

Vaccine failures: assessing yellow fever, measles, varicella, and mumps vaccines

Falhas vacinais: avaliando vacinas febre amarela, sarampo, varicela e caxumba

Fallos en vacunas: evaluando vacunas de fiebre amarilla, sarampión, varicela y parotiditis

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Abstract

Vaccination is one of the greatest public health interventions, based on its safety and effectiveness, but vaccination does not always mean immunization. Numerous aspects related both to the individual that receives the vaccine and the specificity of each vaccine administered are part of the process of obtaining adequate immunization, and it is essential to observe the aspects in order to avoid vaccine failures. The analysis of immunogenicity and effectiveness studies for the measles, varicella, and mumps vaccines point to the need to incorporate two doses into the basic vaccination calendars in order to control these diseases. Epidemiological studies that analyzed outbreaks of these diseases identified cases in individuals that received two doses of the vaccine, which may indicate likely secondary failure. For the yellow fever vaccine, the current discussion lies in the ideal number of doses for individual protection. The World Health Organization recommends a single dose for life. Despite the few reports in the literature concerning vaccine failures, immunogenicity studies demonstrate waning protection over the years, mainly in the pediatric age bracket. In the current scenario of elimination and control of diseases, associated with the decrease in the circulation of the wild-type viruses, the role of epidemiological surveillance is crucial for expanding knowledge on the multiple factors involved, culminating in vaccine failures and the emergence of outbreaks. Outbreaks of vaccine-preventable diseases negatively impact the credibility of immunization programs, leading to low vaccination coverage rates and interfering in vaccination's success.

Immunization; Vaccine Immunogenicity; Seroconversion; Vaccines

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Introduction

Vaccination is one of the greatest public health interventions, based on cost, effectiveness, safety, and efficacy. Few other strategies have achieved such a positive long-term effect as vaccination ¹. However, between vaccinating and obtaining protection, that is, immunity, multifactor analyses come into play, and the goal becomes more complex. This process thus requires pharmacovigilance for monitoring adverse reactions to vaccines, immunization errors, and vaccine failures.

The primary response is conferred by the production of specific antibodies via presentation of the vaccine antigen, but the quality of these antibodies, their neutralization capacity, avidity, and long-term maintenance are important for adequate vaccine response. Long-term protection is also linked to the induction of cellular memory and secondary antibody response, induced by additional doses of vaccines ².

The immunization process is also affected by the maintenance of a quality cold chain, with adequate conditions of transportation and storage of vaccines ³.

Vaccine failures occur when one or more of the above-mentioned factors do not occur fully. Primary vaccine failure happens when there is no initial seroconversion to the vaccine, and secondary vaccine failure is when a person contracts a disease against which they had been vaccinated previously, and when initial seroconversion had occurred ⁴.

The study aimed to analyze vaccine failure with the yellow fever, measles, varicella, and mumps vaccines in Brazil and in other countries and to assess the most adequate number of doses based on data from the scientific literature, websites of immunization programs, and relevant publications related to vaccination.

The choice of vaccines for this article was based on criteria of epidemiological relevance and reports of vaccine failures for attenuated viral vaccines. Namely, (1) yellow fever is an important disease for Brazil, with widespread circulation of the virus in the country, which justifies establishing the most adequate vaccination regimen ⁵. The World Health Organization (WHO) recommends a single dose of the yellow fever vaccine for all age brackets, based on the vaccine's good efficacy and the few reports of vaccine failures ⁶. In addition, (2) various studies have demonstrated vaccine failures for other important diseases such as measles, varicella, and mumps, raising the need to evaluate vaccine failures and the setted vaccination regimens ^{7,8,9,10}.

Methodology

The methodology was an integrative review, which provided a synthesis of the knowledge and incorporation of the applicability of results of significant studies in practice. The following databases were used: LILACS, MEDLINE, PubMed, EMBASE, Cochrane Library, websites of immunization programs, and relevant publications on vaccination, such as books and manuals. The following descriptors were used in Portuguese and English: *yellow fever vaccine, measles vaccine, varicella vaccine, immunogenicity, seroconversion, seroprotection*. The inclusion criteria for the selection were articles published in Portuguese, English, and Spanish, indexed in the above-mentioned databases from 2000 to 2019.

Concepts in vaccine failures

Various definitions have been used for vaccine failures, both by regulatory agencies and for epidemiological studies. In Brazil, the criteria are those published in the *Manual on Epidemiological Surveillance of Adverse Events Following Immunization* ⁷, as follows:

- Vaccine failure can be defined according to clinical or immunological criteria that correlate or replace markers of protection against a vaccine-preventable disease. Primary failure (failure of seroconversion or seroprotection) must be distinguished from secondary failure.
- Clinically confirmed vaccine failure is the occurrence of a vaccine-preventable disease in a person with proven vaccination. It requires clinical and laboratory confirmation or epidemiological link of the confirmed case.

