

**The potential impact of Varicella vaccination in
Low to Middle Income Countries: A feasibility modeling study**
**Report to the SAGE working group on Varicella and Herpes Zoster
vaccines**

Marc Brisson^{1,2,3*}, *PhD*

Étienne Racine¹, *PhD*

Mélanie Drolet^{1,2}, *PhD*

1. Centre de recherche du CHU de Québec, Québec, Canada
2. Département de médecine sociale et préventive, Université Laval, Québec, Canada
3. Department of Infectious Disease Epidemiology, Imperial College, London, United Kingdom

*** Author to whom correspondence should be addressed:**

Centre de recherche du CHU de Québec, Hôpital Saint-Sacrement

1050 Chemin Sainte-Foy, Québec, Canada, G1S 4L8

Telephone: (418) 682-7386

FAX: (418) 682-7949

e-mail: marc.brisson@uresp.ulaval.ca

SUMMARY

A dynamic transmission model was constructed to inform SAGE recommendations for varicella vaccination in low and middle income countries (LMIC). The model suggests that in most LMICs there is a high risk of shifts in the age at infection and increased mortality following 1-dose vaccination when coverage is between 20% and 80%. Furthermore, vaccination coverage must be greater than about 60% to produce substantial reductions in morbidity. However, LMIC with very low seropositivity (less than 20-30% in 20 year olds) and the highest burden of disease are expected to have little to no shifts in the age at infection and important reductions in varicella-related mortality and morbidity, at intermediate levels of vaccination coverage. The Immunization and Vaccines Related Implementation Research Advisory Committee (IVIR-AC) found the model to be appropriate. Areas of future work to strengthen the model and thus conclusions include capturing uncertainties in seroprevalence data, case-fatality ratios and morbidity estimates. In terms of data needs, better information is required on varicella incidence and morbidity in LMICs. Future research will focus on extending the work to calculate cost-effectiveness of vaccination.

INTRODUCTION

Concerns prior to varicella vaccination in High Income Countries (HIC)

Prior to the implementation of routine varicella vaccination, important concerns were raised. Firstly, there were concerns related to the high number of varicella cases in vaccinees in the clinical trials¹⁻⁴. Secondly, vaccination could lead to a shift in the average age at infection from children to adults where risk of complication is greater. The worry was that by increasing incidence in adults, varicella vaccination programs could lead to an overall reduction in public health. Mathematical models however predicted that this was unlikely to happen⁵. Thirdly, there were concerns that vaccination could increase the incidence of zoster. It has long been hypothesized that exposure to varicella might reduce the risk of reactivation (zoster) by boosting specific immunity to the Varicella Zoster Virus (VZV)⁶. Two epidemiological studies have

suggested that this mechanism plays an important role in protection against zoster^{7, 8}. Modeling based on these results predicted that, by reducing circulating VZV, universal varicella vaccination could lead to a significant increase in zoster^{5, 7, 9, 10}.

Post-vaccination empirical evidence of the impact of varicella vaccination in HIC

Vaccine effectiveness (concern 1): In HIC, immediate and important declines in varicella-related consultations and hospitalizations have been reported¹¹⁻¹⁶. However, post licensure studies have confirmed some of the above concerns. Breakthrough varicella has been reported following 1-dose varicella vaccination. Surveillance studies have reported 80-85% against all varicella (>90% moderate-severe varicella)¹⁷⁻²¹. Furthermore, it seems that protection wanes with time^{22, 23} with breakthrough varicella cases generally mild and less contagious than varicella in unvaccinated persons^{20, 22}. The population-level effectiveness of 2-dose varicella vaccination has been reported to be >90% against all varicella²⁴⁻²⁷.

Shift in the age at infection (concern 2): It is still too early to measure whether shifts in the age at varicella are occurring in HIC due to herd-immunity effects²⁸. Model results suggest that there is a risk of increased morbidity due to shifts in the age at infection when vaccination coverage is between 30-70%^{9, 29}. Furthermore, models predict that the risk of increases in post vaccination varicella morbidity, due to shifts in the age at infection, increases: 1) with higher vaccine efficacy (e.g. 2-dose vaccination), 2) when contact mixing is proportional, and 3) when severity/morbidity increases significantly with age (e.g. mortality)^{9, 29}.

Increase in herpes zoster (concern 3): Surveillance studies in the U.S. and elsewhere have shown a small increase in zoster^{22, 30-35}. However, it is too early to link these increases with varicella vaccination as increases in age-specific zoster incidence rates have been observed prior to varicella vaccination programs^{16, 36}.

Key issues for Low to Middle Income Countries (LMIC)

LMIC may be at greater risk of shifts in the age at infection and increased morbidity after varicella vaccination because they: 1) are at higher risk of moderate vaccination coverage, 2) have less assortative mixing patterns³⁷, and 3) have greater morbidity and case-fatality in older ages³⁸. Furthermore, given differences in contact patterns, the potential impact of varicella vaccination on herpes zoster is unknown.

OBJECTIVE

The objective of the feasibility modeling analysis was to examine the potential impact of 1-dose varicella vaccination in LMIC on: 1) natural & breakthrough varicella (concern 1) and 2) shifts in the age at infection & morbidity (concern 2). The analysis was performed to inform SAGE recommendations for varicella vaccination in LMICs. Given that this work was part of a feasibility study, a sample of LMICs from across the world was selected for the modeling analysis. Furthermore, we did not examine the potential impact of varicella vaccination on herpes zoster (concern 3).

