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ORIGINAL ARTICLE

## Measles and new perspectives: clinical, epidemiological and social aspects

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### Abstract

**Objective:** Bring together data about measles presenting since the clinical conditions provoked by the disease until instructions related to its vaccine, and bring a both national and international panorama about several aspects related to measles. **Methods:** Non-systematic national and international literature review, relating scientific articles found through the following search descriptors: measles; vaccine; pneumonia; diarrhea; recommendations. **Results:** There was an increase in the number of records of this virus evolved over the last years probably by the emergence of a possible facilitator, which was the anti-vaccine movement, although immunization is mandatory in the pediatric age group. Clinical suspicion and laboratory confirmation, whenever available, are important for the prevention of complications inherent of the disease. In addition, in view of the pandemic currently faced by the new coronavirus, the prevention of infection by the measles virus can't be overlooked, with the authorities playing an important role in tackling the two diseases.

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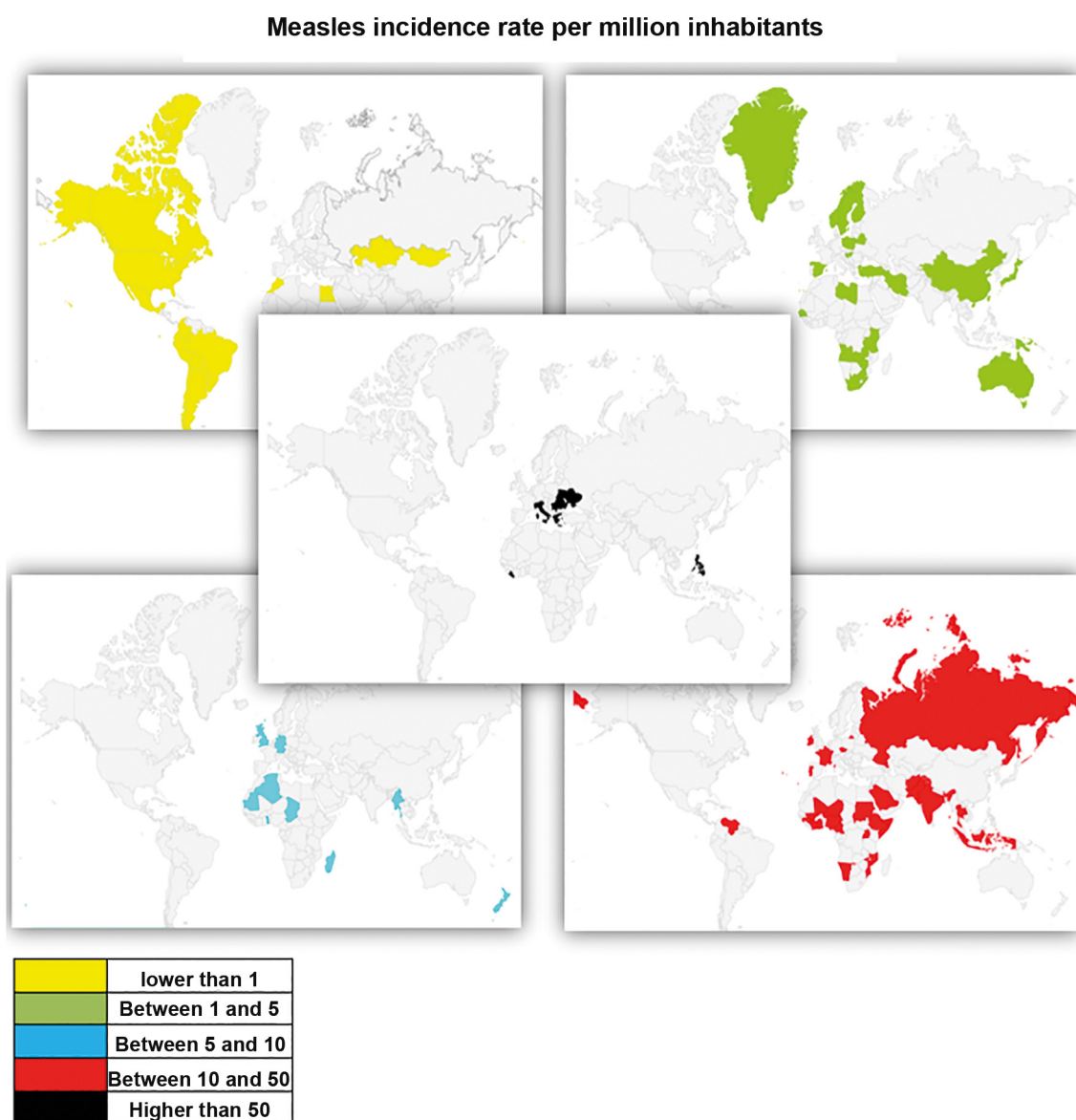


