Estimation of childhood vaccine scale-up rates by country and vaccine

Natalie Galles

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Jonathan Mosser
Hmwe Kyu

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Abstract

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Natalie Galles

Chair of the Supervisory Committee:

Jonathan Mosser

Department of Health Metric Sciences

Background

The development and integration of new vaccines into national immunization schedules has dramatically reduced the number of children experiencing preventable morbidity and mortality. Introduction and scale-up of these newer vaccines remain global health priorities, featured in global vaccine targets like the Immunization Agenda 2030 (IA2030). Analyses of country-specific scale-ups for six childhood vaccines provide insight into trends and trajectories of current delivery systems.

Methods

Using meta-regression – Bayesian, regularised, trimmed (MR-BRT), we estimated newer vaccine coverage controlling for underlying Expanded Programme on Immunization (EPI) vaccine coverage and years of vaccine introduction utilizing data from the Global Burden of Diseases, Injuries and Risk Factors Study 2020, Release 1. Scale-ups occurring between 1980-2019 were assessed using EPI reference coverage aligned by country and calendar year. We analyzed relationships between scale-up, national government spending on immunization, and Gavi support status.

Findings

First-dose rubella-containing vaccine (RCV1) had the highest scale-up in the first year of introduction (94.3%) compared to completed Rotavirus (RotaC; 40.6%) and third-dose pneumococcal conjugate vaccine (PCV3; 52.4%). RotaC was the only vaccine to not reach 95% scale-up at any point in the estimated time series. High variation in vaccine scale-up in the first year of introduction was observed across the distribution of available dollars per capita of national government spending, and countries currently experiencing Gavi support in 2019 demonstrated at least 95% scale-up for 5 of the 6 estimated vaccines. By 2019, only 75 (36.8%) of 204 estimated countries had all six vaccines introduced.

Interpretation

Differences in scale-up between vaccines emphasize the need for context-specific strategies prioritizing immunization equity. These findings also highlight that both vaccine introductions and scale-ups must be improved in addition to bolstering existing routine immunization delivery systems more broadly. Continued assessment, then implementation, of such approaches will be necessary to meet the IA2030 targets.

Introduction

The development and integration of new vaccines in national immunization systems has had dramatic, positive effects on reducing avertable childhood mortality due to infectious diseases.[1–4] Building from the Expanded Programme of Immunization (EPI) list of priority vaccinations (primarily including Bacillus Calmette–Guérin [BCG], third-dose diphtheria-tetanus-pertussis [DTP3], first-dose measles-containing vaccine [MCV1] and third-dose polio [Pol3]),[5] newer vaccines including third-dose hepatitis B vaccine (HepB3), third-dose *Haemophilus influenzae* type b (Hib3), second-dose MCV (MCV2), third-dose pneumococcal conjugate vaccine (PCV3), first-dose rubella-containing vaccine (RCV1), and completed rotavirus (RotaC) have been introduced in many countries around or after the year 2000. Vaccine introduction and scale-up was recognized as a formal health priority with the creation of Gavi, a partnering organization alongside other global health agencies like Bill & Melinda Gates Foundation (BMGF), World Health Organization (WHO), UNICEF, and World Bank, which prioritizes funding of vaccination-related services in eligible low- and middle-income countries around the world. Gavi services include but are not limited to support of new vaccine development and integration into national schedules. Since 2000, Gavi contributed over US$150 billion to vaccine scale-up.[6] Recent studies have found that global vaccination has increased dramatically over the past four decades, but coverage rates of relatively newer vaccines are often lower in comparison to rates of DPT3 or MCV1.[7] The recency, duration, and cumulative health toll of the COVID-19 pandemic further highlights the threats posed by infectious diseases unchecked by robust vaccination programs and the importance of swift, effective, and equitable vaccine delivery to minimize ongoing health loss.[8] To continue to prioritize global vaccine coverage progress, quantification of routine vaccine scale-up can be used to motivate focused assessment of the drivers and mechanisms of introduction and scale-up programs.

