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Global mortality reduction impact of rotavirus vaccination in the pre-COVID-19 era: a modelling analysis

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Outline

- Background
- Aims
- Method overview
- Results
- Main findings
- Conclusion

Background

- Rotavirus vaccines are widely considered to have had an important impact on rotavirus gastroenteritis (RVGE) deaths globally in infants <5 years .
- Generating reliable estimates of the impact has several challenges.

What current evidence is there?

- Estimates of RVGE deaths aged <5 years over time from three groups.
- Estimates of vaccine impact (2006 onwards) from three separate groups.
- Estimates differ.

Why does this matter?

- It is important to establish the contribution rotavirus vaccines have made to global public health, to inform potential areas of improvement going forward.

Aims

- Provide updated estimates of the global historical impact of rotavirus vaccination pre-COVID-19 era (2006-2019).
- Combine RVGE mortality datasets to help build consensus on the historical impact of rotavirus vaccination.
- Assess how sensitive they are to the use of different RVGE mortality datasets and vaccine impact modelling assumptions.

Method: Model overview

- UNIVAC—a decision support model that assesses impact and cost-effectiveness of multiple vaccines.

- Developed in Excel, with a user-friendly excel-based interface.

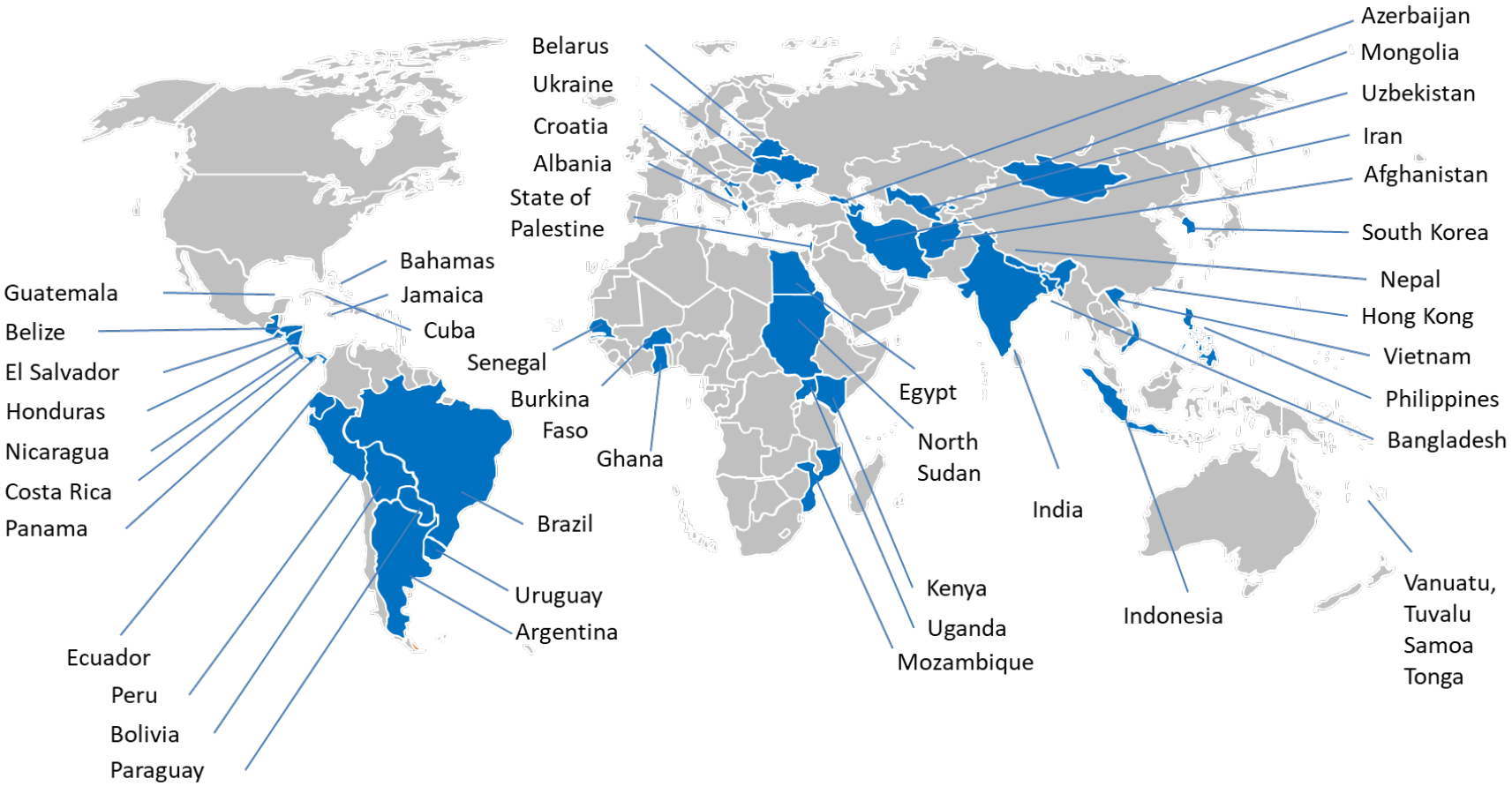
UNIVAC Pakistan, ROTARIX, 2006-2019

Instructions	**Setup**	Inputs	Results	Charts	Scenarios	PSA

Step 1.	?	**Choose country**
Step 2.	?	**Choose vaccine**
Step 3.	?	**Choose vaccine schedule**
Step 4.	?	**Define disease categories**
Step 5.	?	**Choose period of vaccination and other options**
Step 6.	?	**Choose input parameter preferences for each disease category/outcome**
Step 7.	?	**Define options for healthcare cost inputs**