## INTRODUCTION

In 2019, Brazil lost the Clearance Certificate granted by the Pan American Health Organization (PAHO), after registering more than 10,000 cases in the previous year, mainly concentrated in the states of Roraima and Amazonas<sup>1</sup>. Also in 2019, until November, 13,489 cases of the disease were recorded - including 15 deaths, concentrated in the state of São Paulo, according to data from the Ministry of Health<sup>2</sup>. Before that, the last measles outbreaks had been recorded in 2013 and 2014 in Pernambuco and Ceará, respectively.

Vis-à-vis the world scenario, on the five continents, the cities with the lowest vaccination rates suffered the most. The most efficient way to prevent measles is the vaccine, which is available free of charge at public health centers in Brazil. In 2018 alone, 142,000 measles deaths were recorded worldwide<sup>3</sup>, according to data from the World Health Organization (WHO)<sup>4</sup> [figure 1].

The importance of measles as one of the metrics of reducing infant mortality, according to the Millennium Summit, held in 2000, promoted by the United Nations (UN) was remarkable. Indicator 15 of Goal 4 of the Millennium Development Goals aimed to expand measles



**Figure 1.** Global measles situation, 2018 SOURCE: Carvalho AP et al. Atualização sobre sarampo, 2018.<sup>4</sup>

vaccination coverage in 1-year-old children. As a result of this strategy, there was a 78% reduction in measles deaths worldwide, considered one of the main advances among all the Millennium Development Goals<sup>5</sup>.

### The disease

Measles is a highly contagious disease caused by a virus belonging to the Morbillivirus group that affects the entire world. The main group involved are children under 5 years of age. Transmission occurs by air, through aerosols, spread by coughing, sneezing, talking or even breathing close to healthy people<sup>6</sup>. Approximately 90% of susceptible individuals nearby can be infected. Its clinical picture involves different types of manifestations at different times. In the acute stage, the patient may present the following symptoms<sup>4</sup>:

- High fever, greater than or equal to 38.5°C;
- Generalized maculopapular rash;
- Cough;
- Runny nose;
- Conjunctivitis;
- Intense malaise;
- *Koplik's spots* - usually precede the rash and are characterized by small whitish-blue spots on the buccal mucosa, on the inner lining of the cheeks, most commonly in the region opposite the molar teeth<sup>7</sup> [figure 2].



**Figure 2.** Koplik spots. Source: screen print – Available on: <https://www.fetalmed.net/surto-de-sarampo-que-as-gestantes-e-tentantes-precisam-saber/manchas-de-koplik/><sup>7</sup>

The rash usually occurs 14 days after exposure to the virus, and contagion tends to happen 4 or 5 days before to 4 days after the appearance of the skin lesions. The incubation period lasts from 6 to 21 days - 13 days on average. The manifestations can be divided into 3 specific periods<sup>8</sup>:

a) **Infection period:** with an average duration of 3 days, the prodromal period begins, characterized by fever, productive cough, runny nose, anorexia, conjunctivitis with photophobia and tearing (occasionally, a marginal cross-sectional line may be seen in the lower palpebral conjunctiva – Stimson's line). At the end of this period, Koplik's spots can be seen, which disappear from 24 to 48 hours after the rash onset. On the 4th day, the maculopapular skin rash appears red, starting in the retroauricular region, with a descending character (craniocaudal projection), which, in 3 days, affects the entire body in a centripetal distribution without sparing the palmoplantar region, concomitantly with the worsening of the prostration.

b) **Toxemia:** viral or bacterial superinfection is facilitated by the low host resistance against the disease. Complications are common, especially in children up to 2 years of age, especially those malnourished, and young adults.

c) **Remission:** decrease in symptoms with decline in fever. The rash becomes darkened, greyish-brown, and furfuraceous scaling may appear, with a flour-like appearance. The temperature drops if there is no secondary infection and the rash disappears. Cough may persist for 1 to 2 weeks.

