



Duration of immunity to measles, rubella and mumps during the first year of life



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ARTICLE INFO

Article history:

Received 14 December 2018

Received in revised form 13 May 2019

Accepted 19 May 2019

Available online 28 May 2019

Keywords:

Measles
Rubella
Mumps
Passive antibodies
MMR vaccine
ELISA

ABSTRACT

Introduction and objectives: The MMR vaccine was included in the official vaccination schedule in Spain in 1981. Currently, most women of childbearing age are vaccinated and have not been naturally infected. Several studies have shown that vaccinated women have a lower antibody concentration than that achieved after natural infection, and a shorter duration of transplacentally acquired antibodies in their children. The objective of this study was to determine the antibody titer in mothers and their infants at birth and throughout the first year of life under current epidemiological circumstances.

Material and methods: Single-center, observational, descriptive and prospective study conducted between October 2013 and December 2014. One sample of serum and another of a dried blood spot on filter paper were taken from each mother. Dried blood spot samples on filter paper were taken from the children at birth, and at 3, 6, 9 and 12 months. In all the samples, levels of antibodies to the measles, rubella and mumps viruses were measured using standardized quantitative assays.

Results: 146 mother-child pairs were included. 78.4%, 86.9% and 67.1% of mothers had antibodies to measles, rubella and mumps, respectively. A decrease in the antibody titer in children was observed after 3 months, and no antibodies against the three diseases were detected by the age of 6 months. Comparisons revealed no statistically significant differences between the antibody titers of children of mothers born before or after 1981 during the first year of their life.

Discussion: The rapid loss of transplacentally acquired antibodies against measles, rubella and mumps, under current epidemiological conditions, suggests that bringing the MMR vaccination forward to 9 months might be justified. Larger population studies are needed to confirm these results.

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1. Introduction

Monovalent vaccines were introduced in Spain in 1978 against measles for children at special risk, and against rubella in adolescent girls, to reduce the risk of congenital rubella syndrome. Since 1981, the official calendar recommended by the Spanish Ministry of Health has included the MMR vaccine (measles-mumps-rubella) at 15 months of age. The coverage was less than 86% until 1986 but has been high (>95%) nationally since 1989, resulting in a

substantially modified incidence of measles, mumps, and congenital rubella [1].

Among the Health for All in the 21st Century objectives [2], approved by the European Region of the WHO in 1998, the elimination of endemic measles and the control of congenital rubella were identified as priorities. However, at present, this objective is far from being achieved, and measles outbreaks have occurred in European countries in recent years, especially those where vaccination coverage has decreased [3–5].

In Spain, following the recommendations of the Interterritorial Council of the National Health System [6], the MMR vaccine is administered in a two-dose schedule: the first at 12 months of age and the second between 3 and 4 years. This vaccination regimen, which is the same as that adopted by many other countries

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throughout the world, is based on the protection conferred by maternal antibodies during the first months of life [7]. The concentration and duration of these antibodies in newborns depend on their concentration in the mother [8]. Currently, most mothers from countries with high vaccination coverage have received the vaccine and have not experienced natural infections. This is an important aspect, since the antibodies specific to these viruses occur at a lower concentration and are of shorter duration in vaccinated mothers than in mothers who have acquired the infection naturally. Several studies have shown a more rapid loss of protection in children of vaccinated mothers [9–13]. In addition, in many countries, the average age of mothers has increased, so the interval between their vaccination and the birth of their children is longer, with the consequence that a lower level of protection may be transmitted [14]. There is a window in which infants are susceptible to infection due to the loss of these antibodies before they are first vaccinated. It would be desirable to minimize this period by early initiation of vaccination, for which reason two fundamental factors should be taken into account: the duration of protection conferred by maternal antibodies, and the immune capacity of infants to respond to vaccination [15].

The aim of this study was to determine the titer and duration of antibodies to measles, rubella and mumps in a group of mothers and their children during their first year of life under the current epidemiological circumstances in Spain. To this end, the concentration of antibodies against the MMR viruses was determined at birth and at 3, 6, 9 and 12 months of age, evaluating the antibody titer in mothers and children in relation to the pregnant women's exposure to the vaccine.

2. Material and methods

Women who gave birth between October 2013 and December 2014 at the Puerta de Hierro University Hospital (HUPH) (Majadahonda, Spain) were offered the opportunity to participate in the study. The following inclusion criteria were adopted: gestational age ≥ 37 weeks, adequate birth weight, possibility of follow-up during the first year of life, and informed consent of parents or guardians. Cases with a family history of immunodeficiencies, administration of immunosuppressants, immunomodulators or immunoglobulins during pregnancy were excluded from the study. The study was approved by the Clinical Research Ethics Committee of the HUPH (Act number 286, dated 25/03/13).

