Eradicating measles: a feasible goal?

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Measles has been the greatest cause of vaccine-preventable mortality in the world, killing approximately six million individuals annually prior to the advent of vaccination. Measles vaccines, first available in 1963, offer the opportunity to prevent this terrible burden. Measles is no longer an endemic disease in the Western hemisphere or the Americas, demonstrating the feasibility of interrupting transmission globally. Worldwide efforts to reduce measles mortality have resulted in an estimated 60% decrease in measles deaths from 1999–2005. Measles meets biologic criteria to be considered a potentially eradicable disease: first, humans are necessary for maintaining transmission; second, accurate diagnostic tests are available; third, there is an effective intervention and, last, sustained transmission has been terminated in large geographic areas. Nevertheless, there are substantial hurdles to eradication, including obtaining and sustaining the political will and resources necessary, and overcoming problems such as lack of security in some countries, concerns about measles vaccine safety and urban crowding.

Measles is one of the major killers of children in the world. Before the advent of vaccination, approximately six million people, primarily children aged under 5 years died of the disease each year [1]. The licensure of measles vaccines in 1963 offered the opportunity to prevent this terrible burden [2]. In 1966, the USA began an effort to eradicate the disease within its own borders [3,4]. After a series of successes and setbacks, in 2000, 34 years after the initial goal was announced, measles was declared no longer to be endemic in the USA [5]. In 1994, the Pan American Health Organization set a goal to eliminate measles in the Western hemisphere [6]. By the end of 2002, it appeared that there was no sustained transmission within the Americas [7]. As of May 2007, three of the other five WHO Regions had goals to eliminate indigenous measles transmission [8]. In addition, major efforts during the early part of this decade resulted in a 60% reduction in estimated measles deaths – from 873,000 in 1999 to 345,000 in 2005 [8]. Recent successes in terminating measles transmission in many countries and substantially reducing transmission in others again raises the question of whether measles, like smallpox before it, could be eradicated from the globe [9]. In this article, we review criteria that make a disease a candidate for eradication and whether measles fits those criteria.

Eradication

Eradication is the permanent reduction to zero of the worldwide incidence of infection caused by a specific agent as a result of deliberate efforts [10,11]. Smallpox is the only disease to date that has been eradicated. In 1988, the World Health Assembly (WHA) set a goal to eradicate polio by 2000. While substantial progress has been made in reducing the incidence of polio, there were at least four endemic countries at the beginning of 2007 and there are still outbreaks occurring in countries that had previously terminated polio transmission, as a result of importations primarily from the endemic countries [12]. In the past, eradication has been taken to mean that intervention measures such as vaccination could be terminated. However, now with the potential for bioterrorism and concerns that some infectious agents might escape from laboratories, either in specimens known to contain infectious agents or where specimens might unknowingly be contaminated with the organism, complete cessation of control measures may not be a wise policy.

Two major sets of criteria must be met to consider a disease an eradication candidate. First, eradication must be biologically feasible [11,13]. Second, there are a number of other challenges to implementation of eradication strategies that must be overcome including the need for global political will and resources available to implement the selected eradication strategy. All countries must participate fully in the eradication effort. Otherwise, any countries that do not could remain reservoirs of virus that could re-infect the other countries. In addition, an

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eradication effort must address other barriers including security concerns, crowding, HIV prevalence and vaccine safety concerns [13,14]

Criteria for biologic feasibility

Three major criteria must be met to consider a disease eradicable [11,13]. First, humans are essential for maintaining transmission (there is no animal or environmental reservoir). Second, the disease can be accurately diagnosed and, third, there is an effective intervention that can terminate transmission. In addition, some authors have called for a fourth criterion: there must be demonstration that disease transmission can be eliminated in large geographic areas over an extended period [13]. Each of these criteria is discussed below with regard to measles.