- Clinical suspicion of vaccine failure is defined as the occurrence of the disease in a person with proven vaccination, but in whom the disease is not confirmed, for example, invasive pneumococcal disease of an unknown serotype in a provenly vaccinated person, taking into account the incubation period and the necessary time for production of antibodies after immunization.
- Immunologically confirmed vaccine failure occurs when the immune response is tested in laboratory. An example is the assessment of seroprotection against hepatitis B.
- Suspicion of immunological vaccine failure occurs when the antibody titration is only performed years after the vaccination, and since the testing time is inappropriate, immunological failure is possible but not confirmed.

Various factors can be related to vaccination failures. Host factors include primary and secondary immunodeficiencies, immune senescence, interference from infectious agents (non-polio enterovirus and oral polio vaccine), maternal antibodies, or underlying diseases. Vaccine-related factors include inadequate coverage of types, serotypes, genotypes, antigenic variants or mutations that can cause the disease, and antigenic interference or interactions between co-administered vaccines ⁷.

Correlates of protection

The immune system's complexity is reflected when analyzing correlates of protection for the currently used vaccines. For many vaccine-preventable diseases, no reliable serological marker has been determined that represents a true correlate of protection. Thus, for some diseases we use the term assumed correlate, characterized as a correlate of protection that is not totally defined, but is statistically related to protection, as occurs with the pertussis and yellow fever vaccines, for example. In fact, there is a wide range of correlates and assumed correlates, linked both to antibodies and to cellular response, varying widely between different vaccines ⁸. We will now discuss the vaccine failures related to the yellow fever, measles, varicella, and mumps vaccines.

Yellow fever vaccine

Yellow fever is an arbovirus infection, endemic to Sub-Saharan Africa and tropical regions of South America. After an incubation period of three to nine days, the disease evolves with three stages, with viremia for three to four days in the initial phase of the infection, followed by a period with remission of symptoms, evolving from there to cure or to a more severe stage with jaundice and hemorrhage. The clinical spectrum of the disease varies from asymptomatic infection (55% of cases), mild forms (33% of cases), to a more severe condition, with the presence of jaundice and hemorrhage, fatal in 20-50% of these cases. The variability of clinical forms, mainly mild and moderate cases, makes the diagnosis more difficult, especially during the occurrence of sporadic cases, when the degree of suspicion is lower. The available treatment is merely symptomatic, making prevention via vaccination highly important ^{6,9}.

The YFV-17D attenuated yellow fever vaccines are considered highly efficacious and present lasting immunity, with few reported cases of vaccine failure. The available vaccines in Brazil are 17DD (Bio-Manguinhos/Fiocruz) and 17D204 (Sanofi Pasteur) ^{6,8,9}.

Tests using a log₁₀ neutralization index (LNI) showed that LNI > 0.7 was heavily correlated with protection in an animal model. It is considered an assumption of protection. Plaque reduction neutralization test (PRNT) is used for diagnosis and follow-up of studies, detecting presence or absence of neutralizing antibodies ⁹. Although the serological correlates of protection for yellow fever are unknown, seronegativity in vaccinated individuals may indicate primary failure of vaccination or decreased immunity at levels below the threshold for protection ¹⁰. Recent data suggest that besides neutralizing antibodies, innate and cell-mediated immunity also contributes to the initial immune response and to maintenance of long-term protection against the yellow fever virus in vaccinated persons ⁹.

The Collaborative Group for Studies with the Yellow Fever Vaccine, using the 17DD vaccine (Bio-Manguinhos/Fiocruz), found 82% seroconversion in children 6 to 8 months of age, 72% in 9 to 11 months (measles vaccine was recommended at that time at 9 months), and 88% in children 12 to

23 months¹⁰. Seroconversion in adults was assessed in two other studies with the above-mentioned vaccine and obtained similar results of 98%^{11,12}.

A study involving the simultaneous administration of vaccines against yellow fever and measles/mumps/rubella (triple viral) in children at 12 months of age found a decrease in the immune response for yellow fever, mumps, and rubella when the vaccines were administered on the same day. The study suggests that the yellow fever and triple viral vaccines should be administered with a 30-day interval in the second year of life¹³.

