

A cost-benefit analysis of varicella vaccination in Aragón

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ABSTRACT

Background. Varicella, a contagious and infectious disease that is usually benign in children, may become complicated among adults and vulnerable children and may even be life-threatening. There are effective vaccines. A retrospective study was conducted about costs and resulting hospitalizations related to this disease in the population of Aragón in the 2004-2014 period. Costs were compared to the expenses that would have been incurred if those people had received the vaccine and also to the expenses of vaccinating the 1-year-old population over the entire period. A cost-benefit analysis was done to assess the economic impact of varicella vaccination.

Method. Data for the 11-year period were provided by the Autonomous Community of Aragón (Spain) and included annual varicella incidence, hospital discharges of varicella cases, costs of primary health care visits and hospitalizations for each year, costs of each workday as per the minimum annual salary and of drugs used). Capitalized costs were estimated and compared to capitalized expenses of vaccination, and a sensitivity analysis was performed.

Results. A benefit-cost ratio of 1.6 was obtained considering that all children who had varicella had been vaccinated and had received a booster dose. A benefit-cost ratio of 1.24 was obtained considering that the vaccine had been administered to every 1-year-old individual at a price of EUR 28.59 per vaccine. Over the 11-year period, 53% of hospitalizations corresponded to children younger than 5 years old.

Conclusions. Public campaigns for the immunization of children younger than 4 years old with 2 doses lead to cost savings and are cost-effective because the vaccine price results in a benefit-cost ratio greater than 1. A major reduction is expected in the number of hospitalizations among children aged 3-4 years.
Key words: varicella, vaccines, cost-benefit analysis, economy in health care and organizations.

<http://dx.doi.org/10.5546/aap.2017.eng.432>

To cite: Peña Blasco G, Blasco Pérez-Aramendía J. A cost-benefit analysis of varicella vaccination in Aragón. *Arch Argent Pediatr* 2017;115(5):432-438.

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Funding:
Guillermo Peña received external funding from the Government of Aragón and the European Social Fund (Public Economics Research Group).

Conflict of interest:
None.

Received: 8-7-2016
Accepted: 2-20-2017

INTRODUCTION

Varicella is an infectious, contagious disease caused by varicella-zoster virus which mainly affects children. It is usually benign but 12% of patients may suffer some sort of complications. It is also highly contagious. Patients should remain in isolation and miss school for several days. In a large population, this also supposes parental absenteeism from work and minor medical expenses for the symptomatic relief of symptoms.

Perinatal varicella, which develops from 5 days before to 2 days after delivery, may be very severe in 30% of cases. Varicella complications may lead to hospitalizations during childhood, including death, especially among immunocompromised children. In adults, the rate of complications is 25 times higher.¹ Hospitalization expenses and workplace absenteeism due to varicella imply a large social disbursement. In the United States, it has been estimated that varicella is the most common cause of death attributed to vaccine-preventable diseases.

The varicella vaccine was initially registered for its use exclusively in patients at risk in Europe (1984) and Japan (1986). It was later approved for its general use in South Korea (1988), the United States, Sweden, and Germany (1995).³ In Spain, it has been used in hospitals since 1997 and approved for sale at pharmacies in 2005. At present, in Spain, there are two live, attenuated virus (OKA strain) vaccines.^{1,4} In the Autonomous Community of Aragón (1325 million inhabitants in 2014), the vaccine was introduced in the immunization schedule in 2007 for children aged 11 years and a booster dose was introduced in 2009. In Spain, it is

administered free of charge by the Public Health System. Two vaccine doses provide an overall coverage of 100%,⁵ and are very well-tolerated. The Spanish Society of Pediatrics' immunization schedule indicates the first dose for 1-year-old infants and a booster dose as of 2-3 years.⁴ In 2016, the varicella vaccine was introduced at a national level in Spain for children aged 15 months old with a booster dose at 3-4 years.⁶

Some countries provide the measles, mumps, rubella and varicella (MMRV) vaccine to infants with the corresponding booster dose.^{1,7}

Varicella vaccine critics claim an increase in the incidence of herpes zoster. However, large population-based prospective studies have detected a reduction in the incidence of herpes zoster among vaccinated children compared to those who had wild-type varicella, although additional years of follow-up are required.⁸

In this study, the number of varicella cases in the general population of Aragón over an 11-year period (2004-2014) was assessed. Varicella-related hospitalizations and the resulting related costs were studied. The objective of this study is to assess varicella vaccination cost-effectiveness, either paid by patients or by the Public Health Administration, provided to the entire 1-year-old population as per the immunization schedule. Our hypothesis is that having varicella is more expensive than receiving the vaccine, even two doses.

