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Modeling the hepatitis A epidemiological transition in Thailand

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ABSTRACT

Background: In most low- and middle-income countries, hepatitis A virus (HAV) is shifting or expected to shift from high endemicity to intermediate or low endemicity. A decreased risk of HAV infection will cause an increase in the average age at infection and will therefore increase the proportion of infections that results in severe disease. Mathematical models can provide insights into the factors contributing to this epidemiological transition.
Methods: An MSLIR compartmental dynamic transmission model stratified by age and setting (rural and urban) was developed and calibrated with demographic, environmental, and epidemiological data from Thailand. HAV transmission was modeled as a function of urbanization and access to clean drinking water. The model was used to project various epidemiological measures.
Results: The age at midpoint of population immunity remains considerably younger in rural areas than in urban areas. The mean age of symptomatic hepatitis A infection in Thailand has shifted from childhood toward early adulthood in rural areas and is transitioning from early adulthood toward middle adulthood in urban areas. The model showed a significant decrease in incidence rates of total and symptomatic infections in rural and urban settings in Thailand over the past several decades as water access has increased, although the overall incidence rate of symptomatic HAV is projected to slightly increase in the coming decades.
Conclusions: Modeling the relationship between water, urbanization, and HAV endemicity is a novel approach in the estimation of HAV epidemiological trends and future projections. This approach provides insights about the shifting HAV epidemiology and could be used to evaluate the public health impact of vaccination and other interventions in a diversity of settings.

1. Introduction

Hepatitis A virus (HAV) is associated with inadequate water and sanitation as well as poor hygiene; increases in water access lead to reduced risk of waterborne HAV transmission, and the improved hygiene stemming from water access also reduces the rate of person-to-person transmission. The clinical presentation of hepatitis A varies with age. Few children younger than 6 years show symptoms, while most older children and adults develop an icteric infection (jaundice). Following infection, patients usually acquire a life-long immunity against HAV with no chronic development of the disease [1].

HAV endemicity can be conveniently characterized in a region by using the age at midpoint of population immunity, which is the youngest age at which at least 50% of the population is HAV-seropositive [2]. The prevalence of HAV infection varies across geographical regions, with low endemicity in Western Europe, Northern America, Japan and Australia, and intermediate or high endemicity in most of Central and South America, Africa and South Asia [3,4]. However, most low- and middle-income countries are shifting or are expected to shift toward lower risk of HAV infection and therefore toward lower endemicity in the coming years. As the HAV incidence decreases, the average age at infection increases from early childhood toward adolescence and adulthood [3,5]. Because the severity of symptoms increases with age, delayed age at infection can lead to a higher disease burden in populations that do not adopt appropriate vaccination strategies.

In both urban and rural regions of countries where endemicity is shifting to lower levels or is foreseen to do so, mathematical models of current and future HAV epidemiology may inform the public health community by providing insight about where HAV vaccination may be needed to reduce the burden of HAV disease [6,7]. In previous HAV models, the risk of a susceptible individual contracting HAV – that is, the *force of infection* (FOI) – has usually been modeled as a decreasing function of calendar time

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[8–10]. These transmission models generally have not attempted to account for changes in HAV transmission over time as a consequence of improvements in socioeconomic conditions and hygiene, even though field studies and meta-analyses have shown a significant correlation between these factors and HAV incidence [4,8]. There is a particularly strong association between the HAV FOI and access to clean drinking water [8].

In Thailand, seroprevalence data indicate that an epidemiological shift to lower endemicity has occurred in both rural and urban areas, although rural areas continue to have higher seroprevalence rates [11–13]. Studies conducted in the late 1970s reported that about half of all 5-year-olds had already developed immunity to hepatitis A as a result of prior infection and that nearly all adults had anti-HAV antibodies [14–16]. By the late 1980s, the age at midpoint of population immunity had risen to about 10 years [17,18]. By the early 2000s, the midpoint had shifted toward early adulthood [13,19–22], though the age at midpoint of population immunity remained in childhood in some rural areas [12,23,24]. This shift to lower incidence has enlarged the frequency and scale of outbreaks of symptomatic hepatitis A disease in Thailand [25].

In Thailand, urbanization is occurring at a rapid rate. The percentage of the population living in urban areas increased from 17% in 1950 to 44% in 2010, and is projected to rise to 72% in 2050 [26]. Access to clean drinking water has also increased since 1970, especially in rural areas that previously had very limited access to safe water [27]. These conditions make Thailand an excellent case study for exploring the HAV endemicity shift that occurs as a function of urbanization and access to clean drinking water. This paper presents the results of a new HAV model applied to rural and urban data from Thailand.

