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Economic Evaluation

The Public Health Benefits and Economic Value of Routine Yellow Fever Vaccination in Colombia

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ABSTRACT

Objectives: To evaluate the public health benefits and economic value of live-attenuated yellow fever (YF) 17D vaccine in Colombia. **Methods:** A decision tree model was used to assess the theoretical impact of routine YF vaccination of 1-year-olds (no "catch-up") during the interepidemic period from 1980 to 2002, avoiding capturing the impact of YF vaccine introduction in 2003. The vaccine was assumed to be 99% effective, to provide lifetime protection, and to cover 85% of the target population. Costs per disability-adjusted life-year (DALY) averted were computed from payer and societal perspectives. Univariate sensitivity analyses were performed. **Results:** During the interepidemic period, routine YF vaccination would have averted 2223 nonfatal cases of YF and 65 deaths, leading to an overall reduction of 1365 DALYs. The net cost of this vaccination would have been $25 964 813 (payer's perspective) and $16 535 465 (societal perspective). Cost per DALY averted was $19 022 and $12 114 from payer and societal perspectives, respectively (all costs in 2015 US dollars). Vaccination was considered cost-effective from both perspectives (ie, between 1- and 3-fold the gross domestic product per capita, $7158) and remains so if price per dose was $2.75 or less and $4.66 from payer and societal perspectives, respectively. Underreporting had the largest impact on the results. **Conclusions:** Routine toddler YF vaccination in Colombia would have been considered cost-effective in the prevaccination era. This study provides insights on the value of vaccination in an upper middle-income country.

Keywords: Colombia, cost-benefit analysis, economic evaluation, vaccine, yellow fever, yellow fever vaccine

Introduction

Yellow fever (YF) is a mosquito-borne viral hemorrhagic fever. The YF virus is considered the prototypic member of the family *Flaviviridae*, a group that includes dengue, Japanese encephalitis, and Zika.[1,2] It is most commonly found in tropical Africa and South America where a population of up to 1 billion people is at risk.[3,4] Most infections are asymptomatic. YF infection is generally categorized as being 1 of 3 phases. In the initial acute phase, symptomatic cases are usually self-limiting, nonspecific febrile illnesses with symptoms such as muscle pain, headache, and prostration. Patients then move to the second phase (remission) during which the fever and the intensity of the symptoms subside. Nevertheless, approximately 15% of patients with symptoms go on to the third toxic phase during which they may develop jaundice, organ failure (generally), liver and kidney dysfunction, or die. The case-fatality rate (CFR) of severe YF ranges from 20% to 50%.[4-6] An estimated 200 000 YF confirmed clinical cases and 30 000 associated deaths occur annually worldwide[7-9]; these estimates are likely limited by underreporting of the disease and capacity of national surveillance systems, as well as lack of diagnostic capability in many endemic regions.

There are no antiviral treatments available and therefore vaccination has become the major element in controlling the disease.[5] The live-attenuated YF 17D vaccine has been available for decades and has been shown to be safe and efficacious.[3,10] The vaccine confers lifelong immunity in most cases.[11-14] The World Health Organization (WHO) recommends immunizations for all

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individuals 9 months or older in areas or countries at risk of YF.[9] In Colombia, the YF 17D vaccine was initially included in the National Immunization Program in 1998 for 1-year-old children in high-risk areas, but was made mandatory in 2003 for all children 12 to 23 months old throughout the entire country.[15] In 2006, it was estimated that YF vaccine coverage was 88% of the target population.[16]

The value of the YF 17D vaccine as one of the most successful interventions for controlling disease has not been well documented and this has contributed to a lack of appreciation of the overall value of YF vaccination. In particular, the value for money of a routine immunization program against YF has never been described for an endemic country in Latin America. Therefore, the objective of our study was to evaluate the public health benefits and economic value of routine toddler YF vaccination in Colombia.