Method: Model overview

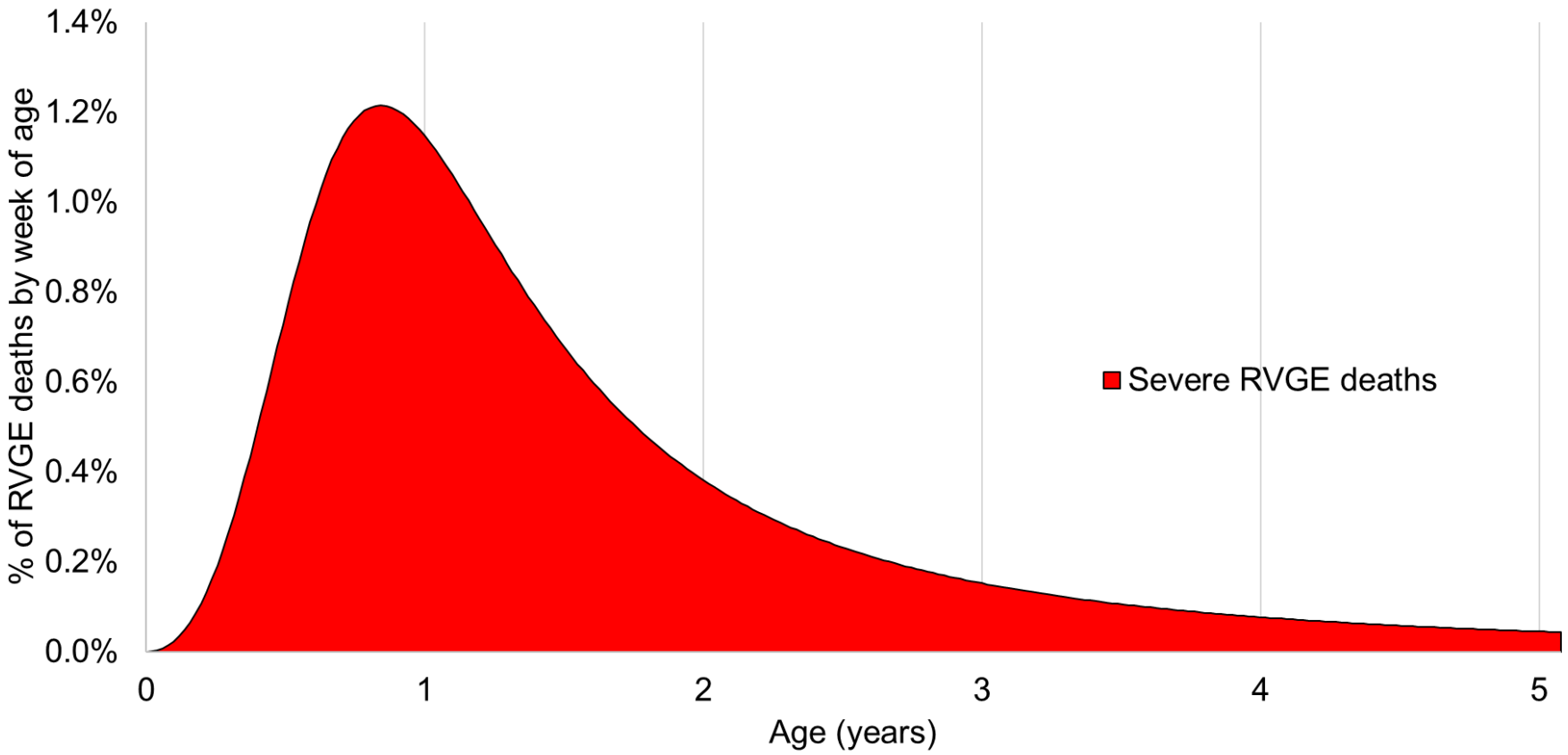
Country-led economic evaluations using UNIVAC (or predecessor model)



Method: Model overview

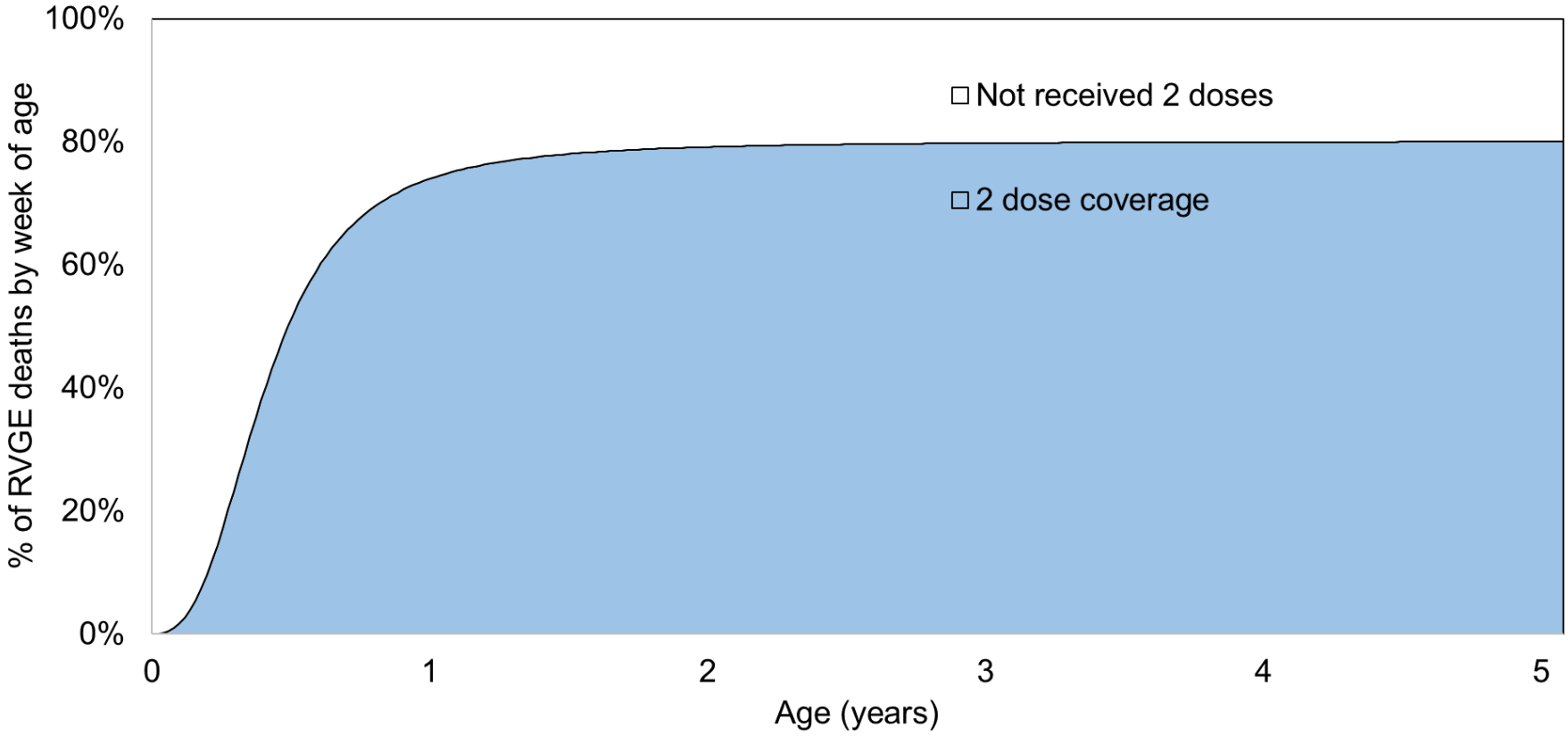
- 186 countries included.
- Time period: 1st January 2006 – 31st December 2019 (a period unaffected by COVID-19).
- Primary outcome measure: RVGE deaths aged <5 years prevented.
- Country-specific coverage and vaccine brand/schedule.
- Direct effects of vaccine only—benefits of vaccine amongst those vaccinated.
- Alternative scenarios:
  - MCEE mortality dataset only
  - WHO/CDC mortality dataset only
  - GBD mortality dataset only
  - Age restricted (first dose <15w, last dose <32w)
  - 2-dose schedules have 3-dose schedule impact