A dried blood spot sample on filter paper and a serum sample were taken from each mother participating in the study. Dried blood spot samples from the children were obtained on filter paper by heel puncture at birth and at 3, 6, 9 and 12 months. Levels of antibodies against the three viruses in these samples were determined. A previously established elution procedure was employed to study the antibodies in dried blood spots [16]. Due to the almost complete absence of vaccination records, it was assumed that mothers with protective antibodies against any of the three diseases who were born before 1981 had been naturally infected, while those born subsequently had received the vaccination as part of the vaccination schedule. We chose 1981 as a cut-off because the protection of mothers born before that year must have been due to natural infection.

Mothers were classified into two groups with respect to their MMR coverage level:

- Mothers born before and after 1981, year of introduction of vaccine, with low coverage levels (<30%);
- Mothers born before and after 1985, with coverage levels <75%.

The levels of IgG against measles, rubella and mumps in dry blood spots were determined by the indirect ELISA technique (Enzygnost Measles IgG, Enzygnost Rubella IgG, and Enzygnost Mumps, Siemens, Marburg, Germany), following modifications to a previously described procedure [17]. Briefly, five 3-mm discs were cut from Whatman paper, to which 156 μL of sample diluent were added in an Eppendorf tube, shaken for 15 min at room temperature, and kept at 4 °C overnight without agitation. Samples were then stirred again for 15 min at room temperature and centrifuged for 10 min at 2200g (5500 rpm). Supernatants were collected, which corresponded to a 1:21 dilution of the samples. From this material, a 1:231 dilution was obtained, with which the IgG levels against the three viruses were determined. This was carried out automatically in an ELISA processor (Behring ELISA Processor III, Siemens). The quantitative results were measured in mIU/ml (measles), IU/ml (rubella) and as the titer (mumps). The assay for determining the levels of IgG against the three viruses is accredited, for serum and dry blood spot samples, in accordance with ISO15189. Whenever sample availability permitted, the children's follow-up samples were studied in parallel with previous samples.

The cut-off values of the assays were established as follows: optical density (OD) < 0.100: negative; OD between 0.100 and 0.200: indeterminate; > 0.200, positive. The values for specific antibodies were quantified as described elsewhere [18], the established values being as follows: for measles (mIU/ml): positive > 300, negative < 150, indeterminate 150–300; for rubella (IU/ml): positive > 10, negative < 4, indeterminate 4–10; and for mumps (titer): positive > 580; negative < 230; indeterminate 230–580. In the quantitative calculations, half the cut-off value was assigned to the negative samples (measles: 75 mIU/ml; rubella: 2 IU/ml; mumps: 115 titer) [19,20].

Categorical variables were summarized as absolute and relative frequencies; numerical variables were summarized as means (and standard deviation [SD]), or medians (with 25 and 75 percentiles, respectively), depending on whether they were normally or non-normally distributed, respectively. Titers are shown as medians and percentiles because of the great variability observed. To visualize the evolution of titers over time, three plots for panel data have been produced, showing the median and 25 and 75 percentiles over time in each case, using the `xtgraph` command in Stata.

A sensitivity analysis was carried out to determine whether the introduction of the vaccine in 1981 into the immunization schedule was associated with different levels of antibody titers. The Mann-Whitney *U* test was used to assess differences between measles, rubella and mumps titers in women born before or after 1981.

The level of statistical significance was set at $p < 0.05$. Analyses were carried out using Stata / IC v 15.1 (StataCorp 2017, College Station, TX, USA).

3. Results

3.1. Population and sample

An initial sample of 146 mother–child pairs was studied, with a follow-up throughout the study period of 67.8% ($n = 99$) at 3 months, 52.7% ($n = 77$) at 6 months, 43.2% ($n = 63$) at 9 months and 20.5% ($n = 30$) at 12 months. The average age of mothers was 33.1 ± 4.6 years. 57.3% were born before 1981. 79.6% were of Spanish nationality. Demographic data of mothers are shown in Table 1.

82% of births were vaginal deliveries. The mean weight of newborns was $3.260 \text{ kg} \pm 0.416 \text{ kg}$. All of them were of adequate weight for their gestational age. 41.5% of newborns were girls.

Table 1
Demographic data of mothers.

