Breakthrough Infections in Measles Elimination

Subjects: Health Policy & Services

Contributor: Clara Fappani, Maria Gori, Marta Canuti, Mara Terraneo, Daniela Colzani, Elisabetta Tanzi, Antonella Amendola, Silvia Bianchi

Measles is one of the most contagious diseases known to man. Despite the existence of a safe and effective live attenuated vaccine, measles can appear in vaccinated individuals. Paradoxically, breakthrough cases increase as vaccination coverage in the general population rises. In measles endemic areas, breakthrough cases represent less than 10% of total infections, while in areas with high vaccination coverage these are over 10% of the total. Two different vaccination failures have been described: primary vaccination failure, which consists in the complete absence of humoral response and occurs in around 5% of vaccinated individuals; and secondary vaccination failure is due to waning immunity or incomplete immunity and occurs in 2–10% of vaccinees. Vaccination failures are generally associated with lower viral loads and milder disease (modified measles) since vaccination limits the risk of complicated disease. Vaccination failure seems to occur between six and twenty-six years after the last vaccine dose administration.

Keywords: measles ; breakthrough infection ; measles vaccine ; vaccination failures

1. Introduction

Measles is one of the most contagious diseases known to humankind, with a basic reproduction number (R_0) assumed to be between 12 and 18. It spreads through coughing and sneezing, close personal contact, or direct contact with infected nasal or throat secretions. The disease is typically characterized by an erythematous and blotchy red (maculopapular) rash that starts from the face, upper neck, and behind the ears and then spreads to the trunk reaching hands and feet. The rash lasts for 3–4 days and then fades, disappearing from the face first [1][2]. Most measles-related deaths are caused by complications associated with the disease, such as: blindness, encephalitis, severe diarrhoea and related dehydration, ear infections, or severe respiratory super-infections such as pneumonia [1].

Measles is caused by measles virus (MV). MV is a single-stranded, negative-sense, enveloped, non-segmented RNA virus belonging to the species *Measles morbillivirus* of the genus *Morbillivirus*, within the family *Paramyxoviridae*. MV genome consists of 15,894 nucleotides and encodes eight proteins. The non-structural proteins V and C are involved in the cellular response to infection. The hemagglutinin (H), essential for viral binding to cellular receptors, and fusion (F) proteins mediate fusion of the viral envelope with the host cell membrane and are the main targets of neutralizing antibodies. Together with the matrix protein (M), which is important for virus assembly, they represent the three membrane-associated proteins. The ribonucleoprotein (RNP) complex consists of the nucleocapsid (RNA bound to RNA-binding nucleocapsid proteins N) with a polymerase-associated phosphoprotein (P), and a large protein (L, including an RNA-directed RNA polymerase (RdRP), mRNA guanylyl- and methyltransferases, and methylation functions required for the capping of mRNAs) [2][3]. MV is related to several viruses infecting animals (e.g., Canine Distemper Virus, Rinderpest virus) and humans are its natural host [2].

According to the World Health Organization (WHO) guidelines, measles cases classification should be conducted according to clinical, epidemiological, and/or laboratory criteria. Any individual presenting with fever, maculopapular rash lasting 3 or more days, and at least one additional symptom among cough, coryza, or conjunctivitis fulfills clinical criteria for measles. Epidemiological criteria are met when contact tracing evidences an epidemiological connection that could have been the source of interhuman transmission. Laboratory criteria must meet at least one of the following parameters: isolation of MV from a clinical specimen (throat or nasopharyngeal swabs, nasal aspirates, or 10 to 50 mL of urine, collected as soon as possible after the rash onset [4]), detection of MV nucleic acid in a clinical specimen (the same samples collected for isolation can be used, as well as oral fluids and dried blood [4]), identification of anti-MV specific antibody response characteristic of the acute infection (1–10 days) in serum or saliva, or detection of MV antigen by a direct fluorescent assay in a clinical specimen (nasopharyngeal and throat swabs, and urine specimens [5]) using MV specific monoclonal antibodies. Laboratory results need to be interpreted according to the vaccination status, and specific virological investigations (i.e., the detection of a wild viral strain) are required to confirm the diagnosis in recently vaccinated patients (see the following sections for more details) [6].

