

Modeling the impact of vaccination for the immunization Agenda 2030: Deaths averted due to vaccination against 14 pathogens in 194 countries from 2021 to 2030[☆]

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ABSTRACT

Background: The Immunization Agenda 2030 (IA2030) Impact Goal 1.1. aims to reduce the number of future deaths averted through immunization in the next decade. To estimate the potential impact of the aspirational coverage targets for IA2030, we developed an analytical framework and estimated the number of deaths averted due to an ambitious vaccination coverage scenario from 2021 to 2030 in 194 countries.

Method: A demographic model was used to determine annual age-specific mortality estimates associated with vaccine coverage rates. For ten pathogens (Hepatitis B virus, Haemophilus influenzae type B, human papillomavirus, Japanese encephalitis, measles, Neisseria meningitidis serogroup A, Streptococcus pneumoniae, rotavirus, rubella, yellow fever), we derived single measures of country-, age-, and pathogen-specific relative risk of deaths conditional upon coverage rates, leveraging the data from 18 modeling groups as part of the Vaccine Impact Model Consortium (VIMC) for 110 countries. We used a logistic regression model to extrapolate the relative risk estimates to countries that were not modeled by VIMC. For four pathogens (diphtheria, tetanus, pertussis and tuberculosis), we used estimates from the Global Burden of Disease 2019 study and existing literature on vaccine efficacy. A future scenario defining years of vaccine introduction and scale-up needed to reach aspirational targets was developed as an input to estimate the long-term impact of vaccination taking place from 2021 to 2030.

Findings: Overall, an estimated 51.5 million (95 % CI: 44.0–63.2) deaths are expected to be averted due to vaccinations administered between the years 2021 and 2030. With immunization coverage projected to increase over 2021–2030 an average of 5.2 million per year (4.4–6.3) deaths will be averted annually, with 4.4 million (3.9–5.1) deaths be averted for the year 2021, gradually rising to 5.8 million (4.9–7.5) deaths averted in 2030. The largest proportion of deaths is attributed to Measles and Hepatitis B accounting for 18.8 million (17.8–20.0) and 14.0 million (11.5–16.9) of total deaths averted respectively.

Interpretation: The results from this global analysis demonstrate the substantial potential mortality reductions achievable if the IA2030 targets are met by 2030. Deaths caused by vaccine preventable diseases disproportionately affect LMICs in the African region.

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Table 1
14 pathogens included in the analysis.

No	Pathogen	Universal vaccine ^a	Immunization schedule (in the models)	Models
1	Hepatitis B virus	Yes	Birth dose and three infant doses (<1 year)	Center for Disease Analysis (dynamic); Imperial College London (dynamic); independent model developed by Goldstein and colleagues (static)
2	<i>Haemophilus influenzae</i> type B	Yes	Three infant doses (<1 year)	Johns Hopkins University (static); LSHTM (static)
3	Human papillomavirus	Yes	Two doses for adolescent girls (9–14 years)	Harvard School of Public Health (static); LSHTM (static)
4	Japanese encephalitis	No	One infant dose (<1 year)	National University of Singapore (dynamic); University of Notre Dame (dynamic)
5	Measles	Yes	First dose at ≤ 1 year, second dose at < 2 years	LSHTM (dynamic); Pennsylvania State University (dynamic)
6	<i>Neisseria meningitidis</i> serogroup A (MenA)	No	One infant dose (<1 year)	University of Cambridge (dynamic); Kaiser Permanente Washington (dynamic)
7	<i>Streptococcus pneumoniae</i> (PCV)	Yes	Three infant doses (<1 year)	Johns Hopkins University (static); LSHTM (static)
8	Rotavirus	Yes	Two infant doses (<1 year)	Emory University (dynamic); LSHTM (static)
9	Rubella	Yes	First dose at <1 year, second dose at <2 years	Johns Hopkins University (dynamic); Public Health England (dynamic)
10	Yellow fever	No	One infant dose (<1 year)	Imperial College London (static); University of Notre Dame (static)
11	Diphtheria	Yes	Three infant doses (<1 year)	Data from Global Burden of Disease study
12	Pertussis	Yes	Three infant doses (<1 year)	Data from Global Burden of Disease study
13	Tetanus	Yes	Three infant doses (<1 year)	Data from Global Burden of Disease study
14	TB(BCG)	Yes (only in countries specified)	Birth dose	Data from Global Burden of Disease study

Universal^a: universally recommended vaccines according to WHO recommendations for routine immunization <https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/who-recommendations-for-routine-immunization—summary-tables>.

1. Introduction

In August 2020, the 73rd World Health Assembly endorsed the Immunization Agenda 2030 (IA2030), a global strategy to achieve the vision of a world where everyone, everywhere, at every age fully benefits from vaccines for good health and well-being [1]. Three impact goals were developed to track progress towards this vision. By 2030, the global community aims to “(1) reduce mortality and morbidity from

vaccine-preventable diseases for everyone throughout the life course, (2) leave no one behind, by increasing equitable access and use of new and existing vaccines, and (3) endure good health and well-being for everyone by strengthening immunization within primary health care and contributing to universal health coverage and sustainable development” [1].

Robust measurement of progress towards these goals is critical to the implementation of IA2030 at all levels. Since the inception of the WHO’s Expanded Programme on Immunization (EPI) in 1974, countries have made significant advances in the introduction and uptake of routine childhood vaccines [2]. While there is an extensive body of evidence on the role of vaccines and immunization programs in reducing mortality and morbidity [3,4,5,6] challenges measuring deaths and cases directly through vital registration records and surveillance remain in many locations. In such cases, mathematical models have been used to extrapolate existing data to generate impact projections in other settings and quantify uncertainty in the predictions [7,8].

