

Economic Evaluation of Universal Varicella Vaccination in Mexico

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Background: Universal varicella vaccination has proven to be cost-effective (CE) in countries where implemented. However, this has not been evaluated for Mexico.

Methods: The yearly disease burden (varicella cases/deaths, outpatient visits, and hospitalizations) was derived from Mexican seroprevalence data adjusted to the 2020 population. The yearly economic burden was calculated by combining disease with Mexican unit cost data from both health care and societal perspectives. Four different vaccination strategies were evaluated: (1) 1 dose of varicella vaccine at 1 year old; (2) 2 doses at 1 and 6 years; (3) 1 dose of varicella vaccine at 1 year, and quadrivalent measles-mumps-rubella-varicella vaccine at 6 years; (4) 2 doses of measles-mumps-rubella-varicella vaccine at 1 and 6 years. We developed an economic model for each vaccination strategy where 20 consecutive birth cohorts were simulated. Vaccination impact (number of avoided cases/deaths) was evaluated for a 20-year follow-up period based on vaccine effectiveness (87% and 97.4% for 1 and 2 doses), and assuming a 95% coverage. We estimated annual costs saved, incremental cost-effectiveness ratio, and costs per life year gained.

Results: Avoided cases during the 20-year follow-up with 1, and 2 doses were 20,570,722 and 23,029,751, respectively. Strategies 1 and 2 were found to be cost saving, and strategy 3 to be CE. Strategy 4 was not CE. Strategies 1 and 2 would allow saving annually \$53.16 and \$34.41 million USD, respectively, to the Mexican society.

Conclusions: Universal varicella vaccination, using 1 dose or 2 doses, would result in a cost-beneficial and CE public health intervention in Mexico.

Key Words: varicella, varicella vaccine, pharmacoeconomics, cost-effectiveness

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Varicella is generally a benign, self-limiting disease in immunocompetent children. It is often more severe in adults and immunodeficient subjects and is associated with severe complications. Infection usually confers immunity for life although rare second varicella infections may occur.^{1–4} Reactivation of the virus can result in Zoster, which may occur at any time following primary infection but is seen more frequently in the elderly.

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The World Health Organization (WHO) recommends the introduction of universal varicella vaccination (UVV), at least 1 dose at 12–18 months of age, and sustaining vaccine coverage of 80% or above to countries where varicella is an important public health burden.⁵

Varicella vaccine was first developed in Japan in the 1970s,⁶ and the United States was the first country to introduce UVV in its National Immunization Program (NIP) in the Americas.⁷

In the United States, comparing pre- (1993–1995) to post-vaccination (1996–2004), varicella-related ambulatory visits were reduced by 66%, as well as hospitalization rates by 70%.⁷ In 2005, as a consequence of breakthrough cases, the United States introduced a second varicella vaccination at 6 years of age, resulting in a further decline in incidence, hospitalizations, and deaths (>90% compared with the prevaccination period). In addition, UVV was shown to be cost-effective (CE) in the United States using either 1 or 2 doses.⁸

In Latin America, the more relevant data proving UVV as a CE public health intervention come from Colombia⁹ and Brazil.¹⁰ In these studies, UVV can lead up to \$5278 USD of cost per life year gained (LYG) and savings of \$132,015,282 USD to the society, respectively.

In Mexico, varicella is not a notifiable disease. Only 220,039 cases were reported according to the “Unique System of Epidemiologic Surveillance from the General Direction of Epidemiology” of Mexico.¹¹ However, with an annual birth cohort of 2,162,535 individuals in 2018,¹² this shows that cases are severely underreported, resulting in an underestimation of both the disease and economic burdens. We therefore conducted this study to estimate the burden and cost of varicella infection in Mexico, and to develop a pharmacoeconomic evaluation of UVV using 4 different varicella vaccination strategies.

