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Editorial

Measles in Spain at the elimination phase: The enemy knocking on the door

El sarampión en España en la etapa de su eliminación: el enemigo a las puertas

Measles is a highly transmissible immune-preventable infection caused by the genus *Morbillivirus*, family *Paramyxoviridae*. Other viruses belonging to this genus that affect mammals include the rinderpest virus (RPV), the peste-des-petites-ruminants virus (PPRV), the canine distemper virus (CDV) and the phocine distemper virus (PDV).[1] Measles virus has several structural proteins, among them, the envelope fusion protein (F) and the attachment protein (H) define the existence of a single serotype.[2] At the molecular level, the wild type viral genotype has been divided into eight clades (designated as A–H) with 24 different genotypes.[2,3] A new genotype is considered when the nucleotide sequence encoding the nuclear (N) and H proteins differs from a previous defined genotype at a certain level.[4] Since 1990 nineteen genotypes have been described in human infections (A, B2, B3, C1, C2, D2, D3, D4, D5, D6, D7, D8, D9, D10, D11, G2, G3, H1 and H2).[3] However, from 2005 to 2019 twenty genotypes were eliminated after immunization campaigns.[5] In 2019 only the circulation of genotypes B3, D4, D8, and H1 was reported.[5]

Cattle were domesticated approximately 10,000 years ago in the Euphrates Valley. This historical milestone propitiated the close contact between livestock and humans, what facilitated the trans-species jump of the bovine *Morbillivirus*. Later, the human measles virus required a critical community size of around 300,000 people in order to become endemic and gain stable transmission. It has been suggested that among the first cities large enough to allow measles circulation would be the ancient Sumerian capital of Ur, and later other biblical towns as Babylon.[6]

Measles spreads by aerosolized particles and respiratory droplets. Clinically is characterised by the maculopapular rash accompanied by the marker triad of fever, cough, coryza and/or conjunctivitis. The incubation is about twelve-thirteen days after the exposition. Patients are suspected to be contagious between four days before to four days after the appearance of the rash.

The incidence of this disease is today affected by factors related to a globalized society that facilitates the movement of infected people from developing countries, and by the decrease in the rate of immunization and herd immunity in developed countries, partially as a consequence of movements against vaccination that generate pools of susceptible individuals in places with high population density. The control phase of an infectious agent as measles is directed to restrict virus circulation in the population. Measles is part of global immunization programs since 1974, when the 27th World Health Assembly established the Expanded Program on Immunization.[7] The current Plan of the World Health Organization (WHO) for the elimination of measles and rubella in Spain was set up in 2001. In 2012, the WHO Regional Office for Europe established the Regional Verification Commission (RVC) to confirm the elimination of measles at the regional level.[8] The WHO established measles elimination as a goal for 2020 but, unfortunately, this objective was not reached.[7] Hence, the elimination goals are now part of the Measles and Rubella Strategic Framework (MRSF) 2021–2030.[9] The interruption of the dissemination of measles requires the absence of endemic transmission. The evidence of the elimination of endemic measles is the demonstration of interruption of transmission for at least thirty-six consecutive months.[10] In the year 2017 the WHO declared the elimination of measles in Spain, assuming that isolated cases and outbreaks were due to imported sources. For several years in the WHO European Region, we have witnessed a sort of "honeymoon" towards the elimination of measles, with a drastic decline in the number of cases. Although in 2020 the 9th Meeting of the European RVC concluded that more than half of the states (including Spain) provided evidence for the elimination of measles, some countries (including France, Georgia, Germany, Italy, Kazakhstan, Kyrgyzstan, Poland, Romania, Russian Federation, Serbia, Turkey and Ukraine) were considered endemic for this infection.[10] Thus, countries like Spain, that has achieved currently the elimination level, are at continuous risk of importing cases from other parts of the World, including neighboring nations in the same continent. Although classically this infection was considered as a "paediatric exanthematic disease", this concept can no longer be maintained as susceptible adults are frequently involved in transmission chains. In the outbreak described in this issue of Enfermedades Infecciosas y Microbiología Clínica by González-Praetorius and colleagues[11] the cases initially corresponded to young adults and subsequently affected non- or incompletely vaccinated children. In Spain, most children over the age of four years are fully vaccinated; however, at the post-elimination phase, there is a growing number of cases of measles among vaccinated individuals. Nowadays, measles is usually an imported infection from endemic