The value of new vaccine introduction and scale-up has also been recognized by the Immunization Agenda 2030 (IA2030), a set of global immunization coverage targets prioritizing high and equitable increases in vaccine coverage for the coming decade.[9,10] IA2030 strategic priority objective 4.3 focuses specifically on the introduction of all recommended vaccines in national schedules; indicator 2.2 builds further, describing a global coverage goal of 90% across all routine vaccinations which overlaps with the intention of indicator 3.b.1 of the Sustainable Development Goals (SDGs). While no standardized indicator nor global evaluation framework for new national vaccine introductions has been named to date, together these targets call for coverage of all vaccines recommended by national immunization schedules to reach within 5 percentage-points of DTP1 coverage by 2030. As such, analyses of historical scale-up rates complement existing published estimates of coverage trends over time[7,11] and are poised to contribute more broadly to development of key monitoring and evaluation indicators to compare vaccine- and country-specific scale-up rates.

Building from the vaccine coverage estimation framework used to produce annual estimates for 11 childhood vaccines for the Global Burden of Diseases, Injuries, and Risk Factors (GBD) Study,[7,12] we quantified scale-up rates for six newer childhood vaccines for 204 countries and territories controlling for underlying EPI vaccine coverage and years of newer vaccine introduction. We additionally assessed scale-ups in relation to government spending on immunization disaggregated by spending category and by categorical indicators of Gavi support. These quantified and directly comparable estimates of vaccine-specific scale-ups provide novel insight into patterns of scale-up and variation by vaccine, filling important research gaps in the global immunization landscape.

Methods

Overview

This work builds upon the data and modeling framework of the GBD 2020 Release 1 (GBD 2020 R1) estimates of global, national-level vaccine coverage.[7] Key coverage indicators included Hib3, HepB3, MCV2, PCV3, RCV1, and RotaC. To quantify and compare different scale-up rates, we used meta-regression – Bayesian, regularised, trimmed (MR-BRT),[13,14] which is a statistical framework for estimation of nonparametric relationships, and GBD 2021 R1 estimates of DTP3 and MCV1 to produce annual estimates of scale-up. Secondary analyses comparing scale-up rates against indicators of government financing and Gavi assistance were completed to further evaluate historical, contextual patterns associated with calculated scale-ups by vaccine.

Data

Vaccine coverage data prepared for GBD 2020 R1 as described elsewhere in detail[7] provided the foundation for vaccine scale-up modeling. In brief, three main types of coverage data were incorporated. First, household survey microdata from children 12-59 months, grouped by birth cohort and assigned to year of expected vaccine delivery following country-specific vaccination schedules, were used as available; in the absence of available microdata, coverage was extracted from survey reports. Last, we used official country-reported estimates of coverage reported through the 2020 Joint Reporting Form (JRF) which we bias-adjusted based on its relationship with available survey data for every possible paired location-vaccine-year. In total we incorporated data from 409 unique data sources, and 86.0% (12,410/14,465) of all included location-vaccine-years were from the JRF country-reports.

To assign vaccine-specific national introduction years, we primarily used country-reported introduction years as reported through the JRF.[15] We incorporated introduction year data from custom searches when absent from the JRF.

The underlying estimates used to support our secondary analyses came from multiple sources. We incorporated estimates of national-level government spending on immunization for 135 countries from 2000-2017, which has been described in detail elsewhere.[16] The specific government spending categories evaluated included spending on vaccines, spending on vaccine delivery, and spending on routine immunization for all vaccines combined. Spending amounts scaled to 2019 USD were converted to per capita totals using GBD 2020 R1 estimates of under-1 populations. Data on Gavi assistance was compiled independently, gathered from online Gavi publications.[6] Gavi countries were grouped by current Gavi support (indicating receipt of Gavi assistance in 2019), past Gavi support (indicating previous support from Gavi terminated prior to 2019), and never Gavi support (indicating that the country never received assistance from Gavi).

MR-BRT cascading spline model

To capture the nonparametric relationship of location-specific vaccine coverage scale-up, we used the statistical framework meta-regression – Bayesian, regularised, trimmed (MR-BRT).[13,14] This tool was designed to facilitate analyses of complex, non-linear relationships between covariates and outcomes. Specifically, the MR-BRT modeling framework used was a cascading spline approach, exemplified elsewhere.[17,18] This approach allowed for country-specific coverage variation standardized to account for differing calendar year of introduction by country and vaccine. In addition, underlying reference vaccine coverage was used as a covariate in the model to help inform predictions in locations with minimal data.