Method: Age distribution



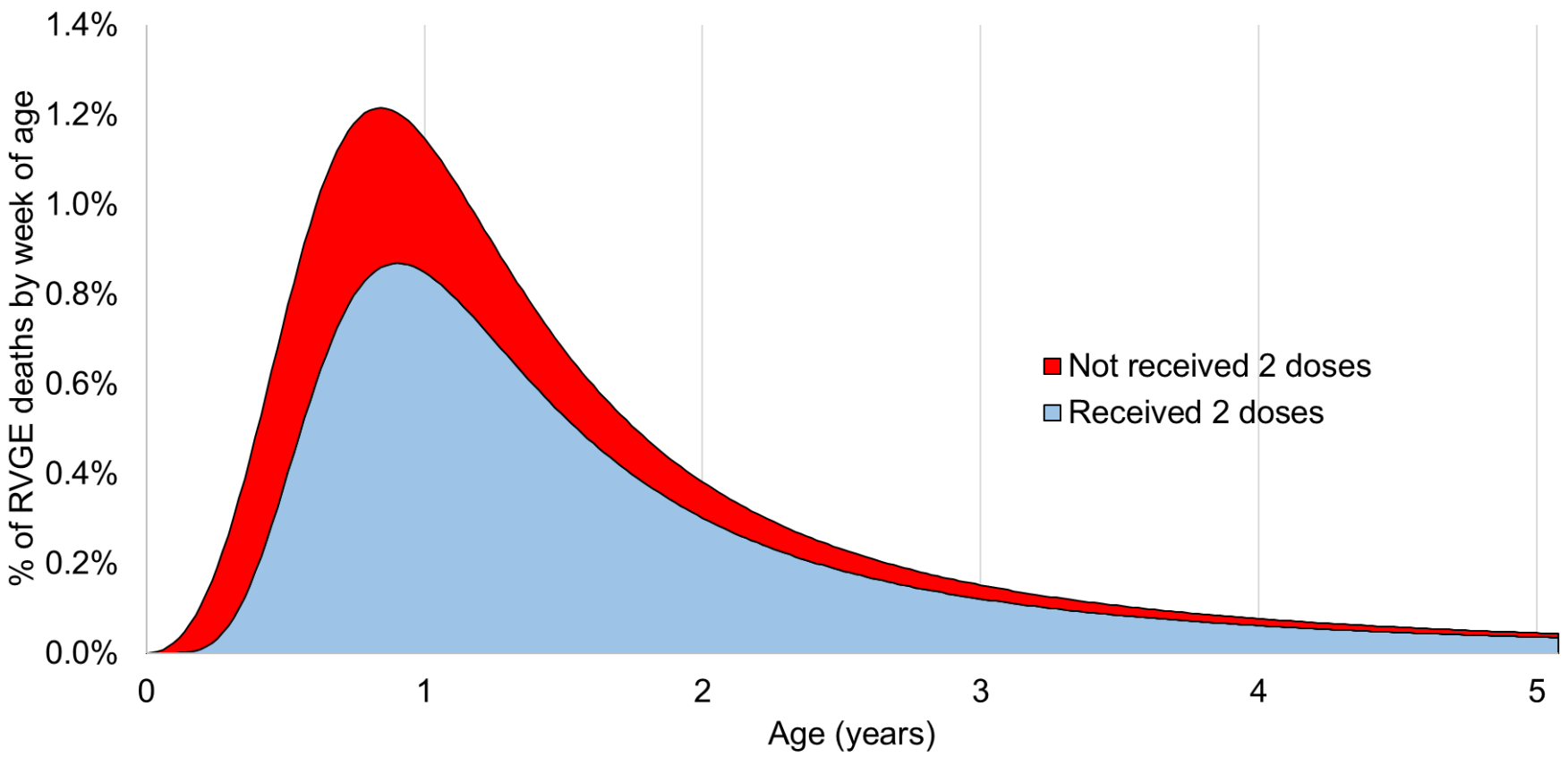
Source of mortality data: GBD, WHO/CDC, MCEE
Source for age distribution: Hasso-Agopsowicz et al, CID 2019

