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ORIGINAL ARTICLE

Epidemiological and clinical characteristics and the approach to infant chickenpox in primary care

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Abstract

Chickenpox is not common in the first year of life (infant varicella) and there is a lack of data on its presentation, especially in primary care. A year-long observational study (July 2015–2016) carried out by a research network of primary care pediatricians throughout Spain.Two hundred and sixty-four pediatricians gathered data from 358 cases of clinically diagnosed chickenpox in infants. The illness was considered mild in 78% of infants < 7 months compared to 65% in those aged 7 to 12 months ($p = 0.0144$). Fever (46%) was present in 35% of children ≤ 6 months compared to 55% in older children ($p = 0.0005$). The number of skin lesions was > 50 in 35% of children ≤ 6 months old compared to 47% in > 7 months ($p = 0.0273$). From the 2% of hospitalized children 86% were younger than 7 months. Oral antiviral treatment was given in 33% of cases ≤ 6 months compared to 18% in older patients ($p = 0.0023$). Doubts about administering the chickenpox vaccine at a later date were expressed by 18% of pediatricians.

Conclusion: Chickenpox is considered benign, having a mild effect on most infants. There is less clinical effect in infants ≤ 6 months although this age group is hospitalized more and is prescribed more antiviral treatment. There are doubts among pediatricians about the subsequent need for vaccination.

What is Known:

- *Chickenpox is uncommon and of uncertain evolution in the first year of life*
- *Hospital admissions for chickenpox are more frequent in the first year of life*

What is New:

- *The course of chickenpox in the first year of life is mild, especially in infants younger than 7 months despite the fact they are hospitalized more and are treated more frequently with antivirals. Antivirals are prescribed to 1 in 4 children with chickenpox under 12 months of age.*
- *Almost 50% of pediatricians recommend a subsequent vaccination against chickenpox especially if it occurs in the first 6 months of life.*

Keywords Chickenpox · Infant · Primary care · Acyclovir · Chickenpox complications

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Abbreviations

PC	Primary care
AR	Autonomous region
SD	Standard deviation
CI	Confidence interval
OR	Odds ratio
PAPenRed	Pediatric Epidemiological Surveillance Network of Spanish Primary Care Pediatrics Association

Introduction

Chickenpox is the most common vaccine preventable disease in developed countries. Without vaccination up to 89–96% of children suffer from the illness, the majority in the first 5 years of life [11, 31, 33]. In Spain, pending the outcome of a generalized vaccination's effect on 1-year old children from 2016, 87% and 53% of cases occur in children under 15 and 5 years of age respectively [25, 33].

Chickenpox has a characteristic appearance that allows accurate diagnosis for pediatricians. However, it is not exempt from error, and, in addition, medical attention is not necessary in many cases [3, 16, 31].

Although chicken pox is considered a benign disease in childhood, it can be associated with mortality [3, 31, 32, 38]. Complications are estimated in 2–6% of cases, 0.3% requiring hospital admission, (most likely in the first year of life) [11, 18, 31]. Fatality rates in hospitalized cases vary in Europe from 0.01–5.4% [11], while the after-effects are 0.4–3.1% [11, 31]. The majority of complications, hospitalizations, and deaths are recorded in previously healthy pediatric patients [13, 20, 35].

The appearance of chickenpox is uncommon in the first year of life (3%) [10, 11], probably due to the protection of passive maternal antibodies (90% of pregnant women), which explains the presence of very mild clinical forms in infants [29]. However, several studies show that maternal antibodies cease to be detected long before the child reaches 6 months of age [14, 19, 24, 27, 28].

Although hospitalization rates are higher in infants [8, 11, 17, 25, 35], explained in part by the perception of a greater vulnerability [23, 35], there are contradictory results in the incidence of complications. Thereby, Blumental et al. found fewer complications in infants admitted for chickenpox [3].

There are few epidemiological studies in literature that describe the appearance and development of chickenpox in infants, even less in the primary care (PC) environment, further reflecting contradictory results [2, 5, 17, 23, 29, 36, 37]. The aim of the present study is to dig deeper into the epidemiology, approach, and evolution of chickenpox up to 12 months of age, using the data collected by the Pediatric Epidemiological Surveillance Network of Spanish Primary Care Pediatrics Association (PAPenRED).