After illness, immunity against measles seems to be established for life, although there are reports of reinfection.

Complications<sup>4,8</sup> possibly resulting from measles in children are:

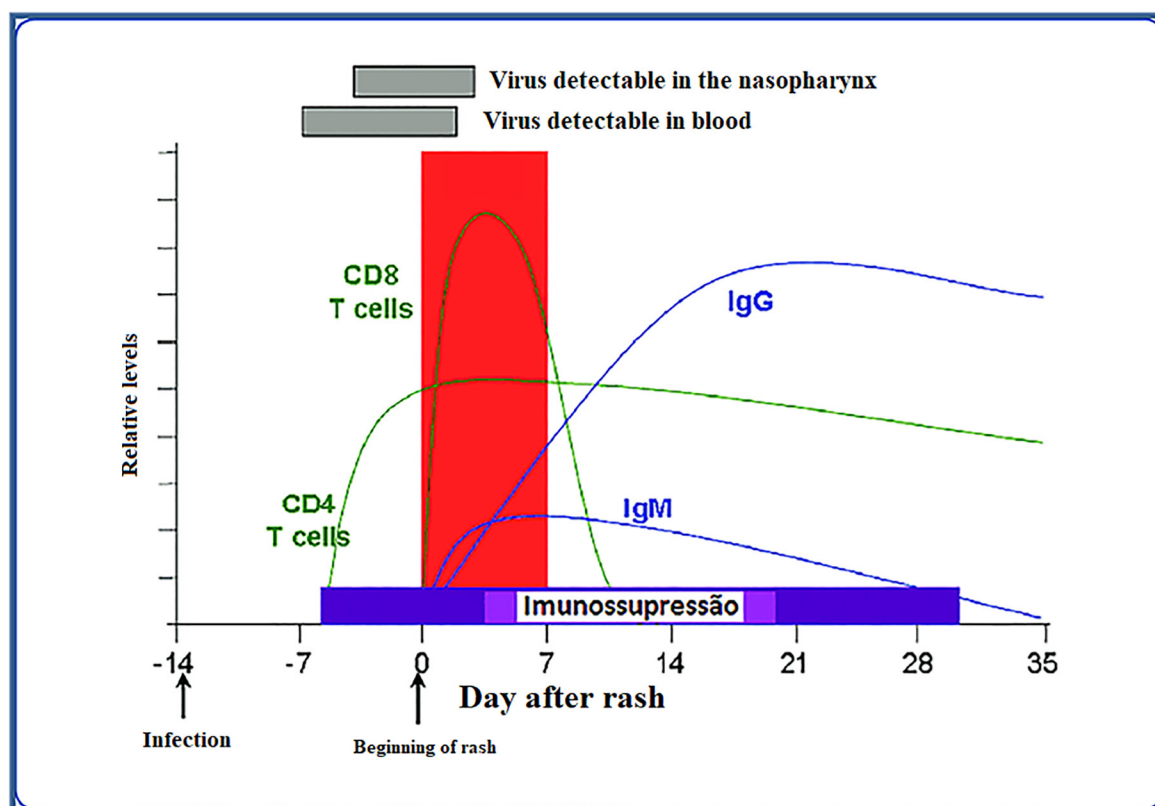
- Pneumonia (1/20 children can develop it, being the most common cause of death from measles in young children – 6% of cases);
- Acute otitis media (this is the most frequent complication and can result in permanent hearing loss);
- Acute encephalitis (1/1000 may develop it, and 10% may die – it can occur even after the 20th day of the disease);
- Death (1 to 3 in every 1000 sick children may die as a result of complications from the disease);
- Respiratory infections such as laryngotracheobronchitis;
- Gastroenteritis;
- Diarrhea, present in 8% of cases;
- Subacute sclerosing panencephalitis – SASP (rare, fatal neurodegenerative disease that can develop 7 to 10 years after measles infection, characterized by intellectual, cognitive and behavioral deterioration, seizures, myoclonus and progresses to spastic decerebration and death – the risk is of about 4 to 11 per 100,000 measles cases).