Method: Coverage and timeliness

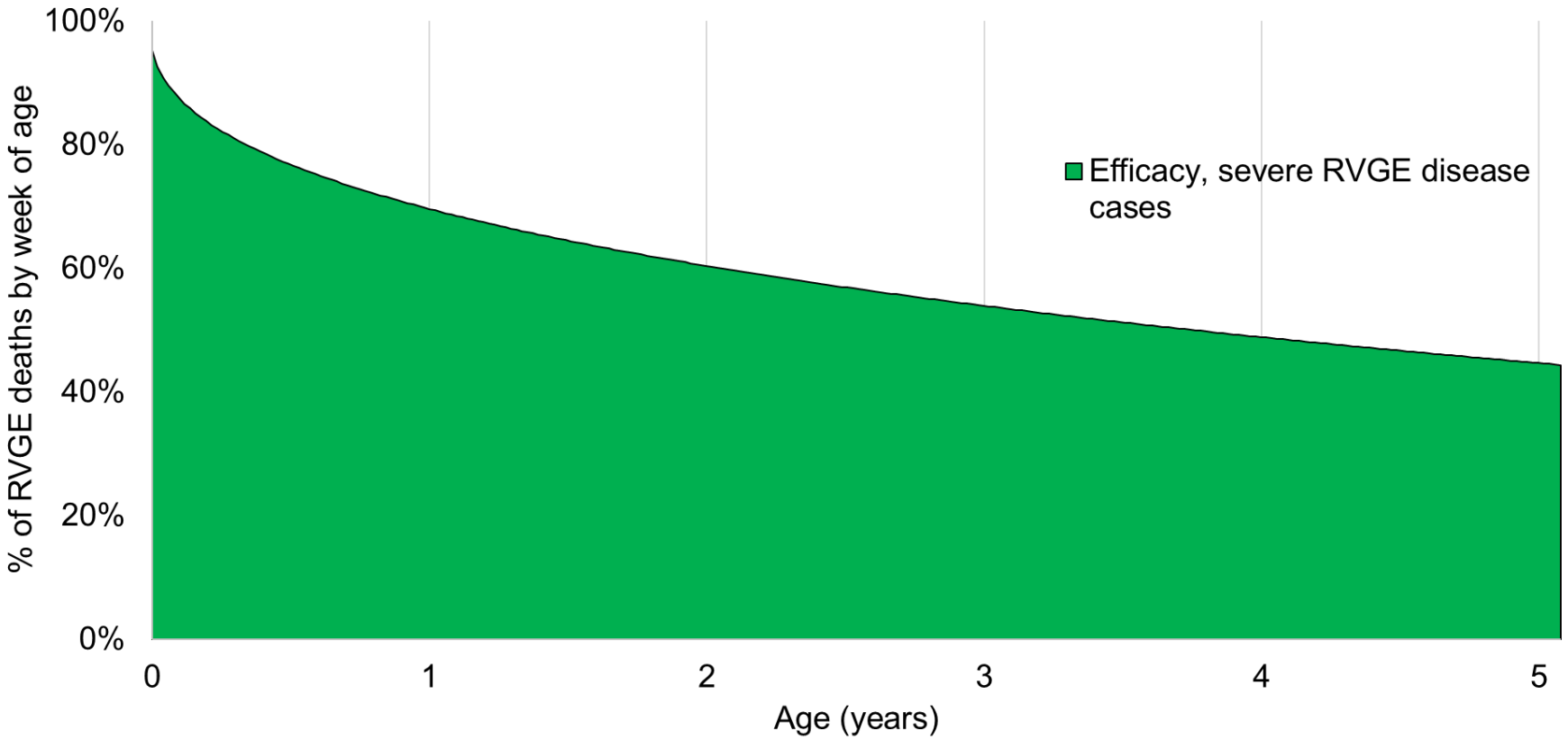


Source: WUENIC, DHS and MICS surveys

Method: Model overview

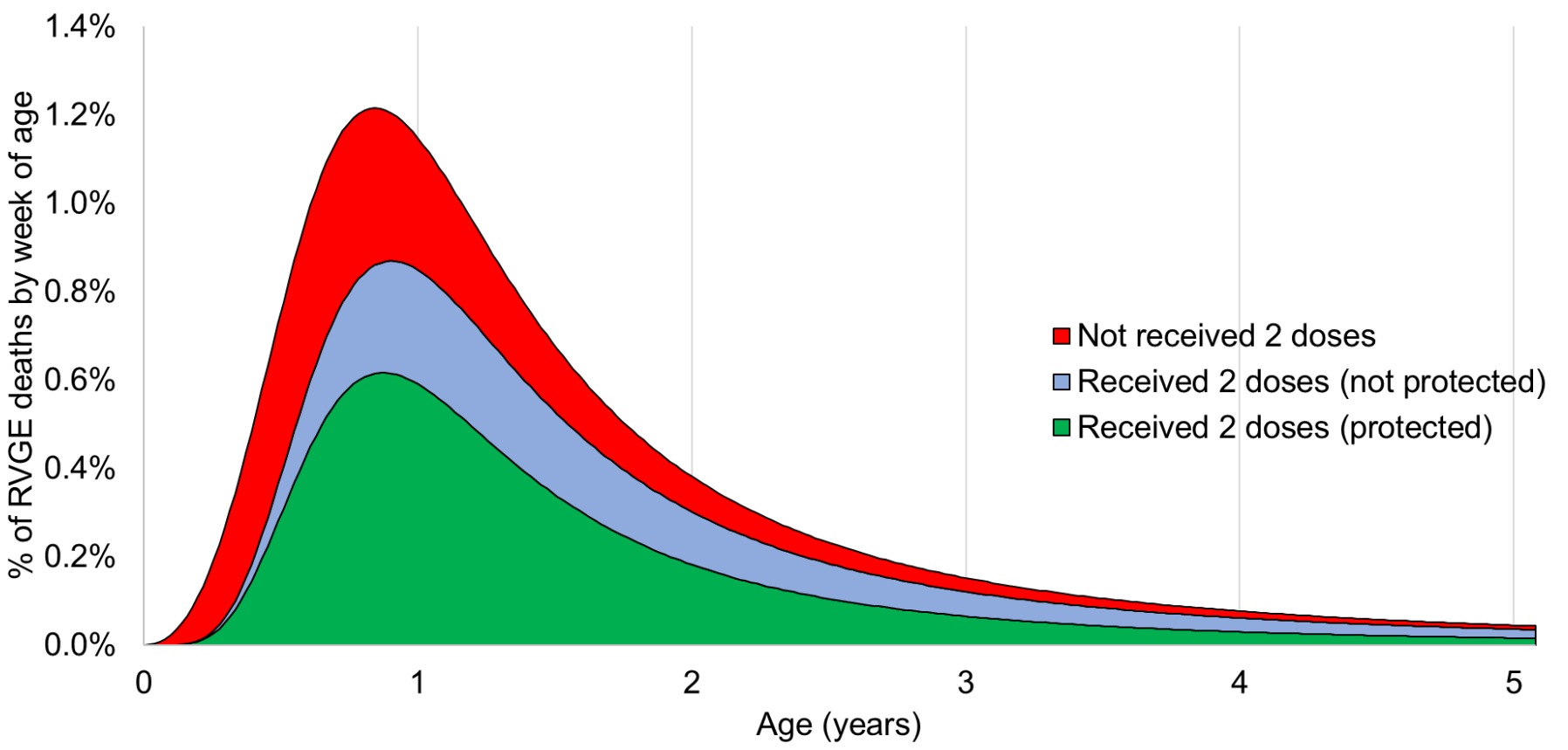


Method: Efficacy and waning

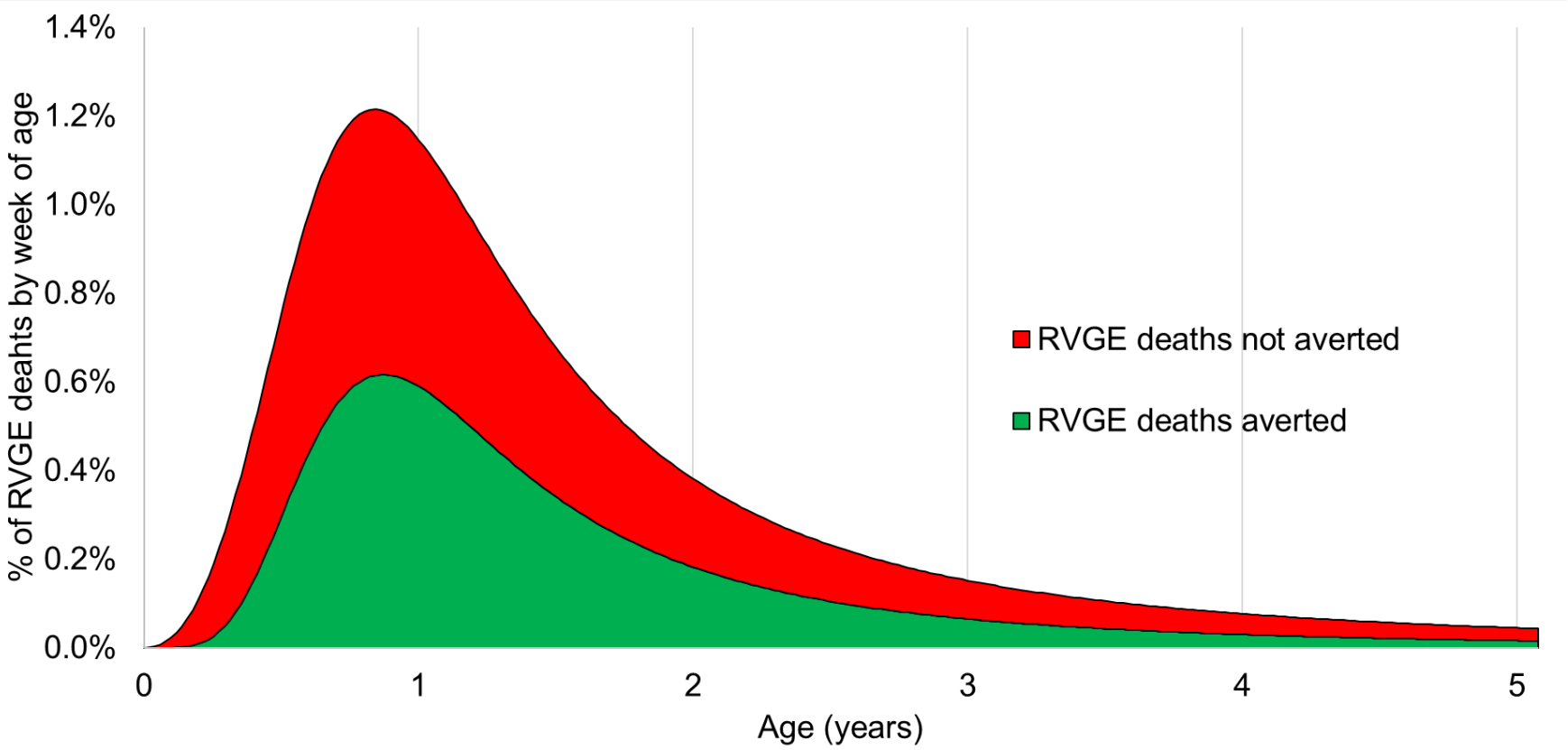


Source: Clark et al, Lancet ID 2019

Method: Model overview



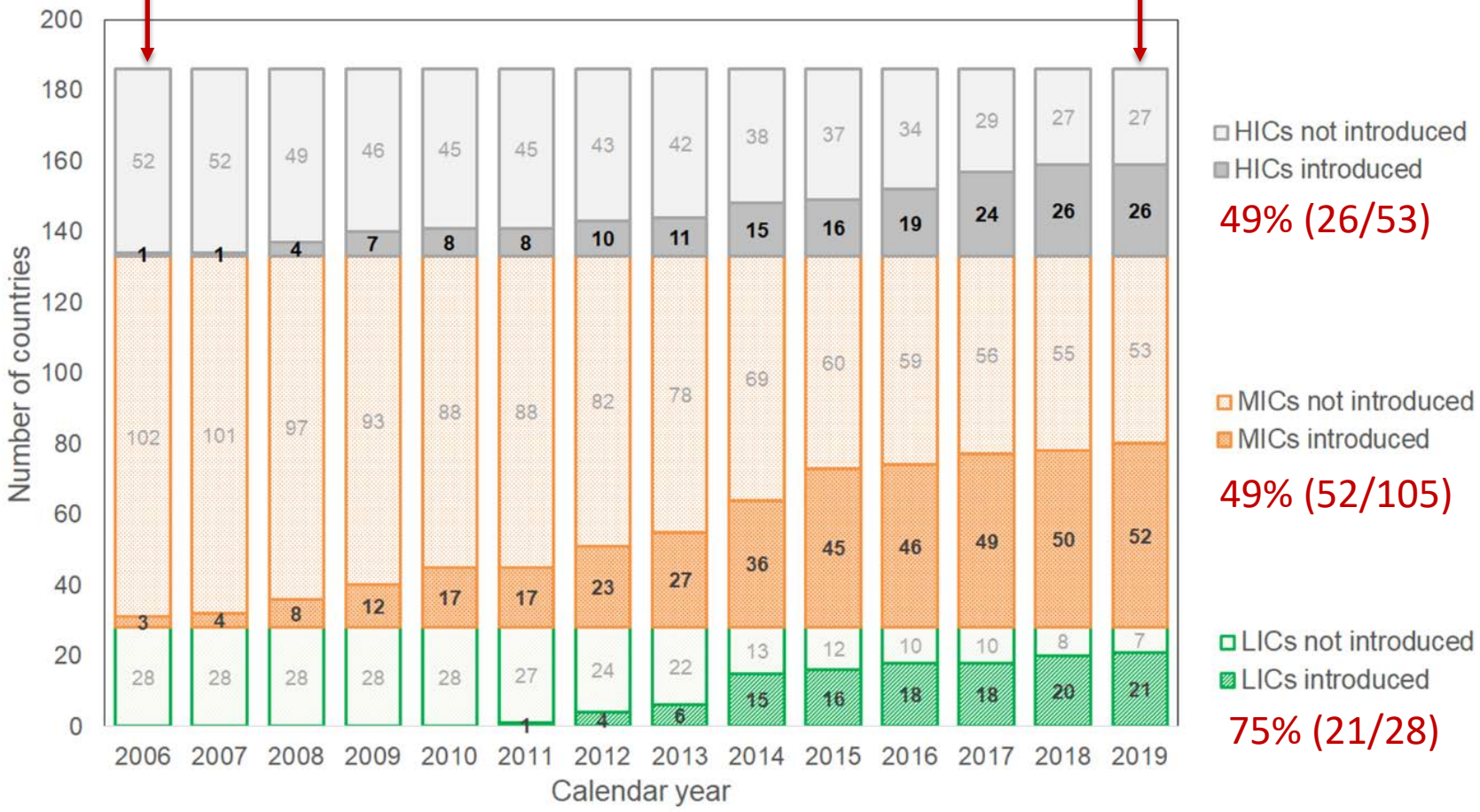
Method: Model overview



Results: Vaccine introduction

2% of countries introduced