Humans as essential for the survival of the organism in nature

Humans are the natural reservoir for the measles virus. While outbreaks in primate colonies have been reported, the size of primate groups in their natural habitat is not large enough to sustain transmission. Sustained transmission in an unimmunized population probably requires populations of at least several hundred thousand [15]. Recent studies of the *Morbillivirus* receptor signaling lymphocytic activation molecule (SLAM or CD150), have shown that measles virus, canine distemper virus, and rinderpest virus use SLAMs specific to their host species (humans, dogs and cattle, respectively) [16]. Mice express a mouse version of SLAM, but can only be infected with measles virus when they express human SLAM as a transgene [17–19].

Mouse SLAM, when expressed on a CHO cell, does not support entry of wild-type measles virus while human SLAM does [20]. Mouse SLAM can be made to serve as a receptor for measles virus only after it has been genetically modified to look more like human SLAM. This suggests host specificity that makes it unlikely for measles virus to infect other nonprimate species.

Furthermore, persons infected by measles are usually contagious for short periods, generally less than 1 week (from the onset of the prodrome, 2–4 days prior to rash, through the first few days of rash) [21]. There are no known chronic shedders of contagious virus that could re-introduce the virus into the population after global termination of transmission. Also, the virus does not survive long on inanimate surfaces [22]. Thus, measles meets this criterion.

Availability of accurate diagnostic tools

Clinical diagnoses of measles are inaccurate, particularly as disease incidence decreases. However, serologic tests are available to accurately identify measles. The most commonly used methods involve detection of IgM in single serum or oral fluid specimens using enzyme immunoassays (EIA) [13,21]. Commercial kits have been estimated to have sensitivities ranging from 83–92% and specificities ranging from 87%–100% [23]. These tests have been critical for documenting the absence of measles transmission in the Americas and are playing a role in other worldwide measles surveillance efforts. While the positive predictive value decreases with decreasing incidence of measles, the assays are still extremely useful. When doubts exist about the validity of the test, a second serum specimen can be obtained to assess whether there is a significant rise in total or IgG antibodies between acute and convalescent sera [21]. Blood spots on filter paper may also facilitate the diagnosis. Thus, measles meets this criterion.

An effective intervention

Measles is highly contagious. Mathematical modelers have estimated the R_0 value (the average number of secondary cases following introduction into a 100% susceptible population) of 12 or more in most populations [24]. This translates into a herd immunity threshold, the level of immunity to prevent sustained transmission, of at least 92%. Live attenuated measles vaccines induce 95–98% seroconversion in persons vaccinated when at least 15 months of age [21,25,26]. Seroconversion rates are lower when vaccine is administered to children who still retain maternal antibodies from transfer across the placenta and may also be lower in field conditions in developing countries. Thus, vaccination of infants at 9 months of age yields seroconversion rates, on average, of 85%, leaving approximately 15% of vaccinees susceptible [27]. In the industrialized world, vaccination is usually recommended from 12–18 months of age to obtain optimal seroconversion. Mothers who were vaccinated as children tend to have lower antibody levels than those with natural infection and infants born to vaccinated mothers tend to lose antibody at younger ages [28]. Thus, in the industrialized world, optimal levels of vaccine-induced immunity can now be obtained through vaccination as young as 12 months of age [29]. However, in the developing world, recommendations for vaccine use must balance the need to induce protection prior to the infant being exposed to measles (which would dictate vaccination at as young an age as possible), and inducing high levels of protection (which would dictate vaccination after maternal antibodies have disappeared). As a result, the first dose of measles vaccine is usually administered at 9 months of age in developing countries. However, if transmission has been interrupted (e.g., in the Americas), the first dose can be delayed to 12 months [6]. Alternatively, if risk of infection is high (e.g., during outbreaks) the first dose may be given as early as 6 months of age.

The contribution of vaccine failure to the accumulation of susceptible individuals has led to the recommendation for a two-dose schedule in most industrialized countries to reduce that susceptibility [21]. Outbreaks have been reported in populations with more than 95% immunity [30]. Seroconversion rates among individuals seronegative following a first dose are generally greater than 90% after the second dose [31].

