

Impact of universal two-dose vaccination on varicella epidemiology in Navarre, Spain, 2006 to 2012

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In 2007 in Navarre, Spain, universal varicella vaccination with two doses of Varivax was introduced in the childhood immunisation schedule for children aged 15 months and three years. This study describes changes in the epidemiology of varicella in the period 2006 to 2012 and evaluates vaccination effectiveness using epidemiological surveillance data. The incidence of varicella in children aged 0 to 14 years decreased by 98.1%, from 50.1 cases per 1,000 inhabitants in 2006, to 1.0 per 1,000 in 2012. Children aged one to eight years were the vaccinated cohorts, and their incidence of varicella decreased by 98.5% ($p<0.0001$). In unvaccinated age groups, important reductions were also achieved between 2006 and 2012: 90.5% ($p<0.0001$) in infants under one year of age, and 89.4% ($p<0.0001$) in children aged nine years. In the period 2006 to 2012, the hospital admissions rate for varicella or its complications decreased by 89.0%, and in 2012, there was only one admission of a newborn with neonatal varicella. Vaccine effectiveness for at least one dose was 96.8% (95% confidence interval: 96.3–97.2%). Universal vaccination with two doses has reduced varicella circulation to minimum levels within five years and has proved highly effective.

Introduction

In the absence of vaccination, varicella-zoster virus (VZV) circulates widely and infects most people during childhood [1]. Varicella typically occurs during the school year, with outbreaks affecting classmates and family members [2–5]. In 1995 the first varicella vaccine, with one dose, was introduced in the childhood vaccination schedule in the United States (US). Subsequent years saw a reduction, not only of cases of varicella, but also of hospitalisations due to its complications [6–8]. In other countries like Australia [9,10], Germany [11] and Italy (Region of Veneto) [12], universal childhood vaccination against varicella has had similar effects.

Despite high one-dose vaccination coverage and the success of the vaccination programme in the US, the

occurrence of continued outbreaks in highly vaccinated populations and an increasing number of vaccine failures [8,13] led the Advisory Committee on Immunization Practices (ACIP) in 2006 to recommend a second dose of the vaccine [4]. The two-dose scheme is expected to have a rapid and pronounced impact on the control of varicella circulation [14].

Thanks to herd immunity, varicella vaccine protects not only those who are vaccinated, but also the unvaccinated, since the probability that susceptible individuals will come into contact with the VZV diminishes [15,16]. This indirect effect could also contribute to the impact of a universal varicella vaccination programme. Most studies have evaluated the impact of varicella vaccination programmes which started with a single-dose scheme or which introduced the second dose after a period of using a one-dose programme. It would be interesting to have evidence on the potential impact of the introduction of varicella vaccination in childhood with a two-dose scheme.

Navarre is a Spanish region with 644,566 inhabitants in 2012, of whom 100,282 were under 15 years-old. The Navarre Health Service provides healthcare, free at point of service, to 97% of the population; it comprises one tertiary hospital in the main city, two small local hospitals, all of them with paediatric wards and emergency rooms, and 54 primary healthcare centres. The clinical reports have been computerised since 2000, and include those from both primary care and hospital admissions. All vaccine doses administered are registered at the vaccination points.

In 2004, Navarre began varicella vaccination for all susceptible individuals (individuals with no history of varicella and who had not been previously vaccinated) at age 14 years for cohorts born since 1990. In 2006, the age of vaccination of susceptible children was lowered to 10 years for all those born since 1996. A school catch-up vaccination was performed for susceptible persons born between 1992 and 1995. In 2007,

universal vaccination with two doses was introduced for all children born since 2006. The schedule calls for the first dose of vaccine at the age of 15 months and a second dose at the age of three years. In order to obtain a rapid decrease in varicella cases, all children born in 2004 and 2005 were offered vaccination with one dose at the age of three years. In addition, vaccination of susceptible individuals continued for all children who had not received universal vaccination (those born between 1996 and 2003). In 2011, a second dose of vaccine was offered to all cohorts who had previously received only one dose.