Methods

Model Structure

A decision tree model was used to evaluate the impact of the introduction of routine YF 17D vaccination of all 1-year-old toddlers on the disease burden in Colombia (Fig. 1). This allowed us to compare the health burden and cost of YF before and after routine vaccine implementation. There were no “catch-up” opportunities considered in the model. When the vaccine was first introduced in Colombia it was used only in a high-risk population. Our model mirrors the current approach to YF vaccination in Colombia as part of the Expanded Immunization Program, which recommended vaccination of only 1-year-old children. The modeling approach chosen was the most appropriate design to address the primary research question, namely, evaluating the cost effectiveness of routine toddler vaccination compared with a no-vaccination scenario using the epidemiology of YF in Colombia in an interepidemic period.

We assumed vaccine efficacy of 99% with lifelong duration of protection, and 85% coverage of the target population.[17] We considered the epidemiology of YF in the prevaccination era in the country so as to estimate the value of vaccination, by comparing outcomes in unvaccinated population with the theoretical impact of vaccination over the same era. Over the decades before Colombia introduced the vaccine, there was constant low to moderate human YF activity with 2 major outbreaks (1978-1979 and 2003-2004). To remain on the conservative side, the model considered only the interepidemic period, 1980 to 2002, during which the mean number of reported YF cases per year was 6.2.[18] To calculate the cost effectiveness of the vaccine itself, it was necessary to use a time period before the introduction of routine YF vaccination because the number of YF cases reported since 2003 would clearly be affected by the impact of the vaccine.

All monetary units were expressed in US dollars. Prices were inflated to 2015 prices as required using the Consumer Price Index.[19] For the conversion of values from Colombian pesos (Col$) to US dollars, the average representative exchange rate reported by the Bank of the Republic was applied ($1 = Col$2321).[20] Both costs and benefits were discounted at 5% in line with Colombian guidelines.[21] The data were analyzed from the healthcare payer perspective (ie, only costs directly incurred by the healthcare system) and the societal perspective (ie, all costs including out-of-pocket expenses, lost earnings, and productivity losses). The vaccine cost-effectiveness price threshold was estimated on the basis of the WHO cost-effectiveness thresholds, which state that an intervention is cost-effective when its incremental cost-effectiveness ratio (ICER) is 1 to 3 times the gross domestic product (GDP) per capita, and highly cost-effective at an ICER of less than 1 time the GDP per capita.[22] Colombian GDP in 2015 was Col$16 613 951 ($7 158) per person.[23]

Data Sources

Data were taken from peer-reviewed publications and both national and international sources. The size of the Colombian population and of the cohort targeted for vaccination were obtained from the *Departamento Administrativo Nacional de Estadística*.[24,25] Vaccine cost data were obtained from the Pan American Health Organization and a previous vaccination study.[17,26-28] The cost of