	Date of birth	
	Before 1981 n = 83	After 1981 n = 63
Age, mean (SD)	36.2 (2.6)	29.1 (3.3)
Country of origin, n (%)		
Argentina	3 (3.6)	1 (1.6)
Bolivia	2 (2.4)	1 (1.6)
Chile	0	1 (1.6)
Colombia	3 (3.6)	1 (1.6)
Cuba	1 (1.2)	0
Dominican Republic	2 (2.4)	1 (1.6)
Ecuador	0	1 (1.6)
France	1 (1.2)	0
Honduras	0	1 (1.6)
Morocco	1 (1.2)	1 (1.6)
Paraguay	1 (1.2)	3 (4.8)
Romania	0	5 (7.9)
Spain	69 (83.1)	47 (74.6)
Mean antibody titer, median (IQR)		
Measles	1200; 695–5650	590; 320–1200
Rubella	32; 14–54	17; 11–38
Mumps	900; 310–1800	850; 350–1300

3.2. Serological results

3.2.1. Measles

78.4% of mothers had antibodies against measles (13.7% indeterminate results). The median antibody titers were 825 mIU/ml (interquartile range (IQR): 330–2400 mIU/ml) for mothers, and 1200 mIU/ml (IQR: 510–3600 mIU/ml) in the newborns ($p = 0.072$) (Table 2). The antibody levels over time are shown in Fig. 1a. 88% of newborns had positive titers and only 19% continued to be positive at 3 months. All of them were seronegative at 12 months (Fig. 2a).

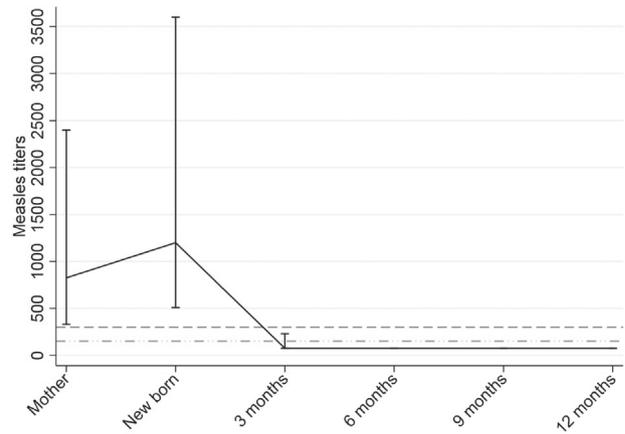
With respect to the year of birth, it was observed that in mothers born before 1981 the median antibody titer was 1200 mIU/ml (IQR: 695–5650 mIU/ml), while those born subsequently had titers of 590 mIU/ml (IQR: 320–1200) ($p < 0.001$). The median antibody titer in newborn children of mothers from the first period was 1900 mIU/ml (IQR: 470–5500 mIU/ml), and that of children of mothers born after 1981 was 710 mIU/ml (IQR: 450–1400 mIU/ml) ($p < 0.001$) (Fig. 3a).

3.2.2. Rubella

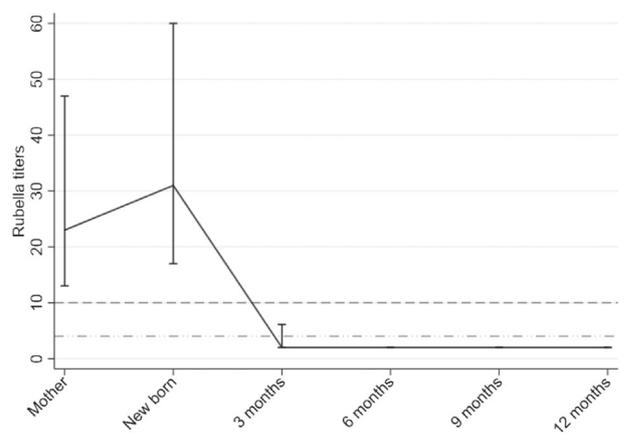
86.9% of mothers had protective antibodies against rubella (10.9% indeterminate titers). The median antibody titer against rubella in mothers was 23 IU/ml (IQR: 13–47 IU/ml) and 31 IU/ml (IQR: 17–60 IU/ml) in newborns ($p = 0.006$) (Table 2). Antibody titers for the various times in the study are shown in Fig. 1b. 91% of newborns had positive titers, and at 3 months 13% continued to be positive, while 32% of them had an indeterminate titer.

Table 2
Median titers for measles, rubella and mumps.

