was explained and the significance of importation into areas where good control had been attained was stressed. An outline was given of the impressive progress achieved in setting up a global measles laboratory network.

Encouraging results were reported with small-particle aerosol delivery of nebulized Edmonston-Zagreb vaccine in Mexico and South Africa. The continuing development of a dry powdered formulation of measles vaccine for aerosol delivery was reported. A small group discussed primate trials that should help to establish the safety and efficacy of these aerosol treatments. In this connection, agreement was reached on the specific details of two safety and immunogenicity trials in macaques. A report was presented on the use of this model to determine the relative merits of other vaccine approaches.

The cost-effectiveness of measles control was considered. Special attention was given to the safety of vaccine delivery and the need for needle-free systems. The cost and regulatory issues related to the introduction of new products or delivery systems were reviewed.

The final day of the meeting was devoted to discussions in working groups and to presentations relating to the following questions.

- What studies should be conducted in order to improve mass campaigns?
- What studies should be conducted on measles immunity and immunopathology?
- What further studies should be undertaken on alternative routes of vaccination and on new products?
- What studies are needed on the cost-effectiveness of measles control and elimination?

Recommendations for further research related to measles control and elimination were developed by the working groups. These recommendations will provide the basis for revision of the priorities for research to be funded and encouraged by the Steering Committee on Research Related to Measles Vaccines and Vaccination and the Expanded Programme on Immunization, Department of Vaccines and Biologicals, WHO.

1. Introduction

Nearly a million deaths were attributed to measles in 1998. The disease thus remains a major cause of vaccine-preventable illness and death. The problem persists even though an effective and safe vaccine has been widely available for three decades. Failure to deliver at least one dose of measles vaccine to all infants remains the primary reason for the preventable morbidity and mortality caused by the disease.

In 1989 the World Health Assembly adopted the goal of achieving reductions in measles morbidity and mortality of 90% and 95% respectively by 1995, relative to estimates of the disease burden in the pre-vaccine era. In 1990 the World Summit for Children adopted the goal of vaccinating 90% of children against measles by 2000. Target dates of 2000, 2010 and 2007 for the elimination of measles were set by the Region of the Americas, the Eastern Mediterranean Region and the European Region of WHO in 1994, 1997 and 1998 respectively.

Global reported measles vaccination coverage declined from 79% in 1997 to 72% in 1998, when 16 countries reported measles coverage below 50%.

The research programme is an important component of WHO activity aimed at the global control and elimination of measles. WHO's Department of Vaccines and Biologicals prepared an inventory of measles-related research activities worldwide. This was a part of the world body's effort to ensure that all priority research issues were addressed rapidly and that the results were widely distributed to support the development and implementation of strategies for measles control and elimination. Of the 902 studies obtained from the Medline database, 269 were selected. The inventory revealed considerable progress in many research areas but in some key areas there were only a few research studies or progress was slow. These areas included safer vaccine delivery systems, vaccination by alternative routes, diagnostics, and co-infection with HIV. Developing countries accounted for 42% of the studies in the inventory. However, only 20% of these were conducted by principal researchers from developing countries. Studies in progress should continue to be analysed in order to facilitate the development of a strategic plan for research in the area of measles control and elimination.

2. Key issues in measles immunology and immunization

Immunological memory: data from field trials

Data from field studies in Guinea-Bissau, southern India, and Senegal suggest declining measles vaccine efficacy and increasing measles infection rates with age and time since vaccination. This effect may be more pronounced for children vaccinated with a single dose at the age of £9 months. Other factors that may be leading to lower population immunity in these settings are:

- reduced transfer of maternal antibodies to infants, causing increased susceptibility at young ages;
- lower antibody levels in immune individuals because of reduced boosting from re-exposure to natural measles.

Subclinical infections may be more common among vaccinated children than children with immunity to natural infection. However, it is unclear whether persons with subclinical infection contribute to measles transmission.

Improved measles control or eradication[2] will require higher immunity levels and better vaccine efficacy. This could be achieved by raising the age of vaccination (e.g. from 9 to 12 months). However, this might result in a short-term increase in measles morbidity and mortality at younger ages. Alternatively, a two-dose strategy could help to improve control. Edmonston-Zagreb measles vaccine may be a better candidate for an early two-dose schedule than Schwarz vaccine but it also suffers from waning immunity. Another alternative would be to conduct mass vaccination campaigns over 5-10 years, as is being done in the Americas. Political instability in some parts of Africa could prevent the implementation of such a strategy. Nevertheless, it would be beneficial to have a measles vaccine that could be given early in life.

This presentation led to discussion about the feasibility of eradication[2] and the need for further study of waning immunity in Africa. Waning immunity has not been a problem in the Americas, Europe and Micronesia.

[2] Measles eradication is defined as the interruption of measles transmission worldwide as a result of deliberate efforts; intervention methods may no longer be needed. Eradication represents the sum of successful elimination efforts in all countries.