MATERIAL AND METHODS

This was a retrospective study that included the number of varicella cases occurred in Aragón between 2004 and 2014 and hospital discharges registered in the entire community; these data were then analyzed. A cost-benefit analysis was subsequently done to compare varicella-related expenses and vaccine costs.

Incidence data were obtained from the Mandatory Reportable Diseases records of the General Council of Aragón and from primary health care medical records of cases diagnosed with varicella (OMI AP code for Aragón: A72).⁹ Hospital discharge records corresponded to the entire health care network of the Autonomous Community of Aragón (public and private hospitals) with varicella infection as the main diagnosis (data source: basic minimum dataset of the Planning and Insurance Management Division, ICD-9-CM 052, varicella, Aragón) over the 2004-2014 period and for the overall Aragón population.

A retrospective cost-benefit analysis was done, which consisted of comparing investment benefits and capitalized costs and establishing its cost-effectiveness. The benefit-cost ratio (BCR) was used to this end. This index measures, in relative terms, the return on investment, and is calculated as the ratio between the capitalized sum of the benefits and costs, respectively. It is also known as profitability index. A BCR greater than 1 indicates that there is a positive return on the investment whereas a BCR lower than 1 means that the investment is not profitable. The minimum expenses resulting from primary health care visits and hospitalizations per each day in the hospital were estimated. The following were taken into account: cost of a single primary health care pediatric visit (as per the service provision rates for each year according to the Billing Service of Zaragoza Health Sector 3), average minimum expenses for treatment at home (pain killers, antiseptic agents, antipruritic agents: EUR 11.75), and costs of missing a workday for one of the parents as per the inter-professional minimum salary for each year according to the corresponding Official Bulletin of the State.¹⁰ In relation to hospitalized patients, the cost of each hospitalization day was estimated (as per the service provision rates, including stay and medications, for each year according to the Billing Service of Zaragoza Health Sector 3) multiplied by the mean length of stay for each year, plus the expenses of missing 5 working days for one of the parents or for an adult working patient (as per the inter-professional minimum salary for each year according to the corresponding Official Bulletin of the State). This was because the mean length of stay every year was greater than 4 days, and the Law for the Conciliation of Labor and Family Life allows to miss 5 working days when a dependent family member is hospitalized.

These data were compared to the hypothetical cost that would have been undertaken if every individual affected by varicella every year had received the varicella vaccine at a retail price of EUR 43.63 during routine nurse checkups—at no additional cost—with a booster dose since 2009. These values were capitalized to the actual price in 2014 at a capitalization factor of 3%.¹¹ Such factor was based on the preference of past over present. The capitalization factor was calculated as follows:

$$(1 + r)^t$$

for each "t" (study years); "r" was the rate of

capitalization. To establish the economic return of implementing the varicella vaccine, the BCR was used.

The costs that would have implied to vaccinate the entire population (100% coverage) of infants born each year in Aragón from 2004 to 2014 (data from the National Statistics Institute of Spain) with the varicella vaccine up to 2009, and with two doses as of that year, were also calculated at a cost price of EUR 28.59 (General Division of Public Health of the Government of Aragón in 2015). Data were capitalized as per 2014 values, and the BCR was calculated in relation to expenses from 2004 to 2014. Expenses that would have been incurred if the varicella vaccine had not been included in the vaccination schedule

were considered returns on the investment, and the money saved by including the vaccine in the schedule was also estimated, whereas the costs of every administered vaccine were considered investment costs. Afterwards, a sensitivity analysis was done with a slight variation in data, for example, changing the capitalization factor from 3% to 6% or the vaccine cost from EUR 43.63 to EUR 28.59 to verify robustness of results obtained and causes of variation.

RESULTS

The number of varicella cases recorded between 2004 and 2014 (*Table 1*) showed an oscillating pattern that ranged from 8741 cases in 2004 to 4371 in 2013.