2. Measles Vaccines and Immunization Programs

Several attenuated measles vaccines are available worldwide, either as single-virus vaccines or in combination with the rubella and mumps vaccines (MMR) or with the rubella, mumps, and chickenpox vaccines (MMRV). Although there are 24 recognized MV genotypes, MV is considered serologically monotypic [7] and most of the available vaccine strains derive from the Edmonston strain, isolated in 1954 [8]. The principal target of human antibodies is the H protein. Sequence analyses of the H gene performed in several studies did not show specific mutations associated with immune escaping, and this antigenic stability could be at the basis of the effectiveness of the present vaccine [9][10][11][12]. Likewise, no significant differences have been found in strains circulating in vaccinated or not vaccinated individuals [13][14].

The measles vaccine induces both humoral and cellular immune responses and antibodies appear between 12 and 15 days after vaccination, peaking at 21 to 28 days [2]. Measles immunization programs consist of the administration of two doses of measles vaccines. Although there are variations between vaccination calendars of the various countries, according to WHO recommendations for routine immunization, the first dose is usually given at the age of approximately nine months in countries with ongoing measles transmission, in which the risk of measles mortality remains high, and, to take advantage of the higher seroconversion rates achieved at an older age, at the age of 12 months in countries with low levels of measles transmission. The second dose should be administered at 15 to 18 months of age or at school entry [15] [16]. However, every opportunity should be taken to vaccinate all children that missed one or both routine doses [16].

3. Measles Virus Infection and Vaccine Failure

Despite the availability of a safe and highly effective live attenuated vaccine, measles can manifest in individuals with a documented vaccination history. During the Cincinnati and St. Louis epidemics of 1971–1973, Cherry et al., and Plotkin et al., described for the first time the existence of measles vaccination failure cases [17][18][19]. Indeed, nowadays it has been observed that the duration of protection conferred by measles vaccine is more variable and shorter than that acquired through measles infection, with an estimated 5% of children losing protective antibody titres 10–15 years after vaccination [2][14][20]. Breakthrough cases, which occur when a person becomes sick with a disease despite having received the vaccine for that disease (vaccine failure), do play an important role in the epidemiology of the disease.

As vaccination coverage increases in the general population, a proportional increase in the frequency of measles cases among vaccinated individuals is expected, as long as MV circulates [21]. This happens because, with fewer non-vaccinated individuals, most of the susceptible subjects are those that did not develop a protective immune response after vaccination (**Figure 1**). Indeed, the portion of breakthrough cases over the total of measles infections is higher in countries with high vaccination coverage, as described in various studies [22][23][24][25].