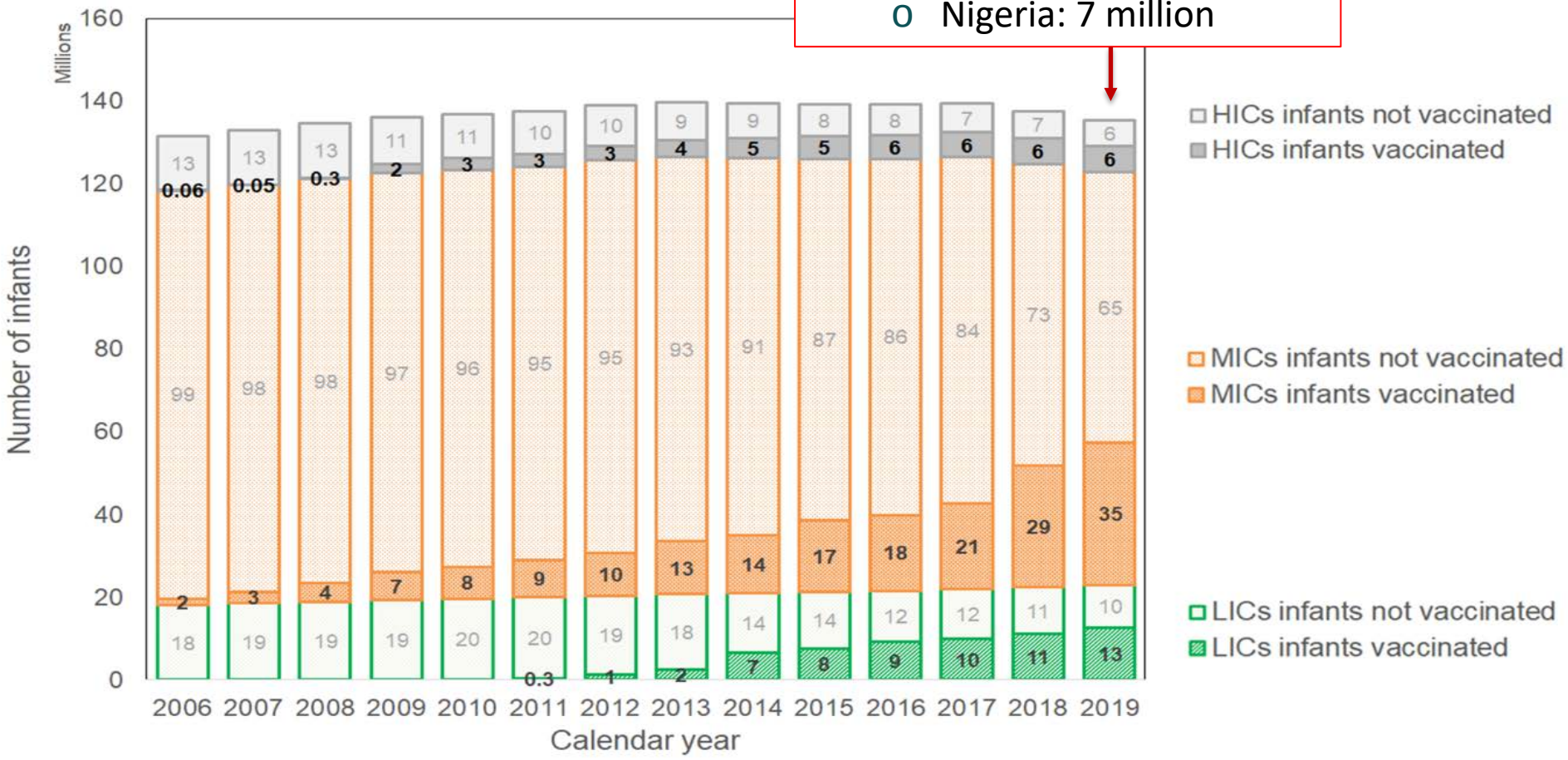
53% of countries introduced



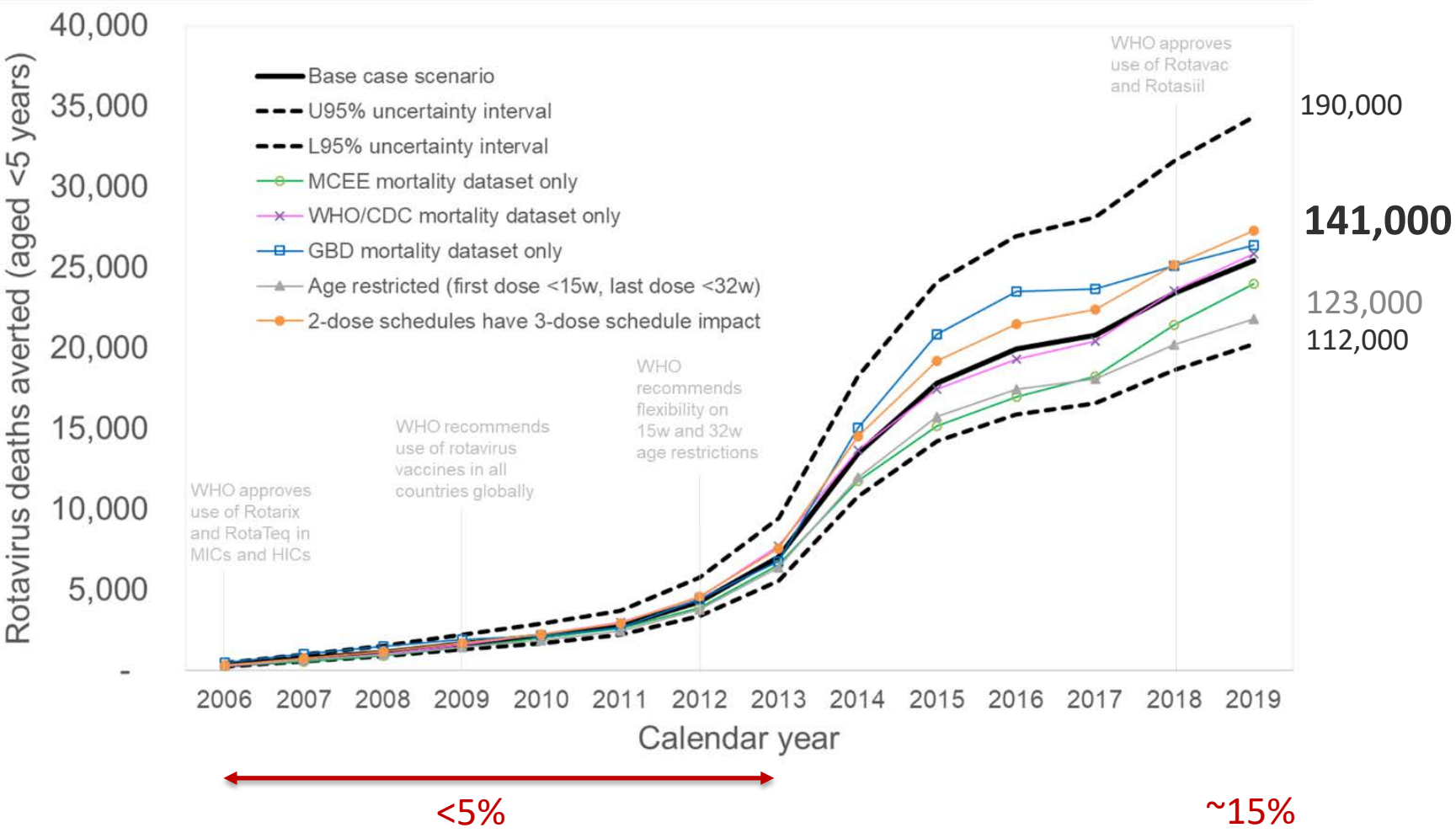
Results: Infants vaccinated

82 million infants unvaccinated

- India: 11 million
- Indonesia: 4.5 million
- Nigeria: 7 million

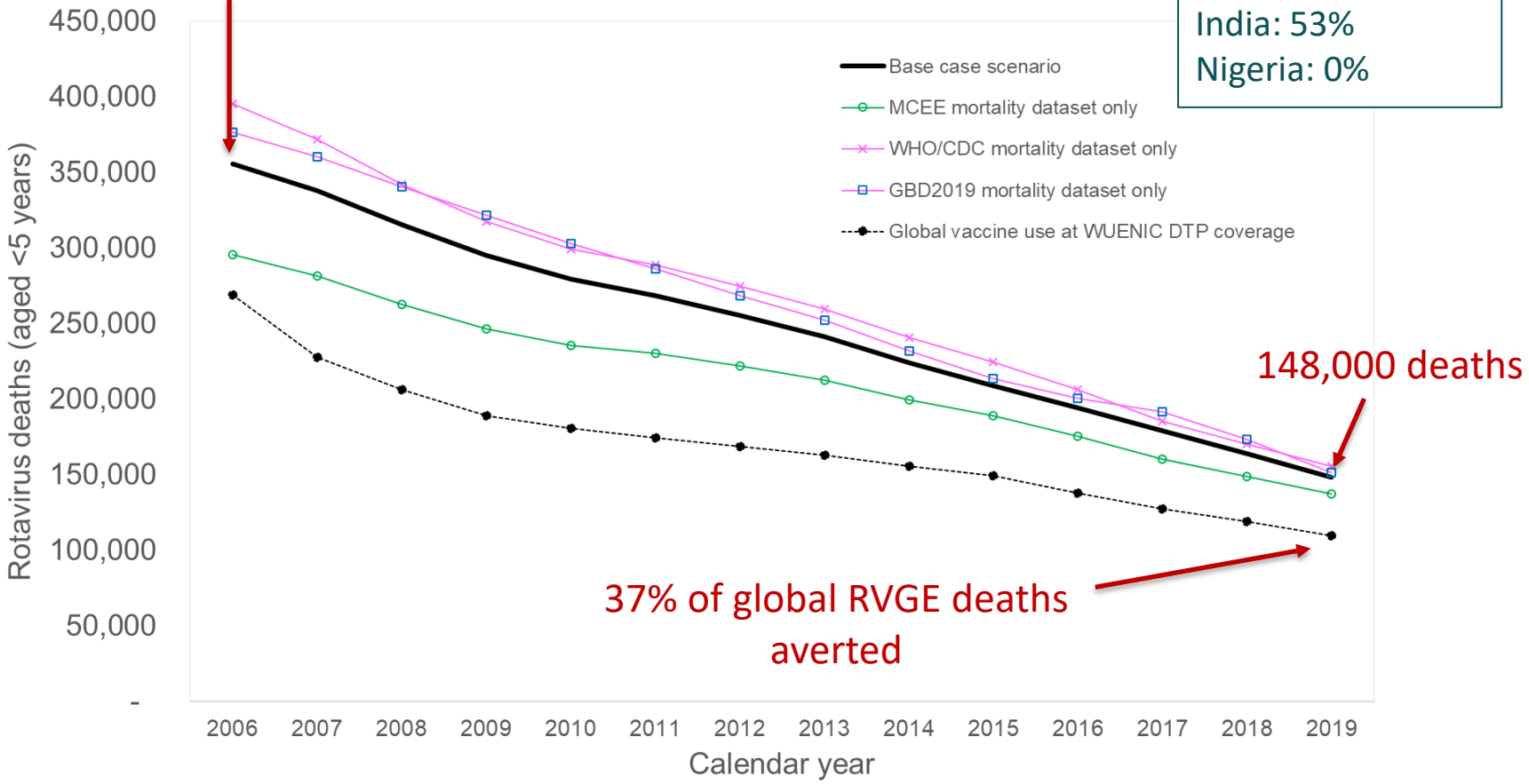


Results: RVGE deaths averted



Results: RVGE deaths <5 years

2019 coverage:
DR Congo: 4%
India: 53%
Nigeria: 0%



Main findings