Varicella and measles-mumps-rubella vaccinations in Navarre are administered at the same time, but in separate vaccines. Varilrix was used for vaccination of susceptible adolescents until the end of 2006, and Varivax was used for all vaccinations after that. In the period from 2009 to 2012, vaccination coverage was around 95% for the first and second doses of measles-mumps-rubella vaccine and the first varicella vaccine dose, and over 89% for the second varicella vaccine dose (data not shown).

The aim of this study is to describe the epidemiology of varicella in Navarre, Spain, since the introduction of universal vaccination with a two-dose scheme, in terms of its impact on both vaccinated cohorts (direct effect) and unvaccinated cohorts (indirect effect), and to assess the vaccine effectiveness.

Methods

Study design and information sources

Varicella is a notifiable disease in Navarre [17]. From the electronic clinical reports of primary healthcare, automatic notification of all diagnoses of varicella (ICPC-2 code A72) is generated according to the International

Classification of Primary Care, Second Edition (ICPC-2) [18], including the date of consultation, date of birth, sex and vaccination history.

Varicella surveillance in hospitals is conducted by trained nurses, who review clinical and laboratory reports daily to search for cases among admitted patients. At the end of each year this information is validated with hospital discharge diagnoses. In the present study, we considered all admissions with a principal diagnosis of varicella (ICD-9 code 052.9) or complication of varicella (ICD-9 codes 052.0, 052.1, 052.7, 052.8) according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) [19]. A unique patient identification number was used to detect and exclude duplicate cases. The number of vaccine doses received, the date and the brand name were taken from the regional vaccination registry.

In the cohorts of vaccinated children, three possible explanations for cases of varicella were considered according to the temporal criteria already described [20]: Cases with onset in the first 14 days after the first vaccine dose were considered as not related to the vaccine; those occurring between 15 and 42 days after receipt of a vaccine dose were attributed to the vaccine virus, and all cases occurring more than 42 days after administration of a dose of varicella vaccine were considered vaccine failures or breakthrough varicella.

Statistical analysis

To calculate incidence rates, we used as the denominator the population of Navarre at the beginning of each year, according to the National Statistics Institute [21] of Spain. To assess the impact of vaccination, we compared the incidence in 2012 with the incidence in 2006, the year before universal vaccination was initiated. We

FIGURE 1

Notified varicella cases, by four-week period, Navarre, 2006–2012 (n=10,477)