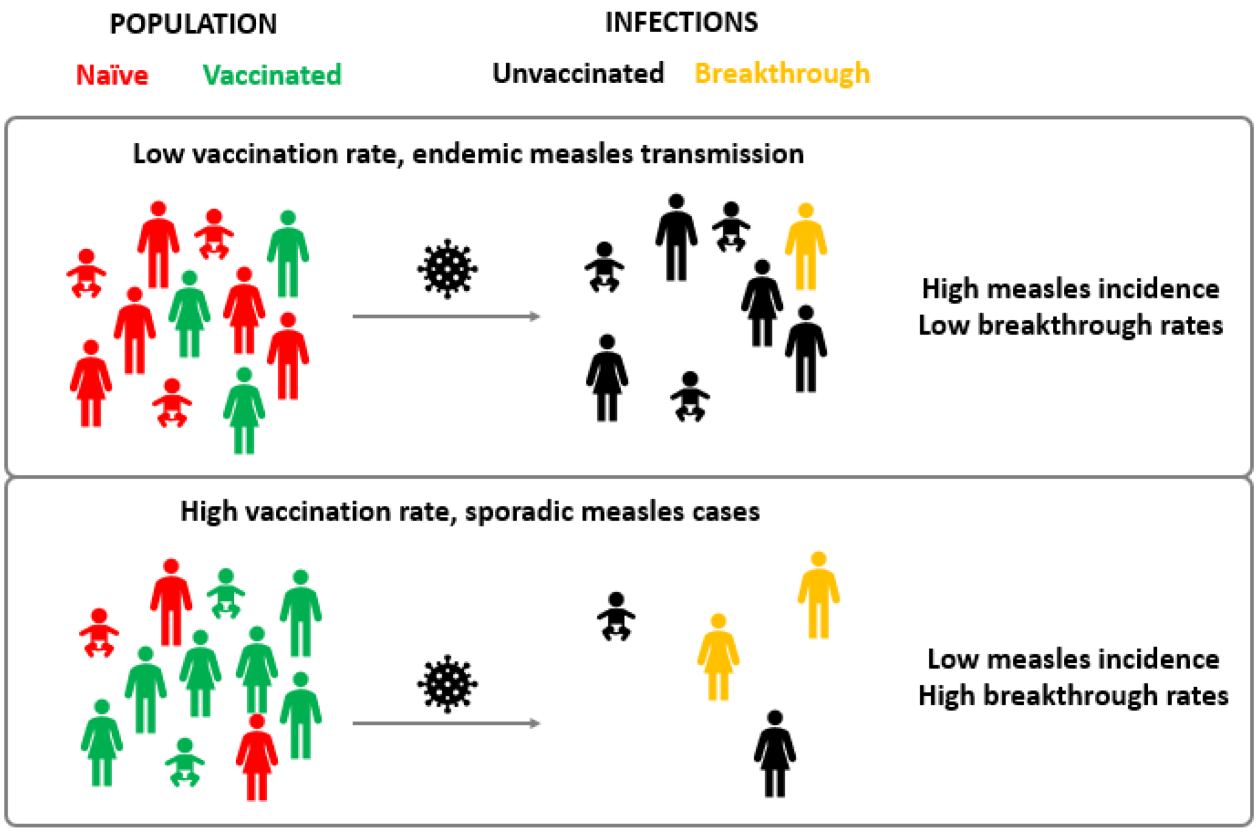

Figure 1. Measles breakthrough cases in countries with endemic or sporadic measles transmission. In populations where the majority of individuals are naïve, MV can circulate endemically and most of the infected individuals will be unvaccinated subjects (top). On the other hand, in populations with high vaccination coverages (and lower MV circulation), the number of vaccination failure cases among susceptible individuals will be higher and so will be the proportion of breakthrough cases (bottom).

4. Vaccine Failure Classification

There are two major factor categories associated with vaccine failures: vaccine-related and host-related factors. Vaccine related factors include incomplete attenuation, incorrect immunization route or schedule, and interruption of the cold chain (attenuated measles vaccines lose potency if not properly stored at 2–8 °C after reconstitution). Host-related factors include host genetics, immune status, age, and health or nutritional status [26]. Single-nucleotide polymorphisms of cytokine and cytokine receptor genes and genetic variants of genes involved in MV infection, inactivating mutations in the type I interferon receptor IFNAR1, the high-affinity interferon α/β receptor IFNAR2, and the transcription factors signal transducer and activators of transcription (STAT) 1 and STAT2 could influence the effectiveness of the response to vaccination [14].

These factors can lead to primary or secondary vaccine failures. Primary vaccine failure is the complete absence of a measurable humoral immune response [26][27]. Subjects that fail to seroconvert after the vaccination are also referred to as non-responders. Secondary vaccination failure consists of a sub-optimal or non-protective response to immunization by the vaccination or in the loss of vaccine-induced immunity over time [27][28][29] (**Figure 2**).

