Measles vaccine: Selected references for the WHO Position paper published in the WER 2 April 2003

Epidemiology, pathogenesis, clinical aspects, laboratory diagnosis


The estimation of the global burden of measles is challenging in the absence of reliable and comparable surveillance systems worldwide. A static model is described that enables estimation of measles morbidity, mortality, and disability for the year 2000 on the basis of country-specific information (i.e., demographic profile, vaccine coverage, and estimates of case-fatality ratios). This approach estimated a global incidence of 39.9 million measles cases, 777,000 deaths, and 28 million disability-adjusted life years. The World Health Organization regions of Africa and Southeast Asia had 70% of incident cases and 84% of measles-related deaths; 11 countries alone (Afghanistan, Burkina Faso, Democratic Republic of the Congo, Ethiopia, India, Indonesia, Niger, Nigeria, Pakistan, Somalia, Uganda) account for 66% of deaths. This approach quantifies the measles burden by considering country-specific indicators, which can be updated, permitting an assessment of country, regional, and global changes in the burden associated with measles infection.


Measles is one of the most important diseases of mankind, which is so highly contagious and evokes such persistent immunity that the virus cannot be sustained in a population of less than about 500,000 persons. The first of the licensed live virus vaccines against measles was developed empirically and was approved in 1963. It provides high level and lasting immunity and is a paradigm for solving major medical problems without really understanding them. In spite of means for control by prophylactic immunization, research on measles infection continues to be part of the effort to understand the pathogenesis of many different viruses, which may have important similarities and differences and provide important insights. Measles, usually, is spontaneously reversible and is a prime model for understanding virus-induced immunodeficiency disease (AIDS) which is rarely reversible. Much has been learned of basic immunology and vaccinology in measles through observation of the inappropriate use of vaccines of appropriate composition, and through inappropriate host response to measles vaccines of inappropriate composition. This review provides a current overview of selected highlights of measles, the virus, its
immunopathogenesis, and its control by use of live virus vaccine which may lead to elimination of the disease and eventually to eradication of the virus.


Measles is the most frequent cause of vaccine-preventable childhood deaths. Infants younger than the recommended age for vaccination are susceptible to the disease, and in developing countries they have a high risk of complications and mortality. Vaccine coverage in excess of 95% interrupts endemic transmission of measles in many countries, but achievement of such coverage almost always requires coordinated supplementary mass vaccination campaigns. There are substantial health gains if countries improve measles vaccine coverage, irrespective of whether or not high coverage is achieved; these gains include much lower measles complication and case fatality rates, long-term interepidemic duration, and possibly non-specific improvements in survival of children. Investigation into the cost-effectiveness of different strategies for measles control, including mass campaigns, two-dose schedules, and young-infant doses, would help countries to formulate control policies appropriate to their setting. Pneumonia is the most common fatal complication associated with measles, and at least 50% of measles-related pneumonias are due to bacterial superinfection. WHO has developed standard case management programmes for measles, but there are several unresolved clinical issues, including optimum indications for antibiotic treatment, the importance of intravenous immunoglobulin, the role of viral coinfection, and the risk of tuberculosis after measles. The priority in worldwide efforts to control measles is to lend support to poor countries, helping them to increase vaccine coverage and sustain improvements to vaccination infrastructure, and to address technical issues with respect to optimum vaccination schedules. Measles represents a specific challenge, whereby partnerships between high-income and developing nations would reduce child mortality in developing countries; such partnerships are not without incentive for high-income countries, since without them imported measles cannot be prevented.


Forty years after effective vaccines were licensed, measles continues to cause death and severe disease in children worldwide. Complications from measles can occur in almost every organ system. Pneumonia, croup, and encephalitis are common causes of death; encephalitis is the most common cause of long-term sequelae. Measles remains a common cause of blindness in developing countries. Complication rates are higher in those <5 and >20 years old, although croup and otitis media are more common in those <2 years old and encephalitis in older children and adults. Complication rates are increased by immune deficiency disorders, malnutrition, vitamin A deficiency, intense exposures to measles, and lack of previous measles vaccination. Case-fatality rates have decreased with improvements in socioeconomic status in many countries but remain high in developing countries.

The optimal timing for collection of a single serum specimen to diagnose measles by using a monoclonal antibody-capture EIA was evaluated. Results of testing paired serum samples from 166 measles cases with at least 1 IgM-positive specimen were analyzed. Among persons whose second samples were IgM-positive, the seropositivity rate for first samples was 77% when collected within 72 h and 100% when collected 4-11 days after rash onset. Among unvaccinated persons whose first samples were IgM-positive, the rate for IgM positivity of second specimens declined from 100% at 4 days to 94% at 4 weeks after rash onset, then declined further to 63% at 5 weeks. Some previously vaccinated persons became IgM-negative during the third week after rash onset. In general, a single serum specimen collected between 72 h and 4 weeks after rash onset can be used to diagnose most cases of measles with an IgM capture EIA.


