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Public health and budget impacts of switching from a trivalent to a quadrivalent inactivated influenza vaccine in Paraguay

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ABSTRACT

This study aimed to investigate the public health and economic benefit of using a quadrivalent influenza vaccine (QIV) instead of a trivalent influenza vaccine (TIV) in past seasons in Paraguay. The budget impact of switching from TIV to QIV in the Immunization Program was also evaluated. The adapted model includes two modules. The first compared retrospectively Health and Economic outcomes resulting from the use of QIV instead of TIV. The second forecast the spending and savings that would be associated with the switch from TIV to QIV. Our findings estimate that the switch from TIV to QIV during the seasons 2012 to 2017 could have prevented around 2,600 influenza cases, 67 hospitalizations and 10 deaths. An alternative scenario using standardized estimates of the burden of influenza showed that 234 influenza-related hospitalizations and 29 deaths could have been prevented. The estimated annual budget impact of a full switch from TIV to QIV was around USD1,6 million both from the payer and societal perspectives. Those results are mainly driven by vaccine prices and coverage rate. In sum, this manuscript describes how the use of QIV instead of TIV could have prevented influenza cases and subsequent complications that led to hospitalizations and deaths. This could have generated savings for the health system and society, offsetting part of the additional investment needed to switch from TIV to QIV.

Introduction

Influenza is an acute respiratory infection caused by viruses that are members of the Orthomyxoviridae family. Four genera of influenza viruses exist (A, B, C and D); however, only types A and B, which co-circulate, cause seasonal epidemics in humans. The other two types of influenza viruses are clinically less important: type C can cause mild illness, while type D infects cattle but infections in humans have not been reported.[1,2]

The burden of seasonal influenza epidemics is still significant. On average, 389,000 deaths worldwide (CI [294,000;518,000]) are attributable to influenza annually (67% occurring in the elderly).[3] Another study estimated that, annually, the influenza infection is responsible for 5,678,000 hospitalizations (95% CI [3,205,000;9,432,000]).[4] In Paraguay, a study in 10 local hospitals from 2011 to 2015 reported that the incidence of influenza-related hospitalization was 20.3/100,000 and the associated mortality was 1/100,000. In the elderly, those estimates were 98.8/100,000 and 16.8/100,000, respectively.[4]

Severe forms of influenza can lead to hospitalization and death, particularly in certain high-risk populations.[5] Populations at risk for severe complications of influenza include young children, the elderly and people with chronic comorbidities.[6] Therefore, the Paraguayan Ministry of Health offers free influenza vaccinations to individuals older than 60 years, children between 6 and 35 months old, and individuals within other age groups with comorbidities, as well as health care workers, pregnant women and other vulnerable groups.[7] Currently, trivalent influenza vaccines (TIVs) containing antigens derived from 2 influenza A virus subtypes (A/H1N1 and A/H3N2) and 1 influenza B virus lineage (either B/Victoria or B/Yamagata lineage, based on World Health Organization South Hemisphere annual recommendations) are available in Paraguay. Nevertheless, analysis of the distribution of influenza B/Victoria and B/Yamagata cases in Paraguay in the years 2010–2017 showed a high level of mismatch between circulating B viruses and the ones included in the TIV.[8] To offer broader protection against influenza B viruses, a quadrivalent influenza vaccine (QIV) containing both influenza B lineages has been developed.

This study aimed to assess the value of the use of a QIV instead of TIV investigating what would have been the public health and economic impacts of using QIV instead of TIV over six past influenza seasons (from 2012 to 2017) in Paraguay. The future budget impact of switching from TIV to QIV in the National Expanded Program Immunization was also estimated and presented.

Materials and methods

Model structural choices

Analysis

A model combining epidemiological and budget impact modules was used to:

- compare the health and economic outcomes that would have occurred if the current population vaccinated with TIV would have received QIV in Paraguay and,
- estimate the potential budget impact of the TIV switch with QIV.

