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Contribution of vaccination to improved child survival: modelling 50 years of the Expanded Programme on Immunization

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Abstract

Background: The World Health Organization, as requested by its Member States, launched the Expanded Programme on Immunization (EPI) in 1974 to make lifesaving vaccines available to all globally. To mark the 50-year anniversary of EPI, we sought to quantify the public health impact of vaccination globally since the programme's inception.

Methods: Using a suite of mathematical and statistical models we estimated the global and regional public health impact of 50 years of vaccination against 14 pathogens in EPI. For the modelled pathogens, we considered coverage of all routine and supplementary vaccines delivered since 1974 and estimated mortality and morbidity averted for each age cohort relative to a hypothetical scenario of no historical vaccination. We then used these modelled outcomes to estimate the contribution of vaccination to globally declining infant and child mortality rates.

Findings: Since 1974, vaccination has averted 154 million deaths, including 146 million among children under 5 years, of whom 101 million were infants. For every death averted, 66 years of full health were gained on average, translating to 10·2 billion years of full health gained. We estimate that vaccination has accounted for 40% of the observed decline in global infant mortality, 52% in the African region. In 2024 a child at any age under-10 is 40% more likely to survive to their next birthday relative to a hypothetical scenario of no historical vaccination. Increased survival probability is observed even well into late adulthood.

Interpretation: Since 1974 substantial gains in childhood survival have occurred in every global region. We estimate that the Expanded Programme on Immunization has provided the single greatest contribution to improved infant survival over the past 50 years.

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Introduction

The Expanded Programme on Immunization (EPI) was established by the World Health Assembly in May 1974, marking a proactive commitment to extend the protective benefits of vaccination to all.¹ Motivated by successful progress towards smallpox eradication, a milestone achieved in 1980, the World Health Organization (WHO) launched the collaborative initiative with the initial goal to vaccinate all children against smallpox as well as against tuberculosis, diphtheria, tetanus, pertussis, polio, and measles by 1990.² EPI now also includes protection against other global and regional specific pathogens, across all ages of the life-course, whose inclusion is determined by country programme decisions. [Box 1] Over the past 50 years, this growth in the number of diseases covered, coupled with catalytic strategies and initiatives, and underpinned by a vision shared by the global community, achieved massive scale-up in breadth of protection and coverage. [Box 1] Global coverage with third dose diphtheria, tetanus, pertussis containing vaccine (DTP3), a proxy for vaccine programme performance, has increased from <5% in 1974 to 86% prior to the COVID-19 pandemic, and currently is 84%.³

In order to quantify EPI impact, we estimated the number of deaths averted, the life years gained, and the years of full health (YFH) gained (disability-adjusted life years averted) by vaccination (henceforth impact) against 14 diseases (diphtheria, *Haemophilus influenzae* type B, hepatitis B, Japanese encephalitis, measles, meningitis A, pertussis, invasive pneumococcal disease, poliomyelitis, rotavirus, rubella, tetanus, tuberculosis, and yellow fever) in 194 WHO Member States between June 1974 and May 2024 through coverage achieved by routine and supplementary immunization activities. We developed a standardised analytical framework to estimate vaccine impact per fully vaccinated person over time, synthesising the results of 23 models and applying regression-based imputation methods to ensure geographical and temporal completeness. We also estimated the attributable contribution of vaccination to the reduction in infant mortality since 1974 and the regional variation in the absolute and relative impact of vaccination.

Methods

We provide here brief details regarding the suite of mathematical and statistical models, a more complete description is given in supplementary material (Especially section Transmission Models and Suppl. Table S6 and section Static Models). We synthesised age-specific vaccine coverage estimates from four data sources: (1) WHO Immunization Information System (WIISE) database (for routine activities), (2) WHO Supplementary Immunisation Activity database and (3) WHO Polio Information System (for supplementary immunization activities), and (4) Vaccine Impact Modelling Consortium (VIMC) coverage estimates.⁴⁻⁶ Where country coverage data 1974 to 1979 were unavailable, for low- and middle-income countries we linearly extrapolated from known coverage in 1980 to an anchored 0% coverage in 1974, for high income countries we used the coverage reported in 1980 (sensitivity analysis in Supplement). In total, we evaluated 24 vaccine activities (stratifying each disease, vaccine, dose number; routine or supplementary), calculating the number of fully vaccinated people (FVP) using population estimates from World Population Prospects (WPP).⁷ Modelling took 3 forms. (1) Impact estimates were derived directly through simulation of published transmission models for measles and poliomyelitis in all 194 countries for the full 50-year analysis period. For measles we used an ensemble of two published dynamic models.^{8,9} For poliomyelitis we ran novel simulations of an existing dynamic model.¹⁰ (2) A suite of VIMC transmission models for *Haemophilus influenzae* type B (Hib), hepatitis B, Japanese encephalitis, invasive pneumococcal disease, rotavirus, and rubella, that estimate impact for 110 countries (fewer for meningitis A and yellow fever) from 2000 was extended by geographical imputation and temporal extrapolation, as

described below.⁶ (3) Published static disease burden models for diphtheria, tetanus, pertussis, and tuberculosis were upgraded (full explication in Supplement).¹¹ For these static models we incorporated estimates reported by the 2021 Global Burden of Disease (GBD) study using three key quantities: (A) GBD estimated country- and age-specific disease-attributable mortality and morbidity; (B) vaccine efficacy (interpreted as the reduction in probability of death or disease) profiles, including effects of waning immunity, and derived distinctly for priming, boosting and pregnancy schedules and vaccine platforms (e.g. acellular and whole-cell pertussis); and (C) country- and age-specific vaccine coverage.¹² The last two quantities are combined to result in an estimate of ‘effective vaccine coverage’, which is then used to estimate disease-attributable mortality and morbidity in a hypothetical scenario of no historical vaccination (Suppl. Figs. S10, S11).

To impute vaccine impact in countries outside of the scope of the VIMC, we fitted time series regression models with the outcome of deaths averted and YFH gained for each vaccine in each country where VIMC estimates were available. Time series regression models regress each time point (here year) of an outcome variable against the same or lagged time points of predictor variables. We used a corrected Akaike Information Criterion (AICc) model selection approach to inform the choice of socioeconomic and demographic covariates, selecting the parsimonious model with best performance, on average, for each region and disease. Using the regional median coefficient for each included predictor variable, combined with local data, we used the selected model to impute the impact in missing countries (Supplement). In order to estimate vaccine impact in time periods not directly modelled, we fitted a functional relationship between model-estimated cumulative impact – in terms of either deaths averted or YFH gained – and the cumulative number of FVP. Four functional forms were fitted for each vaccine in each country: linear (presumes each dose has equal effect, no community herd effect), logarithmic, exponential (each additional dose has respectively lesser/greater effect), and sigmoidal (programme takes time to establish and achieve community effects, then each subsequent dose has less individual impact). Thus we selected functions that best fit locally specific data, thereby capturing locally relevant interaction between individual and population effects of specific vaccines at specific place and time. A Markov Chain Monte Carlo algorithm was used to derive posteriors for all fitted function parameters. The AICc was then used to select the most appropriate functional form for each vaccine in each country. Using these fitted relationships between vaccine coverage (in terms of FVP) and vaccine impact (in terms of deaths averted or YFH gained), we inferred vaccine impact either back or forward in time according to observed coverage in all cases where modelled estimates were not available. The parameter posteriors generated through this functional fitting process were used to propagate uncertainty of final vaccine impact estimates (Suppl. Table S1, Suppl. Figs. S4, S5). Briefly, vaccine coverage and population size sources used are not statistical estimators per se and uncertainty bounds for these are not reported, we took them as given. It was also not possible to propagate uncertainty at all levels of estimation for all the hierarchical underlying models or of the values input into those models. For our own modelling we produced posterior credible intervals but these were of arbitrarily predefined widths, and should not be interpreted as bounds about our final reported outcomes (Supplement).

For all pathogens, deaths averted were estimated by single year of age for each calendar year. For measles, polio, and the VIMC models we estimated YFH gained using the modelled number of cases of specific severity along with disease burden disability weights provided by GBD 2021.¹² For the static models of diphtheria, pertussis, tetanus and tuberculosis, we used an identical approach as for computing deaths averted, but with corresponding GBD estimates for disease burden. Age granularity was derived

using linear interpolation from 5-year bins as provided by GBD. These age-specific results were then directly used along with life expectancy values to estimate Years of Life (YL) saved. We used country- and year-stratified life expectancy values from WPP for this study.

Using population and all-cause mortality estimates from WPP along with our modelled estimates of deaths averted, we estimated child mortality rates in the hypothetical scenario of no vaccination since 1974. Further, by considering a second hypothetical scenario of no decline in child mortality rates over the analysis period, we derived estimates for the attributability to vaccination of the observed global and regional decline in child mortality over the past 50 years. In all scenarios, namely the observed mortality decline due to vaccine and non-vaccine causes, the modelled mortality in absence of historical vaccination, and the baseline comparator (no change to mortality rate since 1974), we assumed that the child population would be of an identical size to that observed. That is, that fertility rates would be higher in scenarios of higher child mortality, which in effect offsets loss of life.

Finally, we assessed age-disaggregated absolute and relative survival gains achieved through vaccination globally and regionally for individuals alive in 2024. That is, the increase for an individual of a given age in the probability of 1 year survival due to global vaccination activities since 1974. This metric was estimated by considering the difference between age-specific mortality rates in 2024 in the real-life scenario compared to the hypothetical no historical vaccination scenario.

Our methods were reviewed by WHO's immunization and vaccines related implementation research advisory committee (IVIR-AC).¹³ Our data sources and analytic code are available, making our findings reproducible and extendable: <https://github.com/WorldHealthOrganization/epi50-vaccine-impact>

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Results

Over the last 50 years, (June 1974 – May 2024) we estimate that vaccination programmes targeting the 14 modelled pathogens have averted 154 million deaths [Fig. 1A], including 146 million in children under 5 years of age among whom 101 million were infants. The number of years of life gained were 9·0 billion [Fig. 1B], and the years of full health gained (i.e. disability-adjusted life years averted) were 10·2 billion [Fig. 1C], or over 200 million healthy life years gained per year globally. For each life saved, an average of 58 years of life and 66 years of full health were gained, with 8% (0.8 billion of 10.2 billion) of years of full health gained attributable to poliomyelitis cases averted. Overall, measles vaccination accounted for over 60% (93.7 million of 154 million) of the total benefit of vaccination over this 50-year period. Measles vaccination was the single greatest driver of lives saved by vaccination, over all years in every region and across all World Bank income strata. [Suppl. Table S1, Suppl. Figs. S1 – S2]

Since 1974, global infant mortality has declined substantially [Fig. 2A]. We estimate that vaccination is directly responsible for 40% of this achievement, varying from 21% in the Western Pacific region to 52% in the African region. [Figs. 2A, 2B and Suppl. Fig. S3]. The relative contribution was especially high during

the 1980's, a period of intense scale-up of coverage of the original EPI vaccines, BCG, DTP, measles, and poliomyelitis vaccines. [Fig. 2C] In the 21st century, the increasing impact of other interventions is notable, highlighting the need for sustained investment and implementation efforts, bringing together immunisation and primary health care services.

We assessed the vaccination-mediated increase in survival probability over the life-course, taking a snapshot of survival rates in 2024 under two distinct scenarios: a baseline scenario where vaccination activities occurred as observed, and a hypothetical scenario of no vaccinations since 1974. We estimate that in 2024, children turning 10 are about 44% relatively more likely, 25-year-old adults are 35% more likely, and 50-year olds 16% more likely to survive to their next birthday. [Fig. 3A] These results highlight the continued positive effect of vaccination throughout the life course, even in the context of waning vaccine immunity and an analysis focused on infant- and child-specific schedules, which does not include HPV, influenza, or COVID-19 vaccination programmes. In terms of absolute impact, the African region has seen the largest vaccine-induced gains in life course survival probability over the past 50 years, with the European region seeing the lowest absolute gains. [Fig. 3B] This result showcases the high vaccine impact attainable in regions with the highest infectious disease burden. Conversely, in terms of relative impact, the European region has seen the largest gains in life course survival probability, and the African region amongst the lowest, given a higher burden of competing risks. [Fig. 3A] This contrasting result highlights the potential for further gains in some regions.

Discussion

The eradication of smallpox achieved through vaccination is among humanity's great achievements. Building on the smallpox programme, at a time when a child born anywhere remained at risk of death from infection in infancy and childhood, the EPI program expressed a belief that it was humanly possible to build a world where all were free from preventable infectious death. On the occasion of the 50th anniversary of EPI we present the most comprehensive analysis of historical vaccine programme impact yet conducted.

We estimate that the modelled vaccines have saved more than 154 million lives since 1974, 95% of these in children under 5 years. This equates to 9·0 billion years of life saved and further considering the added benefit of reduced morbidity, 10·2 billion healthy years of life have been gained due to vaccination. Measles vaccination has been the single greatest contributor and is likely to remain so.^{6,11} Vaccination has accounted for close to half the total global reduction in infant mortality, and in some regions to the majority of these gains [Suppl. Fig. S3]. As a result of 50 years of vaccination, a child born today has a 40% increase in survival through each year of infancy and childhood. The survival benefits of infant vaccination extend to beyond 50 years of age, a finding all the more remarkable excluding as it does both smallpox and the anticipated benefits of HPV, influenza, SARS-CoV-2, Ebola, MPox and other vaccines affecting adult mortality.

Many vaccines protect in two ways, by direct reduction of risk to the vaccinated individual, and for most vaccines (although notably not tetanus) by reducing the community transmission and exposure to infectious diseases. Paradoxically, as vaccination programmes reduce community transmission, the measurable marginal direct individual benefit of vaccination becomes more modest since there is less circulating disease to prevent. We accounted for both the individual and communal benefits of vaccine programmes and their complex non-linear interactions. Though not modelled as an outcome, as part of

method development we found that many of our models fit the local data better when the function presumed community effects (Suppl. Fig. S18). The relationship suggests that even small reductions in community vaccine coverage can result in dramatic increased risk of disease, which further work will explore. Indeed, a worldwide resurgence of large measles outbreaks is underway consequent to pandemic associated declines in measles vaccine coverage.^{14,15} Measles outbreaks are a tracer for vaccine programme performance under the Immunisation Agenda 2030 (IA2030, Box 1). Historically, the annual mortality reduction impact of measles vaccination peaked contemporaneously with global scale up of first dose coverage. Vaccine coverage then plateaued, while other non-vaccine factors that reduce infant and child mortality were introduced, though this varies by region [Suppl. Figs. S4, S5, Box 1]. These non-vaccine factors also contributed to lowering the risk of dying from measles, given infection. Despite this, forecasting suggests that measles vaccination will remain the preeminent intervention that will maximise lives saved well into the future.^{11,15}

Unlike measles vaccination which breaks communal chains of transmission, tetanus vaccinations serve only to protect the vaccinated individual or her newborn through placental transfer of immunity. Absence of plateauing population-level effects means per-dose impact remains high [Suppl. Fig. S4, S5]. Maternal and newborn tetanus elimination can be achieved through concerted effort to achieve sufficient, timely access to immunization for pregnant women and their newborns, leading to large relative reductions in newborn disease. Pertussis vaccination was a major contributor to lives saved. Nevertheless pertussis mortality remains a persistent preventable cause of death in young infants in all settings. In many settings the acellular vaccine is used since it is less reactogenic but it is now known to provide less durable protection, making booster doses in pregnancy important. The contribution of tetanus and pertussis highlights the importance of maternal immunisation programmes. Strengthening and extending these to include influenza, RSV and Group B Streptococcus provide further opportunities for saving future lives, and efficacy and sufficiently powered safety studies of prenatal delivery can support increased adherence. Despite being the oldest and most ubiquitously used vaccine, neonatal Bacille Calmette-Guérin (BCG) vaccine impact on tuberculosis mortality was modest. This is explained by the vaccine's low biological efficacy that varies by strain, and the likely waning efficacy by adulthood.¹⁶ New generation tuberculosis vaccines are in development.¹⁷ This analysis did not include BCG or measles vaccine putative effects on mortality from causes other than tuberculosis and measles, which some evidence suggests may be substantial. Vaccination against polio has had modest impact on mortality, averting 1% of deaths, but has led to substantial public health gains by reducing poliomyelitis-induced paralysis accounting for 8% of the 10.8 billion healthy life years gained. The impact of poliomyelitis vaccines on life-long disability must remain part of our intergenerational memory, lest we forget the world-changing impact of polio vaccines, and lest we forgo the opportunity to again eradicate an ancient scourge, as we did with smallpox. The closer we get the greater is the challenge, but so is the commensurate obligation to complete the task.

We secondarily aimed to evaluate vaccine impact by region and other predictors. We found that larger absolute gains occurred in regions with initially high mortality, though relative benefit has been lower in such areas, because of competing mortality risks. Vaccines promote equity by saving more lives in places where more deaths occur. The contribution of vaccines to the total reduction in infant mortality varied across regions, being higher in the WHO African and European regions, regions in which the absolute mortality burden are quite different. Correctly interpreting such findings require consideration of both the relative and absolute effects. In both Africa and Europe vaccines have contributed to a substantial proportion of the reduced infant mortality, but in Africa this has meant many more lives are saved in

absolute terms. Interestingly over the life course, EPI vaccines increase current survival probability at every age in Africa in both relative and absolute terms, but in persons born more recently the measurable impact is less than among those born in earlier decades. This is consistent with the finding that, despite the enormous contribution of vaccines for infant survival, in recent years non-vaccine interventions are saving an increasing proportion of lives. The IA2030 places vaccination squarely within the remit of Primary Health Care and the Alma Ata Declaration. Vaccine programmes often serve as the backbone for systems that provide other life-saving healthcare delivery. We plan to extend our analyses to examine the impact of sociodemographic factors on impact achievable by vaccination programmes and examine underlying explanatory differences across and within regions.

The analysis presented is a minimum conservative estimate. We accounted for external factors that reduce infectious case fatality and diminish the vaccine-attributable impact on mortality. We did not include flow-on downstream benefit of vaccine on non-communicable disease mortality (e.g. of diarrhoea on malnutrition) nor broader economic benefit or community development gains that vaccination might facilitate, since the magnitude of causal attribution is more difficult to quantify.¹⁸ We also did not include possible heterogenous effects of vaccines on epitopically non-specific immune training or other potential mechanisms. Such effects may mean we underestimated the benefits of some vaccines (e.g. BCG and measles) or did not sufficiently discount the benefits of others (e.g. DTP containing vaccines). Our methods are well suited for a more thorough treatment of possible population impacts of potential heterologous effects, but this is beyond the current scope. We cannot claim a complete analysis of the impact of immunization, since we exclude vaccines such as those against COVID-19, which is arguably yet to achieve equilibrium; influenza, which is subject to local-level variation in seasonality and immunity profiles and HPV, a vaccination programme which can anticipate a rapid increase in impact in the coming years. We did not include vaccines used for outbreaks such as cholera or Ebola. We did not include vaccines targeting disease occurring in adult life, nor those used largely in high income settings such as varicella/herpes zoster or mumps, and our counterfactual assumed a smallpox free world, meaning we did not account for the enormous benefit achieved by its eradication. The coverage assumption we made for 1974 to 1979 was a conservative choice, though sensitivity analysis on this showed little material difference (not shown) given low coverage achieved by 1980. We foresaw the risk of ‘double counting’: one individual’s death being averted for multiple diseases. Using a Bernoulli approach, we demonstrated that this limitation would have a small (0.01%) impact on our overall estimates (Supplement). We have presented global and regional findings, this delimits the geographical resolution at which conclusions may be drawn. Ongoing work to extend our models in consultation with Member States is underway. We captured the calendar year impact of vaccination over the last 50 years. Compared to birth cohort-based or year-of-vaccination approaches which require longer term projection based on broad assumptions, the calendar year based approach does not fully account for any post-2024 lifetime impact of vaccination especially for diseases that occur later in life, implying a substantial underestimate for diseases like hepatitis B.¹⁹ For the above reason, HPV, first licensed in 2006 and introduced more widely in 2010s, was excluded from the analysis due to incomparability of timeframe.

