

Chapter 9

Measles Control and the Prospect of Eradication

W.J. Moss

Contents

Introduction	174
Goals and Strategies	174
Mortality Reduction	175
Regional Elimination	176
Eradication	177
Progress in Measles Mortality Reduction and Elimination	178
Global Goals and Progress	178
Regional Progress in Mortality Reduction and Elimination	179
Feasibility of Measles Eradication	180
Biological Feasibility of Measles Eradication	181
Technical Feasibility of Measles Eradication	181
Logistical Feasibility of Measles Eradication	182
Challenges to Global Measles Eradication	182
Challenges to Achieving High Levels of Measles Vaccine Coverage	182
Challenges to Achieving High Levels of Population Immunity	184
Challenges to Sustained Measles Eradication	185
Prospects for Measles Eradication	185
References	186

Abstract Remarkable progress has been made in reducing measles incidence and mortality as a consequence of implementing the measles mortality reduction strategy of the World Health Organization (WHO) and United Nations Children's Fund (UNICEF). The revised global measles mortality reduction goal set forth in the WHO-UNICEF Global Immunization Vision and Strategy for 2006–2015 is to reduce measles deaths by 90% by 2010 compared to the estimated 757,000 deaths in 2000. The possibility of measles eradication has been discussed for almost 40 years, and measles meets many of the criteria for eradication. Global measles eradication will face a number of challenges to achieving and sustaining high levels

W.J. Moss

Department of Epidemiology and the W. Harry Feinstone Department of Molecular Microbiology and Immunology, Johns Hopkins University Bloomberg School of Public Health, Baltimore MD, USA, e-mail: wmoss@jhsph.edu

of vaccine coverage and population immunity, including population growth and demographic changes, conflict and political instability, and public perceptions of vaccine safety. To achieve the measles mortality reduction goal, continued progress needs to be made in delivering measles vaccines to the world's children.

Introduction

Measles virus (MV) has caused millions of deaths since its emergence as a zoonosis thousands of years ago. Prior to the introduction of measles vaccine, more than 130 million cases and 7–8 million deaths due to measles were estimated to have occurred annually, and almost everyone was infected during childhood. Measles mortality declined in the first half of the twentieth century in developed countries as a consequence of improvements in living conditions, better nutritional status, and the availability of antibiotics for secondary bacterial infections. The introduction of measles vaccines beginning in the 1960s led to substantial reductions in measles incidence, morbidity, and mortality in both developed and developing countries. Measles vaccines were not available for many of the world's children, however, until the World Health Organization (WHO) launched the Expanded Programme on Immunization (EPI) in 1974, which provided vaccines against six target diseases including measles. Global vaccine coverage against EPI targeted diseases increased from less than 5% at the start of the program to almost 80% by 1990.

More recently, remarkable progress has been made in reducing measles incidence and mortality as a consequence of implementing the measles mortality reduction strategy of the WHO and United Nations Children's Fund (UNICEF). This strategy focuses on 47 priority countries and includes: (1) achieving and maintaining more than 90% coverage with the first dose of measles vaccine in every district by the age of 12 months; (2) ensuring that all children receive a second opportunity for measles vaccination; (3) surveillance for measles cases and serological confirmation; and (4) provision of appropriate case management (WHO/UNICEF 2001). Support for these efforts comes from the Measles Initiative, a partnership started in 2001 and led by the American Red Cross, the United Nations Foundation, UNICEF, the United States Centers for Disease Control and Prevention, and the WHO.

Goals and Strategies

The key to measles control is achieving and sustaining high levels of measles vaccine coverage (Fig. 9.1). Different goals for measles control have been established, necessitating different vaccination strategies. Three broad goals can be defined: mortality reduction, regional elimination, and global eradication.

Mortality Reduction

Mortality reduction, the least demanding of the three goals, calls for a reduction in measles mortality from a predetermined level through reductions in incidence and case fatality. Although reducing case fatality through appropriate case management is an important component, measles mortality reduction is achieved largely through a reduction in incidence. To reduce incidence, measles vaccine is administered as a single dose through routine immunization services (Fig. 9.2), with the optimal age

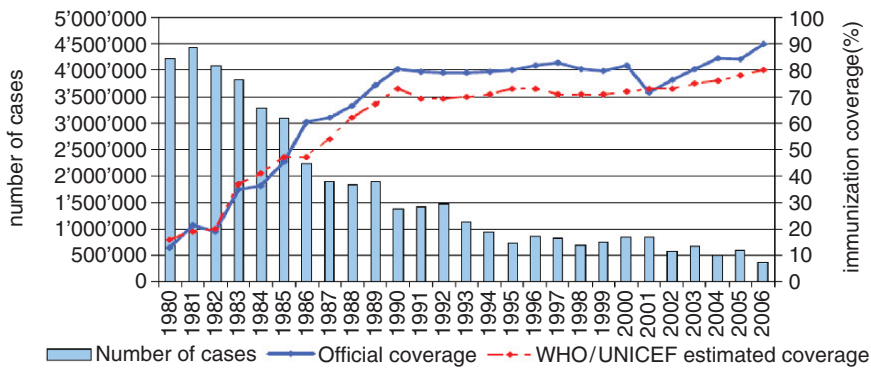


Fig. 9.1 Global annual reported measles incidence and measles vaccine coverage, 1986–2006. From World Health Organization 2007a