The problem in the developing world has been high levels of susceptibility to measles as the result of failure to provide a first dose of vaccine to a large proportion of the population, particularly in difficult to access areas. Vaccine failures from the first dose contribute to a lesser extent. In the developing world, the WHO has recommended a strategy giving two opportunities for vaccination [6,32], The first dose is recommended at 9 months of age as part of the routine delivery of immunizations, usually in the context of overall health services delivery. A country embarking on the two-opportunity policy usually starts with a mass campaign targeting all children aged 9 months through 14 years, regardless of prior vaccination status, using social mobilization techniques and going beyond the routine delivery system. Thus, the second opportunity results in a second dose provided to those who had previously received a first and, perhaps more importantly, it offers a first dose to children who had not been accessed through the routine health system. Following this campaign, routine immunization with a single dose continues. In some countries, the decreased transmission allows increase of the routine age for vaccination from 9 months to 12 months, which improves seroconversion rates. Every 3–5 years, follow-up campaigns are undertaken to reach children born since the previous campaign. In countries where sufficiently high coverage can be reached through provision of a second dose through routine services, a routine two-dose strategy may be implemented. Immunity levels achieved through this two-opportunity strategy have been sufficient to terminate measles transmission in many countries [33].

Global production capacity of measles vaccine, much of which is now produced in developing countries, appears adequate to support an eradication effort [101].

Waning vaccine-induced immunity with time since vaccination has been reported but has not played a significant role in sustained measles transmission in the industrialized world [13,34,35]. The major cause of measles vaccine failure appears to be lack of seroconversion following a first dose. While waning immunity has been suggested in some investigations among those vaccinated at under 1 year of age, it should be counteracted by the two-opportunity strategy [36,37].

Thus, there is an effective intervention, measles vaccine, and an effective strategy to use the intervention to terminate transmission.

Termination of transmission in large geographic areas over extended periods

Measles was declared 'not endemic' in the USA in 2000 [5]. Measles cases remain at record or near record low levels. All cases have been documented to be (or are believed to be) the result of international importations with limited spread [38]. There is no endemic genotype and most cases are either sporadic, with recognized or unrecognized international sources, or occur in small outbreaks from international importations [39]. Likewise, in the Americas, the epidemiologic and virologic evidence is consistent with absence of endemic measles since November 2002 and the outbreaks that have occurred have been linked to importations from outside the Western hemisphere [40]. South Korea recently declared indigenous measles had been eliminated from that country [41]. Thus, measles meets this criterion.

Thus, measles eradication is feasible from biological, technical, and epidemiological perspectives. Other challenges are discussed below.

Political will

As of 2007, there is no global goal to eradicate measles. The WHA passed a resolution in 2003 to reduce global measles mortality by 50% from 1999 levels by 2005, a goal that has been met using the two-opportunity strategy [8]. The

Global Immunization Vision and Strategies document was welcomed by all member countries at the WHA in 2005 and contains a goal to reduce global measles mortality by 90% by 2010 compared with the level in 2000 [8]. However, a resolution calling for measles eradication is not on the horizon. Member countries and the WHA as a whole may be reticent to support measles eradication until successful polio eradication is achieved or imminent. It has been 19 years since the WHA established a goal for the global eradication of polio and despite an investment of over US$ 4 billion, transmission persists in a handful of countries, albeit at record low levels [12,42]. While there has been broad-based support for the measles mortality reduction goals, measles eradication does not yet enjoy the same support. For polio eradication, there was a major private sector partner, Rotary International, which contributed $600 million for the effort and continues to play a major role in overseeing the initiative [43,101]. There is an active partnership supporting measles mortality reduction efforts, comprising the American Red Cross, Becton Dickinson, Bill and Melinda Gates Foundation, Canadian International Development Agency, Church of Jesus Christ of Latterday Saints, Exxon Mobil, Global Alliance for Vaccines and Immunization, International Federation of Red Cross and Red Crescent Societies, United Nations Foundation, UNICEF, Izumi Foundation, US Centers for Disease Control and Prevention, Vodaphone Foundation, and the WHO [8]. But none of the organizations involved in the measles initiative has yet called for measles eradication or committed to acquiring the additional resources that would be necessary.