Reference vaccine coverage was represented by either country-specific DTP3 or MCV1 coverage based on the recommended schedule of each newer vaccine, as DTP3 and MCV1 have generally been introduced the longest[5] and broadly capture capacity of country-specific childhood vaccine delivery systems. DTP3 was the reference vaccine for HepB3, Hib3, PCV3, and RotaC, and MCV1 the reference vaccine for MCV2 and RCV1.

The cascading design included a "stage 1" global model including all data from all locations. The subsequent "stage 2" or country-specific models were fit using available country-specific data for each vaccine, respectively, and the coefficient from the spline in the global model as a prior. Specifically, the underlying model framework followed:

$$logit(p_t) = \beta_0 + \beta_1 * logit(X_t) + \beta_2 * spline(t)$$

where p_t was the proportion of children vaccinated in year t of vaccine introduction; β_0 was the intercept; X_t was modeled reference EPI vaccine coverage (DTP3 or MCV1); and $spline(t)$ was a random, cubic spline on years of vaccine introduction. Spline knots were positioned at the minimum, 10th, 20th, 40th, 60th, and maximum percentiles of the available data distribution. More knots were used earlier in the distribution of data to better capture scale-up in early years when coverage tended to change more quickly compared to later years. The model was parameterized such that the model fit was linear beyond the maximum year of vaccine introduction available from the data distribution. In addition, it was constrained to monotonically increase with increases in years of introduction and reference vaccine coverage, assuming an underlying trend in coverage patterns over time. To reduce implausible variation particularly in locations with sparse or no data, the coefficient distribution of the spline passed down as a prior to the stage 2 models was fixed to be the mean solution from the stage 1 model. Coverage estimates for HepB3, Hib3, MCV2, PCV3, RCV1, and RotaC were each produced independently but all used these same model specifications. Supplementary results table S1 describes the magnitude of β_1 per global model of each vaccine.

The direct output of this model was expected vaccine coverage per year of vaccine introduction. These coverage estimates were aligned with calendar year using country-reported introduction years matched to years of vaccine introduction as included in MR-BRT. Estimates prior to the first year of introduction were forced to 0, aligning with the standard GBD coverage estimation framework to only produce estimates for nationally-introduced vaccines.

Vaccine scale-up calculation

Using each time series of modeled coverage per vaccine and location, scale-up was assessed via direct ratio comparison to the underlying reference vaccine (DTP3 or MCV1, as described above), aligned by calendar year. We evaluated all scale-ups occurring between 1980 and 2019, aligning with GBD estimation years.[12] High scale-up was considered if the newer vaccine achieved 95% of reference vaccine coverage in each year. Additionally, we evaluated how scale-up rates compared using DTP1 instead of DTP3 as the reference vaccine as described in the proposed IA2030 Global Strategic Priority Objective Indicators.[10]

Secondary analyses

We conducted two secondary analyses to broadly evaluation the association between country- and vaccine-specific scale-up ratios and national government spending on immunization and categorization of current, past, or never Gavi support, respectively. We evaluated the relationship between country-

specific vaccine scale-up rates in the first year of introduction and government spending converted to USD per capita by immunization spending category using local regression (LOESS) for all scale-up estimates by location and year for which financing data was available. LOESS was used instead of another nonparametric function to evaluate how spending and scale-up varied over the distribution of dollars spent per capita without having to prescribe a functional form for the relationship. To look at the influence of Gavi assistance, we evaluated the first year average scale-up by vaccine met or exceeded the threshold of 95% scale-up for groups of current, past, and never-supported Gavi countries separately, focusing specifically at scale-up patterns in the first five years of introduction.

Results

Trends and patterns in vaccine introduction and scale-up

On average, global scale-up rates increased across all six estimated vaccines during the first five years of introduction (figure 1a). In the first year of introduction, scale-up of RCV1 was the highest compared to all other vaccines at mean scale-up of 94.3%; RotaC and PCV3 had the lowest average rates of initial scale-up at 40.6% and 52.4%, respectively. For all of the estimated vaccines, the largest gains in scale-up were observed between the first and second years of introduction. RotaC experienced the largest gain in scale-up (36.4 percentage points) followed by PCV3 (23.0 percentage points), both surpassing scale-up proportions of MCV2 by their second year. Across all estimated years and vaccine introductions occurring between 1980 and 2019, 5 of 6 vaccines reached at least 95% average scale-up within the time series (figure 1b). However, steady growth or consistent scale-up levels were not experienced by all vaccines; RotaC never reached 95% average global scale-up within the estimated time series, instead reaching a maximum of 89.5% in its 6^{th} year of introduction. Further, RotaC was the only vaccine to experience a decline of more than 5 percentage points (6.2 percentage points) by 2019 following its maximum observed scale-up earlier in the time series.