Materials and methods

An observational, cross-sectional study carried out in Spanish National Health Service PC centers between July 1, 2015 and June 30, 2016. Data collection was performed by PAPenRED (310 sentinel PC pediatricians in every Autonomous Region [AR] proportionally). Two-stage stratified sampling was used to select pediatricians. AR was the first stage units and the second stage units, the healthcare zones. In the Spanish public health service system, there are PC pediatricians so children are treated directly by a specialist at the first level of healthcare. Pediatricians of primary care in Spain are the gateway to health care for Spanish children in the public health system. Each one has a quota of about 900 children under 14 years, and they attend consultations on demand for illness, and on specific programs including prevention and health education. The ease of access to pediatric PC in Spain makes it unlikely that varicella cases in the first year of life are not a reason for consultation.

Study subjects: children from 0 to 12 months treated in pc pediatric surgeries, throughout the national territory (except ceuta and melilla) with a clinical diagnosis of chickenpox.

Inclusion criteria: age between 0 and 12 months, clinical diagnosis of chickenpox, and having attended a PC pediatric surgery during the study period with availability of clinical and epidemiological data of the episode. All patients included in the study went to their pediatrician of PC when the symptoms started or in the follow-up of the disease, including those that require hospital admission. Cases prior to the year of data compilation were also included in the study provided that the data was available in the clinical records.

Exclusion criteria: lack of sufficient data in clinical records. Studying prevalence of the early varicella is not among the aims of our work. Refusal of parents/guardians to participate in the study.

Data collection: the subject's age at the time of diagnosis was recorded as the main variable, and, as secondary variables sex; number of siblings; birth order; nursery school attendance; place and source of infection; pathology or previous treatments; related cases; situation with regard to mother's chicken pox (the collaborating pediatricians asked the mothers if they suffered varicella or if they had positive antibodies against it measured before or during pregnancy); signs and symptoms (the intensity and duration of the fever was obtained from the interrogation of the parents or caregivers), number of vesicles (three possible answers in relation to the approximate number of vesicles in each case: less than 50, between 50 and 100 or more than 100 lesions), treatments, hospital admissions, and the recommendation or not to a subsequent

vaccination. Depending on the impairment of health conditions, the complications and the evolution of the disease, each pediatrician classified the episode as mild, moderate, or severe. Mild: uncomplicated and the following symptoms (fever lower than 38.5 °C and it presents less than 3 days, number of vesicles less than 50). Moderate: fever up than 38.5 °C and it presents more than 3 days, number of vesicles more than 50–100. Severe: life risk and/or permanent disabilities. The data was uploaded to a dynamic database created in Google Drive: (https://www.aepap.org/sites/default/files/documento/archivos-adjuntos/carta_de_presentacion_estudio_varicela-zosster.pdf).

Statistical procedures: the mean, standard deviation (SD), median, and interquartile range for quantative variables were calculated. For qualitative statistics, the proportions of each category with a 95% confidence interval (CI 95) were calculated. Seasonal incidence patterns were established and for the comparison of variables odds ratios (OR) with their respective CI 95 were calculated. When considering statistical significance, a p value ≤ 0.05 was taken.

Results

Two hundred and sixty-four network pediatricians participated (80% of the total). From this number, 184 referred cases and 80 reported not having cases. A total of 358 cases of chickenpox were compiled from children of 0 to 12 months of age. One hundred nineteen of them happened before to the year of study, the oldest case corresponding to October 2000. The distribution by sex was almost equal: girls 51.12% compared to 48.88% boys.

The mean age was 7.50 months (SD 3.22; range 0.10 to 12.80 months); 44% were less than 7 months old (Fig.1).

With regard to seasonal manifestations, spring was the season with the highest prevalence (48.6% of cases). Autumn provided 9.2% of cases, summer 19.8%, and winter 22.3%.

In this study, 21.5% of children had no siblings. The largest group had one brother or sister (58.7%), 2 siblings 15.1%, 3 siblings 4.5%, and 4 siblings 0.3%. There were no cases of precocious chickenpox in twins in our study.

The majority of children did not attend day care centers (76.82%), especially the youngest (87.3% of infants of less than 7 months did not attend nursery compared to 68.5% in those of 7 or more months). In Spain, attendance to day care in children under 6 months old is usually lower than older children.

Regarding the suspicion of contagion, it was attributed to family contact in 61.7% (84.1% by an older sibling), 12.3% in day care, 0.8% to a non-family carer, 5.0% to contact with other people, and in 20.1% contagion was of unknown origin.