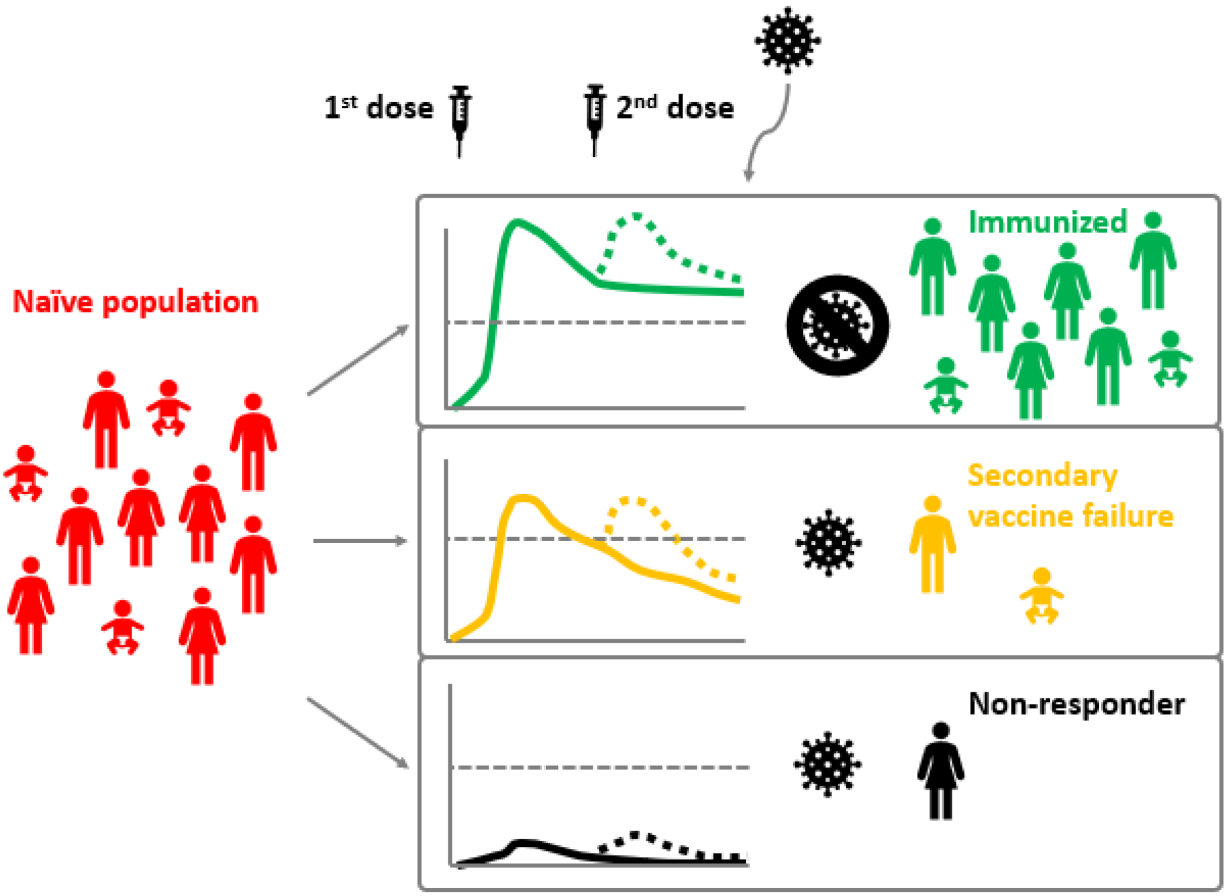

Figure 2. Possible vaccine outcomes in relation to type G immunoglobulins (IgG) levels. Immunization with a first vaccine dose causes the development of an immune response and the production of long-lasting levels of IgG (continuous lines) while a second vaccine dose causes a boost of IgG levels (dotted lines) that increases protection duration. Successfully immunized individuals maintain, already after the first dose, or develop after the second dose, an immunity that protects them from future infections and IgG levels are above the protective level (grey lines). Secondary vaccine failure occurs when the level of IgG drops below the protective level (although IgG can still be detected in these individuals), while non-responders are those subjects that never develop protective immunity (unmeasurable IgG levels).

The best method to differentiate breakthrough infections is the presence or absence of type G immunoglobulins (IgG), which develop later during the infection and persist for long periods of time, and the avidity enzyme immunoassay, which allows to differentiate a recent (low avidity IgG) from a past (high avidity IgG) infections [30] (**Figure 3**). During the acute

phase of a breakthrough infection, non-responders are recognized by the absence of IgG or, during a post-acute stage of the infection (beyond 10 days), by the presence of IgG of low avidity as the only antibodies detectable in these individuals are those produced during the reinfection. Individuals with a secondary vaccination failure are characterized by the presence of high-avidity IgG during the acute infection phase as these patients possess IgG from past infections that, however, did not protect them from a reinfection. Both non-responders and secondary vaccine failure cases can develop IgM during the reinfection. Notably, subjects with low post-vaccination antibody titers could still maintain protective antibody levels and have an adequate response against MV infection [27].