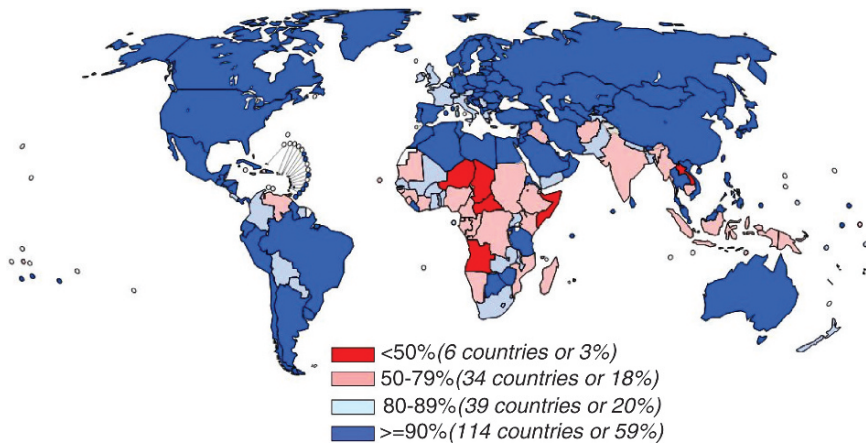


Fig. 9.2 Immunization coverage with measles containing vaccines in infants, 2006. From World Health Organization 2008

of immunization determined by the average age of infection and the rate of decline of maternal antibodies. In areas where measles is endemic, and the average age of infection is low, measles vaccine is routinely administered at 9 months of age in accordance with the EPI schedule (WHO 2004). In countries where MV transmission has been significantly reduced, the age at first vaccination is often increased to 12–15 months, resulting in a higher proportion of children who develop protective immunity. If vaccination coverage is sufficiently high, substantial reductions in incidence and mortality occur, the period between epidemics lengthens, and the age distribution shifts toward older children and young adults, further contributing to a reduction in measles case fatality.

Mortality reduction can also be achieved by proper case management, including the administration of vitamin A to persons with measles (D'Souza and D'Souza 2002) and prompt antibiotic treatment of secondary bacterial pneumonia (Duke and Mgone 2003). Provision of vitamin A through polio and measles vaccination campaigns further contributes to the reduction in measles mortality (WHO 2005).

Regional Elimination

Measles elimination is the interruption of MV transmission within a defined geographic area, such as country, continent, or WHO region. Small outbreaks of primary and secondary cases may occur following importation from outside the region, but sustained transmission does not occur. Because of the high infectivity of MV and the fact that not all persons develop protective immunity following vaccination, a single dose of measles vaccine does not achieve a sufficient level of population immunity to eliminate measles. A second opportunity for measles immunization is necessary to provide protective immunity to children who fail to respond to the first dose, as well as to immunize those children who were not previously vaccinated. Two strategies to administer the second dose of measles vaccine have been used. In countries with sufficient health infrastructure, and where children routinely receive well-child care beyond the 1st year of life, the second dose of measles vaccine is administered through routine immunization services, typically prior to the start of school (4–6 years of age). High coverage levels can be ensured by school entry requirements (CDC 2007). A second approach, first developed by the Pan American Health Organization (PAHO) for South and Central America (PAHO 1999) and modeled after polio eradication strategies, involves mass immunization campaigns (called supplementary immunization activities or SIA) to deliver the second dose of measles vaccine. This strategy was successful in eliminating measles in South and Central America (de Quadros et al. 1996, 2004) and has resulted in a marked reduction in measles incidence and mortality in much of sub-Saharan Africa (Otten et al. 2005; WHO 2006b).

The PAHO strategy consists of four subprograms: catch-up, keep-up, follow-up, and mop-up. The catch-up activity consists of a one-time, mass immunization campaign that targets all children within a broad age range regardless of whether they

have previously had wild-type MV infection or measles vaccination. The goal is to rapidly achieve a high level of population immunity and interrupt MV transmission. These campaigns are conducted over a short period of time, usually several weeks, and during a low transmission season. Under the PAHO strategy, children 9 months to 14 years of age were targeted for vaccination, a substantial proportion of the total population in many countries. The appropriate target age range depends upon the age distribution of measles cases. In regions where measles is endemic, the majority of older children are likely to be immune. Nevertheless, seroprevalence studies usually are not conducted prior to catch-up campaigns, and this broad age range first adopted by PAHO has been widely used in sub-Saharan Africa and Asia. These campaigns require significant financial investments and the commitment of large numbers of personnel; extensive logistical planning to transport and store vaccines, maintain cold chains, and dispose of syringes and needles; and community mobilization to ensure participation. If successful, SIA are cost effective (Dayan et al. 2004; Uzicanin et al. 2004) and can abruptly interrupt MV transmission, with dramatic declines in incidence and mortality.

Keep-up refers to the need to maintain greater than 90% coverage with the first dose of measles vaccine through routine immunization services. Follow-up refers to periodic mass campaigns to prevent the accumulation of susceptible children. Follow-up campaigns typically target children 9 months to 4 years of age, a narrower age group than targeted in catch-up campaigns. Follow-up campaigns should be conducted when the estimated number of susceptible children reaches the size of one birth cohort, generally every 3–5 years after the catch-up campaign. These campaigns need to be conducted indefinitely because of the potential risk of MV importation, or until the health infrastructure is sufficiently developed so that the second opportunity can be provided through routine immunization services. Mop-up campaigns target difficult-to-reach children in areas of measles outbreaks or low vaccine coverage. Difficult to reach children include those living on the street or in areas of conflict.

Measles elimination also requires active surveillance for measles cases to assist outbreak response (Grais et al. 2008) and to monitor progress in mortality reduction and elimination. Blood samples should be collected from all suspected measles cases for confirmation by detection of IgM antibodies to MV. Measles outbreaks require serological investigation of the first five to ten cases (WHO/UNICEF 2001), with other cases linked epidemiologically. Less invasive oral fluid or dried blood spot samples also may be used, and urine or nasopharyngeal specimens should be obtained for virus isolation and genetic characterization (Bellini and Helfand 2003). To support these activities, the WHO established the Global Measles Laboratory network in 2000 and the Measles and Rubella Laboratory Network (LabNet) in 2003, comprising over 700 laboratories in more than 160 countries (CDC 2005).