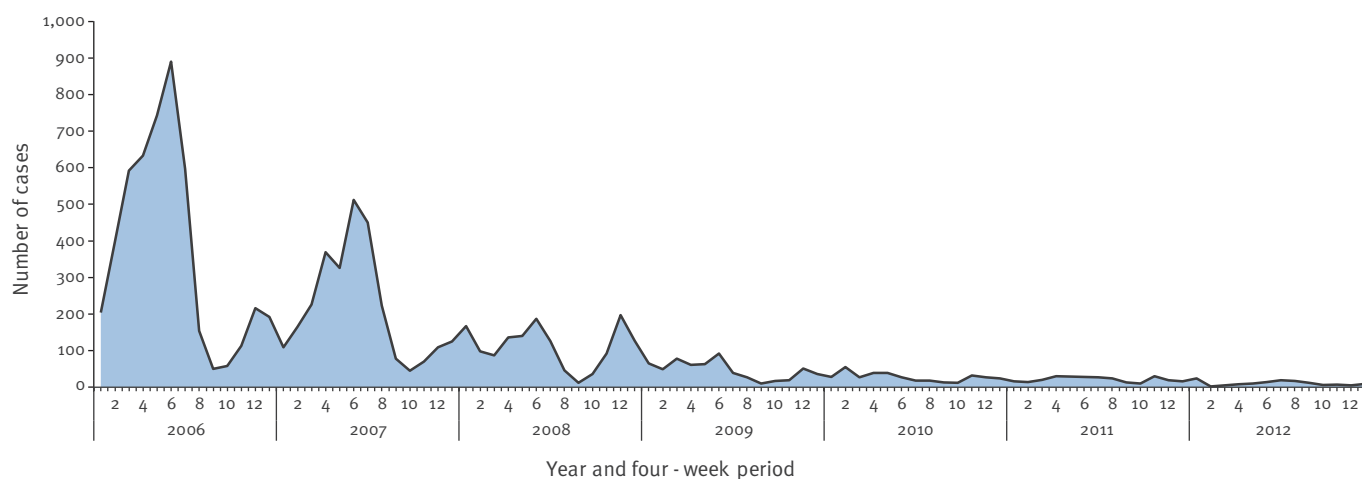
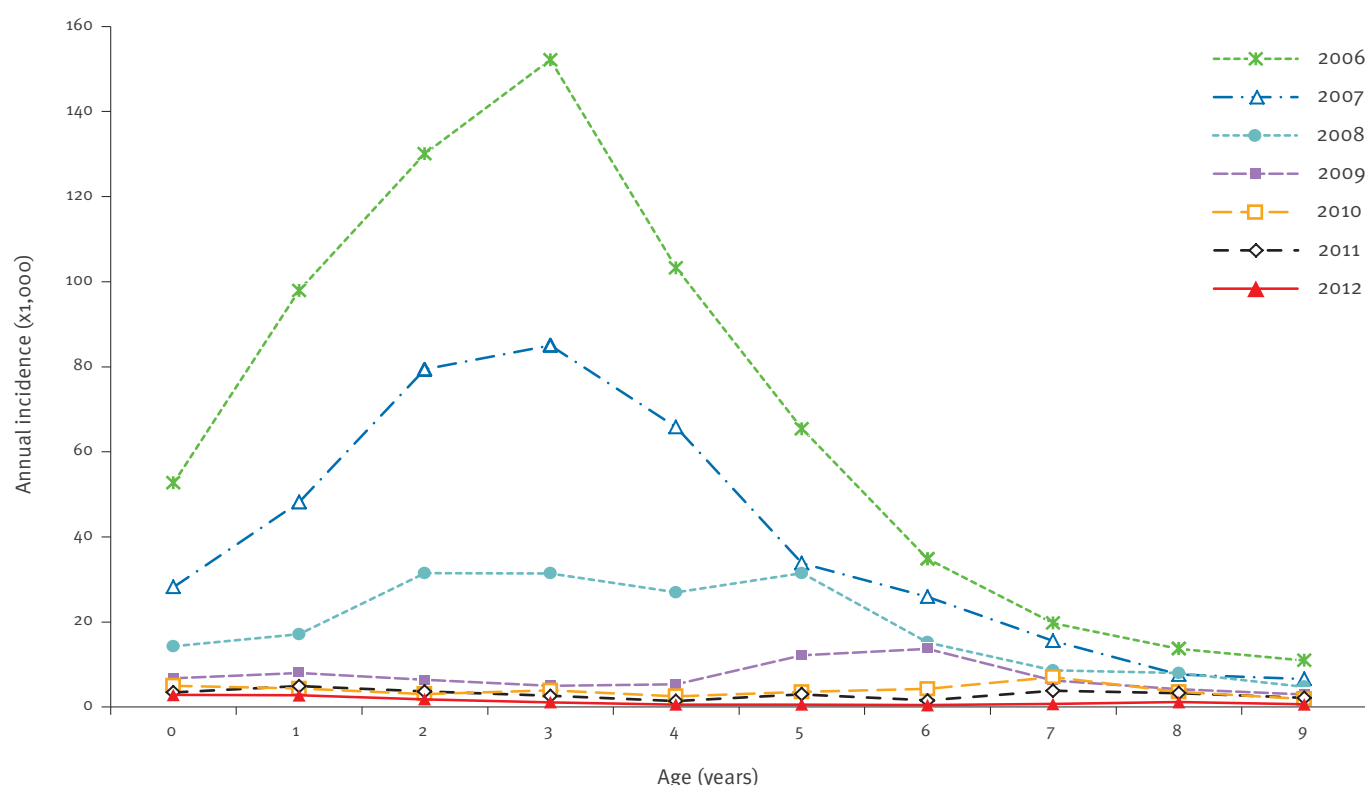