TABLE 1. *Varicella-related expenses, in Euros, for Aragón over the 2004-2014 period*

Year	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Number of varicella cases	8741	6779	6183	8602	5202	7561	4441	5768	7087	4371	7174
Primary health care cases	8683	6711	6126	8535	5170	7519	4407	5732	7042	4343	7136
Visit expenses	44.03	51.18	50.97	54.33	56.18	58.15	58.09	57.51	72.53	71.23	70.02
Volumen of visit expenses	382312.49	343468.98	312242.22	463706.55	290450.6	437229.85	256002.63	329647.32	510756.26	309351.89	499662.72
Expenses for missing 1 workday	15.855	17.1	18.03	19.02	20	20.8	21.11	21.38	21.38	21.51	21.51
Treatment expenses	11.75	11.75	11.75	11.75	11.75	11.75	11.75	11.75	11.75	11.75	11.75
Family expenses	239694.215	193612.35	182432.28	262621.95	164147.5	244743.45	144814.02	189901.16	233301.46	144448.18	237343.36
Total primary health care expenses	622006.705	537081.33	494674.5	726328.5	454598.1	681973.3	400816.65	519548.48	744057.72	453800.07	737006.08
Number of hospital discharges	58	68	57	67	32	42	34	36	45	28	38
Length of stay in days	7.2	7.5	5.2	6	7.9	6.6	4.8	6.9	5.6	6.6	5.2
Expenses per day in the hospital	327.6	342.02	340.6	363.09	418	432	443	496	526	556	591
Hospitalization expenses	136805.76	174430.2	100953.84	145962.18	105670.4	119750.4	72297.6	123206.4	132552	102748.8	116781.6
Volume of expenses for missing 5 workdays	4597.95	5814	5138.55	6371.7	3200	4368	3588.7	3848.4	4810.5	3011.4	4086.9
Total expenses for hospitalized patients	141403.71	180244.2	106092.39	152333.88	108870.4	124118.4	75886.3	127054.8	137362.5	105760.2	120868.5
Period	0	1	2	3	4	5	6	7	8	9	10
Volumen of final expenditure	763410.415	717325.53	600766.89	878662.38	563468.5	806091.7	476702.95	646603.28	881420.22	559560.27	857874.58
Capitalized volume of final expenditure	562957.259	545333.147	470847.061	709944.129	469353.486	692218.371	422021.694	590137.355	829328.285	542773.462	857874.58
Total capitalized volume of final expenditure	6692788.83										

A total of 505 hospital discharges for varicella infection were recorded in Aragón in the 11-year period (Table 1). There were 67 hospitalizations in 2007, and 32 in 2008. The percentage of hospitalizations by number of varicella cases ranged between 1% (68 hospitalizations out of 6779 cases) in 2005 to 0.52% (38 hospitalizations out of 7174 cases) in 2014.

When considering hospitalized patients' age, among 505 hospital discharges, 267 (53%) patients were 0-4 years old; 37 (7%), 5-14 years old; 128 (25%), 15-39 years old; 50 (10%), 40-64 years old; and 23 (5%) were older than 65 years old.

The mean length of stay throughout the study period was 6.3 days per hospitalized patient, ranging from 4.8 days in 2010 to 7.9 days in 2008 (Table 1). The length of stay ranged from 1 to 35 days. The length of stay was 2-7 days in 361 patients (71.5%).

In Table 1, under "total primary health care expenses" it is worth noting that EUR 744 057.72 were spent in 2012 versus EUR 400 816.65 spent in 2010. Under "total expenses for hospitalized patients" it is observed that the expenses per hospitalization were EUR 180 244.2 in 2005 and EUR 75 886.3 in 2010. Under "total capitalized volume of final expenditure" it is shown that EUR 6 692 788.83 were spent over the 11-year period in relation to varicella in Aragón.

In Table 2, under "total capitalized patient vaccination costs" up to 2014, it is observed that the total hypothetical expenses accounted for EUR 4 156 649.35, with a BCR of 1.610.

Table 3 shows a total capitalized population vaccination cost of EUR 5 380 499.29, with a BCR of 1.244.