Another impediment to gaining the political will is the ongoing debate over the degree to which eradication programs can detract from efforts to strengthen routine health services. This has been a major concern with the polio eradication program, although evaluations indicate the additional resources contributed through the program have actually enhanced the overall health system [44]. Support for an eradication goal would likely require demonstration of the ultimate cost-effectiveness of eradication and its relative value compared with other interventions. Models have been developed to estimate the costs and benefits [45].

Security & other societal disruptions

Armed conflicts afflict many areas of the world, making delivery of vaccination difficult. Mass vaccination campaigns for polio have been conducted in many such conflict zones with the agreement of the various groups involved to allow for days of tranquility that permit health workers to administer vaccines [46]. Measles eradication would require similar negotiations to allow for implementation of the two-opportunity strategy and for surveillance of disease to take place. Other factors can also disrupt implementation of eradication strategies such as natural disasters, national financial crises, changes in governments, modifications of donor policies, and so on. While it is difficult to anticipate how much these other factors could adversely impact measles eradication, the polio eradication effort has been able to overcome most of these, suggesting they could be addressed with regard to measles eradication.

Urban crowding

Owing to the high level of contagiousness of measles, there is concern regarding interrupting transmission in densely populated urban areas of the developing world where contact rates are extremely high, facilitating connections between transmitting cases and susceptible persons in the population, even if immunity levels are high [13]. However, measles has been eliminated from some crowded cities such as Sao Paulo, Brazil and Mexico City, indicating that the two-opportunity strategy, if appropriately implemented, can interrupt transmission [7,47]. Interruption of measles transmission has yet to be demonstrated in one or more of the most rapidly expanding megacities in Africa or Asia.

HIV prevalence

Some areas of Africa have HIV prevalence rates of 30% or higher, based on surveys of mothers giving birth. In the absence of substantial efforts to reduce perinatal transmission of HIV, concern has been raised about high levels of immunocompromise in such populations, leading to failure of vaccination programs to reach the level of immunity needed to interrupt transmission [48]. Available data suggest that most HIV-infected individuals can respond to measles vaccine and that current levels of HIV will not prevent interruption of transmission. Measles mortality has been eliminated, at least transiently, in some countries with high HIV prevalence [49]. While immune response to measles vaccine in young HIV infected children has been variable, severe adverse events have not been observed or reported.

Vaccine safety concerns

Measles vaccine is extremely safe [21]. The major adverse events attributable to vaccine include fever, rash and febrile seizures, which usually have benign outcomes. Whether measles vaccine can cause encephalitis in the normal host is not clear. If it does so, the occurrence is extremely rare. The measles vaccine virus can cause severe disease in immunocompromised persons who receive it, primarily those with T-cell abnormalities [50,51].

However, allegations that measles vaccine, when combined with mumps and rubella (MMR) vaccines, could cause autism have led to decreases in acceptance of measles vaccine and outbreaks of measles in some industrialized countries [52,53]. Overwhelming scientific information favors rejection of a role of MMR in autism, but unfounded fears still persist in some countries [52–54]. Countering these types of unfounded assertions will be critical to any effort to eradicate measles.

Low measles vaccine coverage in many industrialized countries

In contrast to polio, which was considered a serious threat in industrialized countries, leading to effective termination of transmission through vaccination prior to the establishment of a goal for global eradication, measles has not received the same societal priority in a number of developed countries. Measles remains endemic in many industrialized countries more than 40 years since the first vaccines were developed [55].