Eradication

The Dahlem Conference on Disease Eradication (1997) defined eradication as the permanent reduction to zero of the global incidence of infection caused by a specific

pathogen as a result of deliberate efforts, with the consequence that interventions would no longer be necessary (Dowdle and Hopkins 1998). The pathogen need not be extinct. Smallpox virus, for example, exists in government laboratories in the United States and Russia, although the disease is eradicated and vaccination activities have ceased (Stone 2002). Eradication is the most ambitious goal, requiring sustained high levels of financial investment, political commitment, and public cooperation. Presumably, measles eradication would be achieved using strategies similar to those described for elimination but applied and coordinated globally.

Progress in Measles Mortality Reduction and Elimination

Global Goals and Progress

In 2003, the World Health Assembly endorsed a resolution to reduce the number of deaths attributed to measles by 50% by the end of 2005 compared with 1999 estimates. This target was met. Global measles mortality in 2005 was estimated to be 345,000 deaths (uncertainty bounds 247,000 and 458,000 deaths), a 60% decrease from 1999 (Wolfson et al. 2007). Further reductions in global measles mortality were achieved in 2006, with an estimated 242,000 deaths (uncertainty bounds 173,000 and 325,000 deaths) (Fig. 9.3) (WHO 2007b). These estimates are not based on active surveillance for measles deaths but instead are derived from models of measles incidence and mortality, using estimated measles vaccine coverage and case fatality rates.

The revised global measles mortality reduction goal set forth in the WHO-UNICEF Global Immunization Vision and Strategy (GIVS) for 2006–2015 is to reduce measles deaths by 90% by 2010 compared to the estimated 757,000 deaths in 2000 (WHO/UNCF 2005). The financial resources required to achieve the

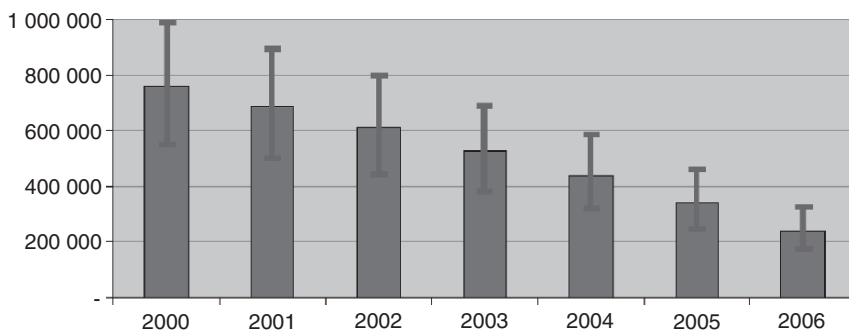


Fig. 9.3 Estimated global measles deaths, 2000–2006. Note the estimated number of global deaths is similar to the reported incidence shown in Fig. 1 because of the different methods used to derive the estimates. From World Health Organization 2007a

measles control goals for 2001–2005 was estimated to be US \$984 million, with approximately two-thirds for the operational costs of conducting SIA and one-third for the purchase of vaccines and injection equipment (WHO/UNICEF 2001). The cost of scaling up childhood immunization services to reach the WHO-UNICEF GIVS goal of reducing mortality due to all vaccine-preventable diseases by two-thirds by 2015 was recently estimated to be US \$35 billion (range US \$ 13–40 billion) for the 72 poorest countries of the world, including US \$8.7 billion for the purchase of vaccines (Wolfson et al. 2008).

Regional Progress in Mortality Reduction and Elimination

Four WHO regions set measles elimination goals: Americas (2000), Europe (2010), Eastern Mediterranean (2010), and Western Pacific (2012). Measles elimination was achieved in the United States in 2000 and in the Americas by November 2002. The two regions where most measles deaths occur (Table 9.1), Africa and South-East Asia, have measles mortality reduction goals, although many countries in these regions have implemented the WHO-UNICEF strategy of providing a second opportunity for measles vaccination through SIA, resulting in dramatic declines in

Table 9.1 Estimated number of deaths from measles and coverage of first-dose measles vaccine through routine immunization services, by WHO region, 2000 and 2006

WHO region	2000		2006		% Decrease in measles deaths 2000–2006
	% Coverage with 1st dose of measles vaccine	Measles deaths (uncertainty bounds)	% Coverage with 1st dose of measles vaccine	Measles deaths (uncertainty bounds)	
Africa	56	396,000 (290–514,000)	73	36,000 (26–49,000)	91
Americas	92	<1000	93	<1000	–
Eastern Mediterranean	73	96,000 (71–124,000)	83	23,000 (16–34,000)	76
Europe	91	<1000	94	<1000	–
South-East Asia	60	240,000 (173–316,000)	65	178,000 (128–234,000)	26
Western Pacific	86	25,000 (17–35,000)	93	5,000 (3–7,000)	81
Total	72	757,000 (551–990,000)	80	242,000 (173–325,000)	68

Adapted from World Health Organization 2007b

incidence and mortality. The largest decrease in measles mortality was in Africa, where measles mortality decreased 91% from 2000 to 2006, accounting for 70% of the global reduction in measles mortality (WHO 2007b). Progress in measles mortality reduction in the South-East Asia region was not as marked because several populous countries have not conducted SIA and routine immunization coverage remains suboptimal (WHO 2007b). Low vaccination coverage and susceptibility among adults hinder measles elimination in parts of Europe and Australia (Andrews et al. 2008). Conflicts and political instability in several countries of the Eastern Mediterranean region, including Afghanistan, Iraq, Lebanon, Somalia, and Sudan, have impeded measles control, but a catch-up SIA was conducted in parts of Pakistan in 2007 (CDC 2008c).