2. Methods

2.1. Modeling key steps and data used

The main steps to the modeling process, and the key data inputs (Table 1), were as follows:

(1) Fit parametric models to age-specific seroprevalence data from several sites to obtain two cross-sectional synthesized seroprevalence curves, one for rural settings [12,13] and one for urban locations [13] (Supplement A).
(2) Estimate the demographic model parameters by calibrating the demographic model outcomes to United Nations data and projections about total population sizes by age [28], and the percentage of the population living in urban areas [26] (Fig. 1A, Supplement B). Aging takes place continuously over time in the model. The model assumed a fixed population age distribution before 1950 [29], but the demographic model is fully dynamic after 1950, with migration rates from rural to urban areas estimated by calibrating the demographic model to the calendar-year-specific percentage of the national population living in urban areas. Finally, the model also uses age-specific mortality rates [28,30].
(3) Estimate the parameters of the transmission model by calibrating age-specific HAV-seropositive prevalence rates in rural and urban areas projected by the model to the two synthesized seroprevalence curves, one for rural and one for urban areas. The decrease in HAV transmission is modeled as a function of the access to clean drinking water over time in each of the two settings [27] (Fig. 1B, Supplement C). The model is deterministic and there are no confidence intervals on the estimated parameters. Their estimation by minimizing the total sum of squares between the model-projected seroprevalence and the two synthesized seroprevalence curves allowed the projected seroprevalence curves by age in each setting (rural and urban) to be as close as possible to the two synthesized seroprevalence curves.
(4) Use the model with the best-fit parameter estimates to project epidemiological outcomes over time. Those outcomes are the youngest age at which 50% are HAV-seropositive, the mean age of symptomatic infection, and the incidence rates of HAV infections (all infections and symptomatic infections) over time. There are no confidence intervals on the model outcomes as the model is a deterministic one.

All numerical simulations were carried out in MATLAB R2013a (The MathWorks Inc., Natick, MA, USA).

2.2. MSLIR model of HAV natural history

A MSLIR compartmental deterministic dynamic transmission model (referred to as the *transmission model* in the sequel) with five infection states was used for the natural history of HAV: protection by maternal antibodies (M), susceptibility to HAV (S), a latent state of being infected by HAV but not yet infectious (L), an infectious period (I), and a recovered state in which infection has conferred life-long natural immunity (R). Individuals flow from one state to another continuously over time, with individuals flowing from an infection state in a given age group to the same infection state in the next age group. The age-specific proportions of symptomatic HAV infections used the model of Armstrong and Bell [9] (Supplement D). The duration in each state is assumed to have an exponential distribution with a mean duration of protection by maternal antibodies of 9 months [31,32], a mean duration in the latent state of 14 days, and a mean duration of infectiousness of 21 days [33].

The model is stratified by (1) age, with one-year age groups from 0–1 up to 99–100 years, to account for evolving demographics and age-specific percentages of icteric infections [9], and (2) setting (separate compartments for rural and urban areas). There is one compartment for each combination of infection state, age group and setting (1000 compartments in total). The model assumed random mixing with respect to age due to the difficulty in estimating relative rates of direct and waterborne transmission of HAV and to reduce model complexity. For the setting stratification, the model assumed that contacts between individuals only occur within the same setting. The only interactions between rural and urban areas are related to rural-to-urban migration over time.

2.3. Force of infection

For a given setting, the FOI was considered to be the sum of the risk caused by person-to-person transmission and the risk from all other causes. The risk caused by person-to-person transmission was assumed to be the most important quantitatively and to depend multiplicatively on three factors: (1) the percentage of infectious individuals in that setting, (2) a setting-specific transmission parameter, β_s, accounting for the contacts between individuals and the per-contact risk of HAV transmission, and (3) a time-varying factor accounting for the decrease in HAV transmission over time, modeled as a setting-specific parametric function of the setting-specific percentage of the population having access to clean drinking water. More precisely, the FOI in setting s (rural or urban) at time t, is given by:

$$FOI_s(t) = F_s(W_s(t)) \times (A_s + \beta_s \times I_s(t))$$

where

- F_s is the factor of HAV transmission in setting s, with F_s modeled as a decreasing parametric function of $W_s(t)$.

Table 1
Data sources.