Mathematical models of vaccine preventable diseases have increasingly been used to inform global level strategic planning and decision making. Among the first efforts to estimate mortality reduction by vaccination at a global scale through multiple mathematical models is the study by Lee et al 2013 which projected 23.3 million deaths averted due to vaccination against ten pathogens from 2011 to 2020, in 73 countries supported by Gavi, the Vaccine Alliance [9]. The Global Vaccine Action Plan (2011–2020) projected 24.6–25.8 million deaths averted during the same time period [10]. Among global health advocates, it has been frequently cited that globally “2.5 million lives” or “2–3 million lives” are saved every year due to vaccination, although these figures lacked clear sources and methods used [11,12,13]. More recently, the Vaccine Impact Modelling Consortium (VIMC), comprising of 18 modeling groups, estimated that vaccination of ten pathogens between 2000 and 2030 will have averted 69 million (95 CI: 52–88) deaths over the same time period, and 120 million (93–150) deaths over the lifetime of birth cohorts born during this time period in 98 low- and middle-income countries [14]. While the latest analytic developments have contributed significantly to the field of immunization, the scope of the previous work was limited to a subset of countries and vaccines [15].

The vision of IA2030 provides impetus for further advancing the efforts to capture the full impact of vaccination across the globe. Building on existing evidence, we aim to expand the analytical scope to all 194 countries that are Member States of the WHO and project the number of deaths averted by year of vaccination from 2021 to 2030 according to the aspirational coverage targets for IA2030. The results of this analysis are being used as targets for IA2030 Impact Goal indicator 1.1 “Number of future deaths averted through immunization.” [1].

2. Methodology

2.1. Scope of the analysis

The analysis targets 14 pathogens that were selected based on assessment criteria encompassing strategic priorities and availability of existing models and data, with input from partners from the global immunization community (Table 1). For ten pathogens (Hepatitis B virus, *Haemophilus influenzae* type B, human papillomavirus, Japanese encephalitis, *Neisseria meningitidis* serogroup A, *Streptococcus pneumoniae*, rotavirus, rubella, yellow fever), we used pathogen-specific vaccine impact estimates for 110 countries from mathematical models from the 18 modeling groups that are part of the VIMC [14]. For four pathogens (diphtheria, tetanus, pertussis and tuberculosis), we used estimates of cause-specific mortality from the Global Burden of Disease 2019 study along with estimates of pathogen-specific vaccine efficacy [16]. For 194 countries (all WHO Member States), we estimated future deaths averted due to vaccination taking place from 2021 to 2030 under the assumption that aspirational targets set by the IA2030 coverage scenario are met not taking into account backslide in routine immunization coverage due to

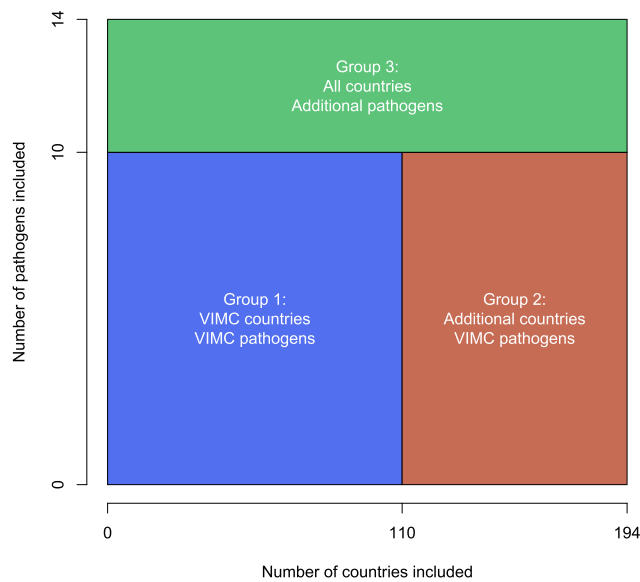


Fig. 1. Countries and pathogens included in the analysis.

the COVID-19 pandemic. The main results are based on estimates of deaths averted under the aspirational scale-up coverage scenario compared to no vaccination to capture the full impact of vaccination. We varied this assumption by comparing the estimates to the baseline level (coverage rates in 2019) to assess the incremental impact of improvement in vaccine introduction and coverage rates.

2.2. Data input

Demographic data on population size and rates of survival, fertility and migration from the UN World Population Prospects 2019 were used to calibrate a demographic model using the cohort component method of population projection (CCMPP) [17]. This approach was used to determine annual estimates of single-year age-specific all-cause mortality that were included as inputs to the relative risk calculation and model. A more detailed explanation on the demographic model is available in Appendix 1.

Country- and year-specific historical vaccine coverage estimates came from WHO-UNICEF Estimates of National Immunization Coverage (WUENIC), published in July 2019 [18]. The VIMC provided estimates of deaths averted due to vaccination against 10 pathogens for 110 countries as well as summary estimates of impact (“impact ratio”) quantified in terms of deaths-averted per fully vaccinated persons (“deaths-averted per FVP”) [19]. The estimates, disaggregated by age and calendar year, were calculated from two or three modeling groups per pathogen [Appendix 2] [19]. The impact ratio is a key summary measure used to estimate the number of individuals that will be saved over their lifetimes due to a particular year’s vaccination activities, capture the long-term impact of vaccines, which is critical for HepB and HPV [20]. For the four pathogens not estimated by VIMC, we obtained estimates of observed deaths from the Global Burden of Disease 2019 study, which employed different modeling strategies for each pathogen and locations, contingent upon availability of high quality mortality data [21]. Both deaths averted estimates and impact ratios were extrapolated to remaining countries and pathogens that were not modeled by the VIMC. To extrapolate the VIMC estimates to remaining 84 countries, we used socio-demographic Index (SDI) [21] and Healthcare Access and Quality Index (HAQI) [22] as covariates for the relative risk model described below.

2.3. Relative risk calculation and model

The analytical approach varies for each of the three groups in Fig. 1. More detailed information on the derivation of the equations is available in Appendix 3.

2.3.1. Group 1: 10 pathogens for 110 countries modeled by VIMC (blue quadrant)

The estimate of deaths averted were drawn directly from the VIMC and used to calculate the relative risk of death attributable to absence of vaccination. We defined the age-specific all-cause relative risk attributable to vaccine preventable antigen c at time t in each location as:

$$RR_{c,t} = \frac{E[\mu_t | \rho_{c,t} = 1]}{E[\mu_t | \rho_{c,t} = 0]} = \frac{\mu_t - \lambda_{c,t} \frac{1 - \rho_{c,t}}{\rho_{c,t}}}{\mu_t + \lambda_{c,t}}$$

where μ_t represents observed age-specific all-cause deaths at time t , and $\mu_{a,t}$ represents observed total deaths in age a at time t and $\lambda_{a,c,t}$ and $\rho_{c,t}$ represent age-specific estimated deaths-averted and observed vaccine coverage, respectively, for antigen c at time t . The numerator represents the hypothetical number of deaths under 100 % coverage, assuming a linear relationship between vaccine coverage and deaths averted. The denominator is the expected number of deaths in the absence of vaccination – observed deaths plus deaths averted. We explored alternative functional forms, including fractional exponentiation of coverage, which would allow for a non-linear relationship but found minimal improvement over the linearity assumption.