Although measles was declared eliminated from the United States in 2000, recent outbreaks highlight the challenges in sustaining elimination. First, despite very high levels of measles vaccine coverage and population immunity overall (McQuillan et al. 2007), clustering of susceptible persons can lead to outbreaks. In 2005, a 17-year-old girl with measles returned to Indiana from Romania and attended a church gathering of over 500 people (Parker et al. 2006). Despite 98% measles vaccination coverage in the state of Indiana (among sixth-graders), 34 cases of measles resulted, of whom 94% were unvaccinated. Second, the widespread circulation of MV and ease of global travel allows for MV importation. Perhaps surprisingly, these importations frequently arise from countries with ample resources for measles control. A multistate outbreak of measles in 2007 occurred at an international sporting event after importation from Japan (CDC 2008a), the country responsible for the most imported cases of measles into the US over the past several years (Takahashi and Saito 2008). Thousands of measles cases occur annually in Japan as a consequence of low vaccination coverage resulting from the relaxing of vaccination requirements after an outbreak of aseptic meningitis from the Urabe mumps vaccine strain (Gomi and Takahashi 2004). Third, as measles control efforts are increasingly successful in reducing disease incidence, public perceptions of the risk of measles diminish and are replaced by concerns of possible adverse events associated with measles vaccine. An outbreak of measles in San Diego in 2008, imported from Switzerland, resulted in 11 additional cases in unvaccinated children and two generations of secondary cases (CDC 2008b). Among the nine cases older than 1 year of age, eight were unvaccinated because of personal exemption beliefs.

Feasibility of Measles Eradication

The possibility of measles eradication has been discussed for almost 40 years (Sencer et al. 1967), beginning in the late 1960s when smallpox eradication was nearing completion and the long-term protective immunity induced by measles vaccine became evident. Three criteria are deemed important for disease eradication: (1) humans must be critical to transmission; (2) sensitive and specific diagnostic tools must exist; and (3) an effective intervention must be available

(Dowdle and Hopkins 1998). Interruption of transmission in large geographical areas for prolonged periods further supports the feasibility of eradication. Measles is thought by many experts to meet these criteria (de Quadros 2004; Orenstein et al. 2000).

Biological Feasibility of Measles Eradication

MV meets many of the biological criteria for disease eradication. MV has no non-human reservoir, infection can be readily diagnosed after onset of a rash, and MV has not mutated to significantly alter immunogenic epitopes (Moss and Griffin 2006). Although MV displays sufficient genetic variation to conduct molecular epidemiologic analyses (WHO 2006a), the epitopes against which protective antibodies develop have remained stable, likely because of functional constraints on the amino acid sequence and tertiary structure of the MV surface proteins (Frank and Bush 2007).

Where MV differs from smallpox and polio viruses is that it is more highly infectious, necessitating higher levels of population immunity to interrupt transmission. Outbreaks can occur in populations in which less than 10% of individuals are susceptible. The contagiousness of MV is best expressed by the basic reproductive number R_0 , which represents the mean number of secondary cases that would arise if an infectious agent were introduced into a completely susceptible population. R_0 is a function not only of the infectious agent, but also of the host population. The estimated R_0 for MV is 12–18, in contrast to 5–7 for smallpox and polio viruses and 2–3 for SARS-coronavirus. The high infectivity of MV implies that a high level of population immunity (approximately 92%–94%) is required to interrupt MV transmission (Gay 2004).

Technical Feasibility of Measles Eradication

Measles vaccines are safe and effective and have interrupted MV transmission in large geographic areas, providing the critical tool for measles eradication. Despite progress in measles mortality reduction and elimination, there are several limitations of the licensed vaccines that may make measles eradication more challenging. First, attenuated measles vaccines are inactivated by heat and a cold chain must be maintained to support measles immunization activities. Second, in contrast to oral polio vaccines, measles vaccines must be injected subcutaneously or intramuscularly, necessitating trained healthcare workers, needles, syringes, and proper disposal of hazardous waste. Third, both maternally acquired antibodies and immunological immaturity reduce the protective efficacy of measles vaccination in early infancy, hindering effective immunization of young infants (Gans et al. 1998). Fourth, the attenuated measles vaccine has the potential to cause serious adverse events, such as lung or brain infection, in

severely immunocompromised persons (Angel et al. 1998; Monafo et al. 1994). Lastly, a second opportunity for measles vaccination must be provided to achieve sufficient levels of population immunity to interrupt MV transmission.

The duration of immunity following measles vaccination is more variable and shorter than following wild-type MV infection, but persists for decades even in countries where measles is no longer endemic and immunological boosting from wild-type MV infection does not occur (Amanna et al. 2007; Dine et al. 2004). Although antibody levels induced by vaccination may decline over time and become undetectable, immunological memory persists and most vaccinated persons produce a MV-specific immune response without clinical symptoms following exposure to wild-type MV.

Logistical Feasibility of Measles Eradication

The elimination of measles in large areas, such as the Americas, suggests that measles eradication is feasible with current vaccination strategies (CDC 1997; de Quadros 2004; Meissner et al. 2004). Perhaps the major logistical challenge to measles eradication will be sustaining the financial resources, political will, and public confidence to implement widespread and coordinated measles vaccination and surveillance activities.

Challenges to Global Measles Eradication

Global measles eradication will face a number of challenges to achieving and sustaining high levels of vaccine coverage and population immunity. Serious discussion of measles eradication is not likely to take place before polio eradication is achieved. Garnering the necessary political and public support for measles eradication will be extremely difficult should polio eradication efforts fail.