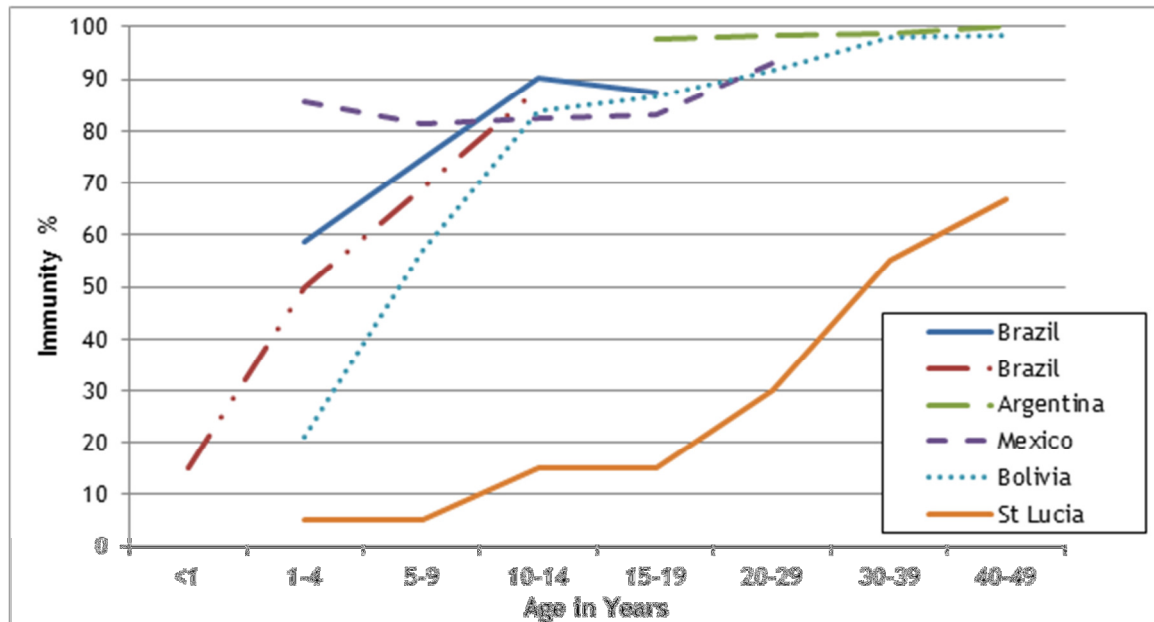
Methods

Selection of Countries

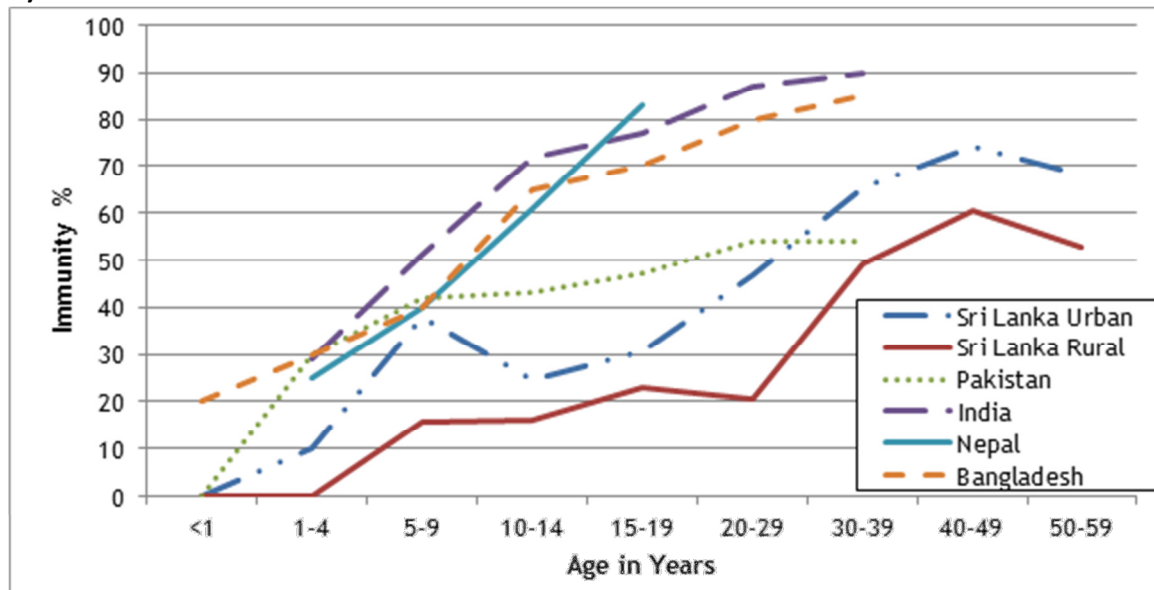
We used a literature review to identify seroprevalence data from LMICs across different world regions (Greenaway, McGill University; see figure 1 for references and results). For the modeling analysis, we chose countries representing the range of seroprevalence from three world regions: Latin America & Caribbean (Maximum seroprevalence=Brazil, Medium=Bolivia, Minimum=St Lucia), South Asia (Maximum=India, Medium=Sri Lanka urban, Minimum=Sri Lanka rural), East Asia & Pacific (Maximum=Thailand, Medium=Malaysia, Minimum=Singapore). Only one seroprevalence study was available from Africa (Nigeria).

Figure 1. VZV seroprevalence from: a) Latin America & Caribbean, b) South Asia, and c) East Asia & the Pacific. References: Brazil: Yu, Epidemiol Infect (2001); Argentina: Dayan, J Clin Epidemiol (2004); Mexico: Munoz, Arch Med Res (1999); Bolivia: Bartoloni, Trop Med Int Health (2002); St Lucia: Garnett, Epidemiol Infect (1993); Sri Lanka [Urban and Rural]:Liyanage, Indian J Med Sci (2007); Pakistan: Akram, Southeast Asian J Trop Med Public Health(2000); India and Nepal: Sengupta, Current Pediatric Reviews(2009); Bangladesh: Saha, Ann Trop Paediatr (2002); Australia: Gidding, Epidemiol Infect (2003) & O'Grady, Trop Med Int Health (2000); Indonesia: Juffrie, Southeast Asian J Trop Med Public Health (2000); Malaysia and Philippines: Lee, Trop Med Int Health(1998); Singapore: Ooi, Southeast Asian J Trop Med Public Health (1992); Taiwan: Chang, Med Mal Infect (2007), Lolekha, Am J Trop Med Hyg(2001) & Migasena, Int J Infect Dis (1997).

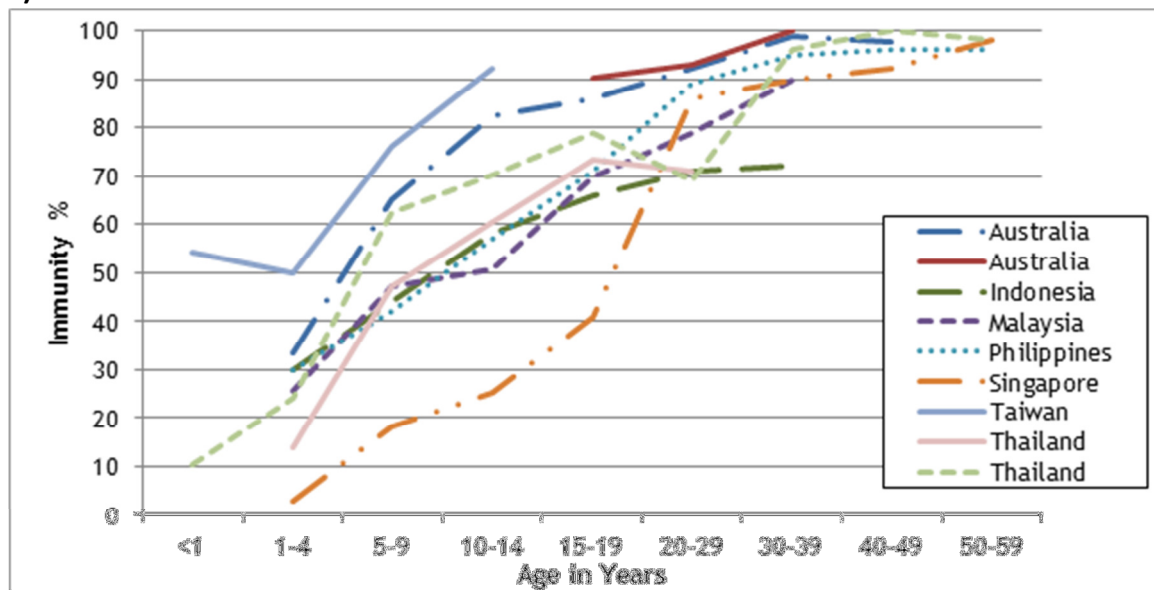
a)



b)



c)

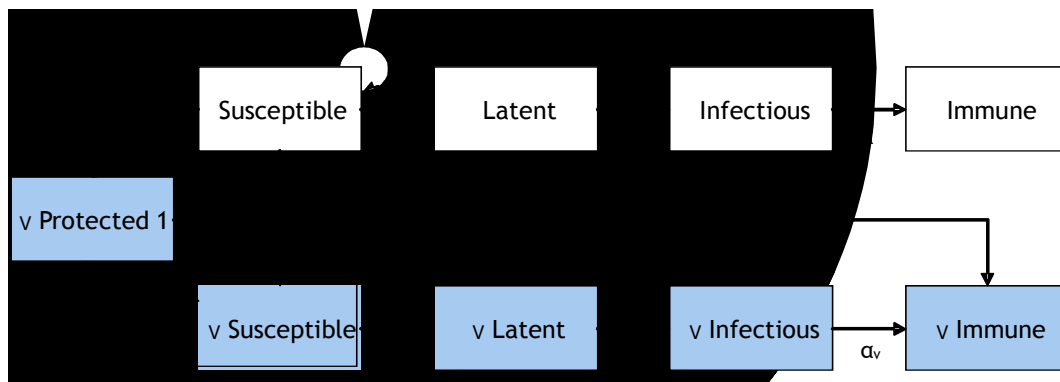


Model Structure

We adapted a transmission dynamic model previously developed to predict the impact of 1-dose varicella vaccination in Canada, the UK and Australia^{9, 10, 39}. The transmission model is a realistic, age structured, deterministic model (RAS) based on a set of ordinary differential equations. The natural history of varicella is represented by 4 mutually exclusive epidemiological states: Susceptible, Latent, Infectious, Immune, Susceptible to Boosting, Zoster and Zoster Immune. Given the objectives of the report, we only present the varicella portion of the model (see figure 2). At 6 months of age, children enter the susceptible class (Susceptible) and if infected pass through the latent (Latent - i.e. infected but not infectious) and infectious (Infectious) periods. After varicella infection, individuals acquire lifelong immunity to varicella (Immune). Following 1-dose vaccination (Figure 2, blue boxes), individuals either remain in the fully susceptible class (Susceptible) due to primary failure or move into one of two classes: 1) a temporary protection class (V_Protected 1) in which individuals are immune to infection but may lose protection over time, and 2) a partially susceptible class (V_Susceptible) in which individuals are partially protected against infection. Vaccinated protected individuals

can also be boosted through exposure to VZV and develop immunity to varicella (V_Immune).

