Model-based projections of the population-level impact of hepatitis A vaccination in Mexico

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Abbreviations: HAV, hepatitis A virus; m, months; y, years; WAIFW, who acquires infection from whom; WHO, world health organization

There are indications of a shift in the pattern of hepatitis A (HAV) in Mexico from high to intermediate endemicity, progressively increasing the mean age of infection and the proportion of cases which are symptomatic.

This study estimated the potential impact of universal infant HAV vaccination in Mexico with two doses of Havrix™ at 12 and 18 months of age on all HAV infections and symptomatic HAV infections. We developed a dynamic transmission model that accounts for changes in demography and HAV epidemiology. It was calibrated using Mexican age-specific seroprevalence and symptomatic HAV incidence data.

With 70% first-dose coverage and 85% second-dose coverage, the calibrated model projected that HAV vaccination would reduce the incidence of all HAV infections (symptomatic and asymptomatic) after the first 25 years of vaccination by 71–76% (minimum and maximum for different transmission scenarios). The projected reduction in cumulative incidence of symptomatic HAV infections over the first 25 years of vaccination was 45–51%. With 90% first-dose coverage and 85% second-dose coverage, the projected reduction in incidence of all HAV infections was 85–93%, and the projected reduction in the cumulative incidence of symptomatic HAV infections was 61–67%, over a 25-year time frame. Sensitivity analyses indicated that second-dose coverage is important under the conservative base-case assumptions made about the duration of vaccine protection.

The model indicated that universal infant HAV vaccination could substantially reduce the burden of HAV disease in Mexico.

Introduction

Hepatitis A virus (HAV) is the most common cause of viral hepatitis in Latin America.¹ It is transmitted mainly by the fecal-oral route, and thus the incidence of HAV infection is strongly correlated with socioeconomic factors.¹ There is only one HAV serotype, and lifelong immunity is gained after natural infection.² In regions of high endemicity, nearly all children become infected early in life, and therefore most cases are asymptomatic and outbreaks are uncommon.^{1,2} In regions of moderate endemicity, the mean age of HAV infection increases and outbreaks are common.² As the clinical severity of hepatitis A increases with age,³ an increase in the mean age of infection may also increase the number of symptomatic cases.

Changes in socioeconomic conditions in Mexico could have an impact on the pattern of HAV infection. Seroprevalence studies conducted prior to 2000 suggested that in Mexico HAV endemicity was mostly high, with lower seroprevalence levels in higher socioeconomic groups.^{1,2} Recent seroprevalence studies indicate that the seroprevalence pattern for HAV has shifted from high to intermediate endemicity levels.^{4,5} Moreover, this

shift in HAV seroprevalence in Mexico has been confirmed by a recent systematic review and meta-analysis from the World Health Organization (WHO).⁶ Shifting from high to medium HAV endemicity may progressively result in an increase in symptomatic clinical cases among older children, adolescents and adults, and therefore a higher potential for disease outbreaks.²

Vaccines against HAV are available. After a full two-dose course of vaccination, models estimate that detectable anti-HAV antibodies would be expected to persist for at least 25 y after primary vaccination in 95% to 97% of recipients.^{7–9} Universal infant HAV vaccination has been demonstrated to reduce the burden of hepatitis A disease in Israel,¹⁰ Argentina,¹¹ and the US.¹² Mexico is currently considering the introduction of universal infant HAV vaccination, and thus it is important to evaluate the potential impact on the incidence of all HAV infections and symptomatic HAV infections in Mexico.

In addition to the potential impact of vaccination on HAV transmission dynamics, changes in epidemiology, demography and socioeconomic conditions may affect HAV transmission dynamics in Mexico. Furthermore, indirect herd protection may also influence HAV incidence in the unvaccinated population,

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depending on transmission dynamics and the vaccine coverage rates obtained.^{3,13} All these factors need to be taken into account when evaluating the potential impact of HAV vaccination on public health, and therefore dynamic mathematical modeling is the most appropriate method to estimate the impact of vaccination. Coverage rates and the number of doses can also be modeled and can be used to provide data for an economic evaluation of a universal mass vaccination (UMV) program.

We have developed a dynamic transmission model for HAV to estimate the expected population-level impact of universal infant HAV vaccination using the hepatitis A vaccine Havrix™ (GlaxoSmithKline Biologicals S.A., Rixensart, Belgium) on the incidence of all HAV infections and symptomatic HAV infections in Mexico.