A medical record of immunosuppression was recorded in 1 case. He was a child of 6 and a half months old in treatment with high doses of corticosteroids to take care of the worsening of the bronchopulmonary dysplasia that he suffered.

Only 3 children had been vaccinated with one dose of chickenpox (0.8%).

The mothers' immunity status against chickenpox was unknown in 22.3% of cases. The largest group (74.6%) had a medical record of chickenpox or the existence of antibodies had been established (Fig. 2).

Fever was present in 46.1% of cases. Infants of 7 months or more exhibited significantly more fever (55%; CI 95 48–62%) than younger children (34.8%; CI 95% 27–42%) (OR 2.29; CI 95 1.49–3.52; $p = 0.0005$). The general condition was classified as good in 92.7%.

Less than 50 lesions were found in 58.1% of children (Fig. 3); numbers were significantly higher in children ≥ 7 months, who in 47% (CI 95 40–54%) had more than 50 lesions compared to 35% (CI 95 28–43%) in children younger than that age (OR 1.62, CI 95 1.05–2.48; $p = 0.0273$).

Complications were present in 8.1% of cases; those in children of 7 or more months were more frequent but not by a significant number: 10% (CI 95 5–14%) compared to 6% (CI 95 3–10%) in children 7 months old (OR 1.55; CI 95 0.70–3.4). Among the complications, the frequency of lesion superinfection stands out and if we add impetigo, acute media otitis, and perianal disease, the hypothetical superinfection by *Streptococcus pyogenes*/*Staphylococcus aureus* would account for 86% of the complications. Complications separated by age groups are included in Table 1.

The majority of cases were classified as mild (70.9%) and 1.1% as severe. The diagnosis of moderate or severe forms was significantly more frequent in children ≥ 7 months: 35% (CI 95 28–42%) compared to 22% (CI 95 15–28%) respectively in children less than 7 months old, OR 1.96 (CI 95 1.22–3.17; $p = 0.0145$). There were no differences in age in severe cases (three cases were considered to be serious, two in children under 7 months old and one older. They presented bacterial superinfection of the lesions and high fever. The fourth case had a significant initial affectation of the general state and high fever on debut, and required hospital observation with oral antiviral treatment).

Oral acyclovir was administered in 24.3% of cases. A significantly higher percentage was administered to children under 6 months (33% of treated cases, CI 95 26–40%) than in older children (18%, CI 95 12–23%) (OR 2.31; CI 95 1.41–3.79; $p = 0.0023$). When acyclovir was prescribed, the pediatricians tend register a significantly condition worse general health of the children (13% poor health condition, 95% CI 6 to 20%) as compared with the cases when the patients were not treated (6% poor health, 95% CI 3 to 8%) (OR 2.47; 95% CI 1.09 to 5.60, $p = 0.050$). The use of antiviral treatment was not significantly higher in those who had fever, greater number of lesions or were classified