Serum-based measles-specific IgM EIAs are the recommended laboratory assays for diagnosis of acute measles infections and appear to be sufficient for measles control programs. However, serum samples are not ideal for molecular characterization of measles virus. Although neither laboratory nor field-based diagnostic tests that rival the EIAs have been developed, laboratory surveillance could be improved if specimen collection were simplified. Ideally the collection method should be noninvasive, have no requirement for a cold chain, and/or have no requirement for technically sophisticated equipment. Two alternative specimen collection technologies appear promising and can be used for both diagnostics and for collecting pertinent genotyping information: oral fluid and filter paper collection methods. These methods are compared along with their respective utilities in supporting measles diagnosis and strain surveillance.

Measles vaccines


High morbidity and mortality from measles among infants under 9 months of age is an obstacle to measles control in many developing countries. In this paper, we review 30 studies conducted on the serological response to measles vaccine in infants aged less than 9 months. Among children aged under 9 months, Edmonston Zagreb and AIK-C vaccines produce higher seroresponse rates than Schwarz vaccine of equivalent titre. For Edmonston Zagreb and Schwarz vaccine, seroresponse rates increase with increasing vaccine titre. The absolute rate of seroresponse to Edmonston Zagreb
vaccine in 6-month old infants varied greatly between studies because of differences in methods of vaccine titer measurement, serological assays, definitions of seroresponse, and maternal antibody profiles of the populations studied. Seroconversion rates to Edmonston Zagreb or AIK-C vaccines at 6 months of age were generally similar to those to Schwarz vaccine at 9 months of age, but antibody levels were lower after vaccination below 9 months of age. Although the increased mortality documented in other studies after use of high titer vaccines in 4-6 month old infants led to withdrawal of these vaccines, this review of vaccine trials highlights the need for standardization of study methods and for a better understanding of the biological action of measles vaccines.


BACKGROUND. In the 1970s measles, mumps, and rubella were rampant in Finland, and rates of immunization were inadequate. In 1982 a comprehensive national vaccination program began in which two doses of a combined live-virus vaccine were used. METHODS. Public health nurses at 1036 child health centers administered the vaccine to children at 14 to 18 months of age and again at 6 years, and also to selected groups of older children and young adults. Vaccination was voluntary and free of charge. In follow-up studies, we focused on rates of vaccination, reasons for noncompliance, adverse reactions, immunogenicity, persistence of antibody, and incidence of the three diseases. Since 1987, paired serum samples have been collected from all patients with suspected cases of measles, mumps, or rubella. RESULTS. Over a period of 12 years, 1.5 million of the 5 million people in Finland were vaccinated. Coverage now exceeds 95 percent. The vaccine was efficient and safe, even in those with a history of severe allergy. No deaths or persistent sequelae were attributable to vaccination. The most frequent complication requiring hospitalization was acute thrombocytopenic purpura, which occurred at a rate of 3.3 per 100,000 vaccinated persons. The 99 percent decrease in the incidence of the three diseases was accompanied by an increasing rate of false positive clinical diagnoses. In 655 vaccinated patients with clinically diagnosed disease, serologic studies confirmed the presence of measles in only 0.8 percent, mumps in 2.0 percent, and rubella in 1.2 percent. The few localized outbreaks were confined to patients in the partially vaccinated age groups. There are now fewer than 30 sporadic cases of each of the three diseases per year, and those are probably imported. CONCLUSIONS. Over a 12-year period, an immunization program using two doses of combined live-virus vaccine has eliminated indigenous measles, mumps, and rubella from Finland. Serologic studies show that most reported sporadic cases are now due to other causes, but a continued high rate of vaccination coverage is essential to prevent outbreaks resulting from exposure to imported disease.

The vast majority of adverse reactions following immunisation of children with live measles-mumps-rubella (MMR) vaccine were shown in a double-blind, placebo-controlled, cross-over study in 581 twin pairs to be only temporally but not causally related to the vaccination. The true frequency of side-effects caused by MMR vaccine, estimated from the discordance rates of individual signs and symptoms between MMR vaccinees and their placebo-injected twins, was between 0.5 and 4.0%. Moreover, respiratory symptoms, nausea, and vomiting were observed more frequently in the placebo-injected group than in the MMR vaccinated group.