Figure 2. Flow diagram of the natural history of varicella and zoster with and without vaccination. The mutually exclusive compartments represent the different VZV epidemiological states. Arrows represent the flow between these states. w = Waning rate from vaccine protected to vaccine susceptible; T = % who become temporarily protected after vaccination; F = % for which vaccine fails completely; $1-b$ = Degree of protection in vaccinated susceptibles; k = % vaccine protected who become immune due to contact with varicella; m = Rate of varicella infectiousness of vaccinees compared to non-vaccinees; λ = Force of infection; $1/\sigma$ = Duration of natural varicella latent period; $1/\alpha$ = Duration of natural varicella infectious period; $1/\sigma_v$ = Duration of breakthrough varicella latent period; $1/\alpha_v$ = Duration of breakthrough varicella infectious.



Demographic parameters

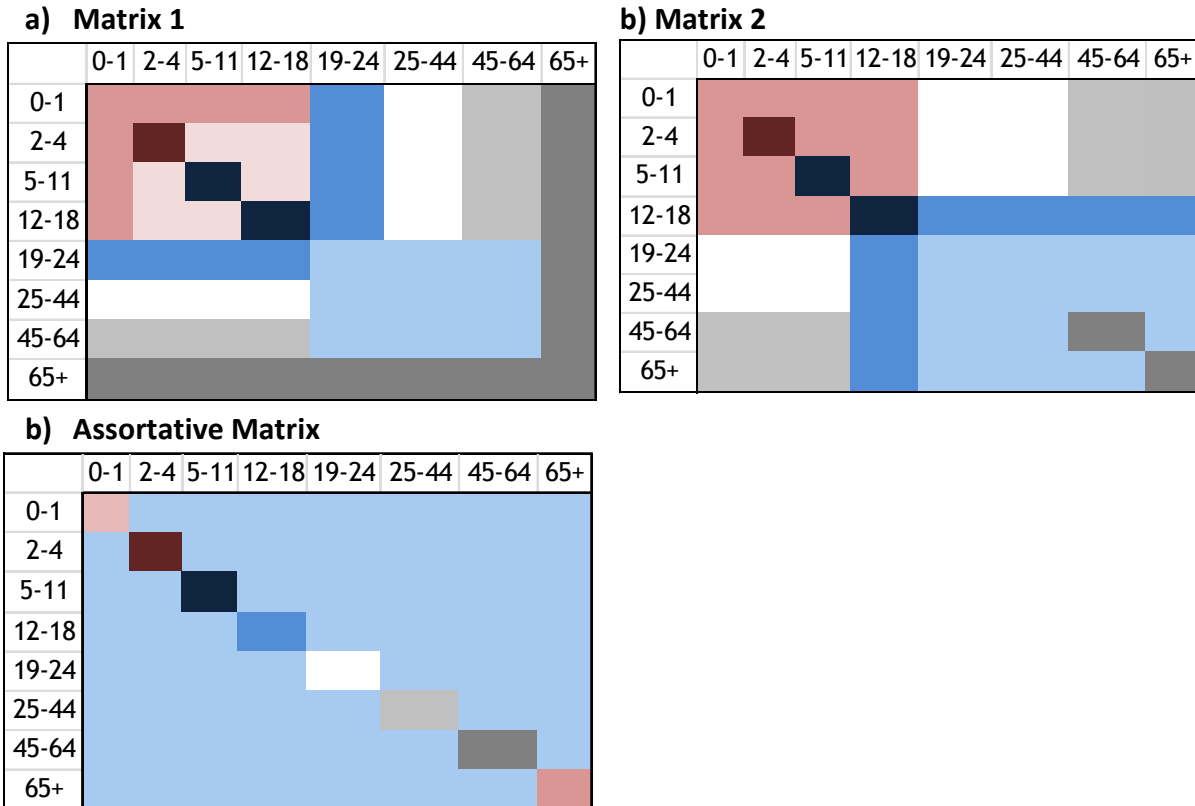
The modelled populations are assumed to be stable and are stratified into 101 age cohorts (0,1,...,100+). The birth rate is constant through each year, and age-specific all-cause mortality rates for each modelled country were taken from the World Health Organization's Global Health Observatory Data Repository [<http://apps.who.int/gho/data/node.main.692>].

VZV Natural History and Transmission Parameters

Mixing. We used Who-Acquired-Infection-From-Whom (WAIFW) matrices to take into account country-specific age-dependant mixing patterns. The WAIFW matrix represents the rate at which an infective of age X infects a susceptible of age Y (effective contact rate). Given the absence of empirical data in LMICs, we used, in this feasibility study,

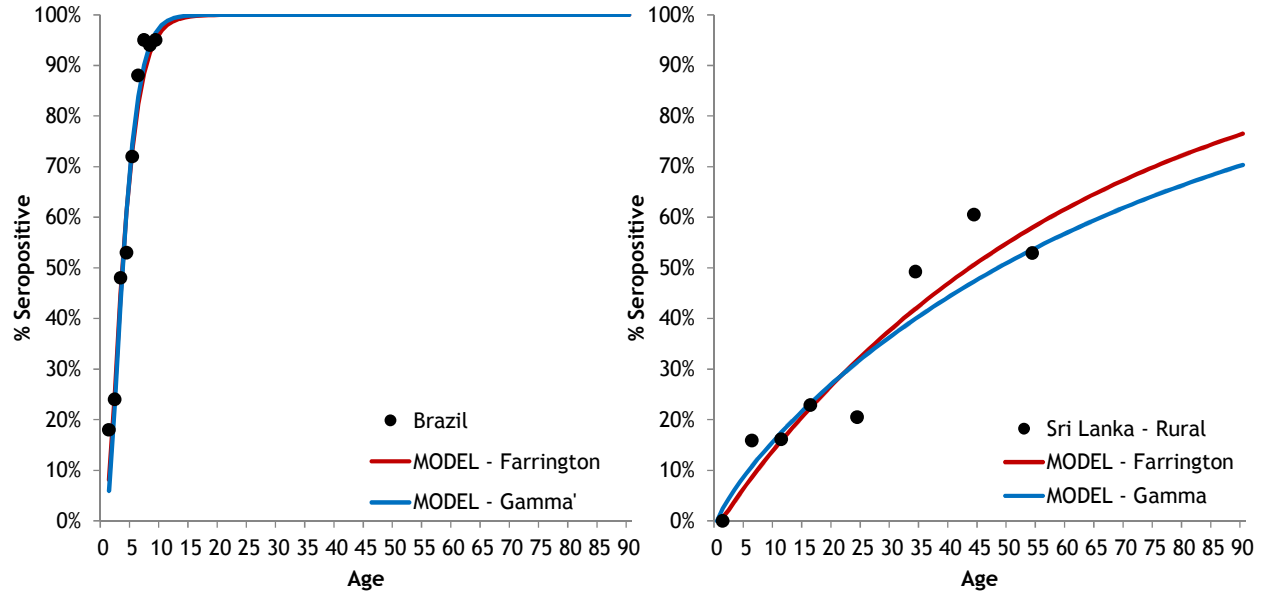
three different matrix structures (see figure 3). These matrices were loosely based on contact patterns measured in Europe⁴⁰ and in Vietnam³⁷.

Figure 3. Mixing patterns (WAIFW matrices) used to model country-specific force of infection. Each colour represents a different element of the effective contact matrices (i.e., different effective contact rate values between age classes).



