Risk Analysis for Measles Reintroduction After Global Certification of Eradication

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Background. Measles virus will continue to exist after certification of global eradication as virus stocks and infectious materials held in laboratories, in persistently and chronically infected individuals, and possibly in undetected foci of transmission. A literature search was undertaken to identify and evaluate the main risks for reintroduction of measles transmission in the absence of universal measles immunization.

Methods. A qualitative risk assessment was conducted following a series of literature searches using the PubMed database.

Results. If the criteria for global certification of eradication are stringent and require rigorous validation, then the risk of undetected measles transmission after certification is very low. Risk of unintentional reintroduction from any source, including persistent infections and laboratory materials is low to very low but depends on the extent of measles vaccine use. If immunization levels decrease, measles will become a credible agent for bioterrorism through intentional release.

Conclusions. Posteradication risks are low and should not deter any attempt at measles eradication. More information on measles transmission dynamics and the role of atypical infections is required to determine requirements for global certification of eradication. Posteradication risks would be minimized through development and implementation of an international risk management strategy, including requirements for a posteradication vaccine stockpile.

By any reasonable definition of eradication, measles virus will continue to exist after global certification of eradication, as virus stocks and infectious materials held in laboratories, in persistently and chronically infected individuals, and as measles vaccine strains maintained as vaccine stocks. This study was undertaken to determine the extent of the risk of measles reintroduction in a post-eradication world. Risks examined include continuing wild-type measles transmission in undetected human reservoirs, transmission of vaccine-derived virus, persistent and chronic infections, nonhuman primate reservoirs, laboratory-acquired infections and virus escape into the community, and intentional release.

If universal or near-universal coverage with measles vaccine is continued after global eradication, the risk of measles reintroduction will be minimal. It is likely that a number of national authorities will choose to continue current routine immunization activities after eradication. Some authorities may adopt a modified immunization schedule, such as a single-dose immunization policy, or some form of campaign strategy, whereas some national authorities, either through decision or default, will cease routine measles immunization. For the purposes of this analysis it was assumed that universal immunization against measles would not be continued and that an increasing global population would be susceptible to measles infection in the years after certification.

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METHODS

A qualitative risk assessment was conducted following a series of internet literature searches predominantly using the PubMed database (http://www.ncbi.nlm.nih.gov/pubmed), with additional searches using the JSTOR (http://www.jstor.org) and ScienceDirect (http://www.sciencedirect.com) databases.

RESULTS

Risk of Continuing Wild-Type Measles Transmission in Undetected Human Reservoirs

A key factor in determining the risk of continuing transmission is the critical community size required for maintaining measles virus circulation. Accurately predicting the critical community size is difficult due to the large number of variables involved, but direct observation and several deterministic and stochastic models suggest that a population of 250,000–400,000 with 5000–10,000 births per year is required to maintain transmission [1]. High levels of immunization coverage, low population density, a low birth rate, and good public health care facilities increase the critical community size. Low vaccine uptake, high population density, high birth rates, high levels of immunodeficiency and poor public health care facilities decrease the critical community size [2].

Another important potential risk factor is the extent to which asymptomatic infections contribute to transmission. Control strategies assume that virus transmission occurs through chains of clinically recognizable measles cases, and surveillance systems largely rely on the identification of these cases for detecting and responding to outbreaks. Convention holds that asymptomatic measles infections are rare, but there is a significant body of published evidence of acute measles infection among people who are exposed to measles virus but who do not develop classic symptoms [3–5]. It has also been recognized that measles virus can infect previously immune persons, producing classic symptoms of measles in some but mild or no symptoms in most [6]. The estimated rates of mild or asymptomatic measles infections after exposure to measles cases are varied, however, in part because of different diagnostic techniques and different case definitions used or because of the different types of exposure. It is possible that mild or asymptomatic measles infections are common among measles-immune persons exposed to measles cases and may be the most common manifestation of measles during outbreaks in highly immune populations [3]. No conclusive evidence of virus transmission from persons with asymptomatic infection has been published. If such transmission does occur, it is likely to be very rare and is unlikely to be efficient enough to sustain transmission, especially in the highly vaccinated populations expected in the years immediately after global certification of eradication.