Results

Prior to vaccination (model calibration). For each of the eight sets of assumptions considered regarding transmission (0–< 1 and 1–< 5 y or 0–3 and 3–< 5 y for the first two age groups for the contact pattern, and 70%, 80%, 90% or 100% of risk of HAV infection assumed to be caused by person-to-person transmission), the best-fit model outcomes were close to both the age-specific seroprevalence data and the age-specific HAV disease incidence data. The **Supplemental Material** provides data on the value of the objective function, quantifying the quality of fit, of the best-fit model for each of the eight sets of transmission assumptions, obtained by minimizing the weighted sum of squares of relative differences between model outcomes and observations.

Figure 1 shows model vs. observed data for the scenario with 80% person-to-person transmission and 0–< 1, 1–< 5 y for the two first age groups for the contact pattern. The quality of the model fit is similar for the other scenarios (data not shown). **Figure 1A** shows the mean percentage of the population projected by the model to be HAV-positive, by age group, in 2006 compared with the observed seroprevalence data the same year.⁴ **Figure 1B** shows the mean incidence of symptomatic HAV infections during the period 2004–2008, by age group (accounting for the estimated under-reporting of symptomatic HAV infections) projected by the model compared with observed incidence during that period.¹⁴

Figure 1C shows the year-by-year model-projected incidence rate during the period 1990–2008 pooled across all age groups, compared with the incidence reported during the same period.¹⁴ The model did not fit the year-by-year data as closely as the mean incidence data shown in **Figure 1B**; however, as incidence fluctuates from year to year, the model was calibrated only on the mean incidence during the period 1990–2003 and on the age-specific mean incidence between 2004 and 2008 (**Fig. 1B**).

The model estimated a 14–16-fold under-reporting of symptomatic HAV cases and a 1.9 to 2.4-fold decrease in HAV transmission from 1990 onwards. The sigmoidal function of time estimated for the best model used as a factor for the transmission rates is shown in **Figure 1D**, for the same assumptions about transmission as in **Figure 1A–C**.

Model projections with vaccination—base case. **Figure 2A** shows the projected incidence rate of symptomatic HAV infections (cases per 100,000) over time for the base case, without vaccination, with 70% coverage for the first dose and 85% for the second dose, and with 90% coverage for the first dose and 85% coverage for the second dose. **Figure 2B** shows the corresponding projected percentage reduction in the incidence of symptomatic HAV infections over time for the base case with the same coverage rates as **Figure 2A**. For each first-dose coverage rate (no vaccination, 70% or 90%), the four curves in **Figure 2A and B** correspond to different transmission scenarios (two first age groups for contact pattern and 80% or 90% of HAV risk caused by person-to-person transmission).

Table 1 presents the projected percentage reduction in the incidence of all HAV infections (whether symptomatic or not) and the incidence of symptomatic HAV infections after the first 25 y of vaccination, as well as the projected percentage reduction in the cumulative incidence of symptomatic HAV infections over the first 25 y of vaccination, with 70% and 90% vaccination coverage for the first dose and 85% coverage for the second dose. Despite the increase of the mean age at infection after vaccination, the model projects a decrease in the incidence and cumulative incidence of symptomatic HAV infections in each age group after/over the first 25 y vaccination. **Figure 3** shows the age-specific cumulative incidence of symptomatic HAV infection (by 10 y age groups) with vaccination (90% vaccination coverage first dose and 85% vaccination coverage second dose) and without vaccination.

Sensitivity analyses. **Table 2** shows the projected percentage reductions in the incidence of all HAV infections, the incidence of symptomatic HAV infections and the cumulative number of symptomatic HAV infections, for different combinations of assumptions about the first-dose vaccination coverage (70% and 90%), second-dose vaccination coverage (85%, 70%, 0% of those who received the first dose), waning of vaccine protection (base case or no change in waning rate), and time window post-vaccination (25 y, 40 y and 100 y).

The projected reductions in the incidence were slightly smaller over a 40-y or 100-y time window than over a 25-y time window, for both first-dose coverage rates (**Table 2**). Projected reductions in cumulative symptomatic HAV incidence were larger over 40 y than over 25 or 100 y (**Table 2**).

