Vaccine supplement

**Title:**

Modeling the impact of vaccination for the Immunization Agenda 2030: deaths averted due to vaccination against 14 pathogens in 194 countries from 2021-2030

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**Conflict of interest**

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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. In order to estimate the potential impact according to the aspirational coverage targets for IA2030, we developed an analytical framework and estimated the number of deaths averted due to vaccination from 2021-2030 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, 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). We used a logistic 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 data from the Global Burden of Disease 2019 study and existing literature on vaccine efficacy. A future scenario defining years of vaccine introduction, scale-up and aspirational targets was developed as an input to estimate the long term impact of vaccination taking place from 2021-2030.

*Findings*

Overall, an estimated 51.0 million (95% CI: 48.5 – 53.7) 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  5.1 million per year (4.9 – 5.4) deaths will be averted annually, with 4.4 million(3.6- 5.1) deaths be averted for the year 2021, gradually rising to 5.8 million(4.9-6.6) deaths averted in 2030. The largest proportion of deaths is attributed to Measles and Hepatitis B accounting for 18.8 million (16.7-21.1) and 14 million (13.6-14.4) of total deaths averted respectively.

*Interpretation*

The results from this global analysis demonstrate the major impact of mortality reductions if the IA2030 targets are met by 2030. Deaths caused by vaccine preventable diseases disproportionately affect LMICs in the African region.

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 have been 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, significant advances have been made to the increase in 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,3456 the challenges of 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 the existing data in specific settings to generate projections in other settings and quantify uncertainty in the predictions.78

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 2011-2020, 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 based on an analysis by WHO, Gavi, the Bill Melinda Gates Foundation and PATH.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 source and methods used.111213 More recently, the Vaccine Impact Modelling Consortium (VIMC), comprising of 18 modeling groups, estimated that vaccination of ten pathogens will have averted 69 million (95 CI: 52-88) deaths between 2000 and 2030, and 120 (93-150) deaths over the lifetime of birth cohorts born during this time period in 98 low- and middle-income countries.14 VIMC’s estimates have informed Gavi and BMGF’s strategic decisions, facilitated monitoring of the progress of their strategies and supported advocacy and resource mobilization efforts. 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 members of WHO and project the number of deaths averted by year of vaccination from 2021-2030, according to the aspirational coverage targets for IA2030. The results of this analysis will be used as targets for IA2030 Impact Goal indicator 1.1 “Number of future deaths averted through immunization.”1

**Methodology:**

**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 all 194 WHO countries, we estimated future deaths averted due to vaccination taking place from 2021-2030 under the assumption that aspirational targets set by the IA2030 coverage scenario are met. The main results are based on the 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.

**Data input**

As the first step, demographic data on population size and rates of survival, fertility and migration from the UN World Population Prospects 2019 were used to construct 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 mortality that can be linked to annual estimates of vaccine coverage, ultimately deriving the changes in pathogen-specific mortality due to vaccination within the same demographic envelope. 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 quantified (“impact ratio”) 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 measure used to estimate the number of individuals that will be saved due to a particular year’s vaccination activities and capture the long-term impact of vaccines, which is critical for HepB and HPV.20 For four remaining pathogens not provided 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.

**Relative risk calculation and model**

The analytical approach could be broken down into three groups in Figure 1. More detailed information on the derivation of the equations is available in Appendix 3.

*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 relative risk attributable to vaccine preventable cause c at time t as:

Where represents the age *a* per population deaths-averted for cause *c* at time *t*.

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

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

Where for age *a* and antigen *c* at time *t* in location *i*, is an intercept, for are fixed effects on SDI, HAQI, all-cause mortality, and year, respectively, is a b-spline on age, and is an error term. Predicted relative risk values are only used for countries not modeled by VIMC. Total deaths averted are calculated by :

Where the , mortality estimates at age *a* and at time *t*, come from the demographic model and is the vaccine coverage level for antigen *c* at age *a* and at time *t*.

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

For BCG (tuberculosis), Diphtheria, Tetanus and Pertussis, we used an approach that applies the following equation to calculate relative risk. 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:

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Where is proportion covered by vaccine *c* at time *t*, is observed deaths from the cause of deaths associated with vaccine *c* at time *t*, and is the mortality reducing efficacy of vaccine. We used the same equation as above to calculate the total deaths and deaths averted conditional upon coverage. The vaccine efficacy is 0.97 (0.94-0.98) for Diphtheria23, 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 model detailed for Group 2 was then used to extrapolate the relative risk estimates beyond the final year of cause-specific mortality data.

**Procedure for alignment and calibration**

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 long term 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 person (FVP). FVP is the product of vaccination coverage and cohort size. Once we generated deaths averted, FVPs and impact ratio 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 median bias correction across locations for each pathogen and applied to out-of-sample locations. For DTP and BCG, 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.

**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), 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.

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,27 Defeating meningitis by 2030: a global road map,28 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:

Where t0 and T are the baseline and target years, respectively. 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 the IA2030 coverage scenario is available in Appendix 4.