Subclinical measles infection

It has been documented that MV-specific virus neutralizing serum antibody levels below 120 international units per litre may not protect an individual from clinical measles, and that both symptoms and antibody responses may be seen in persons exposed to measles who have higher titres than this. Subclinical measles is commonly defined as a fourfold rise in measles-specific antibody following exposure to natural measles in a person who remains asymptomatic. A difficulty arises with this definition because of overlapping laboratory test results. Cases of subclinical measles might also be defined as those with measles-specific IgM, positive virus isolation or positive RT-PCR signals. However, contamination of clinical specimens may result in false positive MV antigen tests in PCR.

Subclinical measles has been described in macaque monkeys, infants with maternal antibodies, vaccinees with waning immunity, and adults with a history of natural measles in childhood. MV has been isolated from the urine of naturally immune, subclinically infected individuals. In macaque monkeys it appears that the amount of viral replication correlates negatively with the level of pre-existing antibodies. In a hospital in the Netherlands a measles case occurred in which, notwithstanding extensive epidemiological investigation, there had been no known exposure to any other case of clinically manifest measles. It was concluded that there must have been exposure to another subclinically infected individual.

It is possible that subclinical measles cases can transmit virus. However, the frequency with which this occurs is unknown. The key question concerns the extent to which subclinically infected individuals contribute to the epidemiology of measles. Can MV continue to circulate by means of a chain of transmission between subclinically infected individuals?

Measles in HIV-infected individuals

Will the HIV pandemic be a barrier to a future measles eradication effort? How can this question be answered? The following areas were covered during the meeting:

- immunogenicity of measles vaccine;
- vaccine effectiveness;
- vaccine safety;
- transmission of infection;
- immunity in adults.

Immunogenicity of measles vaccine

Studies in the USA demonstrate that children with HIV have more primary and secondary vaccine failures than other children and have a poor response to repeated vaccinations. The limited data available from developing countries also suggest a reduced response to vaccination. In order to determine the optimal age for vaccination in countries with high rates of HIV a six-month and nine-month vaccination schedule in Malawi and a one-dose nine-month schedule in Zambia will be tested in children with and without HIV infection.

Vaccine effectiveness

Limited data are available on the effectiveness of measles vaccine in children with HIV infection. Studies on this matter would require very large samples. Outbreak investigations and surveillance in countries with endemic HIV which are embarking on measles elimination will help to evaluate the feasibility of interrupting transmission in these settings.

Vaccine safety

No increase in serious adverse events has been noted in HIV-infected children. In the USA a serious adverse event occurred in a young adult 10 months after receiving measles vaccine. The studies in Malawi and Zambia will collect additional data on adverse events, as will an autopsy study that is proceeding in Zambia. The monitoring of adverse events during mass campaigns will be invaluable in throwing light on vaccine safety in older children.

Transmission of infection

There are few data indicating whether HIV-infected individuals are more infectious than other people. Studies are proceeding in Kenya one the possibility of chronic shedding of vaccine virus. A prospective study in Zambia and a cross-sectional study in Uganda will evaluate the possibility of chronic shedding of wild-type virus. Studies are in progress in Zambia and planned in Côte d'Ivoire to evaluate the frequency of rashless measles in children with HIV infections and respiratory illnesses. An autopsy study is under way to determine the role of wild-type or vaccine virus in children who die of respiratory illnesses with and without rash.

Immune response to measles vaccine in HIV-infected children and adults

HIV-infected adults in the USA maintain pre-existing antibodies, both those that are vaccine-induced and those attributable to natural disease, but respond poorly if they are antibody-negative and re-vaccinated. A study is under way in Kenya to evaluate the immune response to measles in HIV-infected adults. An investigation is necessary into the maintenance of vaccine-induced immunity in HIV-infected adults in developing countries.

Long-term effect of measles infection on child health

A study was conducted in Bangladesh to investigate the hypothesis that measles leads to increased morbidity from other illnesses, and to determine the duration of any increased morbidity. Weekly interviews were conducted for six months with 117 hospitalized and 137 non-hospitalized acute measles patients and with age -matched control children in hospital and in the community who did not have measles. Among the outcomes considered were diarrhoea, ALRI, hospital admission, weight for height, and clinic visits for diarrhoea. Morbidity was increased for 6-8 weeks after measles but there was no increased morbidity or wasting beyond 8 weeks after the onset of measles. These results support recent findings that measles is not associated with an increase in delayed morbidity and mortality.

The mechanism of the suppression of cell-mediated immunity following measles is unclear. Well-designed studies are needed to understand the biological basis of immune suppression associated with measles and its relationship to increased morbidity. Because vaccination protects against measles and its complications there is a need to improve vaccination programmes, especially in settings where coverage is low.

Data from Guinea-Bissau suggest that persons with uncomplicated measles survive longer than persons who do not contract measles. In Senegal, index cases were found to have better survival than secondary cases. Among unvaccinated children in Bangladesh, those with measles had higher mortality up to two months after measles than other children, mainly because of chronic diarrhoea. Mortality was lower between three months and a year after acute measles, possibly because of a survivor effect.