Over a 25-y time window, the assumption of no change in vaccine waning rate had little impact on the projected results compared with the more conservative base-case assumption of a higher waning rate after the first 10 y (1 dose) or 25 y (2 doses). Using 70% and 85% coverage for the first and second dose, the model projected a reduction of 58–69% in the incidence and a reduction of 45–52% in the cumulative incidence of symptomatic HAV for the first 25 y with no change in waning rate, compared with reductions of 57–68% and 45–51%, respectively, in the base case. Using 90% coverage for the first dose, the model projected 82–91% reduction in the incidence and 61–68% in the cumulative incidence of symptomatic HAV for the first 25 y with no change in waning rate, compared with 82–91% and 61–67%, respectively, in the base case (**Table 2**). As the time window was extended to 40 y or 100 y, the assumption of no change in vaccine waning

Figure 1. Epidemiological data in Mexico: model vs. observed data (calibration). (A) HAV seroprevalence by age group. Solid line: modeled seroprevalence. Dotted/dashed line with * data points: observed seroprevalence. Dashed lines: exact 95% confidence interval for observed seroprevalence. Only shown with 0—< 1 and 1–5 y for two first age groups for the contact pattern and assuming person-to-person accounts for 80% of the mean force of infection in 2004–2008. (B) Mean incidence rate (cases per 100,000) by age group during the period 2004–2008. Model vs. observed only shown with 0—< 1 and 1–5 y for two first age groups for the contact pattern and assuming person-to-person accounts for 80% of the mean force of infection in 2004–2008. Solid line: modeled. Dashed line: observed. (C) Incidence of symptomatic HAV infections (pooled across age groups), over time, between 1990 and 2008. Solid line: modeled. *: observed data. (D) Estimated time-varying sigmoidal function used as a factor for the transmission rates.

resulted in larger projected reductions in incidence and cumulative symptomatic HAV incidence, compared with the base case (Table 2).

The model projections also indicated the importance of sustaining a high coverage for the second vaccine dose, especially with sub-optimal coverage at the first dose. With 70% and 70% coverage for the first and second dose, the model projects a 50–63% reduction in the incidence and 41–49% reduction in cumulative incidence of symptomatic HAV for a 25-y time frame, compared with 57–68% and 45–51%, respectively, with 70% first-dose and 85% second-dose coverage. The effect of lower (70%) coverage at the second dose was less important if higher coverage was achieved at the first dose: with 90% first-dose coverage and 70% second-dose coverage, the model projected

a reduction of 79–89% in the incidence and 59–66% in the cumulative incidence of symptomatic HAV for the first 25 y, only slightly lower than the projections of 82–91% and 61–67%, respectively, with 90% first-dose and 85% second-dose coverage.

The model results also indicated that under the conservative base-case assumptions of waning of vaccine protection, a two-dose schedule was key. Indeed, while a single dose (0% second dose coverage) was still projected to reduce all HAV infections, the projected reduction in symptomatic HAV was small after 25 y, with a projected reduction of 19–34% in incidence and 25–34% reduction in cumulative incidence of symptomatic HAV with 70% first-dose coverage (Table 2). In the long-term, it was even projected to lead to an increase in symptomatic HAV incidence, with a projected change of 0% to a 19% increase after 100 y even

Figure 2. Model projections over time of (A) incidence of symptomatic HAV and (B) percentage reduction in incidence of symptomatic HAV. Solid lines: without vaccination. Dotted lines: 70% vaccination coverage first dose, 85% vaccination coverage second dose. Dashed lines: 90% vaccination coverage first dose, 85% vaccination coverage second dose. The four lines within each group represent the four different combinations of assumptions considered regarding transmission ($0 < 1$ and $1-5$ y or $0 < 3$ and $3 < 5$ y two first age groups for contact pattern, and 80% or 90% of HAV risk assumed to be caused by person-to-person transmission).

Table 1. Base case, percentage reduction in outcomes for 25-y time window

Coverage dose 1	Coverage dose 2 (of those receiving first dose)	Percentage reduction in the outcome (min-max)*:		
		Incidence HAV infection	Incidence symptomatic HAV infection	Cumulative incidence symptomatic HAV infection
		25-y time window		
70%	85%	71–76%	57–68%	45–51%
90%	85%	85–93%	82–91%	61–67%

Base case assumptions: person-to-person transmission assumed to account for 80–90% of risk of infection; vaccine protection assumed to wane over time at a rate of 0.12% per year for the first 25 y and a rate of 0.62% per year thereafter in individuals who have received two doses, and at a rate of 1.62% per year for the first 10 y and 2.67% thereafter in individuals who have received one dose; vaccination coverage 70% or 90% at first dose and 85% (of those receiving first dose) at second dose. Note: *percentage reduction in the outcome: minimum and maximum over different scenarios considered for transmission ($0 < 1$ and $1-5$ y or $0 < 3$ and $3 < 5$ y two first age groups for contact pattern, and 80% or 90% of HAV risk assumed to be caused by person-to-person transmission) HAV, hepatitis A virus.

at 90% first-dose coverage. However, the model still projected a decrease of 14–28% in cumulative symptomatic HAV over the first 100 y. Those outcomes are related to the shift in the mean age at infection combined with much faster waning (2.67%) assumed after the first 10 y with a single vaccine dose.