On average, global scale-up rates were 7.4 percentage points lower over the first five years of introduction when using DTP1 instead of DTP3 as the reference vaccine for HepB3, Hib3, PCV3 and RotaC following the proposed recommendation put forth in the IA2030 agenda (figure 2). In 2019, DTP1-based scale-ups ranged from as low as 21.8% (RotaC in first year of introduction) to 100% (Hib3, scale-up in 23 years of introduction). Ultimately, fewer vaccines reached at least 95% average scale-up when compared against DTP1 versus DTP3 with only HepB3 and Hib3 reaching this threshold.

By 2019, Hib3 and HepB3 were the most widely introduced of the estimated newer vaccines, with 198 and 196 out of 204 estimated countries recommending the vaccine, respectively (table 1). RotaC had the lowest number of national introductions, recommended in just 111 locations. While schedules varied by location, 99.5% (203/204) of countries had any nationally-introduced newer vaccine at or above 95% scale-up in 2019 (89.7% [183/204] when DTP1 is used instead of DTP3). However, only 36.8% (75/204) of countries had all nationally-recommended newer vaccines at or above 95% scale-up (26.0% [53/204] when DTP1 is used instead of DTP3) and just 38.2% (78/204) had all six estimated newer vaccines fully introduced.

Scale-up and national immunization financing

High variation was observed between national vaccine scale-up and amount of government spending on immunization in the first year of introduction (figure 3). Across mutually exclusive categories including spending on vaccines, spending on vaccine delivery, and spending on routine immunization, there was no singular association between amount of dollars contributed (converted to 2019 USD) and scale-up in

the initial year of vaccines. While 50% (248/496) of available country-vaccine data observations contributed less than or equal to US$23.00 per capita in the year of introduction on aggregate spending on immunization, scale-ups varied from 0.466% (Indonesia, PCV3) to 150% (Equatorial Guinea, HepB3) in this range.

Scale-up and Gavi support

Since 2000, Gavi has supported 78 total countries in varying capacities. In 2019, Gavi supported 57 countries while 21 had since transitioned out of or became ineligible for continued assistance. Based on categorizations of Gavi support in 2019, 95% scale-up was observed within the first five years of introduction on average for 4 of the 6 estimated vaccines (Hib3, PCV3, RCV1, RotaC) among countries with current Gavi assistance (figure 4). Countries that had received Gavi support in the past but not in 2019 only had 95% scale-up on average for 3 of the 6 estimated vaccines (Hib3, PCV3, and RCV1) within the first five years. Among countries in this grouping, the inaugural year that 95% scale-up was reached was consistently later compared to those achieved by countries supported by Gavi in 2019, shifting back by one year for all three vaccines. The 126 countries with vaccine scale-ups between 1980 and 2019 that never received Gavi support only had average scale-up meet 95% for 2 of the 6 vaccines (Hib3 and RCV1); scale-ups for all other vaccines did not reach 95% within the first five years, if at all by 2019.

Discussion

Disparities in vaccine introduction and scale-up between 1980 and 2019 underscore the need to address context-specific barriers associated with uptake so more children can be protected against vaccine-preventable diseases. Variation over 50 percentage-points in scale-up during the first year of introduction suggests that each introduction must be thoughtfully strategized and considered in the context of existing delivery systems. For example, the relatively high and consistent rates of Hib3 scale-up may largely be facilitated by transition from a DTP vaccine to a Hib-containing pentavalent vaccine in many countries. While initial vaccine receipt may lag at the introduction of combination vaccines, case studies across low- and middle-income countries have observed higher rates of uptake post-introduction with minimal disruption to underlying DTP coverage proportions and the broader health system.[19] In comparison, addition of new, separate vaccine products to like PCV3 and RotaC may face more barriers or hesitation to acceptance and subsequent delivery;[20] however, their delivery may be aided by complementing the schedule of DTP3 vaccine delivery, so additional health care visits are not required for vaccine receipt. MCV2 scale-up may lag other vaccines throughout the entire estimated time series because it is recommended to an older age group, requiring an additional interaction with the vaccine delivery system. Lack of parental awareness or sensitization, combined with general health system weaknesses, may prompt slow uptake and large drop-out between first and second MCV doses.[21] National vaccine delivery systems will need to recognize, assess, and implement context-specific strategies to reduce the disparities between these vaccines if all vaccines are to meet at least 95% scale-up and also attain high levels of average coverage.