3. Immunosuppression induced by measles virus

Protective immunity against measles is characterized by high levels of neutralizing antibody. The mechanisms involved in inducing and sustaining this type of immune response are not completely understood. An important component is the generation of type 2 cytokines that promote the expansion and differentiation of measles antibody-secreting B cells, and type 1 cytokines that suppress cellular immune responses characterized by macrophage activation and lymphocyte proliferation. The suppression of cellular immune responses may therefore be a necessary correlate of the induction of sustained high levels of antibody. There are suggestions that the ability of measles vaccines to induce prolonged protective immunity may depend on the age at immunization, the presence of other infections that alter immune responsiveness (e.g. HIV), and the strain of vaccine administered.

The ability of MV infection to induce immune suppression has been recognized for more than a century, but the mechanism of this transient immunosuppression is not clearly understood. Delayed-type hypersensitivity responses to recall antigens (e.g. tuberculin) and lymphoproliferative responses to mitogens are suppressed. The increased susceptibility to other infections is a major cause of the morbidity and mortality associated with measles. It is likely that immunosuppression is multifaceted, with some components that are specific to measles and others that are shared with similar but milder decreases in immune function associated with the immune responses to other viral diseases. In addition to the study of measles patients a number of model systems have been used to elucidate the mechanisms of measles immunosuppression. Information gained from multiple approaches was presented and discussed.

Lymphocytopenia occurs early during the viraemic phase of measles. Peripheral blood mononuclear cells collected during this phase and after the onset of rash undergo apoptosis when cultured in vitro. This suggests that the lymphocyte life span in vivo is shortened, even though few, if any, lymphocytes are infected. The direct inhibitory effects of the expression of MV proteins H and F at the cell surface on the proliferation of cocultured lymphocytes has been demonstrated in vitro and in cotton rats in vivo. This suggests direct interaction of uninfected lymphocytes with MV-infected cells, which may result in impaired lymphocyte function.

In vivo, naive T lymphocytes are most likely to interact with dendritic cells, which are important antigen-presenting cells susceptible to infection with MV in vitro. Such infection leads to the differentiation of dendritic cells and the formation of syncytia. Infected dendritic cells have a decreased ability to express the costimulatory molecule CD40 and to produce IL-12. Dendritic cells also produce IFN-a/b, which is induced by vaccine but not by wild-type strains of MV.

MV-infected dendritic cells are induced to express the tumour necrosis factor-related apoptosis-inducing ligand (TRAIL). Tumour cells cocultured with MV-infected dendritic cells undergo apoptosis and this is mediated through TRAIL. These studies indicate that lymphocytopenia during the active phases of MV replication in vivo may be mediated through the interaction of T cells with MV-infected cells, particularly MV-infected dendritic cells.

Lymphocytopenia gradually resolves as the immune response is induced, the viraemia is cleared and the rash appears. During this time there is considerable activation of CD4 and CD8 T lymphocytes, with the appearance of cytokine-secreting and cytotoxic T lymphocytes. T cell activation includes increased expression of cell surface receptors such as *Fas,* which increase susceptibility to the induction of apoptosis. CD4 T cells remain activated longer than CD8 T cells. Cytokines are produced primarily by CD4 T cells. The cytokine response is skewed towards type 2 cytokines IL-4 and IL-5. There is concomitant eosinophilia. This type 2 cytokine skewing may be explained by an MV-induced suppression of IL-12, the cytokine responsible for inducing the synthesis of type 1 cytokines, for instance IFN-a and IL-2. A type 2 skewing of the cytokine response suppresses delayed-type hypersensitivity skin test responses and lymphoproliferation in vitro and promotes B cell proliferation and differentiation, leading to antibody production.

Transgenic mice incorporating the human receptor CD46 for MV were recently used to study measles pathogenesis, including immunosuppression. After infection with MV the mice had lower responses to new and recall antigens and had an increased susceptibility to infection with the bacterium *Listeria monocytogenes.* This model may prove useful for further study of the mechanisms of measles-induced immunosuppression.

The need was emphasized to understand the biological mechanisms underlying MV-induced immunosuppression and its relationship to immunosuppression induced by measles vaccine. This required further research concentrating on how observations made in tissue culture systems and animal models related to the events occurring during measles and measles immunization in humans.

4. Measles mucosal immunization

South African study

A report was presented on a block randomized study conducted in Durban, South Africa, comparing aerosolized Edmonston-Zagreb vaccine (EZae), aerosolized Schwarz vaccine (SWae), subcutaneous Edmonston-Zagreb vaccine (EZsc) and subcutaneous Schwarz vaccine (SWsc). Children aged 6-12 years were studied at intervals of a month, a year and two years after vaccination. Four outcome parameters were measured: percentage seroconversion (fourfold rise in antibodies), average rise in antibody titres, geometric mean titres (GMTs), and percentage seronegativity. The haemagglutination inhibition test was performed in the laboratory. SWae lost its activity after a few simulated doses and was not included in subsequent analyses.