2.3.2. Group 2: 10 pathogens for remaining 84 countries (red quadrant)

VIMC estimates were extrapolated to remaining 84 countries, using a logistic model:

$$\text{logit}(RR_{a,c,t,i}) = \beta_0 + \beta_1 SDI_{i,t} + \beta_2 HAQI_{i,t} + \beta_3 \mu_{a,t,i} + \beta_4 t + \sum_j \alpha_j B_j(a) + \epsilon_{a,c,t,i}$$

where for age a and antigen c at time t in location i , β_0 is an intercept, β_k for $k=1, 2, 3, 4$ are fixed effects on SDI, HAQI, all-cause mortality, and year, respectively, $\sum_j \alpha_j B_j(a)$ is a b-spline on age, and ϵ is an error term. Predicted relative risk values from this model are only used for countries not modeled by VIMC. Total deaths averted are calculated from our relative risk estimates by:

$$\lambda_t = \sum_c \lambda_{c,t} = \mu_{a,t} \sum_c \frac{\rho_{c,t}(1 - RR_{c,t})}{1 - \rho_{c,t}(1 - RR_{c,t})} = \mu_t \sum_c PAF_{c,t} \left(\frac{1}{1 - \rho_{c,t}} - 1 \right)$$

Here, $PAF_{c,t}$ is the population attributable fraction; exposure equates to being unvaccinated and the relative risk is the risk of death for unvaccinated individuals compared to vaccinated individuals (i.e. the elevated risk of death associated with being unvaccinated). The unvaccinated relative risk is equal to the inverse of the vaccinated relative risk. We believe this equation may be useful to others looking to calculate averted burden as a fraction of observed burden, the “burden averted fraction” (BAF):

$$BAF = PAF \left(\frac{1}{1 - \rho} - 1 \right)$$

2.3.3. Group 3: Four pathogens for all 194 countries (green quadrant)

For BCG (tuberculosis), Diphtheria, Tetanus and Pertussis, we assumed that the observed deaths under observed vaccination coverage is the difference between the hypothetical deaths if coverage was 0 and hypothetical deaths averted based on the vaccine efficacy and observed coverage. The relative risk is defined as the ratio of deaths under the scenario of full coverage to the scenario of no vaccination:

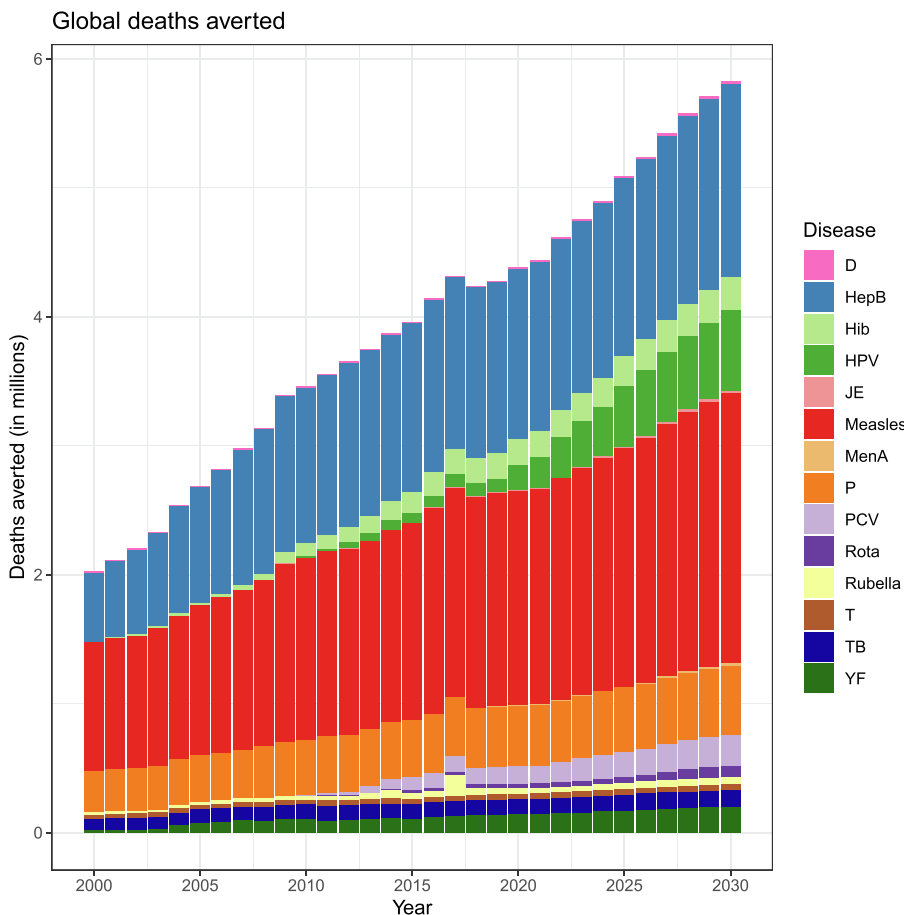


Fig. 2. Total deaths averted by pathogen, global, 2021–2030. Legend: HepB (Hepatitis B), Hib (*Haemophilus influenzae* type b), HPV (Human papillomavirus), JE (Japanese encephalitis), Measles (Measles), MenA (*Neisseria meningitidis* serogroup A), P (Pertussis), PCV (*Streptococcus pneumoniae*), Rota (Rotavirus), Rubella (Rubella), T (Tetanus), TB (Tuberculosis) and YF (Yellow Fever). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

$$RR_{c,t} = \frac{E[\mu_t | \rho_{c,t} = 1]}{E[\mu_t | \rho_{c,t} = 0]} = \frac{\mu_t - \mu_t^c - (1 - \eta_c)E[\mu_t^c | \rho_{c,t} = 0]}{\mu_t - \mu_t^c + E[\mu_t^c | \rho_{c,t} = 0]}$$