FIGURE 2

Annual incidence of varicella per 1,000 inhabitants by age, Navarre, 2006–2012



evaluated the direct effect of vaccination in age groups in which universal vaccination was offered, and the indirect effect (herd immunity) in unvaccinated age groups. The chi-square test and Fisher's exact test were used for the statistical analysis.

Varicella vaccine effectiveness for at least one dose was calculated using the screening method proposed by Farrington [22], based on a comparison of the proportion of vaccinated persons among the cases and the population. Vaccine effectiveness (VE) is then given by the expression:

$$VE = 1 - \left[\frac{PCV}{(1 - PCV)} \times \frac{(1 - PPV)}{PPV} \right]$$

where PCV is the proportion of cases vaccinated and PPV is the proportion of the population vaccinated. We estimated vaccine effectiveness in the birth cohorts born between 2004 and 2010 that had received the vaccine between 2007 and 2012.

Results

Figure 1 shows the time trend of varicella incidence in Navarre in 2006 to 2012. Of note is the marked seasonality in the first years, with peaks in late spring, and a rapid reduction in incidence during the study period.

Incidence of varicella

From 2006 to 2012, 10,477 cases of varicella were diagnosed in primary healthcare, 50.7% in males, 62.5% in children under five years-old, and 87.6% in those younger than 15 years. The incidence of varicella decreased progressively, from 8.04 cases per 1,000 inhabitants in 2006 to 0.21 per 1,000 in 2012, a reduction of 97.3% ($p < 0.0001$). The incidence of varicella in children aged 0 to 14 years decreased from 50.1 cases per 1,000 inhabitants in 2006 to 1.0 cases per 1,000 in 2012, which represented a 98.1% reduction.

While 82.9% of cases occurred in children under age 15 in 2006, this percentage decreased to 70.3% in 2012. Furthermore, the peak incidence of varicella have moved, from the three year-olds in 2006 to a situation with two small peaks in 2012, corresponding to children under 15 months-old and children aged nine years, as these children have not yet been vaccinated (Figure 2).

Impact of varicella vaccination

In children aged one to eight years, the cohorts vaccinated in the universal vaccination programme, the incidence of varicella decreased by 98.5% ($p < 0.0001$). Important reductions were also observed in cohorts vaccinated at age 10 to 21 years. The incidence declined by 93.8% ($p < 0.0001$) among the 10 to 16 year-olds and

TABLE 1

Annual incidence of varicella per 1,000 inhabitants among age groups included in universal vaccination (1–8 years) and vaccination of susceptibles (10–21 years), Navarre, 2006–2012

Age groups	2006	2007	2008	2009	2010	2011	2012	% reduction 2006–2012
Universal vaccination								
1 year	70.1	32.8	19.2	8.5	5.3	5.1	2.9	95.9% ^c
2 years	117.9	67.3	11.3	7.3	3.8	3.6	2.7	97.7% ^c
3 years	133.0	78.0	46.7	5.2	3.6	3.5	1.4	99.0% ^c
4 years	142.8	86.3	15.3	5.4	3.3	1.3	0.7	99.5% ^c
5 years	94.9	49.3	43.0	4.5	2.8	2.2	0.3	99.7% ^c
6 years	51.7	30.0	21.4	21.7	3.5	2.5	0.7	98.6% ^c
7 years	28.3	19.7	9.5	7.4	6.3	1.6	0.3	99.0% ^c
8 years	14.4	12.5	9.8	5.2	5.9	5.0	0.7	94.9% ^c
Total 1–8 years	92.1	52.6	23.9	8.5	4.1	2.8	1.2	98.5%^c
Vaccination of susceptibles								
10–16 years^a	7.3	2.0	1.6	1.5	0.6	0.4	7.3	95.6%^c
17–21 years^b	2.7	1.4	0.6	0.6	0.4	0.2	0.3	90.1%^c

^a Vaccinated at 10 years of age.