MATERIALS AND METHODS

Disease Burden

The annual number of varicella cases was derived from the seroprevalence by age group (0–4, 5–9, 10–14, 15–19, and 20–95 years) described in the study by Conde et al.¹³ We used a catalytic model¹⁴ to estimate the average age-specific force of infection. First, the seroprevalence was estimated for the upper limit of all age groups by considering midage group seroprevalence and assuming a constant increase in seroprevalence within each age group. The cumulative incidence was then calculated for each age group, and from age “a” to age “a+k” was defined as the difference between seroprevalence at age “a+k” and seroprevalence at age “a.” Then, assuming a constant incidence within the age group, the annual incidence was obtained by dividing the cumulative incidence by the width of the interval. Finally, the annual number of varicella cases was obtained by multiplying each annual incidence by the corresponding Mexican population size, estimated at 128,919,791 as of January 2020.¹⁵

Furthermore, there is also no Mexican data on varicella-related hospitalizations, accordingly, we used data from a Brazilian

pharmacoeconomic study¹⁰: accordingly, we assumed that the hospitalization and case-fatality rates were the same in natural and breakthrough varicella cases, with estimation of hospitalization rates of 0.297%, 0.129%, 0.147%, 0.269%, 0.246%, 1.08%, and 3.36% for <1, 1–4, 5–9, 10–14, 15–44, 45–64, and ≥65 years of age, respectively, and death rates of 0.0106%, 0.0027%, 0.0018%, 0.0031%, 0.0249%, 0.2583%, and 1.1685%, for <1, 1–4, 5–9, 10–14, 15–44, 45–64, and ≥65 years of age, respectively.¹⁰

Economic Burden

The annual direct cost of varicella (Cost_direct) was estimated as follows, using an Excel spreadsheet:

$$\text{Cost_direct} = \sum_i n_Hosp_i * c_Hosp * u_Hosp + n_Out_i * c_Out$$

where i represents every age group; n_Hosp is the number of hospitalizations, c_Hosp the unit cost of a 1-day hospitalization, and u_Hosp the length of hospitalization; n_Out is the number of doctor (outpatient) visits; and c_Out the unit cost of an outpatient visit.

The overall annual indirect cost of varicella (Cost_indirect) was determined separately for children (≤20 years) and adults (>20 years) patients:

$$\text{Cost_indirect_children} = \sum_i c_Wage * (n_Out_i * u_Care + n_Hosp_i * u_Hosp)$$

$$\text{C_indirect_adults} = \sum_i c_Wage * (n_Out_i * u_Pati + n_Hosp_i * u_Hosp + n_Death_i * \text{WorkYr})$$

where c_Wage represents the minimal daily wage, u_Care the number of workdays lost by caregiver (assuming 1 caregiver per child outpatient per day), u_Pati the number of workdays lost by the adult outpatient, n_Death is the number of varicella-related deaths and WorkYr the number of workdays lost because of premature death.

Unit costs of varicella in Mexico were obtained from a retrospective study in which net costs of both outpatient and hospitalized varicella cases were analyzed based on the unitary costs by the Mexican Institute of Social Security (IMSS).^{16,17} The indirect costs were estimated based on the average daily wage in Mexico (2020) of \$16.6 USD.¹⁸ In addition, 2.5 and 6.7 days (ie, average hospitalization duration) of caregiver/patient work loss were assumed respectively per outpatient and inpatient case.¹⁶ For varicella-related deaths, as the number of days of work lost in any given year could theoretically range from 1 to 365 days, we assumed that 182 days of work were lost because of premature death in an adult case.

We calculated the average cost per case of varicella by dividing total annual costs (direct and indirect costs) by the annual number of varicella cases in this age group. The cost was estimated from the health care (HC) perspective (only direct costs) and from the societal perspective (both direct and indirect costs).

All cost estimates collected in Mexican currency were converted to 2020 USD.

All direct and indirect costs are listed in detail in Tables 1 and 2, respectively.

Economic Evaluation

We estimated the incremental cost-effectiveness ratio (ICER), defined as the net cost of vaccination per averted varicella case and as the net cost per life-years gained (LYG) for the 4 following varicella vaccination strategies:

Strategy 1: One dose of a single varicella vaccine at 1 year old, at the same visit for vaccination against measles-mumps-rubella (MMR) vaccine, based on the Mexican NIP.¹⁹

Strategy 2: 2 doses of single varicella vaccine at 1 and 6 years old, along with MMR.

Strategy 3: One dose of a single varicella vaccine at 1 year old, along with MMR, and measles-mumps-rubella-varicella (MMRV) vaccine at 6 years.

Strategy 4: 2 doses of MMRV at 1 and 6 years.