$$= \frac{\mu_t - \mu_t^c + (1 - \eta_c) \frac{\mu_t^c}{1 - \eta_c \rho_{c,t}}}{\mu_t - \mu_t^c + \frac{\mu_t^c}{1 - \eta_c \rho_{c,t}}}$$

where μ_t^c is observed deaths from the cause c at time t and η_c is the mortality reducing efficacy of vaccination for cause of death c . We used the same equation as above to calculate the total deaths and deaths averted conditional upon coverage. The vaccine efficacy used was 0.97 (0.94–0.98) for Diphtheria [23], 0.99 (0.80–1.00) for Tetanus [24], 0.80 (0.71–0.86) for Pertussis [25], and 0.66 (0.08–0.88) for BCG [26]. The same logistic regression model detailed for Group 2 was then used to extrapolate the relative risk estimates beyond the final year of cause-specific mortality data and convert relative risk estimates to deaths averted.

2.4. Procedure for alignment and calibration

After initial estimation, we then calibrated the modeled estimates for all countries and vaccines through multiple steps. To align with the measure used by the VIMC and capture the long term benefits of vaccination, especially for diseases where mortality and morbidity occur later in life, we used the Year of Vaccination (YoV) method by Echeverria-Londono et al. which attributes the lifetime effects of a particular year's vaccination activities to that year [20]. The YoV method requires calculation of the “impact ratio,” defined as vaccine impact (deaths averted in this case) divided by fully vaccinated persons (FVP). FVP is the product of vaccination coverage and cohort size. Once we generated deaths averted, FVPs and impact ratios stratified by

activity type, we compared the observed values to the predicted values and generated scaling factors to ensure the exact replication of VIMC estimates. Pathogen-specific summary values of these scaling factors were then applied to the out of sample estimates using two approaches to ensure relative consistency in the estimates derived. For the 10 pathogens modeled by VIMC, a single pathogen-specific scalar was obtained from the median bias correction across locations for each pathogen and applied to out-of-sample locations. For DTP and BCG, the median bias correction across all pathogens for routine vaccines was used, as these align with potential biases present in the extrapolation of DTP and BCG estimates.

2.5. IA2030 coverage scenario

A future coverage scenario for IA2030 was developed as an input to calculate the number of deaths averted using calibrated model and population projection. The coverage scenario reflects the vision of IA2030 where countries introduce all recommended vaccines in national immunization schedules and reach aspirational target coverage rates for the vaccines by 2030. The aspirational targets are derived from Impact Goal indicator 2.1 and 2.2 of which country-specific achievements for DTPcv-1 and subsequently DTPcv-3 coverage can be approximated from the calculation of 50 % reduction in zero dose children by 2030 (Appendix 4) [1]. These country-specific endpoints were applied to all vaccines except HPV, for which each country reaches 90 % coverage rate by 2030 based on the ambitious goals set by the Cervical Cancer Elimination Initiative (CCEI) [27], and some countries using JE, YF and BCG vaccines for subnational introduction or targeted vaccination strategies. We used the WUENIC estimates in 2019 as baseline levels for all vaccines. To reflect limited progress due to COVID-19 pandemic, the 2019 baseline level is held constant through 2021.

Table 2
Estimated deaths averted due to vaccination from 2001 to 2030, 194 countries (in million).

	Deaths averted due to vaccination		
	2001–2010	2011–2020	2021–2030
Total	29.7 (26.6–33.1)	39.5 (36.7–42.4)	51 (48.5–53.7)
<i>By pathogen</i>			
Hepatitis B virus	9.7 (8.4–11.6)	13 (11.1–15.7)	14 (11.5–16.9)
<i>Haemophilus influenzae</i> type B	0.4 (0.2–0.6)	1.6 (0.9–2.8)	2.3 (1.3–3.9)
Human papillomavirus	0 (0–0.1)	0.9 (0–3.1)	4.7 (0.3–15.7)
Japanese encephalitis	0 (0–0)	0 (0–0.1)	0.1 (0.1–0.2)
Measles	12.9 (12.2–13.8)	15.5 (14.7–16.6)	18.8 (17.8–20)
<i>Neisseria meningitidis</i> serogroup A (MenA)	0 (0–0)	0 (0–0)	0.1 (0–0.4)
<i>Streptococcus pneumoniae</i> (PCV)	0 (0–0)	0.9 (0.5–1.8)	2 (1.2–3.7)
Rotavirus	0 (0–0)	0.2 (0.1–0.3)	0.5 (0.3–0.9)
Rubella	0.3 (0.2–0.4)	0.6 (0.4–0.7)	0.5 (0.4–0.6)
Yellow fever	0.7 (0.6–0.9)	1.2 (1–1.5)	1.7 (1.4–2.1)
Diphtheria	0.1 (0.0–0.3)	0.1 (0.1–0.3)	0.2 (0.1–0.3)
Pertussis	4 (1.9–6.8)	4.5 (2.1–7.6)	5 (2.3–8.6)
Tetanus	0.4 (0.1–0.7)	0.4 (0.1–0.8)	0.4 (0.1–0.8)
TB(BCG)	1.1 (0.2–3.1)	1.1 (0.2–3.2)	1.2 (0.2–3.5)
<i>By WHO region</i>			
AFRO	8.8 (7.9–9.9)	14.4 (13–16.1)	23 (18.9–29.1)
EMRO	3.1 (2.8–3.4)	4.4 (4–4.9)	5.6 (5–6.3)
EURO	1.8 (1.6–2.2)	2.1 (1.8–2.7)	2 (1.7–2.6)
PAHO	3.5 (3.1–4.2)	3.6 (2.9–5.5)	3.6 (2.9–5)
SEARO	6.4 (5.3–7.9)	8.5 (7.1–10.3)	10.5 (8.6–14)
WPRO	6.2 (5.6–7)	7.1 (6.3–8.2)	6.8 (5.9–8.3)
<i>By World Bank income group</i>			
High income	2 (1.7–2.4)	2.1 (1.6–2.9)	2.3 (1.7–3.1)
Upper middle income	10.4 (9.4–12)	11.8 (10.3–14.1)	11.5 (9.8–14.8)
Lower middle income	12.5 (10.8–14.7)	17.9 (15.7–20.8)	24.8 (20.7–31.5)
Low income	4.8 (4.4–5.3)	8.4 (7.6–9.1)	13 (11–16.4)
<i>By Gavi status</i>			
73 countries supported by Gavi	17.2 (15.1–20.1)	26.3 (23.4–30.1)	37.9 (31.8–47.4)
121 remaining countries	12.5 (11.2–14.3)	13.9 (12.1–16.6)	13.6 (11.6–17.1)