Type	Details and source
Demographic data	Population size over time (stratified by 5-year age groups, by 5 calendar years periods) [28] Mortality with age-specific death rates [28,30] Country-specific percentages of urban and rural population [26]
Epidemiological data	Urban seroprevalence data from three cities (Chaingrai, Nakhonsrithammarat, and Udonthani), with 2-year seroprevalence rates for pediatric age groups and 10-year rates for adult age groups [13]; the mean prevalence across the three cities for each age group was taken as the overall urban prevalence for the age group Rural seroprevalence data for Chonburi (near Bangkok) [13] and Umphang (near the Thai–Myanmar border) [12]; a separate best-fit curve was fit to each dataset and the mean of the two fits was used as synthesized curve in rural Thailand
Access to clean drinking water	Percentage of the population with access to clean drinking water over 1970–2008 [27]; data were adjusted to ensure access increased monotonically over time, and a linear increase in access was assumed for 1950–1970 due to lack of data

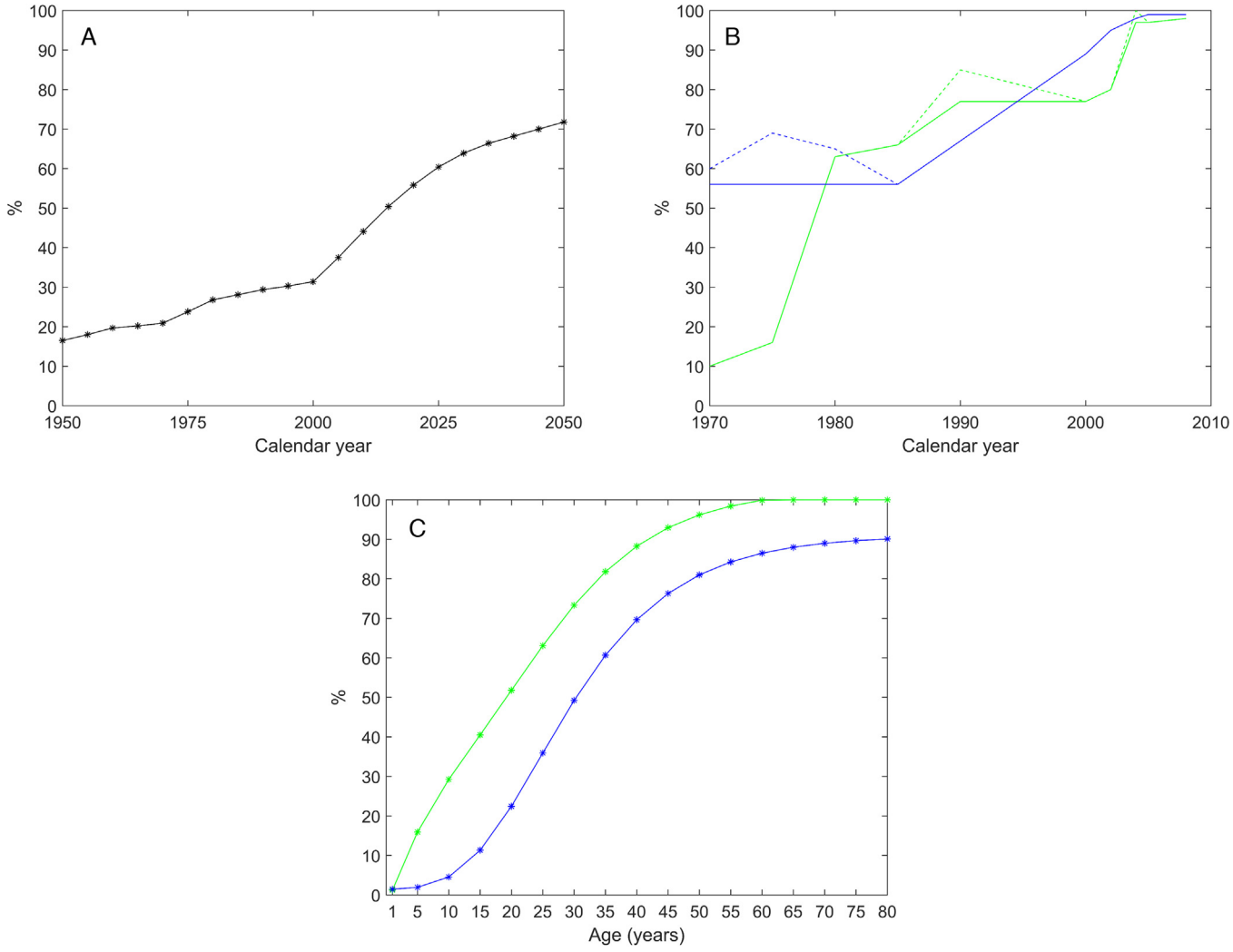

Fig. 1. (A) Percentage of the total population in urban areas, over time, by 5 calendar years; (B) percentage with access to clean drinking water over time; (C) percentage of HAV-seropositive by age (synthesized seroprevalence curves by setting). Dashed lines: data; continuous lines: adjusted data; green: rural setting; blue: urban setting.