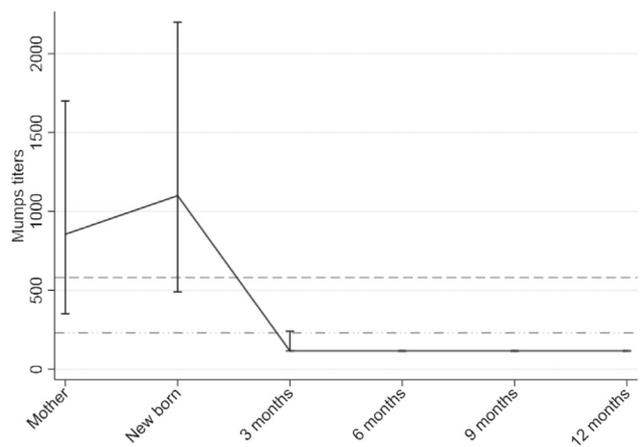
	Measles		Rubella		Mumps	
	n	Median (P25; P75)	n	Median (P25; P75)	n	Median (P25; P75)
Mother sample	146	825 (330; 2400)	146	23 (13; 47)	146	855 (350; 1700)
Newborn	142	1200 (510; 3600)	142	31 (17; 60)	141	1100 (490; 2200)
3 months	99	75 (75; 230)	100	2 (2; 6)	98	115 (115; 240)
6 months	76	75 (75; 75)	77	2 (2; 2)	77	115 (115; 115)
9 months	62	75 (75; 75)	62	2 (2; 2)	62	115 (115; 115)
12 months	30	75 (75; 75)	30	2 (2; 2)	30	115 (115; 115)