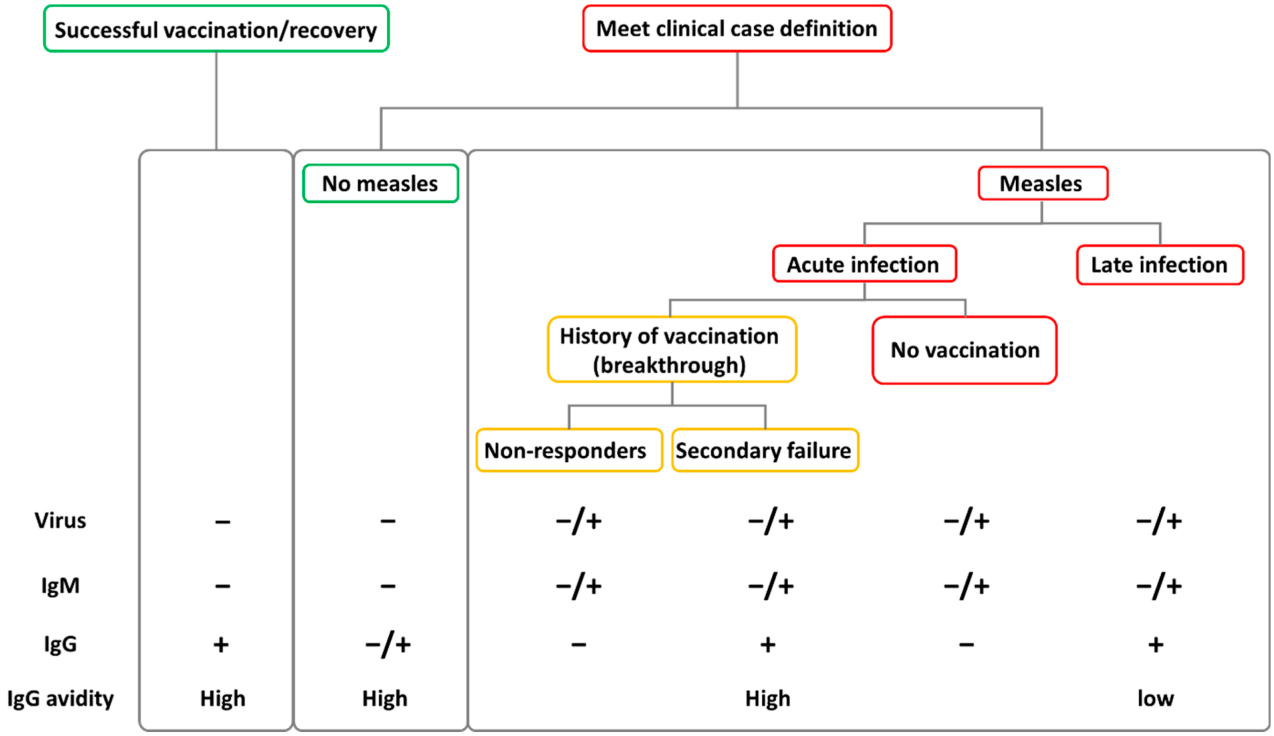

Figure 3. Graphical representation of molecular and serological profiles that can be detected during diagnostic tests in different cases after MV infection compared to non-infected subjects. A primary infection usually causes the development of both IgM, which disappear in later stages of the infection, and long-lasting IgG. When a case meets the clinical definition of measles the presence of IgM and/or the detection of the virus indicates the occurrence of an active acute infection (right panel), while their absence implies a different infection causing the symptoms (middle panel). During an acute infection, a non-immunized subject will not yet present measurable IgG while, in a post-acute infection (beyond 10 days), low-avidity IgG (indicating a recent infection) will be measurable in these subjects (while IgM and virus levels drop) (red boxes in the right panel). During reinfection, IgG would not be measurable in non-responders while high-avidity IgG (indicating a past infection) can be detected in secondary vaccination failure (yellow boxes in the right panel). During a post-acute reinfection non-responders can present low-avidity IgG. A recovered or successfully vaccinated individual will present no acute infection markers (IgM and virus) while possessing high-avidity IgG (left panel).

5. Clinical Manifestations of Breakthrough Cases and Diagnostic Challenges

Different studies recognized a milder disease in breakthrough cases (modified measles), especially in secondary vaccination failure cases and in fully vaccinated individuals. Indeed, despite sometimes insufficient immunization to adequately protect against the infection develops, measles vaccination still limits the risk of complicated measles [31]. However, these subjects do not always present with signs and symptoms typical of measles, making the clinical diagnosis more challenging [22][30]. For instance, rash may not follow the usual progression, the initial sites may be the trunk and arms rather than the face, and the infection may result in a full body rash [32]. Fully vaccinated secondary vaccine failure cases are less likely than unvaccinated patients, those vaccinated with only one dose, or non-responders to have cough, coryza, conjunctivitis and fever [22][25][33] and/or to be hospitalized [13][14][22][34], demonstrating a protection against the severe forms of the disease. Primary vaccination failure cases, despite being less likely to be hospitalized compared to unvaccinated cases [13][23], are more likely to display typical measles symptoms [23][32].