To reflect the targeted population, it was stratified by age and risk status: 6 months to 3 years of age; 4 to 19 years of age with chronic comorbidities (referred to as high risk), 20 to 59 years of age at high risk, and 60 years of age and older.

The impact on the seasonal number of influenza cases, related consultations to the general practice, hospitalizations and deaths, as well as the associated costs were estimated. From the societal perspective, absenteeism due to sick leave was also considered. Long-term consequences of influenza infections, such as productivity losses due to premature death, were not taken into account.

The model included two modules: retrospective and prospective (i.e., epidemiological and budget impact).

Retrospective module

The retrospective epidemiological module (Figure 1) was based on the structure published by Reed et al. and adapted for several countries.[9–12] It assessed retrospectively how many influenza-related outcomes and associated expenditures would have been prevented by using QIV instead of TIV from 2012 to 2017 in Paraguay.

To simulate the number of cases in the vaccinated populations, the influenza-related attack, consultation, hospitalization and mortality rates from an unvaccinated population were adjusted by:

- the vaccination coverage rate observed in the included populations,
- the vaccine efficacy against the specific influenza virus type (A, B lineage included in the vaccine) and,
- the percentage of cases due to each strain.

A level of cross-protection was assumed for the B lineage not included in the vaccine. The outcome rates being obtained from surveillance data in the general population were corrected to estimate the rates in a hypothetically unvaccinated population.

Prospective module

The prospective budget impact module (Figure 2) estimated the impact of switching from TIV to QIV on public spending over the subsequent five years. It compared the additional investment necessary to introduce QIV to the National Program Immunization to potential savings resulting from the use of QIV instead of TIV. Therefore, on top of the cost items previously cited, the model included the vaccination costs (i.e., prices of vaccine doses and administration costs). The model then projected the influenza-related outcome rates estimated in the retrospective module over the next five years (considering annual vaccine coverage rates and market share projections).

Population parameters

Local inputs were used when available. All inputs were automatically recalculated to match the age groups included in the model, assuming a uniform distribution of individuals in each year within an age group.