Challenges to Achieving High Levels of Measles Vaccine Coverage

Sustainability of Current Measles Control and Elimination Strategies

To eradicate measles, high levels of population immunity need to be sustained through coverage with two doses of measles vaccine. Because the first dose of measles vaccine is administered through routine immunization services, strengthening the primary healthcare system will further this goal. However, the long-term sustainability of mass vaccination campaigns is unclear as these activities make

additional demands on the resources and staff of the primary healthcare system and require continued public support in the face of decreasing disease burden and perception of public health importance. The polio eradication campaign in Nigeria, for example, was perceived negatively to trigger a massive outbreak response for just three confirmed cases of polio in Adamawa State in 2005, whereas hundreds of deaths due to measles did not result in a comparable response (Schimmer and Ihekweazu 2006). Countries dependent upon SIA to deliver the second dose of measles vaccine will need to strengthen their primary health care systems to provide this dose beyond the 1st year of life. Ensuring the necessary supply of measles vaccine as eradication efforts progress will be critical (Costa et al. 2003), requiring close collaboration with vaccine manufacturers and the understanding that vaccination may decrease or cease should eradication be achieved.

Public Perceptions of Vaccine Safety and Public Health

Loss of public confidence in vaccines can significantly impair control efforts, as demonstrated by the poliovirus outbreaks in northern Nigeria, which subsequently spread across several continents (Katz 2006). Numerous measles outbreaks have occurred in communities opposed to vaccination on religious or philosophical grounds (CDC 2000) or because of unfounded fears of serious adverse events (Feikin et al. 2000). Garnering the political will and public support for measles eradication is likely to be difficult in countries where the burden of disease due to measles is not recognized and unfounded fears of serious vaccine adverse events are common.

Much public attention has focused on a purported association between measles-mumps-rubella (MMR) vaccine and autism following publication of a report in 1998 hypothesizing that MMR vaccine may cause a syndrome of autism and intestinal inflammation (Wakefield et al. 1998). The events that followed, and the public concern over the safety of MMR vaccine, led to diminished vaccine coverage in the United Kingdom and provide important lessons in the misinterpretation of epidemiologic evidence and the communication of scientific results to the public (Offit and Coffin 2003). As a consequence, measles outbreaks became more frequent and larger in size (Jansen et al. 2003). Several epidemiological studies and comprehensive reviews of the evidence rejected a causal relationship between MMR vaccination and autism (DeStefano and Thompson 2004; Madsen et al. 2002).

Conflict and Political Instability

Maintaining high levels of measles vaccine coverage in areas of conflict and political instability is challenging (Senessie et al. 2007), and devastating measles outbreaks occur frequently in refugee populations and internally displaced populations (Connolly et al. 2004). Measles case fatality rates in such settings have been as high as 20%–30% (Salama et al. 2001). Progress in global control has made outbreaks of

measles less likely in some regions, although outbreaks continue to occur in refugee and internally displaced populations with low levels of immunity (Kamugisha et al. 2003). Polio vaccination campaigns have been successfully conducted during scheduled cease-fires in regions of conflict (“days of tranquility”) (Tangermann et al. 2000) and similar results should be achievable for measles vaccination campaigns, although more highly skilled healthcare workers are needed to administer parenteral measles vaccine than oral poliovirus vaccine.

Population Growth and Demographic Changes

The world’s population is predicted to increase 2.5 billion from 2007 to 2050, from the current 6.7 billion to 9.2 billion (UN 2007). This increase is equivalent to the total number of people in the world in 1950. Population growth will be greatest in the less developed regions of the world, increasing from 5.4 billion in 2007 to 7.9 billion in 2050 (UN 2007), where the proportion of people younger than 15 years of age is greatest. Specifically, the population of the 50 least developed countries will likely more than double, increasing from 0.8 billion in 2007 to 1.7 billion in 2050 (UN 2007). This increase in global population, particularly in less developed countries, will require additional resources, personnel, and vaccine supplies just to maintain current levels of vaccine coverage.

Most of the predicted population growth will take place in urban areas of less developed countries (Cohen 2003). Currently, more than half of the world’s population lives in urban areas, and one in three urban residents live in slums, with a much higher proportion in sub-Saharan Africa and Asia (Dye 2008; UNPF 2007). Measles elimination may be particularly difficult in impoverished areas of large cities in Africa and Asia where several factors converge to facilitate MV transmission, including the high population density and difficulties in achieving high vaccination coverage. A critical question regarding measles eradication is whether the epidemiological conditions are sufficiently different in the large, densely populated cities of Africa and Asia than in the Americas to hinder measles eradication efforts.

Challenges to Achieving High Levels of Population Immunity

Impact of the HIV-1 Pandemic

In regions of high HIV prevalence and crowding, such as urban centers in sub-Saharan Africa, HIV-infected children may play a role in the sustaining MV transmission (Moss et al. 1999). Children with defective cell-mediated immunity can develop measles without the characteristic rash (Moss et al. 1999), hampering diagnosis, and HIV-infected children have prolonged shedding of MV RNA (Permer et al. 2001), potentially increasing the period of infectivity. Children born to HIV-infected mothers have lower levels of passively acquired maternal antibodies,

increasing susceptibility to measles at an earlier age than children born to uninfected mothers (Moss et al. 2002; Scott et al. 2007), and protective antibody levels following vaccination wane within 2–3 years in many HIV-infected children not receiving antiretroviral therapy (Moss et al. 2007), creating a potential pool of susceptible children (Tejiokem et al. 2007). Thus, population immunity could be reduced in regions of high HIV-1 prevalence despite high levels of measles vaccine coverage.

Counteracting the increased susceptibility of HIV-infected children is their high mortality rate, particularly in sub-Saharan Africa, such that these children do not live long enough to build up a sizeable pool of susceptible children (Helfand et al. 2005). Successful control of measles in the countries of southern Africa suggests that the HIV-1 epidemic is not a major barrier to measles control (Biellik et al. 2002; Otten et al. 2005). This may change with increased access to antiretroviral therapy, which may prolong survival without enhancing protective immunity in the absence of revaccination. Using a dynamic, age-structured mathematical model, the prevalence of measles increased after introduction of antiretroviral therapy into a hypothetical population of children with a high prevalence of HIV-1 infection (Scott et al. 2008).