Twenty consecutive birth cohorts of the Mexican population (2,162,535 individuals in year 2018)¹² were simulated in an Excel spreadsheet. The impact of vaccination (ie, number of cases and deaths avoided by vaccination) was assessed for a 20-year follow-up period, calculated for every vaccination strategy and each birth cohort in the follow-up. We assumed a vaccine efficacy (VE) of 87% and 97.4% with 1 and 2 doses, respectively.²⁰ The VE was considered to be constant throughout the 20 years of follow-up. We assumed a vaccination coverage of 95%, which is the required vaccination coverage for impeding measles to spread according to WHO.²¹

We considered the following unit costs of varicella vaccination: \$16.59 USD by the Pan American Health Organization per dose of varicella vaccine.²² MMRV price of \$47.45 USD was obtained from personal communication with GSK-Mexico, then subtracted \$2.75 USD from the MMR (Zagreb strain) price by Pan American Health Organization,²² giving an adjusted price of \$44.7 USD. For all 4 strategies, vaccine administration cost was of \$1.2 USD per dose.²³

We adjusted the model for time discounting considering a constant annual discount rate of 3% for costs and benefits, as recommended by the US Panel of Cost-effectiveness in Health and Medicine²⁴ and the World Bank Global Burden of Disease Project.²⁵

The LYG were estimated based on the number of life-years lost assuming a 75-year life expectancy.²⁶

Finally, a sensitivity analysis was conducted by modifying the vaccination coverage to 85%.

RESULTS

Varicella Disease Burden

In year 2020, the total number of varicella cases of varicella in Mexico was estimated at 2,041,296 resulting in 1,177,606 outpatient visits, 5290 hospitalizations, and 188 deaths.

Economic Burden

The annual direct and indirect costs were estimated at \$115,565,315 and \$49,806,746 USD, respectively, with a total of \$165,372,061 USD. Unit direct and indirect costs were \$56.61 and \$24.39 USD, respectively, with a total of \$81.00 USD (Fig. 1).

Vaccination Strategies

On a 20-year-time horizon, varicella vaccination strategies 1 (1 dose) and 2–4 (2 doses) could avoid 20,570,722, and 23,029,751 cases, respectively. This would drop to 18,405,383 and 20,605,566, respectively, with a coverage of 85%.

Vaccination strategies 1 and 2 were found to be cost saving with saved annual costs ranging (85–95% vaccination coverages) from \$49,495,999 to \$53,156,846 USD for strategy 1, and \$30,789,596 to \$34,411,901 USD for strategy 2 (see Table 3).

Since strategies 1 and 2 were found to be cost saving, ICER estimation was estimated only for strategies 3 and 4.

ICER per averted case for strategy 3 was of \$6.05 and \$30.45 USD from societal (SOC) and HC perspectives, respectively, with a total ICER of \$36.5 USD. For strategy 4, ICER per averted case was of \$44.8 USD and \$68.88 USD from SOC and HC perspectives, respectively, with a total ICER of \$113.36 USD (see Table 3).

TABLE 1. Estimated Individual-unitary Direct Costs (Outpatient and Hospitalized), and Varicella Deaths Proportions in Mexico (Expressed in US Dollars)

Event	Unit	Source (Reference)	Unit	Source (Reference)
Outpatient care/day	\$87.00 USD	16	No. of outpatient visits	36
Outpatient visits (years)	%	36	Average No.	36
<1	57		1.7	
1–4	47		1.2	
5–9	38		1.1	
10–14	44		1.2	
15–44	72		1.6	
45–64	74		1.9	
≥65	81		1.6	
Hospitalization/day	\$370.00 USD	16	Varicella death	10
*Hospitalization (left), or death (right columns) (years)	%	10	%	
<1	0.297		0.0106	
1–4	0.129		0.0027	
5–9	0.147		0.0018	
10–14	0.269		0.0031	
15–44	0.246		0.0249	
45–64	1.08		0.2583	
≥65	3.36		1.1685	

*Hospitalization/day first left column, varicella death % last right column, both columns corresponding to same age groups.

TABLE 2. Estimated Individual-unitary Indirect Costs (Only Loss of Wage Days) of Varicella in Mexico (Expressed in US Dollars)

Event	Unit	Source (Reference)
Outpatient work loss days	2.5	16
Hospital work loss days	6.7	16
Daily salary (wage)	\$16.7 USD	18

Hence, as recommended by the WHO, a strategy should be considered CE if the costs per LYG are lower than the per capita gross domestic product,²⁷ which was \$9673.4 USD in Mexico of in 2020.²⁸ Accordingly, for strategy 3, LYG was of \$1539 and \$7740 USD from society and HC perspectives, respectively, and for strategy 4 of \$11,305 and \$17,507 USD from society and HC perspectives, respectively, making strategy 3 a CE intervention (see Table 3; Fig. 2).