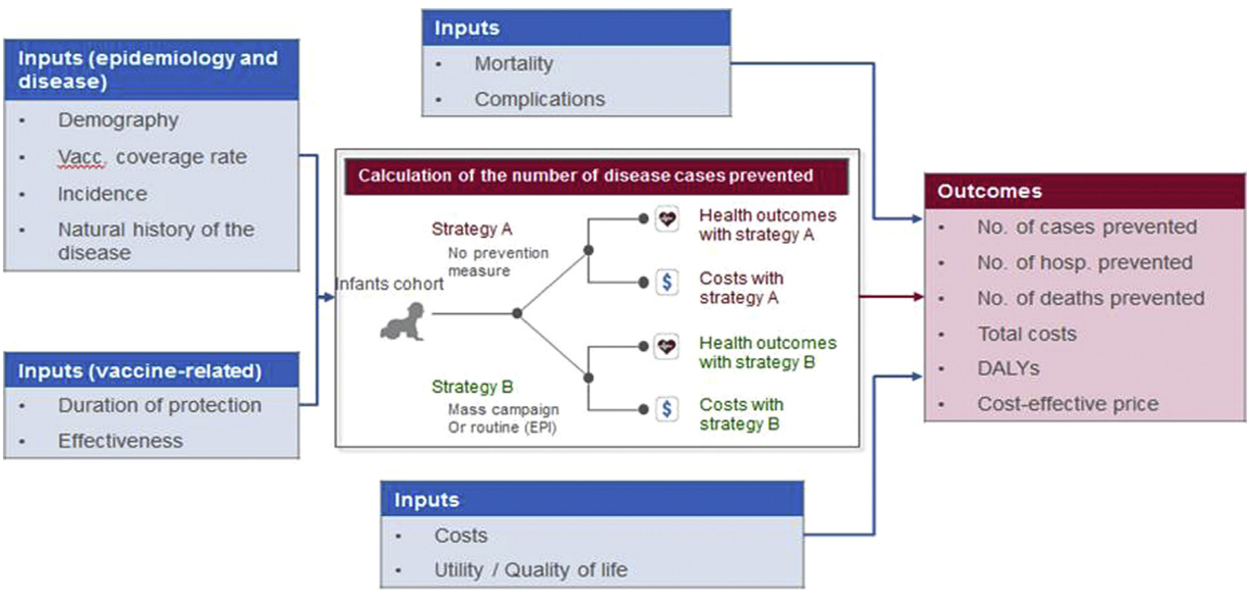

Fig. 1 – Analytical decision tree—allows a prediction of prevented cases and their related costs with the live-attenuated YF vaccine vs no vaccination. DALY indicates disability-adjusted life-year; EPI, expanded program of immunization; YF, yellow fever.

the vaccine in 2015 was $1.10 per dose.[28] Disease incidence rates were estimated on the basis of cases notified to WHO over the nonepidemic period (1980-2002). WHO recognizes that most of these cases are likely to be patients in the toxic phase of YF because of the similarity of the early signs and symptoms of YF with other fever-producing illnesses, and notification is therefore unlikely until YF can be confirmed in more serious, hospitalized cases.[29] The data on the proportion of patients who entered the YF toxic phase and subsequently died and on the duration of the toxic phase in those who survived were all taken from a previous YF study.[30] YF is considered as a reportable disease according to International Health Regulations; nevertheless, the precise extent of illness and death due to YF is not known. There have been several attempts to quantify the degree to which YF is underreported, ranging from 3- to 100-fold levels of underreporting estimated by WHO[17,29] to 10- to 1000-fold, confirmed as a realistic estimate by a recent study[31] (although it should be noted that none of these estimates was specific to Latin America only). Recognizing that many cases of YF therefore go unreported, we used a conservative underreporting factor of 5 (ie, for every severe case reported, there are 5 that are unreported), which was based on the most recent WHO expert opinion.[31] Therefore, although the average number of reported cases per year in Colombia during the interepidemic period (1980-2002) was approximately 6.2, the number of actual toxic cases was considered to be approximately 31 per year.

The costs of the acute and toxic phases of illness as well as the loss of productivity because of premature death were all taken from Colombian government data[32-34] or the International Labor Organization.[35] An allowance was made for labor and vaccine wastage within these costs. The morbidity and mortality caused by both acute and toxic YF were calculated using the WHO Global Burden of Disease methodology[36] and a previously published YF study.[37] Full details of all the values used in the base case and the sources of data are presented in Table 1.

Sensitivity Analysis

Sensitivity analyses were performed to assess the magnitude of uncertainty and to define key drivers. Univariate sensitivity analyses were performed on the following key variables: CFR, programmatic costs (eg, syringes, delivery, and wastage), wastage rate, and the underreporting factor. These parameters were varied within their plausible ranges taken from published sources; details are presented in Table 2.

Table 1 – Input parameters (base case) and sources.