Challenges to Sustained Measles Eradication

Potential Use of Measles Virus as an Agent of Bioterrorism

The high infectivity of MV is a characteristic suitable to a bioterrorist agent, but high levels of measles vaccination coverage throughout the world would protect many persons from the deliberate release of MV. Genetic engineering of a MV strain that was not neutralized by antibodies induced by the current measles vaccines would likely have reduced infectivity, as suggested by the fact that wild-type MV has not mutated to alter neutralizing epitopes. Whether the threat from bioterrorism precludes stopping measles vaccination after eradication is unclear but, at the least, a single-dose rather than a two-dose measles vaccination strategy could be adopted (Meissner et al. 2004).

Prospects for Measles Eradication

The measles eradication end-game is likely to be different than that for smallpox or polio viruses (Gounder 1998; Morgan 2004). In contrast to polioviruses, prolonged shedding of potentially virulent vaccine viruses and environmental viral reservoirs will not be challenges to measles eradication. Although MV can be carried by persons during the incubation period, transmission from mobile, asymptomatic carriers is not as common as with poliovirus. However, higher levels of population immunity are necessary to interrupt MV transmission, more

highly skilled healthcare workers are required to administer measles vaccines, and containment through case detection and ring vaccination will be more difficult for MV than smallpox virus because of infectivity before rash onset. New tools, such as aerosol administration of measles vaccines (Low et al. 2008), will facilitate mass vaccination campaigns, allowing less highly trained workers to administer vaccine and diminishing the medical waste disposal problems. Critics of eradication programs claim they can divert resources from primary healthcare and are imposed on countries or communities from outside. Enormous resources and efforts may be required to eradicate the few remaining measles cases, and the economic and social costs of eradication need to be carefully considered (Cutts and Steinglass 1998). Despite enormous progress, measles remains a leading vaccine-preventable cause of childhood mortality worldwide, and continues to cause outbreaks in communities with low vaccination coverage rates in industrialized nations. To achieve the measles mortality reduction goal, continued progress needs to be made in delivering measles vaccines to the world's children.

References

- Amanna IJ, Carlson NE, Slifka MK (2007) Duration of humoral immunity to common viral and vaccine antigens. *N Engl J Med* 357:1903–1915
- Andrews N, Tischer A, Siedler A, Pebody RG, Barbara C, Cotter S, Duks A, Gacheva N, Bohumir K, Johansen K, Mossong J, Ory F, Prosenec K, Slacikova M, Theeten H, Zarvou M, Pistol A, Bartha K, Cohen D, Backhouse J, Griskevicius A (2008) Towards elimination: measles susceptibility in Australia and 17 European countries. *Bull World Health Organ* 86:197–204
- Angel JB, Walpita P, Lerch RA, Sidhu MS, Masuredar M, DeLellis RA, Noble JT, Snyderman DR, Udem SA (1998) Vaccine-associated measles pneumonitis in an adult with AIDS. *Ann Intern Med* 129:104–106
- Bellini WJ, Helfand RF (2003) The challenges and strategies for laboratory diagnosis of measles in an international setting. *J Infect Dis* 187 [Suppl 1]:S283–S290
- Biellik R, Madema S, Taole A, Kutsulukuta A, Allies E, Eggers R, Ngcobo N, Nxumalo M, Shearley A, Mabuzane E, Kufa E, Okwo-Bele JM (2002) First 5 years of measles elimination in southern Africa: 1996–2000. *Lancet* 359:1564–1568
- Centers for Disease Control (1997) Measles eradication: recommendations from a meeting cosponsored by the World Health Organization, the Pan American Health Organization, and the CDC. *MMWR* 46:1–20
- Centers for Disease Control (2000) Measles outbreak—Netherlands, April 1999 – January 2000. *MMWR Morb Mortal Wkly Rep* 49:299–303
- Centers for Disease Control and Prevention (2005) Global Measles and Rubella Laboratory Network, January 2004–June 2005. *MMWR Morb Mortal Wkly Rep* 54:1100–1104
- Centers for Disease Control and Prevention (2007) Vaccination coverage among children in kindergarten – United States, 2006–07 school year. *MMWR Morb Mortal Wkly Rep* 56:819–821
- Centers for Disease Control and Prevention (2008a) Multistate measles outbreak associated with an international youth sporting event – Pennsylvania, Michigan, and Texas, August–September 2007. *MMWR Morb Mortal Wkly Rep* 57:169–173
- Centers for Disease Control and Prevention (2008b) Outbreak of measles – San Diego, California, January–February 2008. *MMWR Morb Mortal Wkly Rep* 57:203–206