## Laboratorial diagnosis

**Laboratorial diagnosis** helps confirm the disease<sup>4</sup>. It consists of the detection of immunoglobulins of the IgM class in the blood in the acute phase of the disease, from the first day to 1 month after the rash. In regions with a high prevalence of the virus, with low vaccination coverage, the WHO establishes the serum concentration of antibodies of this class as a diagnostic standard. IgG class antibodies may occasionally appear at this stage and remain detectable throughout life [figure 3]. The following techniques can be used:

- Enzyme immunoassay (ELISA): IgM and IgG levels – this is used by the Brazilian public laboratory network;
- Hemagglutination Inhibition (HI): measurement of total immunoglobulins;
- Immunofluorescence (IF): dosage of both classes;
- Plaque neutralization: detects specific antibodies;
- RT-PCR: virus identification in any organic material.

All these tests have sensitivity and specificity between 85 and 98%. Samples collected within the first 28 days after the rash are considered timely. The IgM test with a reactive or inconclusive result must always be notified immediately for the continuity of the investigation and collection of the second blood sample, which is mandatory for the final classification of cases. The second collection must be carried out between 20 and 25 days after the first. For complete epidemiological surveillance, it is necessary to collect clinical specimens for viral identification by genotyping, differentiating an autochthonous case from an imported case or one related to the vaccine virus. This can be identified in urine, nasopharyngeal secretions, blood, cerebrospinal fluid or tissues by the PCR technique. These samples should be collected up to the 5th day after the rash, preferably the first 3 days. Molecular analysis is important in order to map the virus transmission pathways that possibly help to link cases or not and may suggest a source for imported cases. Furthermore, it is the only way to distinguish between infection caused by the wild-type virus itself and a lesion caused by a recent measles vaccination<sup>4</sup>.



**Figure 3.** Laboratorial Diagnosis Source: Carvalho AP et al. Atualização sobre sarampo, 2018.<sup>4</sup>

## Vaccination

The best and most efficient way to prevent measles is through vaccination. The criteria for vaccine indication<sup>9</sup> are periodically reviewed by the Ministry of Health, which considers clinical characteristics, age, the fact of having had measles before, occurrence of outbreaks, among others. Currently, 2 doses of the vaccine are recommended. The first dose is given at 12 months of age and the second at 15 months of age, as shown in the official vaccination schedule [figure 4]. When the two recommended doses are used, the effectiveness of protection against measles exceeds 99%<sup>10</sup>. There are scientific discussions about recommending extra doses for certain groups of people, such as infants aged 6 months to 1 year traveling to risky areas, or young people aged 15 to 29 years due to a recent outbreak. There are 3 types of vaccine against the measles virus, they are: double viral (protection against measles and rubella); MMR (measles, mumps and rubella); viral tetra (measles, mumps, rubella and chickenpox).

Those who have a record of vaccination are considered regularly vaccinated, otherwise, it is recommended to apply one or two doses depending on the situation, spaced for a minimum period of one month. People with a confirmed history of the disease do not need to be vaccinated. Due to the inhomogeneity of vaccination coverage among children under 5 years of age, the group with the most reported cases, the public vaccination campaign takes priority for this public.

The possible adverse effects<sup>4,8</sup> involving the vaccine are:

- Local reactions (burning, redness, pain, and lump formation may be present s in less than 0.1% of vaccinated people);
- High fever (higher than 39.5°C, appears 5 to 12 days after vaccination, occurring in 5 to 15% of those vaccinated);
- Febrile seizure without serious consequences;