Force of infection. The age-specific force of varicella infection (per susceptible rate of infection) for each selected country was estimated using a 2 step procedure. First, we estimated the age-specific seroprevalence from available empirical studies (see Figure 1 for seroprevalence studies) using two functions: Gamma⁹ and Farrington⁴¹. Best fit estimates were identified through least squares. Secondly, through least squares, we fit the dynamic model to the estimated seroprevalence using the different WAIFW matrix structures illustrated in figure 3. Model predictions were performed using the best fit for each country (see figure 4 for examples of model fit to seroprevalence data).

Figure 4. Example of model fit to seroprevalence data.



Other parameters. Duration of varicella latent and infectious periods, and vaccine efficacy parameters were assumed to be the same as those previously reported in Brisson *et al.*⁹, see table 1. Given lack of data, we used the same varicella case-fatality rates and morbidity parameters for all LMICs. Base case age-specific case-fatality was taken from a Brazilian study⁴² and the morbidity outcome was inpatient days⁴³.

Table 1. Model Parameters

Model Parameters	Value
Biologic Parameters ⁹	
Duration of varicella (days) [6]:	
Duration of latent period (1/β)	14
Duration of infectious period(1/β)	7
Mobidity & Mortality Parameters	
Mean inpatient days per 100 case of varicella by age group ⁴³ :	
<1	9.9
1-4	2.0
5-9	0.9
10-14	1.8
15-44	12.2
45-64	19.4
>65	
Case-fatality (per 100 case of varicella) ⁴² :	
<1	0.011
1-4	0.003
5-9	0.002
10-14	0.003
15-44	0.025
45-64	0.258
>65	1.169
Vaccine Efficacy Parameters ⁹	
Rate at which temporarily protected individuals become partially susceptible to varicella (1/year) (W)	0.031
% individuals who become temporarily protected after vaccination (T)	93%
% individuals for which vaccine fails completely (P)	4%
Rate of varicella acquisition of vaccinees compared to non vaccinees (b)	73%
Proportion of temporarily protected individuals who become immune due to contact with varicella (k)	91%
Rate of varicella infectiousness of vaccinees compared to non-vaccinees (m)	50%

Results

Modelled seroprevalence and burden of varicella in LMICs, by region

Figure 4 shows that there are important variations in age-specific varicella seroprevalence within world regions, and these variations are greater than between regions. These results are similar to those of a recent study⁴⁴, which suggests that climate and other country specific factor is a key determinants of seroprevalence rather than world region. Table 2 shows the predictions of pre-vaccination burden of varicella by country.

Table 2. Pre-vaccination estimated burden of varicella by country

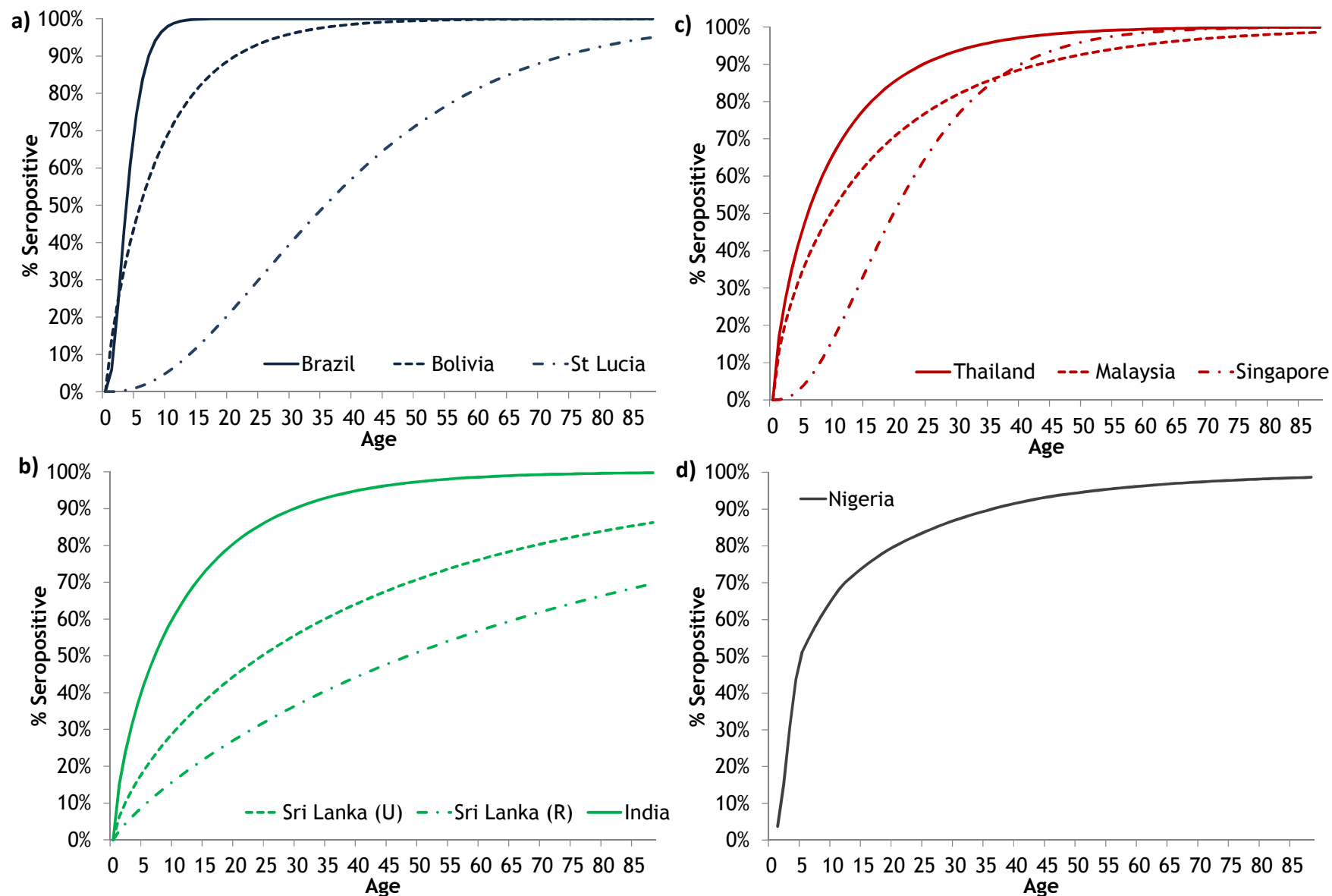
	Population (millions)	Cases	Deaths		Case-fatality (/100)	
			Min	Max	Min	Max
Brazil	200	2,892,437	80	221	0.3%	0.8%
Bolivia	10	227,996	17	47	0.7%	2.1%
St Lucia	0.2	2,405	2	5	8.1%	22.2%
Thailand	70	879,814	109	298	1.2%	3.4%
Malaysia	30	528,927	101	278	1.9%	5.3%
Singapore	5	58,468	21	58	3.6%	9.9%
India	1,310	26,001,129	2769	7616	1.1%	2.9%
Sri Lanka	20	172,000	219	601	12.7%	34.9%

MIN: Brazil case-fatality (Valentim, Vaccine 2008)

MAX: Chili case-fatality (Sengupta, Current Pediatric Reviews 2009)

Age-specific Population numbers: United Nations, Department of Economic and Social Affairs, Population Division (2011). World Population Prospects: The 2010 Revision, CD-ROM Edition.