At a month after vaccination, virtually all children given EZae, EZsc or SWsc were seropositive. EZae outperformed EZsc and SWsc in respect of the other three parameters. At one and two years after vaccination, EZae outperformed EZsc and SWsc in respect of all the parameters. At a month and a year after vaccination, EZsc outperformed SWsc in respect of all the parameters, but at two years the differences were no longer statistically significant except with regard to seronegativity: the proportions seronegative at this time were 6%, 13% and 19% respectively for EZae, EZsc and SWsc.

The potential advantages of aerosol vaccine, in addition to its superior immunogenicity, include the following: it mimics the natural route of infection; it can multiply locally without being neutralized by pre-existing antibodies; it is non-invasive and consequently there are none of the problems associated with injections. It is cost-effective if used in mass campaigns, and may improve the secretory IgA response. Because they may differ between manufacturers, all vaccines should be field-tested in a nebulizer before being recommended for aerosol vaccination. In conclusion, the use of aerosol vaccination could significantly advance global efforts to eliminate measles.

Mexican studies

Results were presented from two trials in which measles vaccine and measles-rubella vaccine (MR) were administered in aerosol to schoolchildren in Mexico. All samples were tested by an ELISA, and 11% were also tested by plaque reduction neutralization (PRN). The following indicators were measured: % seropositive, % seroconversion (twofold rise), and GMT.

In the first study, SWsc, EZsc, low-dose aerosolized Edmonston-Zagreb (EZae-low), and standard-dose aerosolized Edmonston-Zagreb (EZae-st) were compared. The frequency of adverse events was low in all groups but was significantly lower in the aerosol groups than in the others. In each group, 97%-100% of children were seropositive as indicated by ELISA after vaccination; all those tested had a PRN titre = 120 mIU. The % seroconversion and the GMT achieved were higher for both the aerosolized vaccines than for the subcutaneous vaccines.

In the second study, subcutaneous MR (rubella component = RA 27/3) was compared with aerosolized MR. As in the first study, the frequency of adverse events was low in all groups but was significantly lower for the aerosol groups. All children became seropositive in both groups by PRN, although the children in the subcutaneous group had lower rates of seropositivity by EIA. In addition, the rate of PRN seroconversion and the GMT were significantly higher for children in the aerosol group. Responses to rubella vaccine (EIA) were similar for both groups.

Thus seroconversion was high for all vaccines but highest for aerosol vaccines, and although all groups achieved high rates of seropositivity for measles the antibody titres were higher for the aerosolized groups. These are the first studies showing that measles and rubella vaccines can be given together successfully in aerosol form. The successful use of low-dose measles vaccine in aerosol, with an administered dose of about 1000 pfu in 0.1 ml, suggests that currently available Edmonston-Zagreb vaccine in standard titre can be reconstituted as directed for injection or that the administration time should be increased beyond 30 seconds for potencies below 5000 pfu per 0.5 ml. In Mexico there are plans to conduct phase I and phase II studies using aerosolized MMR vaccine as a booster dose to school-age children. In addition, studies are planned on cellular immunity after aerosol vaccination of infants and on mucosal immunity after aerosolized vaccination of preschool children. Cost-benefit studies of the use of aerosol vaccination will also be performed.

The experience of giving vaccine in the presence of upper respiratory tract infection (URI) was discussed. In Mexico, some 5% of children were excluded because of URI. In South Africa, such children were not excluded and although the response was slightly decreased it was still greater than the response in children receiving subcutaneous vaccine.

The best assays for measuring protection against disease are PRN for measles and possibly a neutralization test for rubella. There was speculation as to whether the induction of higher antibody levels might reflect increased immunosuppression.

The data indicated that the immunogenicity of the aerosol vaccine when used as a booster dose appeared superior to that of the subcutaneous vaccines, although the clinical significance of the increase has not been verified. The advantages of the aerosol route include painlessness and the absence of injection safety issues and of a need to dispose of needles and syringes. However, there will be major difficulties in licensing the aerosol route of administration. More information is needed on the requirements for licensing. There was disagreement as to whether additional large-scale human trials should be undertaken immediately or whether more safety

data should be collected first. Although several aerosol studies have involved immunologically naive children, some participants felt the aerosol route should only be used for booster doses in such children because of possible hazards, especially those that might be encountered in immunocompromised hosts (e.g. possible risk of pneumonitis or giant cell pneumonia).

The following matters were also discussed:

- Serum IgA may be a surrogate of mucosal IgA.
- It would be helpful to determine exactly how far aerosolized vaccine should penetrate into the pulmonary tract in order to be effective. Questions were raised about the possible importance of deposition in the upper respiratory tract.
- The establishment of a smaller working group could be useful with a view to determining what other questions should be answered in order to develop the use of aerosolized vaccine in booster doses, to test its use as a first dose, and to evaluate its use for countries with high rates of HIV infection.
- The active involvement of representatives from regulatory agencies and developing countries is important in order to determine the requirements for promoting aerosol vaccination and the time frame for attaining the objective.
- How will a decision to use aerosolized measles or MR vaccine affect the decisions of countries that are moving towards the use of MMR?
- Is there a possibility that aerosol administration of the vaccine could lead to extension into the central nervous system via the cribriform plate? An animal model could be used to investigate this matter

Measles vaccination in the macaque model

Results were presented on four alternative candidate vaccines and application routes in the macaque monkey model.