We compared our modelling against previously conducted estimates that were restricted in time and space, parsing our findings accordingly. In each case, our results fell within existing published error margins. Other estimates projecting future impact as part of IA2030 that include high coverage targets for HPV vaccine have suggested an even greater number of annualized deaths averted over the life course are achievable.^{6,11,20} This is highly dependent on achieving post-pandemic recovery and restoration of the

trajectory to IA2030 targets, achieving and maintaining universally high coverage with measles-containing vaccine (a principle aim of the Big Catchup initiative (Box 1)), and achieving universal high coverage with HPV vaccine (a “Must-Win” for Gavi, The Vaccine Alliance) – currently reaching only 21% of adolescent girls globally, still far from the coverage targets of the WHO Cervical Cancer Elimination strategy which aims to achieve HPV vaccination for 90% of all adolescent girls by 2030 – and the introductions of much anticipated malaria, RSV and other potential high impact vaccines.^{15,21}

The first post-pandemic release of the WHO and UNICEF Estimates of National Immunization Coverage (WUENIC) showed that countries that had sustained improvements in vaccine coverage in the years before the pandemic, also made more resilient recoveries from pandemic impacts on the programme.¹⁵ Our findings make the related point that the remarkable achievements of vaccination are accumulated through consistent layered data driven and operationally realistic efforts over years. We need to protect the gains of EPI, sustain coverage, target remaining gaps, and think of immunization programmes as the foundation of pandemic preparedness and of strong and resilient health systems. We are at a watershed moment in the history of infectious disease control. The large and ubiquitous gains that can be achieved have, through concerted collaborative effort, been achieved. The next 50 years of what has now become the Essential Programme of Immunization, will require improvements in targeting and reach, most especially with measles vaccines, amidst future complex realities for un- and under-vaccinated children and communities. Continuous engagement of communities in vaccine uptake is critical since hard won gains can so easily be lost. The next fifty years hold great promise, but like all promissory notes, need collective and sustained determination to deliver.

Box 1 Key milestones that increased global access to vaccines.

1974 WHO Expanded Programme on Immunization (EPI)
<ul style="list-style-type: none">The 27th World Health Assembly resolution formally established the Expanded Programme on Immunization (EPI) against diphtheria, pertussis, tetanus, measles, poliomyelitis, tuberculosis, smallpox and other diseases, where applicable, according to country-specific epidemiological situation.¹
1979 PAHO Revolving Fund
<ul style="list-style-type: none">The Pan American Sanitary Conference resolution established the working capital for the PAHO revolving fund, a mechanism facilitating pooled procurement and increasing access to vaccines, syringes, and cold-chain equipment at affordable prices.²²
1982 UNICEF Child Survival & Development Revolution
<ul style="list-style-type: none">UNICEF launched the Child Survival and Development Revolution with a focus on four measures: growth monitoring, oral rehydration therapy, promotion of breastfeeding, and immunization (GOBI).²³
1984 EPI's first standardized schedule
<ul style="list-style-type: none">EPI revised the standardized vaccination schedule building on WHO's 1961 schedule, and including vaccinations for tuberculosis (BCG vaccine at birth), diphtheria, tetanus, and pertussis and poliomyelitis vaccinations (DTP vaccine at 6,10, and 14 weeks), and measles vaccination at (9 months), and poliomyelitis (6,10, and 14 weeks).²⁴
1988-ongoing Disease eradication & elimination initiatives
<ul style="list-style-type: none">Since WHO declaration of smallpox eradication in 1980, nine eradication/elimination strategies have been established: Global Polio Eradication Initiative (1988), Maternal and Neonatal Tetanus Elimination (MNTE), Measles & Rubella Initiative (2001), the End TB strategy (2015), Global Health Sector Strategy on viral Hepatitis (2016), Global technical strategy for malaria (2016), Eliminate Yellow Fever Epidemics Strategy (2017), Global strategy to accelerate the elimination of cervical cancer (2020), and Global Roadmap to Defeat Meningitis (2020).²⁴
1990 Declaration of Manhattan, Children's Vaccine Initiative
<ul style="list-style-type: none">Children's Vaccine Initiative aimed to accelerate efforts to develop vaccines that could enhance the performance of EPI.²⁵
1999 The Strategic Advisory Group of Experts (SAGE) on Immunization
<ul style="list-style-type: none">SAGE was established by the Director-General of WHO to advise WHO on overall global policies and strategies, ranging from vaccines and technology, research and development, to delivery of immunization and its linkages with other health interventions.²⁶
2000 Global Alliance of Vaccines and Immunization (GAVI)
<ul style="list-style-type: none">Gavi, the Vaccine Alliance (previously GAVI) was established as a public-private partnership to address market failure in lower income countries and accelerate equal access to new and under-utilised vaccines.²⁷
2000s-ongoing Acceleration of new vaccine introduction
<ul style="list-style-type: none">Accelerated Development and Introduction Plans (ADIPs) for pneumococcal conjugate vaccines and rotavirus vaccines and the Hib Initiative expedited vaccine introduction in Gavi-supported countries.²⁸The pneumococcal Advance Market Commitment (AMC) contributed to scaling up PCV supply and coverage.²⁹The Meningitis Vaccine Project (MVP) led to development, testing, licensure and introduction of a meningococcal A conjugate vaccine (MenAfriVac®)³⁰Malaria Vaccine Implementation Programme (MVIP) evaluated the public health use of RTS,S malaria vaccine and informed the first WHO SAGE recommendation for a malaria vaccine.³¹
2017 Coalition for Epidemic Preparedness Innovations (CEPI)
<ul style="list-style-type: none">As a global response to Ebola, Zika, and SARS outbreaks, CEPI was launched to develop safe and effective vaccines for emerging infectious diseases to prevent future epidemics.³²
2020 Immunization Agenda 2030 (IA2030)
<ul style="list-style-type: none">Building on lessons learned from the Global Immunization Vision and Strategy (2006 – 2015) and the Global Vaccine Action Plan (2011-2020), IA2030 was endorsed by the 73rd World Health Assembly in August 2020.. IA2030 advances the commitment set by EPI and global initiatives to ensure universal access to vaccines, strengthening Primary Health Care and supporting Universal Health Coverage.³³
2020-2023 COVAX and the COVID-19 Vaccine Delivery Partnership
<ul style="list-style-type: none">COVAX was the vaccine pillar of the Access to COVID-19 Tools (ACT) Accelerator partnership, established to speed up development, production, and equitable distribution of COVID-19 tests, treatments, and vaccines, reducing COVID-19 mortality and severe diseases and restoring full societal and economic activity.³⁴

2023-2024 The Big Catch-Up

- The Big Catch-Up initiative aims to restore immunization coverage to pre-pandemic levels, catch-up children whose doses were missed consequent to the pandemic, and strengthen routine immunization systems in order to achieve 2030 targets.³⁵

2024 Essential Programme on Immunization (EPI)

- EPI has expanded to cover vaccines against 13 vaccine preventable diseases across the life-course at the global level (BCG, COVID-19, diphtheria, HepB, Hib, HPV, measles, rubella, PCV, pertussis, polio, rotavirus, tetanus) and over 17 context-specific VPDs (Cholera, dengue, Hep A, influenza, JE, malaria, meningitis, Mpox, mumps, pneumococcus, rabies, RSV, typhoid, tick-borne encephalitis, varicella, yellow fever, zoster, etc).²⁴

Box 2 Research in context.

Evidence before this study

We searched PubMed up to 13 March 2024, without date limits, using the search terms (((vaccine) AND (impact)) AND (model)) AND (countries)) AND (mortality OR morbidity). Studies were included if they used modeling approaches to estimate health impact of vaccination in multiple countries for at least one pathogen that is covered by EPI. Of 1268 results, 87 studies met the inclusion criteria. The vast majority of the studies (81 studies) focused on the impact of a single vaccine in more than one country. Six studies considered the impact of multiple vaccines with a broader geographic scope. Of these, five studies were published by the Vaccine Impact Modelling Consortium (VIMC). Two studies estimated the number of deaths and disability adjusted life years (DALYs) averted due to vaccines against ten pathogens supported by Gavi, the Vaccine Alliance in low- and middle-income countries between 2000-2030. Other three studies focused on the lasting impact of COVID-19 related disruptions on routine and non-routine immunization services, their implications of recovery and catch-up, and effect of different recovery scenarios in these countries. One study by WHO and its partners estimates the potential impact of reaching aspirational coverage targets of the Immunization Agenda 2030 (IA2030) for vaccines against 14 pathogens from 2021-2030 in 194 countries. No study existed that estimated the global impact of the EPI since its commencement.

Added value of this study

This study is the most comprehensive modeling analysis of historical vaccine impact to date. It covers 14 pathogens with a 50-year timeframe (1974 – 2024) at the global level (194 countries). Furthermore, the analysis advances the previous work by Carter et al by incorporating additional sources of coverage estimates for non-routine immunization activities, improving characterization of disease epidemiology for the static component of modelling, and capturing the impact of vaccination on reducing morbidity in addition to mortality. It contributes to the existing literature on global vaccination impact modelling by developing novel approaches to synthesizing diverse sources of model estimates, accounting for non-linearity in vaccine impact, and extrapolating model outputs to locations without such estimates.

Implications of all the evidence

Vaccination in the last half century has made the greatest contribution of any health intervention to mortality reduction and years of full health gained. Vaccine impact modeling estimates have played a critical role in informing advocacy, decision making, and monitoring and evaluation in the immunization field. The results from this study demonstrate high impact of vaccination on infant and child mortality and morbidity reduction over the last 50 years, and protective effects persist throughout the life-course. The greatest contribution being due to measles vaccination. Substantial gains in childhood survival highlight the importance of sustained efforts to protect gains from the past decades and extend further benefits to un- and under-vaccinated children and missed communities, especially with measles vaccine.

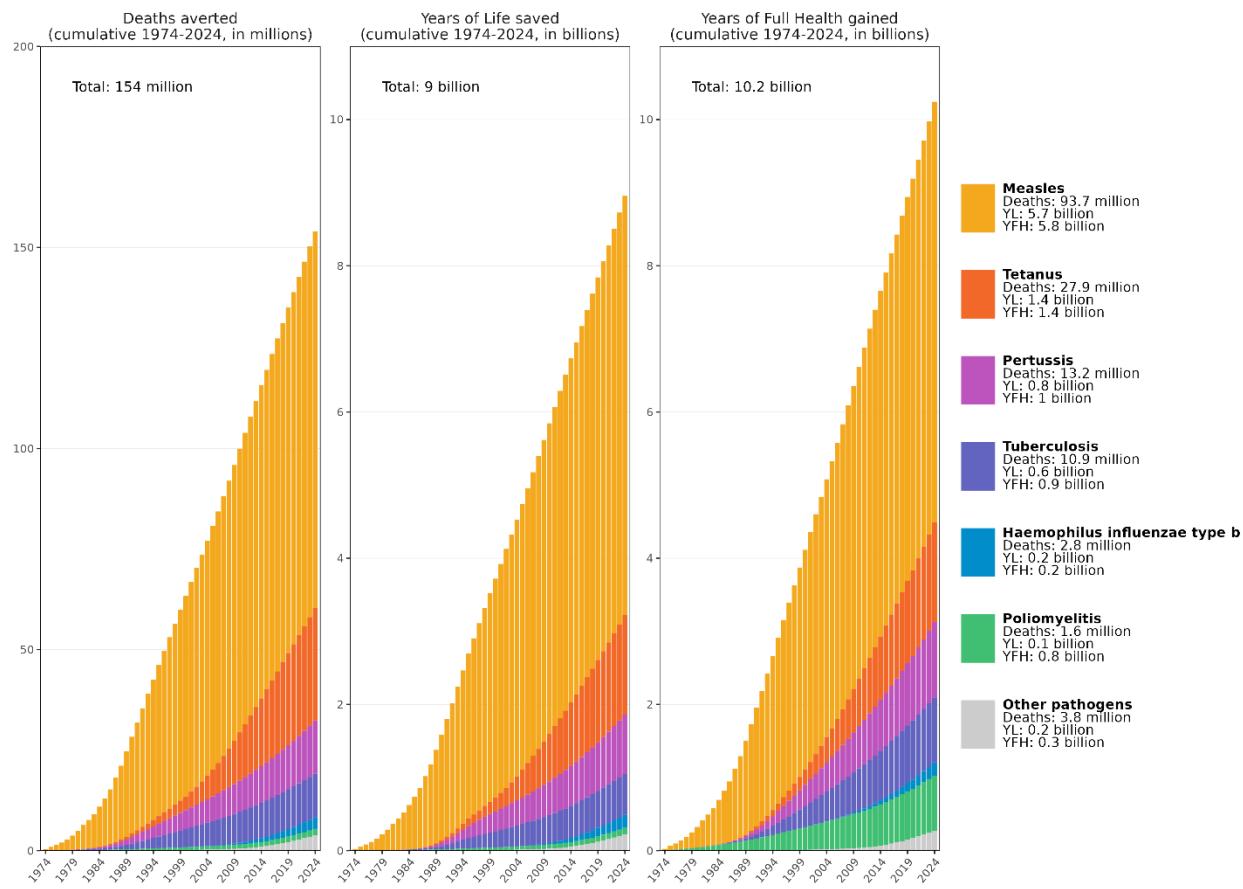


Figure 1 Deaths averted, years of life saved, years of full health gained due to vaccination.

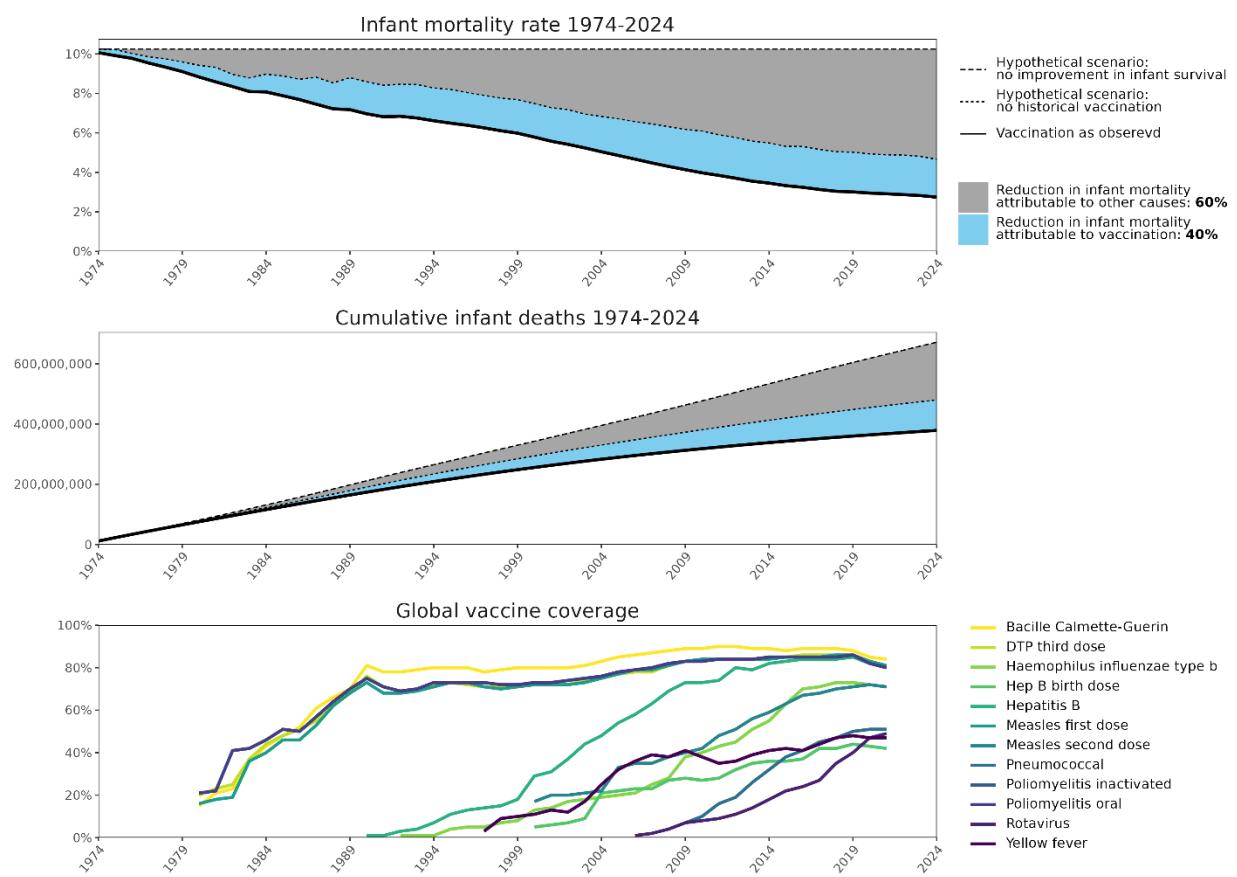


Figure 2 Infant mortality over 1974-2024, the proportional effect of vaccination to overall decreasing trends and global vaccine coverage.

Historical vaccination compared to hypothetical no vaccination

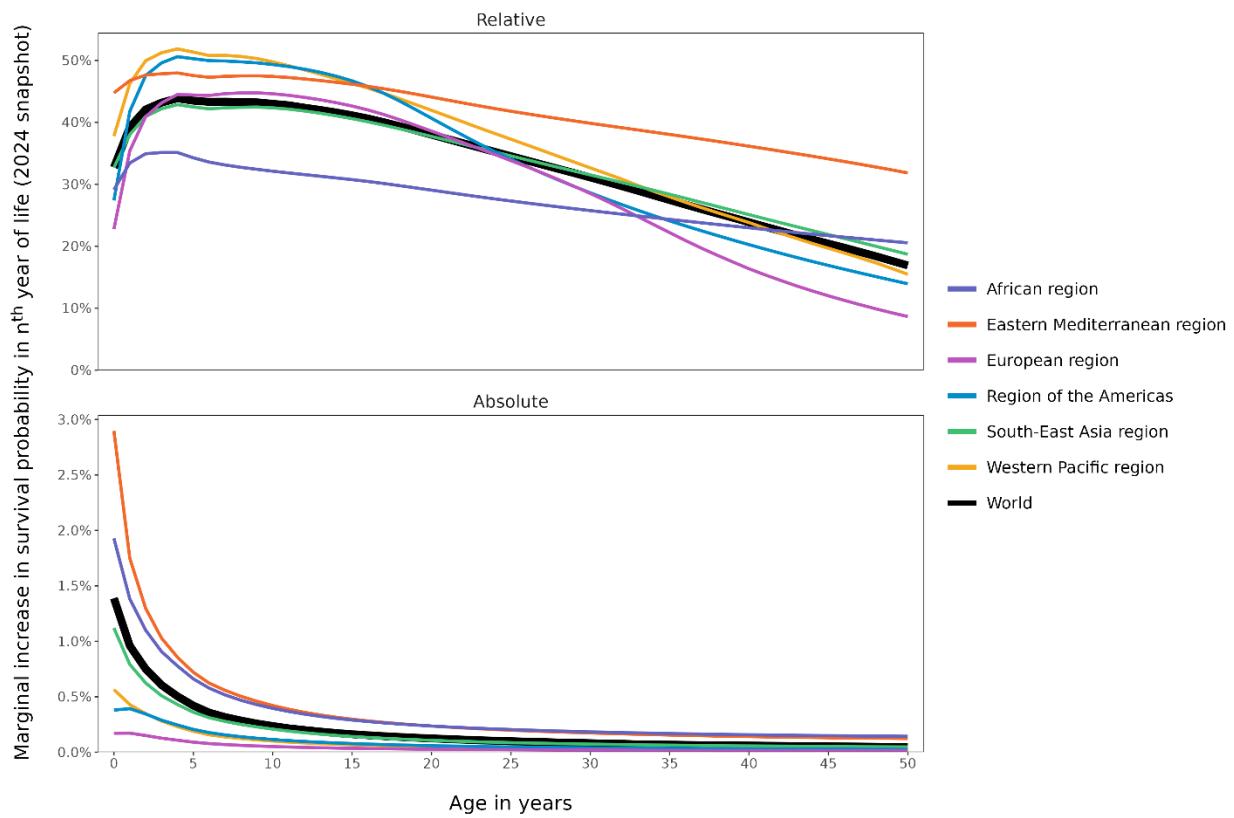


Figure 3 Marginal increase in survival probability in n^{th} year of life in 2024 compared to hypothetical scenario of no historical vaccination, by WHO Region. Relative means proportional percent change in this baseline risk. Absolute means percentage point reduction in 2024 risk of death for the next year for a person of a given age.