Parameters	Values	References
Total population	48 203 405	DANE[25]
No. of people fully vaccinated	669 137	DANE[24]
Vaccine data		
Vaccine price ($)	$1.10	PAHO[28]
Administration cost (delivery, syringe, wastage)	$2.49	PAHO[28] Castañeda-Orjuela et al[27] Ministerio de Salud y Protección Social[26]
Vaccine efficacy	99%	World Health Organization[17]
Duration of immunity	Lifelong	
Vaccination coverage	85%	
Yellow fever data		
Incidence rate (per 100 000/y) accounting for underreporting factor	0.018	Garske et al[31] DANE[24]
Risk of toxic phase	15%	World Health Organization[42]
Risk of sequelae after toxic phase	None	
Case-fatality rate after toxic phase	20%	World Health Organization[43] Monath and Vasconcelos[30]
Acute-phase duration (d)	3	Assumption
Toxic-phase duration before death (d)	8.5	Monath and Vasconcelos[30]
Toxic-phase duration in survivors (d)	14	Monath and Vasconcelos[30]
Cost data		
Cost of acute phase	$148	Instituto de Seguros Sociales[33]
Cost of toxic phase per event for individuals who then die in toxic phase	$488	Ministerio de Salud y Protección Social[32]
Cost of toxic phase per event for individuals who survive the toxic phase	$804	
Loss of productivity after premature death	$121 596	Estimated value according to participation in the minimum wage relative to average wage income in the years 2007-2010 International Labor Organization[35] Banco de la Republica[34]
Morbidity and mortality data		
YLL per death (discounted 5%)	19	World Health Organization[36]
YLD per acute phase	0.012	Labeaud et al[37]
YLD per toxic phase	0.024	Labeaud et al[37]
Discounting		
Discount rate	5%	Instituto de Evaluación Tecnológica en Salud[21]

YLD indicates years of life with disability; YLL, years of life lost.

Table 2 – Univariate sensitivity analyses: parameters and ranges.

Parameter	Range	Source
Case-fatality rate	0%-60%	Assumption World Health Organization[43] Monath and Vasconcelos[30]
No programmatic costs (eg, syringes, delivery, and wastage)	0%	
Wastage rate	10%-57%	World Health Organization[44] Castañeda-Orjuela et al[27]
Underreporting factor	5-1000	World Health Organization[29] World Health Organization[17] Garske et al[31]

Results

During the interepidemic period (1980-2002), routine YF vaccination of 1-year-olds in Colombia might have averted 2223 nonfatal cases of YF and 65 deaths, leading to an overall reduction of 1365 disability-adjusted life-years (DALYs). The net cost associated with routine YF vaccination (deducting costs averted) was estimated to have been $25 964 813 from the payer's perspective and $16 535 465 from the societal perspective, that is, a cost per case prevented of $11 680 and $7 438 from the perspectives of the payer and the society, respectively, and a cost per life saved of $399 459 and $254 392, respectively. The cost per DALY averted was $19 022 (payer perspective) and $12 114 (societal perspective).

From both perspectives considered, the incremental cost with routine vaccination per DALY averted was between 1 and 3 times the GDP per capita, and thus routine vaccination can be considered a cost-effective intervention using the WHO criteria. Vaccination remains a cost-effective strategy if the price per dose is set no higher than $2.75 and $4.66 from the perspectives of the payer and the society, respectively.

Sensitivity Analyses on the Potential Maximum Cost-Effective Price

Because of the wide range in YF underreporting factors used across the literature, sensitivity analyses were performed across the whole range reported. The underreporting uncertainty had the largest impact on the results (Fig. 2). If the underreporting factor was 5 (the lowest level we assessed), then the cost-effective price of the vaccine would be $2.75 (the same as the base case). If we increased the factor to 10 (the lowest level WHO thought plausible), then the cost-effective price would increase to $8.20. At a factor of 100, the cost-effective price would be $110.05 and it would be regarded as highly cost-effective if the price per dose did not exceed $35.82. Of the other factors considered, only CFR and wastage rate had a significant impact on the results (Fig. 3A,B).

Discussion

Our study suggests that the routine vaccination of 1-year-olds in Colombia against YF would have been considered a cost-effective