Population

The age-specific population size was derived from national statistics with projections for 2020 and served as a basis to calculate the percentages at high risk among individuals 36
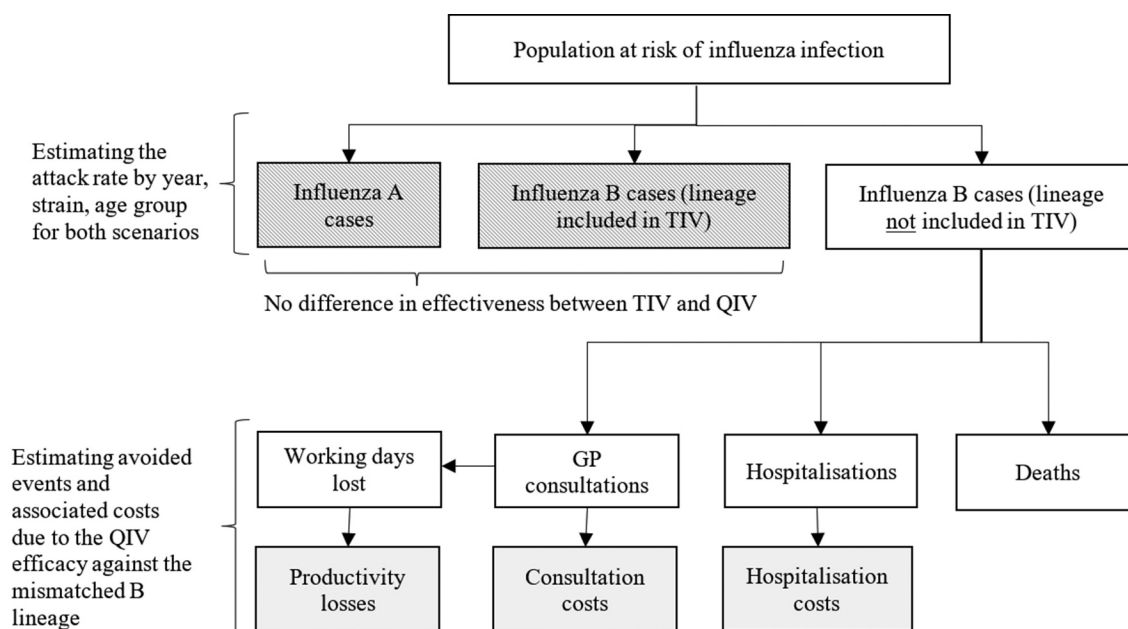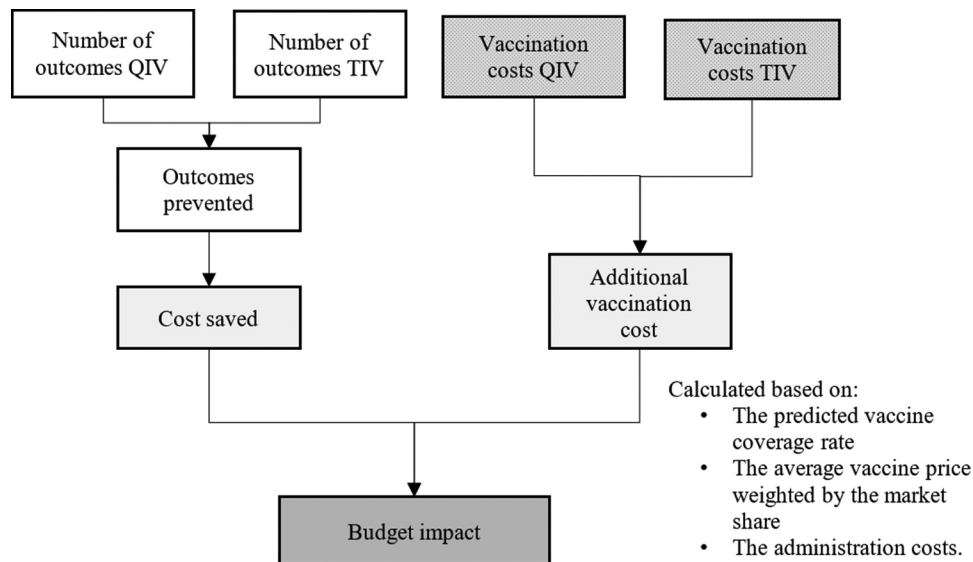

Figure 1. Diagram of the retrospective module. QIV = quadrivalent influenza vaccine; TIV = trivalent influenza.

Figure 2. Diagram of the prospective module. QIV = quadrivalent influenza vaccine; TIV = trivalent influenza vaccine.

months to 19 years of age and those 20 to 59 years of age.[13] The percentage of individuals categorized as "high risk" is the percentage of patients having at least one of the following conditions: HIV/AIDS, tuberculosis, cancers with direct immunosuppression, cancers with possible immunosuppression, cardiovascular diseases, chronic respiratory diseases, chronic liver diseases, obesity, diabetes mellitus, chronic kidney diseases, chronic neurological disorders and sickle cell disorders. This percentage was estimated for Paraguay in 2020 using the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) (2017) and UN population estimates for 2020 which were published by Clark et al. 2020.[14] This work was originally conducted for estimating the percentage of persons at increased risk of COVID-19. However, the conditions listed as risk factors are similar to those included in the recommendations for influenza vaccination.[15]

Vaccination coverage rate

The vaccination coverage rate was calculated as the number of vaccinated individuals provided by the Ministry of Health divided by the population size. The average from 2006 to 2018 was considered. For infants (6 to 35 months old), with no prior vaccination, the recommendation is two doses, each of .25 mL, and for adults and children >4 years of age, the recommendation is one dose of .5 mL. Hence, for infants, the model included the price of two doses. However, no additional efficacy was considered for the second dose. This assumption was informed by the conclusions of a Cochrane review on vaccines for preventing influenza in healthy children, stating that there was no evidence of a difference in the vaccine effect between the group receiving two doses and the group receiving only one dose.[16] The same coverage was considered over the 5-year time horizon of the budget impact analysis.