Because of the milder disease, the identification of secondary vaccination failure cases based only on clinical features is unreliable [32]. Patients with mild measles are less likely to seek medical attention and providers may be less likely to perform tests for measles in vaccinated subjects. Therefore, it is likely that secondary infections occur more frequently than reported and this could be critical in light of the global measles control strategies. To overcome this issue, in a

measles elimination setting, a highly sensitive case-based surveillance is essential for the timely detection of cases/outbreaks and to accurately define the extent of susceptible people and populations [35]. In a study conducted in Spain in the post elimination era, half of the measles cases that occurred in fully vaccinated subjects could have gone undetected because of the lack of the classical set of symptoms that usually trigger surveillance activities [23]. Therefore, the best methods to confirm MV infection in these cases are the detection of MV RNA in oropharyngeal swabs or urine samples by real time RT-PCR, even if the window for RNA detection may be shorter than that of a primary measles case [32], combined with a full serological profiling. Indeed, since IgM antibodies may not be produced, serology could be useful to confirm secondary vaccine failure cases, which usually show in their sera collected during the acute phase highly reactive IgG antibodies of high avidity, consistently with a prior immunological response to MV [32] (**Figure 3**).

6. Onward Transmission from Breakthrough Cases

Although rare, transmission from vaccine failure cases is possible, with vaccinated people acting both as index cases as well as secondary transmitters. Onward transmission from vaccinated cases to susceptible individuals seems to be limited to specific settings where close contacts are more common, such as familiar or nosocomial environments. The low rate of transmission from breakthrough cases may be associated with the elevated and rapid production of neutralizing antibodies that quickly reduce the viral load, but also with the manifestation with milder symptoms (i.e., mild, or unproductive cough) that reduces the likelihood of an effective transmission of the virus [32]. Nevertheless, the fact that a MV infection and onward transmission can both occur for subjects with vaccine failures, underscores the need to maintain a high index of suspicion for measles during an outbreak and to monitor all subjects despite (presumed) prior vaccination or disease [36]. Specifically, the same effort in tracing contacts should be dedicated to identifying possible infections amongst vaccinated and unvaccinated subjects and vaccinated cases should also carefully follow virus containment procedures. This is of particular importance in health care settings.

7. Booster Doses and Catch-Up Vaccination

Breakthrough infections occur between six and twenty-six years after the last measles vaccination [13][14][22][23][37][38]. A progressive decrease in levels of anti-MV antibodies as time since vaccination increases has been observed, as also shown by a prospective cohort study performed in the United States [20]. LeBaron and colleagues, in a study conducted in schoolchildren in a post-elimination environment, observed a decrease in neutralizing antibodies ten years after vaccination, with 4.7% of fully vaccinated children considered potentially susceptible to reinfection (neutralizing titres lower than 120 mIU/mL) [20]. The analysis conducted by Pacenti et al., showed that in over 90% of subjects, antibody titres remained above the level of protection up to 30 years after vaccination [14]. These results were consistent with previous studies [39]. Therefore, even if the percentage of susceptible individuals several years after vaccination seems to be low, population immunity to MV should be monitored, especially in adult age groups, to assess potential declines of protection.

Catch-up vaccination is recommended for all individuals (children, adolescents, and adults) who have not received the first or second dose of MV vaccine. However, in many European countries catch-up vaccination programs are not efficiently conducted or well accepted. Consequently, measles outbreaks are still occurring despite significantly increasing vaccination rates, with many adolescents and young adults (up to 40 years of age) being affected [40]. Furthermore, during 2020, childhood immunization services have been disrupted by the COVID-19 pandemic in about 70 countries, with around 80 million children being affected [41]. Reduced routine vaccination coverage without catch-up vaccination may lead to an increase in measles burden worldwide. The effect of lower measles vaccine coverage has not yet resulted in an increase in the number of cases and deaths, probably because prevention and control measures introduced to reduce the spread of SARS-CoV-2 have also reduced the spread of MV [42]. Nonetheless, it is crucial to implement catch-up vaccination campaigns and close this immunization gap before the consequences of the reduced coverage will start manifesting.

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