- $W_s(t)$ is the percentage of individuals in setting s with access to clean drinking water as a function of calendar time t.
- A_s is the component of the FOI not related to person-to-person transmission in setting s.
- β_s is the transmission parameter in setting s.
- $I_s(t)$ is the proportion of individuals infected in setting s, as a function of calendar time t.

The risk from all causes other than person-to-person transmission, including water, foodborne transmission and importation of HAV, was taken as a small fraction of the setting-specific FOI at the steady state (before 1950) multiplied by the same time-varying factor used for the person-to-person transmission. Because the percentage of residents with access to clean drinking water in both rural and urban settings was nearly 100% by 2008 (Fig. 1B,

Supplement C), the percentage was assumed to remain the same from 2008 onwards.

The transmission model has 10 parameters, of which 5 are specific to each setting:

- the transmission parameter β
- α: percentage of individuals with access to clean drinking water at which $F(p)$ starts to decrease, such that $F(\alpha) = 0.99$ (the maximal value of $F(p)$ being 1)
- δ: percentage of individuals with access to clean drinking water at which $F(p)$ has its inflexion point, counted starting from α (hence, the inflexion point is at the value $\alpha + \delta$)
- f: maximal fold decrease for $F(p)$, from its maximal value (1) to its minimal value.
- p_{1950}: the percentage of the population with access to clean drinking water in 1950 as a fraction of the percentage with access to clean drinking water in 1970.

For each setting (rural and urban), there is a function $F(p)$ with 3 setting-specific parameters α, δ and f, that characterize the decrease of HAV transmission as a function of the percentage of the population with access to clean drinking water p in that setting. $F(p)$ was modeled as a sigmoidal ('S-shape') function. This type of function was chosen because it decreases monotonically without having too many parameters. The function $F(p)$ is given by

$$F(p) = L + H \times (1 - tanh(s \times (p - (\alpha + \delta))))$$

where p is the percentage of the population with access to clean drinking water, $L = 1/f$, $H = (1 - (1/f))/2$, $s = -Atanh(x)/\delta$, $x = (L + H - 0.99 \times (L + 2 \times H))/H$. Note that neither α, $\alpha + \delta$ nor the value of p at which $F(p)$ is ceiling at its minimal value necessarily have to be for a value of $p \leq 100\%$. *tanh* and *Atanh* denote the hyperbolic tangent and inverse hyperbolic tangent functions respectively.

To estimate those five parameters in each setting, the model was calibrated to both synthesized seroprevalence curves simultaneously (Supplement E).

2.4. Base case and sensitivity analyses

For the base case, the per-susceptible risk of HAV infection not related to person-to-person transmission was assumed to be 10% of the setting-specific FOI at steady state (prior to 1950), and the relative difference between the three parameters (α, δ, and f) of the transmission model in the rural and urban settings was constrained to be at most 10%. The main model projections for the base case are presented in Section 3.

A sensitivity analysis was conducted with respect to the per-susceptible rate of HAV infection not related to person-to-person transmission, using alternative values of 0%, 5%, 10%, and 20% of the FOI at steady state prior to 1950. The parameters α, δ, f were either unconstrained, or constrained to have a relative difference of at most 10% or 25% between the rural and urban settings, with or without the same constraint on β (using a maximal relative difference of 25% for the 4 parameters). The transmission model was calibrated to the synthesized seroprevalence curves for 16 scenarios (4 scenarios with respect to the FOI and 4 scenarios with respect to the constraints). The range of the model outcomes for the 8 most relevant scenarios of the sensitivity analyses are presented in Supplement G.

3. Results

3.1. Transmission level as a function of access to water

The calibration of the transmission model to the two synthesized seroprevalence curves shown in Fig. 1C allowed the parameters of the transmission model to be estimated. The model achieved a good fit in both rural and urban settings. The model estimated consistently higher transmission levels in rural than in urban areas, with a 2.4- to 5.3-fold difference in transmission level between settings over the 1950–2008 period. When access to clean drinking water was 100% versus 0%, the model estimated a 3.3- and 4.1-fold decrease in transmission in rural and urban areas, respectively (Fig. 2A). Using the setting-specific access to clean drinking water between 1950 and 2008, a 3.1- and 3.3-fold decrease in transmission was estimated in rural and urban areas, respectively (Fig. 2B).

3.2. Seroprevalence

Fig. 3 shows the projected age-seroprevalence curves every 25 years from 1950 to 2050 in rural (Fig. 3A) and urban (Fig. 3B) areas and at the national level (Fig. 3C). The model also estimated the age at midpoint of population immunity, defined as the first age at which 50% of individuals are HAV-seropositive, to be consistently higher in urban than in rural areas and to have also progressively increased over time in both settings (Fig. 4A and Table 2). At the national level (and in rural and urban areas, respectively), the youngest age at which 50% of the population is estimated to be HAV-seropositive has increased from 6 years (5 and 19 years, respectively) in 1950 to 19 years (15 and 29, respectively) in 2000, and is projected to further increase to 40 years (33 and 45 years, respectively) in 2025 and 61 years (45 and 66 years, respectively) in 2050. Rural areas had a high endemicity level in 1950 and have shifted toward intermediate endemicity, while urban areas had intermediate endemicity in 1950 and have shifted toward low endemicity.