There are, as yet, no definitive criteria for certification of global measles eradication or agreed-upon requirements for validation of these criteria. If the criteria are firm enough and require rigorous validation, then the risk of undetected measles transmission after certification is very low. If the certification criteria are lax or validation requirements are inadequate, the risk will be higher.

Risk of Transmission of Vaccine-Derived Virus

Measles virus is serologically monotypic and is genetically characterized into eight clades (A–H), divided into 23 recognized genotypes [7, 8]. All of the current live attenuated measles vaccines share a remarkable nucleotide sequence similarity and all are members of genotype A [9]. Although current vaccine viruses and their wild-type progenitors share >95% sequence homology, they can easily be distinguished genetically from currently circulating wild-type viruses.

Like wild-type virus, measles vaccine virus replicates effectively in vaccine recipients, inducing both humoral and cellular immune responses similar to natural measles virus infection, and viral RNA can be detected in specimens of urine [10] and respiratory secretions for some days after immunization [11]. Vaccine virus can be isolated from the blood of recent vaccine recipients and has been detected in samples of lung, liver, bone marrow, and brain tissues in the very rare cases of severe acute disease after measles vaccination [12]. There is, however, no published evidence of the transmission of vaccine virus from vaccine recipients. The reasons for nontransmission of vaccine viruses are not fully understood and are likely to be complex. Whatever the reason, it appears that the block on transmission of vaccine viruses is highly effective.

Additional evidence of the nontransmissibility of vaccine virus strains comes from molecular epidemiology data. During the 1950s and 1960s, before vaccination had been started, the majority of measles viruses isolated belonged to what is now recognized as genotype A, and this genotype may have had a worldwide distribution. Over the past 15 years, a massive effort has been put into characterizing measles viruses associated with outbreaks, importations, and sporadic occurrences. Although gaps remain, viruses from most major outbreaks and importations are being sequenced and genetically characterized through the World Health Organization Laboratory Network's activities. Against a background of >7000 isolates characterized [8], very few genotype A viruses have been identified during the past 20 years, and none have been unequivocally associated with outbreaks of measles. Table 1 summarizes the published documentation on detection of genotype A measles viruses since 1990.

Table 1 includes isolates that may represent wild-type lineages that have survived since the prevaccination era. It also includes viruses isolated from very recent vaccine recipients presenting with classic measles symptoms and possible laboratory

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Table 1. Published Documentation on Isolation and Characterization of Genotype A Measles Viruses, 1990–May 2010

Year of detection	Country	State, province, or region	No. of isolates[a]	Reference
1990	Japan	Handai[b]	1 (1)	[13]
1991	Argentina	Buenos Aires	1 (1)	[14]
1993	United Kingdom	Coventry, England	5 (1)	[15]
1995	South Africa	Johannesburg	1	[16]
1996	Russian Federation	Novosibirsk, Siberia	3	[17]
1996	United States	Delaware	1	[18]
1996	China	Hunan	1	[19]
1996	United Kingdom	NA	2	[20]
1996	South Africa	Johannesburg	1	[21]
1998	United Kingdom	Importation from Russia	1	[20]
1999	Argentina	Buenos Aires	2 (2)	[14]
1999	China	Henan	1	[19]
2000	United Kingdom	NA	1	[20]
2001	Spain	Ibiza	1	[22]
2002	Spain	Madrid/Badajos	2	[22]
2003	Spain	Almeria	3 (3)	[22]
2003	China	Xinjiang	1	[19]
2005	Taiwan	Taichung/Taipei	2 (2)	[23]
2007	Taiwan	Tainan/Taipei	2 (2)	[23]
Total	…	…	32 (12)	…

NOTE. NA, not available.

[a] Number of isolates known to be associated with recent receipt of vaccine shown in parentheses.