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regions disseminated in our country by susceptible autochthonous adults. These adults belong to cohorts born in the beginning of the Spanish national vaccine campaigns (mainly between the decades of 70s and 90s), when the coverage could be suboptimal and the circulation of the virus dropped, limiting the natural immunization. Obviously, when the infection reaches an unvaccinated child (i.e., babies under twelve months old) outbreaks can occur in day care centres. In the outbreak described by González-Praetorius and colleagues[11] the virus spreaded from healthcare personnel. During outbreaks, non-immunized healthcare workers are a significant risk group.[12]

In the measles elimination stage, the exhaustive investigation of every suspected case is mandatory. The diagnosis of measles is based on specific serological tests detecting IgM and IgG, and on viral RNA detection by reverse transcriptase polymerase chain reaction (RT-PCR) performed in pharyngeal exudates and/or urine samples.[11] Viral RNA is present at the early phases of the infection, however, IgM response can be delayed up to several days after the onset of rash. The diagnosis can be more problematic in previously vaccinated people presenting milder symptoms. In these cases, IgM may be undetectable by lack of production and/or interference due to high levels of IgG (typical of a secondary immune response). Therefore, the predictive value of a positive IgM for an acute infection is very low in areas with low incidence of measles.[13] In these situations, other alternative serological methods like IgG avidity testing can be relatively useful. The RT-PCR for viral RNA detection is currently the most widely used laboratory technique. In addition, as shown in the outbreak reported by González-Praetorius et al.,[11] RT-PCR methods allow the performance of genotyping and molecular epidemiology studies. After an outbreak, to ensure that the transmission has definitively ended, two incubation periods (estimated in forty-six days) are required without any new cases since the last confirmed positive.[13]

Measles is considered one of the most contagious of all vaccine-preventable diseases. The basic reproductive number (R_0) estimates the transmissibility of an infectious disease, being the average number of secondary cases arising from one index case in a totally susceptible population. The effective basic reproductive number (R) is used when part of the population is immunized. High R indicates high transmissibility, and stopping the transmission of virus can be achieved when the R is ≤ 1.[14] Population density and rural or urban distribution of the communities seems to be a basic covariant for measles transmission. Herd immunity, defined as the indirect protection of susceptible individuals conferred by the "barrier" of immunized individuals that interferes with the transmission of the infection in the population, is critical for elimination.[15] Herd immunity level (h_C) is defined classically as $h_C = 1 - 1/R_0$.[16] Measles has a much higher R_0 than that of other very contagious viruses, for example SARS-CoV-2. Given that the R_0 for measles is estimated between 6 and 13, elevated vaccination coverages are required to prevent outbreaks, so two doses of vaccine are needed in at least 97% of the population.[15] However, the waning of immunity, directly time-related after the last dose of vaccine, can contribute to the occurrence of outbreaks in populations with elevated levels of vaccine inoculation. The waning of immunity becomes more relevant in scenarios of measles elimination, due to the absence of natural boosters, since there is little circulation of the wild virus. The aim of mass immunization interventions is achieving high coverage rates to establish herd immunity in the population. The current schedule for routine immunization of children in Spain includes the first dose of the measles-rubella-mumps vaccine at 12 months of age, with a second dose administered at 3–4 years. This second dose could be administered in a tetra-viral compound by adding the varicella-zoster virus vaccine component. In vaccinated populations, outbreaks can occur if coverage decreases, when pockets of susceptible individuals grow in sufficient number.

