

Review Article

Measles eradication, is it feasible?

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Background:

Measles is a highly contagious viral infectious disease which mainly affects children. Approximately six million people, primarily children aged under 5 years died of the disease each year before proper immunization programmes¹. The introduction of an effective live attenuated virus vaccine in 1963 has dramatically reduced the incidence of measles². In 1980, an estimated 2.6 million deaths occurred due to measles when vaccine was not adopted world wide. By 2015, the Millenium Development Goal 4 (MDG4) sets a goal to reduce two-thirds measles related deaths among children compared with the level in 1990³. In 2010, the 63rd World Health Assembly (WHA) Member States agreed that the following accelerated measles control targets to be achieved by 2015:- exceed 90% coverage with first dose of live measles vaccine nationally and exceed 80% vaccination coverage in every district; reduce annual measles incidence to <5 cases/ million and maintain that level; and reduce measles mortality by ≥95%, compared with cases in 2000 estimated⁴. Global mortality of measles has been reduced from an estimated 733,000 deaths in the year 2000 to 164,000 deaths in the year 2008⁵. The decrease in measles mortality has attributed -23% of the total decrease in childhood mortality since 1990 and for 24% since 2000⁶. All countries, with the exception of India, achieved the 2010 global goal of reducing measles mortality by 90%, two years ahead of the target date⁵. The World Health Organization (WHO) encouraged by reducing measles deaths worldwide, evaluated the feasibility of the global eradication of measles in May, 2008⁷. A comprehensive program of work was performed to explore the biological, programmatic, economic, social, and political aspects of the feasibility of measles eradication. It concluded that measles should be eradicated globally by 2020⁸ and that

is also agreed by the WHO Strategic Advisory Group of Experts (SAGE) in November 2010⁹. The SAGE did not recommend a target date for measles eradication, rather it proposed for sufficient progression toward the 2015 control targets and regional measles elimination goals which will be the basis for establishing a target date for measles eradication. In January 2011, this approach was supported by the Executive Board of the WHA¹⁰.

Small pox is the only disease that has been eradicated. In 1988, the WHA set a goal to eradicate polio by 2000. There were at least four endemic countries at the beginning of 2007 while substantial progress has been made in reducing polio by 2000. Polio outbreaks occurred in countries that previously known as polio eliminated countries as a result of importations primarily from the endemic countries¹¹. Now there is ongoing question to eradicate measles like small pox from the globe. In this review whether measles is fit for criteria of eradication is discussed.

Eradication:

Eradication is the permanent reduction to zero of incidence of an infection caused by a specific agent as a result of deliberate efforts worldwide^{12,13}. Two major criteria must be fulfilled to consider a disease to be eradicable. First, eradication must be biologically feasible^{13,14}. Second, there are some other challenges for implementation of eradication strategies including global political will and resources. To eradicate a disease, all countries must be fully participated in the programme. Other wise, countries that do not participate in this programme may infect other countries who would participate in eradication programme.

Measles as an eradicable disease:

The feasibility of measles eradication has been discussed for more than 30 years, began in 1960s when the long-term protective immunity induced by live measles vaccines was becoming evident¹⁴.

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Three biologic criteria must be fulfilled to a disease for eradication.^{13, 15} First, humans should be the only natural host (there is no animal or environmental reservoir). Second, the disease must be accurately diagnosed, and third, there is an effective intervention method that can terminate transmission. In addition, the disease transmission can be eliminated in large geographic areas over an extended period is considered as fourth criteria by some authors¹⁵. Measles is thought to meet all these criteria by many experts¹⁶. The biological feasibility of measles eradication.

Humans are the only reservoir for measles virus:

Measles virus infection is thought to be sustained through an unbroken chain of human-to-human transmission. There are no known animal or environmental reservoir for measles virus. However, nonhuman primates can be infected with measles virus and can develop an illness similar to measles in humans with rash, coryza, and conjunctivitis. Many primate species are susceptible to measles virus infection, including *Macaca mulatta*, *M. fascicularis*, *M. radiata*, *M. cyclopis*, *Papio cristatus*, *Cercopithecus aethiops*, *Saimiri sciureus*, *Colobus quereza*, *Pan troglodytes*, *Callithrix jacchus*, *Saguinus oedipus*, *S. fuscicollis*, and *Aotus trivirgatus*¹⁷. Much of the evidence for the susceptibility of these nonhuman primates comes from laboratory colonies and the use of nonhuman primates as animal models for the study of measles virus pathogenesis. Interestingly, serological studies have demonstrated proof of previous measles virus infection in free-ranging populations of nonhuman primates in the wilds of southern India and Indonesia^{18, 19}. This infection may be resulted from human-to-animal transmission with limited spread within the primate population due to the absence of critical population size necessary to sustain transmission of highly infectious measles virus. Several hundred thousand persons with ~5000-10,000 births per year is required to maintain measles virus transmission in humans²⁰. As such huge population of susceptible primates in wild is not possible to exist together, transmission and maintenance measles virus is complicated. In addition, receptor used by measles virus for cellular entry is not present in other animals. The Morbilliviruses like; measles virus (Humans), canine distemper virus (Dogs) and rinderpest (Cattle) use same type of receptor for their cellular entry (Signaling Lymphocytic Activation Molecule, SLAM) but there are some dissimilarities between them²¹ and only genetically modified human SLAM can serve as receptor for measles virus²². Therefore transmission of measles virus from human to animal is quite difficult.

Accurate diagnostic tests for Measles

Several diagnostic tests exist for measles, but some are limited by low positive predictive value²³. Measles is diagnosed clinically in the endemic areas or during outbreaks by clinicians, but clinical diagnosis is difficult when incidence is low. Koplik spots are especially helpful for diagnosis because they appear early and are pathognomonic, but it not always recognized by many clinicians. The rash of measles may be absent or delayed in immunocompromised or severely malnourished children with impaired cellular immunity.

Serology is most commonly used method for diagnosis of measles virus infection in laboratory. The Measles virus-specific immunoglobulin M (IgM) antibodies in serum or oral fluid is considered diagnostic of acute infection. Measles virus-specific IgM antibodies may not be detectable until 4 days after the onset of rash and usually it falls to undetectable concentrations within 4-8 weeks.

Measles can be confirmed by isolating measles virus in Vero cell culture from respiratory secretions, nasopharyngeal and conjunctival swabs, blood, or urine. Vero cells are commonly used for neutralization tests using laboratory-adapted measles virus strains. A derivative (B95-a) of the Epstein-Barr virus-transformed marmoset B lymphocyte cell line B95-a has greater sensitivity than Vero cells for the isolation of wild-type strains of measles virus. Expression of the measles virus receptor CD150 (SLAM) on Vero cells enhances the ability to isolate wild-type measles virus strains in tissue culture²⁴.

Measles virus RNA can be detected from clinical specimens by reverse transcriptase-PCR (RT-PCR). These assays permit identification and characterization of measles virus genotypes for epidemiological studies when combined with nucleotide sequencing. Moreover, it can distinguish wild-type and vaccine measles virus strains. Measles virus RNA may persist in both healthy and immunocompromised children for several months and under experimental conditions in macaques²⁵. However, measles virus RNA does not indicate acute infection.

There are limitations of both false negative and false positive results for measles diagnosis especially IgM results. Low concentrations of IgM antibodies during the first three days of the rash may give false negative test results²⁶. Presence of rheumatoid factor and viral coinfections like rubella, parvovirus B19, and human herpes virus 6 may give false positive results. Moreover, laboratory testing is usually performed in suspected cases of measles. Thus, persons with minimal signs or symptoms or with uncharacteristic features of measles may be missed.

Effective Interventions

The effectiveness of measles vaccines has been measured by two broad approaches- firstly, the effectiveness of measles virus specific vaccines in preventing measles, secondly, measurement of vaccine immunogenicity^{27, 28}. The protective antibody concentrations in children following measles vaccination depends on the presence of maternal antibodies and immunologic maturity of the vaccine recipient, as well as the dose and strain of vaccine virus²⁹. However, maternally acquired antibodies may not present in the majority of children in between 6-9 months of age³⁰. It was estimated that when single dose of measles vaccine was given at 9 months of age approximately 85% children develop protective measles antibody concentration while 90-95% develop when vaccinated at 12 months of age^{31, 32}.

Measles virus transmission can be interrupted by vaccinating a large number of populations with live measles vaccines so that probability of an infected case coming in contact with a susceptible individual is low³³. However, a 2-dose measles immunization schedule should take to achieve 95% population immunity necessary to interrupt measles virus transmission.