Vaccine efficacy

The vaccine efficacy against influenza A and B, both for the strain included in the TIV and not (resulting from cross-protection), was derived from a cost-effectiveness analysis conducted by Clements et al.[17] The vaccine efficacy estimates used in the cost-effectiveness analysis were obtained from a meta-analysis of the published clinical data for TIV.[16,18–20]

Epidemiological data

The epidemiological data used in the reference case were obtained from surveillance data in the general population (i.e., in which a part of the population received the vaccine). Therefore, to be populated in the model, those rates were corrected by the observed vaccination coverage and TIV efficacy to estimate the rates that would have been obtained in a fully unvaccinated population.

Virus circulation

Unpublished virologic surveillance data provided by the Central Laboratory of Public Health (Laboratorio Central de Salud Pública, data on file) were considered.[21] However, the distribution of cases attributable to B/Yamagata and B/Victoria lineage before 2014 was not available; therefore, the average distribution over four seasons (from 2014 to 2017) was considered.

Influenza attack rates

The influenza attack rates considered in the reference cases were the number of influenza cases notified to the Directorate General for Health Surveillance (DGVS—Dirección General de Vigilancia de la Salud) and the influenza laboratory-confirmed cases reported by the Central Laboratory of Public Health (Laboratorio Central de Salud Pública—LCSP)".[22]

Consultations

Influenza-related consultation rates were calculated by applying to the influenza cases an average number of consultations per case (opinion from a panel of ten experts) and corrected by the probability of consultation per case.[23]

Hospitalizations

Influenza-related hospitalization rates were obtained from the National Hospital Database (Sistema de Egresos Hospitalarios—SEGHOSP) provided by the Ministry of Public Health (Ministerio de Salud Pública y Bienestar Social—MSPyBS) and the General Directorate of Strategic Health Information (Dirección General de Información Estratégica en Salud—DIGIES).[24] As only the stays in hospitals depending on the MSPyBS were recorded, the population size used as the denominator was corrected to account only for the catchment population of these institutions (i.e., the population served by the facility). To do so, the general population size was corrected by the ratio of the total number of stays in the sentinel centers divided by the total number of stays in all establishments in Paraguay.

The influenza-related outcome rates used for the reference case are presented in Supplementary Table S1.

Mortality

The influenza-related mortality rates were calculated by applying to the hospitalization data the case-fatality ratio per influenza-related hospitalization published in the DGVS weekly epidemiological reports for the years 2010 to 2017.[22]

Standardized approach

Local surveillance data, while being a valuable source of information, are subject to certain limitations. Firstly, the data are collected only if the patients enter the healthcare system, i.e., if they seek medical care. Influenza in its less severe form is well known to resolve without medical care. Therefore, an important proportion of patients choose not to seek medical care in case of influenza illness or influenza-like illness.[23,25] In addition, even patients consulting medical staff (or hospitalized) for influenza are not guaranteed to receive a test to identify the pathogenic agent (depending on local practice), nor guaranteed to get positive test results (depending on the sensitivity of the test). In addition, severe forms of influenza usually aggravate existing comorbidities or become complicated by coinfections and the patient could die weeks after the primary infection, even after discharge. Hence, seasonal influenza is infrequently listed on death certificates of people who die from influenza-related complications. For these reasons, data collected through influenza surveillance and case finding usually represent only a fraction of persons infected with influenza.[26] Finally, to be able to extrapolate data (hospitalizations and mortality) we made assumptions (e.g. regarding catchment population and representativeness of the rates to the whole country) that could diminish the accuracy of our estimates.

To assess this uncertainty, a second scenario was conducted in which a standardized method was adapted for Paraguay. The age-specific attack rates in an unvaccinated population were obtained from pooled data within the control arms of several clinical trials.[27–29] As the effectiveness of the vaccines varies depending on the season (because of the strain circulation and especially, for TIV, the degree of match), the severity of each influenza season included was considered. To account for the seasonal heterogeneity in influenza infections circulation, the rates were distributed over the seasons using a severity coefficient. For each season, the coefficient was calculated as the percentage of positive influenza cases identified for the season divided by the average over the timeframe using the report of the FluNet network.[30] The same approach has already been reported in the literature.[10–12] To these attack rates, we applied probabilities of consultations, hospitalizations and deaths per case from the literature.[23] The alternative rates are presented in Supplementary Table S2.