3.3. Mean age of symptomatic infection

The mean age of symptomatic infection estimated by the model was consistently higher in urban than in rural areas and progressively increasing over time in both settings (Table 2 and Fig. 4B). At the national level (and in rural and urban areas, respectively), the mean age of symptomatic infection was estimated to have increased from 13 years (11 and 21 years, respectively) in 1950 to 18 years (18 and 25 years, respectively) in 2000. The mean age of symptomatic infection is projected to further increase to 29 years (28 and 33 years, respectively) in 2025 and 40 years (38 and 43 years, respectively) in 2050.

3.4. Incidence

The model-projected annual incidence rate of all HAV infections has decreased continuously over time (Table 2 and Fig. 4C). Model-projected incidence rates (per 100,000) of symptomatic HAV infections decreased between 1950 and 2000, from 794 to 665 in rural areas, from 962 to 88 in urban areas, and from 822 to 484 at the country level (Fig. 4D and Table 2). The model shows a relative increase during the next decades, mostly in the rural areas (Table 2 and Fig. 4D). However, the annual incidence rate of symptomatic HAV at the national level is projected by the model to be lower than before 2000 and to remain between about 200 and 300 per 100,000 at the national level between 2025 and 2050 (Table 2 and Fig. 4D).

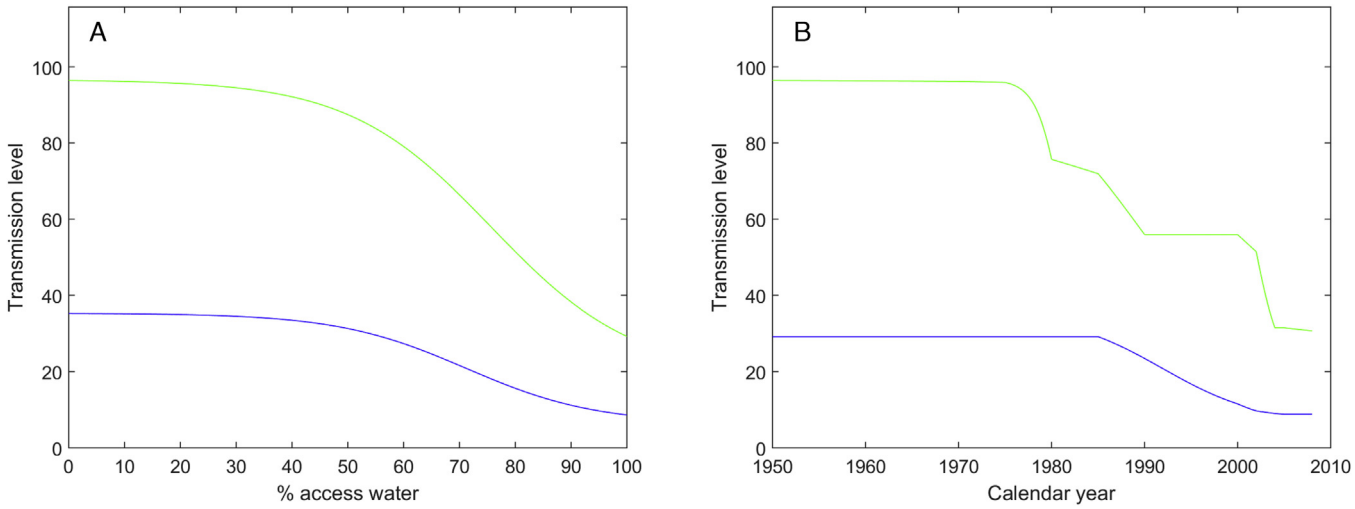

Fig. 2. (A) Transmission level** vs. percentage with access to clean drinking water and (B) derived transmission level** vs. calendar year. **Transmission level = setting-specific transmission parameter (β) times setting-specific factor for transmission; green: rural setting. blue: urban setting.