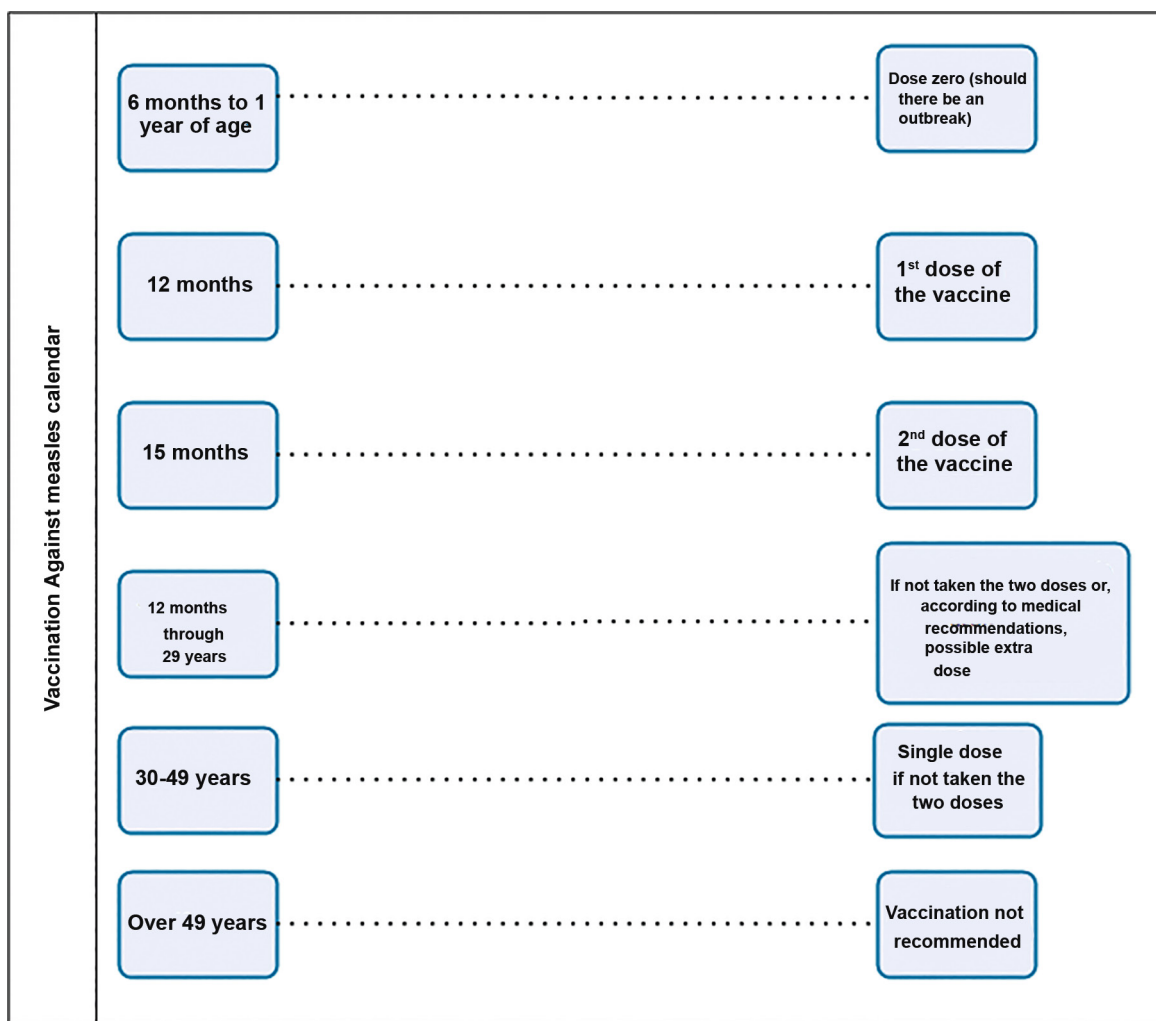


Figure 4. Vaccination calendar. Source: Ministry of Health (MS). Health surveillance guide – Measles. 3<sup>rd</sup> edition. 2019.

- Headache, irritability, low-grade fever, tearing, redness of the eyes and runny nose affect 0.5 to 4% of vaccinated persons;
- Red spots on the body for 2 days in around 5% of those vaccinated;
- Lymphadenopathy in less than 1% of vaccinees after 1 to 3 weeks of vaccination;
- Meningitis usually benign;
- Encephalitis (1 in every 1 million to 2.5 million vaccinated with the first dose);
- Hemorrhagic manifestations – thrombocytopenic purpura;
- Joint pain or arthritis;
- Inflammation of the parotid glands;
- Anaphylaxis;
- Rash.

The chance of a possible adverse reaction to the vaccine is substantially lower than the possibility of it progressing to pneumonia or measles encephalitis, for example.