[b] Region is not certain.

contaminants, because many laboratories historically used vaccine strains as positive controls for virus isolation. It may also include vaccine-derived isolates that have been transmitted from vaccine recipients to unvaccinated contacts. Although some of the genotype A isolates have nucleotide substitutions that distinguish them from vaccine viruses, there is no published documentation identifying a distinct set of genetic markers that consistently differentiate wild-type viruses from attenuated viruses [24]. If vaccine viruses are ever transmitted, it appears to be a very rare and as-yet undocumented occurrence. Available information suggests that the risk of current live, attenuated vaccine viruses reverting to wild-type transmissibility is very low, but it remains a possibility. Genetically modified measles vaccine strains are currently being investigated as vectors for cancer treatment. There may be some, very low, risk associated with the production and clinical use of these vectors, but more experience and information are required before the extent of the risk can be assessed.

Risk From Persistent Infections

In classic measles cases, there is a 10- to 14-day incubation period between infection and the onset of clinical signs and symptoms, and infected persons are usually contagious for 2–3 days before and up to 4 days after onset of the rash. Measles virus has been isolated from peripheral blood mononuclear cells and urine samples up to 1 week and up to 10 days, respectively, after appearance of the rash [25]. Delayed virus clearance has been documented in cases of malnutrition [26] and patients with cellular immunity deficiencies [27]. Detection of measles virus RNA has been reported for up to 4 months in a case of congenital measles [28] and for 1–4 months after uncomplicated infection in 90% of human immunodeficiency virus HIV-1–infected children and >50% of HIV-uninfected children [29, 30]. These data are consistent with studies of rhesus macaques showing that virus clearance occurs over 120–150 days [31], suggesting that normal clearance is a prolonged process. Virus persistence is almost universally associated with wild-type measles infection, not with receipt of vaccine virus. Despite the reported persistence of viral RNA, there have been no reports of infectious virus shedding more than 3–4 weeks after appearance of symptoms.

Persistent infection with wild-type measles virus has definitively been associated with subacute sclerosing panencephalitis (SSPE), a progressive fatal neurological disease with high levels of neuronal infection by measles virus in the central nervous system. SSPE is not associated with receipt of vaccine virus [32]. The average period from initial measles infection to SSPE symptom onset (latency) usually ranges between 4 and 10 years, but it has been reported to occur from 2 months to 23 years [32]. The reported SSPE incidence range is 0.2–40 cases per million population per year, but direct comparison of data from different countries is problematic because methods and quality of

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diagnosis have been inconsistent. Analyses of data from the United Kingdom and United States have calculated the true incidence of SSPE to be 4–11 cases of SSPE per 100,000 cases of measles. A higher risk is associated with earlier infection: the risk after measles infection for persons aged <1 year of age is 18 cases per 100,000 persons, compared with 1.1 cases per 100,000 persons aged ≥5 years in the United Kingdom [32]. Evidence from brain biopsies of SSPE patients indicates that although measles virus can be detected, these viruses contain defective genomes that usually include mutations making ≥1 of the proteins needed for budding from infected neurons nonfunctional [33]. There is no evidence of transmission of measles virus from SSPE cases.

Measles inclusion body encephalitis (MIBE) is a rare central nervous system complication that follows acute measles virus infection. MIBE has also been reported as a very rare result of receipt of measles vaccine [34]. It has been described in children and adults receiving immunosuppressive drugs and, therefore, is thought to chiefly affect immunocompromised hosts. The neurologic disease usually appears 3–6 months after the acute measles rash [35], with a median time of 4 months [36]. Measles antigen is present in the brain, and virus has been isolated directly from the brains of affected individuals [35]. Cases of MIBE without clear measles exposure or infection have been reported. In a review of MIBE, 18% of patients had no documented measles exposure or infection [36]; however, many of these cases occurred in years when measles was more prevalent. There are no published reports of infectious measles virus shedding from MIBE cases.

As described above, measles virus RNA could be detected in samples from 90% of HIV-infected children 1 month after recovery from acute measles [29], but in this study, no attempt was made to culture virus from any samples. In regions with a high prevalence of HIV-1 infection, coinfection with HIV-1 more than doubles the odds of death for hospitalized children with measles [37] and may slow the rate of virus clearance slightly, but there is no evidence that HIV infection leads to an increased risk for persistent measles virus infection. In addition, HIV infection does not appear to present a risk for persistent infection with the measles vaccine virus [38].