The clinical safety of measles and measles-mumps-rubella vaccines has been questioned in recent reports that propose a possible link between measles virus or measles vaccines and the occurrence of juvenile Crohn disease and autism. This article reviews the outcomes of several laboratory investigations which were carried out independently to identify the presence or absence of measles virus in the intestinal tissues derived from cases of inflammatory bowel disease. One research group reported the presence of measles virus particles and genomic RNA in inflammatory bowel disease tissues, but this could not be confirmed by other groups, despite use of techniques that are highly specific and sensitive for the detection of measles virus nucleic acid in clinical specimens down to the molecular level. Based on the published data reviewed here, it can be concluded that there is no direct association between measles virus or measles vaccines and the development of Crohn disease, a conclusion which is supported by most epidemiological findings.


BACKGROUND: Several disorders have been attributed to measles-mumps-rubella (MMR) vaccination during the past decade. The aim of this prospective follow-up study was to identify serious adverse events causally related to MMR vaccination. METHODS: When the MMR vaccination program was launched in Finland in 1982, a countrywide surveillance system was set up to detect serious adverse events associated with MMR. To obtain detailed case histories vaccinees' clinical charts were reviewed. Serum samples were analyzed to trace concurrent infections. SETTING: All hospitals and health centers in Finland from 1982 through 1996. RESULTS: Immunization of 1.8 million individuals and consumption of almost 3 million vaccine doses by the end of 1996 gave rise to 173 potentially serious reactions claimed to have been caused by
MMR vaccination. In all, 77 neurologic, 73 allergic and 22 miscellaneous reactions and 1 death were reported, febrile seizure being the most common event. However, 45% of these events proved to be probably caused or contributed by some other factor, giving an incidence of serious adverse events with possible or indeterminate causal relation with MMR vaccination of 5.3 per 100,000 vaccinees or 3.2 per 100,000 vaccine doses. CONCLUSIONS: Causality between immunization and a subsequent untoward event cannot be estimated solely on the basis of a temporal relation. Comprehensive analysis of the reported adverse reactions established that serious events causally related to MMR vaccine are rare and greatly outweighed by the risks of natural MMR diseases.


In the planning and implementation of mass immunization campaigns, vaccine delivery has always been a priority. However, safety issues have gained increasingly more attention and grown in importance, and campaign planners must now take them into prime consideration. The World Health Organization has released guidelines to assist with the design and implementation of safety surveillance systems, primarily for developing countries, and these include a new monograph for measles mass campaigns. Experience in the past decade with mass campaigns (primarily in developed countries) shows that measles vaccine performs in these settings as anticipated from pre- and post-licensure studies. Serious adverse events are rare, even under the increased scrutiny extended during a campaign. The experience in developing country settings is growing. The implementation of safety surveillance for mass campaigns offers a unique opportunity for countries to avoid crisis situations and to begin vaccine safety monitoring in routine immunization programs.


Measles immunization campaigns are effective elements of a comprehensive strategy for preventing measles cases and deaths. However, if immunizations are not properly administered or if immunization waste products are not safely managed, there is the potential to transmit bloodborne pathogens (e.g., human immunodeficiency virus and hepatitis B and hepatitis C). A safe injection can be defined as one that results in no harm to the recipient, the vaccinator, and the surrounding community. Proper equipment, such as the exclusive use of auto-disable syringes and safety boxes, is necessary, but these alone are not sufficient to ensure injection safety in immunization campaigns. Equally important are careful planning and managerial activities that include policy and strategy development, financing, budgeting, logistics, training, supervision, and monitoring. The key elements that must be in place to ensure injection safety in measles immunization campaigns are outlined.
Vaccination policy


The accelerating progress in reducing measles incidence and mortality in many parts of the world has led to calls for its global eradication during the next 10-15 years. Three regions have established goals of elimination of indigenous transmission of measles. The strategy used in the Americas of a mass 'catchup' campaign of children 9 months to 15 years of age, high coverage through routine vaccination of infants, intensive surveillance and follow-up campaigns to prevent excessive build-up of susceptibles has had great success in reducing measles transmission close to zero. However, while these developments are impressive, much remains to be done to reduce measles-associated mortality in western and central Africa, where less than half of children are currently receiving measles vaccine and half a million children die from measles each year. The obstacles to global measles eradication are perceived to be predominantly political and financial. There are also technical questions, however. These include the refinement of measles elimination strategies in the light of recent outbreaks in the Americas; the implications of the HIV epidemic for measles elimination, issues around injection safety, and concerns about the possibility that secondary vaccine failures will contribute in sustaining transmission in highly vaccinated populations. The global priorities are to improve measles control in low income countries, increase awareness among industrialized countries of the importance of measles, and conduct studies to answer the technical questions about measles elimination strategies.