For example, 5–10 thousand cases occur annually in Japan, leading to substantial morbidity in that country as well as exportation of measles to other countries [56].

Two recent importations into the USA came from individuals who visited France and Germany, where outbreaks were presumably occurring [38].

Thus, successful measles eradication will require the buy-in of industrialized countries, which have thus far not made measles elimination a priority.

Mass campaigns with a vaccine that requires a cold chain & injections

Successful measles eradication will require successful delivery of a thermolabile vaccine through mass campaigns using needles and syringes. While efforts are underway to develop mass delivery tools that do not require injections, at the moment, injections are needed. This raises concerns regarding injection safety, maintenance of the cold chain and appropriate training of vaccinators. The current policies and practices requiring use of single-use autodisable syringes with safety boxes for disposal have significantly lowered the risk of immunization-related transmission of blood-borne agents to healthcare workers or to the general population. Despite concerns regarding injection safety, current measles control strategies require implementation of the same strategies and have successfully led to an estimated 60% reduction in measles deaths between 1999–2005 [8]. Overall, measles mortality has already been reduced by more than 90% since vaccination efforts began.

Future perspective

Measles eradication is biologically feasible. Maintenance of human-to-human transmission is essential for survival of the virus and interrupting those chains will eliminate the reservoir. Sensitive and specific laboratory assays are available and have been used throughout the world. Measles vaccination in a two-opportunity strategy (with the first dose delivered through routine health services and a second dose or second opportunity for vaccination delivered through special mass campaigns to reach children not reached for a first dose) can achieve the immunity levels needed to interrupt transmission. In addition, measles is no longer endemic in the Americas, demonstrating that eradication, from a technical standpoint, can be achieved. Three WHO regions, in addition to the Americas, have adopted goals of measles elimination [8]. However, the political will essential for a global eradication program has not yet been developed and may await demonstrated or imminent global polio eradication. Thus, eradication does not seem likely in the near future. If the polio eradication goal is achieved and the measles mortality reduction and regional elimination goals are met, the stage for future worldwide eradication may be set.

In the meantime, achieving a 90% reduction in measles deaths by 2010 is the most ambitious global goal ever undertaken and will depend on a 'bottom-up' approach with increased commitment in the high-burden countries to implement the recommended strategies, as well as ongoing technical and financial support from partner agencies.

Executive Summary
Measles is a major vaccine-preventable killer of children. As recently as 2005, more than 300,000 persons, primarily children aged under 5 years of age died from the disease.
Measles vaccines offer the opportunity to prevent this terrible health burden.
Eradication of measles is biologically feasible. Humans are essential for maintaining transmission, accurate diagnostic tests are available, effective interventions have been developed and sustained transmission has been terminated in large geographic areas.
Effective interventions with measles vaccines include the ‘two-opportunity strategy’. A dose of measles vaccine is provided routinely, usually at 9 months in the developing world and 12–18 months in the industrialized world. In the developing world, a second opportunity is offered through mass campaigns, initially targeting children aged 9 months to14 years, regardless of vaccination status. Follow-up campaigns are conducted every 3–5 years.
The second opportunity offers a first dose to persons missed by routine health services and a second dose to the children not protected by the first dose, to reduce vaccine failure. Countries that achieve high coverage with the first dose often adopt two-dose schedules without the need for mass campaigns.
Obstacles to measles eradication include: lack of political will and resources; concerns that measles eradication will detract from building better routine health services; lack of security to conduct eradication programs in a number of countries; intense crowding in some of the mega-cities of Africa and Asia; high prevalence of HIV in some areas and vaccine safety concerns.
There is widespread support for measles mortality reduction and a group of private and public organizations are supporting a goal for reducing measles mortality by 90% from 2000 levels by 2010.
Four WHO regions have goals to eliminate indigenous measles.
While eradication is not on the immediate horizon, success in mortality reduction and elimination in multiple WHO regions may lead to consideration of eradication in the future.

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