It is worth noting that individuals who have fever and rash are not considered contagious. Furthermore, the chance of adverse effects with the second dose is significantly lower than in the first.

Contraindications<sup>4,8</sup> of the vaccine involve suspected cases of measles, pregnant women, infants under 6 months of age, immunosuppressed patients, people with a previous history of anaphylactic reaction. HIV-exposed or infected children in categories N, A and B with CD4  $\geq$  15% can be vaccinated as directed by their physician. Those who have severe symptoms and/or severe immunosuppression (CD4 < 15% for children under 5 years and CD4 < 200 cells/mm<sup>3</sup> for people over 5 years) should not be vaccinated. Adults living with HIV/AIDS with a CD4 count of between 200 and 350 should receive advice from their doctor, while those with a CD4 count of less than 200 should not be vaccinated. People undergoing cancer chemotherapy should only be vaccinated 3 months after stopping the treatment. Those medicated with immunosuppressive drugs need to receive guidance from their doctor, who will assess the risk of treatment discontinuation and propose a minimum interval. Bone marrow transplant recipients can only be vaccinated 12 to 24 months after the procedure. Vaccinations should be delayed for 3 to 11 months in patients who received antibody preparations or blood products, as a result of the potential interference of these products in the vaccine response. They should also be delayed for 6 months after treatment in patients undergoing therapy with biologics such as anti-B-cell immunoglobulins.

## Treatment

There is no specific treatment for measles. Although ribavirin has demonstrated in vitro activity against measles virus, there are no controlled studies to demonstrate the benefit of its use in humans<sup>11</sup>. Some healthcare professionals advocate its use in children younger than 6 months with

measles pneumonia, patients older than 12 months with pneumonia when pulmonary ventilation support is needed, and extremely immunosuppressed patients<sup>11</sup>. In such cases, the dose of ribavirin varies from 15 to 20mg/kg per day orally in 2 divided doses for 5 or 7 days. Another widely discussed factor is the relationship of vitamin A with the disease. The deficiency of this compound contributes to a delay in recovery and favors a high rate of complications. The use of retinol in children is associated with a decrease in morbidity and mortality. It should be administered once a day on 2 consecutive days, at the following dosages<sup>11</sup>:

- In infants under 6 months of age, 50000 IU orally;
- For infants 6 to 11 months of age, 100,000 IU orally;
- For children 12 months of age and older, 200,000 IU orally.

In some cases, a third dose should be given 4 to 6 weeks later for children with retinol deficiency.

## Notification

Notification is essential in order to maintain measles elimination through sensitive, active and timely epidemiological surveillance, ensuring relevant control measures. Measles is a “must notify” disease, which must be carried out following two criteria that vary according to the clinical situation, they are:

- Suspected case: any patient, regardless of age and vaccination status, who has fever and maculopapular rash accompanied by one or more of symptoms such as cough and/or runny nose and/or conjunctivitis, or any individual who has recently traveled to risk areas in the last 30 days, or from contact with people who traveled in the same period.
- Confirmed case: any suspected case confirmed as a measles case according to at least one of the following criteria:
  - o Laboratory criteria: suspected cases whose laboratory test had a reagent or positive result for IgM and the epidemiological clinical analysis indicative of confirmation.
  - o Epidemiological link: suspected cases that have had contact with one or more laboratory-confirmed measles cases, and that showed the first signs of the disease between 7 and 18 days after exposure.

Suspected measles cases must be notified to the Municipal Health Department (MHD) within the first 24 hours, followed by blood collection for serology and material for viral isolation, identification and investigation, which must occur

within 48 hours so that vaccination blocking can be carried out within 72 hours.

Immunosuppressed persons, susceptible pregnant women and infants under six months of age in contact with a measles case should receive intramuscular immunoglobulin (IMIG) or intravenously (IVIG) within the first six days after contact.

Hospitalization<sup>4</sup> is indicated in cases of children under six months of age, pregnant women, severely malnourished patients, immunodeficient patients or people who present at least one of the following clinical signs:

- Dehydration;
- Persistent vomiting;
- Significant diarrhea;
- Inability to ingest liquids and food;
- Presence of a large number of ulcers in the oral cavity;
- Respiratory discomfort;
- Stridor;
- Pneumonia;
- Seizure;
- Motor deficit;
- Sensory alteration.