- Centers for Disease Control and Prevention (2008c) Progress toward measles mortality reduction and elimination – Eastern Mediterranean Region, 1997–2007. *MMWR Morb Mortal Wkly Rep* 57:262–267
- Cohen JE (2003) Human population: the next half century. *Science* 302:1172–1175
- Connolly MA, Gayer M, Ryan MJ, Salama P, Spiegel P, Heymann DL (2004) Communicable diseases in complex emergencies: impact and challenges. *Lancet* 364:1974–1983
- Costa A, Henao-Restrepo AM, Hall SM, Jarrett S, Hoekstra EJ (2003) Determining measles-containing vaccine demand and supply: an imperative to support measles mortality reduction efforts. *J Infect Dis* 187 [Suppl 1]:S22–S28
- Cutts FT, Steinglass R (1998) Should measles be eradicated? *BMJ* 316:765–767
- Dowdle WR, Hopkins DR (1998) The eradication of infectious diseases: report of the Dahlem Workshop on the eradication of infectious diseases, Berlin, March 16–22, 1997. Wiley, New York
- D’Souza RM, D’Souza R (2002) Vitamin A for the treatment of children with measles – a systematic review. *J Trop Pediatr* 48:323–327
- Dayan GH, Cairns L, Sangruejee N, Mtonga A, Nguyen V, Strebel P (2004) Cost-effectiveness of three different vaccination strategies against measles in Zambian children. *Vaccine* 22:475–484
- de Quadros CA (2004) Can measles be eradicated globally? *Bull World Health Organ* 82:134–138
- de Quadros CA, Olive JM, Hersh BS, Strassburg MA, Henderson DA, Brandling-Bennett D, Alleyne GA (1996) Measles elimination in the Americas. Evolving strategies. *JAMA* 275:224–229
- de Quadros CA, Izurieta H, Venczel L, Carrasco P (2004) Measles eradication in the Americas: progress to date. *J Infect Dis* 189 [Suppl 1]:S227–S235
- DeStefano F, Thompson WW (2004) MMR vaccine and autism: an update of the scientific evidence. *Expert Rev Vaccines* 3:19–22
- Dine MS, Hutchins SS, Thomas A, Williams I, Bellini WJ, Redd SC (2004) Persistence of vaccine-induced antibody to measles 26–33 years after vaccination. *J Infect Dis* 189 [Suppl 1]:S123–S130
- Duke T, Mgone CS (2003) Measles: not just another viral exanthem. *Lancet* 361:763–773
- Dye C (2008) Health and urban living. *Science* 319:766–769
- Feikin DR, Lezotte DC, Hamman RF, Salmon DA, Chen RT, Hoffman RE (2000) Individual and community risks of measles and pertussis associated with personal exemptions to immunization. *JAMA* 284:3145–3150
- Frank SA, Bush RM (2007) Barriers to antigenic escape by pathogens: trade-off between reproductive rate and antigenic mutability. *BMC Evol Biol* 7:229
- Gans HA, Arvin AM, Galinus J, Logan L, DeHovitz R, Maldonado Y (1998) Deficiency of the humoral immune response to measles vaccine in infants immunized at age 6 months. *JAMA* 280:527–532
- Gay NJ (2004) The theory of measles elimination: implications for the design of elimination strategies. *J Infect Dis* 189 [Suppl 1]:S27–S35
- Gomi H, Takahashi H (2004) Why is measles still endemic in Japan? *Lancet* 364:328–329
- Gounder C (1998) The progress of the Polio Eradication Initiative: what prospects for eradicating measles? *Health Policy Plan* 13:212–233
- Grais RF, Conlan AJ, Ferrari MJ, Djibo A, Le Menach A, Bjornstad ON, Grenfell BT (2008) Time is of the essence: exploring a measles outbreak response vaccination in Niamey, Niger. *J R Soc Interface* 5:67–74
- Helfand RF, Moss WJ, Harpaz R, Scott S, Cutts F (2005) Evaluating the impact of the HIV pandemic on measles control and elimination. *Bull World Health Organ* 83:329–337
- Jansen VA, Stollenwerk N, Jensen HJ, Ramsay ME, Edmunds WJ, Rhodes CJ (2003) Measles outbreaks in a population with declining vaccine uptake. *Science* 301:804
- Kamugisha C, Cairns KL, Akim C (2003) An outbreak of measles in Tanzanian refugee camps. *J Infect Dis* 187 [Suppl 1]:S58–S62
- Katz SL (2006) Polio: new challenges in 2006. *J Clin Virol* 36:163–165
- Low N, Kraemer S, Schneider M, Restrepo AM (2008) Immunogenicity and safety of aerosolized measles vaccine: systematic review and meta-analysis. *Vaccine* 26:383–398

- Madsen KM, Hviid A, Vestergaard M, Schendel D, Wohlfahrt J, Thorsen P, Olsen J, Melbye M (2002) A population-based study of measles, mumps, and rubella vaccination and autism. *N Engl J Med* 347:1477–1482
- McQuillan GM, Kruszon-Moran D, Hyde TB, Forghani B, Bellini W, Dayan GH (2007) Seroprevalence of measles antibody in the US population, 1999–2004. *J Infect Dis* 196:1459–1464
- Meissner HC, Strebel PM, Orenstein WA (2004) Measles vaccines and the potential for worldwide eradication of measles. *Pediatrics* 114:1065–1069
- Monafo WJ, Haslam DB, Roberts RL, Zaki SR, Bellini WJ, Coffin CM (1994) Disseminated measles infection after vaccination in a child with a congenital immunodeficiency. *J Pediatr* 124:273–276
- Morgan OW (2004) Following in the footsteps of smallpox: can we achieve the global eradication of measles? *BMC Int Health Hum Rights* 4:1
- Moss WJ, Griffin DE (2006) Global measles elimination. *Nat Rev Microbiol* 4:900–908
- Moss WJ, Cutts F, Griffin DE (1999) Implications of the human immunodeficiency virus epidemic for control and eradication of measles. *Clin Infect Dis* 29:106–112
- Moss WJ, Monze M, Ryon JJ, Quinn TC, Griffin DE, Cutts F (2002) Prospective study of measles in hospitalized human immunodeficiency virus (HIV)-infected and HIV-uninfected children in Zambia. *Clin Infect Dis* 35:189–196
- Moss WJ, Scott S, Mugala N, Ndhlovu Z, Beeler JA, Audet SA, Ngala M, Mwangala S, Nkonga-Mwangilwa, Ryon JJ, Monze M, Kasolo F, Quinn TC, Cousens S, Griffin DE, Cutts FT (2007) Immunogenicity of standard-titer measles vaccine in HIV-1-infected and uninfected Zambian children: an observational study. *J Infect Dis* 196:347–355
- Offit PA, Coffin SE (2003) Communicating science to the public: MMR vaccine and autism. *Vaccine* 22:1–6
- Orenstein WA, Strebel PM, Papania M, Sutter RW, Bellini WJ, Cochi SL (2000) Measles eradication: is it in our future? *Am J Public Health* 90:1521–1525
- Otten M, Kezaala R, Fall A, Masresha B, Martin R, Cairns L, Eggers R, Biellik R, Grabowsky M, Strebel P, Okwo-Bele JM, Nshimirimana D (2005) Public-health impact of accelerated measles control in the WHO African Region 2000–03. *Lancet* 366:832–839
- Pan American Health Organization (1999) Measles eradication. Field guide. Washington, DC, Pan American Health Organization
- Parker AA, Staggs W, Dayan GH, Ortega-Sanchez IR, Rota PA, Lowe L, Boardman P, Teclaw R, Graves C, LeBaron CW (2006) Implications of a 2005 measles outbreak in Indiana for sustained elimination of measles in the United States. *N Engl J Med* 355:447–455
- Permar SR, Moss WJ, Ryon JJ, Monze M, Cutts F, Quinn TC, Griffin DE (2001) Prolonged measles virus shedding in human immunodeficiency virus-infected children, detected by reverse transcriptase-polymerase chain reaction. *J Infect Dis* 183:532–538
- Salama P, Assefa F, Talley L, Spiegel P, van Der V, Gotway CA (2001) Malnutrition, measles, mortality, and the humanitarian response during a famine in Ethiopia. *JAMA* 286:563–571
- Schimmer B, Ihekweazu C (2006) Polio eradication and measles immunisation in Nigeria. *Lancet Infect Dis* 6:63–65
- Scott S, Moss WJ, Cousens S, Beeler JA, Audet SA, Mugala N, Quinn TC, Griffin DE, Cutts FT (2007) The influence of HIV-1 exposure and infection on levels of passively acquired antibodies to measles virus in Zambian infants. *Clin Infect Dis* 45:1417–1424
- Scott S, Mossong J, Moss WJ, Cutts FT, Cousens S (2008) Predicted impact of the HIV-1 epidemic on measles in developing countries: results from a dynamic age-structured model. *Int J Epidemiol* 37:356–367
- Sencer DJ, Dull HB, Langmuir AD (1967) Epidemiologic basis for eradication of measles in 1967. *Public Health Rep* 82:253–256
- Senessie C, Gage GN, von Elm E (2007) Delays in childhood immunization in a conflict area: a study from Sierra Leone during civil war. *Confl Health* 1:14