a. Median and IQR titers for measles



b. Median and IQR titers for rubella

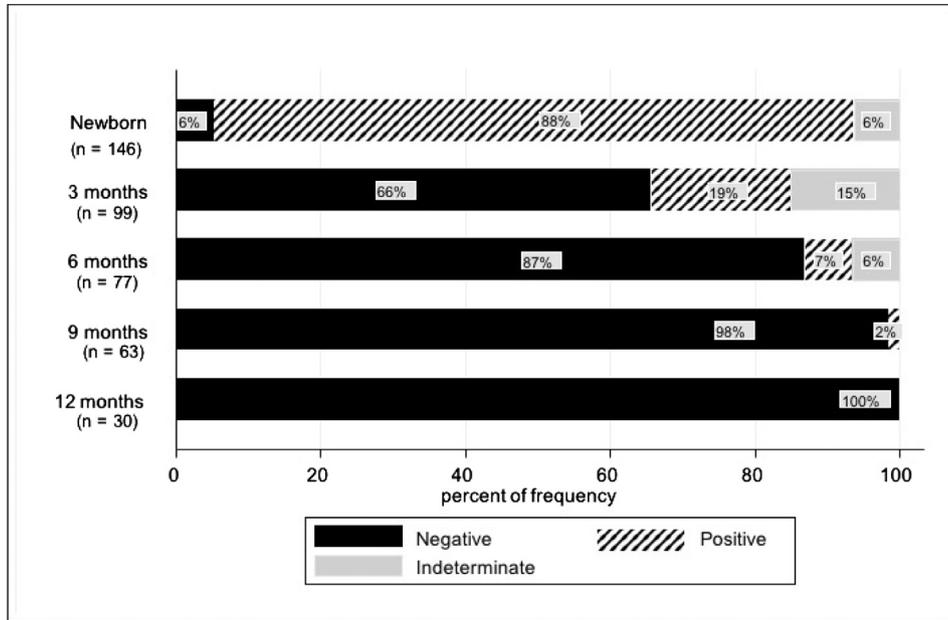


c. Median and IQR titers for mumps

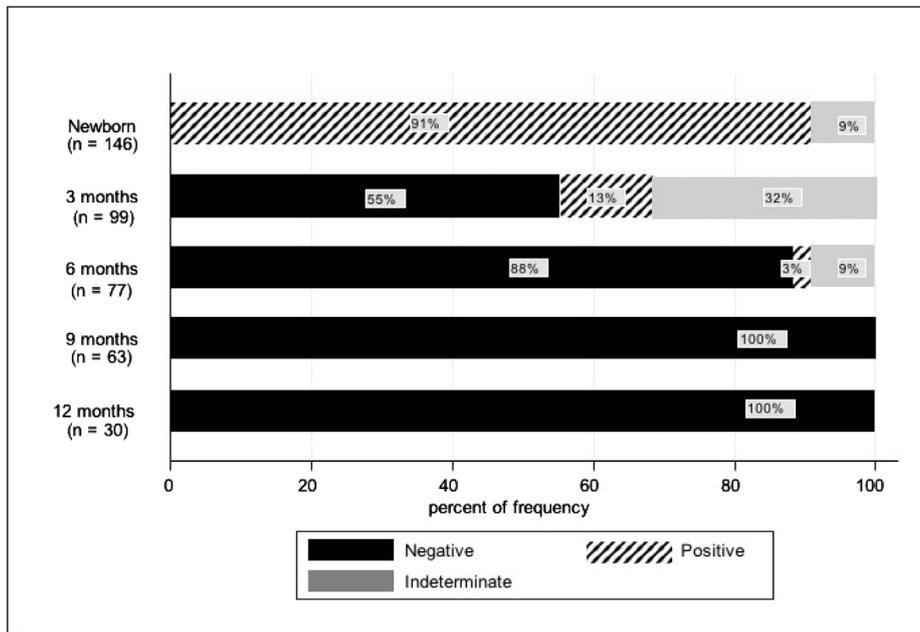
Fig. 1. Median and IQR titers for measles (mIU/ml), rubella (IU/ml) and mumps of mothers and children during follow-up (lower dashed line: negative; upper dashed line: indeterminate).

Protective antibodies against rubella were not detected in any of the children analyzed at 9 and 12 months of age (Fig. 2b).

In relation to the year of birth, mothers born before 1981 had a median antibody titer of 32 IU/ml (IQR: 14–54 IU/ml), while those born afterwards had a median titer of 17 IU/ml (IQR: 11–38 IU/ml) ($p < 0.001$). The median antibody titer for infants born to mothers



a. Evolution of time to negative antibody level against Measles



b. Evolution of time to negative antibody level against Rubella

Fig. 2. Evolution of time to negative antibody level of antibodies against.

in the first period was 31 IU/ml (IQR: 15–61 IU/ml), and 29.5 IU/ml (IQR: 17–60 IU/ml) in those of mothers in the second period ($p = 0.770$, NS) (Fig. 3b).

3.2.3. Mumps

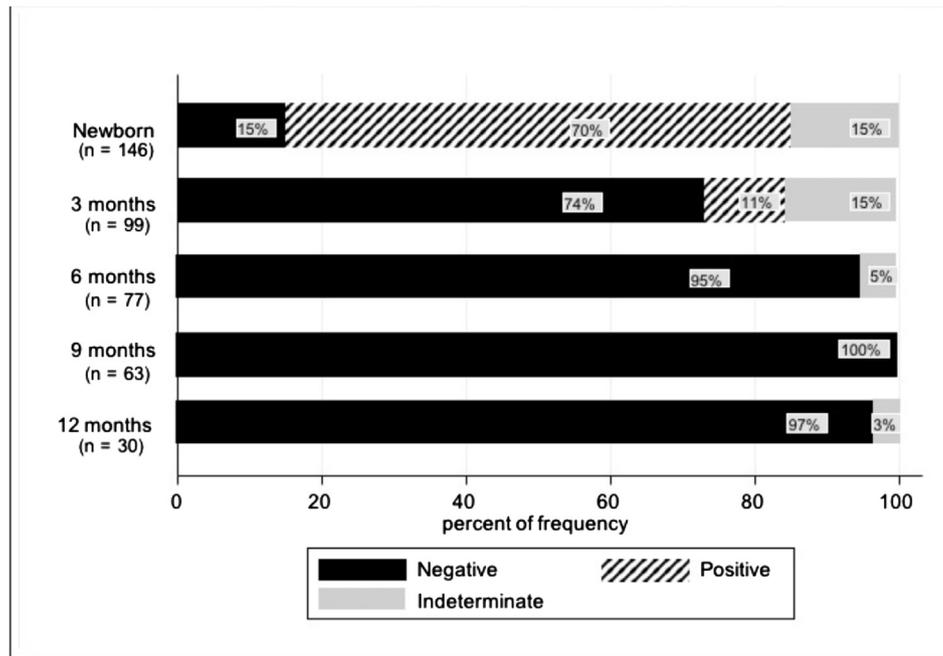
67.1% of mothers had a positive antibody titer against mumps (21.2% indeterminate titers). The median titer of mumps antibodies was 855 (IQR: 350–1700) in mothers and 1100 (IQR: 490–2200) in their newborns ($p = 0.036$) (Table 2). Antibody titers at the various times during the study are shown in Fig. 1c. 70% of newborns had positive titers and only 11% remained positive at 3 months. By 9 months, all of them were seronegative (Fig. 2c).