- Live attenuated vaccine in tablet form was not immunogenic when administered intraintestinally, even when enteric-coated tablets were used. It was concluded that the intestine was not a favourable site for MV replication, nor, therefore, for vaccination.
- DNA vaccination with gold particles coated with plasmids encoding the MV F, H and/or N proteins were administered intradermally by means of a gene gun on two occasions separated by eight weeks. Very low levels of F and H antibodies and a single N-specific antibody rise were observed. Upon challenge with live MV a year later, neutralizing antibody was not detectable and the macaques were not protected. However, those that had received the DNA-N construct showed reduced viral loads in lung lavages and blood. These data do not support the use of this method for measles vaccination.
- Recombinant modified vaccinia virus Ankara (MVA) encoding the measles haemagglutinin and fusion protein (MVA-FH) was evaluated using a two-dose schedule, both in the absence and presence of passively transferred MV-neutralizing antibodies. All animals immunized with this live, replication-deficient vaccine developed MV-specific neutralizing antibodies

and CD4+ and CD8+ T cell responses. The levels of immunity induced in the absence of passively transferred antibodies were slightly lower than those induced by Schwartz vaccination, but in the presence of passively transferred antibodies MVA-FH induced much higher responses than Schwartz. All animals were essentially protected from challenge infection a year after vaccination. No safety problems were encountered when testing this candidate vaccine in immunocompromised macaques. MVA-FH may be a promising candidate vaccine in measles elimination campaigns, either alone or in boosting regimes.

- ISCOM. Studies are continuing in three groups with five animals in each.

Another investigator reported a protective response to gene gun vaccination using DNA vaccines.

Further use of the monkey model was recommended for evaluating the safety, immunogenicity and protective activity of new forms of measles vaccine.

5. Measles vaccination strategy and disease surveillance

Two-dose schedules

Two current studies of two-dose measles vaccination schedules in Guinea-Bissau were reported.

The first was a trial comparing children vaccinated with standard-titre measles vaccine at six and nine months with controls vaccinated with inactivated polio vaccine at six months and measles vaccine at nine months. A blood sample was taken from each child at 18 months to test antibody levels. So far 5500 children have been recruited. The first 590, recruited between March and August 1995, received Edmonston-Zagreb vaccine (EZ); the others received Schwarz vaccine (SW). Among the children given EZ there was no difference in antibody levels at 18 months between those who had received one dose and those who had received two doses. However, for SW, antibody levels at 18 months were twice as high after one dose at nine months than after two doses at six and nine months. Because the two vaccines were used at different times it was possible that natural boosting contributed to the observed difference between them. For all vaccines and schedules, more than 90% of the children had protective antibody levels at 18 months. The incidence of measles was too low to permit good estimates of the efficacy of the different schedules to be derived. There was no difference in overall mortality between the two groups.

The second study was designed to test the impact of offering additional measles vaccine to all children aged 9-59 months. A hundred clusters of 100 women and their children are being followed in a prospective study. The children in half the clusters were offered two additional doses of measles vaccine separated by an interval of six months.

More research is needed to discover the best options for two-dose strategies. Further investigation of the non-specific effects of measles vaccination and infection on child survival should be conducted in order to clarify the role of the vaccine strain employed.

Role of laboratory confirmation in measles surveillance

Laboratory confirmation of acute measles infection is based on the detection of IgM antibodies in serum or oral fluid. Several acceptable commercial assays are available, all of them ELISA-based. In a setting with a measles elimination goal, high specificity is of paramount importance in order to maximize the positive predictive value. One possibility for a confirmatory test involves the detection of low-avidity IgG, but this has not been evaluated. There are many commercial assays of varying quality for the detection of IgG. The interpretation of low antibody levels in terms of protection is problematic.

Considerable progress has been made in the use of oral fluid as an alternative to serum for both IgM and IgG testing. (Oral fluid is also suitable for virus detection by PCR.) ELISAs for IgM and IgG have high sensitivity and specificity. Oral fluid testing is more acceptable to patients than serum testing, and has been conducted successfully in Brazil, Ethiopia, India, South Africa, and the United Kingdom. Since 1995, all suspected measles cases in the United Kingdom have been offered laboratory confirmation based on oral fluid testing, and over 14 000 samples have been tested.

Susceptibility profiles and vaccination strategies

Rational decisions on vaccination strategy are based on knowledge of the susceptibility profile. Coverage data and age-stratified case reports can be used to estimate susceptibility, but such data are often unavailable, incomplete or unreliable. Serological surveys of antibody prevalence provide robust data on which to base strategy.

Mathematical models have been developed to predict the duration of the impact of mass vaccination campaigns. However, coverage data are often of insufficient quality to allow useful guidance to be obtained on the basis of such calculations. Improving the accuracy of routine and campaign coverage data is crucial in evaluating the impact of campaigns.

Measles eradication presents many challenges additional to those of elimination. The potential for measles to be sustained by transmission between unvaccinated communities, especially those refusing vaccination, should be assessed.