Economic inputs

All the costs were converted into US dollars using the exchange rate of the appropriate year and normalized to 2020 using the annual consumer price indices when necessary.[31]

Consultations and hospitalizations

Consultations and hospitalizations were based on a public survey that estimated the costs for the year 2009, including the human resource costs (based on the health care workers' incomes) and the costs of supply and medicine in the public and private sector.[32]

Administration

Costs of vaccine administration were based on the study reported by Peña Kieninger et al.[33]

Vaccine price and market share

Those data were derived from the Pan American Health Organization (PAHO) in 2018.[34] A full switch from TIV to QIV is considered.

Productivity losses due to an acute influenza illness

The rate of absenteeism was informed by expert opinion. An average monthly wage for 2018 was obtained from the Encuesta Permanente de Hogares Continua (EPHC),[35] converted to a daily rate and adjusted by the employment rate.

The inputs considered in the model are summarized in Table 1.

Approach to uncertainty

We conducted the previously described scenario analysis using alternative influenza-related outcome rates based on international references.

In addition, to assess the uncertainty around the parameters of the model, we conducted a deterministic sensitivity analysis. Input values were varied within the bounds of a plausible interval. The ranges of the results obtained using the extreme values of the parameter (either total costs that could have been prevented or total budget impact) were calculated and displayed on tornado diagrams.

Table 1. Parameters with intervals for the sensitivity analysis to inform the model.

Parameters	Value	Interval for sensitivity analysis	Reference
Population size			National statistics,[14]
6–35 months	494,400	N/A	
36 months to 19 years—HR	83,075		
20–59 years -HR	748,102		
≥60 years	720,211		
Vaccination coverage, %			Unpublished data from the Ministry of Health
6–35 months	30.9%	Assumption ± 20%	
36 months to 19 years—HR	24.8%		
20–59 years -HR	25.1%		
≥60 years	40.7%		
Vaccine efficacy against influenza A, %			[17]
6–35 months	59.0%	[.41; .71]	
36 months to 19 years—HR	60.9%	[.48; .70]	
20–59 years -HR	61.0%	[.48; .70]	
≥60 years	58.4%	[.38; .72]	
Vaccine efficacy against matched B, %			
6–35 months	66.0%	[.12; .53]	
36 months to 19 years—HR	76.3%	[.12; .62]	
20–59 years -HR	75.7%	[.12; .59]	
≥60 years	66.9%	[.16; .53]	
Vaccine efficacy against mismatched B [a]			
6–35 months	44.0%	[.08; .82]	
36 months to 19 years—HR	51.1%	[.19; .72]	
20–59 years -HR	49.0%	[.12; .90]	
≥60 years	44.6%	[.09; .85]	
Vaccine cost, USD			Public prices[36]
TIV	5.14	Assumption ± 20%	
QIV	2.65		
Cost of vaccine administration, USD	1.22	Assumption ± 20%	[33]
Cost of GP visit, USD	54.1	Assumption ± 20%	[32]
Cost of hospitalization, USD	1,261.3	Assumption ± 20%	
Workdays lost [b],			
6–35 months	2		Advisory board
36 months to 19 years—HR	2	Assumption ± 20%	
20–59 years—HR	7		
≥60 years	7		
Daily wages, USD[c]	12.7	N/A	[35]

HR = high risk; GP = general practitioner; QIV = quadrivalent influenza vaccine; TIV = trivalent influenza. vaccine.
For TIV only.
Productivity losses in children reflected those incurred by their caregivers.
Corrected by the employment rate.