By year of birth, it was observed that mothers born before 1981 had a median antibody titer of 900 (IQR: 310–1800), while those

born later presented titers of 850 (IQR 350–1300) ($p = 0.616$). The median antibody titer for children of mothers from the first period was 980 (IQR: 425–2050), and 1200 (IQR: 560–2300) in the newborns of mothers from the second period ($p = 0.540$, NS) (Fig. 3c).

4. Discussion

The results of this study show that even before 9 months of age, infants do not have high titers of antibodies against measles, rubella or mumps. Also, although the antibody titer is higher in mothers born before the systematic introduction of the MMR vaccine into the immunization schedule than in those born after, loss



c. Evolution of time to negative antibody level against Mumps

Fig. 2 (continued)

of protection in infants occurs in a similar manner in both groups of women.

A clear decrease in the levels of antibodies to the three viruses was observed by the age of 3 months. This loss continued up to 6 months of age, with more than 50% and 90% of the children being seronegative by these respective ages. None of the children were seropositive for any of the viruses after 9 months of age, except one child who had measles IgG. These results coincide with previous published studies from other European countries, in which positive antibodies were also not detected at 9 and 12 months of age [9,21,22]. This aspect has also been studied in infants from Orthodox Protestant communities in the Netherlands (unvaccinated and exposed to outbreaks) against infants of the general population, finding that the estimated duration of protection conferred by maternal antibodies to measles was 2 months longer in infants born in Orthodox communities, with no significant differences for rubella and mumps [23]. In a study carried out in provinces of China with a high incidence of measles, the authors observed a rapid decrease in protective antibody titers from 90% at birth to 15% at 8 months of age [8].

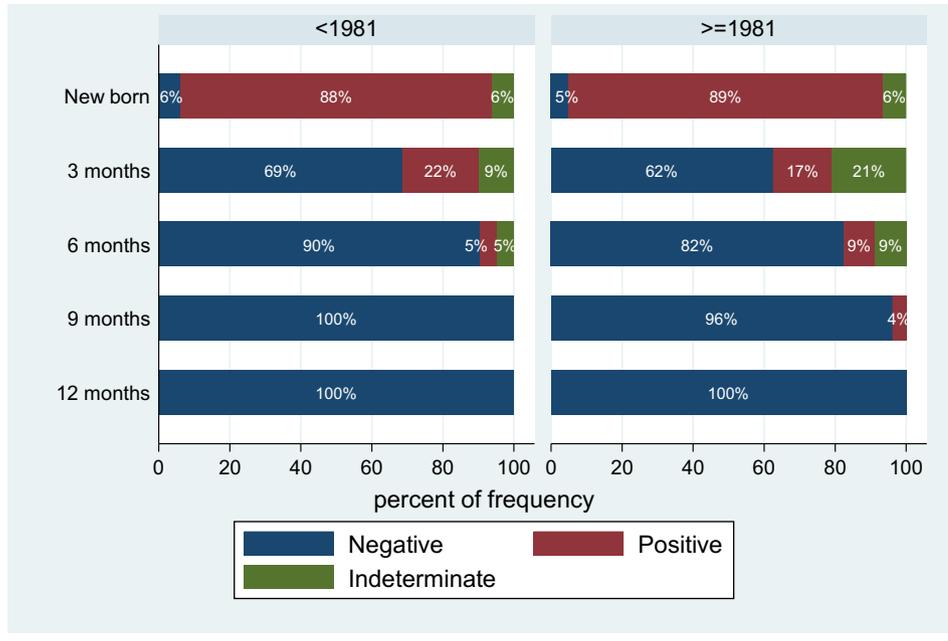
In the present study, statistically significant differences were observed in the titer of maternal antibodies to measles and rubella for mothers born at different times. Titers were clearly higher in women born before 1981, the year the MMR vaccine was included in the vaccination schedule. The most likely explanation is that vaccination induces lower antibody titers than does the natural infection, and that, in addition, given the current low circulating rate of these viruses, there is no reinforcement to increase antibody levels. While the presence of IgG is accepted as indicative of protection in the case of mumps, reinfections occur, and the detection of specific IgGs cannot be considered as synonymous with protection. The differences in the antibodies titers for mothers born at different times observed in measles and rubella is not seen in the titers for mumps. This could be because, despite the generalization of the vaccine, the mumps virus continues to circulate and infect the population, and so mothers now have an antibody response to mumps equivalent to that of the prevaccine era. We think this

is the reason why we have not observed differences in the antibody titers of the newborns in relation to their mothers' year of birth, or at any of the times during the study. In the case of measles, significantly higher titers were found in newborns of naturally immunized mothers, but there were no significant differences at 3, 6, 9 or 12 months.