- Stone R (2002) Smallpox. WHO puts off destruction of U.S., Russian caches. *Science* 295: 598–599
- Takahashi H, Saito H (2008) Measles exportation from Japan to the United States, 1994 to 2006. *J Travel Med* 15:82–86
- Tangermann RH, Hull HF, Jafari H, Nkowane B, Everts H, Aylward RB (2000) Eradication of poliomyelitis in countries affected by conflict. *Bull World Health Organ* 78:330–338
- Tejiokem MC, Gouandjika I, Beniguel L, Zanga MC, Tene G, Gody JC, Njamkepo E, Kfutwah A, Penda I, Bilong C, Rousset D, Pouillot R, Tangy F, Baril L (2007) HIV-infected children living in central Africa have low persistence of antibodies to vaccines used in the Expanded Program on Immunization. *PLoS ONE*:e1260
- United Nations, Department of Economic and Social Affairs Population Division (2007) World population prospects: the 2006 revision, highlights. United Nations, New York
- United Nations Population Fund (2007) State of the world population 2007: unleashing the potential of urban growth. United Nations Population Fund
- Uzicanin A, Zhou F, Eggers R, Webb E, Strebel P (2004) Economic analysis of the 1996–1997 mass measles immunization campaigns in South Africa. *Vaccine* 22:3419–3426
- Wakefield AJ, Murch SH, Anthony A, Linnell J, Casson DM, Malik M, Berelowitz M, Dhillon AP, Thomson MA, Harvey P, Valentine A, Davies SE, Walker-Smith JA (1998) Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 351:637–641
- Wolfson LJ, Strebel PM, Gacic-Dobo M, Hoekstra EJ, McFarland JW, Hersh BS (2007) Has the 2005 measles mortality reduction goal been achieved? A natural history modelling study. *Lancet* 369:191–200
- Wolfson LJ, Gasse F, Lee-Martin SP, Lydon P, Magan A, Tibouti A, Johns B, Hutubessy R, Salama P, Okwo-Bele JM (2008) Estimating the costs of achieving the WHO-UNICEF Global Immunization Vision and Strategy, 2006–2015. *Bull World Health Organ* 86:27–39
- World Health Organization (2004) Measles vaccines. *Wkly Epidemiol Rec* 79:130–142
- World Health Organization (2005) Progress in reducing measles mortality – worldwide 1999–2003. *Weekly Epidemiol Rec* 80:78–81
- World Health Organization (2006a) Global distribution of measles and rubella genotypes – update. *Wkly Epidemiol Rec* 81:474–479
- World Health Organization (2006b) Impact of measles control activities in the WHO African Region, 1999–2005. *Wkly Epidemiol Rec* 81:365–371
- World Health Organization (2007a) Expanded Programme on Immunization of the Department of Immunization, Vaccines and Biologicals. WHO vaccine-preventable diseases: monitoring system. 2007 global summary. WHO/IVB/2007. World Health Organization, Geneva
- World Health Organization (2007b) Progress in global measles control and mortality reduction, 2000–2006. *Wkly Epidemiol Rec*. 82:418–424
- World Health Organization (2008) Immunization surveillance, assessment and monitoring. http://www.who.int/immunization_monitoring/diseases/measles/en/. Cited 28 May 2008. World Health Organization, Geneva
- World Health Organization/United Nations Children’s Fund (2001) Measles mortality reduction and regional elimination strategic plan 2001–2005. World Health Organization, Geneva
- World Health Organization/United Nations Children’s Fund (2005) Global Immunization Vision and Strategy 2006–2015. World Health Organization, Geneva