Many clinical studies found 80 to 100% of individuals with neutralizing antibodies, even 10 years after vaccination. In 2013, this motivated the WHO, through its Strategic Advisory Group of Experts on Immunization, to recommend the vaccine's application in a single dose, independently of age bracket, thus suspending the indication of booster doses^{6,9}. However, other recommendations, differing according to the number of doses, were postulated according to this publication, questioning the use of a single dose in adults and especially in children^{10,14}. A recent Brazilian publication involving 824 children from nine months to 12 years of age demonstrated that the seropositivity rate dropped sharply over the course of the two target periods, from 86.7% in recently vaccinated individuals to 59% and 42.2%, respectively, in the subgroups vaccinated 31-72 months and 73-100 months previously¹⁵. Another study assessed the immune status of adults that received two or more doses of the 17DD yellow fever vaccine. The reference group, which had received a dose of the vaccine more than 10 years previously, presented 69% seropositivity before the second dose and 100% after revaccination. The seropositivity rate dropped as the interval increased between the first and second doses, varying from 90% when there were 1 to 5 years between the two doses to 86% with 6 years or more¹⁶.

There are few data on vaccine failures in the literature. During the yellow fever outbreak in Central Brazil in 1972/1973, with 295 confirmed cases, 7.5% of vaccine failures were identified¹⁷.

According to data from investigations by the Brazilian Ministry of Health from 2007 to 2011, 110 cases of yellow fever were confirmed, ten of which were proven to have been in vaccinated individuals, including one case with two doses more than ten years before the death. There were 60% of deaths among the vaccinated cases. It was not possible to establish a pattern between vaccine failure and the time transpired since receiving the vaccine¹⁸.

During the yellow fever epidemic in Minas Gerais State in the year 2017, 16 cases of proven vaccine failures were identified with vaccination records, based on epidemiological links to epizootics or cases in humans and confirmatory tests of the disease. Median age was 21 years (7 to 86 years) and 68.7% were males. Median time since receiving the vaccine was 15 years (9 months to 78 years), and two vaccinated individuals evolved to death (12.5%). One individual received two doses of the vaccine¹⁹.

The need for a booster dose for adults is questioned, but especially for children, due to evidence of the need for long-term maintenance of protective antibodies, but the ideal number of doses remains inconclusive^{15,16}. Brazil's vaccination calendar adopted the second dose of the vaccine for children, but maintained the single dose starting at five years of age²⁰.

Measles vaccine

Measles is an acute febrile disease, highly contagious, transmitted by respiratory droplets. The etiological agent is an RNA virus belonging to genus *Morbillivirus* of the Paramyxoviridae family. The incubation period varies from 7 to 21 days, from date of exposure to the appearance of rash. The transmissibility period ranges from 4 to 6 days before the rash until 4 days after, and is greatest 2 days before until 2 days after onset of the rash. The clinical picture is characterized by fever greater than 38.5°C, cephalocaudal morbilliform maculopapular exanthema, dry cough (initially), coryza, non-purulent conjunctivitis, and Koplik spots (small white spots on the oral mucosa opposite the third molar, preceding the rash). Persistence of fever for more than 3 days after the appearance of rash is a warning sign and may indicate the appearance of complications such as respiratory infections, otitis, diarrhea and neurological diseases, when hospitalization may be necessary, mainly in malnourished and immunocompromised children²¹.

In some parts of the world, measles is still one of the principal causes of morbidity and mortality among children under five years of age. The disease spreads easily in areas with high population

density, with no predisposition according to race, sex, or age. Higher case-fatality is associated with unfavorable socioeconomic conditions. Measles virus is highly contagious, and in the presence of non-immunized persons, it can maintain endemic levels with seasonal behavior, producing recurrent epidemics²².

All persons are susceptible to the measles virus. Infants whose mothers have had measles or were vaccinated may have transient passive immunity from transplacental antibodies. An estimated 85% of children lose these maternal antibodies around 9 months of age²³. This immunity may last until the end of the first year of life, with potential interference in the response to vaccination in children under 12 months of age, which explains the fact that in basic immunization calendar, the vaccine is administered at 12 months to confer a protective immune response.

The endemic-epidemic behavior of measles depends basically on the relationship between the degree of immunity and the population's susceptibility, as well as circulation of the virus in the area. In places where vaccination coverage is not homogeneous and falls below 95%, the disease tends to behave endemically, with epidemics approximately every 2 to 3 years²⁴.

The development of an effective and efficacious live-attenuated virus vaccine against measles made the disease elimination possible. Measles caused by the wild-type virus produces lasting immunity, and the vaccine is also expected to produce the same kind of immunity. However, one unanswered question is the duration of immunity among vaccinated individuals²⁵.

The measles vaccine has the following presentations: (i) monovalent, used in the early 1970s and currently no longer recommended; (ii) combined with rubella (double viral vaccine); (iii) combined with mumps and rubella (triple viral vaccine); and (iv) combined with mumps, rubella, and varicella (quadruple viral vaccine). The immune response to the combined vaccine is similar to that of the vaccine administered alone. The U.S. Centers for Disease Control and Prevention (CDC) recommends administering the triple viral vaccine between 12 and 15 months and between 4 and 6 years of age^{21,22,24}. Brazil's National Immunization Program (PNI) recommends the triple viral vaccine at 12 months of age and the quadruple viral vaccine (measles, mumps, rubella, and varicella) at 15 months²².