Figure 4. Modelled Seroprevalence by region: a) Latin America & Caribbean, b) South Asia, c) East Asia & the Pacific and d) Africa. Brazil: Yu, Epidemiol Infect (2001); Bolivia: Bartoloni, Trop Med Int Health (2002); St Lucia: Garnett, Epidemiol Infect (1993); Thailand: Migasena, Int J Infect Dis (1997); Malaysia: Lee, Trop Med Int Health(1998); Singapore: Ooi, Southeast Asian J Trop Med Public Health (1992); India: Sengupta, Current Pediatric Reviews(2009); Sri Lanka: Liyanage, Indian J Med Sci (2007); Nigeria: Bugaje Nigerian Journal of Paediatrics (2011)

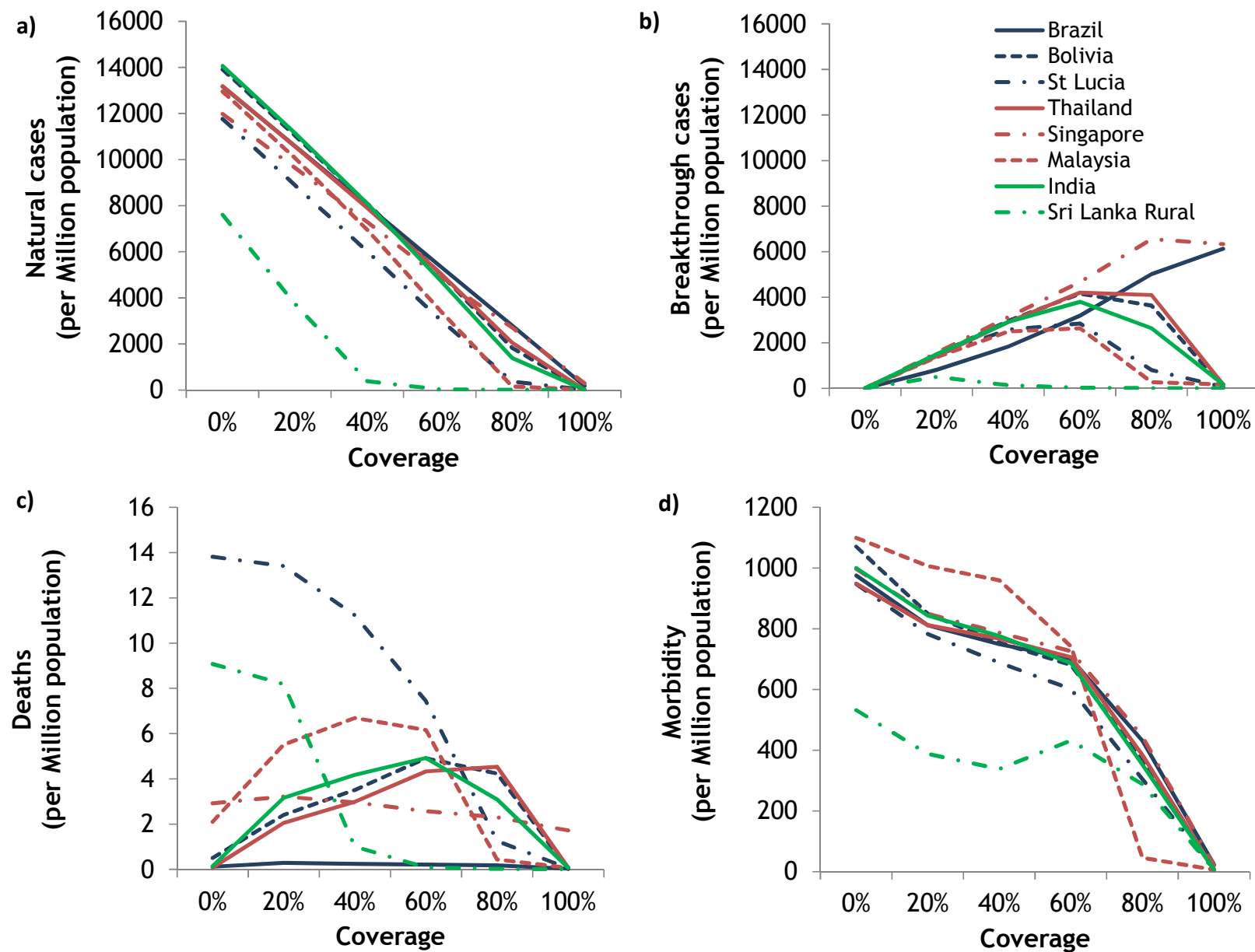


Impact of vaccination & Shift in the age at infection

Figure 1 shows the potential long term (equilibrium) impact of 1-dose varicella vaccination in selected LMIC as a function of vaccination coverage. For all modelled LMICs, the post-vaccination equilibrium incidence of natural varicella declines linearly with increasing vaccination coverage (figure 5a). LMICs with the lowest pre-vaccination seropositivity (e.g., Sri Lanka and St Lucia), reach incidence levels close to elimination at lower coverage than the other countries. As expected, breakthrough varicella rates increase with increasing population-level coverage (as the number of people vaccinated in a country increases) until varicella transmission is significantly reduced in the population (i.e., coverage greater than 80% in most countries).

The model suggests that, prior to vaccination, countries with the lowest predicted population-level incidence (lower seropositivity), have the highest varicella-related mortality. This is because countries with lower force of infection (lower incidence) have higher ages at infection, and case-fatality increases exponentially with age. However, in these countries, the number of varicella-related deaths are predicted to decrease rapidly with increasing coverage (figure 5c), because varicella transmission is more easily controlled through vaccination due to smaller forces of infection and R_0 . Hence, there are little or no shifts in the age at infection predicted for these LMICs (figures 6-7). On the other hand, LMICs with higher seropositivity (most countries) are predicted to have greater mortality rates following varicella vaccination when coverage is between 20-80%, due to shifts in the age at infection (figures 8-9). Finally, the model predicts that, for most LMICs, vaccination coverage must be greater than about 60% to produce substantial reductions in morbidity (figure 5d).

Figure 5. Predicted incidence of a) natural varicella, b) breakthrough varicella, c) varicella-related deaths and d) morbidity at post-equilibrium by country and vaccination coverage. 1-dose base case vaccine efficacy, Equilibrium=80 years post-vaccination, Morbidity=Inpatient days, Seroprevalence/force of infection estimated using the Farrington function.