^b Vaccinated at 11, 12, 13 or 14 years of age.

^c p value <0.001.

by 90.1% ($p<0.0001$) in persons aged 17 to 21 years (Table 1).

Also in unvaccinated age groups, important reductions were achieved between 2006 and 2012: 90.5% ($p<0.0001$) in infant under the age of one year, and 89.4% in nine-year old children. In people older than 21 years, the overall reduction was 92.4% ($p<0.0001$) (Table 2).

Before the introduction of universal vaccination, most cases (77.7%) occurred in winter and spring, with a peak in weeks 21 to 24 (second half of May to first half of June). A slight change in the seasonality of varicella was observed, in that in 2012, only 52.2% of cases

occurred in that period. Moreover, due to an overall reduction in varicella incidence, cases in 2012 were distributed more homogeneously throughout the year, especially from autumn to spring.

Varicella in vaccinated individuals and breakthrough varicella

Between January 2007 and March 2013, 42,860 children born between 2004 and 2011 were vaccinated against varicella: 14,617 received only one dose and 28,243 had two doses. In these birth cohorts, 2,448 cases of varicella were diagnosed until December 2012, 260 of which (10.6%) occurred in vaccinated children. Considering the time interval between the last dose and symptom onset, 22 cases were considered to be vaccine cases (0.9%) and 238

TABLE 2

Annual incidence of varicella per 1,000 inhabitants in unvaccinated age groups (indirect effect), Navarre, Spain, 2006–2012

Age groups	2006	2007	2008	2009	2010	2011	2012	% reduction 2006–2012	p
< 1 year	12.5	8.7	5.5	1.9	1.5	1.3	1.2	90.5%	<0.0001
9 years	11.7	6.3	5.9	3.0	2.4	2.9	1.2	89.4%	<0.0001
22–24 years	1.6	1.2	0.6	0.4	0.3	0.1	0.1	96.8%	<0.0001
25–44 years	1.6	0.9	0.6	0.3	0.2	0.2	0.05	92.4%	<0.0001
45–64 years	0.2	0.2	0.1	0.08	0.06	0.07	0.04	84.6%	0.0015
≥65 years	0.1	0.07	0.04	0.03	0.02	0.02	0.01	91.7%	0.0526
Total ≥22 years	0.8	0.5	0.3	0.2	0.1	0.1	0.06	92.4%	<0.0001

TABLE 3

Hospital admissions with diagnosis of varicella (ICD-9-CM code 052.9) and varicella with complication (ICD-9-CM codes 052.0, 052.1, 052.7 and 052.8), Navarre, Spain, 2006–2012 (n=71)

	2006	2007	2008	2009	2010	2011	2012	% reduction 2006–2012
Total population								
Hospital admissions	25	22	11	7	1	2	3	88%
Average stay (days)	5.9	5.0	3.4	5.0	6.0	1.5	4.3	NA
Admissions per 100,000	4.2	3.6	1.8	1.1	0.3	0.3	0.5	89% ^a
Number of complicated varicella	10	10	2	3	0	0	0	NA
Children <15 years								
Hospital admissions	18	14	9	2	0	0	1	94%
Average stay (days)	5.9	4.6	3.2	4.0	NA	NA	3.0	NA
Admissions per 100,000	20.9	15.9	9.9	2.1	0	0	1.0	95% ^a
Number of complicated varicella	5	6	1	1	0	0	1	NA

NA: not applicable.

^a p value =0.0001.

as vaccine failures or breakthrough varicella (9.7%). One medical consultation for varicella attributable to the vaccine virus was produced for every 3,231 doses administered: one consultation for every 2,381 first doses, and one for every 7,060 second doses. About 82% of vaccine-attributable cases of varicella occurred after administration of the first dose.