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Contributors' statement

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AJS, HCJ, SYS and NBZ directly accessed and verified the underlying data.

NBZ confirms that all authors have seen and approved of the final text.

Conflict of Interest Statements

CT and KAM assert that their employer, Imperial College, receives funding for the Vaccine Impact Modelling Consortium from the Bill & Melinda Gates Foundation, Gavi, the Vaccine Alliance and the Wellcome Trust. CT has received consulting fees from GSK for attending an advisory board meeting on CMV vaccines in May 2022. CT is pro bono chair of the Scientific Advisory Panel of the Meningitis Research Foundation.

HF asserts that her employer, London School of Hygiene and Tropical Medicine, receives funding for the Vaccine Impact Modelling Consortium from the Bill & Melinda Gates Foundation.

JFM asserts that his employer, University of Washington, receives grant funding from Gavi, The Vaccine Alliance and from the Bill & Melinda Gates Foundation.

KB and KMT assert that their organization Kid Risk Inc. holds a cooperative agreement with the US Centers for Disease Control and Prevention, and holds grants from the Bill & Melinda Gates Foundation.

MF asserts that his employer, Penn State University, is a subrecipient of funds from Imperial College for a grant from Gavi, The Vaccine Alliance and that he holds grants from the Bill & Melinda Gates Foundation and the US National Science Foundation.

MJ asserts that his employer, London School of Hygiene and Tropical Medicine, receives funding from the UK National Institute of Health Research, RCUK, the Bill & Melinda Gates Foundation, Gavi, the Vaccine Alliance, the Wellcome Trust, the World Health Organization, the European Commission, the US Centers for Disease Control and Prevention, the Hong Kong SAR Government, and the Task Force for Global Health.

RAH and SPS assert that their employer, University of Capetown, receives grant funding from the African Field Epidemiology Network, the US Centers for Disease Control and Prevention

RGW asserts that he receives funding from the Wellcome Trust (218261/Z/19/Z), NIH (1R01AI147321-01, G-202303-69963, R-202309-71190), EDTCP (RIA208D-2505B), UK MRC (CCF17-7779 via SET Bloomsbury), ESRC (ES/P008011/1), BMGF (INV-004737, INV-035506), and the WHO (2020/985800-0).

All other authors assert that they have no conflicts of interest.

Data sharing statement

All data sources and analytic code are available at <https://github.com/WorldHealthOrganization/epi50-vaccine-impact>

The entire repository can be downloaded here: <https://zenodo.org/records/10980462>

Supplementary Information

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Supplementary results

The following results complement those presented and discussed in the main manuscript. All results and figures can be reproduced by running the code associated with this analysis. See the *code library and reproducibility* section for details. Table S1 provides a complete disease breakdown of the results presented in Figure 1 of the main manuscript, including uncertainty bounds, which represent 95% credible intervals generated from 100 samples of Monte Carlo Markov Chain posteriors from impact function fits. See also the *uncertainty of estimates* section.

Figure S1 presents the results shown in Figure 1 of the main manuscripts disaggregated by WHO region. Figure S2 shows the equivalent disaggregated by World Bank income status. Note that for consistency of results, we selected the World Bank classification in 2024 for this figure.

Table S1 Total 1974-2024 deaths averted and years of full health gained by disease, globally and by region. All values rounded to the nearest thousand.

Pathogen	Total deaths averted 1974-2024	Total YFH gained 1974-2024
Global results		
Diphtheria	357,000 [325,000 - 387,000]	24,721,000 [23,647,000 - 25,669,000]
<i>Haemophilus influenzae</i> type B	2,845,000 [2,798,000 - 2,878,000]	180,334,000 [177,878,000 - 181,669,000]
Hepatitis B	464,000 [446,000 - 481,000]	60,293,000 [58,532,000 - 62,635,000]
Japanese encephalitis	29,000 [28,000 - 30,000]	3,310,000 [3,174,000 - 3,416,000]
Measles	93,712,000 [90,464,000 - 97,216,000]	5,754,556,000 [5,550,037,000 - 5,956,605,000]
<i>Neisseria meningitidis</i> A	2,000 [2,000 - 3,000]	187,000 [169,000 - 200,000]
Pertussis	13,173,000 [12,611,000 - 13,573,000]	1,041,506,000 [985,847,000 - 1,086,071,000]
Poliomyelitis	1,570,000 [1,570,000 - 1,570,000]	755,344,000 [755,344,000 - 755,344,000]
Rotavirus	396,000 [389,000 - 403,000]	22,306,000 [21,893,000 - 22,614,000]
Rubella	286,000 [255,000 - 313,000]	21,271,000 [19,151,000 - 23,024,000]
<i>Streptococcus pneumoniae</i>	1,628,000 [1,597,000 - 1,646,000]	100,923,000 [99,479,000 - 101,941,000]

Tetanus	27,948,000 [26,941,000 - 28,777,000]	1,368,121,000 [1,302,389,000 - 1,418,242,000]
Tuberculosis	10,874,000 [10,612,000 - 11,105,000]	876,988,000 [807,157,000 - 911,495,000]
Yellow fever	554,000 [534,000 - 567,000]	31,541,000 [30,588,000 - 32,241,000]
African region		
Diphtheria	210,000 [203,000 - 216,000]	16,017,000 [15,346,000 - 16,580,000]
<i>Haemophilus influenzae</i> type B	1,534,000 [1,518,000 - 1,546,000]	95,341,000 [94,323,000 - 96,087,000]
Hepatitis B	129,000 [126,000 - 131,000]	16,250,000 [15,907,000 - 16,511,000]
Measles	28,660,000 [27,761,000 - 29,524,000]	1,510,601,000 [1,461,081,000 - 1,555,606,000]
<i>Neisseria meningitidis</i> A	2,000 [2,000 - 3,000]	192,000 [177,000 - 203,000]
Pertussis	4,197,000 [4,031,000 - 4,338,000]	344,870,000 [325,741,000 - 360,807,000]
Poliomyelitis	151,000 [151,000 - 151,000]	73,993,000 [73,993,000 - 73,993,000]
Rotavirus	228,000 [224,000 - 232,000]	12,832,000 [12,571,000 - 13,021,000]
Rubella	45,000 [34,000 - 53,000]	3,811,000 [2,997,000 - 4,557,000]
<i>Streptococcus pneumoniae</i>	1,026,000 [1,012,000 - 1,035,000]	64,791,000 [63,840,000 - 65,333,000]
Tetanus	9,544,000 [9,161,000 - 9,874,000]	424,254,000 [400,946,000 - 438,454,000]
Tuberculosis	6,568,000 [6,368,000 - 6,752,000]	553,101,000 [486,077,000 - 587,975,000]
Yellow fever	549,000 [530,000 - 560,000]	30,899,000 [30,070,000 - 31,582,000]
Eastern Mediterranean region		
Diphtheria	30,000 [29,000 - 32,000]	2,013,000 [1,882,000 - 2,126,000]
<i>Haemophilus influenzae</i> type B	422,000 [416,000 - 424,000]	28,961,000 [28,608,000 - 29,111,000]
Hepatitis B	27,000 [25,000 - 28,000]	3,065,000 [2,949,000 - 3,154,000]

Measles	12,887,000 [12,474,000 - 13,324,000]	796,715,000 [771,696,000 - 823,346,000]
Pertussis	1,861,000 [1,776,000 - 1,918,000]	143,973,000 [135,547,000 - 150,910,000]
Poliomyelitis	119,000 [119,000 - 119,000]	57,638,000 [57,638,000 - 57,638,000]
Rotavirus	67,000 [65,000 - 68,000]	3,823,000 [3,768,000 - 3,863,000]
Rubella	34,000 [30,000 - 37,000]	2,523,000 [2,267,000 - 2,774,000]
<i>Streptococcus pneumoniae</i>	284,000 [281,000 - 287,000]	19,202,000 [18,973,000 - 19,375,000]
Tetanus	8,501,000 [8,252,000 - 8,691,000]	408,393,000 [386,467,000 - 424,055,000]
Tuberculosis	822,000 [809,000 - 833,000]	61,601,000 [59,359,000 - 63,139,000]
Yellow fever	1,000 [1,000 - 1,000]	28,000 [28,000 - 28,000]
European region		
Diphtheria	3,000 [2,000 - 4,000]	146,000 [136,000 - 155,000]
<i>Haemophilus influenzae</i> type B	36,000 [36,000 - 37,000]	2,605,000 [2,583,000 - 2,625,000]
Hepatitis B	24,000 [21,000 - 27,000]	1,230,000 [1,194,000 - 1,260,000]
Measles	6,562,000 [6,251,000 - 6,855,000]	456,491,000 [435,741,000 - 477,387,000]
Pertussis	231,000 [218,000 - 242,000]	16,511,000 [15,539,000 - 17,268,000]
Poliomyelitis	244,000 [244,000 - 244,000]	116,329,000 [116,329,000 - 116,329,000]
Rotavirus	4,000 [4,000 - 4,000]	259,000 [256,000 - 261,000]
Rubella	14,000 [13,000 - 15,000]	1,073,000 [1,004,000 - 1,132,000]
<i>Streptococcus pneumoniae</i>	31,000 [30,000 - 32,000]	903,000 [881,000 - 913,000]
Tetanus	21,000 [16,000 - 25,000]	1,120,000 [924,000 - 1,280,000]
Tuberculosis	108,000 [106,000 - 110,000]	7,967,000 [7,853,000 - 8,068,000]

Region of the Americas		
Diphtheria	7,000 [4,000 - 10,000]	237,000 [202,000 - 269,000]
<i>Haemophilus influenzae</i> type B	181,000 [170,000 - 191,000]	4,858,000 [4,785,000 - 4,897,000]
Hepatitis B	18,000 [17,000 - 20,000]	269,000 [251,000 - 284,000]
Measles	14,894,000 [14,192,000 - 15,577,000]	1,018,337,000 [966,478,000 - 1,065,230,000]
Pertussis	367,000 [337,000 - 390,000]	28,742,000 [26,436,000 - 30,684,000]
Poliomyelitis	218,000 [218,000 - 218,000]	104,804,000 [104,804,000 - 104,804,000]
Rotavirus	31,000 [31,000 - 31,000]	961,000 [952,000 - 968,000]
Rubella	30,000 [28,000 - 31,000]	2,094,000 [1,973,000 - 2,167,000]
<i>Streptococcus pneumoniae</i>	69,000 [69,000 - 70,000]	2,325,000 [2,297,000 - 2,342,000]
Tetanus	65,000 [60,000 - 70,000]	2,697,000 [2,573,000 - 2,801,000]
Tuberculosis	231,000 [229,000 - 233,000]	14,239,000 [13,826,000 - 14,582,000]
Yellow fever	8,000 [8,000 - 8,000]	276,000 [264,000 - 284,000]
South-East Asia region		
Diphtheria	84,000 [72,000 - 95,000]	5,430,000 [5,037,000 - 5,791,000]
<i>Haemophilus influenzae</i> type B	603,000 [593,000 - 604,000]	44,116,000 [43,113,000 - 44,203,000]
Hepatitis B	73,000 [70,000 - 75,000]	10,427,000 [10,110,000 - 10,666,000]
Japanese encephalitis	20,000 [19,000 - 20,000]	2,150,000 [2,109,000 - 2,187,000]
Measles	20,517,000 [19,996,000 - 21,083,000]	1,264,122,000 [1,228,062,000 - 1,299,750,000]
Pertussis	4,437,000 [4,325,000 - 4,541,000]	367,325,000 [353,176,000 - 376,984,000]
Poliomyelitis	347,000 [347,000 - 347,000]	168,577,000 [168,577,000 - 168,577,000]

Rotavirus	62,000 [61,000 - 64,000]	4,139,000 [4,076,000 - 4,208,000]
Rubella	112,000 [105,000 - 117,000]	8,410,000 [7,891,000 - 8,955,000]
<i>Streptococcus pneumoniae</i>	137,000 [134,000 - 138,000]	10,128,000 [9,869,000 - 10,204,000]
Tetanus	9,218,000 [8,911,000 - 9,498,000]	503,168,000 [482,006,000 - 518,968,000]
Tuberculosis	2,416,000 [2,396,000 - 2,434,000]	189,866,000 [188,034,000 - 191,495,000]
Western Pacific region		
Diphtheria	23,000 [12,000 - 34,000]	871,000 [756,000 - 952,000]
<i>Haemophilus influenzae</i> type B	71,000 [67,000 - 73,000]	5,203,000 [5,063,000 - 5,285,000]
Hepatitis B	203,000 [198,000 - 206,000]	27,617,000 [26,985,000 - 28,419,000]
Japanese encephalitis	10,000 [10,000 - 10,000]	972,000 [937,000 - 994,000]
Measles	10,192,000 [9,803,000 - 10,537,000]	708,290,000 [684,998,000 - 737,889,000]
Pertussis	2,058,000 [1,936,000 - 2,149,000]	143,136,000 [131,171,000 - 152,059,000]
Poliomyelitis	491,000 [491,000 - 491,000]	234,002,000 [234,002,000 - 234,002,000]
Rotavirus	4,000 [4,000 - 5,000]	338,000 [307,000 - 352,000]
Rubella	50,000 [47,000 - 53,000]	3,403,000 [3,172,000 - 3,552,000]
<i>Streptococcus pneumoniae</i>	70,000 [70,000 - 71,000]	4,049,000 [3,950,000 - 4,096,000]
Tetanus	586,000 [563,000 - 598,000]	25,040,000 [24,289,000 - 25,605,000]
Tuberculosis	756,000 [747,000 - 762,000]	51,580,000 [50,547,000 - 52,303,000]

Historical impact by WHO region and income status

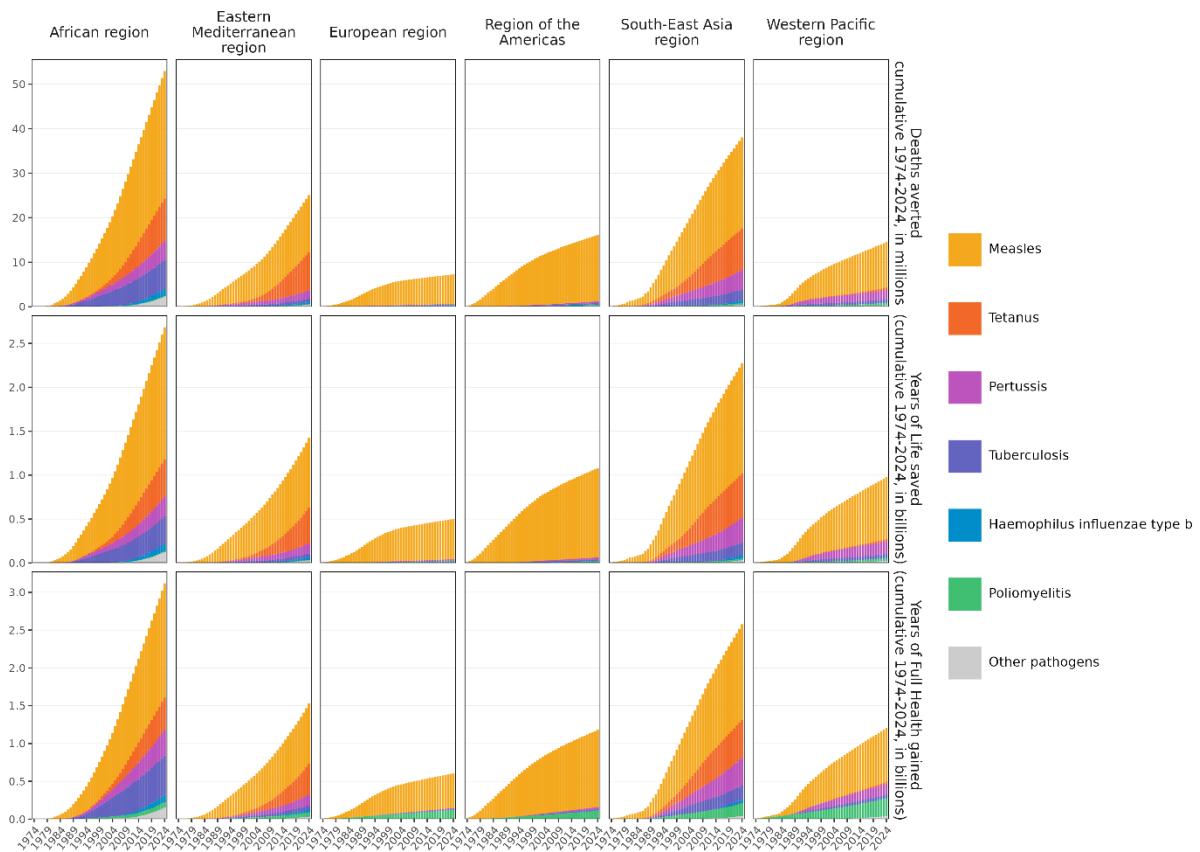


Figure S1 Deaths averted, years of life saved, years of full health gained due to vaccination by WHO region.

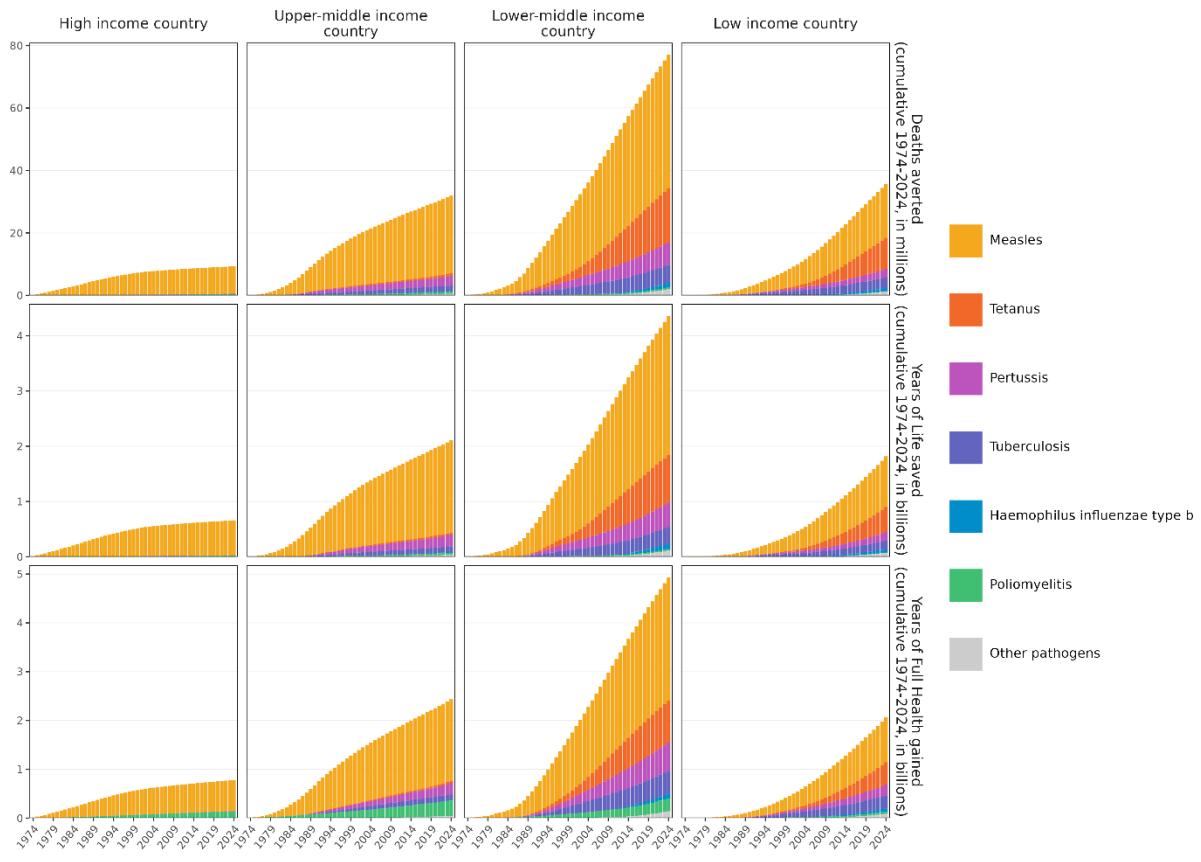


Figure S2 Deaths averted, years of life saved, years of full health gained due to vaccination by World Bank income status (as classified in 2024).