Available information suggests that the relatively small number of persistent measles virus cases, including those that may result from coinfection with HIV, pose a very low risk for reintroduction of measles.

Risk From Nonhuman Primates

A wide range of nonhuman primate species are susceptible to experimental infection with measles virus [39, 40]. As expected from an effective animal model, many species respond to infection in a manner very similar to humans [41]. Inadvertent transmission of either measles (from humans) or the closely related canine distemper virus (from dogs) to captive nonhuman primates has caused numerous outbreaks with significant morbidity and mortality [40]. Nonhuman primates in the wild appear to be free from measles, only contracting infection when they come into contact with infected humans [42]. Serological evidence of measles infection in free-ranging populations of nonhuman primates has been documented [43], and evidence exists for measles infection in nonhuman primate populations that have frequent contact with human populations, as well as in wild populations that have minimal human contact [40, 43].

Because human populations represent the largest reservoir of the measles virus, it is most likely that measles epizootics in nonhuman primate populations are initiated by human-to-nonhuman primate transmission and subsequently spread by animal-to-animal transmission. Because of their relatively small numbers, it is unlikely that natural populations of nonhuman primates are significant or sustainable reservoirs of measles virus [40].

Available information suggests that infections in nonhuman primates pose a very low risk for reintroduction of measles.

Risk From Laboratory-Acquired Infections and Virus Escape Into the Community

Laboratory-associated measles risk after eradication will exist at 2 levels: occupational risk of exposure among laboratory staff and community risk of laboratory-associated measles exposure.

A series of surveys for laboratory-acquired infections conducted in the United Kingdom [44, 45] and the United States [46, 47] failed to include measles among the listed infections. A recent review of principles for prevention of laboratory-associated infections also failed to make mention of measles [48]. An extensive literature search failed to find documented evidence of laboratory-acquired measles infection. This leaves 3 possibilities: laboratory-acquired measles infections have not occurred; the infections that have occurred have been below the threshold of sensitivity of the surveillance systems; or measles has been considered a trivial disease and infections have not been reported.

Measles virus is not physically robust. It is viable for <2 h at ambient temperatures on surfaces and objects, and the aerosolized virus typically remains infective for only 30 min to 2 h, depending on environmental conditions. Virus in maintenance medium loses at least 2 logs of titer when stored at +6°C for 14–20 weeks and loses all infectivity after 1 year at this temperature. Storage at −30°C offers little advantage over storage at +6°C, with a 1- to 2-log loss of titer over 1 year. Storage at −72°C or below results in very little loss of virus infectivity, and infectious materials maintained at this temperature should retain infectivity for many years [49].

Community members may be exposed to infectious measles virus from contaminated laboratory workers, infected laboratory workers, contaminated air effluents, transport of infectious materials, and escaped infectious animals. No published evidence exists regarding the escape of infectious measles virus

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from the laboratory into the community. Given the rapid inactivation of measles virus under normal environmental conditions, the length of time available for infectious virus to be carried out of the laboratory and into the community, either on the body or clothes of a contaminated worker or in contaminated air effluents, is probably limited to 2 h. This reduces the risk to a very low level.

In a measles posteradication world without routine universal immunization, measles laboratories (and measles live vaccine production facilities) will pose a very low but increasing risk for reintroduction of measles.

Risk of Intentional Release of Measles Virus

The devastating effect of measles on susceptible populations in the prevaccination era has been well documented [50]. This is particularly true for the islands of the Pacific, where mortality rates in excess of 25% were associated with epidemics in the 19th and early 20th centuries. Advances in medical treatment make it unlikely that similar mortality rates would be inflicted after measles eradication, but deliberate release would cause extensive disruption to medical, public health, and social services and would probably incur enormous containment costs. The risk of deliberate release of measles will be very low at the time of global eradication but will rise rapidly with accumulation of unvaccinated measles-susceptible populations. Measles is not currently included in the Centers for Disease Control and Prevention Bioterrorism Agent Categories, but a review of this status will be needed after eradication.

Table 2 provides a summary of the risks considered and an assessment of risks posed.