A multitude of social, political, and situational factors likely also affect the success of each newer vaccine introduction. To move from benchmarking and measuring scale-up trends year-to-year to designing and better implementing robust and effective scale-up programs, it will be important to understand the kinds of drivers underpinning the variation between countries and years. In light of trends known to affect vaccine uptake such as increases in vaccine hesitancy in most countries[22] and health service staffing, supply, and engagement,[23] these drivers must be understood and addressed so equitable gains

can be achieved and these barriers overcome. Additional disruptions caused by the COVID-19 pandemic in 2020[18,24] reverted past scale-up gains and likely jeopardized imminent vaccine introductions as more attention and health services were allocated to addressing the impacts of the pandemic,[25] which threatens the likelihood of reaching national and global immunization targets in the next decade. As simply increasing dollars per capita spent on immunization in the initial year of vaccine introduction nor having Gavi backing necessarily leads to higher or faster scale-up, exploring more context-specific strategies and their interactions should be prioritized in the future.

There is much progress to be made in the next decade in order to reach the proposed IA2030 scale-up goals, as less than 40% of countries with all introduced newer vaccines have scaled-up to at least 95% of reference coverage, and a similar percentage of countries even have all six newer vaccines currently introduced. Continued global progress towards these goals will stall unless more countries introduce more vaccines into their national schedules. Average global differences of nearly 10% between DTP1- and DTP3-based scale-ups also highlight that reducing dropout rates will be an important component for reaching IA2030 goals. Such work must prioritize equity in vaccine delivery and will require context-specific strategies, close coordination with government, community, and technical partners, and concerted engagement in monitoring and evaluation efforts.[9,26,27] In addition, as IA2030 also focuses on the need to reduce the number of zero-dose children which is approximated by those never receiving a dose of the DTP series,[10,28,29] scale-up targets will need to be routinely reviewed and updated in order to not reinforce current inequities in vaccine coverage and access. In seeking to serve and understand the immunization barriers to new vaccine uptake for the most underserved groups, countries should be able to achieve improved vaccine scale-up and progress.

In consideration of continued measurement of the IA2030 scale-up indicators, use of a statistical framework to benchmark and further estimate trends in vaccine scale-up provides a variety of benefits. For instance, noticed particularly around the year of introduction, utilization of a flexible model fit allows for capture of high variation in the initial years of vaccine introduction. The stage 2, location-specific model fits from this model also allow for country-to-country variation based on the underlying available data, while locations without or with minimal data can still get meaningful estimates produced by leveraging the relationship between covariate values and the average global prior. As the framework for reporting and measuring the scale-up indicators for IA2030 are finalized, a dynamic modeling strategy will be critical to produce timely and directly comparable estimates.

Limitations

This study has important limitations. First, the underlying coverage data used in the MR-BRT scale-up models assumes negligible effects due to migration, survivor bias, and catch-up vaccination in the data processing, as described elsewhere in detail.[7] This may result in an over-estimation of true coverage, particularly in locations where marginalized populations are not included in official census data or national sampling frames. In addition, as the newer vaccines themselves are relatively data sparse, especially for survey data, effects of administrative bias propagations based on trends in the reference vaccine may be more influential when estimating coverage of the newer vaccine directly. Second, the MR-BRT model is unable to integrate acute vaccine stock data nor data on vaccine phase-out or discontinuation, and its parameterization does not facilitate capture of large increases or decreases in newer vaccine coverage independent from the reference vaccine. The model also does not incorporate inherent dose-specific vaccine constraints, for example, MCV2 having lower estimated coverage than MCV1 in each location nor year, or exactly equal Hib3 and DTP3 coverage in locations using a tetravalent