DISCUSSION

In our study, we estimated varicella incidence by performing a similar approach as Bollaerts et al,²⁹ using seroprevalence estimates by age group.¹³ By implementing this methodology, the estimated number of annual varicella cases (2,041,296 cases) was 10-fold higher compared with reports made to the “Unique System of Epidemiologic Surveillance from the General Direction of Epidemiology” of Mexico.¹¹ It can be assumed that the latter represents only medically attended and reported varicella cases, and the real incidence is underestimated.

It is difficult to compare our estimated annual number of cases to other countries, due to 3 main reasons—first, varicella is not a reportable disease in Mexico; second, different estimation of incidence calculation; and third, different incidences in the different climate zones of the country, temperate versus tropical, with higher rates in the former.³⁰

Thus, when comparing to Brazil, another Latin American country (with in large part tropical, like Mexico) of 210.15 million inhabitants by 2019,³¹ the annual varicella incidence was of 2,915,294 cases before UVV implementation,¹⁰ which is a very similar incidence than in our study (1.39 vs 1.57/100). In Brazil,

the methodology used to estimate varicella incidence has been obtained by “pesquisa system,” a combination of both active and passive surveillance,³² while in our study, as mentioned, incidence was estimated by using a calculation from seroprevalence, as described in the Materials and Methods section.

We found UVV with 1 or 2 doses of a stand-alone varicella vaccine to be cost saving and a mix of stand-alone varicella and MMRV vaccination to be CE. Although not explicitly tested, a strategy with 2 MMRV vaccinations may not be cost-effective in the current Mexican setting due to the incremental vaccine costs, which overcome the additional cold chain and other delivery costs of separate administrations.

In the United States, a study published in 2008 by Zhoyu et al³³ was crucial as a confirmation of UVV as CE by using 2 doses of varicella vaccine, since this 2-dose schedule was introduced in 2005. Two formulations of varicella vaccine are available in the United States: monovalent varicella vaccine and MMRV (introduced in 2006). A 1-dose varicella vaccination program would result in 4937 years of life saved and 14,425 quality of life year saved. The societal net savings was \$1055.8 million USD. The direct and societal BCRs for the 1-dose varicella vaccination program were 1.00 and 4.37, respectively. The 2-dose varicella vaccination program would result in 5324 years of lives saved, and 15,804 quality of life year saved. The societal net savings would be \$951.8 million USD. The direct and societal BCRs with 1 dose would be 0.61 and 2.73, respectively. The direct and societal BCRs for the second dose were 0.13 and 0.56, respectively. An important perspective of this study is that UVV with 2 doses was already performed in the United States, and prices from both private and public sectors were known, as well as percentages of children vaccinated with varicella vaccine alone, or with MMRV, making this analysis much more precise. In our study, the pharmacoeconomic estimation was performed in a country where UVV has never been performed and thus, was based on modeling 4 different strategies using either varicella vaccine alone, or combined with MMRV. Our results indicated that UVV is a CE intervention for all scenarios tested.

In Latin American countries, few studies looking at the economic impact of UVV have been done, all of which have only evaluated varicella vaccine alone, not with MMRV.³⁴

In Argentina, just before UVV was introduced in their NIP, in a study³⁵ with 150 children with varicella (75 inpatient and 75