Contribution of vaccination to decrease in infant mortality by region

Figure S3 presents regional results corresponding to Figure 2 from the main manuscript. That is, the absolute all-cause decrease in infant mortality between 1974 and 2024 (yellow bars), the relative all-cause decrease (orange bars), and – crucially – the estimated contribution of vaccination to the decrease in infant mortality over the past 50 years (green bars). They grey bars represent the global totals, as presented in Figure 2 in the main manuscript. Of particular note, we found that over 50% of the considerable 50-year decrease in infant mortality in the African region is directly attributable to vaccination. That is, in the African region, vaccination has been the majority driver in increased infant survival over the past 50 years.

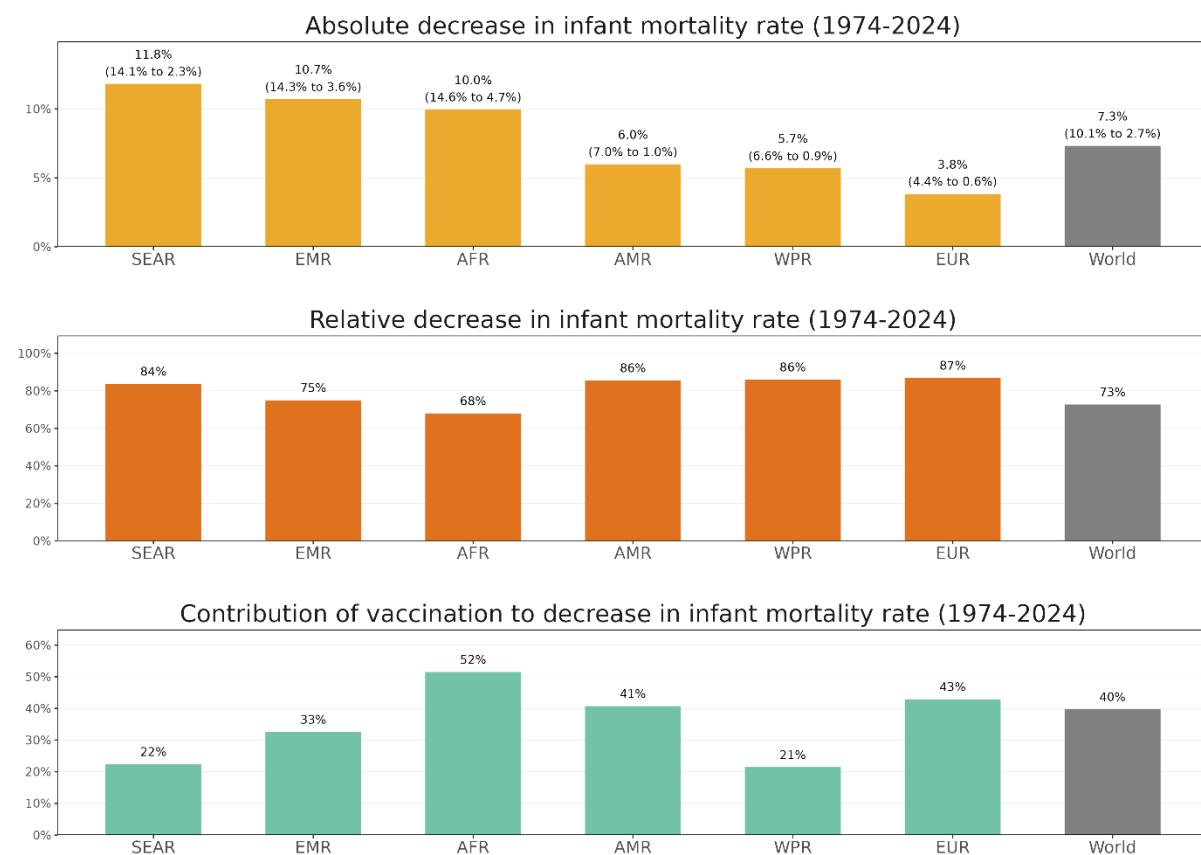


Figure S3 Absolute and relative decrease in infant mortality and contribution of vaccination to the decrease in infant mortality, by region, 1974 – 2024.

Temporal impact by disease

Figure S4 illustrates the annual number of deaths averted for each of the 14 modelled pathogens by WHO region. The corresponding results for YFH gained are presented in Figure S5. Best estimates (solid lines) are presented with uncertainty bounds, which represent 95% credible intervals generated from 100 samples of Monte Carlo Markov Chain posteriors from impact function fits. See *uncertainty of estimates* section for further details of uncertainty estimation.

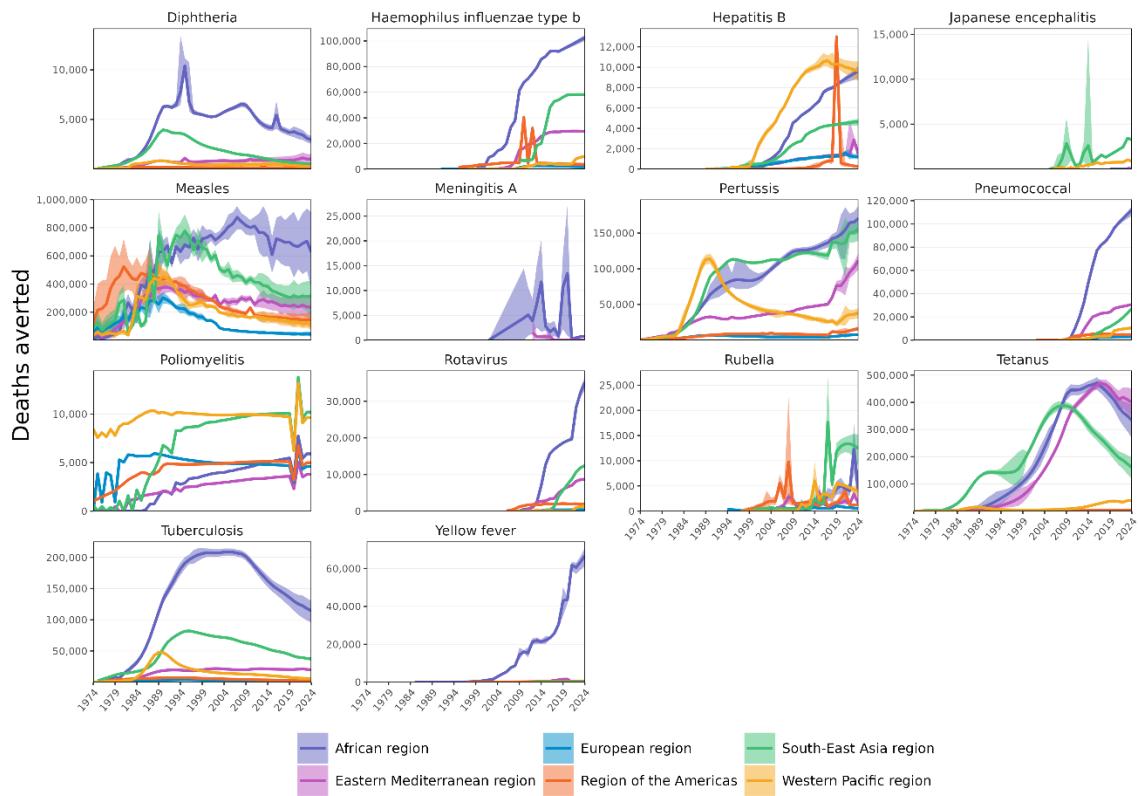


Figure S4 Estimated number of deaths averted by each pathogen, in each WHO region.

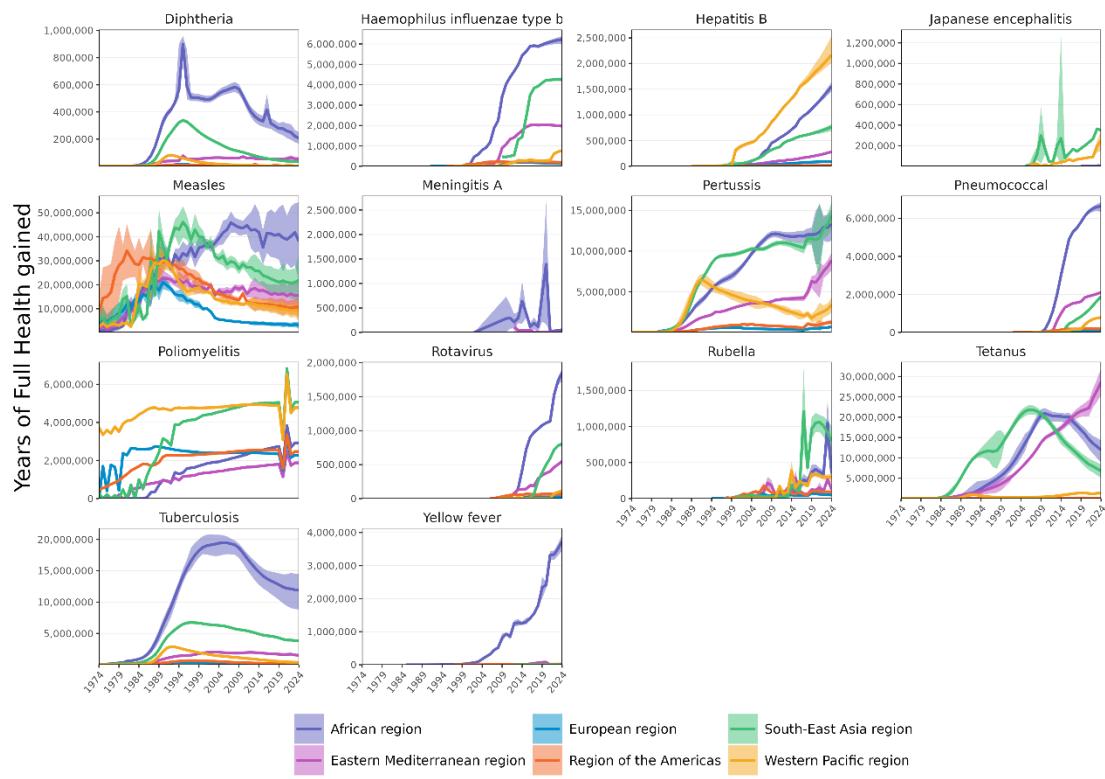


Figure S5 Estimated number of years of full health gained by vaccination against each pathogen, in each WHO region.

Supplementary methods

Categorization of vaccine impact estimation

The 14 pathogens considered in this analysis can be categorized into three mutually exclusive groups in terms of the techniques used to quantify vaccine impact (Table S2).

Table S2 Approaches to quantifying vaccine impact.

Form	Description	Pathogens
Form 1	Novel simulation of previously published transmission models.	Measles Poliomyelitis
Form 2	Using outcomes from previously published transmission models in the Vaccine Impact Modelling Consortium (VIMC) portfolio.	<i>Haemophilus influenzae</i> type B Hepatitis B Japanese encephalitis <i>Neisseria meningitidis</i> A Rotavirus Rubella <i>Streptococcus pneumoniae</i> Yellow fever
Form 3	Using previously published static modelling approach built upon disease burden estimates from the Global Burden of Disease (GBD) study.	Diphtheria Pertussis Tetanus Tuberculosis

In the case of forms 2 and 3, vaccine impact estimates were only available for a subset of the 1974-2024 analysis period. Further, in the case of form 2, vaccine impact estimates were only available for a subset of the 194 WHO Member States included in this study. Therefore, we used two separate extrapolation methods to estimate vaccination impact for the full 50-year global scope of this analysis:

- i. Geographically, for countries not included in the VIMC portfolio
- ii. Temporally, to extend to dates for which values are not explicitly calculated through the above methods

These five sources (three forms and two extrapolations) of vaccine impact are described in detail in this supplement. Figure S6 illustrates the extent to which each of these impact estimation approaches are used in this analysis, in terms of the number of people vaccinated. Table S3 presents a summary in tabular form.

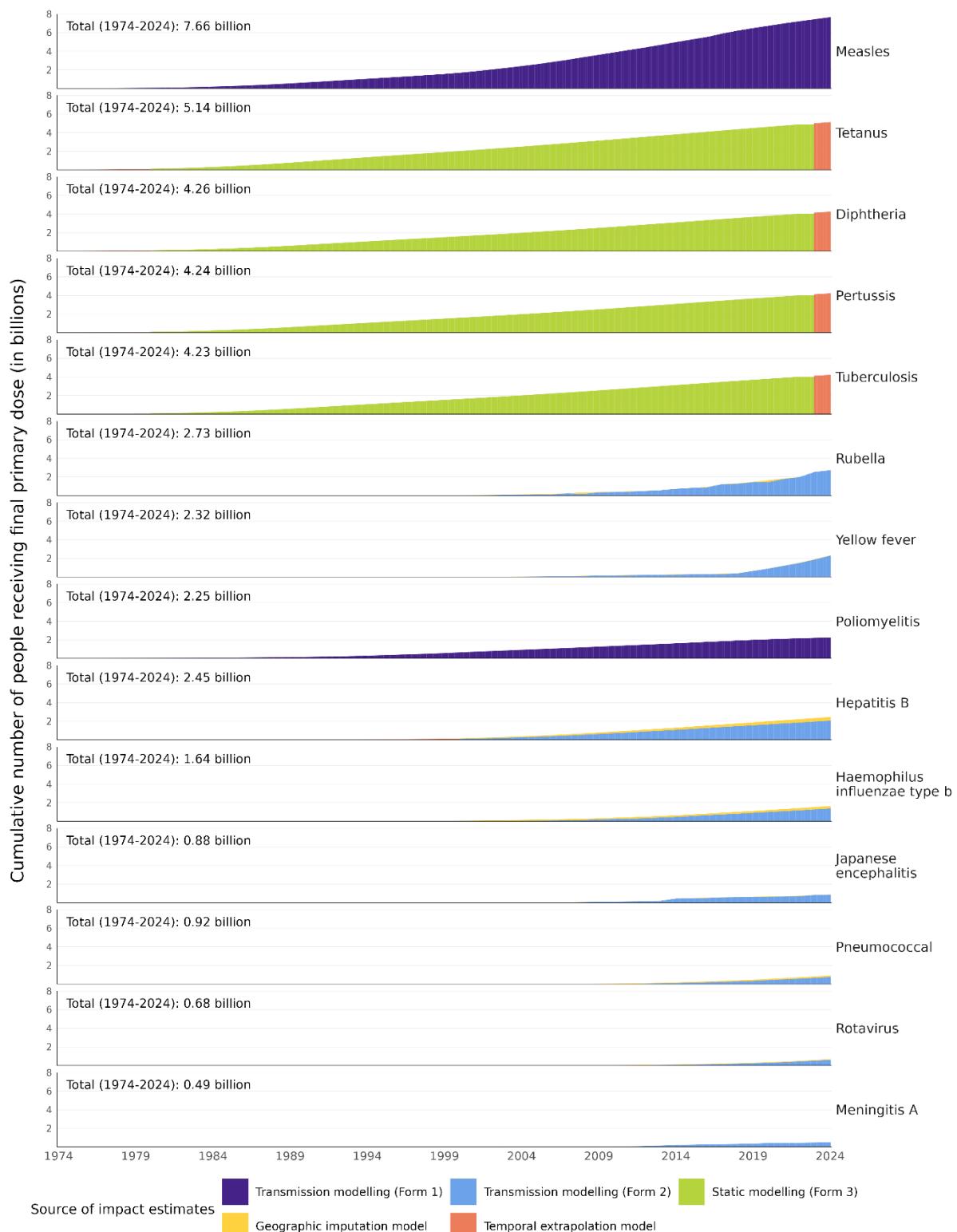


Figure S6 The relative contribution of vaccine impact estimation methods.

Table S3 Completeness of vaccine impact estimates, by form, geographical coverage and time.

Pathogen	Geographical scope	Of which requires geographical imputation	Temporal scope	Of which requires temporal extrapolation
Form 1				
Measles	194 countries	None	1974-2024	None
Poliomyelitis	194 countries	None	1974-2024	None
Form 2				
<i>Haemophilus influenzae</i> type B	194 countries	84 countries	1991-2024	1991-1999
Hepatitis B	192 countries	82 countries	1994-2024	1994-1999
Japanese encephalitis	23 countries	5 countries	2005-2024	None
<i>Neisseria meningitidis</i> A	26 countries	None	2002-2024	None
Rotavirus	152 countries	42 countries	2006-2024	None
Rubella	133 countries	23 countries	1994-2024	1994-1999
<i>Streptococcus pneumoniae</i>	178 countries	68 countries	2002-2024	None
Yellow fever	69 countries	36 countries	1998-2024	1998-1999
Form 3				
Diphtheria	194 countries	None	1974-2024	1974-1989 2020-2024
Pertussis	194 countries	None	1974-2024	1974-1989 2020-2024
Tetanus	194 countries	None	1974-2024	1974-1989 2020-2024
Tuberculosis	177 countries	None	1974-2024	1974-1989 2020-2024

Vaccination coverage assumptions

Prior to describing each vaccine impact estimation method, we first define key concepts and present assumptions regarding vaccination coverage.

Concept of disease-vaccine-activity

Broadly, where evidence exists that different delivery modalities for a given vaccine may result in differing levels of per-dose impact, we attempt to capture such heterogeneity in the analysis. We do this through the concept of disease-vaccine activity. We provide a brief description of the various disease-vaccine-activities represented in this analysis here, and give further details where relevant in the following methodology sections.

For impact estimates derived from transmission models (forms 1 and 2), we consider routine and supplementary vaccine activities separately. In order to do this, we estimate impact attributable to each disease-vaccine activity by running full factorial of scenarios where routine and supplementary activities are introduced independently and synergistically, and then take the proportional difference of impact between these scenarios.

For impact estimates derived from static models (form 3), we make an assumption regarding how routine and supplementary activities contribute to an overall vaccination coverage and then model these activities together. However, primary and booster schedules are modelled separately (where appropriate), as are vaccine doses for pregnant women. Technical details are provided in the ‘static models’ section.

A complete list of all disease-vaccine-activities considered in this analysis are provided in Table S4.

Table S4 Disease-vaccine-activities classifications.