Results

Public health and economic impact

Our simulation estimated that the greatest benefits were observed for the seasons 2016 and 2017, where the level of mismatch and disease severity (i.e., higher influenza-attributable hospitalization rates) were the highest. Our study estimated that from 2012 to 2017, the replacement of TIV with QIV would have resulted in preventing 67 additional hospitalizations and 10 deaths leading to a saving of almost USD400K from the third-party payer perspective and about USD450K from the societal perspective. When considering alternative influenza-related outcome rates, however, the use of QIV instead of TIV could have prevented 234 hospitalizations and 29 deaths attributable to influenza, resulting in a saving of almost USD850K from the third-party payer perspective and more than USD1 million from the societal perspective. The results per year and age groups are presented in Table 2.

Budget impact

Changing from TIV to QIV would have required covering additional vaccination costs of almost USD1,8 million per year, to vaccinate 654,227 individuals (i.e., the estimated total addressable population). Meanwhile, we estimated that the switch would generate savings of around USD73K from a payer perspective and USD84K from a societal perspective. The annual budget impact of a full switch from TIV to QIV from year 1 (assuming an average influenza season, i.e., an average of the outcome rates, mismatch) was around USD1.6 million both from the payer and societal perspectives. The budget impact over five consecutive years was USD8.4 million from a payer perspective and USD8.3 million from a societal perspective. When considering an alternative set of inputs for the epidemiological parameter, the budget impact over five consecutive years was around USD7.6 million from a payer perspective and USD7.4 million from a societal perspective.

Deterministic sensitivity analysis

In the public health and economic impact module, the efficacy against the mismatched strain (i.e., resulting from cross-protection) and the percentage of cases due to the B strain were the most important drivers of the results. The total medical costs saved ranged from USD0 when assuming that the TIV offers complete protection against the mismatched B-strain, to USD3 million when assuming a lower efficacy

Table 2. Costs and savings due to the replacement of TIV with QIV by seasons.

Measure	2012 season	2013 season	2014 season	2015 season	2016 season	2017 season	Total reference case	Total scenario analysis
% of mismatched cases	17.5%	11.2%	11.2%	5.9%	19.9%	27.9%		
Number of additional events avoided:								
Influenza cases	337	249	219	221	858	792	**2,675**	**13,343**
GP consultations	704	517	463	461	1,832	1,626	**5,602**	**10,215**
Workdays saved	1,721	1,332	1,112	1,176	4,374	4,516	**14,230**	**38,263**
Hospitalizations	7	10	6	5	19	22	**67**	**234**
Deaths	1	2	1	1	3	3	**10**	**29**
Costs saved, USD								
GP consultations	38,087	27,977	25,064	24,921	99,119	87,980	**303,149**	**552,757**
Hospitalizations	8,606	12,006	7,018	5,973	23,567	27,267	**84,437**	**295,012**
Productivity losses	189,475	126,255	111,465	109,102	349,302	333,196	**60,925**	**285,062**
Costs saved, payer perspective, USD	46,693	39,983	32,082	30,894	122,687	115,247	**387,585**	**847,769**
Costs saved, societal perspective, USD	236,168	166,238	143,547	139,996	471,988	448,443	**448,511**	**1,132,830**

GP = general practitioner; QIV = quadrivalent influenza vaccine; TIV = trivalent influenza vaccine.