Three sources of uncertainty were incorporated into the uncertainty in the deaths averted associated with the IA2030 coverage scenario. First, VIMC provided uncertainty intervals for the deaths averted estimates that served as inputs to this analysis. We identified the standard deviation that corresponds to the interquartile range and sampled from a normal distribution centered at the mean deaths averted with the calculated standard deviation to generate draws. Second, the vaccine efficacy estimates used for Group 3 relative-risk calculations came with uncertainty intervals. To generate draws from these distributions, we identified mean-preserving maximum likelihood beta distribution parameters and sample from the corresponding distributions. Finally, for Group 2 locations, we used the coefficient of variation in the impact factor scalars to derive a standard deviation that aligned with mean deaths averted estimates and, again, sampled from a normal distribution centered at the mean deaths averted with the calculated standard deviation to generate draws. Two hundred draws were generated to use as inputs to uncertainty interval calculations.

**Results**

Overall, an estimated 51.0 million (95% CI: 48.5-53.7) deaths are expected to be averted due to vaccinations administered between the years 2021 and 2030, inclusive (Figure 2). With immunization coverage projected to increase over 2021-2030 an average of  5.1 million per year (4.9 – 5.4) deaths will be averted annually, with 4.4 million(3.6-5.1) deaths be averted for the year 2021, gradually rising to 5.8 million(4.9-6.6) deaths averted in 2030. The largest proportion of deaths is attributed to Measles, which accounts for 18.8 million (16.7-21.1) (37%), followed by Hep B, accounting for 14 million (13.6-14.4) (27%) of total deaths averted (Table 2).

The expected number of deaths averted is also summarized by the World Bank income Group29 (Figure 3) . Approximately 49% of the total deaths (24.8 million (95%:22.4-26.9)) are averted in lower middle income countries, compared to 26% in low income countries (13.0 million (12.2-13.8)), 22% in upper middle income countries (11.2 million (10.5-12)) and 4% in high income countries (2.0 million (1.7-2.4)) . In the absence of vaccination, the vaccine preventable diseases will disproportionately affect low income countries considering that they account for 10% of the total world population averaged across 2021-2030. Measles and Hep B account for large proportions of the total deaths averted across income groups.

In terms of the distribution of deaths averted by WHO country group30, the AFRO region accounts for 45% of total deaths averted (23.0 million (21.1-25.0)), followed by 21% in WHO SEARO (10.5 million (9.1-11.9)), 13% in WPRO (6.7 million (6.2-7.3)), 11% in EMRO (5.7 million (4.9-6.4)), 6% in PAHO (3.2 million (2.9-3.6)) and 4% in EURO (1.9 million (1.7-2.1)) (Figure 4). The breakdown of deaths averted by pathogen provides a distinct picture for each region. While Measles accounts for the largest proportions of deaths averted in AFRO, EMRO and SEARO, more deaths averted are attributed to HepB in EURO, PAHO and WPRO.

The results by Gavi status demonstrates 74%(72-76) of the total deaths averted are in 73 countries supported by Gavi that account for 48% of the total world population (Figure 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. From 2001-2010, the total number of deaths averted based on historical WUENIC estimates is 29.7 (26.6-33.1), which increases to 39.5 million (36.7-42.4) during the last decade and 51 million (48.5-53.7) for the coming decade.

The main results are based on the number of deaths compared to no vaccination. 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 simply 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.

**Discussion :**

The results from this analysis demonstrate the impact of mortality reductions if the IA2030 targets are met by 2030. To attain these benefits in the next decade, the global community should strive towards the aspirational goals of improvement in vaccine introduction and coverage as well as the maintenance of past achievements. This will require comprehensive efforts from community, national, regional and global stakeholders in all strategic priority areas of IA2030. The changing context and ongoing challenges, including but not limited to the COVID-19 pandemic, conflict and political instability, climate change and public trust, call for effective coordination and partnerships to strengthen immunization programs and primary health care.

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. Gavi continues to play an important role in increasing vaccine introduction and coverage in these countries including those that have transitioned from Gavi support. More efforts should be devoted to improving equity within countries by reaching the most marginalized and vulnerable populations that are still without access to vaccines. The achievement of the IA2030 vision will require sustained investment as well as public and political commitment 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, 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, any limitations inherent to the VIMC models and outputs are also present in this analysis. 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. At the midpoint of IA2030 (2025), 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.

**Conclusions:**

The results show that vaccination generates significant health impact at the global level. To attain these benefits in the next decade, the global community should strive towards the aspirational goals of improvement in vaccine introduction and coverage as well as the maintenance of past achievements. The results will be used as an Impact Goal indicator 1.1 for IA2030 to measure the progress of the implementation of IA2030. The achievement of the IA2030 vision will require sustained investment as well as public and political commitment. The demonstrated benefits call for stronger support from the global community to make this vision a reality.

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**Tables**

**Figures**