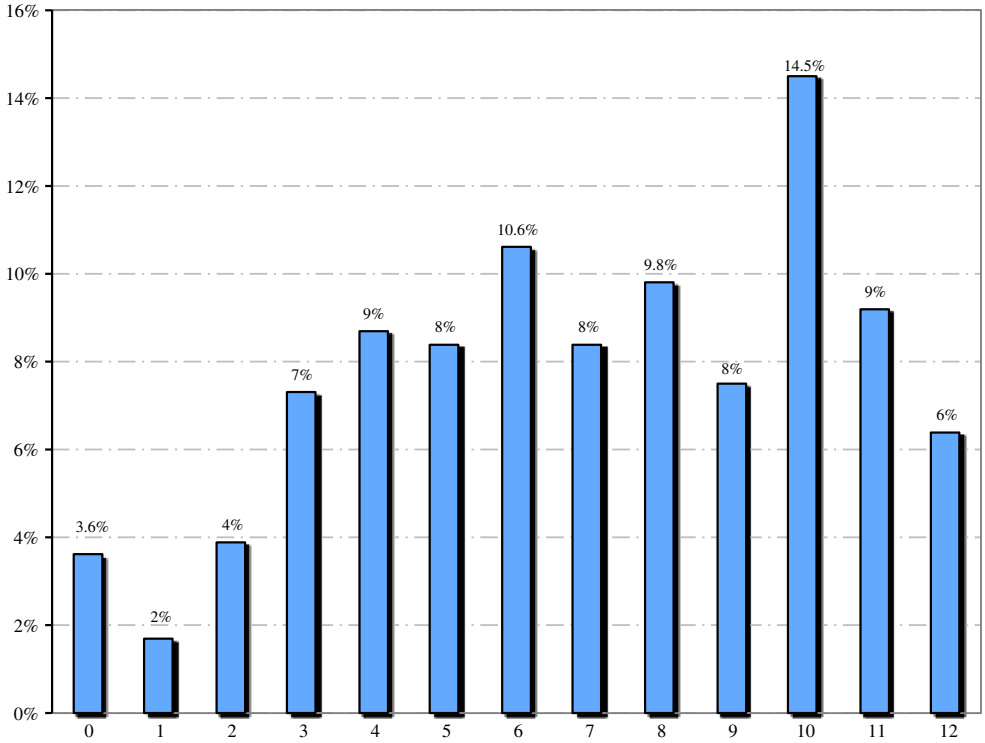

Fig. 1 Case series distribution by age in months. The results are shown as percentages of the total sample

as more severe at the end of the episode. The evolution of the disease was good both in treated and untreated patients (9% of complications in untreated versus 5% in treated; OR 2.11; 95% CI 0.71 to 6.24). A percentage of 81.3 received symptomatic treatment in this study. No significant differences were observed between the group receiving treatment with the antiviral acyclovir and the group which was not treated. From those treated with acyclovir 75.9% received: paracetamol (33.3%), paracetamol + antihistamine (19.7%), paracetamol + antipruritic lotion (16.7%), ibuprofen (4.5%), oral antibiotics (3%), topical antibiotics (3%), and other treatments 19.78%. From those who did not receive antiviral remedies, 83.0% received symptomatic treatment: paracetamol (18.2%); paracetamol + antihistamine (19.7%), paracetamol + antipruritic lotion (22.7%), topical antibiotics (4%), oral antibiotics (3.5%), ibuprofen (2.2%), and other treatments (19.3%).

Hospital admissions were more frequent (4%) in infants up to 6 months old (CI 95 1 to 7%), compared to 1% in those of 7 months or more (CI 95 0–1%), although the figure is not significant (OR 7.86, CI 95 0.94–65.94). Table 2 summarizes the differences between the two groups of children, those younger than 6 months and those from 7 to 12 months.

In 18.4% of cases, the pediatrician doubted as to whether or not a subsequent vaccination was needed. It was recommended in 44.9% of cases. This recommendation was significantly more frequent in infants younger than 6 months (56%, CI 95 49–64%) than in older children (36%, CI 95 29–43%) (OR 2.29; CI 95 1.30–3.51; $p = 0.0003$).

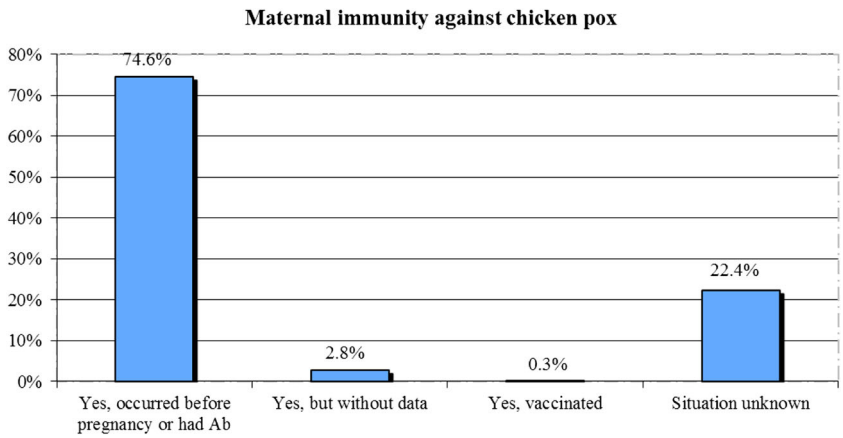

Fig. 2 Situation regarding mothers' chickenpox. The results are expressed as percentages of the total sample (Ab, antibodies)