Measles vaccination and the target for herd immunity are based on two premises: first, vaccine is assumed as protective as the wild strain and, second, the virus remains with a single serotype.[4] The level of protection after the administration of two doses of measles vaccine it is generally reported to be excellent (95% or higher), however there is a variation in the reports provided by different studies.[4] The effectiveness of the vaccine decreases over time. In this way, neither the documented administration of two doses of vaccine, nor a positive measles serology can be considered definitive evidence of immunity.[4] There are two recognized mechanisms of vaccine failure: primary failure, indicating absence of humoral response after vaccination, and secondary failure, when specific IgG response is present but is not fully protective. When a natural infection occurs in a vaccinated subject experimenting primary failure, the typical serological response is produced, with an initial elevation of IgM followed by an elevation of IgG. In cases of secondary vaccine failure, there is usually a lack of production of IgM and a secondary immune response characterized by the generation of high-avidity specific IgG.[4] All vaccine strains belong to the viral genotype A.[3] It has been suggested that, since the vaccine strains were isolated more than half a century ago, some epitope changes may have occurred over time, allowing selection of measles strains that could escape the vaccine.[4] However, this hypothesis has not been proven. The fact that the circulation of most genotypes has been reduced over the last years[5] does not support this idea.

In the last Spanish seroprevalence survey study, carried out between May 2017 and May 2018, the seroprevalence of IgG was below 95% in the age range of 10–15 years to 30–39 years (corresponding to cohorts born between 1978 to 2002). By age groups, the percentages of positive measles IgG were 94.5% in 10–14 years old children, 90.2% in 15–19 years old youngsters, 86.9% in 20–29 years old adults, and 91.5% in the 30–39 years old range.[17] This phenomenon can be explained by a possible waning of immunity after the second dose of vaccine without natural booster by lack of wild circulating strains. These low levels of measles IgG alerts of possible outbreaks and recirculation of the virus in our country in the future. Among immigrants, specifically these attended during 2018–2019 in Madrid, the seroprevalence of measles was also low (88%).[18] African immigrants had higher seroprevalence rates (>90%) than persons coming from other parts of the world, like Latin America (<85%).[18] This fact could be related to the natural circulation of the virus in Africa and an irregular measles vaccination in Latin America.

In addition to the economic conditioning factors that are a big problem in developing countries, "vaccine hesitancy" in developed countries is considered the main challenge for the prevention of measles. In some settings, this problem is motivated by religious beliefs or by belonging to ethnic-cultural communities. Romani people, with low vaccine coverage, has been secularly at risk of measles in Spain.[12] However, the spreading of misinformation, fake news and doubts related to safety, and pseudoscience are now the leading causes of vaccine hesitancy. Surprisingly, vaccine objectors usually have a high level of education.[7]

The COVID-19 pandemic has affected the course of other infections, measles included. Since the routes of transmission of measles and SARS-CoV-2 are alike, prevention interventions directed to COVID-19 have impacted on the incidence of measles. Measures such as international travel disruption, limitations of social contact, improving of disinfection and hygienic habits, and the use of face mask seem to have prevented in some situations the expansion of measles. The number of measles cases has decreased in the European Union in 2020. In Spain a drastic fall in measles notifications was noted, with a decrease from 287 cases in 2019 (at week 52) to 90 cases in 2020 (at week 52). At the time of this writing (week 52) only two cases (imported and epidemiologically related) have been recorded in 2021. However, some biases like healthcare services disruptions, associated to a sub-optimal quality of surveillance and underreporting would have affected the level of notification of measles cases in our country. In addition, the pandemic and the interruption of social and working activities have weakened the strength of healthcare systems in developing countries.[9] The negative impact of COVID-19 in routine immunization has disrupted vaccination campaigns in some countries, what may facilitate the surge of measles cases in these endemic countries.[9] This, together to the secular poverty, social instability and the armed conflicts, aggravates the situation in many regions. Some African countries have experienced a re-increase in the number of measles cases during the COVID-19 pandemic.[19] In the Americas in 2021, Brazil and the United States have reported measles cases.[20]

Considering the multiple factors involved in the epidemiology of measles, such as the widespread circulation in a large number of countries, the globalization process and international travels, the decrease of herd immunity and the growing anti-vaccine movements at the elimination phase of this infection, cause the virus to become an uninvited but potentially occasional recurrent visitor in Spain.

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