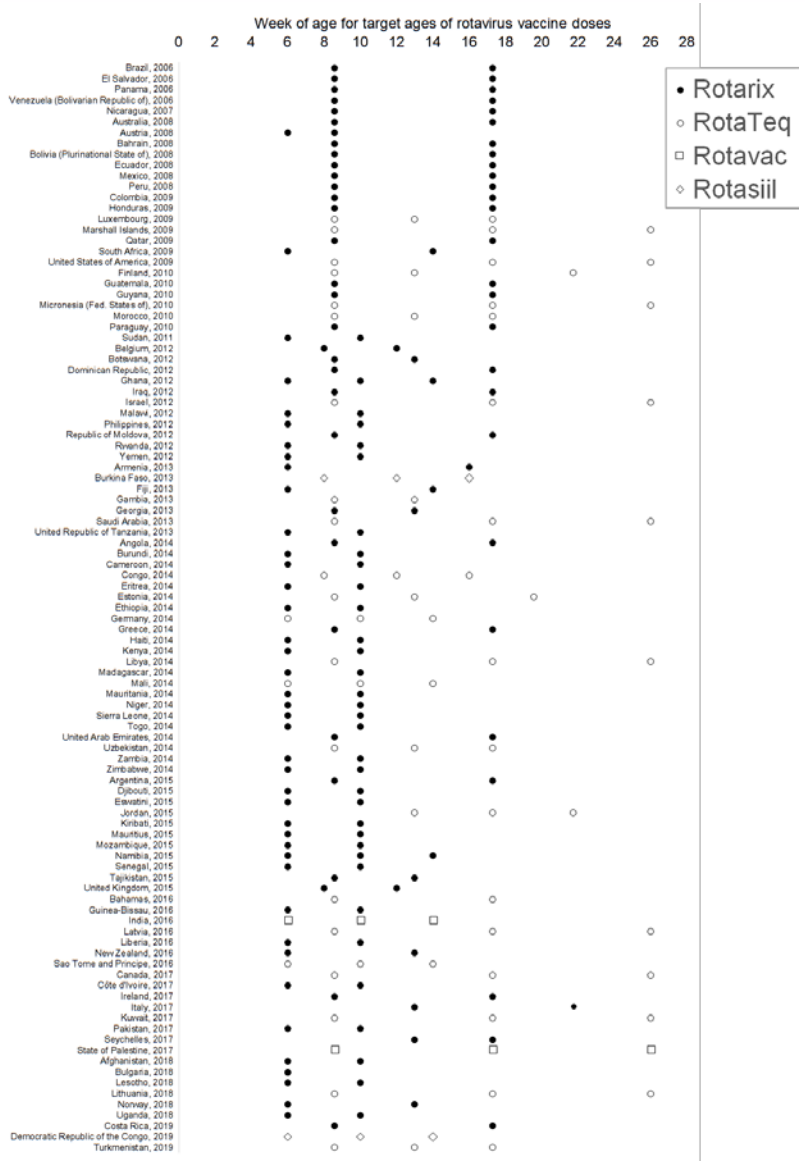
- 141,000 deaths prevented in infants <5 years.
- This will increase as more countries introduce rotavirus vaccine and improve coverage rates.
- Rotavirus vaccination prevented <5% each year in the first 8 years, and 15% in 2019.
  - WHO recommendation to expand use of vaccines to all countries in 2009.
  - Donor support by Gavi, the Vaccine Alliance.
- Highlights potential limitations in existing vaccinations.
  - 99% of deaths were in LMICs.
  - Maximum global reduction (direct effects) unlikely to >40% without more effective vaccines and prevention strategies.
- Estimates were sensitive to choice of mortality dataset.
  - Broad agreement between the 3 sources.
  - Rapid decline in RVGE deaths in absence of rotavirus vaccination.
- Highlights the potential importance of removing age restrictions in 2012.