A combined vaccine against measles, mumps, and rubella (MMR, or triple viral) was first used in Brazil in 1992 in the São Paulo State, and since 1996 it has been used in the routine of immunization rooms in Brazil. The triple viral vaccine used by the PNI is a mixed lyophilized preparation of attenuated viral strains for measles (Schwarz strain), mumps (RIT 4385 strain, derived from the Jeryl Lynn strain), and rubella (Wistar RA 27/3 strain). This vaccine's efficacy in measles control was demonstrated by the drop in incidence of the disease worldwide and especially in the Americas, since implementation of vaccination programs for the elimination of measles, started in Brazil in 1992²². The vaccine against Schwarz strain measles is an international reference, with good immunogenicity and low reactogenicity. Seroconversion is approximately 98%, 28 days after vaccination in seronegative individuals over 15 months of age with geometric mean titers (GMT) of 1:16, similar to that obtained with other strains²⁵.

Various seroprevalence studies have been performed in countries that follow cohorts vaccinated with one and two doses, demonstrating greater than 95% immunity. In Australia, a follow-up study of measles cases reported to the national surveillance service from 2006 to 2012 stratified cases according to vaccination history of one, two, and no doses of vaccine, matched by controls obtained from the immunization program's database. The age-stratified analysis found efficacy levels for the vaccine with a single triple viral dose (MMR) of 97.9% (95%CI: 95.8-98.9) in children 0 to 5 years, 98.6% (95%CI: 91.8-99.8) in 6 to 10 years of age, and 82.7% (95%CI: 58.9-92.7) in the age bracket 11 to 15 years. Among these groups, the vaccine's estimated efficacy ranged from 99.3% to 99.8% for two doses, suggesting that the vaccine was effective at the population level. Still, reports have shown that pockets of susceptible individuals may have contributed to the measles outbreaks, representing barriers to the sustainability of elimination²⁶.

Two European studies on follow-up of lasting immunity in vaccinated individuals using IgG serology (ELISA) and GMT showed seropositive rates of 98.5% three years after immunization and a 90% rate among 348 vaccinated children^{27,28}, respectively. In a seroprevalence study of blood donors (n = 174), all vaccinated previously with one or two doses of the triple viral vaccine, 163 individuals presented 93.7% (95%CI: 89.0-96.8) of anti-measles IgG with protective titers; this seropositive rate did not differ according to the number of vaccine doses received. Time from the last dose of the vac-

cine to collection of the blood sample for serology was approximately 20 years ($6,000.8 \pm 2,777$ days). Multivariate analysis showed that the serological status of anti-measles IgG antibodies was not associated with gender, age, number of vaccine doses, or time since last dose of vaccine, but that the GMT was correlated with the individual's age. Since GMT may decline progressively with the reduction in circulation of the virus, future studies are needed to answer the question of correlation between GMT and progression of the age of individuals vaccinated in childhood²⁸. Various follow-up studies of measles cases in the world have detected the disease in previously vaccinated individuals. About 10-11% of measles cases diagnosed and followed for 10 to 25 years occurred in individuals vaccinated with two doses^{29,30,31}. A measles outbreak in healthcare workers in the Netherlands confirmed that six cases occurred in those who had received two doses of the vaccine, and that all these workers had low neutralizing antibody titers before exposure, with an estimated mean efficacy of the measles vaccine for exposed workers of only 52%³². Another study on persistence of antibodies to measles, mumps, and rubella in a cohort of individuals vaccinated in childhood with two doses of the triple viral vaccine and 20-year follow-up of the cohort, with blood samples drawn at 1, 8, and 15 years after the second dose, showed that antibodies induced by vaccination decline significantly throughout life after the second dose. In this study to assess immunogenicity via ELISA, the authors call attention to the decline in protective measles antibodies during low incidence of the disease in Finland and the absence of natural boost in protective antibody titers gained by immunization. The authors showed that 15 years after the second dose of triple viral vaccine, the seropositive rates were 95% for measles, 74% for mumps, and 100% for rubella. However, the GMT for antibodies against the three viruses declined significantly compared to the titers acquired after the second dose of the triple viral vaccine, with a slower deceleration in the last seven years³³.

Various studies on the duration of immunity have attempted to explain the cause of susceptibility to the measles virus even after the administration of two doses of triple viral vaccine, based not only on the observation of low vaccination coverage. The susceptible population to measles increases when vaccination coverage falls below 95%, leaving pockets of susceptible individuals every year and decreasing herd immunity.