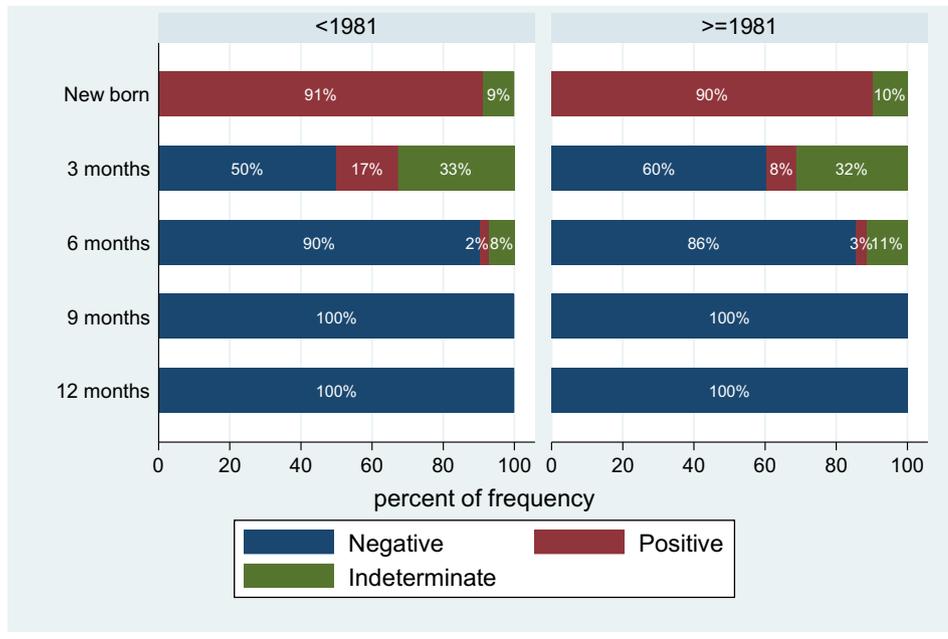
This aspect has been analyzed in previous studies, producing disparate results. Leuridan et al found significant differences in the titers of mothers vaccinated against mumps compared with naturally infected mothers. They also observed a directly proportional association with the titers at birth of children of non-vaccinated women. The children of vaccinated women had significantly fewer antibodies at birth compared with the offspring of naturally immune women [9]. These results agree with studies conducted in European countries with a similar methodology to ours [23,24]. Our results are consistent with those of studies conducted in China, which also established two groups based on the year of maternal birth and found no significant differences in the average levels of antibodies among newborns according to the type of maternal immunity [8]. Other studies have evaluated the immunosuppression status of the mother as a factor determining the transfer of maternal antibodies [25,26].

In relation to the study findings, and under the current epidemiological circumstances, infants younger than one year of age may be considered to be unprotected from the serological point of view in the face of infection by the measles, rubella and mumps viruses. The current vaccination schedule for the MMR vaccine starts in Spain at the age of 12 months. The latest systematic review of the duration of protective antibodies against measles in environments considered by the WHO to be free of infection concluded that infants are susceptible to measles at an earlier age than that at which routine immunization commences [27].

As described in our study, there is a considerable period during which infants are susceptible to infection by these viruses, since, according to current recommendations, they will not yet have benefited from the protection afforded by the vaccine. To solve this lack of protection it would be necessary to lower the age at which



a. Time to negative antibody level of antibodies against measles by time of maternal birth (newborn n = 146, 3 months n = 99, 6 months n = 77, 9 months n = 63, 12 months n = 30)