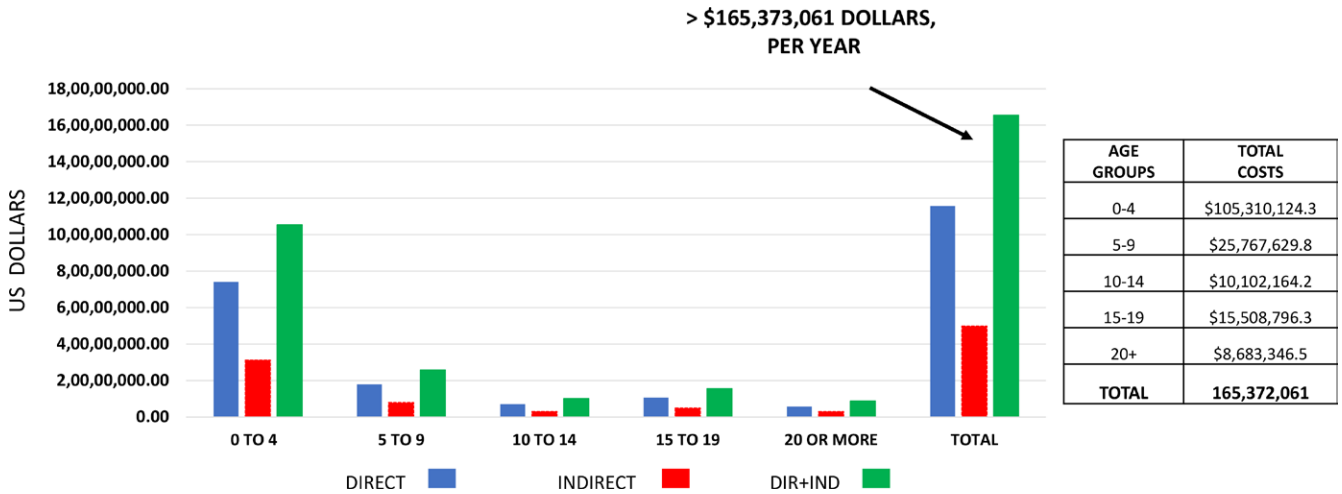


FIGURE 1. Total estimated annual economic burden of Varicella in Mexico (expressed in US dollars). [full color online](#)

TABLE 3. Annual Saved Costs Per Vaccination Strategy vs. No Vaccination, With 95% COV; ICER for Each Vaccination Strategy, and costs per LYG, All From Both SOC and HC Perspectives (Expressed in Us Dollars)

Program	Annual Saved Costs HC/SOC Perspective*	ICER HC/SOC Perspective†	Costs Per LGY HC/SOC Perspective‡
No vaccination	NA§	NA§	NA§
Strategy 1	\$53,156,846	NA§	NA§
Strategy 2	\$34,411,901	NA§	NA§
Strategy 3	NF¶	\$36.5	\$1539
Strategy 4	NF¶	\$113.36	\$11,305

*Annual saved costs with 95% vaccination coverage, from both HC and SOC perspectives.
 †ICER, from both HC and SOC perspectives.
 ‡Costs per LYG, from both HC and SOC perspectives, Mexican per capita Gross Domestic Product = \$9,6734 US Dollars.
 §Not applicable.
 ¶Results of strategies 3 and 4, not favorable in annual saved costs.
 COV indicates coverage; HC, health care; ICER, incremental cost-effectiveness ratio; LYG, life year gained; SOC, societal.

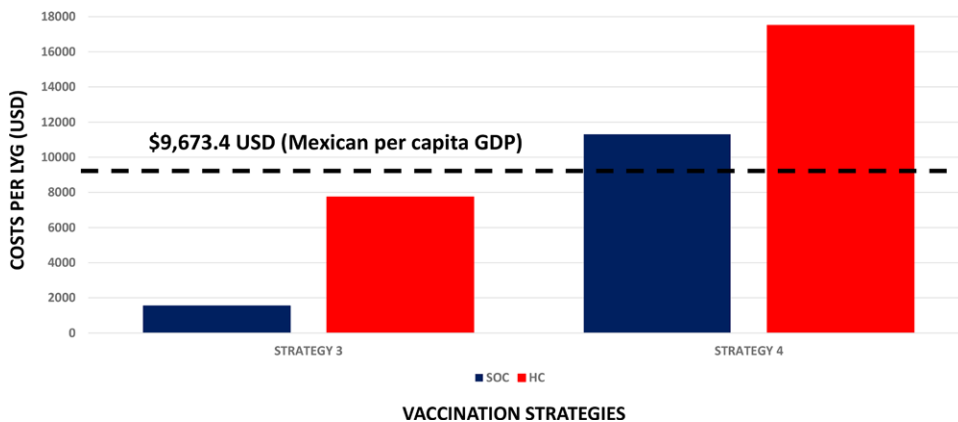


FIGURE 2. Costs per LYG: costs from SOC (indirect and direct costs) and HC (only direct costs) perspectives. Vaccination strategies 3 and 4 (95% vaccination coverage). Expressed in US dollars. GDP indicates gross domestic product; HC, healthcare; LYG, life year gained; SOC, society. [full color online](#)

outpatient), the total combined direct and indirect costs per varicella case were \$2947.7 USD (inpatients) and \$322.7 USD (outpatients). The overall annual cost of varicella in Argentina for children ≤14 years of age in 2015 was estimated at \$40,054,378 USD, suggesting that these costs should be reduced with the recent

implementation of UVV. Nonetheless, a CE analysis was not performed in this study.