Figure 4 shows the percentage reduction in symptomatic HAV incidence for a two-dose schedule compared with a single-dose schedule over time, for 70% and 90% first-dose coverage rates and the four scenarios considered about transmission. For the first few years after the start of vaccination, all the curves were close to zero indicating little difference between a single-dose and two-dose schedule. After a few years the curves began to diverge, accelerating after approximately 10 to 15 y, indicating that the single-dose schedule would become progressively less effective in reducing symptomatic HAV incidence compared with the two-dose schedule.

Discussion

The present study used a dynamic transmission model to estimate the potential impact of universal infant HAV vaccination using the hepatitis A vaccine *Havrix*TM on the incidence of all HAV infections and symptomatic HAV infections in Mexico. To our knowledge, this is the first published dynamic model of HAV in Mexico. The model projections indicated that universal infant HAV vaccination with two doses of *Havrix*TM in Mexico could reduce the cumulative incidence of symptomatic HAV cases over a 25-y time window, compared with no vaccination, by 45% to 51% with coverage of 70% for the first dose and 85% (of those who received the first dose) for the second dose, and by 61% to 67% with first-dose coverage of 90% (and 85% for second dose).

The calibrated dynamic HAV model presented here fits well observed data on the age-specific incidence of symptomatic HAV infections and age-specific HAV seroprevalence in Mexico.

The model results indicated that the reduction in symptomatic HAV incidence would be greater at higher vaccine coverage. This implies that the public health impact of a HAV vaccination program in Mexico would be influenced by the success of the program in achieving high coverage rates. A study of preventive interventions in Mexico found that the completion rate for vaccination programmes (BCG, diphtheria influenza, measles, rubella, pertussis) in children aged 0–10 y was around 90% for 2003–2006,¹⁵ indicating that high coverage rates are achievable in Mexico. The first dose of the measles-mumps-rubella (MMR) vaccine, administered at age 12 mo, has a coverage rate of 70% for children aged < 18 mo in Mexico, and the fourth dose of the pentavalent vaccine administered at age 18 mo has a coverage rate of 83% in children aged 18–19 mo.¹⁶

The time window used for the model also affected the projected impact of vaccination. Over a 40-y time window, the projected reductions in HAV incidence were smaller than over a 25-y time window for a given level of vaccine coverage. In the very long-term, over a 100-y time window, the projected reductions in HAV incidence were smaller still. The difference was also more marked for the incidence of symptomatic HAV than for all HAV. This reflected a combination of two factors: the shift in the mean age at infection induced by a reduction in HAV transmission; and the assumed waning of vaccine protection. As the incidence of infection declines, people tend to be infected later in life when HAV infection is more likely to be symptomatic. It is important to note that the longer the time window, the greater the uncertainty in projections regarding aspects such as demography, population mixing, hygiene and long-term vaccine protection. Thus, projections over the shorter time period of 25 y are expected to be more reliable than projections over 40 or 100 y.

The recommended administration schedule for *Havrix*TM is two doses.⁷ Our model therefore evaluated a two-dose schedule, given at 12 and 18 mo of age, in the base case, with coverage rates of 70% or 90% for the first dose and 85% (of those receiving the first dose) for the second dose. However, another country in the region, Argentina, introduced universal infant HAV vaccination in 2005 and opted for a single-dose schedule.¹¹ We therefore explored the effect of a single-dose HAV schedule (reducing the coverage of the second dose to 0%) in Mexico as part of the sensitivity analyses in the present model. Our results indicated the importance of a two-dose schedule under the conservative base-case assumption made about the rate of waning of vaccine protection. When the second-dose coverage was set to 0% in the sensitivity analyses, the projected reductions in all HAV incidence and symptomatic HAV incidence were much lower than with second-dose coverage set at 70% or 85% (of those receiving a first dose) at all modeled levels of first-dose coverage. This is consistent with the findings of a cost-effectiveness evaluation of HAV vaccination in Argentina published by Ellis and colleagues, using a Markov (static) model and vaccine waning assumptions similar to ours, which also projected that two HAV vaccine doses would produce a greater reduction in HAV infection than a single