Assumptions about new vaccine introduction vary across pathogens. For universally recommended vaccines, we assumed that introductions are spread equally between 2023 and 2027, with countries with higher DTPcv-3 coverage endpoints introducing vaccines first. For HPV, we exceptionally used assumptions from the coverage forecast developed by CCEI. For vaccines recommended for certain regions, we applied assumptions from disease-specific initiatives such as the Eliminating Yellow fever Epidemics (EYE) strategy [28], Defeating meningitis by 2030: a global road map [29], or based on regional priorities for JE. Once introduced, all vaccines are assumed to be scaled up in a non-linear fashion described in the following equation:

$$\rho_t = 1 - (1 - \rho_0) e^{\log\left(\frac{1 - \rho_t}{1 - \rho_0}\right) \frac{t - t_0}{T - t_0}}$$

where t_0 and T are the baseline and target years, respectively. This equation results in faster initial scale-up of coverage followed by slower convergence to the final value. Based on the past experience of more rapid scale up enabled by change in vaccine presentation (e.g. from quadrivalent to pentavalent), we applied the average ratio of Hib to

DTP3 and HepB to DTP3 coverage in the first two years and assumed that they will reach the DTP3 coverage rate by year three. We compared the main scenario with three other scenarios, varying introduction and scale-up assumptions to see their impact on the results. More detailed information about construction of the IA2030 coverage scenario is available in Appendix 4.

In an effort to effectively propagate uncertainty, we ran our entire analysis at the draw-level, using draw-level uncertain inputs when available and selecting sets of inputs using Latin hypercube sampling (LHS). The set of uncertain inputs were VIMC deaths averted, vaccine efficacy, and GBD deaths and HAQI. First, For the VIMC and GBD inputs, we identified the standard deviation that corresponds to the inter-quartile range and sampled from a normal distribution centered at the mean deaths averted with the calculated standard deviation to generate draws. The vaccine efficacy estimates used for Group 3 relative-risk calculations reported 95 % uncertainty intervals. To generate draws from these distributions, we identified mean-preserving maximum likelihood beta distribution parameters and sampled from the corresponding distributions. Using LHS on ranked draws to select sets of inputs assisted with efficiently spanning the co-distribution of inputs, allowing us to constrain the total computation required for our analysis.

3. Results

Overall, an estimated 51.5 million (95 % CI: 44.0–63.2) deaths are expected to be averted due to vaccinations administered between the years 2021 and 2030, inclusive (Fig. 2). With immunization coverage projected to increase over 2021–2030, an average of 5.2 million per year (4.4–6.3) deaths will be averted annually, with 4.4 million (3.9–5.1) deaths averted for the year 2021, gradually rising to 5.8 million (4.9–7.5) deaths averted in 2030. The largest proportion of deaths is attributed to Measles, which accounts for 18.8 million (17.8–20.0) (37 %), followed by Hep B, accounting for 14.0 million (11.5–16.9) (27 %) of total deaths averted (Table 2).

The expected number of deaths averted is also summarized by World Bank income group [30] (Fig. 3). Approximately 49 % of the total deaths (24.8 million (95 %: 20.7–31.5)) are averted in lower middle income countries, compared to 26 % in low income countries (13.0 million (11.0–16.4)), 22 % in upper middle income countries (11.5 million (9.8–14.8)) and 4 % in high income countries (2.3 million (1.7–3.1)). In the absence of vaccination, vaccine preventable diseases will disproportionately affect low income countries considering that they project to account for only 10 % of the total world population averaged across 2021–2030. Measles and Hep B account for large proportions of the total deaths averted across all income groups.

In terms of the distribution of deaths averted by WHO country group [31], among the WHO regions the African region accounts for 45 % of total deaths averted (23.0 million (18.9–29.1)), followed by 21 % in South East Asian Region (10.5 million (8.6–14.0)), 13 % in the Western Pacific Region (6.8 million (5.9–8.3)), 11 % in the Eastern Mediterranean Region (5.6 million (5.0–76.3)), 6 % in PAHO (3.6 million (2.9–5.0)) and 4 % in European Region (2.0 million (1.7–2.6)) (Fig. 4). The breakdown of deaths averted by pathogen provides a distinct picture for each WHO region. While Measles accounts for the largest proportions of deaths averted in the African, Eastern Mediterranean and South-East Asian Region, more deaths averted are attributed to HepB in the WHO regions of Europe, the Americas and the Western Pacific.

The results by Gavi status demonstrate 73 % (69–77) of the total deaths averted are in the 73 countries supported by Gavi, which account for 48 % of the total world population (Fig. 5). The number of deaths averted in these countries increases over time during the next decade, compared to countries that are not supported by Gavi, which is explained by improvement in vaccine introduction and coverage in low and lower middle income countries.

The historical trend demonstrates that the impact of vaccination has steadily increased over time, due to both population growth and