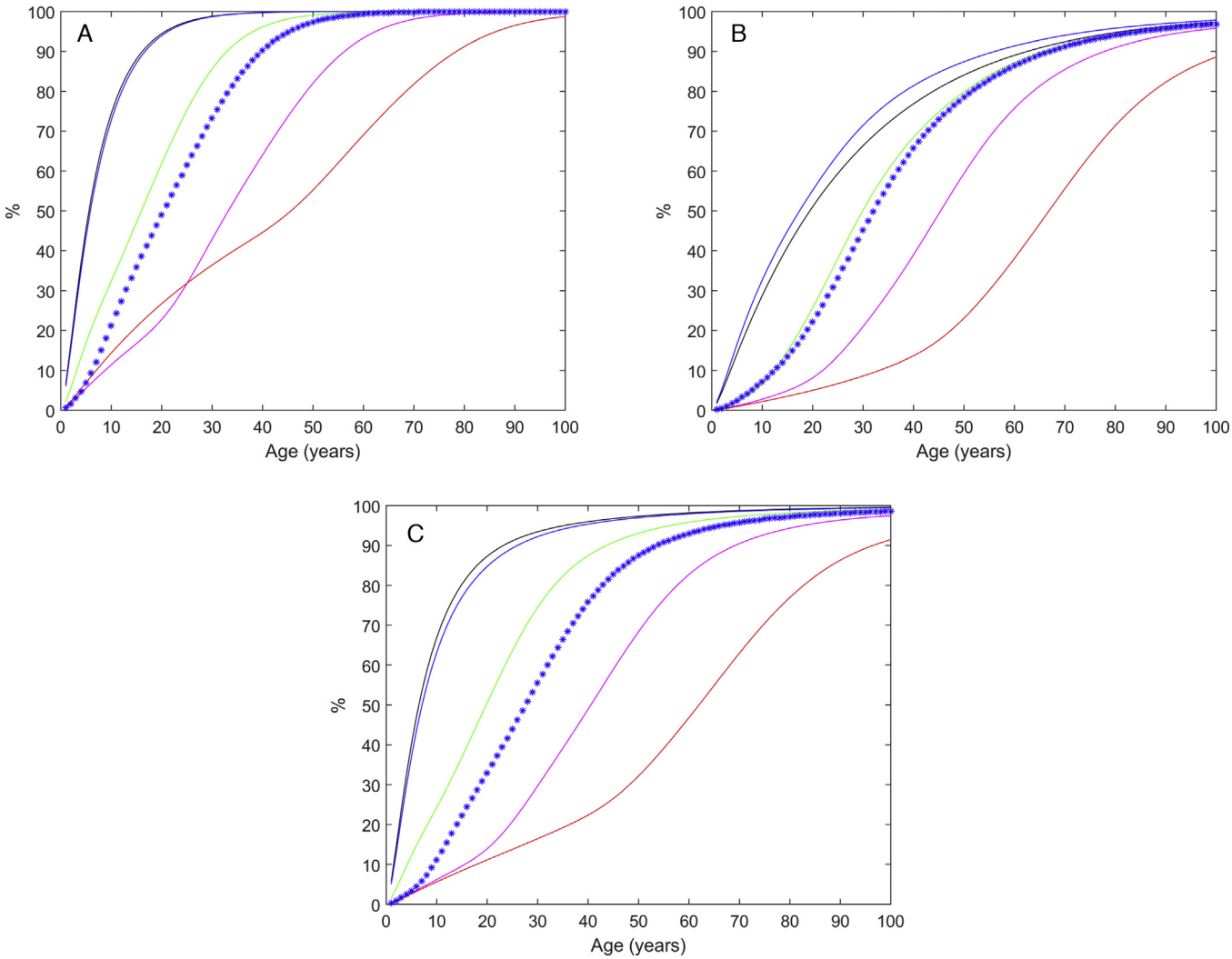

Fig. 3. Model-projected percentage anti-HAV IgG seropositive in rural (A), urban (B) and national (C) settings. Black: 1950; blue: 1975; green: 2000; magenta: 2025; red: 2050; blue stars: years of surveys (2005–2010 for the rural setting, 2005 for the urban setting, 2010 as reference year at the national level).