Varicella vaccine

Varicella, the disease caused by the varicella-zoster virus (VZV), is usually benign and self-limiting, but in immunocompromised patients it can present complications and even lead to death.

The attenuated varicella virus vaccine is considered effective in prevention of the disease, but cases can occur in vaccinated individuals, which is considered vaccine failure. Protection against moderate or severe varicella reaches 95% after the first dose. A second dose provides additional protection against any form of the disease. It is considered safe and effective, including for susceptible contacts, but cases of adverse events and vaccine failure have been reported.

Before varicella vaccination was established, the United States reported annual incidence of 4 million cases of the disease, with annual hospitalizations ranging from 11,000 to 15,500 and 100 to 150 deaths (0.4 to 0.6 per million inhabitants). The case-fatality rate in the pre-vaccination era was 2.6 per 10,000 cases in the United States⁸.

In Brazil, varicella vaccine was introduced in 2013 in the routine calendar of the PNI, combined with the triple viral vaccine at 15 months, for the prevention of moderate and severe varicella. A second dose started to be provided in January 2018 for children aged 4 to 6 years³⁴. Titers greater than or equal to 5U/mL (gp-ELISA) six weeks after vaccination is a correlate of protection³⁵.

The OKA strain was developed in 1974 in Japan and is still used in practically all the vaccine formulations. The available vaccines contain a mixture of variants of the OKA strain with similar sequences to the wild-type virus, which rarely impacts virulence in vaccinated individuals⁸.

According to a study in the United States, the first dose conferred 96% protection in vaccinated individuals, and the second dose applied 3 months later increased the seroconversion rate to 99.5%³⁶. Other studies have shown seroconversion rates from 80 to 100% after the first dose, so one dose of the vaccine may result in vaccine failure^{37,38,39}. The second dose, administered 3 months or years later, results in a boost in both humoral and cellular immunity.

Immunity persists for many years after vaccination, especially in regions where the varicella virus is still circulating. It is not clear if immunity is maintained for a prolonged time in places without circulation of the wild-type virus. According to a study in California, 11,000 children vaccinated with one dose were followed by active surveillance, and among those who developed varicella at more than 5 years after the vaccine, the odds of occurrence of moderate or severe disease were higher. Incidence of the disease was 1.6 cases per 1,000 persons/year in individuals that presented varicella within a year after vaccination, 9 cases per 1,000 persons/year in the case of vaccination within 5 years, and 58.2 cases per 1,000 persons/year if the vaccination was at least 9 years before. Thus, a single dose was not sufficient to confer protection from the disease ⁴⁰.

The effectiveness of the varicella vaccine has been assessed by various studies with different approaches. In studies that use clinical case definition, effectiveness is underestimated in relation to those requiring laboratory confirmation.

One dose of the vaccine is 81% effective against any clinical presentation and 95% effective against moderate and severe varicella. The second dose provides additional protection against any form of the disease. Between 15 and 20% of children vaccinated with one dose are susceptible to varicella, either because they did not respond or because they developed a partial response to the vaccine ⁴¹.

Both the wild-type virus and the vaccine virus can cause symptoms in vaccinated individuals ¹. The time between vaccination and the onset of clinical illness is used to differentiate between the illness caused by the vaccine virus (within 42 days after vaccination and consisting of a varicella-like rash from vaccine failure) and that caused by the wild-type virus, which occurs after this period ¹.

The wild-type virus can cause disease in vaccinated individuals and is normally milder in severity and duration when compared to varicella in unvaccinated individuals. Symptoms usually consist of maculopapular rash with few or no vesicles (less than 50 lesions), but in some cases they may be severe. Atypical presentations with mild symptoms and few lesions may also occur, and the differential diagnosis with varicella should be considered, even in vaccinated individuals, when clinically plausible ¹⁸.

A literature review published in 2017 retrieved 34 articles describing cases of vaccine failure with severe varicella, 25 of which described cases involving other organs besides the skin. These patients had received only one dose of the vaccine, and the clinical picture was similar to varicella in unvaccinated individuals. There were five deaths from varicella in vaccinated individuals in the United States from 1997 to 2013, and all the cases had received only one dose of the vaccine. According to publications with data on active post-registration surveillance, cases of severe or complicated varicella are more frequent in unvaccinated individuals. Only four cases of hospitalization were reported, without involving other organs, in individuals that received two doses. No reports were found of involvement of other organs besides the skin in cases of vaccine failure in individuals vaccinated with two doses, while in unvaccinated individuals, disseminated infections with the involvement of various systems were described. Countries that rely on programs of vaccination against the disease showed a decline in cases, hospitalizations, and deaths ⁴².