Conclusion

- Rotavirus vaccines have made a valuable contribution to global public health in the pre-COVID-19 era but there remains a substantial RVGE mortality burden.
- While there is clearly an immediate need to scale-up the use of rotavirus vaccines in high-mortality settings, our analysis also highlights the potential limitations of live oral vaccines in these settings.
- To address the full RVGE mortality burden in the post-COVID-19 era, enhanced diarrhoea prevention strategies will be needed, including more durable and effective rotavirus vaccines for LMICs.

Extra slides

Parameter	Base case (95% CI)	Probability distribution	Source
Population projections for the 2006-2019 birth cohorts			
Population by single age/year between birth and 5.0 years	Country-specific	Beta-PERT (mid = UNPOP medium variant, range = UNPOP low/high variant)	UNPOP, 2022
Disease burden estimates			
Rate of RVGE deaths <5 years	Country-specific	Beta-PERT (mid = mean of 3 sources of country estimates, range = 95% CI)	GBD, MCEE, WHO/CDC
Age distribution of RVGE deaths			
Log Logistic scale parameter[$]	Country-specific	Beta-PERT (mid = best fit for country/U5MR stratum, range = 95% CI for country/U5MR stratum)	Hasso-Agopsowicz, 2019
Vaccine coverage			
Doses with DTP1, DTP2 or DTP3	Country-specific	Beta-PERT (mid = WUENIC 2015, range = WUENIC 2015 +/-10%)	WUENIC, WHO
Vaccine timeliness			
Log Logistic scale parameter[$]	Country-specific	Beta-PERT (mid = best fit for country or schedule stratum, range = country IQR or median IQR for region)	Clark, 2009
Vaccine efficacy against RVGE mortality[$]			
Low mortality	99.6% (99.4 - 100%)	Beta (alpha = 5377, beta = 22, [A] = 0%, [B] = 100%)	Clark, 2019
Medium mortality	91.4% (89.8 - 92.7%)	Beta (alpha = 1394, beta = 132, [A] = 0%, [B] = 100%)	Clark, 2019
High mortality	78.9% (75.5 - 82.3%)	Beta (alpha = 434, beta = 116, [A] = 0%, [B] = 100%)	Clark, 2019
Mean duration of vaccine efficacy in months [$]			
Low mortality	176.8 (114.7 - 268.0)	Gamma (alpha = 21.82, beta = 8.41)	Clark, 2019
Medium mortality	121.9 (81.3 - 182.4)	Gamma (alpha = 24.01, beta = 5.28)	Clark, 2019
High mortality	13.2 (9.0 – 20.5)	Gamma (alpha = 22.99, beta = 0.62)	Clark, 2019
Relative efficacy of 1 dose versus 2/3 doses			
Low- and middle-income countries (LMICs)	0.63 (0.51-0.79)	Beta (alpha = 27.05, beta = 15.68, [A] = 0, [B] = 1)	Clark, 2019
High income countries (HICs)	0.90 (0.84-1.00)	Beta (alpha = 14.06, beta = 0.46, [A] = 0, [B] = 1)	Jonesteller, 2017


Week of age for target ages of rotavirus vaccine doses
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28
Brazil, 2006
El Salvador, 2006
Panama, 2006
Venezuela (Bolivarian Republic of), 2006
Nicaragua, 2007
Australia, 2008
Austria, 2008
Bahrain, 2008
Bolivia (Plurinational State of), 2008
Ecuador, 2008
Mexico, 2008
Peru, 2008
Colombia, 2009
Honduras, 2009
Luxembourg, 2009
Marshall Islands, 2009
Qatar, 2009
South Africa, 2009
United States of America, 2009
Finland, 2010
Guatemala, 2010
Guyana, 2010
Micronesia (Fed. States of), 2010
Morocco, 2010
Paraguay, 2010
Sudan, 2011
Belgium, 2012
Botswana, 2012
Dominican Republic, 2012
Ghana, 2012
Iraq, 2012
Israel, 2012
Malawi, 2012
Philippines, 2012
Republic of Moldova, 2012
Rwanda, 2012
Yemen, 2012
Armenia, 2013
Burkina Faso, 2013
Fiji, 2013
Gambia, 2013
Georgia, 2013
Saudi Arabia, 2013
United Republic of Tanzania, 2013
Angola, 2014
Burundi, 2014
Cameroon, 2014
Congo, 2014
Eritrea, 2014
Estonia, 2014
Ethiopia, 2014
Germany, 2014
Greece, 2014
Haiti, 2014
Kenya, 2014
Libya, 2014
Madagascar, 2014
Mali, 2014
Mauritania, 2014
Niger, 2014
Sierra Leone, 2014
Togo, 2014
United Arab Emirates, 2014
Uzbekistan, 2014
Zambia, 2014
Zimbabwe, 2014
Argentina, 2015
Djibouti, 2015
Eswatini, 2015
Jordan, 2015
Kiribati, 2015
Mauritius, 2015
Mozambique, 2015
Namibia, 2015
Senegal, 2015
Tajikistan, 2015
United Kingdom, 2015
Bahamas, 2016
Guinea-Bissau, 2016
India, 2016
Latvia, 2016
Liberia, 2016
New Zealand, 2016
Sao Tome and Principe, 2016
Canada, 2017
Côte d'Ivoire, 2017
Ireland, 2017
Italy, 2017
Kuwait, 2017
Pakistan, 2017
Seychelles, 2017
State of Palestine, 2017
Afghanistan, 2018
Bulgaria, 2018
Lesotho, 2018
Lithuania, 2018
Norway, 2018
Uganda, 2018
Costa Rica, 2019
Democratic Republic of the Congo, 2019
Turkmenistan, 2019
Rotarix
RotaTeq
Rotavac
Rotasiil

- Our estimates can be improved by adjusting each year to reflect the true product combination in use at the time.

- Our estimates focused entirely on RVGE mortality and did not capture the potential full health benefits.

- Our estimates did not capture the potential indirect effects (herd effects) that may be associated with rotavirus vaccine. Evidence suggests this may be limited in LMICs.

- Our estimates were not adjusted for subnational inequity in coverage rates.
-
- We assumed reported efficacy against RVGE hospital admissions was a reasonable proxy for efficacy against RVGE deaths.

Results: RVGE deaths