Figure 3. Model projection of the age-specific cumulative incidence of symptomatic HAV infection over first 25 y vaccination, by 10 y age group. Dashed lines (with squares): projection without vaccination continuous lines (with stars): projection with 90% vaccination coverage first dose and 85% second dose among those who received the first dose). The four lines within each group represent the four different combinations of assumptions considered regarding transmission (0–< 1 and 1–5 y or 0–< 3 and 3–< 5 y two first age groups for contact pattern, and 80% or 90% of HAV risk assumed to be caused by person-to-person transmission).

dose.¹⁷ The difference in projected symptomatic HAV incidence between a single-dose schedule and a two-dose schedule was small for the first few years after vaccine introduction, beginning to increase approximately six years after introduction and sharply increasing a decade or more after introduction. This pattern reflects two factors. First, the rate of waning was assumed to be higher after a single dose than after two doses, so more children become susceptible to infection again after receiving a single vaccine dose as an infant than after receiving two doses. Second, most HAV infections in children are asymptomatic, so most of the children who lose vaccine protection and are infected by HAV at a young age in the first few years after vaccination will not have symptomatic HAV infections; the incidence of symptomatic HAV infections begins to rise substantially only as the individuals who have lost vaccine protection reach an age at which HAV infection is likely to be symptomatic. These projections indicate that it may be some years before the effectiveness of the single-dose schedule introduced in Argentina in 2005 can be fully evaluated.

The model by Ellis et al.¹⁷ also projected a 72.5% reduction in HAV cases with 76% coverage with 2 doses at 12 and 18 mo, in the range of the 64% to 77% reduction projected by our population-based model over 100 y with 77% (90% × 85%) 2 doses coverage. Two population-based models of HAV by Lopez et al. (in Argentina¹⁸), and Bauch et al. (in Canada¹⁹), projected slightly higher reductions in symptomatic HAV infections with vaccination than our model.^{18,19} However, the projections from these models cannot be directly compared with the projections presented here due to country-specific

Table 2. Sensitivity analyses, percentage reduction in outcomes

Coverage dose 1	Coverage dose 2*	Waning of vaccine protection	Time window (years)	Percent reduction in the outcome (min-max**)		
				Incidence All HAV	Incidence symptomatic HAV	Cumulative incidence symptomatic HAV
70%	85%	Base case	25	71–76%	57–68%	45–51%
			40	67–73%	52–61%	49–57%
			100	57–65%	31–41%	42–51%
		No change in waning rate	25	71%–77%	58%–69%	45%–52%
			40	68%–74%	54%–63%	49%–57%
			100	63%–70%	45%–53%	48%–56%
	70%	Base case	25	68–73%	50–63%	41–49%
			40	64–70%	44–55%	44–53%
			100	52–60%	20–32%	34–44%
		No change in waning rate	25	69%–74%	52%–65%	42%–50%
			40	65%–71%	48%–59%	45%–54%
			100	59%–66%	35%–45%	42%–51%
	0%	Base case	25	52–56%	19–34%	25–34%
			40	47–51%	11–25%	21–33%
			100	28–35%	–29%––14%	–2–11%
		No change in waning rate	25	56%–60%	27%–42%	29%–38%
			40	52%–56%	21%–34%	27%–38%
			100	36%–43%	–11%–3%	10%–23%
90%	85%	Base case	25	85–93%	82–91%	61–67%
			40	81–91%	75–87%	68–76%
			100	72–85%	54–74%	64–77%
		No change in waning rate	25	85%–93%	82%–91%	61%–68%
			40	82%–91%	77%–88%	68%–76%
			100	80%–89%	71%–83%	71%–81%
	70%	Base case	25	83–92%	79–89%	59–66%
			40	79–90%	71–84%	66–74%
			100	67–81%	43–66%	57–73%
		No change in waning rate	25	84%–92%	80%–90%	60%–66%
			40	81%–90%	74%–86%	66%–75%
			100	75%–86%	61%–77%	65%–77%
	0%	Base case	25	68–73%	43–56%	42–50%
			40	61–69%	33–45%	41–50%
			100	37–50%	–19%–0%	14–28%
		No change in waning rate	25	74%–79%	56%–67%	47%–54%
			40	68%–76%	48%–58%	49%–57%
			100	48%–61%	6%–24%	31%–43%