Among the 42,860 vaccinated children, 238 cases of breakthrough varicella were diagnosed (0.56%). About 85% of vaccine failures (n=202) occurred after administration of the first dose, corresponding to 1.38% of those vaccinated with one dose), while 36 vaccine failures occurred after the second dose (0.13% of those vaccinated with two doses; $p<0.0001$). One medical consultation for breakthrough varicella was produced for every 299 doses administered: one consultation for

every 212 first doses, and one for every 785 second doses.

Hospitalisations due to varicella

The incidence rate of hospitalisations for varicella declined by 89%, from 4.2 per 100,000 inhabitants in 2006 to 0.5 per 100,000 in 2012 ($p<0.0001$). In children under 15 years the rate declined by 95%, from 20.9 to 1.0 per 100,000 ($p<0.0001$), with only one hospitalisation of a newborn with neonatal varicella (Table 3).

Effectiveness of varicella vaccine

Between 2007 and 2012, 36,971 of the 47,908 children born between 2004 and 2010 had received at least one dose of varicella vaccine (77.2%). In the same period, 2,422 cases of varicella were diagnosed in children

TABLE 4

Estimated vaccine effectiveness of any dose of varicella vaccine in vaccinated cohorts (children born between 2004 and 2010), Navarre, 2007–2012

Birth year	Population			Varicella cases			Vaccine effectiveness (95% confidence interval)	
	n	Vaccinated n (%)		n	Vaccinated n (%)			
2004	6,723	2,357	(35)	678	19	(3)	94.7	(91.6–96.6)
2005	6,612	3,104	(47)	819	23	(3)	96.7	(95.1–97.8)
2006	6,869	6,004	(87)	355	86	(24)	95.4	(94.2–96.3)
2007	6,881	6,207	(90)	271	47	(17)	97.7	(96.9–98.3)
2008	7,135	6,587	(92)	147	29	(20)	98.0	(97.0–98.6)
2009	6,917	6,434	(93)	87	24	(28)	97.1	(95.5–98.2)
2010	6,771	6,278	(93)	65	10	(15)	98.6	(97.2–99.3)
2004–2010	47,908	36,971	(77)	2,422	238	(10)	96.8	(96.3–97.2)

born between 2004 and 2010, and 238 of these cases had previously been vaccinated (9.8%). Accordingly, the effectiveness of at least one dose of varicella vaccine was 96.8% (95% confidence interval: 96.3–97.2%). Table 4 shows the effectiveness for each birth cohort, which ranged from 94.7% to 98.6%.

Discussion

Universal varicella vaccination with a two-dose scheme has greatly reduced the impact of this disease in the whole population of Navarre. The reduction was particularly great in the vaccinated cohorts of children aged one to eight years, with a 98.5% decline in incidence within a period of only five years, higher than that reported in other places where universal vaccination has been introduced, such as the US and the Veneto region in Italy [6,12,23–25]. An important reduction in varicella incidence was also noted in persons aged 10 to 21 years, in cohorts included in the strategy of vaccination of susceptibles. Such marked declines may be explained by the introduction of universal vaccination with two doses from the beginning, and the high coverage achieved since the first year.

Varicella incidence also decreased considerably in the unvaccinated cohorts, especially in infants under the age of one year (90.5%), which can be attributed to a herd immunity effect due to reduced circulation of VZV [16]. In children aged nine years and persons over the age of 21 years, significant reductions are also noted, whereas the impact in older adults was lower given that the incidence of the disease in this group had already been low before. All these changes have led to a slight forward shift in the age pattern of this disease. The proportion of cases under 15 years-old have declined, and the peak incidence, which typically occurred at the age of three years, has shifted to the age groups not yet vaccinated, and is now much less pronounced than before.

Rates of hospitalisation for varicella declined markedly (88%), more pronounced and quickly than reported in other countries [7,26–28]. In children under the age of 15 years, there was only one hospitalisation in 2012, showing that vaccination has had a substantial impact in reducing severe and complicated forms of varicella.