Disease	Vaccine	Activity
Forms 1 and 2		
Hepatitis B	Hepatitis B	Routine vaccination
	Hepatitis B birth dose	Routine vaccination
<i>Haemophilus influenzae</i> type B	<i>Haemophilus influenzae</i> type B	Routine vaccination
Japanese encephalitis	Japanese encephalitis	Routine vaccination
		Supplementary Immunization Activity
Measles	Measles-containing vaccine (dose 1)	Routine vaccination

	Measles-containing vaccine (dose 2)	Routine vaccination
	Measles-containing vaccine	Supplementary Immunization Activity
<i>Neisseria meningitidis</i> A	Meningitis A	Routine vaccination
		Supplementary Immunization Activity
Poliomyelitis	Inactivated polio vaccine	Routine and supplementary activities combined
	Oral polio vaccine	
Rotavirus	Rotavirus	Routine vaccination
Rubella	Rubella-containing vaccine	Routine and supplementary activities combined
<i>Streptococcus pneumoniae</i>	Pneumococcal vaccine	Routine vaccination
Yellow fever	Yellow fever	Routine vaccination
		Supplementary Immunization Activity

Form 3

Diphtheria	Diphtheria-containing vaccine	Primary schedule
		Booster schedule
Pertussis	Whole cell pertussis-containing vaccine	Primary schedule
	Acellular pertussis-containing vaccine	Primary schedule
Tetanus	Tetanus-containing vaccine	Booster schedule
		Dose for pregnant women
		Primary schedule
Tuberculosis	Bacille Calmette-Guérin	Primary schedule

Definition of a ‘Fully Vaccinated Person’

In this analysis we work with two complementary metrics relating to vaccine uptake: 1) vaccination coverage, and 2) Fully Vaccinated Persons (FVP). Vaccination coverage is defined in the classical sense. That is, the number of people vaccinated at some given point in time in some given population divided by the size of that population, resulting in a proportion between zero and one. FVP describes the total number of living people at some given point in time in some given population that have received a ‘full’ schedule of a given vaccine.

We stress here that FVP is a quantity defined for each disease-vaccine-activity independently. That is, there is no inter-vaccine dimension to this value. The number of doses required for an individual to be classified as a FVP for each disease-vaccine-activity is given in Table S5. In general, using FVPs only to quantify vaccine impact – and dismissing the potential impact of partially vaccinated people – could be considered a conservative approach. However, this assumption serves to offset the potential over-estimate of those receiving a specific dose of a vaccine; commonly an individual is considered to have received dose n if they receive a dose at the time dose n should be given, regardless of whether they have indeed received all prior doses. As such, the recorded coverage on dose n of a given vaccine can be considered an upper bound for the true value (assuming completeness of data).

We note here that an individual may be classified as a FVP for the primary schedule of a given vaccine e.g. diphtheria, but not for the corresponding booster schedule (Table S5). Thus, an individual receiving four doses of diphtheria-containing vaccine would be considered an FVP for diphtheria primary, but not for diphtheria booster. In the case of diphtheria (and also tetanus and pertussis), whilst this lack of consideration for an effect on a partial booster series may be considered conservative, this is offset by the assumption of sterile immunity following a full schedule of booster doses (see Figure S9).

The concept of FVP is used in this study primarily as a means in which to quantify cumulative effects of vaccine distribution. Vaccination coverage – being a proportion defined annually and bounded above by one – becomes meaningless in cumulative space over numerous years and is thus poorly equipped for such a use case. Consider a simple example of two consecutive years of 80% coverage for a cohort of 100 children for a single dose vaccine. The cumulative number of FVP in the case would be 160, which has a concrete meaning in our context. There is no meaningful equivalent for the vaccine coverage metric. Cumulative FVP are central concepts in both our temporal extrapolation and geographical imputation statistical models, described below.

Table S5 Definitions of fully vaccinated people (FVP) by disease-vaccine-activity.

Disease/vaccine	Scheduled doses	Notes
Diphtheria primary	3	
Diphtheria booster	3	Six doses required in total
Hepatitis B	3	
Hepatitis B birth dose	1	

<i>Haemophilus influenzae</i> type B	3	
Japanese encephalitis	2	
Measles: MCV1	1	Full temporal and geographical scope directly modelled, so FVP redundant concept for measles
Measles: MCV2	1	
<i>Neisseria meningitidis</i> A	1	
Pertussis primary (whole cell)	3	
Pertussis primary (acellular)	3	
Pertussis booster (acellular)	3	Six doses required in total
Polio myelitis: IPV	4	Full temporal and geographical scope directly modelled, so FVP redundant concept for polio
Polio myelitis: OPV	4	
Rotavirus	3	
Rubella	2	
<i>Streptococcus pneumoniae</i>	3	
Tetanus primary	3	
Tetanus booster	3	Six doses required in total
Tetanus pregnancy	1	
Tuberculosis: BCG	1	
Yellow fever	1	

Vaccination coverage estimates

We use four sources for vaccination coverage in this analysis:

1. WHO Immunization Information System (WIISE) database (for routine activities)
2. WHO Supplementary Immunization Activity (SIA) database
3. WHO Polio Information System (POLIS)
4. VIMC coverage estimates

We note here that VIMC coverage estimates are themselves a triangulation of multiple sources including WIISE and SIA databases, explained in detail by Toor et al⁶ and illustrated in the VIMC dataviz tool.³⁶ For pathogens and countries within the scope of VIMC, we use VIMC vaccination coverage estimates. For all pathogens and/or countries outside the scope of VIMC, we calculate vaccination coverage using WIISE and SIA databases.

Figure S7 illustrates the contribution of each data source to overall coverage estimates by vaccine. The dashed line shows the total number of people (in billions) receiving a full course of vaccine within this activity. Figure S8 illustrates the age distribution of all data by source of coverage estimates. The wider, less targeted age range of SIA doses is prominent.

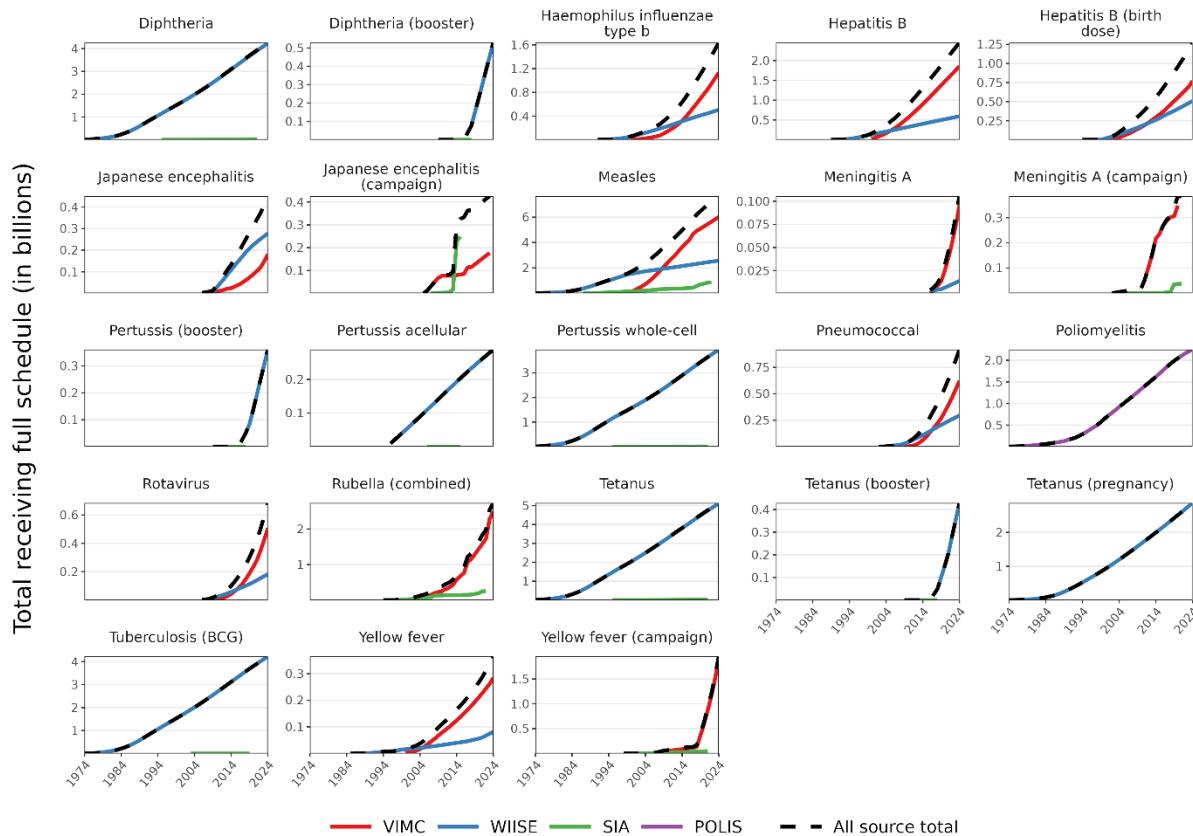


Figure S7 Vaccination coverage by data source.

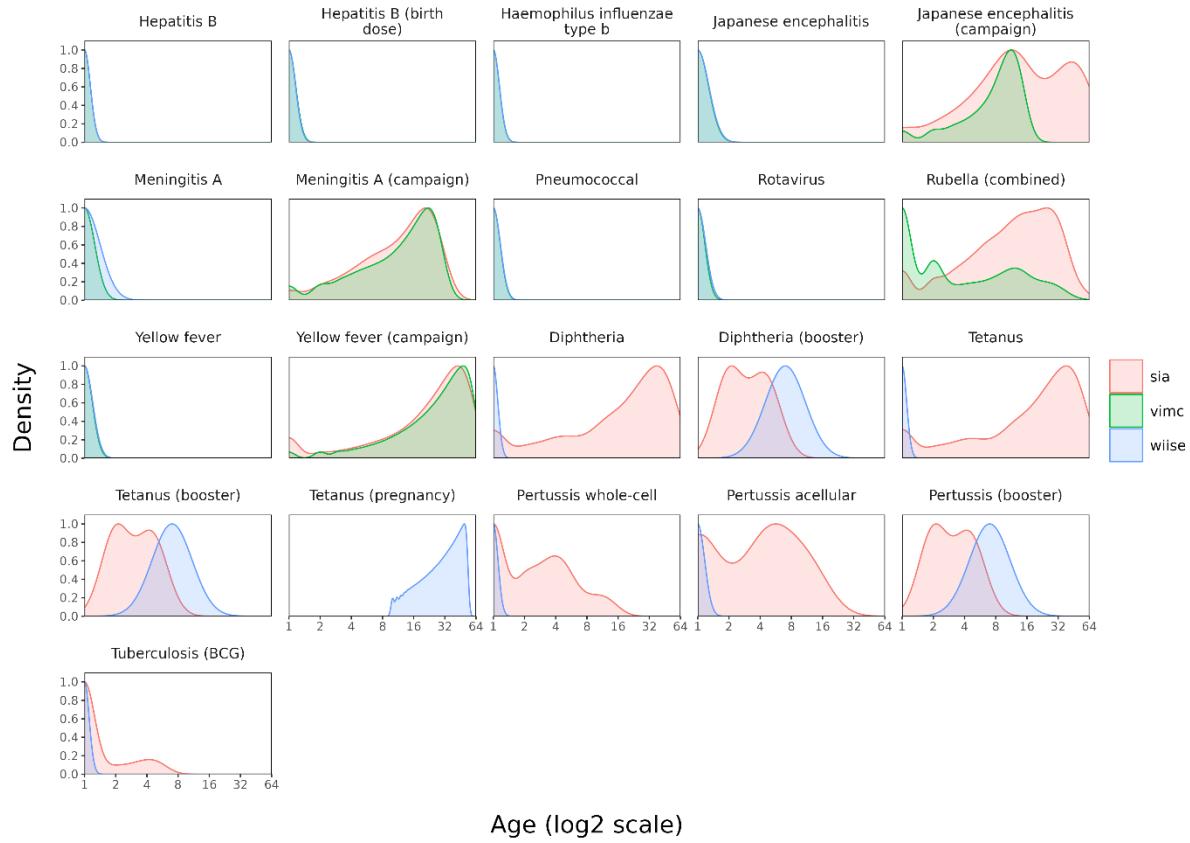


Figure S8 Age distribution of vaccination, by data source.

Relationship between routine and supplementary coverage

To derive an overall vaccination coverage estimate that incorporates both routine and supplementary coverage estimates (required for the static modelling approach (form 3)), we assume the synergistic effect follows the cumulative distribution function of the binomial distribution. That is, overall vaccination coverage, c , is defined as:

$$c_{k,y,a} = 1 - (1 - r_{k,y,a})(1 - s_{k,y,a})$$

for a given country k , year y , age group a , where r is coverage of routine vaccination, s is the coverage of supplementary activities. By using such a relationship, the underlying assumption is that supplementary doses are untargeted and therefore are proportionally likely to be received by an individual already vaccinated as they are by an unvaccinated individual. We note here that coverage remains capped at 100% by construction of this function.

Coverage assumptions over the period 1974-1979

Data is available for the period in 1980-2022 in the majority of cases, where applicable. For the 17 month post-data period we modelled (up to May 2024), we assumed vaccination coverage was constant from 2022 levels. For the period 1974-1979, we used vaccination coverage in 1980 for the pathogens available at that time (DTP, BCG, measles, and polio vaccines) along with one of two assumptions:

1. Vaccination coverage was constant over the 1974-1980 period for countries with **high-income** World Bank status in 1980.
2. Vaccination coverage linearly increased from zero over 1974-1980 period for countries with **middle- or low-income** World Bank status in 1980.

We note here that assumption 2 is a conservative approach for estimating vaccine coverage in non-high-income countries over this pre-1980 period. We also simulated the more ambitious assumption of constant coverage over 1974-1979 (set at 1980 levels) for middle- and low-income countries, resulting in an additional 0.6% deaths averted (950,000 deaths) over this period. Figure S6 illustrates the general post-1980 scale up of vaccine coverage for available vaccines.

[Switch between whole-cell and acellular pertussis vaccines](#)

There are two formulations of pertussis vaccine in extant use, whole-cell (essentially killed, wP) and acellular (subunit, aP) pertussis vaccines. Acellular pertussis vaccine is generally better tolerated with lower reactogenicity. However in the acellular formulation clinical protection wanes faster, and susceptibility returns from about 10 years from vaccination. Since young adults may be susceptible, and pregnant women with low antibody titres provide little to no transplacental transfer to newborns, young infants born to susceptible families are at risk of infection and severe disease. wP is given in many low- and middle-income countries as part of the Pentavalent vaccine (DwPT, Hib, HepB), though in March 2024 a wP hexavalent vaccine that includes injectable polio vaccine achieve prequalification. In many high-income countries an aP hexavalent formulation is in use. The Strategic Advisory Group of Experts on Immunization position policy of 2015 reiterates standing policy and states: “National programmes may therefore consider the vaccination of pregnant women with 1 dose of TdAP in the 2nd or 3rd trimester and at least 15 days before the end of pregnancy where despite high infant coverage there would still be some infant mortality”. Although this is a global recommendation, in practice aP has been introduced mainly in high income countries. To the best of our knowledge, country specific data on switch from wP to aP are not systematically available. We make the following assumptions in this analysis:

- Countries with **high-income** World Bank status in 1995 are assumed to have switched from wP to aP vaccines. From 1995 onwards, all pertussis vaccines in these countries (primary and booster schedules) are assumed to be the acellular formulation.
- Countries with **middle- or low-income** World Bank status in 1995 are assumed to be using whole-cell pertussis vaccines for the entire analytical timeframe.
- We assume all booster doses given are of acellular formulation, regardless of country income status and formulation used for primary schedule.

Transmission models (forms 1 and 2)

For measles, we used the mean of two previously published models to estimate measles impact.^{8,9,37} While these models are part of the VIMC portfolio, we ran a novel simulation with these two models using available data for historical measles coverage rate.

For polio, we collaborated with Kid Risk, Inc. who provided deaths, paralytic cases, and DALYs averted with the number of doses for OPV and IPV, building on a prior retrospective model that characterised the reduction in poliovirus cases due to historical poliovirus immunization through 2021 compared to the counterfactual scenario of no poliovirus vaccines.¹⁰ The current analysis extends the model to account for poliovirus importation events and OPV and IPV vaccine delivery that occurred through mid 2024. For this analysis, the counterfactual scenario assumes no seasonality, but otherwise applies the same assumptions as previously reported.¹⁰ To characterise mortality, the results conservatively assume fatality rates for paralytic polio cases based on the observed rates reported to the WHO and curated in WHO's polio information system POLIS. For the no vaccine scenario, this assumption assumes the development of sufficient global resources for respiratory support to maintain the observed vaccine scenario fatality rate during outbreak surges, which implies maintenance and expansion of polio wards in hospitals with iron lungs. In the absence of this capacity, greater fatality rates could have occurred during outbreaks than considered for the counterfactual scenario.

For eight pathogens, we used previously reported outcomes from 17 transmission models reporting to the Vaccine Impact Modelling Consortium (VIMC) (Table S6). The version of VIMC modelling estimates used in this study are associated with the identification number: 20240318-082736-d6c0daf9, as used in Toor et al.⁶ These VIMC estimates are based upon short-term default coverage extrapolations from 2021 to mid-2024.

Table S6 Models contributed by the Vaccine Impact Modelling Consortium (VIMC).

Pathogen	Model name/institution	Model details
Hepatitis B	PRoGReSs, Centre for Disease Analysis Foundation ³⁸	A dynamic, deterministic disease burden model of HBV infection that calculates the annual HBV prevalence, incidence, and mortality by stage of liver disease, serologic status (low-viral load, high-viral load, on-treatment), sex, and age.
	Imperial College London ^{39,40}	A dynamic, population-level, deterministic, transmission model structured by age, sex, and region. The model contains acute (Severe Acute and Non-severe Acute) and chronic (Immune Tolerant, Immune Reactive, Asymptomatic Carrier, Chronic Hepatitis B, Compensated Cirrhosis, Decompensated Cirrhosis and Liver Cancer) mutually exclusive disease states.
	Goldstein ⁴¹	A static deterministic model that examines the mortality outcomes due to hepatitis B virus (HBV) infection, including deaths of fulminant hepatitis, and deaths of liver cirrhosis

		and hepatocellular carcinoma as results of chronic hepatitis B.
<i>Haemophilus influenzae type B</i>	The Lives Saved Tool (LiST), Johns Hopkins University ⁴²	A static, deterministic, linear mathematical model for estimating the health impact of changes in coverage of 80 health interventions, including vaccines. LiST generates estimates of Hib pneumonia and meningitis cases and deaths averted by the coverage scale-up of Hib vaccine.
	Universal Vaccine Decision Support model (UNIVAC), LSHTM ⁴³	A static cohort model with a finely disaggregated age structure (weeks of age <5 years, single years of age 5–99 years) that calculates impact (% reduction in cases, clinic visits, hospitalisations, lifelong sequelae, deaths and DALYs). UNIVAC included estimates for non-severe Hib pneumonia, severe Hib pneumonia, Hib meningitis and Hib non-pneumonia/non-meningitis in children aged <5 years.
Japanese encephalitis	National University of Singapore ⁴⁴	A dynamic, deterministic model is a basic catalytic model for the force of infection. A 'bottom up' approach was used to generate deaths and cases i.e. from infection rates applying parameters governing the proportion of infections that are symptomatic and the proportion that die (case fatality ratio).
	University of Notre Dame ^{45,46}	A static, stochastic model of Japanese encephalitis virus transmission with a constant force of infection to calculate infections, cases and deaths.
Measles*	DynaMICE, London School of Hygiene and Tropical Medicine (LSHTM) ^{9,37}	A dynamic, age-structured compartmental transmission model.
	Pennsylvania State University (PSU) ⁸	A dynamic, age-structured, discrete time-step, annual SIR model which estimates the aggregate number of cases over one-year time steps.
*While LSHTM and PSU models are part of VIMC portfolio, we ran a novel simulation with these two models using available data for historical measles coverage rate for this analysis		
<i>Neisseria meningitidis A</i>	University of Cambridge ⁴⁷	A dynamic, compartmental transmission model of Neisseria meningitidis group A carriage and disease. Model developed for MenAfriVac.
	Kaiser Permanente Washington ⁴⁸	A dynamic, stochastic, age-structured, compartmental transmission model of NmA.
<i>Streptococcus pneumoniae</i>	The Lives Saved Tool (LiST), Johns Hopkins University ⁴²	LiST generates estimates of pneumococcal pneumonia and meningitis cases and deaths averted by the coverage scale-up of PCV.
	Universal Vaccine Decision Support model (UNIVAC), LSHTM ⁴³	UNIVAC included estimates for non-severe Pneumococcal pneumonia, severe Pneumococcal pneumonia, Pneumococcal meningitis, severe Pneumococcal non-pneumonia/non-meningitis in children aged <5 years, and cases of Pneumococcal acute otitis media.