Cost-effectiveness

There are few data on the cost of improving routine measles coverage, only one longitudinal study having been published. In Africa, however, measles coverage is often well below BCG coverage, suggesting that significant improvements should be possible at reasonably low cost. The cost-effectiveness of improving measles coverage depends on local factors, including current measles coverage and epidemiology. A recent study found that improving routine measles coverage was considerably more cost-effective than introducing vaccination against hepatitis B virus. The cost and effectiveness of measles campaigns are likely to show more local variation. New technology, involving the use of alternative routes of immunization, may significantly reduce the cost of vaccination campaigns. Further work is urgently needed on the cost of improving routine measles coverage, particularly to high levels.

The elimination of measles infection is not the most cost-effective option for measles control. As elimination is neared, each marginal improvement in coverage produces smaller and smaller benefit at greater and greater cost. The most cost-effective option falls short of elimination. However, global eradication may be cost-effective and possibly even cost-saving. The net present value of the cumulative savings to the USA resulting from measles eradication has been estimated as US$ 0.5-4.1 billion. Countries with measles elimination programmes should conduct similar studies in order to calculate how much they should contribute to global eradication. An estimate of the cost of measles eradication could be derived by suitable scaling of the costs for polio eradication.

Laboratory network

A network of national, regional and specialized measles reference laboratories is based on the polio network, with extensions to include extra laboratories, especially in Africa. There are two global strain banks, one in the Public Health Laboratory Service of the United Kingdom and the other attached to the Centers for Disease Control and Prevention (CDC) in the USA. The procedures for assessing and selecting laboratories for the network were described. Support was provided for equipment, supplies and training. The difficulty of retaining trained staff was highlighted. This problem was particularly acute in Africa, where only 25% of staff trained in 1991-1999 were still in post. The network could be strengthened by the development of large-volume panels of standard sera for validation and quality control, the validation of new IgM assays, the promotion and development of non-serum testing, and the development of stabilized transport media for molecular detection.

Measles virus strains

In countries pursuing measles elimination the genetic characterization of wild-type MVs is a key component of laboratory surveillance. Molecular data, analysed in conjunction with standard epidemiological data, can help to monitor transmission pathways of the virus. The lack of any indigenous strain suggests that cases result from importations; such a pattern has been observed in the USA since 1993. The global distribution of genotypes is emerging. Since the publication of the standardized nomenclature for describing MVs in 1998 there has been an increase from 15 to 19 in the number of proposed genotypes. The continued discovery of new genotypes suggests that the list is still incomplete. Progress is hindered by the difficulty of obtaining appropriate specimens. Although most authors now use the standardized nomenclature to describe strains and genotypes, many still do not follow the recommended protocol for analysis.

Simple diagnostic tests

WHO specified the following requirements for a simple test for the diagnosis of measles infection: any person with basic health care skills should be able to perform it; it should not require electricity or running water; it should be stable at a wide range of temperatures; and it should be as sensitive and specific as an IgM-capture ELISA. Previous attempts to develop a test based on a rapid dot-blot immunoassay failed. In 1997-1999, WHO commissioned three institutions to develop a simple test, and each proposed a different format of immunochromatographic technology.

In addition, WHO provided technical support for studies to develop simpler tests for use in primary health care and/or diagnostic laboratories. Prototypes of two of these tests were evaluated on a panel of 91 sera in two WHO global reference laboratories. The IgM-capture gelatin particle agglutination test (Serodia), a simple overnight laboratory assay read by eye, was easy to use and gave good agreement with established assays. In contrast the IgM dipstick test, designed to produce a band on the stick in the event of a positive result, was difficult to read, and there was poor agreement between observers. This test may have some potential but further development is needed.

The use of filter paper blood samples for serology and PCR was reported. Such samples were stable at room temperature and the results correlated well with standard IgM serology in a study of 125 samples. Intermediate levels of IgM in early samples can be confirmed through virus detection by means of PCR.

The type of test required depends on its expected role in surveillance and, in particular, on what the response to a positive test would be. The need for a rapid laboratory test was discussed in view of other delays in the diagnostic process. In many settings the greatest delay would be in getting the samples to the laboratory, in which case an overnight test would not introduce significant extra delay. A rapid test would probably sacrifice some sensitivity and specificity. There was general agreement that development should prioritize ease of performance, with no requirement for specialized equipment, rather than speed. Simpler laboratory tests were needed, not bedside tests. Single-sample tests with built-in controls would be advantageous. Two approaches for resolving low positive samples were suggested: PCR in regional laboratories, or the development of testing for low avidity.

Measles bank of reagents

The status of the measles bank of reagents was summarized. Reagents such as antigens, cell lines, monoclonal antibodies and vaccine recombinants were made available to researchers throughout the world by this bank.