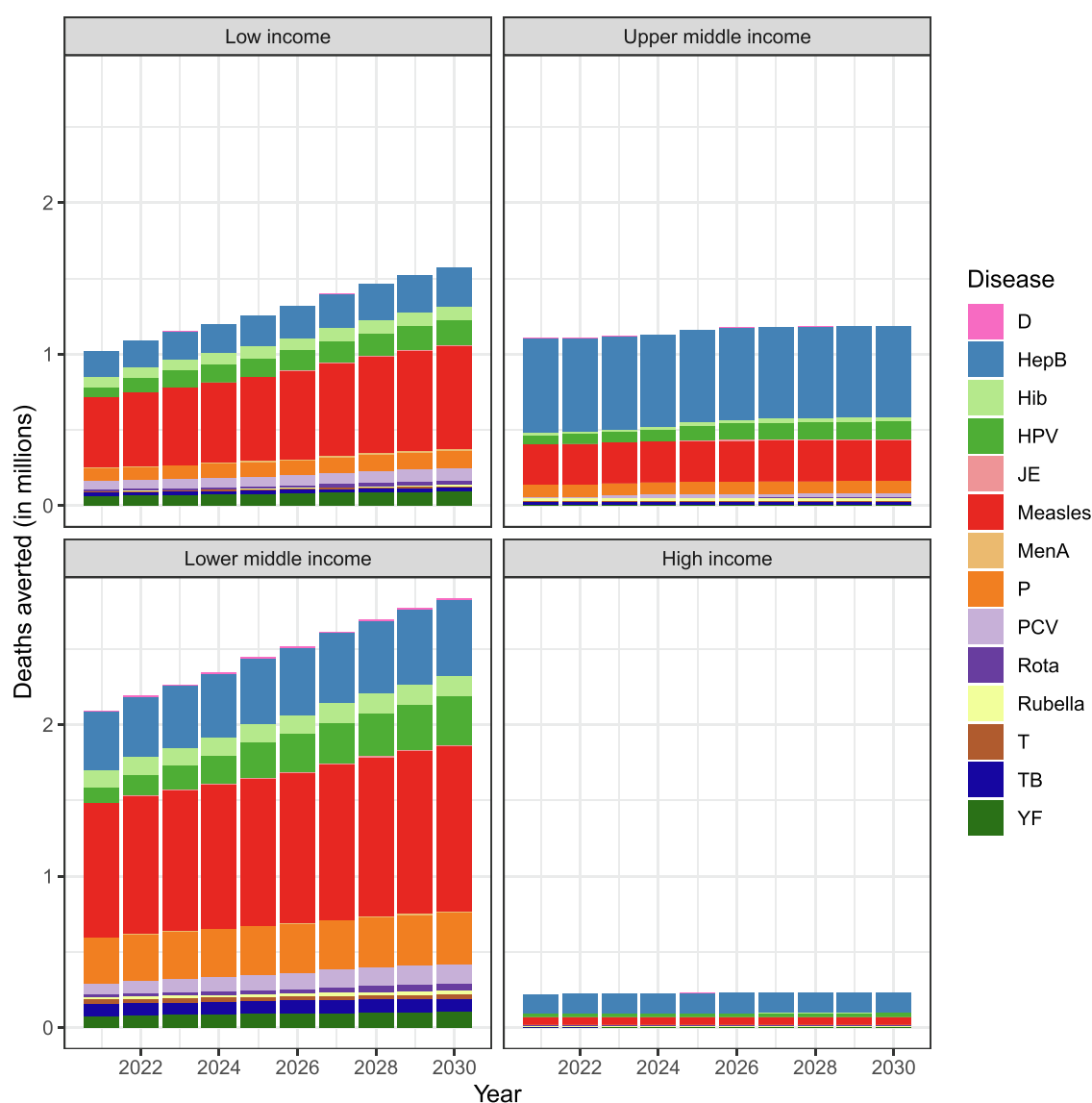


Fig. 3. Deaths averted by pathogen and by income group, 2021–2030. Legend: HepB (Hepatitis B), Hib (*Haemophilus influenzae* type b), HPV (Human papillomavirus), JE (Japanese encephalitis), Measles (Measles), MenA (*Neisseria meningitidis* serogroup A), P (Pertussis), PCV (*Streptococcus pneumoniae*), Rota (Rotavirus), Rubella (Rubella), T (Tetanus), TB (Tuberculosis) and YF (Yellow Fever). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

increased vaccine coverage. From 2001 to 2010, the total number of deaths averted based on historical WUENIC estimates is 29.7 (26.6–33.8), which increases to 40.2 million (36.0–45.2) during the last decade and 51.5 million (44.0–63.2) for the coming decade.

The main results are based on the observed and forecasted number of deaths compared to a no vaccination counterfactual. We additionally estimated the number of deaths relative to the 2019 baseline coverage level to capture the incremental impact of improvement in vaccine introduction and coverage. We did so by taking the difference between projected total deaths averted in future years and subtracting the total deaths averted in 2019. This additional set of results can be found in Appendix 5.

4. Discussion

The results from this analysis demonstrate the potential impact of mortality reductions if the IA2030 targets are met by 2030. The demonstrated benefits in the next decade are grounded on the assumption that countries would make continuous progress towards the

aspirational goals of improving vaccine introduction and coverage as well as reducing the number of children completely missing out on vaccination. During the first years of the new decade, disruptions to routine immunization services caused by the COVID-19 pandemic have led to historic backsliding in global vaccination coverage rate likely affecting equity in vaccine access compared to pre-pandemic times [32]. Furthermore, other challenges such as conflict [33,34], political instability and climate change [35–37] continue to present significant risks in the future for maintaining achieved vaccination coverage and making progress to attain modelled benefits.

Faced with the urgent need for recovery, all stakeholders at the national, regional and global level should intensify their efforts to implement catch-up vaccination and campaigns to reach missed children, address missed opportunities for vaccination and prevent outbreaks while continuing to build trust in vaccines and immunization. Furthermore, stronger partnerships and concerted action between the representatives from ministries of health, government agencies, pharmaceutical companies, funding entities, civil society organizations, academia, United Nations organizations and agencies will be needed to