The Colombian study⁹ estimated that, in an average year, there would be 700,197 varicella cases and 60 deaths in the country in the absence of vaccination (estimates of disease burden based on

previous reports of varicella-zoster virus seropositivity within the country), with HC costs of around US \$88,734,735 USD, 2008–dated (\$101,023,480 USD, 2017–dated), with an estimate of \$2.05 USD per case only from direct costs with discount, considering a population of 49.07 million inhabitants in Colombia in 2017 (88). Accordingly, it was estimated that HC costs for all cases during a 30-years period could be around \$88,734,735 USD. Cost per LYG of 1-dose vaccination was \$2519 USD, and by using a 2-dose scheme of \$5728 USD. The authors concluded that in their country UVV is CE.

The study from Brazil¹⁰ is the one with more substantially representative data in Latin America. In this publication, assuming a single-dose schedule, with VE of 85% and coverage of 80%, the vaccination program could prevent 74,422,058 cases and 2905 deaths. It would cost R\$ 3,178,396,110 (\$635,679,222 USD) and save R\$ 660,076,410 (\$132,015,282 USD) to the society, and R\$ 365,602,305 (\$73,120,461 USD) to the HC system. The program is CE (R\$ 14,749 (\$2.95 USD) and R\$ 16,582 (\$3.32 USD) per life-year saved under the societal and the HC systems perspectives, respectively.

These 3 Latin American publications, with the exception of the Colombian estimation, showed higher costs associated with varicella compared with our study, and all these countries have economic, HC, and societal similarities when compared with Mexico. Nevertheless, our study was consistent with the Latin American publications analyzing CE: UVV is cost-effective, and, as mentioned before, we also modeled varicella vaccination alone \pm MMRV.

Indeed, our estimates of economic burden of varicella could be even conservative since, as mentioned, indirect or society perspective costs used came only from work loss wage days.

In parallel to our study, the budget-impact of multiple vaccination strategies in Mexico was recently analyzed.³⁶ The annual disease burden assumptions were almost identical—2,010,002 yearly cases compared with 2,041,296 in our study. However, the annual economic burden of varicella was estimated at \$311,095,966 USD, much higher than the \$165,372,061 USD we found. An explanation for this difference is that whilst both studies calculated outpatient direct costs mostly from IMSS,¹⁷ for hospitalized direct costs, Graham et al³⁶ used information from a Mexican panel of experts, while we estimated inpatient costs from real-published data.¹⁶

Our study has several limitations. First, we did not impute the impact of herd immunity induced by vaccination which would have had a positive bias. But we also did not include waning of immunity, which would have impacted the epidemiologic and health economics outcome negatively. We neither took into account the impact of vaccination on Herpes Zoster as data from United States and elsewhere in developed countries are inconsistent about the impact of UVV on HZ incidence.^{37–39} We also did not include cost of vaccination failures or increasing vaccine hesitancy so that our coverage rates might be too high. However, we did a sensitivity analysis with lower coverage, which did not materially affect the outcome. Second, and with respect to health economic calculations, the current thresholds based on per capita gross domestic product as guides for policy makers have been subject to criticism. However, other available approaches have also substantial weaknesses such as benchmark interventions, or league tables.⁴⁰ Despite these limitations, our study makes a strong case of introducing UVV in the Mexican NIP and follow other Latin American countries.

In conclusion, the disease and economic burden of varicella in Mexico is substantial. UVV, regardless of the vaccination strategy would result in a high reduction of Varicella cases.

UVV, using 1 dose or 2 doses of a stand-alone varicella vaccine, would result in annual savings of \$53.16 million and

\$34.41 million, respectively, to the Mexican society. Combining a stand-alone dose with a MMRV dose would also be CE, but not the strategy using 2 doses of MMRV, nonetheless, the MMRV cost obtained in our study was if this vaccine is purchased individually; hence, it is well possible that a universal vaccination scheme would result in a lower purchase price, thereby improving the ICER.

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