Rotavirus	Emory University ⁴⁹	A dynamic, deterministic, age-structured compartmental transmission model that simulates rotavirus transmission and estimates disease incidence/burden in a given country.
	The Lives Saved Tool (LiST), Johns Hopkins University ⁴²	LiST generates estimates of rotavirus diarrhoea cases and deaths averted by the coverage scale-up of rotavirus vaccine.
	Universal Vaccine Decision Support model (UNIVAC), LSHTM ⁴³	UNIVAC includes estimates of rotavirus deaths <5 years and cases (non-severe and severe)
Rubella	Johns Hopkins University ⁵⁰	A dynamic, discrete-time, stochastic, age-structured, compartmental transmission model. A 'bottom up' approach was used to calculate CRS cases, and deaths, from modeled output.
	Public Health England ^{51,52}	A dynamic, deterministic, age and sex-structured, compartmental, transmission model that calculates congenital rubella syndrome (CRS) cases and deaths.
Yellow Fever	Imperial College London ^{53,54}	A static force of infection (FOI) epidemiological model that uses published values of the proportion of infections which are severe and of the CFR to calculate the burden of disease.
	University of Notre Dame ^{53,55}	A static transmission model that assumes a constant force of infection for each endemic country. Scaled estimates were used to project the annual number of infections, and this quantity is multiplied by probabilities of disease and death.

More detailed model descriptions are available in VIMC's second consortium-wide paper.⁶

Acknowledgement: Vaccine Impact Modelling Consortium

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Static models (form 3)

Static models were developed to estimate vaccine impact for four diseases: diphtheria, tetanus, pertussis, and tuberculosis. A more basic formulation of these static models has been previously published.¹¹ Several enhancements to these static models have since been incorporated, and thus we fully derive these models here. The 2021 Global Burden of Disease estimates (GBD 2021) for four diseases were used for this analysis.⁵⁶⁻⁵⁹ Broadly, vaccine impact – in terms of deaths averted and DALYs averted (or equivalently YHL gained) – is derived for each disease-vaccine-activity using three key quantities:

1. Disease-attributable mortality and morbidity as estimated by GBD¹²
2. Vaccine efficacy profiles
3. Vaccination coverage

Effective vaccine coverage

The last two quantities are combined to result in an estimate of ‘effective vaccine coverage’, which is then used to estimate disease-attributable mortality and morbidity in a hypothetical scenario of no historical vaccination. Vaccine impact is then calculated as the difference between the outcomes in this hypothetical ‘no vaccine’ scenario and the GBD burden estimates.

In this context, vaccine efficacy is interpreted as the reduction in probability of disease or death. Where appropriate, distinct vaccine efficacy profiles are derived for the primary schedule and any subsequent booster schedule, allowing for unique initial efficacy and waning immunity characterisations. For vaccines for pregnant women, a distinct efficacy profile is used for the effect on the newborn. In the case of pertussis, we derive distinct efficacy profiles for whole-cell and acellular vaccines.

The data used to inform each vaccine efficacy profile is detailed in Table S7. In most cases, data refer to initial efficacy (efficacy in the year of vaccination) or half-life (number of years taken for efficacy to decay to half of initial efficacy). Upon visual inspection of the data available, and following expert consultation, a functional form was assumed for each vaccine efficacy profile (Table S7). Generally, exponential decay functions were assumed for primary schedule and constant functions assumed for booster schedules, with the interpretation being that once an individual has received all doses in the primary and booster schedules (six doses for DTaP) immunity no longer decays. The BCG vaccine for TB was a special case, in which we assumed a sigmoidal decay. We fitted the parameters of the designated functional form using an Adaptive Stochastic Descent optimisation algorithm.⁶⁰ The optimisation process was repeated ten times for each disease-vaccine-activity using different initialisations to maximize the probability that the global optimum was identified. Table S7 states the fitted parameters for each pre-defined disease-vaccine-activity functional form. Figure S9 illustrates the resulting vaccine efficacy profiles along with the data used.

Table S7 Details of functional form used to represent vaccine efficacy – in terms of reduction in death or disease – for each statically modelled disease.

Disease	Vaccine	Activity	Efficacy data used [efficacy, years from vaccination]	Assumed functional form	Fitted parameters
Diphtheria	Diphtheria-containing vaccine	Primary schedule	<i>Initial efficacy:</i> $[0.87, 0]^{61}$ $[0.95, 0]^{62}$ <i>Half-life (of 87% initial efficacy):</i> $[0.44, 19]^{63}$ $[0.44, 27]^{64}$ <i>Half-life (of 95% initial efficacy):</i> $[0.48, 19]^{63}$ $[0.48, 27]^{64}$	<i>Exponential decay</i> $y = ae^{-bt}$	$a = 0.90$ $b = 0.29$
		Booster schedule	<i>Booster efficacy:</i> $[0.95, 0]^{65,66}$	<i>Constant</i> $y = a$	$a = 0.95$
Pertussis	Whole cell pertussis-containing vaccine	Primary schedule	<i>Initial efficacy:</i> $[0.94, 0]^{67}$ $[0.92, 0]^{68}$ $[0.99, 0]^{69}$ <i>15 year half life (expert opinion):</i> $[0.46, 15]$	<i>Exponential decay</i> $y = ae^{-bt}$	$a = 0.95$ $b = 0.046$
	Acellular pertussis-containing vaccine	Primary schedule	<i>Initial efficacy:</i> $[0.84, 0]^{67}$ $[0.80, 0]^{70}$ <i>75% efficacy drops 35% after 5 years:</i> $[0.49, 5]^{71}$ <i>Vaccine efficacy of 41% after 8 years:</i> $[0.41, 8]^{70}$	<i>Exponential decay</i> $y = ae^{-bt}$	$a = 0.82$ $b = 0.093$
		Booster schedule	<i>Efficacy similar to primary series (expert opinion):</i> $[0.80, 0]^{70}$	<i>Constant</i> $y = a$	$a = 0.80$

Tetanus	Tetanus-containing vaccine	Primary schedule	<i>Initial efficacy:</i> [0.95, 0] ⁷² <i>Half-life:</i> [0.48, 11] ⁶³ [0.48, 14] ⁶⁴	<i>Exponential decay</i> $y = ae^{-bt}$	$a = 0.95$ $b = 0.054$
		Booster schedule	<i>Booster efficacy:</i> [0.95, 0] ⁷³	<i>Constant</i> $y = a$	$a = 0.95$
		Pregnancy schedule	<i>Maternal immunity among neonates:</i> [0.45, 0] ⁷⁴ [0.65, 0] ⁷⁵ [0.94, 0] ⁷⁶	<i>Step function</i> $y = \begin{cases} a, & t < 1 \\ 0, & t \geq 1 \end{cases}$	$a = 0.68$
Tuberculosis	Bacille Calmette-Guerin	Primary schedule	<i>Initial efficacy:</i> [0.66, 0] ⁷⁷ [0.66, 15] ⁷⁸ <i>Half-life of 20 years (expert opinion):</i> [0.33, 20] [0.10, 40]	<i>Sigmoidal decay</i> $y = a + \frac{b - a}{1 + (t/c)^{-d}}$	$a = 0.68$ $b = 0.097$ $c = 19.3$ $d = 10.0$

Maternal immunity assumptions

For vaccines delivered during pregnancy, we assume the effect on the pregnant women is equivalent to a booster dose. For the effect on the newborn, we use a distinct vaccine efficacy profile (Table S7 and Figure S9). The efficacy in the newborn is assumed to remain during the neo-natal phase (first 4 weeks of life) and then decay to zero. In effect, only neonates receive any benefit of maternal immunity, with no residual effect for post-neonatal infants.

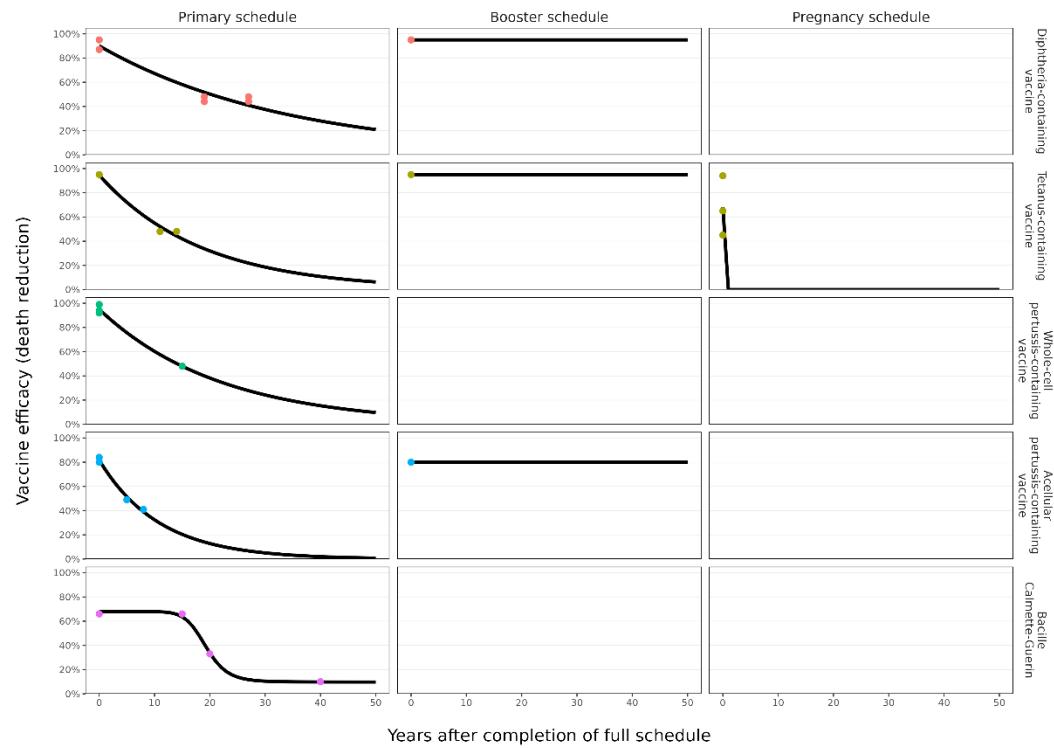


Figure S9 Derived assumptions of effective protection of diphtheria, tetanus, pertussis and BCG vaccines against death, throughout the life course. Note that the efficacy associated with 'pregnancy schedule' is the effect on newborns, which decays to zero effect after the neonate phase of 28 days.

Model formulation

For each disease-vaccine-activity x , we derive effective vaccine coverage e in each country k for each year y and single-year age group a as:

$$e_{x,k}(y, a) = 1 - \prod_{i=y-a}^y \left(1 - c_{x,k}(i, y-i+a) \cdot \varepsilon_x(y-i)\right)$$

Where $c_{x,k}(y, a)$ is vaccine coverage in year y for age a , and $\varepsilon_x(t)$ is vaccine efficacy t years after vaccination for the specific disease-vaccine-activity. Note that commonly only one term in this equation is non-trivial, given that routine vaccinations (which make up the vast majority of doses in the case of diphtheria, pertussis, tetanus, and tuberculosis) are generally targeted at a specific age group – commonly infants – each year.

It remains to aggregate effective vaccine coverage for a given disease. First, we aggregate effective vaccine coverage for each vaccine v that targets disease d , noting that two distinct vaccines are modelled for pertussis (whole cell and acellular). This process involves weighting between primary and booster schedule effect such that those receiving boosters are not double counted. Let disease-vaccine-activity $x = p_v$ represent the primary schedule for vaccine v , and $x = b_v$ the booster schedule, then we define:

$$e_{v,k}(y, a) = e_{p_v,k}(y, a) \left[1 - \frac{c_{b_v,k}(y, a)}{c_{p_v,k}(y, a)}\right] + e_{b_v,k}(y, a)$$

That is, effective coverage in the primary schedule is reduced by the proportion of primary FVP that are not booster FVP. We then aggregate up to effective vaccine coverage for disease d by considering the effects of each relevant vaccine to be additive. That is:

$$e_{d,k}(y, a) = \sum_v e_{v,k}(y, a)$$

Figure S10 illustrates global effective vaccine coverage of each vaccine in each year between 1974 and for age groups 0 to 50 years. Figure S11 represents the corresponding effective vaccine coverage summarised at disease level.

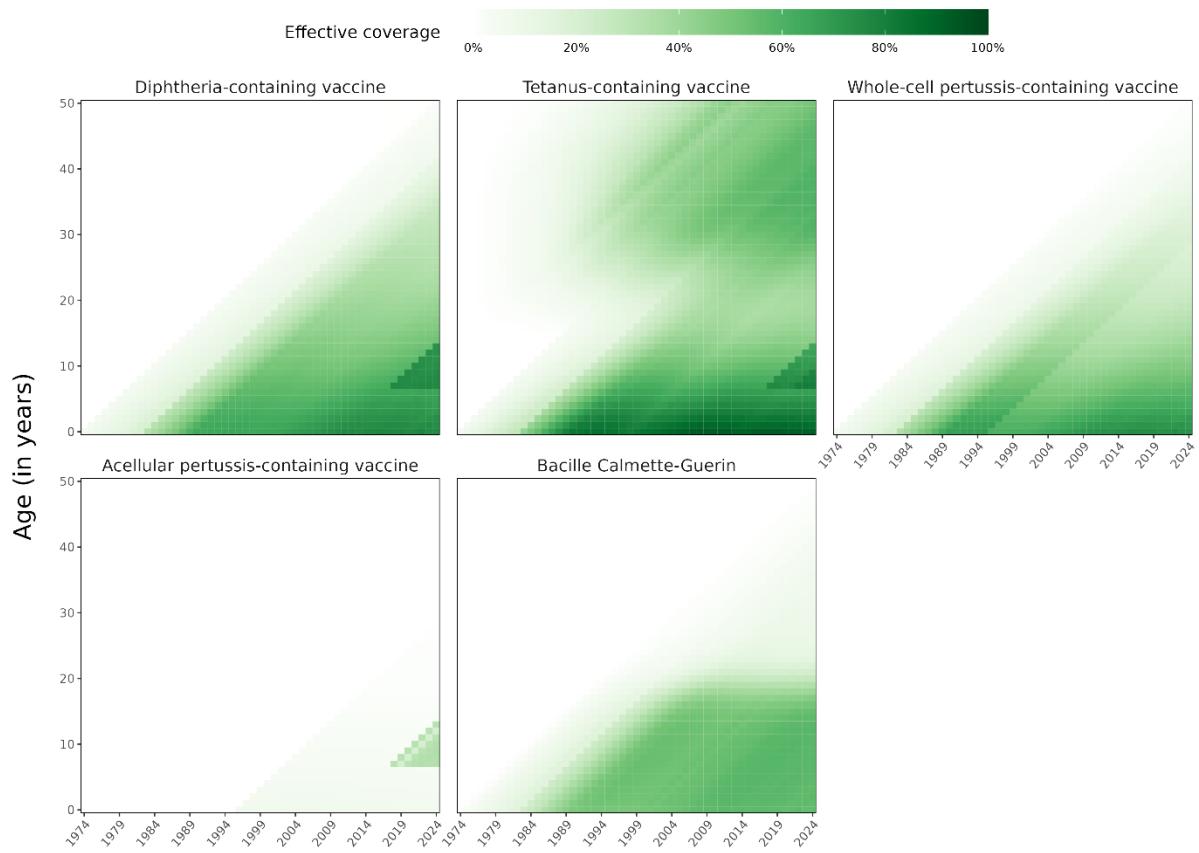


Figure S10 Effective vaccine coverage for each vaccine.

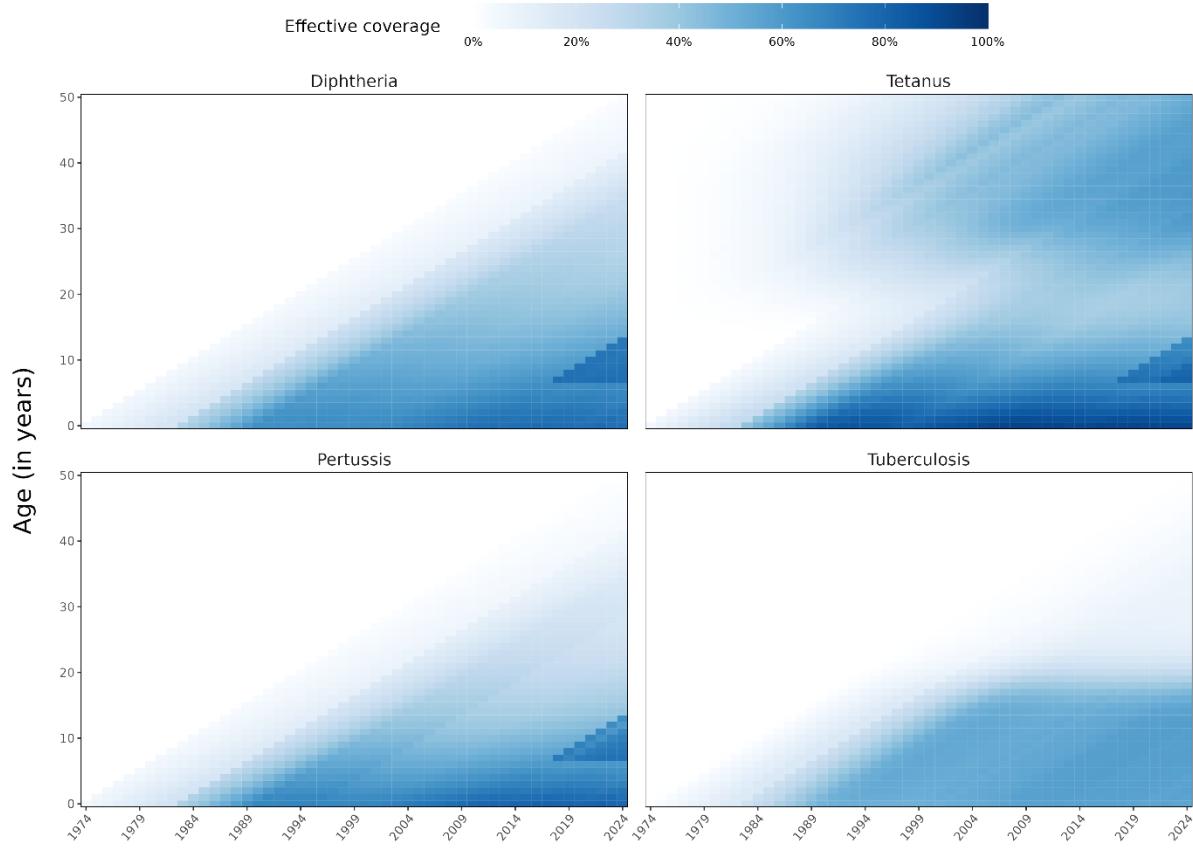


Figure S11 Effective vaccine coverage aggregated for each disease.

It remains to calculate disease burden averted using the disease-specific effective vaccine coverage values illustrated in Figure S10 in conjunction with disease-attributable mortality or mortality as estimated by GBD.¹² Disease-attributable mortality and morbidity estimates, as reported by GBD, are presented at the aggregated global level with broad age stratifications in Figure S12. Here we derive the model for estimating deaths averted. The model for DALYs averted / LFH gained is equivalent.