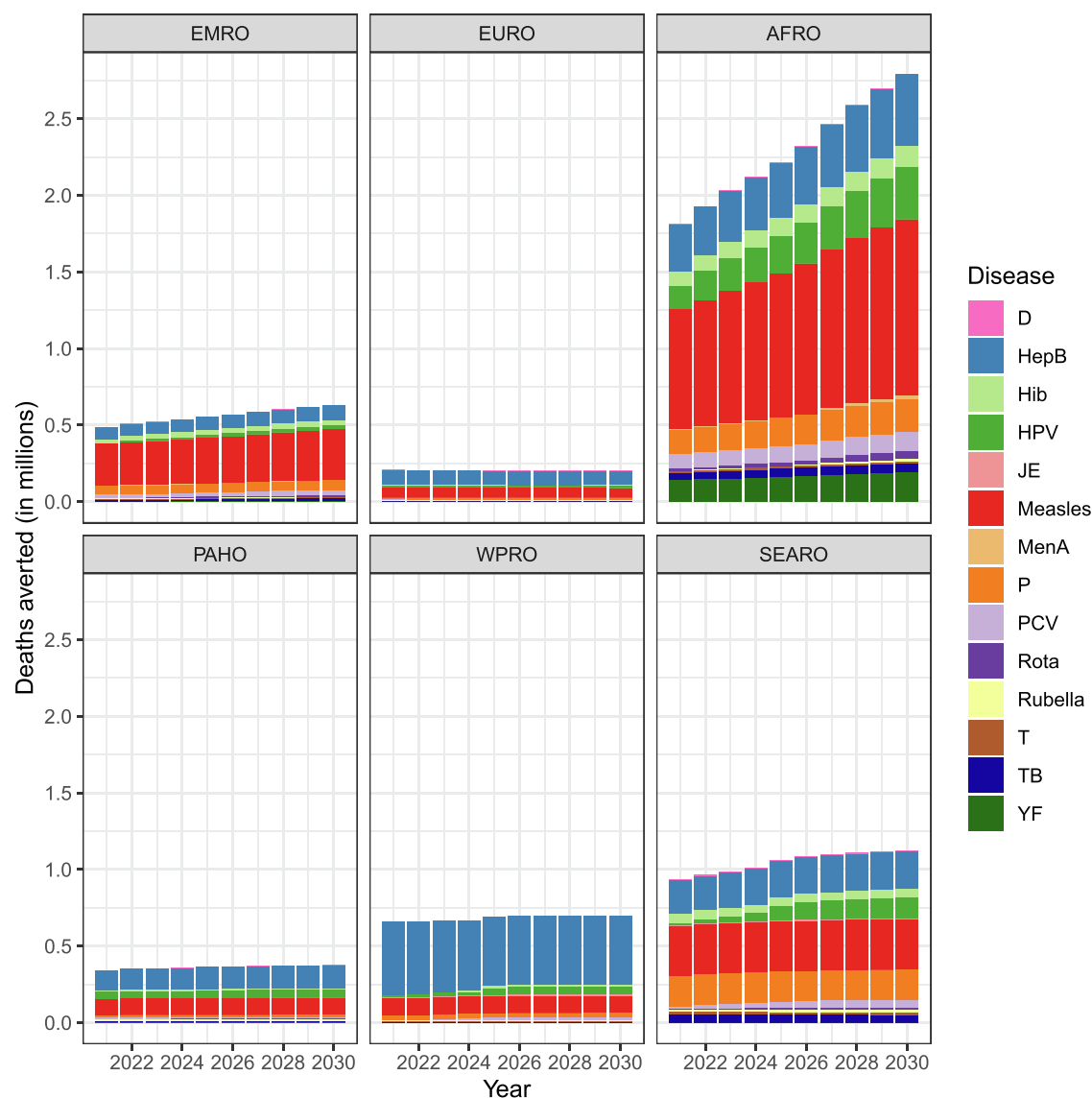


Fig. 4. Deaths averted by pathogen and by region, 2021–2030. Legend: HepB (Hepatitis B), Hib (*Haemophilus influenzae* type b), HPV (Human papillomavirus), JE (Japanese encephalitis), Measles (Measles), MenA (*Neisseria meningitidis* serogroup A), P (Pertussis), PCV (*Streptococcus pneumoniae*), Rubella (Rubella), T (Tetanus), TB (Tuberculosis) and YF (Yellow Fever). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

strengthen immunization programs across the life course embedded within primary health care (PHC), contributing to Universal Health Coverage.

Deaths caused by vaccine preventable diseases disproportionately affect low and lower middle income countries in the African region. It is critical to share the benefits of vaccination among countries in a more equitable manner by increasing access to under-used and new vaccines, reaching the most marginalized and vulnerable populations that are left unprotected against vaccine preventable diseases. As echoed in the previous statements by WHO Member States during the 74th World Health Assembly [38], the achievement of the IA2030 vision will require increased political commitment and investments to extending the benefits of vaccination across the globe, based on robust measurement and monitoring of progress.

The analysis has several limitations. First, the current scope includes 14 pathogens only and does not fully capture all existing vaccines in the national immunization schedules. It is also limited to mortality impact, underestimating the benefits of vaccines through morbidity reductions. Another source of underestimation comes from the exclusion of SIA data

since the analytical framework focuses on routine immunization. Since we used the data from low- and middle-income countries for extrapolation to high income countries using the relative risk model, there is uncertainty in the estimates generated for HICs and corresponding vaccines. Future work by the authors will apply the analytical framework to a broader set of pathogens (including malaria and COVID-19), develop a framework for reliable projection of SIA, and validate modeled estimates from this analysis with empirical data and/or setting-specific modeled evidence specifically from HICs. Group 3 pathogens using disease burden data and vaccine efficacy will benefit from cross-validation with estimates that are directly derived from mathematical models.

In addition, this analysis is based on an optimistic assumption regarding the impact of COVID-19 on routine immunization that informed target setting for the decade. The IA2030 coverage scenario assumes maintenance of 2019 level and does not take into account disruption, recovery or improvement of coverage during the COVID-19 pandemic in 2020 and 2021. This assumption is fixed as the primary aim of the analysis was to set ambitious targets for IA2030. As updated