Engineered vaccine viruses

The development of a reverse genetics system for MV has allowed the manipulation of the genome so as to produce engineered MVs. This system can be used to alter MV so that the roles of particular virus genes of unknown function (e.g. C and V) in virus replication and pathogenesis can be assessed. A further use is to engineer the virus to express other proteins. These proteins are stably expressed and can be reporter proteins allowing the monitoring of virus infection or cytokines that might alter the immune response to the virus. Since the measles vaccine has an excellent safety record it is also possible to express proteins from other pathogens or simultaneous immunization against measles and another disease. The expression of proteins of hepatitis B virus, SIV, HIV and malaria has been accomplished. A problem for use may be the inability of MV to replicate in immune individuals. Attention was drawn to the value of such engineered MVs for studies on pathogenesis and immunity in animal models. Careful evaluation will be necessary of the safety of MVs expressing proteins from other pathogens that might result in altered cellular tropisms and target tissues.

6. Development of new products

Powder formulation of measles vaccine

The technology has been developed and optimized to produce vaccine particles of uniform size of around 5 microns with minimal potency loss during the milling process. However, concerns were raised about the safety of powder vaccines in relation to their content of non-replicable virus as estimated from their potency values before and after milling. It was proposed that preliminary evaluation of the efficacy and safety of powder vaccine should be carried out in the primate model. Several other issues, relating to stabilizers, excipient and the sterility of the vaccine delivery apparatus were discussed. It was indicated that an inexpensive new type of disposable inhaler for single-dose use was being developed. This would prevent the problem of contamination between vaccine recipients.

Needle-free injectors

A discussion was held on progress with needle-free injectors (NFIs) and their suitability and advantages in mass vaccination campaigns. NFIs have great potential for subcutaneous administration of liquid vaccines. Similar injectors have been used successfully in different parts of the world. WHO previously tested four models of NFIs for performance but not for safety.

Contamination through NFIs was reported previously and this issue is currently under investigation. A device (CADB Russia) with disposable nozzle caps and a proprietary system for eliminating contamination is being tested; the results obtained so far have been encouraging. Further testing is required with multiple shoots (300-500). It is expected that introductory trials will be conducted in a number of countries by 2003. Among other matters discussed was the level of injector noise that might frighten children.

Licensing and economic issues related to development of new products

A discussion was held on licensing issues pertaining to new products, with special reference to new formulations of measles vaccines. As these aerosol and powder formulations would be delivered via the respiratory route they would be considered as new products requiring full evaluation. Particular emphasis should be given to vaccine safety and efficacy.

The lack of interest shown by most large companies in the development of new products was attributable to the high capital investment required. The products could be expected to generate low returns over long periods. Furthermore, producers were uncertain about the acceptability of new products.

7. Requirements for further research related to measles control and elimination

7.1 Effectiveness and control of mass immunization campaigns

Highest priority research

- Serological surveys should be conducted before and after campaigns in a range of settings to identify the appropriate age group for campaigns and to evaluate their impact.
- The surveys should include rubella and mumps where there is national interest in these infections.
- Assays based on commercial kits and oral specimens should be developed.

Evaluation of campaigns

Research is needed to develop methods for:

- surveillance of vaccination safety and adverse events;
- evaluation of surveillance systems in countries at different stages of measles control.

The minimum components to consider in the evaluation of a campaign are:

- monitoring of coverage by the campaign and by the routine programme (both overall and in high-risk groups), including the effect of the campaign on routine coverage;
- monitoring of measles incidence and mortality before and after the campaign;
- monitoring of injection practices, including injection safety considerations and/or cold-chain practices;
- monitoring of expenditure on different components of the campaign;
- assessment of the potential uses of molecular epidemiology in campaign evaluation.

7.2 Measles immunity, immunopathology and virus gene function

Considerable progress has been achieved in research on measles immunology and immunopathology during the last few years. Important data on the role of different components of the immune system in protection and immunopathological events were obtained. The potential of engineered MV vaccine strains to induce immunity against other pathogens was demonstrated. In order to improve our knowledge in the areas concerned it is recommended that the following studies be given the highest priority.

- Identification of determinants of longevity of MV-specific immune response, including host-related factors and the effects of its boosting by vaccination and natural infection.
- Identification of correlates of protection from MV infection and disease, with special attention to their relationship with subclinical infection and virus transmission (e.g. transmission by subclinically infected individuals).
- Identification of determinants of quality and quantity of MV-specific immune response, including host-related and environmental factors.
- Identification of molecular determinants of MV virulence, attenuation, immune suppression and cellular/tissue tropism.

In studying these topics, special attention should be paid to MV wild-type and vaccine strains, as well as to the influence of the route of MV infection or immunization. Furthermore, it is emphasized that studies focusing on functional aspects of the humoral and cellular key players of the MV-specific immune response, as well as studies related to the identification of in vivo MV-infected target cells and the changes that such infection causes in the functioning of these and other cells of the immune system, are crucial for studying the above-mentioned topics. The proposed studies could be carried out with materials obtained from MV-vaccinated or naturally infected individuals, and with the help of monkey and rodent models and in vitro systems.

7.3 Alternative routes of vaccination and new products

Jet injectors

Some participants believed that the Russian multi-dose jet injector may be available in four to five years. A major advantage of this device is that it can be used in conjunction with the existing multi-dose vial. In parallel, small business grants at CDC are being awarded for the design of new devices that guarantee safety. One problem with these approaches is the potentially high cost of the devices.