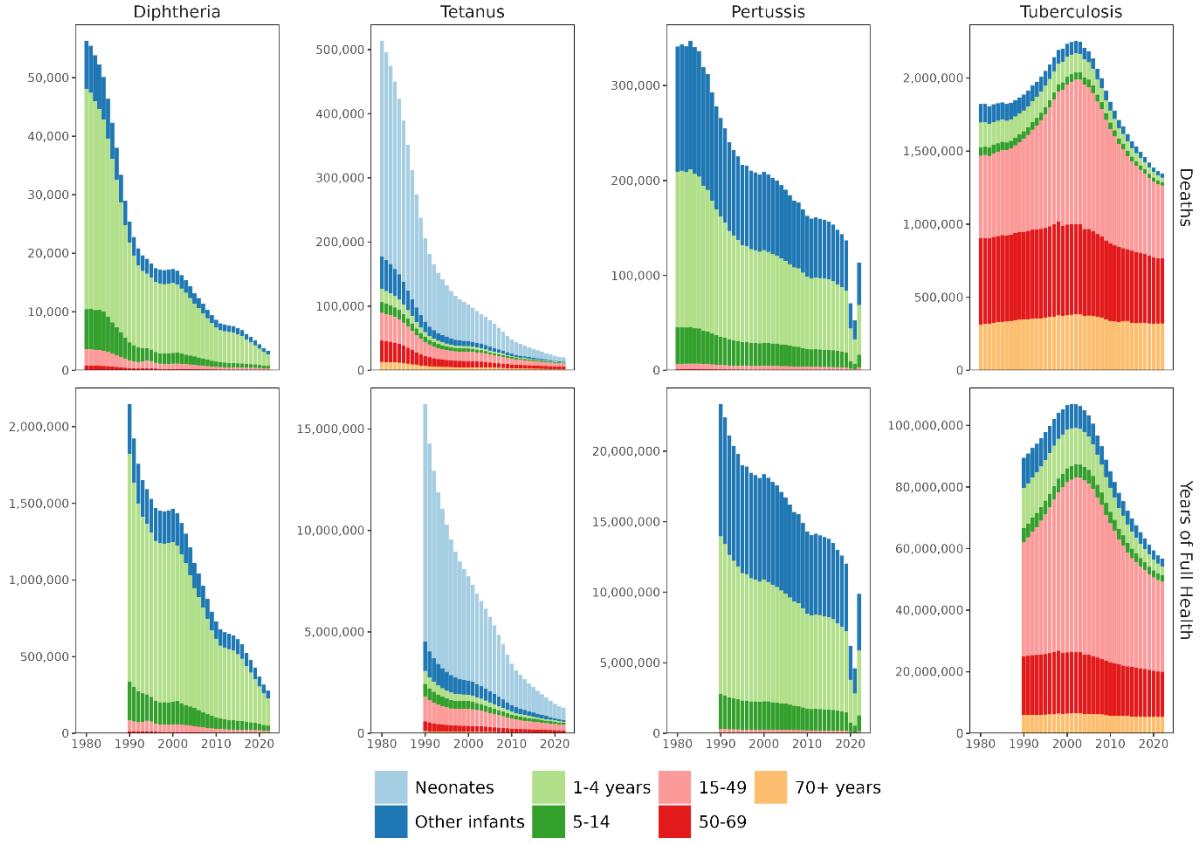


Figure S12 Estimates of the global burden of diphtheria, tetanus, pertussis and TB in terms of deaths and disability-adjusted life years, by age and over time (Source: Global Burden of Disease study).

Let $d_k(y, a)$ be the number of disease-specific deaths in country k , year y , and age a as reported by GBD. We then estimate the equivalent number of disease-specific deaths in the absence of vaccination $w_{d,k}$ using:

$$w_{d,k}(y, a) = \frac{d_k(y, a)}{1 - e_{d,k}(y, a)}$$

We then calculate the number of deaths averted $a_{d,k}$ as:

$$\begin{aligned} a_{d,k}(y, a) &= w_{d,k}(y, a) - d_k(y, a) \\ &= d_k(y, a) \left(\frac{1}{1 - e_{d,k}(y, a)} - 1 \right) \end{aligned}$$

The total number of vaccine-attributable deaths averted for disease d in country k , denoted $A_{d,k}$, is then given by:

$$A_{d,k} = \sum_{y=1974}^{2024} \sum_{a=0}^{100} a_{d,k}(y, a)$$

Global, age-aggregated outcomes of deaths averted for each of the four diseases is presented in Figure S13 alongside GBD-derived estimates of disease-specific deaths. Note that the blue curves represent total values presented in Figure S12. The corresponding results for DALYs averted / YFH gained is presented in Figure S14. We here remark on several observations from these results. We find a substantial effect of vaccination on tetanus mortality. The historical age profile of tetanus – as estimated by GBD – reports a substantial burden of mortality and morbidity in neonatal infants (those under 4 weeks of age) (Figure S12). This age-structure of disease burden coupled with increasing vaccine coverage among pregnant women and a moderate protective effect of maternal immunity on neonates (Figures S9 and S11) results in an expected large impact. Conversely, the effect of BCG on tuberculous mortality is relatively modest. The age profile of tuberculous mortality burden over the past 50 years is much more heavily concentrated in older adults, with over half of deaths in those above 50 years of age (Figure S12). This age-structure, coupled with a vaccine that has a modest initial vaccine efficacy that has decayed to low levels after approximately 20 years (Figure S9) leads to a relatively modest expected impact of vaccination on disease-specific deaths. These two prominent outcomes lead to two conclusions relevant for the future: 1) maternal vaccination against tetanus has great potential to continue saving lives, and 2) innovations in tuberculosis vaccine development for vaccines efficacious in adolescents and adults have considerable scope to prevent future public health burden. We also find a relatively low absolute effect of vaccine impact on averting diphtheria-related deaths. This finding is driven by a low estimated burden of disease in the vaccination era (Figure S12), and can be considered a conservative estimate that is likely an artefact of the relatively simplistic static modelling approach taken.

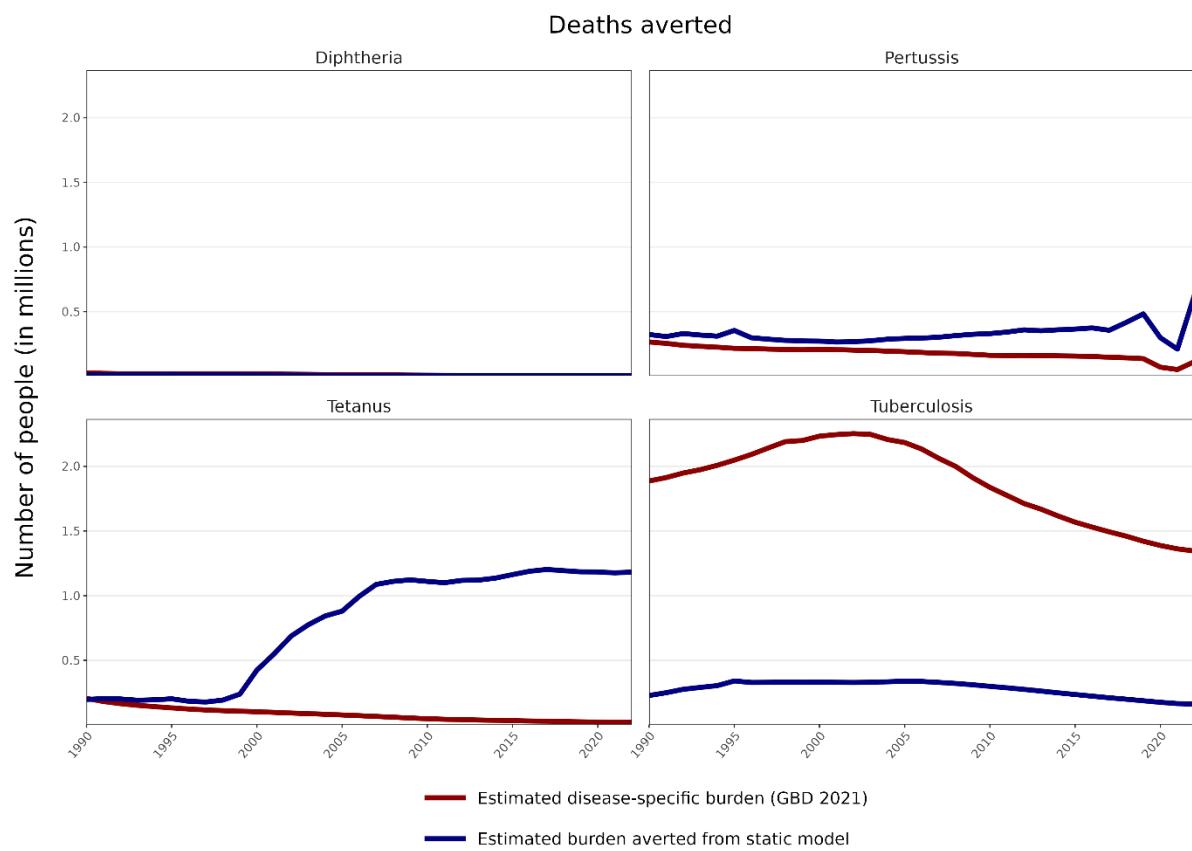


Figure S13 Estimated disease-specific deaths and deaths averted through vaccination.

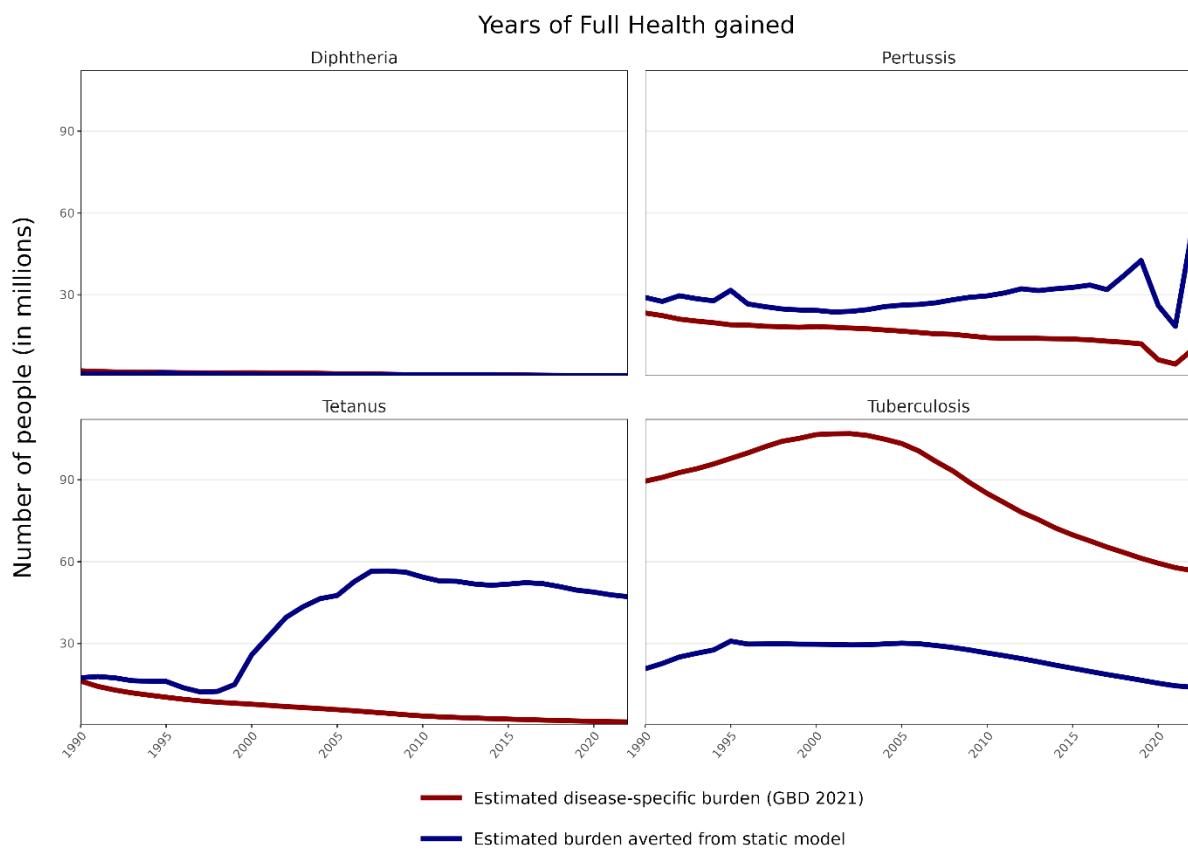


Figure S14 Estimated disease-specific years of full health gained through vaccination.

Extension of model estimates

Geographical imputation

To impute vaccine impact in countries outside the scope of the VIMC, we fitted time series regression models with the outcome of deaths averted and YFH gained for each disease-vaccine-activity (vaccine dose number in routine programmes or supplementary immunization activities) in each country where VIMC estimates were available. Disease-vaccine-activities with fewer than 10 countries were omitted as the sample was insufficient for extrapolation to other settings.

An initial range of predictor variables was selected, encompassing known covariates of vaccination impact, reported in a consistent way globally, over time. Time series regression models evaluate the relationship between the time series of the predictor and the time series of the outcome variable. For predictors where we had prior knowledge of a time-lagged effect, we included offset terms, as summarised in Table S8.

Table S8 Predictor variables included in the model selection for geographical imputation.

Variable	Description	Source
Vaccination coverage (current year, y)	Proportion of the population fully vaccinated, according to the study definition of a fully vaccinated person, in the same calendar year as the outcome variable	As per study
Vaccination coverage (y-1)	As vaccination coverage, with lag of 1 year	As per study
Vaccination coverage (y-2)	As vaccination coverage, with lag of 2 years	As per study
Vaccination coverage (y-3)	As vaccination coverage, with lag of 3 years	As per study
Vaccination coverage (y-4)	As vaccination coverage, with lag of 4 years	As per study
Stunting	Proportion of under-fives falling below minus 2 standard deviations (moderate and severe) and minus 3 standard deviations (severe) from the median height-for-age of the reference population	UNICEF ⁷⁹
Maternal mortality	Maternal deaths from pregnancy or childbirth per 100,000 live births	UNICEF ⁸⁰
Basic water	Proportion of population with access to at least a basic water source	Gapminder Foundation ⁸¹
Basic sanitation	Proportion of population with access to at least basic sanitation	Gapminder Foundation ⁸¹
Male adult literacy	Proportion of males aged 15 years and above who can read and write	World Bank ⁸²
Female adult literacy	Proportion of females aged 15 years and above who can read and write	World Bank ⁸³
Attended births	Proportion of births attended by skilled health workers	Gapminder Foundation ⁸¹

Gini coefficient (current year, y)	Statistical dispersion of income	Gapminder Foundation ⁸¹
Gini (y-1)	As Gini, with lag of 1 year	Gapminder Foundation ⁸¹
Gini (y-2)	As Gini, with lag of 2 years	Gapminder Foundation ⁸¹
Gross domestic product (current year, y)	GDP <i>per capita</i> in constant purchasing power parity US dollars	Gapminder Foundation ⁸¹
GDP (y-1)	As GDP, with lag of 1 year	Gapminder Foundation ⁸¹
GDP (y-2)	As GDP, with lag of 2 years	Gapminder Foundation ⁸¹
Private health spending (current year, y)	Private share of total health spending	Gapminder Foundation ⁸¹
Private health spending (y-1)	As private health spending, with lag of 1 year	Gapminder Foundation ⁸¹
Private health spending (y-2)	As private health spending, with lag of 2 years	Gapminder Foundation ⁸¹
Health spending (current year, y)	Total health spending <i>per capita</i>	Gapminder Foundation ⁸¹
Health spending (y-1)	As health spending, with lag of 1 year	Gapminder Foundation ⁸¹
Health spending (y-2)	As health spending, with lag of 2 years	Gapminder Foundation ⁸¹

Where predictor data were temporally incomplete, we imputed missing values using linear models with a trend component (*forecast* package for R; Hyndman and Khandakar). Since the number of potential predictor combinations was large ($24! = 6 * 10^{23}$) we used a phased approach for model selection. In each phase, we used a corrected Akaike Information Criterion (AICc) to compare models, both within the group and with those from the previous phase. The exercise was conducted for each disease-vaccine-activity combination in each country for which VIMC estimates of vaccine impact were available:

1. In the first phase, the AICc was used to assess how many lagged years of vaccination coverage should be included.
2. Secondly, we assessed the 11 single non-coverage predictors (stunting, maternal mortality, basic water, basic sanitation, male adult literacy, female adult literacy, attended births, Gini coefficient, GDP, total health spending, private health spending) and 55 pairwise combinations of group 2 predictors in combination with the best choice of vaccination coverage inclusion from phase 1.
3. Next, we assessed whether the 66 models in phase 2 could be improved by removing one or more years of lagged vaccination coverage
4. Where predictor combinations included the Gini coefficient, GDP, total health spending or private health spending, we assessed whether a model including lagged values of these variables would be preferable.
5. Finally, we assessed whether the 55 models that already included two non-coverage predictors could be improved by adding a third and, if so, a fourth. In practise, it was unnecessary to continue beyond this point.

The outcome of this stepwise model selection approach was a chosen model for each disease-vaccine-activity in each VIMC country. To avoid complexity (and noting that this may in itself be a form of over-fitting), we grouped countries and selected the most common model choice for the group. Our baseline approach was to group countries by WHO region but we conducted a sensitivity analysis grouping by current World Bank income level and by bands of current DTP vaccination coverage.

The model fit to observed vaccination impact from this approach is shown in Figures S15 and S16.

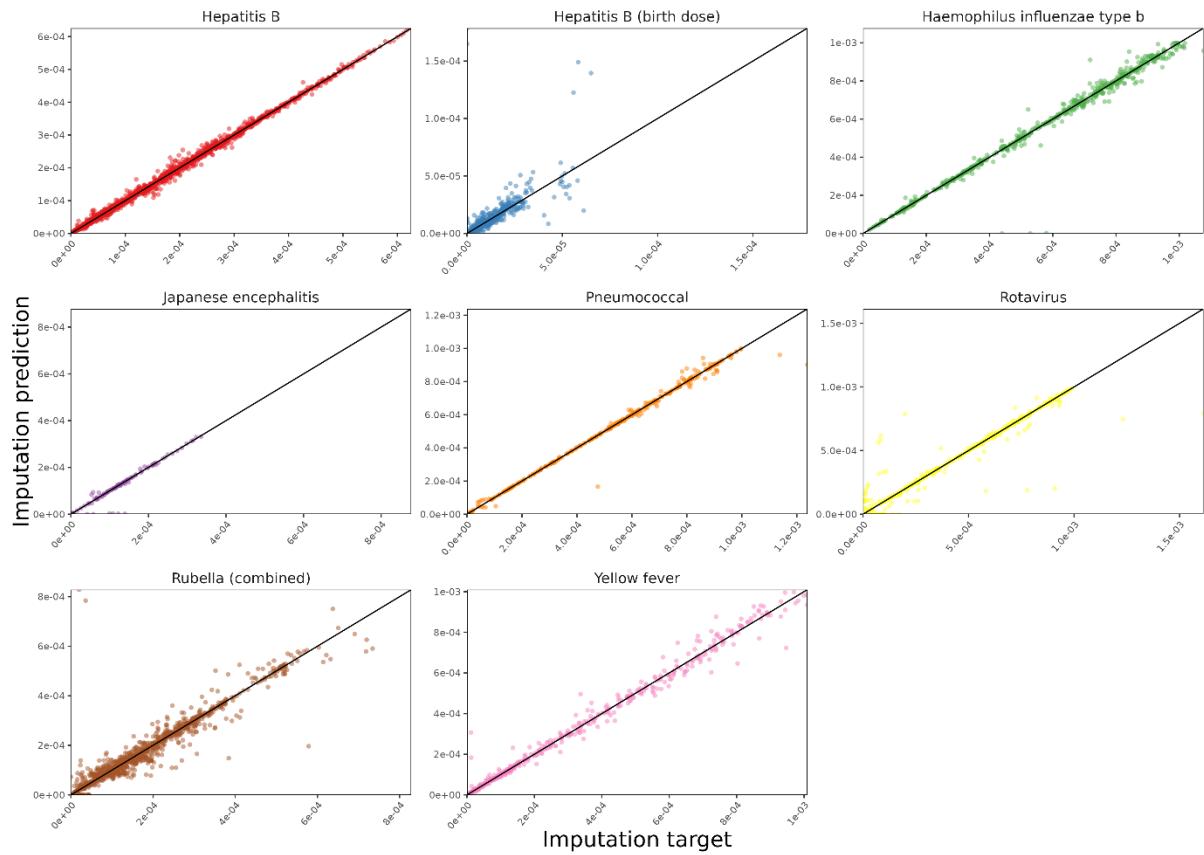


Figure S15 Fit of time series regression models to observed vaccination impact for each disease-vaccine-activity with sufficient observations.