Notes: *of those receiving first vaccine dose **minimum and maximum reductions across the four different scenarios considered regarding transmission (0–< 1 and 1–5 y or 0–< 3 and 3–< 5 y two first age groups for contact pattern, and 80% or 90% of HAV risk assumed to be caused by person-to-person transmission). Base case assumptions: person-to-person transmission assumed to account for 80–90% of risk of infection; vaccine protection assumed to wane over time at a rate of 0.12% per year for the first 25 y and a rate of 0.62% per year thereafter in individuals who have received two doses, and at a rate of 1.62% per year for the first 10 y and 2.67% thereafter in individuals who have received one dose; vaccination coverage 70% or 90% at first dose and 85% (of those receiving first dose) at second dose. HAV, hepatitis A virus.

differences in the force of infection and the way force of infection is modeled in Lopez et al. Furthermore, each model uses somewhat different assumption for vaccine coverage and

the waning rate of vaccine protection. Long-term follow up and mathematical modeling of antibody decay indicate that up to 95% to 97% of vaccinated adults are still protected against HAV

infection up to 25 y after vaccination.⁷⁻⁹ However, there are no data currently available on the long-term effectiveness of HAV vaccination in young children over the timescales involved in the present model, so for the base case of our model we used a conservative assumption of waning vaccine efficacy. For the period of 25 y after two doses, this was based on follow-up data and a mathematical model of antibody decay,⁷⁻⁹ and for longer periods and after one dose the estimates were based on an earlier publication.¹⁷ Although, the estimates of two doses after first 25 y were derived from the opinion of an expert panel,²⁰ those estimates should be interpreted with caution.

Our model has a number of strengths. As the model is dynamic, it can take account of complex factors including changes in demography and epidemiology, and age-specific risk of HAV infection. It also accounts for age-specific risk of symptoms if infected and under-reporting. The projected model outcomes without vaccination matched rather well age-specific seroprevalence and symptomatic HAV incidence data from Mexico, indicating that the model successfully represented HAV transmission patterns. Year-on-year variations in incidence were less closely matched, but given the year-to-year variation the model was calibrated using mean age-specific incidence data and thus would be expected to match mean incidence data more closely than year-by-year data. The model can be used to explore the potential impact of certain features of a vaccination program, such as coverage rates and the effect of different dose schedules, and can be used as the basis for an economic evaluation of universal HAV vaccination in Mexico.

For a preventive intervention such as vaccination, which is expected to produce health effects lasting well into the future, modeling may be the only way to estimate the potential effects on public health at a population level and over a time frame of several decades. Nevertheless, uncertainty surrounds several key parameters, such as the relative contribution of person-to-person and other transmission routes, contact pattern, and the duration of vaccine protection in the long-term. In the present study we have made assumptions about the values of these parameters, and have explored their effects in sensitivity analyses and different transmission scenarios. The sensitivity analyses indicated that the uncertainty around some of these parameters, such as vaccine waning, could have important effects on the projected health benefits of HAV vaccination. Thus, it will be important to update the model in the future as more data on these parameters become available. Future changes in hygiene and sanitation that may result from continued economic development have not been included in the model, and may further alter the transmission dynamics of HAV in the future independent of vaccination. Similarly, if future Mexican demography diverges from the projections used in the model, this may also influence the risk of HAV infection.

Although the main focus of this model was on the impact of vaccination on all HAV infections and symptomatic HAV infections, this model can be easily extended in the future to account for additional outcomes like HAV-related hospitalizations and HAV-related deaths.

The results presented here indicate that universal HAV infant vaccination in Mexico could reduce the cumulative incidence of

Figure 4. Percentage reduction in symptomatic HAV incidence with 85% compared with 0% second-dose coverage. Solid lines: 90% vaccination coverage first dose. Dashed lines: 70% vaccination coverage first dose. The four lines within each group represent the four different combinations of assumptions considered regarding transmission (0–< 1 and 1–5 y or 0–< 3 and 3–< 5 y two first age groups for contact pattern, and 80% or 90% of HAV risk assumed to be caused by person-to-person transmission).

symptomatic HAV by 61–67% over 25 y with 90% first-dose coverage and 85% second-dose coverage among those who received the first dose. This would represent a substantial benefit to public health.