Live attenuated measles vaccines have some limitations to achieve their effectiveness or increase their risk-benefit ratio in some populations. First, these vaccines are not immunogenic in young infants, so vaccine should be administered at 9 months of age or older. Second, measles vaccines are relatively heat-stable in the lyophilized form but lose potency rapidly when exposed to heat. Thus improper storage may reduce effectiveness of measles vaccine. Third, live viral vaccines are potentially harmful to immunocompromised persons leading to cause disease as a result of vaccine virus replication³⁴. A recent systematic review concluded that measles vaccines is safe in children infected with human immunodeficiency virus (HIV), but there is an absence of studies reporting relevant information³⁵. Despite these limitations, the attenuated measles vaccines have been used over the last 40 years and resulted in reductions of measles incidence, morbidity, and mortality.

Sustained Interruption Of Measles Virus Transmission In Large Geographic Areas

Elimination of measles depends on the breakage of transmission chain. Therefore absence of measles for a prolong period of time in large geographical areas is important. Though some small outbreaks of primary and secondary cases occurred following importation from outside the region, measles elimination was achieved in Americas in November 2002^{36, 37}. The WHO regions have set measles elimination goals as such - measles elimination in Eastern Mediterranean, Europe, and

Western Pacific by 2015 or before and the African region by 2020. The remaining WHO region- South-East Asia (SEA), has set a goal to reduce measles mortality by 90% in 2010 compared with the level of measles death in 2000. These ambitious goals have been achieved by successful implementation of the WHO/UNICEF strategy for providing the second dose of measles vaccine through supplementary immunization activities. The largest decrease of measles mortality was achieved in Africa, where measles mortality decreased about 91% from 2000-2006, accounting 70% of the global reduction in measles mortality³⁸.

There are some potential biological barriers that may interrupt eradication. Potential biological barriers include persistent human reservoir to produce disease namely Subacute Sclerosing Panencephalitis (SSPE), sustained transmission through subclinical infection, waning vaccine immunity, measles virus genetic diversity, measles outbreaks in population with high levels of population immunity, impact of the HIV pandemic.

Challenges for eradication:

Many experts have suggested that global measles eradication is biologically feasible. However, the eradication of measles will be more difficult challenge than either polio or smallpox eradication due to some challenges which include global political will, availability of resources and sufficient vaccine supply.

Global political will:

Measles is not considered as a serious problem in many wealthy and middle-income countries, because the development of effective health services system that has reduced the mortality rate. This is particularly relevant for many developed countries in Western Europe and Asia that have not accepted measles as a serious health burden and thus have not made prevention of measles a high priority³⁹.

Availability of resources and sufficient vaccine supply

The gains in measles mortality reduction made over the past decade will be lost if resources are not made available for implementation of planned vaccination activities and laboratory-backed surveillance for measles cases. Reduction in financial support to the Measles Initiative decreased from US\$150 million in 2007 to US\$50 million in 2009, and US\$35 million in 2010. Many priority countries to eliminate measles have not been able to raise the expected 50% of operational costs for measles supplementary immunization activities, which in turn may interrupt measles elimination goal. The WHO has estimated that reduced financial and political commitment to measles control over the period 2010-2013 would result in

an additional 200,000 measles deaths in 2011 and a total of >500,000 measles-related deaths worldwide in 2013 alone⁴⁰. Thus, the world is now at a crossroads regarding whether it has the will and the means to make the sociopolitical and financial commitment to reverse the resurgence by achieving the 2015 mortality reduction target. The availability of an inexpensive and effective vaccine makes measles immunization one of the most cost-effective public health interventions across a range of developmental settings^{39,40}.

Conclusion:

Recent progress in reducing global measles mortality arise the interest in measles eradication. Measles eradication is biologically feasible as no known human reservoir exists, accurate diagnostic tests are available, and live attenuated measles vaccines are effective and immunogenic. 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) can achieve the desired immunity levels for interruption of transmission. Moreover, measles has been eliminated in large geographical areas, including the Americas. Thus, measles eradication is biologically feasible.

However, the eradication of measles will be more difficult than either polio or smallpox eradication. The highly infectious nature of the measles virus and the complex logistical and operational requirements for conducting mass immunization campaigns using an injectable vaccine (rather than an orally administered vaccine as compared with polio), and ensuring safety of injections in developing countries, make this a unique challenge. Another major challenge will be harnessing the political will globally to move forward. Strong management, accountability, communication, advocacy, and resource mobilization at all levels shall play vital and crucial role in achieving measles eradication successfully.

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