## Measles today

Some topics are little discussed when referring to measles, and deserve attention in order to promote possible prevention measures against the disease or to clarify and establish connections between several other diseases.

Pneumonia and diarrhea arise both as complications and as secondary infections from measles, appearing in 10 to 40% of cases<sup>12</sup>.

A study was published in Nigeria, Pakistan, India, Ethiopia and the Democratic Republic of Congo in 2017 on the effect of measles vaccine on acute respiratory infections (ARI) and diarrhea in children aged 12 to 59 months. Vaccinated children were less prone to ARI than unvaccinated children in India and Pakistan. In the other countries, with the exception of Ethiopia, vaccinated children had a lower risk of getting diarrhea compared to unimmunized children. Thus, there was a 15-30% reduction in ARI cases in India and Pakistan and a 12-22% reduction in diarrhea in children who received the

measles vaccine. As a result of this study, the World Health Organization (WHO) and UNICEF introduced the measles vaccine as a preventive measure in the Global Action Plan for Pneumonia and Diarrhea (GAPPD).

Data from the Ministry of Health for 2019 show that measles vaccination coverage in children up to 1 year old was 99.4%<sup>14</sup>. Only 8 states besides the Federal District were below the predicted immunization target of 95%. Until September 2019, only 57.19% of children up to 1 year of age, a highly affected and high-risk group, had received the vaccine.

Retrospectively, it is possible to perceive a pattern of carelessness of the population in relation to the calendar recommended by the PNI. As there was little attention given to measles in 2013, the population seemed to reduce their concern and this opened room for the resurgence of the disease<sup>15</sup>. Faced with the occurrence of a new outbreak between 2013 and 2014, the population returned to protect itself and the coverage rate increased significantly, even though it still remained below expectations, as shown in Figure 5.

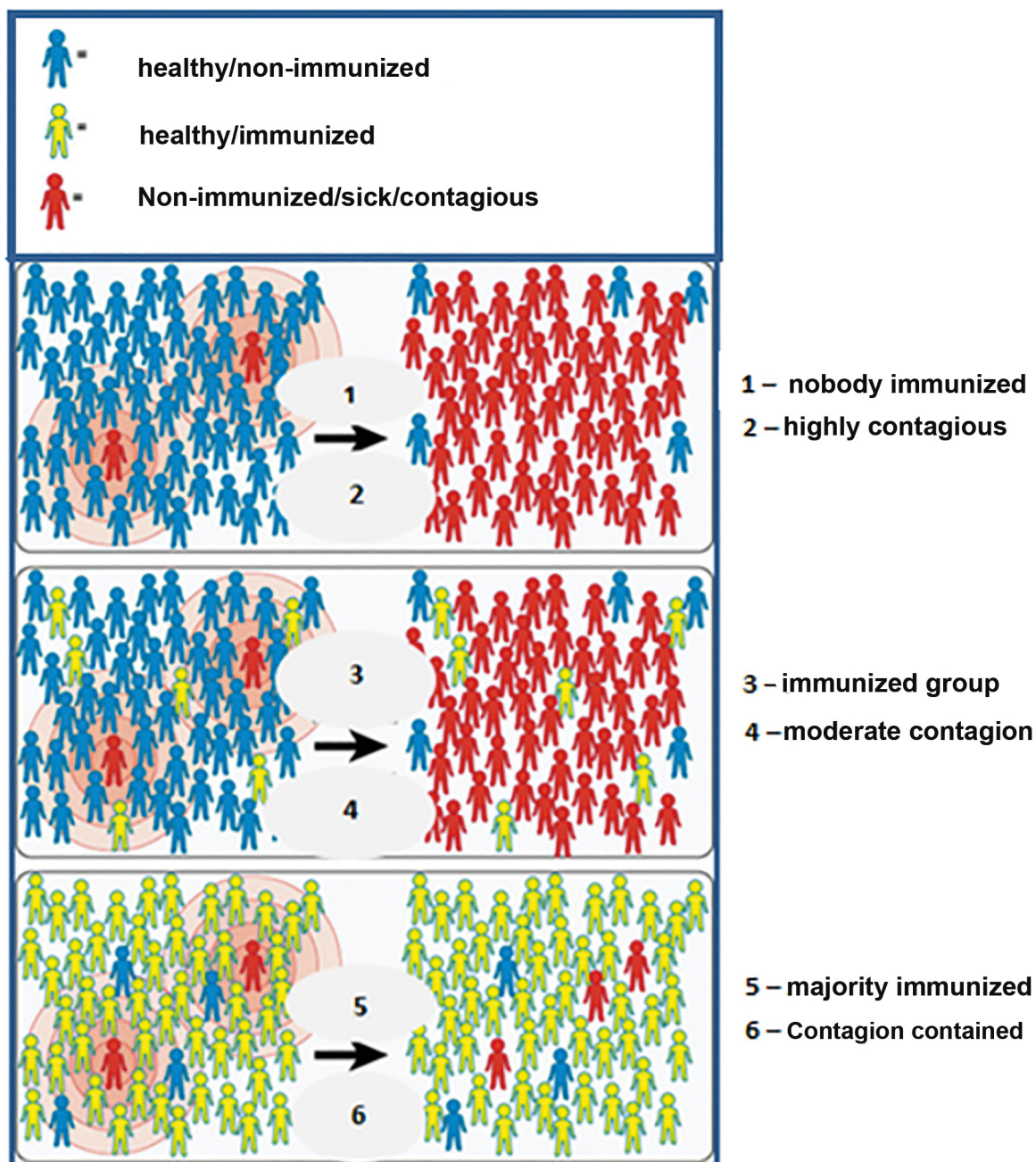
In recent years, the spread of the famous fake news was another factor that contributed to impeding progress against the eradication of various viruses, not just measles<sup>15,16</sup>. The anti-vaccination movement has recently become known and has gained more and more supporters. However, despite the scientific evidence that clearly supports the need for awareness of vaccination, attacking those who are part of the opposing movement can have the unwelcome effect of increasingly dividing both sides.