Methods

A deterministic, compartmental and age-stratified dynamic transmission model of HAV in Mexico was developed and calibrated to country-specific demographic and epidemiological data. We accounted for age-specific risk of HAV infection as a function of age-specific HAV prevalence and contact patterns between age groups, as well as the risk of HAV infection decreasing over the last decades due to improved hygiene and sanitation.^{21,22} The model accounted for the age-specific risk of symptomatic HAV disease in infected individuals and for the under-reporting of symptomatic HAV cases. After model calibration to epidemiological data, the model was used to project the impact of universal infant HAV vaccination with the two-dose vaccine *Havrix*TM at 12 and 18 mo of age under different assumptions about duration of long-term vaccine protection and vaccination coverage after the first and second dose.

Natural history of HAV disease. In the model, the total population of Mexico was stratified into mutually exclusive sub-populations characterized by their common HAV infection/disease status, age and vaccination status (not vaccinated, vaccinated after first dose or vaccinated after second dose). Those sub-populations represent the model states. Individuals flowed continuously between those states when their disease/infection status changed (e.g., by becoming infected or by recovering),

Figure 5. Natural history of HAV disease: states and flows between states.

as they grow older, or when vaccinated. The different disease/infection states were defined in the model as follows: (1) protected by maternal antibodies, (2) latent, i.e., infected but not yet infectious, (3) infected and infectious and (4) recovered and immune (Fig. 5). As the model defined latency as infected but not infectious, individuals in the latent state were assumed to be non-infectious. The time an individual spent in each state was assumed to follow an exponential distribution with a mean duration of 9 mo for maternal antibody protection,^{23,24} 14 d in the latent state,²⁵ and 21 d in the infectious state.²⁵ Recovery from a natural HAV infection was assumed to induce lifelong protection.

Demography. Since both the risk of HAV infection in a susceptible individual and the risk of the infection being symptomatic are age-dependent, the model was also stratified into 105, 1-y age groups (0–< 1 y, 1–< 2 y, etc., up to 104–< 105 y). There were specific model states for each infection/disease state (Fig. 5) in each age group. In any given model state, individuals could either flow to the next infection/disease state or grow older to the next age group in the same infection/disease state. More details on the demography can be found in the **Supplemental Material**.

Transmission. The model included person-to-person transmission (assumed to be the most important risk) and other types of risk such as HAV importation, water and food borne infection. Surveillance is limited in Mexico and outbreaks are not registered and studied, so robust data are absent in Mexico about the contribution of person-to-person transmission to the overall risk. In the absence of such data, the model assumed that person-to-person transmission accounted for a fixed percentage (set at 70%, 80%, 90% or 100%) of the mean per-susceptible risk of HAV infection (i.e., the force of infection) in 2004–2008, with the remainder due to the other types of risk. The component of the force of infection caused by person-to-person transmission depended on the fraction of infected individuals in each of those seven age groups and the contact pattern, using a who-acquires-infection-from-whom (WAIFW) contact pattern matrix,²⁶ whose structure reflected the higher risk in younger age groups, the schooling system in Mexico and contacts between parents and their children.²⁷ The model had seven different age groups for transmission [0–< 1 (or 0–< 3), 1–5 (or 3–5), 6–11, 12–15, 16–19, 20–39 and 40+ y]. To account for the improvement in hygiene and sanitation in Mexico over the last decades,^{21,22} transmission was also allowed to monotonically decrease over time (similarly across all age groups) from some calendar year after 1970 estimated by the model. This was modeled by using a parametric sigmoidal decreasing curve, whose four parameters were estimated by

calibration. The transmission parameters are described in more detail in the **Supplemental Material**.

Risk of symptomatic infections and under-reporting of symptomatic cases. The risk that a HAV infection will cause symptoms (i.e., jaundice) is known to increase with age at infection. In the model, the incidence of symptomatic HAV infections was derived from the incidence of all HAV infections (whether symptomatic or not) by using the symptomatic-to-infection ratio model of Armstrong and Bell (Fig. 6).²⁸ We also assumed that only a fixed percentage of the symptomatic HAV cases are reported. The under-reporting factor used in the model was estimated by calibration.

Impact of vaccination and duration/waning of vaccine protection. We have evaluated the impact on the age-specific incidence of all HAV infections and symptomatic HAV infections of universal infant HAV vaccination with the 2-dose HavrixTM HAV vaccine administered at 12 and 18 mo of age. The vaccine protection effect was assumed to be an all-or-none protection against HAV infection in 97% of vaccinated individuals after dose 1 and 99% after dose 2.^{7,29–31} Vaccine protection was assumed to wane over time (using varying profiles of waning). This was modeled as individuals flowing back from the vaccinated states (in which there is no risk of HAV infection) to the corresponding non-vaccinated states at a constant (waning) rate over time. Although vaccinated individuals in whom vaccine protection has been lost through waning remain vaccinated, when they have lost vaccine protection they have the same immune status as non-vaccinated individuals and were considered as such in the model.