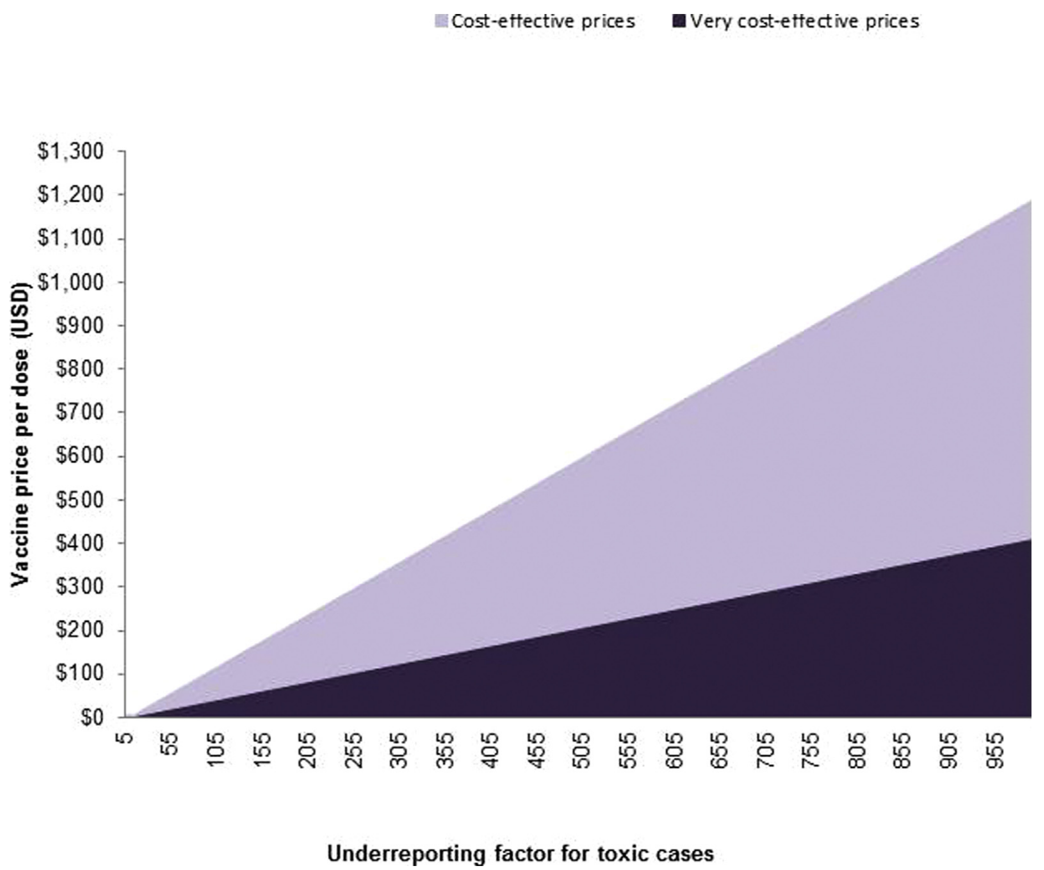

Fig. 2 – Impact of varying underreporting factor on cost-effectiveness of vaccine (payer perspective).

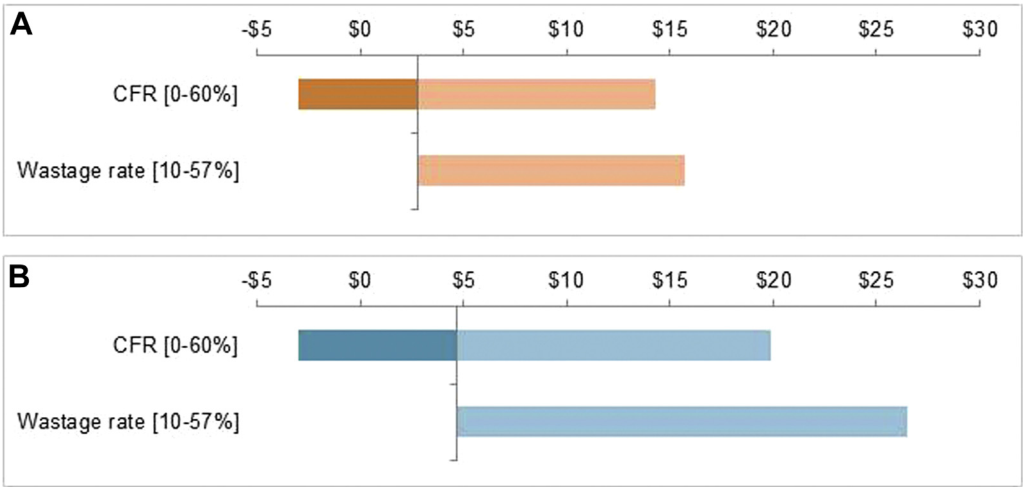

Fig. 3 – Univariate sensitivity analysis on the effect on maximum cost-effectiveness price of the vaccine from payer perspective (A) and societal perspective (B) of varying the CFR and the levels of wastage. CFR indicates case-fatality rate.

strategy in the prevaccination era, even with conservative assumptions on YF incidence, and that its true value is generally not reflected in the actual prices charged for the vaccine.