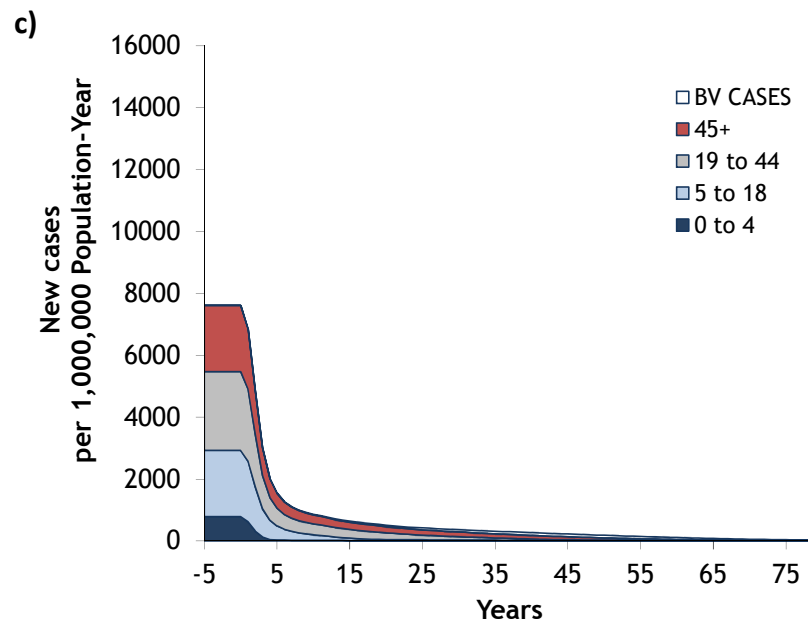
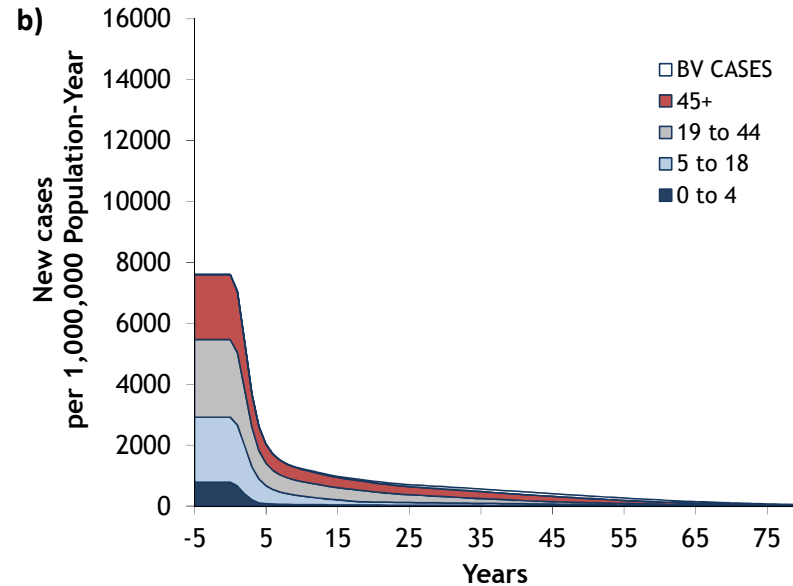
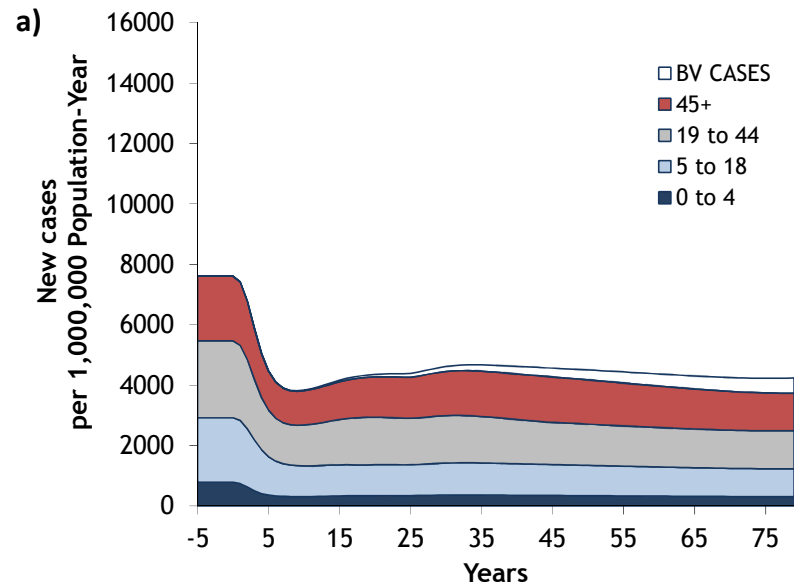
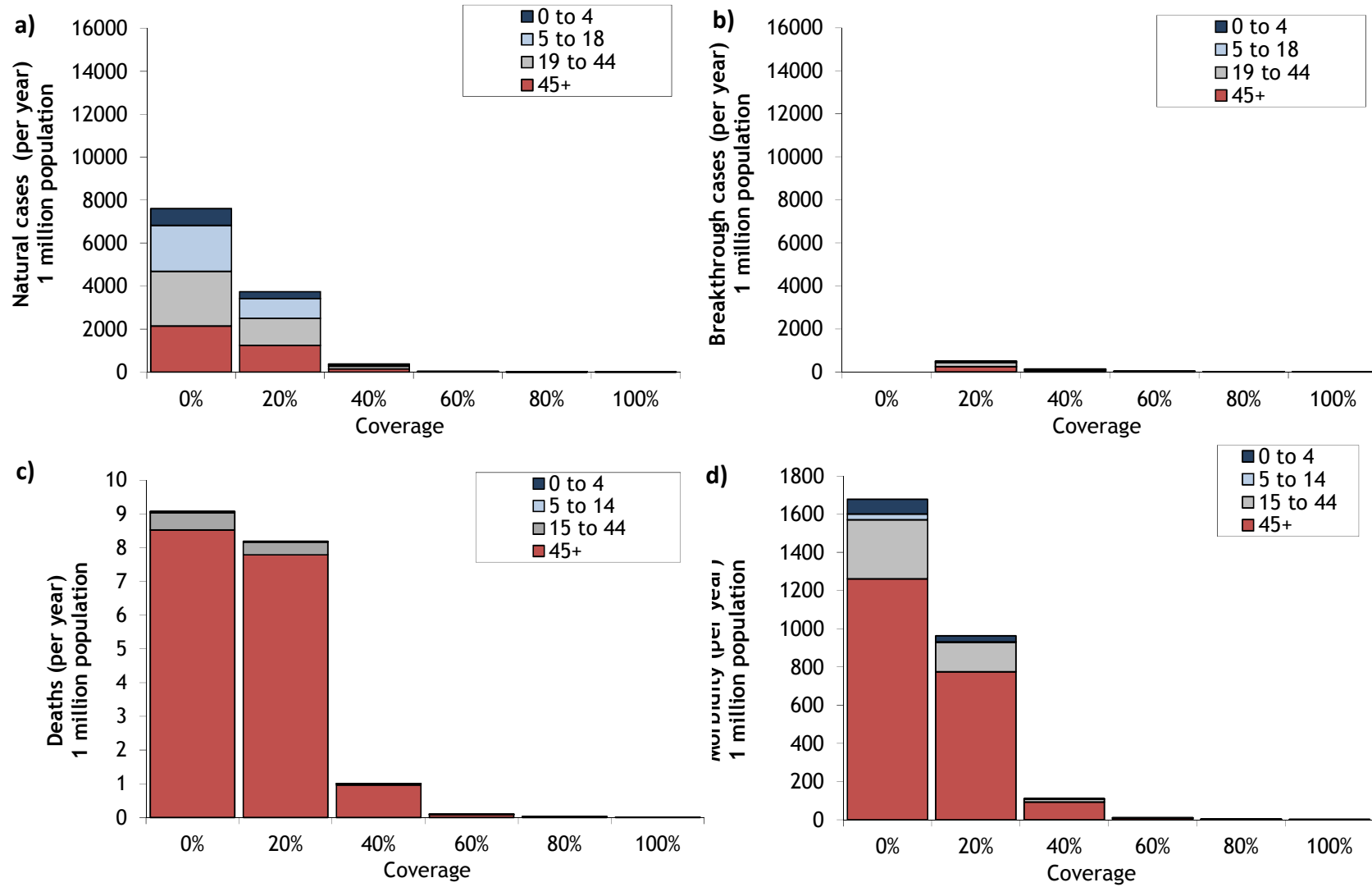


Figure 6. Predicted shift in age distribution for a country with very low seroprevalence. Age-specific number of varicella cases over time since vaccination for a) 20% b) 60% and c) 80% coverage. Country=Sri Lanka, vaccine efficacy=1-dose. The width of each colour band represents the age-specific natural varicella incidence rate (ages are in years). Width of the white band represents overall incidence of breakthrough varicella (BV).

Figure 7. Predicted age distribution of a) natural varicella, b) breakthrough varicella, c) varicella-related deaths and d) morbidity at equilibrium by vaccination coverage (very low seroprevalence, Sri Lanka). The width of each colour band represents the age-specific natural varicella incidence rate (ages are in years). 1-dose base case vaccine efficacy, Equilibrium=80 years post-vaccination, Morbidity=Inpatient days, Seroprevalence/force of infection estimated using the Farrington function.