After introduction of the varicella vaccine in the United States, various varicella outbreaks were identified in daycare centers and schools, confirming the data showing incomplete seroconversion in some individuals after the first dose. Studies that allowed analysis of the vaccine's effectiveness in individuals exposed to the disease during outbreaks demonstrated a linear decline in immunity over time, which may result in increased lifetime susceptibility ⁴³. The influence on the odds of contracting the disease is still the object of discussion, as is the role of repeat exposure to the wild-type virus in stimulating immunity in post-vaccination periods. In the first years after introduction of the vaccine, children under 13 years showed an increase in mean IgG antibody titers, which may be explained by exposure to the wild-type virus that remained in circulation ³⁹.

In a study in the United States after introduction of varicella vaccination, 1,080 individuals developed a clinical picture consistent with disease in 10 years of surveillance, and the rate of moderate or severe cases was higher in the older age brackets both in vaccinated and unvaccinated individuals. Incidence of vaccine failure increased with time since vaccination. Thus, both incidence and severity of the disease increase as the years pass after vaccination. Another fact resulting from the vaccine's introduction in the vaccination calendar is that unvaccinated individuals may be susceptible when they reach adulthood due to decreased exposure to the virus ⁴⁰.

In Brazil, a study on the effectiveness of the single dose was published in 2018, with similar results to those from other countries. A prospective case-control study was conducted in São Paulo and Goiânia (Goiás State) in the two years following the vaccine's introduction in the country ³⁴. The effectiveness with one dose of the vaccine at 15 months was found to be 86% against any form of varicella and 93% against moderate or severe illness, which are comparable results to those of a meta-analysis of 42 studies on effectiveness in the first decade after introduction of the vaccine, with 81% cumulative effectiveness against any form and 98% against the severe form of varicella ⁴¹. Cases of vaccine failure in Brazil were attributed to primary failure, since the cases had been vaccinated on average only 9 months before ³⁴.

Mumps vaccine

Mumps, the disease caused by the mumps virus, is transmitted by direct contact with saliva or droplets from the upper airways. Transmission can occur from a few days before edema of the salivary glands until 5 days after. Other signs and symptoms may be associated, such as fever, headache, muscle pain, fatigue, and loss of appetite.

Complications are rare and occur mainly in adults, including orchitis, oophoritis and/or mastitis, pancreatitis, encephalitis, meningitis, and deafness.

Mumps can be prevented by vaccine, either in the monovalent presentation, combined with measles, with measles and rubella (triple viral vaccine), or with measles, rubella, and varicella (quadruple viral vaccine). Immune response to the combined vaccine is the same as to the single vaccine.

The CDC recommends administering the triple viral vaccine between 12 and 15 months, and between 4 and 6 years of age ⁴⁴. In Brazil, the PNI recommends the triple viral vaccine at 12 months of age and the quadruple viral vaccine at 15 months ⁴⁵.

There are more than 13 strains of the mumps virus in the vaccines developed in the world, such as Jeryl Lynn, RIT 4385 (derived from Jeryl Lynn), Urabe, Leningrad-Zagreb, S-12, and BBM-18 (derived from S-12), among others. Administration is subcutaneous.

Although antibody assays are frequently used as an indirect measure of immunity, the immune response to mumps vaccination provably involves both the humoral and the cellular immune response, but no definitive correlates of protection have been identified ⁴⁶.

A more detailed study revealed that the Jeryl Lynn and Rubini strains induced neutralizing and indirect fluorescent antibodies in the majority of vaccinated individuals, but based on the ELISA, Rubini induced low antibody titers. This result suggests that probably not only the surface antigens of the mumps virus are important for protection. Interestingly, passive immunization against mumps was not shown to be efficacious, again suggesting that other factors are important. The T-cell responses to the mumps vaccine were demonstrated, but their protective effect is unknown. The need to define a correlate for immunity to mumps still exists, due to recent outbreaks in young, previously vaccinated adults who have apparently lost their prior immunity ⁴⁷.

In studies of the combined vaccine with measles and rubella, using the RIT 4385 strain, seroconversion varied from 92 to 96%. In a study that assessed the immunogenicity of the triple viral vaccine made by the Immunological Technology Institute, Oswaldo Cruz Foundation (Bio-Manguinhos/Fiocruz), with the RIT 4385 mumps strain, in infants 12 months old, after one dose of the vaccine, mumps seroconversion was 84.5% (CI: 80.5-88.4), while for measles it was 95% (CI: 92.6-97.4) and rubella 96.3% (CI: 94.2-98.4). This result and those of other studies on the triple viral vaccine's immunogenicity indicate that the mumps component is less immunogenic compared to measles and rubella. After the quadruple viral vaccine, at 15 months of age, in the above-mentioned study, seroconversion to mumps was 97.8% (CI: 96.2-99.4), measles 97.8% (CI: 96.2-99.4), and rubella 98.8% (CI: 97.5-100.0) ⁴⁸.