There have been relatively few studies of the cost-effectiveness of YF vaccination, and those available have generally focused on countries in Africa. A study that included Ghana looked at the cost-effectiveness of adding thermostable single-dose YF vaccines to national vaccination programs and concluded they were potentially cost-effective.[38] Similar findings were reported for YF vaccination in African countries.[39,40] A study in Nigeria showed that routine vaccination of children younger than 2 years would be a cost-effective option, and that in large epidemics it may even be more effective than emergency control vaccination.[39]

Our study is consistent with these previous studies in identifying YF vaccination as a cost-effective approach (with maximum value-based prices of $2.75 and $4.66 per dose from the perspectives of the payer and the society, respectively, which could have been reasonably justified at the time), although differences between countries and years of costing make direct comparison of the actual values difficult. It is apparent from the sensitivity analyses that the underreporting factor is the key driver in determining cost-effectiveness, with CFRs and wastage rates the only other factors to have a significant influence on the ICER.

We did not consider catch-up vaccination in our model; including catch-up vaccination of at-risk groups may have enhanced the cost-effectiveness profile of immunization. Indeed, a retrospective assessment of YF trends between 1998 and 2009 by the *Departamento Administrativo Nacional de Estadística* and the *Instituto Nacional de Salud* identified that inhabitants of the departments located in national territories and Norte de Santander were identified as at an increased risk of illness and death.[41] More specifically, YF deaths occurred primarily in men of working age residing in scattered rural areas in the lowlands of the country, and who were members of the regimen vinculado (those citizens who are entitled to free healthcare because of their income level).[41] This cohort is likely at high risk of YF because of the nature of their occupation/lifestyle and would merit inclusion in any catch-up.

The strengths of our approach are that we used well-recognized data sources and undertook a range of sensitivity analyses to determine the impact of any uncertainty around some of the key parameter values. In addition, we have used conservative estimates in our assumptions, specifically around CFRs (using the lower figure of 20% from Africa as opposed to higher rates of 40%-60% found in South America),[30] wastage (using the highest published rate we could identify),[27] and using an interepidemic period and therefore excluding periods of outbreaks. We also took a low current estimate of the level of underreporting in YF rather than using the higher ones previously published in our base-case analysis, although it should be noted that a factor of 5-fold underreporting has not been confirmed in a Latin American setting. It is clear that the level of underreporting has a great influence on the results and that even relatively modest levels of underreporting would transform the use of routine toddler YF vaccine from being cost-effective to being highly cost-effective, for example, an underreporting factor of 17 would lead to the vaccine being considered highly cost-effective compared at a maximum cost of $1.30 per dose (the price at the time of analysis was $1.10 per dose).

A limitation of our study is that because of the lack of robust surveillance data (prevaccination and current) and the recording of medical costs, the burden of disease is difficult to assess accurately. Also, our analysis only covered a period during which there were no YF epidemics and therefore may well have underestimated the true benefits and value of the vaccine.

Conclusions

The value of the routine YF vaccination of 1-year-olds in Colombia is difficult to assess precisely because of the uncertainty around the number of cases per year and the unpredictable nature of YF outbreaks, but had such a scheme been introduced in the period before 2003, it would appear to have been a cost-effective option. Taking the more conservative range of underreporting factor and epidemiological parameters, we showed that the vaccine was cost-effective. In such a context (where we assume YF activity was only low to moderate), even if the vaccine had to be priced at a level more than double the current price at the time we conducted the analysis ($1.10 per dose), it would still have been regarded as cost-effective from a payer's perspective. This study provides important insights into the value of the YF vaccine in an upper middle-income country.

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