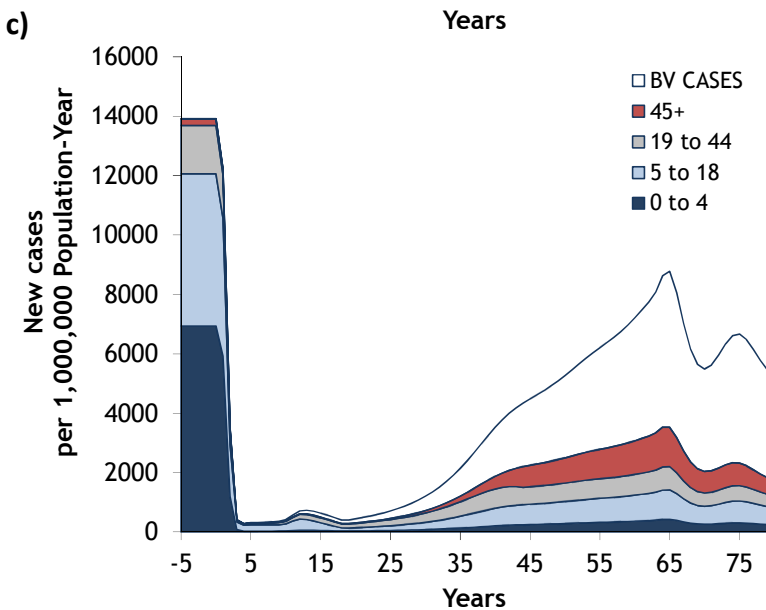
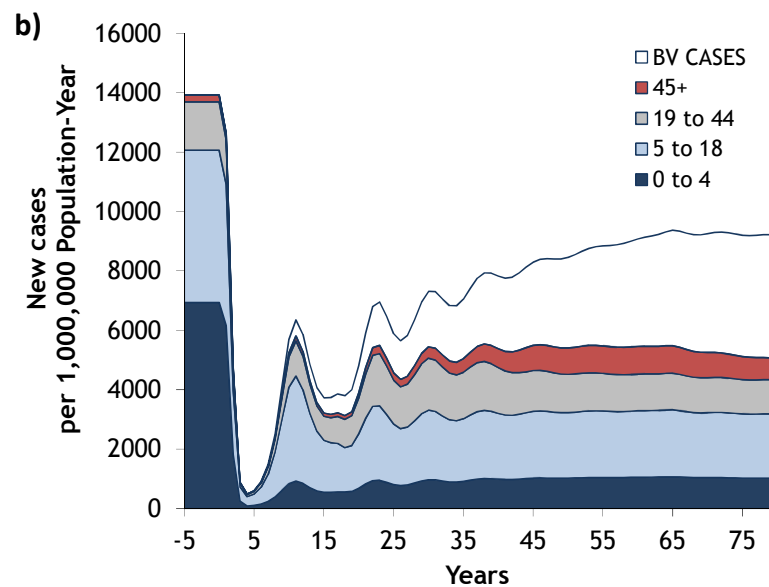
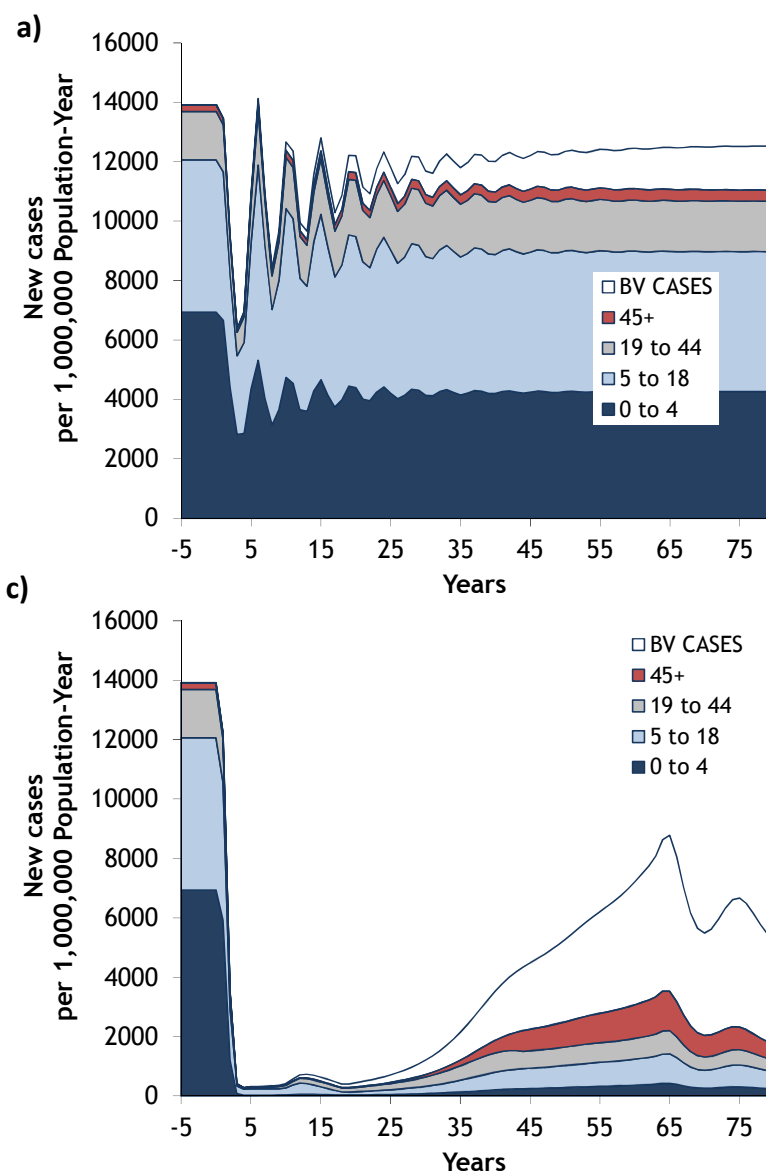


Figure 8. Predicted shift in age distribution for an average LMIC seroprevalence profile. Age-specific number of varicella cases over time since vaccination for a) 20% b) 60% and c) 80% coverage. Country=Bolivia, vaccine efficacy=1-dose. The width of each colour band represents the age-specific natural varicella incidence rate (ages are in years). With of the white band represents overall incidence of breakthrough varicella (BV).

Figure 9. Predicted age distribution of a) natural varicella, b) breakthrough varicella, c) varicella-related deaths and d) morbidity at equilibrium by vaccination coverage (average LMIC seroprevalence profile, Bolivia). The width of each colour band represents the age-specific natural varicella incidence rate (ages are in years). 1-dose base case vaccine efficacy, Equilibrium=80 years post-vaccination, Morbidity=Inpatient days, Seroprevalence/force of infection estimated using the Farrington function.