against the B-strain not included in TIV. These conclusions are intuitive as the added value of QIV relies on the extended protection against an additional B lineage. The vaccination coverage rate, the variation in the influenza-related outcome rates, and the number of workdays lost (from the societal perspective) have less influence on the results.
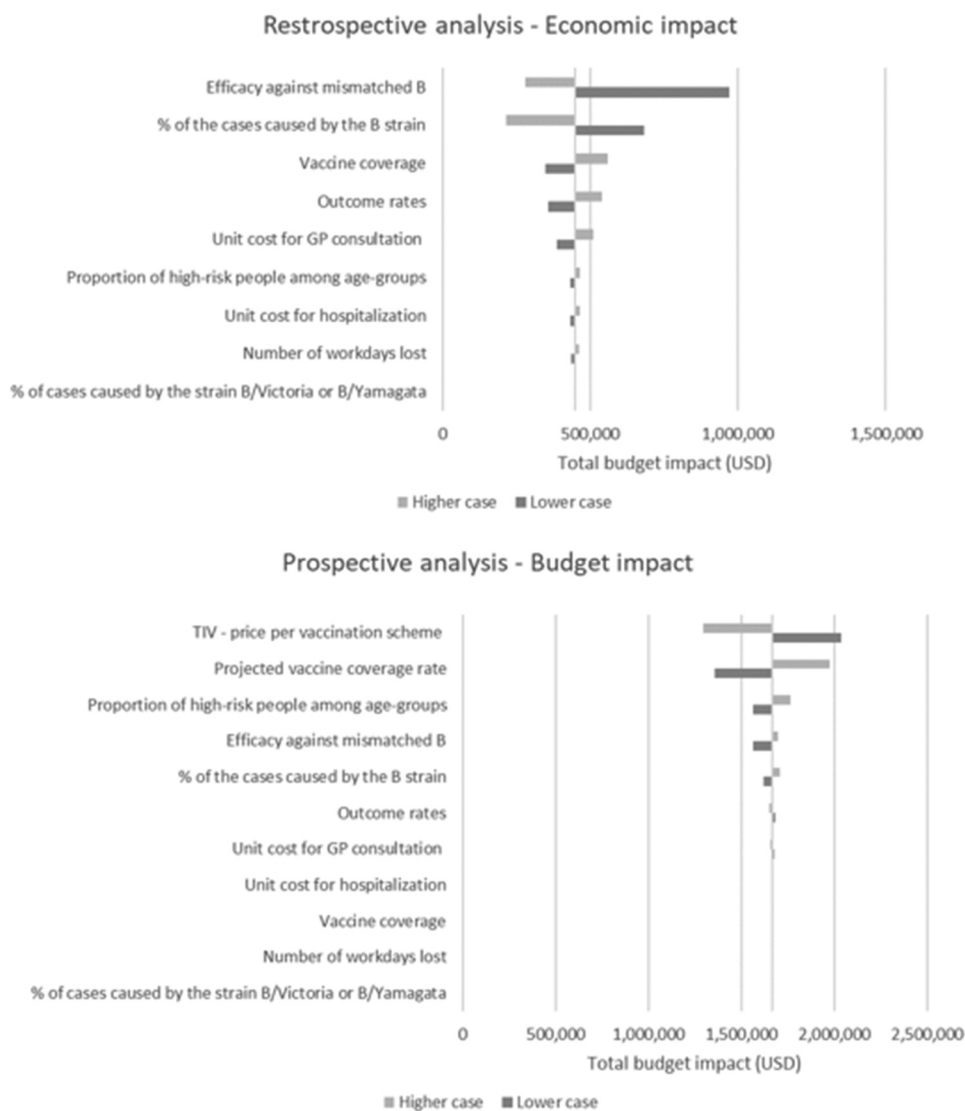
Figure 3. Tornado diagrams (societal perspective). GP = general practitioner; QIV = quadrivalent influenza vaccine; TIV = trivalent influenza vaccine; Yam = Yamagata.

The results of the budget impact module were driven mainly by vaccine prices and coverage rates. These parameters have an impact on the additional vaccination costs due to the switch from TIV to QIV, and thus the total budget impact. The budget impact ranged from USD6.5 million to USD10.6 million depending on the price of TIV, and from USD7.8 million to USD9.3 million, depending on the price of QIV. Other factors impacting the results are the TIV efficacy against the strain not included in the vaccine, the influenza-related outcome rates and the number of workdays lost (from the societal perspective; Figure 3).

Discussion

Influenza immunization has been available in Paraguay since 2006, and vaccination with TIV prevented many cases and associated deaths. However, the severity and relatively high level of mismatch observed during the recent seasons call for broader protection against the B strain.[37]

The results of the reference case estimated that if QIV had been given instead of TIV between 2012 and 2017 in Paraguay, around 2,600 cases of influenza, 67 associated hospitalizations and 10 influenza-related deaths could have been prevented. At the same time, estimated savings on GP consultations and hospitalizations could have amounted to almost USD400K.