A seroepidemiological study in Rio de Janeiro in 2008 and 2009 that assessed immunogenicity in 150 children vaccinated with the triple viral vaccine at 12 months, 30 days after vaccination showed 89.5% seroconversion for mumps (95%CI: 83.3-94.0). High antibody titers and seroconversion were reached after revaccination ⁴⁹.

Clinical studies conducted before licensing of vaccines in approximately 7,000 children found that one dose of the mumps vaccine is approximately 95% effective in prevention of disease. However,

estimates of the vaccine's effectiveness were lower in post-licensing studies. In the United States, efficacy of the mumps vaccine after one dose was estimated at 81% to 91% in primary and secondary schoolchildren and 64% to 76% in household and close contacts. Population and school-based studies in Europe and Canada reported comparable estimates for the vaccine's efficacy (49%-92%).

Few studies have assessed the efficacy of two doses of vaccine containing the mumps component. In the United States, assessment of outbreaks in populations with high coverage for two doses of the mumps vaccine demonstrated 80 to 92% effectiveness in the prevention of clinical disease.

In the 1988/1989 outbreak in secondary school students, the risk of mumps was five times higher in students that received one dose compared to those who received two doses. Population and school-based studies in Europe and Canada estimate that two doses of the vaccine containing mumps have an efficacy of 66% to 95%. Despite the relatively high efficacy of the vaccine with two doses, high vaccination coverage with two doses may not be sufficient to prevent all the outbreaks ⁴⁶.

A systematic review assessed 14 randomized clinical trials with one dose of the quadruple viral or triple viral vaccine with varicella; mumps seroconversion varied from 84.7 to 100% in those that received the quadruple viral vaccine and 91.5 to 100% for the triple viral plus the varicella vaccine separately. In 6 randomized studies with one dose of quadruple viral vaccine and triple viral, seroconversion varied from 71.3 to 97.2% in the quadruple group and from 72.8 to 98.6% in the triple viral group ⁵⁰.

Seroconversion after mumps vaccination does not differ between age brackets after 6 months of age and does not show any association with prematurity ⁴⁴.

Studies indicate that one dose of MMR vaccine can furnish persistent antibodies to mumps. Most persons (70%-99%) assessed approximately 10 years after initial vaccination had detectable antibodies to mumps. In addition, 70% of adults that were vaccinated in childhood presented T-lymphocyte immunity to mumps, compared to 80% of adults that acquired natural infection in childhood. In persons that received two doses, mumps antibodies were detected in most (74%-95%) 12 years after the second dose of the MMR vaccine, but the antibody titers declined over time ⁴⁶.

A study that assessed the decline in antibodies 12 years after the second dose of triple viral vaccine, administered at 4-6 years, showed that most participants were seropositive to the 3 antigens (96% measles, 88% rubella, and 79% mumps). Mumps antibodies declined rapidly, with wide variation, but no demographic or clinical factors were associated with this decline ⁵¹.

Data are limited on the use and efficacy of a third dose of the MMR vaccine to control mumps outbreaks ⁴⁶.

In 2017, the Advisory Committee on Immunization Practices (ACIP) recommended a third dose of an MMR vaccine for groups of persons that public health authorities have determined to be at increased risk of acquiring mumps because of an outbreak. All those that have been determined to belong to a group at increased risk of contracting mumps should receive a dose of MMR vaccine. This includes persons who have no vaccines records that prove they have received two doses of MMR vaccine in the past and persons who have evidence of presumed immunity, or who have not had a record of two doses of MMR vaccine. No additional dose is recommended for persons that have received three or more doses before the outbreak ⁵².

One study assessed the effectiveness of the third dose of MMR vaccine for controlling a mumps outbreak in university students. The study evaluated 20,496 students enrolled in the 2015/2016 school year. Mumps was diagnosed in 259 students. Before the outbreak, 98.1% of them had received at least two doses of MMR vaccine. During the outbreak, 4,783 received a third dose. The attack rate was lower in students that received three doses than in those who had received two doses (6.7 vs. 14.5 cases per 1,000 inhabitants, $p < 0.001$) ⁵³.

Conclusions

The analysis of immunogenicity and effectiveness studies on the measles, varicella, and mumps vaccines are unequivocal concerning the need to incorporate two doses into the basic vaccination calendars to control these diseases. Vaccine failures were identified with two doses and varied between the vaccines, characterizing probable secondary failure. These results emphasize the need to expand the

knowledge on the impact of the natural boost on maintenance of immunogenicity, especially in its absence in vaccinated populations. This scenario also requires closer surveillance of vaccine failures by the National Immunization Program.