BACKGROUND: The World Health Organization recommended strategy for responding to measles outbreaks in developing countries does not promote the use of immunization campaigns due to their high cost, disruptive nature and limited impact. Given the substantial morbidity and mortality associated with such outbreaks, a literature review was conducted as a basis for re-evaluating this policy. METHODS: Reports of supplementary immunization activities that were performed to control measles outbreaks in middle or low income countries were identified. The impact of the immunization activities on the course of each outbreak was evaluated by examining the data provided. RESULTS: Of 66 reports detailing a measles outbreak in a middle or low income country, 17 described supplementary immunization activities which included seven 'non-selective' immunization campaigns, three 'selective' campaigns and one use of an early 2-dose schedule. Eight of the reports commented on the impact of the response, five of which reported a reduction in outbreak morbidity. Only one of the reports, from an isolated island outbreak, provided sufficient data to support a possible reduction in outbreak-associated morbidity. CONCLUSIONS: There are limited data on the impact of measles outbreak immunization activities from developing countries. The available data do not support a change in the WHO recommended strategy for conducting a limited, if any,
immunization response to such outbreaks. Immunization strategies which aim to prevent outbreaks may be more effective than campaigns to interrupt transmission of an outbreak which has already begun.

PIP: Because of their high cost, disruptive nature, and limited impact, immunization campaigns are not recommended by the World Health Organization (WHO) in response to measles outbreaks in developing countries. The authors reviewed the available literature to assess whether that WHO policy should stand or be changed. 66 reports were identified detailing a measles outbreak in middle- or low-income countries. 17 of those reports described supplementary immunization activities to control measles outbreaks which included seven nonselective immunization campaigns, three selective campaigns, and one use of an early two-dose schedule. Eight reports commented upon the impact of the intervention, five of which reported a reduction in outbreak morbidity. Only one report, from an isolated island outbreak, provided sufficient data to support a possible reduction in outbreak-associated morbidity. The available data therefore do not support a change in the WHO-recommended strategy. Immunization strategies to prevent outbreaks may be more effective than campaigns to interrupt transmission of an outbreak which has already begun.


Measles, a highly contagious viral disease, is a major childhood killer in developing countries, accounting for almost 1 million deaths every year globally. Measles virus normally does not cause a persistent infection, no animal reservoir for measles virus exists, no vector is involved in its spread, only one serotype exists, the virus is antigenically stable and vaccination with the currently used live attenuated vaccines proved to be highly effective in preventing disease. Therefore, theoretically measles should be considered eradicable. This article provides a review of past and current measles vaccination efforts and development and need of new generation experimental measles vaccines.


Measles eradication would avert the current annual 1 million deaths and save the $1.5 billion in treatment and prevention costs due to measles in perpetuity. The authors evaluate the biological feasibility of eradicating measles according to 4 criteria: (1) the role of humans in maintaining transmission, (2) the availability of accurate diagnostic tests, (3) the existence of effective vaccines, and (4) the need to demonstrate elimination of measles from a large geographic area. Recent successes in interrupting measles transmission in the United States, most other countries in the Western Hemisphere, and selected countries in other regions provide evidence for the feasibility of global eradication. Potential impediments to eradication include (1) lack of political will in some industrialized countries, (2) transmission among adults, (3)
increasing urbanization and population density, (4) the HIV epidemic, (5) waning immunity and the possibility of transmission from subclinical cases, and (6) risk of unsafe injections. Despite these challenges, a compelling case can be made in favor of measles eradication, and the authors believe that it is in our future. The question is when.


BACKGROUND: In 1994, ministers of health of countries of North and South America established the goal of measles eradication from the western hemisphere by 2000. To accomplish this goal, the Pan American Health Organization (PAHO) developed an enhanced measles vaccination strategy. METHODS: PAHO's measles eradication vaccination strategy has evolved into three principal components; a catch-up measles vaccination campaign, maintenance of high vaccination coverage (keep-up), and periodic follow-up measles vaccination campaigns. To monitor progress towards measles eradication, measles surveillance has been strengthened, including the laboratory investigation of suspected measles cases. FINDINGS: Both the catch-up and follow-up mass campaigns achieved high vaccination coverages in the respective targeted age groups. In 1996, only 2109 confirmed measles cases were reported in the Americas. In 1997, there was a resurgence of measles in the Americas, mostly as a result of a large measles outbreak with over 42000 cases, which occurred mainly among unvaccinated young adults in Sao Paulo State, Brazil. By 1998, there was a reduction in the number of reported confirmed measles cases, with a total of 14474 cases. Reduction of cases continued to the end of 1999, with a total of only 2828 confirmed cases. INTERPRETATION: PAHO's measles eradication strategy has been effective in interrupting transmission and maintaining the absence of measles virus circulation in most parts of the Americas. The PAHO experience provides strong evidence that with full implementation of an appropriate vaccination strategy, measles transmission can be effectively interrupted.

Additional WHO documents related to measles vaccine