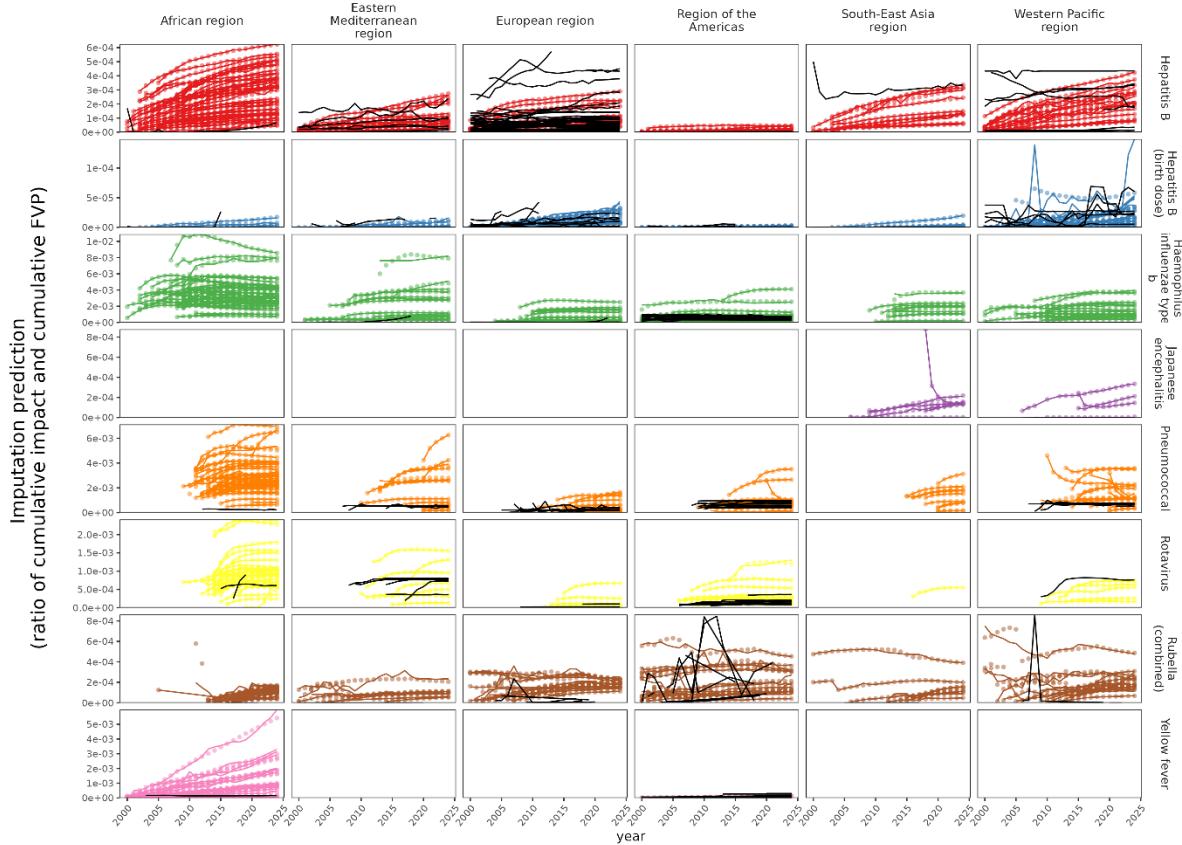


Figure S16 Fit of time series regression models, plotted by disease-vaccine-activity and WHO region. Points represent ‘data’; that is, transmission model estimated cumulative deaths averted divided by cumulative FVP. The corresponding coloured lines represent the regression model fit, grouped by country. Black lines represent the imputed ratio of cumulative deaths averted and cumulative FVP for countries without transmission model estimates.

For countries without primary estimates of vaccination impact we used the selected model for their grouping again using WHO region in the baseline case and conducting a sensitivity analysis of World Bank income level and band of DTP vaccination coverage, using the group median of fitted predictor coefficients to inform the model.

Being conscious that the geographical imputation approach is, in effect, an extrapolation from VIMC to non-VIMC countries, known to be contextually different, we assessed the validity of our estimates against observed measures of vaccination impact in the imputed countries, where available.

Non-linear impact functions and temporal extrapolation

Vaccine impact derived using form 2 (VIMC modelling portfolio, eight pathogens) and form 3 (static models, four pathogens) represent only a subset of the 50 year timeframe of this analysis; 2000-2024 for form 2 and 1980-2021 for form 3. For several of the relevant pathogens, there exists vaccine coverage outside of the directly modelled temporal scope, for which we must extrapolate expected vaccine impact.

Over a short period, it may be reasonable to assume that the per-FVP impact of vaccination may hold constant over time. That is, for a given vaccine each FVP averts a consistent number of deaths (or gains a consistent number of YFH) year on year. However, over a long-term period – such as the 50 years considered in this analysis – such an assumption may not necessarily be suitable. We here offer some justification for this reasoning. Depending on the dynamics of the pathogen and properties of the vaccine itself, two complimentary effects of vaccination may be observed. First, an individual-level benefit that may prevent disease and/or death. Second, a population-level benefit that may break transmission chains (due to reduced bacterial/viral load in infected people and/or due to infection/transmission blocking effects of the vaccine). As vaccine coverage increases, maximal population-level benefits may become realised. Thus, over a given coverage threshold – commonly termed the ‘herd immunity threshold’ – the proportional gain of population benefit relative to individual benefit decreases. As such, the impact per FVP may begin to saturate for high coverage levels. We stress, however, that decreasing coverage would similarly be expected to result in a non-linear impact per drop in FVP; larger negative effects would occur as coverage falls back below herd immunity threshold. Moreover, there may also exist a growth in impact per FVP, especially in the early stages in vaccine rollout. As more of the population are vaccinated (up to a certain threshold), a pathogen may circulate less and therefore a proportional increase in population level benefit over individual level benefit may be observed.

With this reasoning considered, to accurately back or forward project vaccine impact per FVP beyond the directly modelled scope, we hypothesize that cumulative per-FVP impact may follow one of four functional forms: linear growth, exponential growth, logarithmic growth (saturating at high levels of coverage), or sigmoidal growth (initial exponential growth followed smoothly by saturating logarithmic growth). Table S9 describes the four functional forms used in more detail. All functions pass through the zero FVP – zero impact origin by construction.

Table S9 Functions evaluated for impact factor model selection.

Function name	Equation	Number of parameters	Description
Linear gradient	$y = p_1x$	1	Straight line through the origin. Gradient represents an ‘impact factor’.

Logarithmic growth	$y = \frac{p_1}{1 + e^{-p_2x}} - p_1/2$	2	Logarithmic growth function that saturates.
Exponential growth	$y = p_1 e^{p_2x} - p_1$	2	Exponential growth that continues to rise.
Sigmoidal growth	$y = p_1 \left(1 - \frac{1}{1 + (x/p_2)^{p_3}} \right)$	3	Initial exponential rise smoothly continuing into logarithmic saturation. An 'S' shape.

Where the number of modelled cumulative FVP – cumulative deaths averted data is sufficient, each functional form is fitted for each disease-vaccine-activity and country combination. Formally, let k be the number of cumulative FVP – cumulative death averted data points for a given disease-vaccine-activity for a given country. An artificial data point is appended at the origin (that is, zero FVP implies zero vaccine impact), such that each function is fit to $k + 1$ coordinates. For a function with n parameters, we attempt to fit said function to the data only if $n \leq k$. Thus, in the extreme case of $k = 1$, only the linear gradient function is fitted.

For each disease-vaccine-activity and country combination, a Monte Carlo Markov Chain (MCMC) algorithm was used to derive posteriors for all fitted function parameters. The priors used for the MCMC process were derived by an Adaptive Stochastic Descent optimisation algorithm, with the result of this optimisation informing the mean of each parameter prior. The prior for each parameter was assumed to be Gaussian distributed with a unit standard deviation. The MCMC algorithm was run ten times for each disease-vaccine-activity-country instance to ensure the resulting chains converged to the same globally optimal result. Posterior samples were then generated by randomly selecting a subset from the combination of the ten MCMC chains. Finally, a corrected Akaike Information Criterion (AICc) score was used to select the most appropriate functional form for each disease-vaccine-activity and country combination. The AICc model selection criteria helps to ensure the best fitting functional form is selected, whilst reducing the probability of selecting a function that over-fits the data. Figure S17 illustrates the data (presented as points) and resulting fitted functional form (lines) selected for each disease-vaccine-activity. Figure S18 shows the proportion of countries for which each functional form was selected, for each disease-vaccine-activity.

Using these fitted relationships between vaccination coverage (in terms of cumulative FVP) and vaccine impact (in terms of cumulative deaths averted / cumulative YFH gained), we inferred vaccine impact either back or forward in time according to observed coverage in all cases where vaccine impact was not directly modelled.

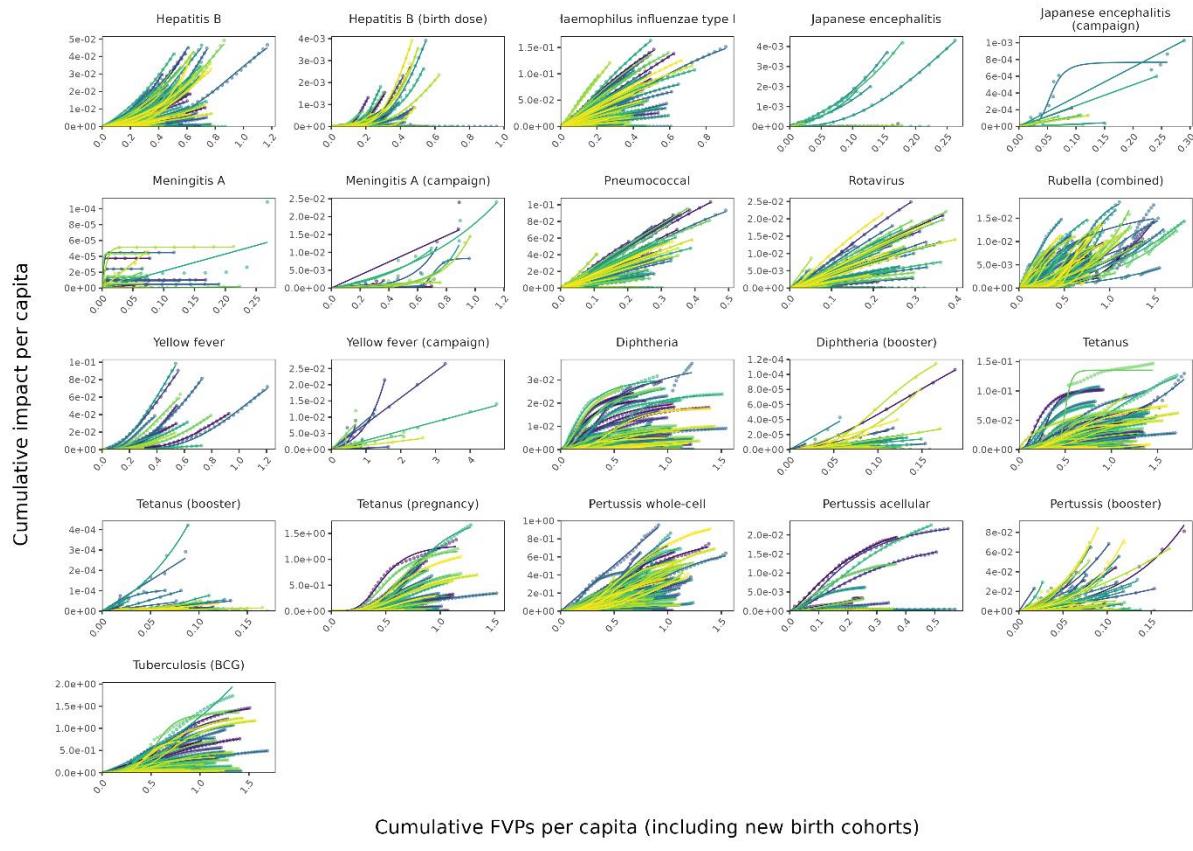


Figure S17 Fitted functional representation of cumulative FVP against cumulative deaths averted per capita. Points represent ‘data’; that is, outcomes from 1) transmission models, or 2) geographical imputation time series models. Lines represent impact function fits. Points and lines are grouped and coloured by country.

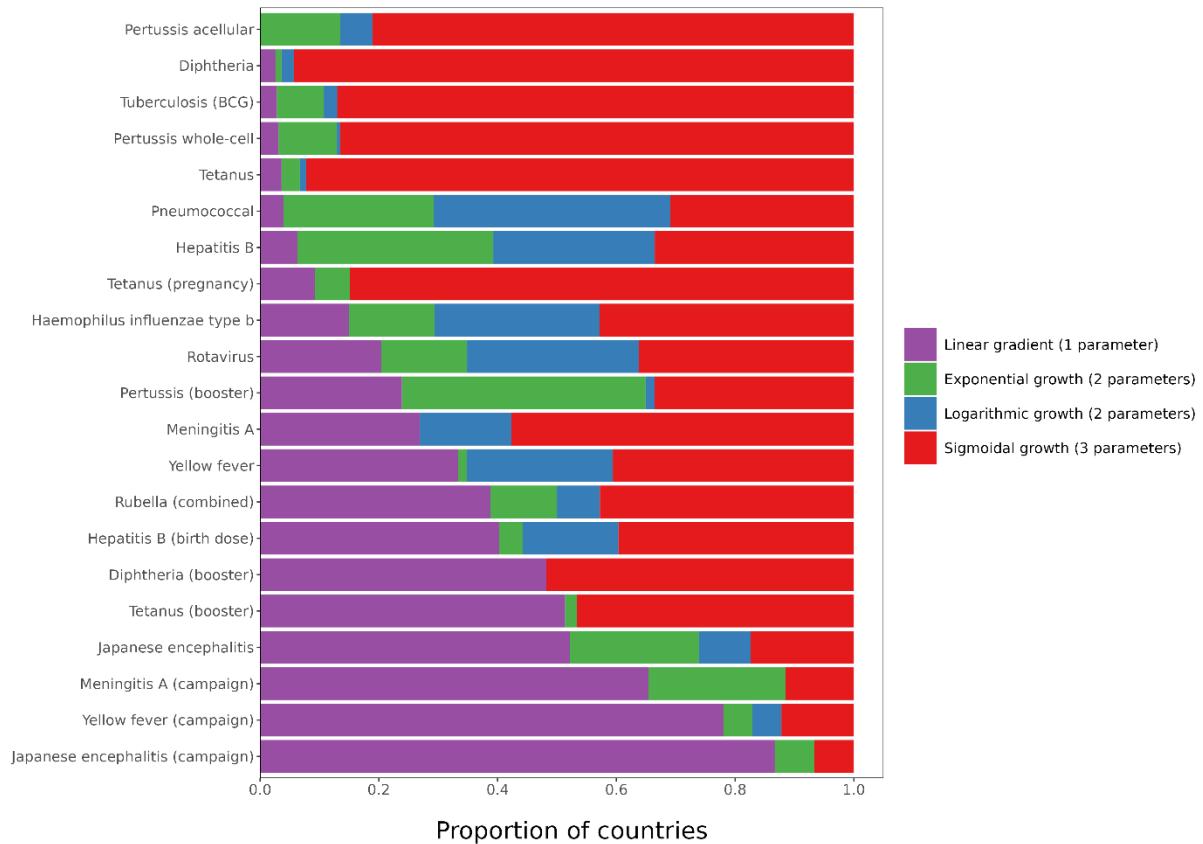


Figure S18 Proportion of countries for which each functional form was selected by disease-vaccine-activity.

Uncertainty of estimates

It is important to appreciate that our uncertainty bounds relate only to the work of our modelling. They are not bounds around the veracity of the estimates themselves. It is not possible to propagate uncertainty at all levels of estimation, of all the hierarchical underlying models or of the values input into the models. For example, we took existing estimates of coverage and of population denominators as such, that is we took them to be true. We used these inputs to conduct our modelling, and we fit functional forms and derived Markov Chain Monte Carlo posteriors. In the process of deriving these posteriors we predefined the magnitude of the allowable uncertainty. In this sense the bounds are arbitrary. They broadly show the scale of uncertainty, but they should not be interpreted as a claim to where the edges of valid estimates possible lie. Bounds we produce do not describe the probability distribution of the true estimator under our assumptions, as bounds of regression say are usually interpreted. Put simply, the bounds are not as big as they should be given the multiple levels of uncertainty, and do not carry the usual meaning.

The coverage estimates that derive from WIISE are those that are produced through the WHO and UNICEF Estimates of National Immunization Coverage (WUENIC). WUENIC numbers are not statistical estimands, and do not have uncertainty bounds. They are based on a logic model that applies predetermined rules to triangulate Member States' official reported coverage against other sources of evidence, to achieve a final determination of national coverage. The methods for

WUENIC are published, and also made available on the WUENIC site. WUENIC numbers form the input for many arising statistical or modelling efforts by academic institutions globally. More importantly they form the basis for country decision making and planning. Further methods, and relevant publications, are available here:

www.who.int/docs/default-source/immunization/immunization-coverage/wuenic_notes.pdf?sfvrsn=88ff590d_6

WPP estimates are produced by the UN Population Division. UNPD produce uncertainty bounds for prospective population projections, but not for past population figures, the latter being relevant for our present analysis. To be sure even retrospective numbers are derived from hierarchical Bayesian models that do incorporate uncertainty bounds, for example with respect to inter alia fertility rate assumptions or sex ratio at birth, cause of death data, international migration, et cet. See for example Liu, P., and A.E. Raftery (2020). Accounting for uncertainty about past values in probabilistic projections of the total fertility rate for most countries. The annals of applied statistics, vol. 14, No. 2, pp. 685-705. WPP methods are described here:

https://population.un.org/wpp/Publications/Files/WPP2022_Methodology.pdf

Interested readers who seek to extend on our work, (we have made public our data and code) will of course need to grapple with the same issues, as we have done.

Accounting for potential double counting

Since we estimate the deaths averted separately by a number of disease-vaccine-activities, we assessed the potential impact of double counting. That is, a life saved from measles may later be saved from invasive pneumococcal disease but should not count as two lives and falsely inflate the overall rate of reduced mortality.

We used a Bernoulli process to provide an estimate of the potential scale of this effect. Although the Bernoulli method for competing risks provides a lower bound, it is accepted as the most robust approach for finding an approximate value. The equation is:

$$\text{mortality}_{\text{combined}} = 1 - \prod_{\text{dva}} (1 - \text{mortality}_{\text{dva}})$$

By calculating the combined mortality in the presence and absence of vaccination, we quantified the potential impact of double counting on the number of deaths averted. For infants aged 12 months and younger, 355,000 deaths may have been counted twice, 0.343% of the total. For the overall population, the number is lower since the rate of deaths averted by each disease-vaccine-activity is lower. Making the limiting assumption that risk in the population is homogenous, it is much less likely that the same person will be affected by two diseases. The potential number of deaths counted twice in the overall population is 25,000 which equates to 0.01% of the total.

Code library and reproducibility

The open source code library for this analysis is publicly available from the World Health Organization GitHub repository:

<https://github.com/WorldHealthOrganization/epi50-vaccine-impact>

For longevity of the code used to generate all results and figures presented here, all files can be downloaded from Zenodo (DOI: 10.5281/zenodo.10980462):

<https://zenodo.org/doi/10.5281/zenodo.10974443>

All input data and configuration files required to reproduce this analysis in full are also open source and contained within this repository. Code is written in the R programming language. An internet connection is required to run the analysis, which can be run on both Windows and UNIX operating systems.

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