For yellow fever vaccine, the current discussion focuses the ideal number of doses for individual protection. The WHO recommends a single lifetime dose. Despite the few reports in the literature on vaccine failures, immunogenicity studies show some degree of loss of protection over the years, especially in the pediatric age group. Although the existing vaccines are highly immunogenic, the persistence of protection over the years has not been determined, and there is no herd protection in this case, thus requiring each individual to be protected when entering regions with YFV circulation. Brazil opted for vaccination with two doses only for children under five years, but an evaluation is in order on the recommended number of doses for the other age brackets. We feel that given the data generated by the various yellow fever outbreaks in Brazil in recent years and mass vaccination of the population, an in-depth analysis of cases of vaccine failures by the PNI could add greater knowledge on the subject and back future decisions on the national vaccination calendar. At any rate, the ideal number of doses has not yet been established.

Vaccine failures exist and vary according to the vaccines and the number of doses, but in a scenario of eradication and control of diseases, epidemiological surveillance plays a key role, and joint work with vaccine manufacturing laboratories can add more knowledge concerning the multiple factors involved in vaccine failures and outbreaks, which can impact the credibility and success of vaccination.

Contributors

All the authors contributed to the article's conception, drafting, and revision and approval of the final version.

Additional informations

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Conflict of interest

The authors work at Bio-Manguinhos/Fiocruz, a laboratory which produces various vaccines for the Brazilian National Immunization Program.

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Resumo

A vacinação é uma das maiores intervenções em saúde pública pela segurança e efetividade, porém nem sempre vacinar significa imunizar. Inúmeros aspectos relacionados tanto ao indivíduo que recebe a vacina quanto à especificidade de cada imunobiológico administrado compõem o processo para a obtenção de uma adequada imunização, sendo essencial que sejam observados para não culminar em falhas vacinais. A análise dos estudos de imunogenicidade e efetividade para as vacinas sarampo, varicela e caxumba apontam para a necessidade de incorporação de duas doses aos calendários básicos de vacinação para o controle das referidas doenças. Estudos epidemiológicos que analisaram surtos dessas doenças identificaram casos em indivíduos que receberam duas doses da vacina, o que pode apontar provável falha secundária. Para a vacina febre amarela, a discussão atual reside no número de doses ideal para a proteção individual. A Organização Mundial da Saúde recomenda dose única para toda a vida. Apesar dos poucos relatos em literatura a respeito das falhas vacinais, os estudos de imunogenicidade demonstram perda de proteção ao longo dos anos, principalmente na faixa etária pediátrica. Num cenário atual de eliminação e controle de doenças, associado à diminuição da circulação de vírus selvagens, o papel da vigilância epidemiológica é fundamental para aprofundar o conhecimento a respeito dos múltiplos fatores envolvidos, que culminam com falhas vacinais e surgimento de surtos. A ocorrência de surtos de doenças imunopreveníveis impacta negativamente a credibilidade dos programas de imunização, acarretando baixas coberturas vacinais e interferindo no êxito da vacinação.

Imunização; Imunogenicidade da Vacina;
Soroconversão; Vacinas

Resumen

La vacunación es una de las mayores intervenciones en salud pública, por su seguridad y efectividad, sin embargo, no siempre vacunar significa inmunizar. Innumerables aspectos relacionados tanto con el individuo que recibe la vacuna, como con la especificidad de cada inmunobiológico administrado, componen el proceso para conseguir una adecuada inmunización, siendo esencial que sean observados para no acabar con fallos en las vacunas. El análisis de los estudios de inmunogenicidad y efectividad para las vacunas sarampión, varicela y parotiditis, apuntan hacia la necesidad de la incorporación de dos dosis a los calendarios básicos de vacunación para el control de las mencionadas enfermedades. Estudios epidemiológicos que analizaron brotes de esas enfermedades identificaron casos en individuos que recibieron dos dosis de la vacuna, lo que puede apuntar un probable fallo secundario. Para la vacuna de fiebre amarilla la discusión actual reside en el número de dosis ideal para protección individual. La Organización Mundial de la Salud recomienda una dosis única para toda la vida. A pesar de los pocos relatos en la literatura, respecto a los fallos en las vacunas, los estudios de inmunogenicidad demuestran una pérdida de protección a lo largo de los años, principalmente en la franja de etaria pediátrica. En un escenario actual de eliminación y control de enfermedades, asociado a la disminución de la circulación de virus salvajes, el papel de la vigilancia epidemiológica es fundamental para profundizar el conocimiento respecto a los múltiples factores implicados, que culminan con fallos en las vacunas y surgimiento de brotes. La ocurrencia de brotes de enfermedades inmunoprevenibles impacta negativamente en la credibilidad de los programas de inmunización, acarreando bajas coberturas de vacunación e interfiriendo en el éxito de la vacunación.

Imunización; Inmunogenicidad Vacunal;
Seroconversión; Vacunas

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