The vaccine, according to the American writer Tara Haelle<sup>17</sup>, assumes two very important roles: inside the body and outside it. In the first, the body creates antibodies that fight the virus if it arrives before it even causes an infection. The second refers to reducing the ability of the virus to spread and circulate, which depends on social solidarity and compassion. This movement is known as herd immunity [figure 6]. This concept is more than relevant since in the case of measles, one person can infect 12 to 18 other people. In addition, thinking about solidarity is essential when we remember those who cannot get vaccinated, even if they want to, such as children under 6 months, immunosuppressed people, pregnant women and cancer patients.

The measles virus deserves redoubled concern in the face of the current world scenario of facing the new

Biologics	2012	2013	2014	2015	2016
D1 viral triple (1 year)	99.5	107.46	112.8	96.07	95.35
D2 Virus triple (1 year)	...	68.87	92.88	79.94	76.71
Source: CGPNI (data taken from <a href="http://pni.datasus.gov.br">http://pni.datasus.gov.br</a> ). in red we see below-the-goal coverage					

**Figure 5.** Vaccine coverage (VC) by vaccine type in children 1 year and younger, Brazil, 2012 through 2016 Source: Cruz A. A queda da imunização no Brasil. Rev Consensus, 25ª edição. 2017.



**Figure 6.** Group immunity. SOURCE: Screen print. Available on: <https://www.flickr.com/photos/niaid/5149339976><sup>19</sup>

coronavirus (Covid19)<sup>18</sup>. With attention focused exclusively on Covid19, the measles vaccination campaign has run out of steam, but it should never be neglected, as its contagion and lethality are significant and, therefore, it should receive assistance in parallel with the current pandemic.

## CONCLUSION

In this paper, the evolution of the disease over the last few years was analyzed from both a national and international perspective. Locations where the disease behaves endemically

were pointed out, in addition to the main risk groups that deserve greater attention from healthcare professionals. In addition, this review demonstrated the social aspect linked to vaccination, such as the difficulty in facing the anti-vaccination movement. It is also worth mentioning the impact of vaccination on cases of pneumonia and diarrhea, common manifestations of the disease with a great contribution to the number of deaths associated with this virus. Measles vaccine coverage has been decreasing and needs to return to the 95% established as ideal, in an attempt to contain the accelerated pace of infection in recent years, especially in times of a Covid19 pandemic.

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