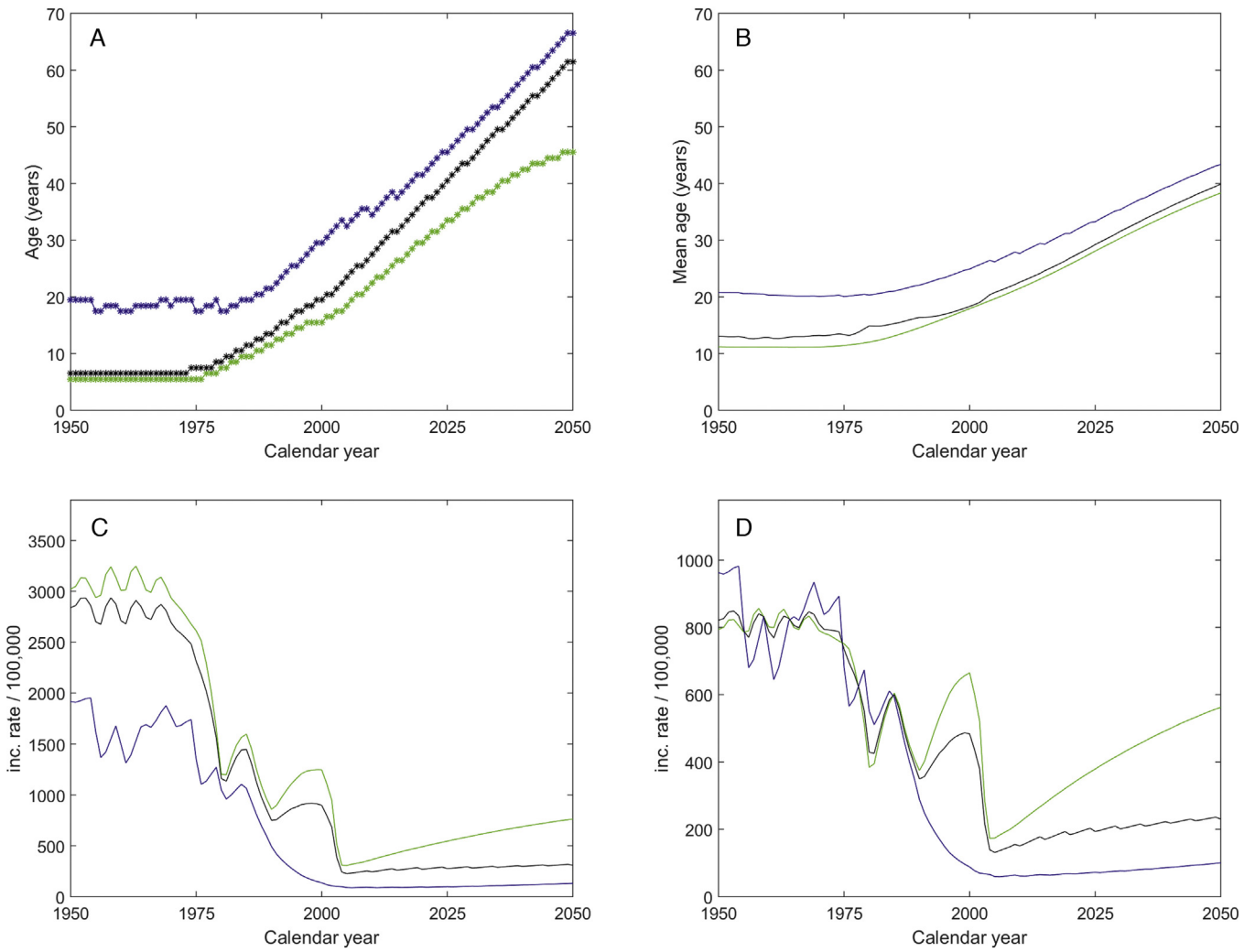

Fig. 4. Epidemiological outcomes over time. (A) Projected youngest age at which 50% of the population is anti-HAV IgG seropositive as result of past infection (the age at midpoint of population immunity or population susceptibility); (B) projected mean age of symptomatic HAV infection; (C) projected annual incidence rate of all HAV infections, per 100,000; and (D) projected annual incidence rate of symptomatic HAV infections, per 100,000. Green: rural setting; blue: urban setting; black: country level.

Table 2
Projections from the model over time.

Outcome	Setting	Calendar year				
		1950	1975	2000	2025	2050
Youngest age at which 50% are HAV-seropositive	Rural	5	5	15	33	45
	Urban	19	17	29	45	66
	Total	6	7	19	40	61
Mean age of symptomatic infection	Rural	11	11	18	28	38
	Urban	21	20	25	33	43
	Total	13	13	18	29	40
Incidence rate of all HAV infections, per 100,000	Rural	3022	2612	1246	545	763
	Urban	1915	1348	136	98	130
	Total	2839	2311	897	275	308
Incidence rate of symptomatic HAV infections, per 100,000	Rural	794	751	665	379	562
	Urban	962	681	88	72	100
	Total	822	735	484	194	231