To address the possible underestimation of surveillance data, as revealed by a comparison with other data or outcomes of neighboring countries,[36] a complementary analysis was conducted, for which an alternative outcome rates data set was used. In this scenario, we estimated that the switch could have prevented around 13,000 influenza cases, 234 hospitalizations and 29 deaths, leading to almost USD850K in savings according to the payer perspective and more than USD1.1 million according to the societal perspective, over 6 past seasons. These results emphasize the advantage of opting for QIV instead of TIV in the immunization program in Paraguay. This complimentary analysis also highlights the importance of influenza surveillance to appreciate the burden of this particularly unpredictable disease.

However, switching from TIV to QIV would require additional investment to cover the additional vaccination costs of USD1,749,316 which could be offset in part by the savings generated from prevented outcomes. The budget impact over 5 subsequent years would have been ~USD8.4 million from the payer perspective and ~USD8.3 million from the societal perspective.

The parameter having the most important impact on the results was related to the vaccine efficacy against the influenza B virus, as the benefit of the QIV is driven by its ability to offer extended protection against the B strains. However, the estimates were derived from a robust primary source (i.e., meta-analysis), and a conservative approach pertaining to the cross-protection was adopted. While the topic of the existence of cross-protection has been discussed,[38–42] our analyses considered a cross-protection factor of 67%. Similarly, there is uncertainty regarding the percentage of cases attributable to the B strain in each season. However, this uncertainty is inherent in the influenza seasonality and its heterogeneity. The model accounted for this factor as adequately as possible by using season-specific epidemiological data to match the outcomes rates, circulation and the strain included in the vaccine.

The sensitivity and scenario analyses also highlight how the influenza-related outcome rates impact the results. We, nonetheless, used in the reference case the most robust data available for Paraguay. The rationale for conducting a complimentary scenario analysis was developed previously in the article and indicates that the results presented in the reference cases are conservative.

This study has generated results that provide clear information and elements of consideration for switching from one vaccine to another within the immunization program (public health and budget impacts); using a validated approach with a model structure published in the literature.[9,10,12] Another strength of this model is its adjustments to local characteristics. The model was mainly informed with high-quality local data. Furthermore, the model considers how seasonality, particularly the effect of seasonal severity and virus circulation, affects the vaccine's effectiveness. This is more relevant now that the 2017 and 2018 seasons have shown a high degree of mismatch in Paraguay.

This analysis has several limitations. First, high-risk groups are more likely to develop influenza-related complications,[6,43] but despite this, we applied influenza-related outcome rates characteristic for the overall population to the high-risk population. Such an assumption leads to an underestimation of the number of outcomes avoided for two main reasons: (1) it is reasonable to assume that the number of hospitalizations and deaths related to influenza used to derive the rates mainly occurred in the high-risk population; nonetheless, the whole population count was used to calculate them, leading to lower rates, and (2) these rates were applied not to the whole population but to the high-risk population only. This assumption is conservative, and it underestimates the potential impact of the use of QIV. Second, while we used the best epidemiological data available for Paraguay, the influenza burden reported by local surveillance data is arguably underestimated. The conducted scenario analysis informed that this bias would not favor QIV as it underestimates its additional benefit. Finally, certain outcomes were not included in the present model, e.g., no data were available regarding influenza-related admissions in the emergency department. Therefore, no potential savings associated with this outcome were observed.

The use of QIV instead of TIV could have prevented influenza cases and the subsequent complications, eventually leading to hospitalizations and deaths. This could have generated savings that could have offset, in part, the additional investment necessary to switch from TIV to QIV.

Disclosure statement

AA declares no conflict of interest. CMdC is employed in the Institute of Tropical Medicine, part of the National University of Paraguay, and received a grant from Sanofi Pasteur for the collection of the epidemiological data.

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