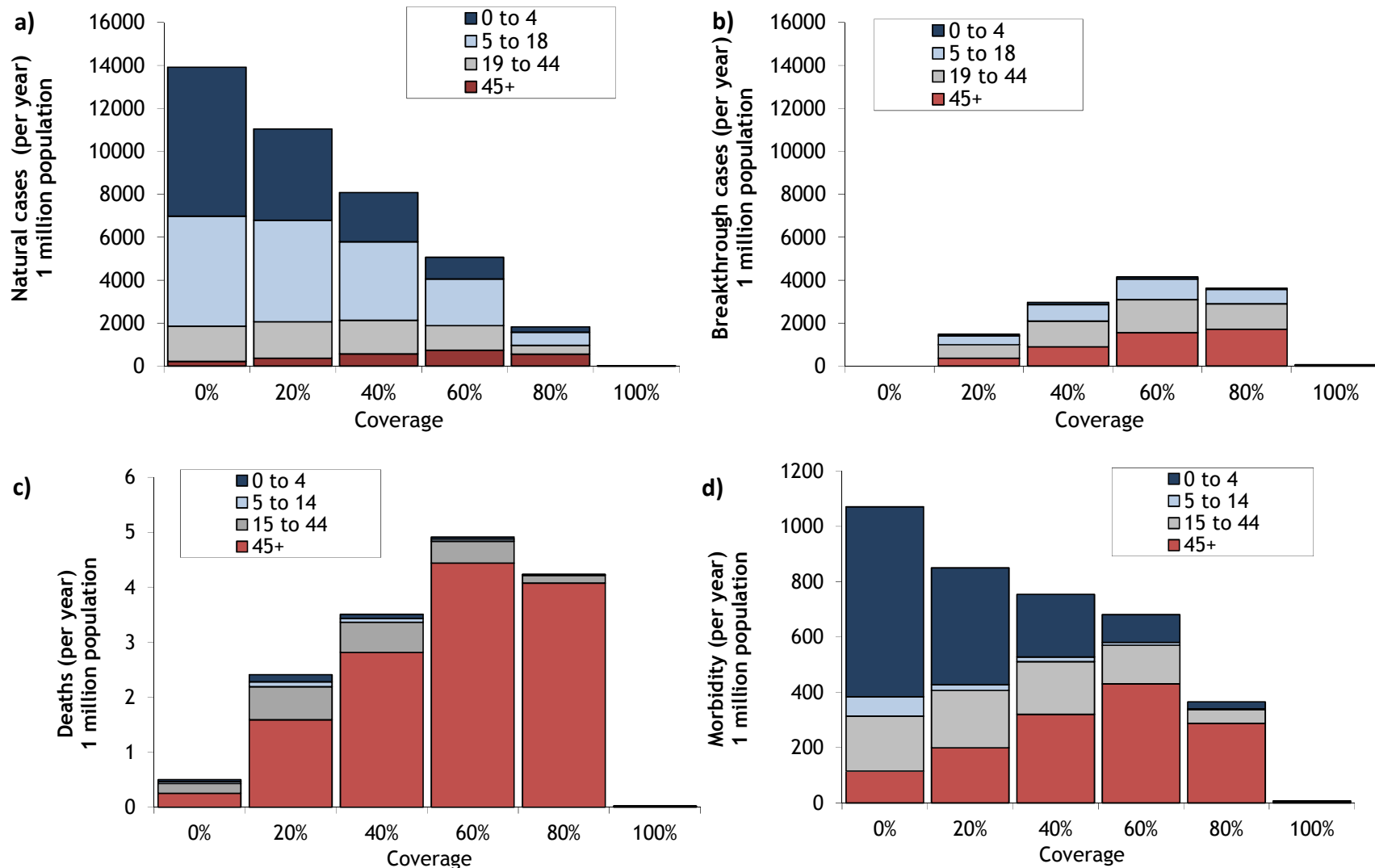
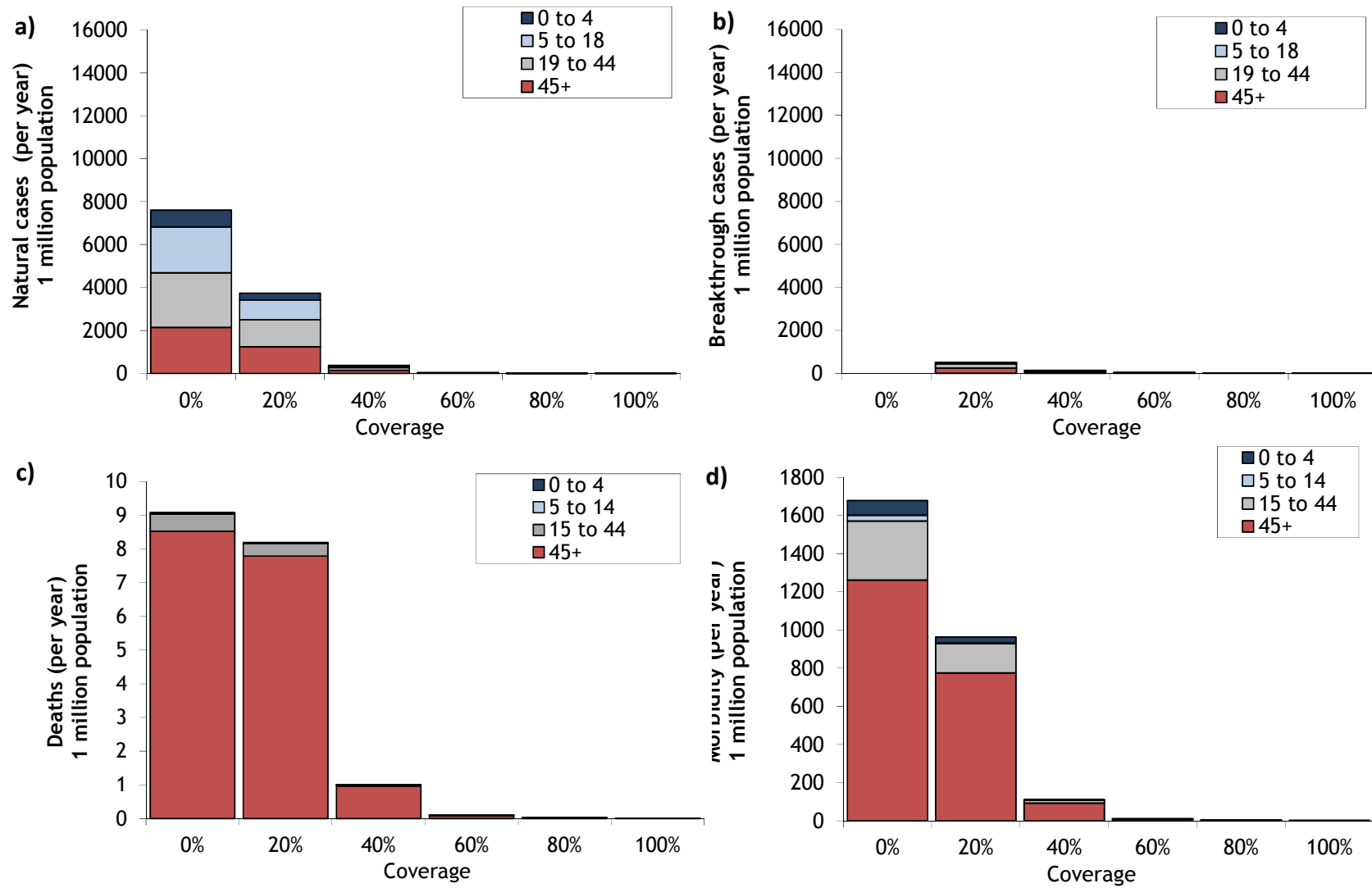


Figure 9. Predicted age distribution of a) natural varicella, b) breakthrough varicella, c) varicella-related deaths and d) morbidity at equilibrium by vaccination coverage (very low seroprevalence, Sri Lanka). The width of each colour band represents the age-specific natural varicella incidence rate (ages are in years). 1-dose base case vaccine efficacy, Equilibrium=80 years post-vaccination, Morbidity=Inpatient days, Seroprevalence/force of infection estimated using the Farrington function.



Discussion

Most LMICs had medium to high varicella seropositivity. In such countries there is a high risk of shifts in the age at infection following 1-dose vaccination at intermediate levels of vaccination coverage. The model predicts that between 20-80% coverage, there is a risk of increased mortality following varicella vaccination, and that vaccination coverage must be greater than about 60% to produce substantial reductions in morbidity. On the other hand, LMICs with very low seropositivity (less than 20-30% in 20 year olds), such as Sri Lanka, are expected to have no shifts in the age at infection and important reductions in varicella-related mortality & morbidity, at intermediate levels of vaccination coverage. This results is due to the low R_0 (basic reproductive number), in these countries.

The results of this study must be used with an understanding of its limits. The impact of vaccination on herpes zoster was not examined in this feasibility study. Hence, the potential increase in herpes zoster following varicella vaccination in LMICs was not examined. In addition, our conclusions are dependent on the quality of the seroprevalence data, the function used to fit seroprevalence, the contact mixing and age-specific morbidity. Firstly, although we conducted a literature review of existing seroprevalence studies, we did not examine the quality of these studies. Of particular importance is whether the seroprevalence data are of sufficient quality to be representative of the country. A recent study suggested that climate is a key driver of varicella force of infection ⁴⁴. If this is the case, seroprevalence may vary significantly even within a country. Hence, recommending the use of varicella vaccination without assurances that high coverage can be attained may be dangerous even in a country with reported low seropositivity, if quality assessment of the seroprevalence data is not performed. Secondly, more sensitivity analysis is required on the mixing matrices as these have been shown to have a significant impact on predictions of shift in the age at infection (see Appendix figure A1 from Brisson et al. ²⁹). If mixing in LMICs is more proportional (e.g. more mixing between children and adults) than assumed, shifts in the

age at infection will be greater than those predicted in this study. Thirdly, the functions used for fitting to seroprevalence data (Gamma and Farrington) are unimodal (force of infection decreases with age). However, contact may be multimodal (e.g., force of infection increases among parents of young children). Hence, more sensitivity analysis is required on the function used to fit seroprevalence. Finally, there is very little data available on age-specific mortality and morbidity related to varicella. More research is needed to better quantify country-specific burden of illness due to varicella

Future steps in modelling varicella vaccination in LMICs should include: 1) cost-effectiveness and affordability analysis, 2) sensitivity analysis on mixing matrices and the functions used for fitting to seroprevalence data, 3) assessment of the quality of seroprevalence and force of infection data and understanding why certain countries differ substantially to others (e.g., Singapore & St Lucia).

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