Because it contains attenuated virus, the varicella vaccine may infrequently cause disease, generally mild, in immunocompromised individuals, although cases have also been described in immunocompetent people [29]. From an epidemiological perspective, only 0.9% of cases of varicella in vaccinated individuals in our study were attributable to the vaccine virus, given that they appeared between 14 and 42 days after vaccine administration.

We observed vaccine failures in children with one and two doses of varicella vaccine, although these cases were generally not confirmed by laboratory. Breakthrough disease can be difficult to accurately

diagnose clinically and may be overreported in the absence of laboratory confirmation [14]; we defined it as a case of varicella that appears in a person who was vaccinated more than 42 days before the onset of symptoms. Other authors have reported that these cases typically exhibit a shorter duration of illness, fewer constitutional symptoms, less than 50 skin lesions, and a rash that may show an atypical appearance (maculo-papular with few or no vesicles) [20,30]. However, breakthrough disease also results in medical consultation and can transmit the virus to susceptible individuals, which may lead to outbreaks [20,25].

The need for a second dose of vaccine has been widely assessed. Brisson et al. estimated that protection wanes by up to 3% per year, with the consequent risk of developing a breakthrough infection if exposed to VZV [31]. As has been suggested, a second dose offers additional protection and reduces the possibility of breakthrough cases [25,32–34]. Our approach to vaccine effectiveness in vaccinated cohorts showed high effectiveness (96.8%) in a programme where most of children had received two doses. One study estimated that vaccine efficacy after a 10-year follow-up was 94.4% for one injection and 98.3% for two injections [35]. Shapiro et al. have estimated that the odds of developing varicella were 95% lower for children who received two doses than for those who received one dose of varicella vaccine in the first 2.5 years after recommendation of a routine second dose in the US vaccination programme [25].

The main limitation of the present study is its ecological design and the fact that it is based on epidemiological surveillance data. The incidence of varicella in the population usually varies over time, but the marked reductions in incidence following the introduction of the vaccine would be difficult to explain by other causes. Varicella surveillance in Navarre during the study period was based on automatic notification from electronic clinical reports, which were fully implemented throughout the healthcare network, making underreporting of cases highly unlikely and ensuring a high level of completeness of information.

Immunity to VZV might be maintained by external boosting of immunity through exposures to varicella or herpes zoster [36]. Exposure to varicella might reduce the risk of zoster [37,38] and on the other hand, its absence would lead to an increase of herpes zoster [34,39]. Although this possible negative effect of the two-dose universal vaccination programme has not been taken into account in this study, recent studies have not demonstrated a relationship between varicella vaccination and increase of zoster disease in the general population [20,40,41]. Moreover, others have reported a reduction in zoster incidence in vaccinated [40,42]. In this context of universal varicella vaccination, long-term studies to monitor zoster incidence will be necessary to assess whether zoster rates increase.

This study was based on clinically diagnosed cases of varicella, which were only occasionally confirmed by laboratory. The clinical diagnosis of varicella is highly specific in the context of wide virus circulation in the population. However, in situations of very low incidence, other diseases with clinical features similar to varicella, although infrequent, may acquire appreciable weight relative to the clinical diagnoses of varicella. In order to maintain a high specificity in varicella diagnosis, it may be desirable to incorporate virological confirmation of varicella cases in populations with high vaccination coverage, especially in breakthrough cases, since, in the absence of a large number of vesicles, they might be confused with other viral syndromes.

In conclusion, five years after the inclusion of two doses of varicella vaccine in the childhood vaccination schedule of Navarre, the incidence of this disease has diminished drastically, not only in vaccinated individuals, but also in the unvaccinated, due to herd immunity. Hospital admission rates are also lower. Varicella vaccine has been shown to be highly effective. In this situation of very low incidence, it is very important to continue varicella surveillance and to assess disease trends over time; laboratory confirmation of varicella cases is also recommended.

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