Long-term follow up and mathematical modeling of antibody decay indicated that up to 95% to 97% of vaccinated individuals are still protected against HAV infection up to 25 y after vaccination.^{7–9} The model assumed an exponential distribution for the duration of time spent in a compartment. With an annual waning rate of 0.12% (0.0012) per year, 97% of individuals would still be protected at year 25 post-vaccination.^{7–9} Therefore, we used a vaccine waning rate of 0.12% per year for the first 25 y after two vaccine doses. Thereafter we used a conservative 0.62% annual waning rate as used in prior models based on an expert panel.^{17,20} In the absence of data on the duration of vaccine protection after a single dose, we assumed an annual waning rate of 1.62% during the first 10 y and 2.67% thereafter like in a prior model of HAV.¹⁷ Given the uncertainty about the duration of vaccination protection after 25 y and after a single dose, we have evaluated the impact of those assumptions about waning rate in sensitivity analyses, using an assumption that the vaccine waning rate remained unchanged throughout (i.e., the annual waning rate after one dose is 1.62% for the first 10 y and thereafter, and the annual

waning rate after two doses is 0.12% for the first 25 y and thereafter).

For the purpose of this model, the vaccination program was assumed to be implemented in 2012.

Model calibration. The model parameters about transmission and the under-reporting factor of symptomatic cases were estimated by simultaneously calibrating the model outcomes to epidemiological HAV data in Mexico:

- Age-specific HAV seroprevalence data from a surveillance seroprevalence study including all Mexican regions in 2006 (24 data points);⁴ (personal communication)
- Mean age-specific incidence rates of reported symptomatic HAV infections from nationwide surveillance data in Mexico during the period 2004–2008 (9 data points);¹⁴
- Mean incidence rate of symptomatic HAV infections from nationwide surveillance data in Mexico pooled across all age groups during the period 1990–2003 (1 data point).¹⁴

More details on the model calibration can be found in the **Supplemental Material**.

Outcomes evaluated from the model. The model was then used to project the impact of universal infant HAV vaccination in Mexico with HavrixTM at 12 and 18 mo of age under different assumptions about vaccination coverage and the long-term duration of vaccine protection after the first and second dose.

The model evaluated the following outcomes:

- The incidence rate of *all* HAV infections (whether symptomatic or not), and of symptomatic HAV infections, over time, with or without vaccination;
- The percentage reduction in the incidence rate of all HAV infections and of symptomatic HAV infections after 25 y, 40 y and 100 y of vaccination, vs. no vaccination;
- The percentage reduction in the cumulative number of symptomatic HAV infections over the first 25 y, 40 y and 100 y of vaccination, vs. no vaccination.

Assumptions for the base case. The following assumptions were made for the base case analysis:

- Person-to-person transmission assumed to account for 80–90% of risk of infection (as a percentage of mean estimated FORCE OF INFECTION in 2004–2008);
- Vaccine protection assumed (conservatively) to wane over time as follows:
 - after first dose, annual rate of 1.62% decrease during the first 10 y and 2.67% thereafter;¹⁷
 - after second dose, annual rate of 0.12% decrease per year during the first 25 y,⁷⁻⁹ and 0.62% per year thereafter.^{17,20}
- Vaccination coverage: first dose at 12 mo of age, 70% or 90%; second dose six months later, 85% of those receiving the first dose.

Sensitivity analyses. Sensitivity analyses evaluated these outcomes under different assumptions: (1) vaccination coverage for second dose, 100%, 70% and 0% among those who received the first dose; and (2) assuming no change in rate of vaccine waning for the duration of the model projections.

Figure 6. Age-specific probability that HAV infection is symptomatic.

All computations were performed using Matlab 7.9.0 software (MathWorks, Cambridge, UK).

Disclosure of Potential Conflicts of Interest

All authors (T.V.E., R.D.A., A.C., L.R.M., C.M.) are employees of GSK Biologicals; T.V.E., R.D.A., A.C. and C.M. also have stock ownership at GSK Biologicals.

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Trademark

Havrix is a trademark of GlaxoSmithKline group of companies.

Supplemental Materials

Supplemental materials may be found here:
www.landesbioscience.com/journals/vaccines/article/20549

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