DISCUSSION

There are, as yet, no definitive criteria for certification of global measles eradication or agreed-upon requirements for validation of these criteria. Without these criteria and the detailed requirements for demonstrating they have been met, it is not possible to accurately estimate the risk presented by undetected continuing transmission.

In drawing up the certification criteria and validation requirements, it will be necessary to engage experts familiar with the development of dynamic and stochastic models of measles transmission, persistence, and elimination. This will be particularly important for determining the certification and validation requirements for low-income, high-density populations. On the basis of the experience gained in polio eradication, this will be most relevant for selected populations in Africa, the Indian subcontinent, and large refugee/migrant population camps.

Important information can also probably be gained from detailed epidemiological and molecular analysis of outbreaks, particularly those occurring in highly immunized populations, in high-density populations, and in generally highly-immunized populations with inadequately immunized subpopulations. If the criteria for global certification of eradication are firm enough, and if they require rigorous validation, then the risk of undetected measles transmission after certification is very low. If the certification criteria are lax, or if validation requirements are inadequate, the risk will be higher.

The currently licensed live, attenuated measles vaccines are safe and efficient and have been used successfully to protect many millions of individuals and prevent measles transmission. If currently licensed attenuated measles vaccines are to be used in a posteradication world, more information on the nature of the changes caused by attenuation and the potential for reversion to wild-type characteristics will be required. An alternative would be to speed up development, testing, and introduction of new measles vaccines that do not depend on live, attenuated virus.

More understanding of the nature of the complex interaction between measles virus and the host immune system, including both humoral and cell-mediated responses, would probably benefit continued use of existing vaccines and development of new vaccines. In the years leading up to global eradication, all genotype A viruses detected in association with acute cases of measles should be thoroughly scrutinized. Full epidemiological information will be required, and additional sequence data from both clinical samples and corresponding viral isolates will be necessary to exclude the possibility of transmission of vaccine-derived virus. Thorough genetic analyses, including full genomic

Table 2. Summary of Risks Considered and Assessment of Risks Posed

Risk	Magnitude	Tendency over time
Continuing wild-type measles transmission in humans	Low but depends on certification criteria and validation requirements	Decreasing
Transmission of vaccine-derived virus	Very low	Depends on level of vaccine use
Persistent infections	Very low	Decreasing
Nonhuman primates	Very low	Decreasing
Laboratory-associated infection	Very low but rising after eradication	Increasing
Intentional release	Very low but rising after eradication	Increasing

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sequencing, should be performed on selected vaccine viruses that are associated with common vaccine reactions, as well as on those detected in the very rare severe reactions to vaccination.

Measles virus is a member of the genus *Morbillivirus*, which includes dolphin and porpoise morbillivirus, canine distemper virus, phocid distemper virus, peste des petits ruminants virus, and rinderpest virus. It is theoretically possible that, after the eradication of measles and cessation of measles vaccination, another member of the genus could jump the species barrier to occupy the human niche left by measles. There is very little published information on this, and in the absence of further evidence, the potential risk must be considered to be very low.

Although there is no direct evidence of laboratory-acquired measles infections, it is possible that such infections have occurred among immune laboratory staff and resulted in asymptomatic or very mild infections. Despite the current lack of evidence for laboratory-associated infections or escape of virus into the community, these must be considered possibilities in a post-eradication world. One approach to reducing the risk would be adoption of a strategy to minimize availability of measles virus, through removal of live viruses from the majority of laboratories and securely containing all infectious material that remains. A systematic laboratory containment strategy for measles, learning from the example set by the Polio Eradication Initiative, would be an appropriate starting point.

Another risk-reduction strategy would be to develop a measles vaccine stockpile. This would counter the risk of measles reintroduction from many sources, including deliberate release. The size, nature, and disposition of the stockpile required are difficult to predict without extensive mathematical modeling. Requirements would probably be dynamic, depending on complex variables including the number of susceptible persons accumulating in the community, the effectiveness of the vaccine, transmission dynamics of the virus and the effectiveness with which any event requiring an immunization response was detected, reported, and responded to. Decisions on establishing a measles vaccine stockpile should not be taken in isolation but considered systematically and included in a consensus post-eradication risk management strategy. Development of a risk management strategy should begin as soon as possible.

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