Table 4 shows a sensitivity analysis where it should be noted that the maximum BCR (2.52)

TABLE 2. Costs, in Euros, if varicella patients had been vaccinated, for Aragón

Year	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Number of varicella cases	8741	6779	6183	8602	5202	7561	4441	5768	7087	4371	7174
Vaccine price per person	43.63	43.63	43.63	43.63	43.63	87.26*	87.26	87.26	87.26	87.26	87.26
Patient vaccination costs	381369.83	295767.77	269764.29	375305.26	226963.26	659772.86	387521.66	503315.68	618411.62	381413.46	626003.24
Period	0	1	2	3	4	5	6	7	8	9	10
Capitalized patient vaccination costs	281231.31	224851.85	211425.97	303240.21	189054.04	566569.40	343070.14	459362.63	581863.49	369971.06	626003.24
Total capitalized patient vaccination costs					4156643.35						
BCR**					1.61014267						

* Two vaccine doses are administered as of 2009.

** Benefit-cost ratio.

TABLE 3. Costs, in Euros, for administering the vaccine to the entire 1-year-old population of Aragón

Year	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Number of 0 year-olds	11064.38	11533.2971	11722.00	12392.45	12976.73	13772.63	13129.85	12964.39	12770.35	12007.50	11683.50
Vaccine price per person	28.59	28.59	28.59	28.59	28.59	57.18*	57.18	57.18	57.18	57.18	57.18
Population vaccination costs	316330.75	329736.965	335132.04	354300.24	371004.75	787518.79	750764.61	741303.82	730208.33	686588.88	668062.56
Period	0	1	2	3	4	5	6	7	8	9	10
Capitalized population vaccination costs	233269.93	250676.28	262657.51	286268.51	309036.57	676269.18	664646.51	676567.98	687053.01	665991.21	668062.56
Total capitalized population vaccination costs					5380499.26						
BCR**					1.24389736						

* The booster dose is administered at 3 years old as of 2009.

** Benefit-cost ratio.

for assumption 3 and the minimum BCR (0.795) for assumption 8; in both cases, each vaccine has a cost price of EUR 43.63. Once such cost is reduced to EUR 28.59 but keeping the remaining outcome measures the same, the BCR increased to 1.397 (assumption 12).

DISCUSSION

This study estimates the economic costs of having administered the varicella vaccine to the Aragón population over the past 11 years and shows that immunization in the infant population is cost-effective as long as the Public Health Administration manages to negotiate an adjusted price, as that obtained in 2015. Once hospitalizations for this cause in the Aragón community are analyzed,³ it is observed that more than half of cases occurred in children younger than 5 years old; therefore, it is expected that health expenses will decrease following the first years of the immunization campaign as long as coverage is high.

Over the past decade, the greatest number of cases was reported in 2004 and the lowest, in 2013; values were as expected within a sustained oscillating pattern.⁹ In relation to hospitalizations, it is worth noting that these decreased as of the second half of 2008 compared to previous years. In 2005, the vaccine was marketed and parents started to give it to their children, so it is difficult to establish accurate vaccine coverage rates in our records.³ Based on our data, the greater percentage of hospitalizations per number of cases (1%) was recorded in 2005, which was also the year when the greatest hospitalization expenses were incurred.

This is suggestive of a greater virulence.²

The investment necessary to administer the varicella vaccine is cost-effective in all cases, except for assumptions 6 and 8, with the vaccine given to the entire infant population, providing a booster dose as of 2009, and paying a retail price for the vaccine (Table 4). Our study shows that the BCR for administering an initial and a booster dose to the entire infant population with vaccines at a cost price per dose is cost-effective. It is also cost-effective if parents assume the responsibility for giving the vaccine at a retail price. The sensitivity analysis showed that assumption 3, with the administration of one dose of the vaccine only to sick individuals at a retail price and assuming a capitalization factor of 6%, is the most cost-effective. This assumption is not consistent with the recommendations of the Spanish Society of Pediatrics,⁴ which suggests that greater effectiveness is achieved with two doses.