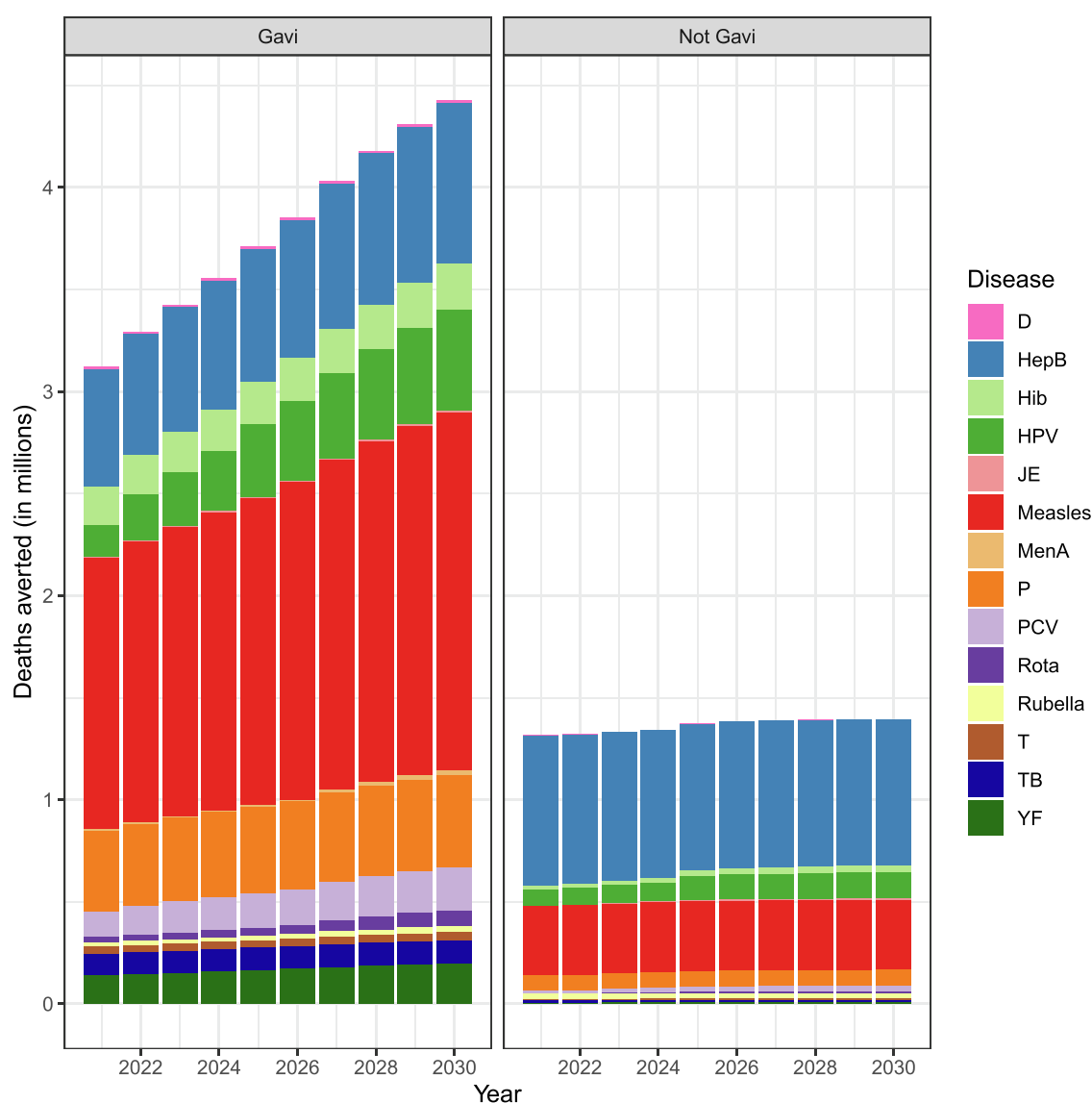


Fig. 5. Deaths averted by pathogen and by Gavi status, 2021–2030. Legend: HepB (Hepatitis B), Hib (*Haemophilus influenzae* type b), HPV (Human papillomavirus), JE (Japanese encephalitis), Measles (Measles), MenA (*Neisseria meningitidis* serogroup A), P (Pertussis), PCV (*Streptococcus pneumoniae*), Rubella (Rubella), T (Tetanus), TB (Tuberculosis) and YF (Yellow Fever). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

WUENIC coverage data become available every year [39], the annual progress has been measured against targets as part of the annual progress report to the Strategic Advisory Group of Experts on Immunization (SAGE) and the scorecard for IA2030 [40]. By running the same model using the updated WUENIC coverage estimates in 2022, which reflect the impact of disruption to vaccine delivery during the pandemic, we found that the observed numbers fall below target numbers in the past two years. The observed number of future deaths averted due to vaccination in 2019, the baseline year, is 4.23 million, and the number in 2020 is 4.16 million.

Finally, any limitations inherent to the VIMC models and outputs are also present in this analysis, and any substantial changes in vaccine impact that may have been caused by the COVID-19 pandemic also affect this study. Uncertainty in demography and coverage is not captured in the model outputs. Sparse temporal or geographically distributed data used as model input adds to uncertainty although it could be improved with increased availability of such data. Model averaging and equal weighting underestimates heterogeneity across models. The approach to calculating impact ratios underestimates

variations in health care access, case fatality ratio or other temporal factors, and does not fully replicate the estimates of dynamic models. Finally, there remains a theoretical risk of “double counting” deaths as disease burden and vaccine impact for each pathogen is generated from separate VIMC models. Recent work by VIMC found that double counting of deaths averted accounts for only a small proportion of impact for 10 pathogens in 112 countries. For cohorts born between 2000 and 2030, the adjustment was 2.36 % (95 % CI [2.00 %, 2.83 %] which reduced to 1.07 % (95 % CI [0.90 %, 1.32 %] for children under age 5 [19]. Conceptually, double counting is justified if we account for the fact that a life can be saved multiple times by different interventions.

Despite the limitations of the current analysis, this is the first attempt to develop an analytical framework to extrapolate existing models and data to estimate the full impact of vaccination on a global scale. In addition, the estimates will contribute to the monitoring and evaluation efforts of the global community. These targets will be compared against estimates using the current model and historical coverage rates to assess the performance. A new target will be set at the midpoint incorporating an expanded scope of pathogens and structural changes with refinement

of underlying models and data. Furthermore, global, regional and country partners could use the results for advocacy and resource mobilization efforts to secure commitment and resources needed to achieve the vision of IA2030.

CRediT authorship contribution statement

Austin Carter: Conceptualization, Methodology, Software, Formal analysis, Writing – original draft. **William Msemburi:** Conceptualization, Methodology, Software, Formal analysis, Writing – review & editing. **So Yoon Sim:** Conceptualization, Writing – original draft, Project administration. **Katy A.M. Gaythorpe:** Data curation, Methodology, Writing – review & editing. **Philipp Lambach:** Supervision, Writing – review & editing. **Ann Lindstrand:** Writing – review & editing. **Raymond Hutubessy:** Supervision, Methodology, Writing – review & editing.

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The authors alone are responsible for the views expressed in this article and they do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Due to required approvals from WHO country representatives, only aggregate level data is available upon request.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2023.07.033>.

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