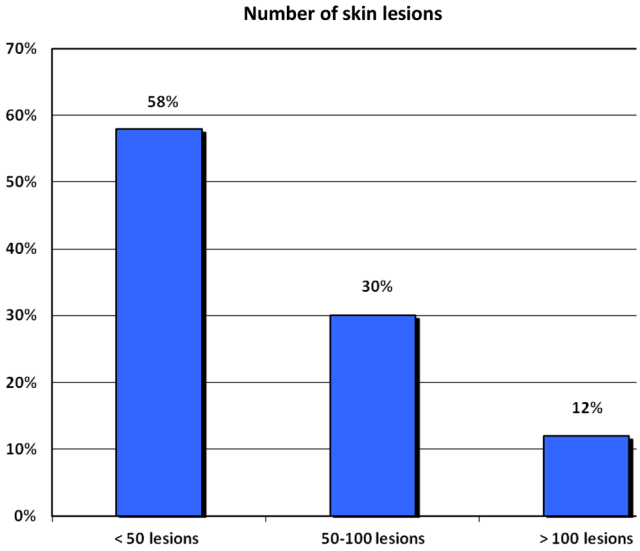

Fig. 3 Number of skin lesions. The number of skin lesions exhibited was counted. The results are expressed as percentages of the total sample

Discussion

This study was developed in PC centers and relied upon the collaboration of 264 affiliated PAPenRED pediatricians [30]. In Spain, chickenpox is a notifiable disease. In 2015, 176,281 cases were declared (http://www.isciii.es/ISCIII/es/contenidos/fd-servicios-cientifico-tecnicos/fd-vigilancias-alertas/fdenfermedades/RENAVE_INFORME_ANUAL_2015.pdf). Records for chickenpox are not mandatory in all European countries [16]. Currently, the data is housed in the European Surveillance System (TESSy) and in the European Centre for Disease Prevention and Control (ECDC) (which coordinates the old EUVAC.NET network) [11]. Besides, there are few seroprevalence studies in Europe [4]. As a result, the sentinel networks in some countries acquire special interest [1, 12, 31].

A total of 358 cases of chickenpox were compiled between July 2015 and June 2016 for children from 0 to 12 months old with a mean age of 7.5 months and a similar frequency in both sexes. The majority of cases occurred in spring following a known seasonal pattern [1]. The Autonomous Regions that registered more cases of infant chickenpox were those with higher hospital admission rates and lower vaccination coverage according to the provided data by Gil-Prieto and collaborators during 2009–2010 [15].

Although considered benign in childhood, chickenpox is highly contagious. In our study almost 71% of the cases were considered mild and more than 50% had family contact as the source of infection as shown by Iseli et al. [22].

Chickenpox, however, is not exempt from high morbidity [31, 32] and can have serious complications. The most common complication was skin superinfection as already described in other studies [3, 9, 32]. Many studies have shown that *Staphylococcus aureus* and *Streptococcus pyogenes* are the bacteria which most frequently produce superinfection in patients with chickenpox [20].

Approximately 3–4% of our patients received antibiotics, oral or topical. Symptomatic treatments (paracetamol, antipruritic lotions, and antihistamine) were prescribed the most, as was recorded by Emery et al. in PC units in France [9]. It is striking that practically one in four infants received oral acyclovir; the figure is significantly more frequent in those under 6 months, specifically those with milder clinical forms. Use of this treatment has been shown to reduce the duration of fever, but not the appearance of new lesions [6]. Probably the greatest use of acyclovir (at ambulatory level) with reference to information provided by other hospital studies [3] is as a consequence of the age of the patients studied, associated with a greater vulnerability. This must also surely explain that the highest number of admissions was in children under 7 months, despite the disease being milder among the younger children in our study. However, other studies have also shown that the majority of hospital admissions for chickenpox occur in children under 5 years of age with a higher age-specific incidence in children under one [3, 18, 20]. This study recorded a hospital admissions rate of 2%, higher than other works [18] [3]. There is some controversy with regard to the frequency of complications within this age range. While there are works that show no differences with respect to age [17], others provide a gradually increasing frequency for the presentation of complications [5] [23] [29]. So, the closer the child approaches to the age of 12 months, the more risk he/she will have of presenting complications. This is due to the drastic decrease of passive antibodies after 3 months of life. After 4 months of life, maternal protection could be lost [28]. In

Table 1 Occurrence of complications in each age group (in absolute terms and in percentage of cases in each age group)