The following studies are needed:

- additional laboratory safety trials;
- evaluation of sheering of the vaccine going through the disposable tip;
- design work to ensure feasibility of mass-production;
- field simulation studies to determine the number of potent doses of vaccine that can be given in the absence of means for continued chilling of vaccine in the multi-dose vial.

Aerosolized vaccines

For this approach, researchers advocate the use of these devices for children aged 5 years or more, and then broadening the approach to include children under 5 years and immunologically naive children. To begin to address some of the safety issues raised by the HIV pandemic, animal studies have been planned for both approaches. Developers and researchers believe that both approaches could be available within the next three to five years, depending on licensing issues.

Nebulized aerosol approach for use in mass campaigns

The researchers note that this approach will not replace subcutaneous administration for individual use. One advantage is that the dose required is significantly smaller than that needed for subcutaneous use, thus offering the prospect of dramatically reducing vaccine requirements. The research on this approach is at an advanced stage but more work is needed on safety and immunogenicity.

Studies are needed on:

- safety data from the Mexican and South African trials (review of the safety of both vaccinees and vaccinators);
- safety, using immunocompetent and immunosuppressed monkeys;
- safety and immunogenicity in immunologically naive younger children;
- use of aerosolized MMR as a booster dose for school-age children (phase I and II);
- evaluation of methods for delivering nebulized vaccine to preschool children;
- cellular immunity after aerosol vaccination (already planned);
- mucosal immunity after aerosol vaccination of preschool children;
- potential suitability of different vaccine strains;
- cost/benefit of aerosol vaccination.

Dry powder formulation

This formulation is at an earlier stage of development but appears promising. The manufacturer advocates a single-use disposable device that could be made inexpensively. Collaboration with a vaccine manufacturer may help to keep it affordable.

Work is needed to:

- make the vaccine formulation less hygroscopic;
- determine the optimum size of vaccine particles for immunization by aerosol;
- evaluate vaccine safety and immunogenicity, first in monkey models and subsequently in clinical studies.

Coordination of studies on alternative routes of vaccination

WHO should convene a meeting that includes regulatory agencies together with companies and researchers developing the three proposed products/vaccines. The meeting should focus on clarifying the steps, time frames and hurdles for bringing the products to the market place. At the end of this meeting, WHO and other collaborators should be able to prioritize the different approaches. Before the regulatory meeting, the developers should indicate to WHO the projected time frame and costs of development and the approximate unit costs for use of the jet injector system, the nebulized formulation and the powder formulation.

Diagnostic tests and new vaccines

- The development of new rapid field tests is not a priority at present.
- Existing commercially available measles antibody assays (IgM and IgG) should be evaluated for use with oral fluid samples.
- The particle agglutination test should be evaluated in Africa with filter paper samples and oral fluid samples.
- Work should continue on evaluating and refining the use of filter paper for measles diagnostics and molecular epidemiology.
- The development of new vaccines is a lower priority for WHO than work on alternative routes and diagnostic tests. However, WHO recognizes the potential value of continuing this line of research.

7.4 Cost-effectiveness of measles control and elimination

Routine immunization

Knowledge of the average costs of routine immunization and the incremental costs of expanding routine coverage is essential when decisions on allocation are being made. There are, at present, very few data on the incremental costs of expanding routine coverage, particularly to higher levels. The following recommendations are made.

- Intervention-evaluation studies should be conducted. These would involve a baseline assessment of immunization services followed by an intervention proposal, implementation and a follow-up assessment. This process would yield average costs as well as incremental costs of expanding coverage. It could be conducted relatively cheaply in areas where baseline studies have recently been performed.
- An alternative study design would involve allocating an additional sum of money to an area and determining whether coverage improved.
- A review should be conducted of PAHO data on the costs of expanding routine coverage to high levels. This could be done relatively quickly and inexpensively.

Introduction of a second dose

- Further studies are needed on the costs and effectiveness of different two-dose schedules.
- If effectiveness studies are being planned, investigators should be strongly encouraged to collect cost data as well.

Campaigns

- Existing data on the cost of campaigns should be collated and disseminated.
- Data on costs should be collected in a comparable fashion from campaigns in progress. This can be done inexpensively.
- It is essential to collect data on costs alongside data on effectiveness in trials using needle-free technologies.
- The costs of unsafe vaccinations in current campaigns should be properly evaluated. This should be a research priority even though substantial efforts would be required.

Elimination/eradication

If global measles eradication is to be considered as a policy option, research should be performed in the near future to determine its feasibility and cost.

- A survey of the current costs of measles surveillance, treatment and vaccination should be performed in countries that have achieved elimination. These costs could be compared with the projected costs of surveillance and vaccination after measles eradication in order to determine the attainable savings.
- Data on the costs of global polio eradication and the relative difference in costs of polio and measles elimination in the Americas could be used to obtain an approximate estimate of the likely costs of measles eradication.
- The current financial global burden of measles should be determined. This would be a substantial study.

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