4. Discussion

The present transmission model is, to the best of our knowledge, the first model explicitly estimating the risk of HAV infection as a function of urbanization and access to clean drinking water. Previous mathematical models have linked socioeconomic development to transmission [8], modeled the FOI from seroprevalence data [34], determined cohort effects [35], applied a catalytic model to determine incidence rates [36] as well as prevalence rates and the FOI [5], assessed periodic oscillations of the FOI [37], used dynamic models to assess the impact of vaccination on HAV infection evolution over time [10,38,39], assessed HAV dynamics by using individual-based models [40], and calculated the cost-effectiveness of vaccination [41]. This new model shows that increases in access to clean water

and urbanization in Thailand can explain the progressive epidemiological shift toward lower endemicity levels. The model's projection of increasing average ages of symptomatic cases and decreased seroprevalence over time are consistent with data from field studies in Thailand [15,17,18,20]. Also, Poovorawan et al. [25] reported a median age at infection of 22 years during an outbreak in 2012 in a rural setting, which lies within the range projected by the model for the mean age of symptomatic infection in the rural setting (18 years in 2000 and 28 years in 2025). The trends projected by this model are a good match to the general pattern for HAV endemicity observed in middle-income countries in every region of the world [3]. In middle-income countries, a significant decrease in seroprevalence typically occurs as access to clean water increases. Studies from middle-income countries also typically show a lag in this epidemiological shift in the rural setting as compared to the urban setting, and this is suspected to be related to a faster increase in access to water and sanitation in urban areas. This model for Thailand builds on what has been observed in field studies in many countries, and the model allows us to make projections into the future and to explore the dynamics of the association between water and transmission in different settings (rural vs. urban).

The model presented here has several strengths. It is fully dynamic from 1950 onwards, in terms of both demography (including urbanization) and epidemiology, and is stratified by age to account for changing demographics and the age-specific risk of symptomatic icteric HAV infections. The model is also stratified by setting, with sub-populations dynamically coupled through the progressive migration from rural to urban areas over time. Rural-to-urban migration is an important cause of the decrease in incidence in Thailand. Even if rural incidence remained high, the migration of a majority of the population to urban areas would be sufficient to cause a national-level shift toward lower endemicity.

However, several limitations require cautious interpretation of the results. The model assumed that rural and urban areas had the same age distributions and that rural-to-urban migration occurred at the same rate for all ages. The model assumed that all newborns were immune at birth due to maternal antibodies, even though an increasing proportion of infants may enter directly into the susceptible state because their mothers remain HAV-seronegative at the time of pregnancy. In the absence of data about the magnitude of the risk of HAV infection caused by contaminated water, importation, or other causes that were not person-to-person transmission, it was assumed in the base case that 10% of the FOI prior to 1950 was not caused by person-to-person transmission. The synthesized age-seroprevalence curves used for calibration of the model combined heterogeneous data from several rural and several urban settings, and no longitudinal data from Thailand were available to allow for more precise validation of changes in HAV susceptibility over time. The model-projected mean age at infection over time is quite robust between the different scenarios considered. Likewise the model projections for the midpoint of population immunity and for the HAV incidence rate (whether all infections or symptomatic infections) are also relatively similar between scenarios during the period from 1950 to 2000, although the projections in the future (after 2000) for those three types of outcomes depend more substantially on the assumptions for the different scenarios. Even with these limitations, the model still offers valuable projections from easily obtainable data such as access to clean drinking water and rates of urbanization.

As of the end of 2014, only 18 middle-income countries were including HAV vaccination in their national immunization programs [42]. This means that at present the changes in HAV epidemiology observed in most middle-income countries are being driven by improved access to clean water and other infrastructural and socioeconomic developments. However, as these countries shift toward lower endemicity, an ever-growing proportion of adults will remain susceptible to HAV infection resulting in an increased risk of severe clinical disease and mortality; the benefit of vaccination should be considered in such an environment [6]. When a growing number of adults contracting HAV require lengthy hospitalization, vaccination may become a cost-effective option for reducing the burden of HAV on the health system. The current model did not examine the impact of vaccination on the epidemiology of hepatitis A in Thailand, because a hepatitis A vaccine is not currently included in the national vaccination program. However, vaccination could be added to the model once the model has been validated in other settings. Such a model could be very useful for identifying countries where the shifting endemicity of hepatitis A makes vaccination a valuable public health intervention.

5. Conclusions

Our model offers valuable mid- and long-term projections of HAV epidemiology in Thailand. A similar modeling approach might also be valuable for projecting mid- to long-term trends in HAV epidemiology in other countries, including those that are undergoing transitions in endemicity level but have little historic or recent data on hepatitis A seroprevalence. A model that includes urbanization and water access projections may also be useful for projecting the public health impact of interventions, including various strategies for targeted or universal vaccination.

Role of the funding source

GSK Biologicals SA was the funding source and was involved in all stages of the conduct and analysis. GSK Biologicals SA also took responsibility for all costs associated with the development and publishing of the present manuscript.

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Conflict of interest: KJ reports receipt of personal fees relating to this research study. TVE and CM are employed by the GSK group of companies and own stock options and restricted shares in the GSK group of companies.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2015.11.052.

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