	< 7 months (%)	≥ 7 months (%)	Total (%)
Impetignization	8 (5%)	12 (6%)	20 (5.6%)
Worsening atopic dermatitis	0	2 (1%)	2 (0.6%)
Acute media otitis	1 (0.6%)	3 (1.5%)	4 (1.1%)
Bronchiolitis	1 (0.6%)	0	1 (0.3%)
Pertussoid cough	0	1 (0.5%)	1 (0.3%)
Estreptococcal perianal disease	0	1 (0.5%)	1 (0.3%)
Intensse hyporexia	1 (0.6%)	0	0

Table 2 Differences in secondary variables by age range

	7–12 m (CI 95%)	0–6 m (CI 95%)	OR (CI 95%)
Fever (46.1%)	55% (48–62%)	35% (27–42%)	2.29 (1.49–3.52)
> 50 skin lesions (41.9%)	47% (40–54%)	35% (28–43%)	1.62 (1.05–2.48)
Moderate or severe forms (29.1%)	35% (28–42%)	22% (15–28%)	1.96 (1.22–3.17)
Complications (8.1%)	10% (5–14%)	6% (3–10%)	1.55 (0.70–3.40)
Hospital admissions (2%)	1% (0–1%)	4% (1–7%)	0.26 (0.05–1.29)
Oral antiviral treatment (24.3%)	18% (12–23%)	33% (26–40%)	0.45 (0.27–0.73)

our study, 74.58% of mothers had had chickenpox, similar to the Pinquier study [28], 2.79% did not know, and only 0.28% had received the vaccine, but antibody titers were not measured.

Chickenpox is a vaccine preventable disease. In 1995, the USA introduced vaccination from early infancy throughout the country followed by Canada, Japan, Australia, North Korea, and Israel. In Europe, however, few countries have implemented vaccination programs for chickenpox [20] [34]. In Spain, the chickenpox vaccine was introduced in 2005 for adolescents at risk [25] and in 2016, a systematic vaccination in early childhood became widespread, with an initial dose given between 12 and 15 months of age and a booster between the ages of 3 and 4.

There is controversy about the need for subsequent vaccination in those under 12 months old who have had chickenpox in the first year of life. Almost half of the participating pediatricians recommend it, especially when the illness develops before 7 months of age and about 20% of pediatricians had doubts about this. Accordingly, there are no solid arguments on the best action to follow given that these are expert opinions. There are recommendations which support not vaccinating patients as long as there is confirmation through laboratory tests and the diagnosis is not in doubt [21]. Others recommend vaccinating children under 6 months and in the case of the older children it would not be deemed necessary if the disease was manifesting a complete and typical clinical syndrome [7]. Others recommend vaccinating whether such circumstances occur or not [26].

This is the first work about varicella in child under 12 months old diagnosed in primary care which data a larger number of cases in a country. Due to the universal vaccination since 2016, it could be difficult to realize a similar work in the future. Nevertheless, this study has some limitations derived from the scope of data collection. The diagnosis had to be exclusively clinical since it was very economically costly (and probably unjustified) to perform serology tests in every case. However, chickenpox is easy to diagnose for pediatric specialists and is a notifiable disease in our country. In addition to the inherent bias in data collection through surveys (noncoverage errors and non-response errors), bias could have been due to the interviewer (mainly of cooperation, since PAPenRED pediatricians participate voluntarily). Case inclusion was not randomized. It was requested that all cases be recorded successively in the study period, but it is possible that the habitual strain on healthcare or in the form of "peaks" has been a factor in case selection. The selection of the sentinel sample by Autonomous Regions ensures proper representation at a national level, so that valid data from the entire country is reflected.

In the future, Spanish mothers will be immunized against varicella, as a result of the current universal vaccination. Our work has shown the benignity of chickenpox in younger infants due to the maternal antibodies protection. It will be interesting compared the clinical implications between maternal antibodies title after vaccination or illness.

Overall, and with a good number of compiled cases, we have found that in our environment, the behavior of this disease in the first level of health care is also benign in children under 1 year of age. However, despite zero lethality rates and few hospital admissions, pediatricians resorted to specific antiviral treatment in one out of every four children.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical considerations The PAPenRED project as a whole has obtained the approval of the Aragon Ethics and Scientific Research Committee (Favorable Ruling, Act No. 19/2013, C.P.-C.I. PI13 / 00154). An information sheet was provided for the parents/legal guardians of the children participating in the study and informed consent was signed for the use of data. To ensure the appropriate patient anonymity, the data was codified so that only the patient's own pediatrician could know their identity.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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