The epidemic curve over the past 11 years in Aragón describes an oscillating pattern⁹ and does not show an alteration due to the marketing of the varicella vaccine, that parents may administer on their own.³

A reduction in hospital discharges has been recorded in the autonomous communities where infants have been vaccinated.¹² Our study also observed that hospital discharges reduced to almost a half as of 2008 (with the vaccine already in the market) compared to previous years. It is not possible to assure that is the result of giving the vaccine to infants outside the immunization schedule, which is consistent with the conclusions of Peña-Rey's study.³

TABLE 4. Sensitivity analysis for the cost-benefit assessment

Assumption	Number of doses	Vaccine dose costs	Population*	r**	BCR***
1	1	43.63	Patients	3%	2.49430924
2	1	43.63	Total population	3%	1.30479171
3	1	43.63	Patients	6%	2.51843916
4	1	43.63	Total population	6%	1.30457957
5	1-2	43.63	Patients	3%	1.61014267
6	1-2	43.63	Total population	3%	0.81510487
7	1-2	43.63	Patients	6%	1.58105354
8	1-2	43.63	Total population	6%	0.79524677
9	1	28.59	Total population	3%	1.991187911
10	1	28.59	Total population	6%	2.293184
11	1-2	28.59	Total population	3%	1.24389736
12	1-2	28.59	Total population	6%	1.397881

* Patients with varicella or overall 1-year-old population with a booster dose at 3 years old.

** r: capitalization rate.

*** Benefit-cost ratio.

In our study, it has been observed that it is cost-effective for parents to give the vaccine to their children, even if they buy it at the retail price. It would be even more cost-effective to give 2 vaccine doses to their children (as recommended since 2009) than paying for health care costs and missing workdays.

The study conducted by Pérez-Rubio in Castile and León¹¹ shows that immunization with one dose only, not two as recommended by the Spanish Society of Pediatrics⁴ is cost-effective. Immunization during adolescence, as demonstrated by Peña-Rey¹³ in their article from 2004, is cost-effective based on the BCR. Other studies have demonstrated the cost-effectiveness of administering the vaccine to children with risk factors.^{2,7}

As part of a public immunization strategy, as conducted in Spain and Aragón, the cost of giving the vaccine to the entire population aged 12-15 months with a booster dose at 3 years old would also be cost-effective, as per our data, if paid at a cost price. However, paying the vaccine at a retail price and giving a booster dose may not be cost-effective.

Other studies⁷ have mostly assessed indirect expenses resulting from missing workdays; in our study, we also analyzed health care expenses related to pediatric office visits and hospitalizations, and petty expenses in relation to giving medications at home.

Based on our findings, it is observed that a single vaccine dose results in a higher BCR and is more cost-effective, but population studies show that a booster dose provides long-lasting immunity, for more than 14 years, and in addition prevents severe varicella cases.^{1-5,7} Outbreaks in schools have been observed with a single dose and coverage close to 99%.⁵ Also with a single dose, the age of varicella onset may be delayed. The bibliography even agrees that this disease is more severe in adults.^{1,3,7} The vaccine effectiveness is very high; public immunization campaigns promoting two doses may help to interrupt varicella transmission in the long term.^{3,7} It has also been seen that cost-effectiveness increases as the cost per dose reduces; the administration of two doses would be essential to optimize vaccination costs (*Table 4*, assumption 12).

In Europe, the varicella vaccine has been given to infants since 2003 in Sicily and Luxembourg, since 2004 in Germany and Greece, since 2008 in Tuscany and Lithuania, and since 2010 in Cyprus.⁷

In America, official immunization schedules

vary depending on the country. In the United States, Canada, and Uruguay, children receive the first dose at 12 months old and a booster dose at 4-6 years. Immunization schedules of Argentina, Brazil, and Mexico include a dose at 15 months. Other countries, like Chile and Peru, have not included the vaccine in their official immunization schedules as of 2016.⁶

It is also evident, according to our results, that hospital discharges for varicella after 4 years of immunization will reduce to a half because 53% of hospitalizations occur in this age group, as described by the Gil-Prieto¹⁴ group in 2014 based on communities where infants were vaccinated.

The marketing of other alternatives, such as the MMRV vaccine,^{1,7} already in use in other countries, may mean an improvement in relation to prices and infant discomfort;^{1,7} however, our study has not considered this assumption.

In short, the economic costs of having administered the varicella vaccine in Aragón over the past 11 years may be improved by giving two doses to the infant population as long as the Public Health Administration manages to negotiate the price, as that obtained in 2015, which allows to obtain a BCR greater than 1. Hospitalizations of children younger than 5 years old will decrease and, therefore, it is expected to observe adequate economic results in a few years following an immunization campaign aimed at the entire infant population with two doses of the varicella vaccine. ■

Acknowledgments

We would like to thank the heads of the different institutions for providing the data.

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