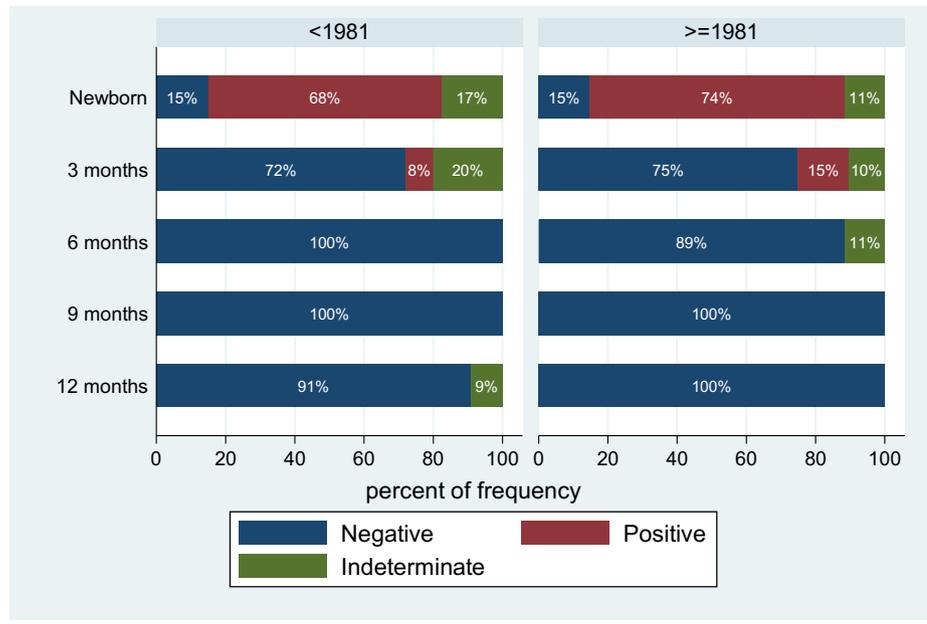
b. Time to negative antibody level of antibodies against rubella by time of maternal birth (newborn n = 146, 3 months n = 99, 6 months n = 77, 9 months n = 63, 12 months n = 30)

Fig. 3. Time to negative antibody level of antibodies by time of maternal birth.

the first dose of MMR vaccine is administered. However, immunization at very young ages may be ineffective, given the immaturity of the immune system of infants less than 1 year old [28]. This is why several studies have been carried out to evaluate the efficacy and safety of MMR vaccination under different guidelines for its administration.

Several studies in the USA and Germany demonstrated that immunogenicity against MMR vaccine was similar at 12 and 15 months, although seroconversion against measles was significantly lower in infants of 9 months [29,30]. Two very similar stud-

ies from the 1990s [31,32] examined infants who were vaccinated with a monovalent measles vaccine at 6 months and revaccinated at 15 months with the MMR vaccine. The authors compared the serological results with those from infants who had only received an MMR vaccine dose at 15 months, and found 74% seroconversion in the group vaccinated at 6 months compared with 100% in the group vaccinated at 15 months. However, after revaccination, all children had protective titers against measles. These studies lead to the conclusion that, when administering a first dose of the MMR vaccine before 12 months of age, it would be prudent to



c. Time to negative antibody level of antibodies against mumps by time of maternal birth (newborn $n = 146$, 3 months $n = 99$, 6 months $n = 77$, 9 months $n = 63$, 12 months $n = 30$).

Fig. 3 (continued)

administer an additional dose at the beginning of the second year of life, according to usual practice.

The work has some limitations. The most important is the high percentage of loss to follow-up due to patient's abandoning the study. The small sample sizes at the later times limit the statistical power of the study to make comparisons. Second, vaccination histories were not available for most women, so we had to assume that mothers born after 1981 had received the MMR and those born before 1981 had been infected naturally. This assumption may have resulted in the misclassification of some women's vaccination and prior infection status.

5. Conclusion

In conclusion, this study describes a decrease in antibody titers from birth, with no infants found to have antibodies against measles, rubella or mumps by 9 months of age, except one child who had measles IgG.

Statistically significant differences exist in antibody titers against measles and rubella among mothers born before and after 1981.

No significant differences were found in the protection conferred by maternal antibodies according to the mothers' year of birth against rubella and mumps. In the case of measles, significantly higher titers were found in children born to mothers who were naturally immunized, although these differences disappeared later in their development.

The majority of children younger than one year of age are susceptible to infection by any of these viruses. This is particularly important, given the clinical importance of measles, with its high mortality and current epidemiological circumstances. Given the findings of our study, we suggest that it may be worth considering administering the first dose of MMR vaccine before 12 months of age, and propose that, under such circumstances, it would be reasonable to bring the administration of the second dose forward to 2–3 years of age. Further studies are needed of the immunogenic-

ity, efficacy and safety of the MMR vaccine in infants younger than 12 months in this context.

Funding

The study was funded by the Fondo de Investigación Sanitaria (FIS PI12/02006), AF-G was funded by CIBER de Epidemiología y Salud Pública (ESPG13).

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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