or pentavalent vaccine. This may result in overestimation or implausible estimates of scale-up in select location-years if these inconsistencies are present in the underlying data. Third, only introductions and scale-ups that occurred within the GBD estimation years (1980 through 2019) were included in these analyses of scale-up. We also did not analyze the relationship between calendar year of introduction and scale-up (for example, if scale-up was faster when vaccines were introduced in 2019 than 2000). This may affect average scale-up calculations, as countries that introduced before 1980 may have demonstrated significantly different scale-up trends, perhaps if earlier introduction is associated with greater national wealth or access to resources, for example, and initial scale-ups were faster on average than vaccines introduced after 1980. Related, the number of countries with each vaccine introduced varies as do national recommendations to introduce certain vaccines in some countries,[30] affecting average scale-up calculations and comparison. Fourth, evaluation of scale-up ratios masks locations with low underlying reference vaccine coverage; while a country may exhibit effective scale-up, having low reference coverage would still leave many children unvaccinated. Finally, associations found between national government immunization financing and Gavi assistance in this study cannot be used as mechanisms to explain country-specific scale-up performance; notably, Gavi support and transitory state was based on country funding status in 2019 due to limitations in publicly available historical information, although all but five of the 21 total countries that transitioned out of Gavi support did so in 2019.[31] Future analyses should explore the multitude and likely interactive relationships between a comprehensive suite of possible covariates across all years and locations to evaluate potential drivers of scale-up patterns observed in a robust and causal estimation framework.

Conclusion

In the first year of introduction, new vaccine scale-up ranged on average from 40.6% (RotaC) to 94.3% (RCV1). While scale-up of most vaccines showed steady growth over time, such trends were not universal. High variation in scale-up success was observed across levels of government spending per capita and type of Gavi engagement. Looking towards goals for the next decade as part of the IA2030 agenda, estimation of newer vaccine introduction and scale-up is important in order to benchmark current levels of progress and the magnitude of gains yet to be achieved. As many countries have yet to introduce and/or scale-up all vaccines to levels similar to reference EPI vaccines, establishing and growing a reliable and comparable framework for monitoring progress will be important alongside elimination of context- and vaccine-specific barriers to high and rapid scale-up. With concerted efforts towards equity in scale-up program implementation, monitoring, and evaluation, it is possible to envision high and effective scale-ups to deliver lifesaving vaccines to all children.

References

1 McGovern ME, Canning D. Vaccination and All-Cause Child Mortality From 1985 to 2011: Global Evidence From the Demographic and Health Surveys. *Am J Epidemiol* 2015; **182**: 791–8.

2 Chang AY, Riumallo-Herl C, Perales NA, *et al.* The Equity Impact Vaccines May Have On Averting Deaths And Medical Impoverishment In Developing Countries. *Health Aff (Millwood)* 2018; **37**: 316–24.

3 Li X, Mukandavire C, Cucunubá ZM, *et al.* Estimating the health impact of vaccination against ten pathogens in 98 low-income and middle-income countries from 2000 to 2030: a modelling study. *The Lancet* 2021; **397**: 398–408.

4 Patel MK, Goodson JL, Alexander JP, *et al.* Progress Toward Regional Measles Elimination — Worldwide, 2000–2019. *MMWR Morb Mortal Wkly Rep* 2020; **69**: 1700–5.

5 WHO | The Expanded Programme on Immunization. https://www.who.int/immunization/programmes_systems/supply_chain/benefits_of_immunization/en/ (accessed Feb 22, 2021).

6 Gavi, the Vaccine Alliance. https://www.gavi.org/ (accessed April 30, 2021).

7 Galles NC, Liu P, Updike RL, et.al . Measuring routine childhood vaccination coverage in 204 countries and territories, 1980-2019: a systematic analysis for the Global Burden of Disease Study 2020, Release 1. *The Lancet*. [In Review].

8 Wouters OJ, Shadlen KC, Salcher-Konrad M, *et al.* Challenges in ensuring global access to COVID-19 vaccines: production, affordability, allocation, and deployment. *The Lancet* 2021; **397**. DOI:10.1016/S0140-6736(21)00306-8.

9 WHO. Immunization Agenda 2030: A Global Strategy To Leave No One Behind. 2020 https://www.who.int/publications/m/item/immunization-agenda-2030-a-global-strategy-to-leave-no-one-behind (accessed Feb 25, 2021).

10 WHO. Implementing the immunization agenda 2030. 2021 https://www.who.int/publications/m/item/implementing-the-immunization-agenda-2030 (accessed June 18, 2021).

11 UNICEF, WHO. WHO and UNICEF reported estimates of immunization coverage time series 2019. July 15, 2020. https://apps.who.int/immunization_monitoring/globalsummary/wucoveragecountrylist.html (accessed July 15, 2020).

12 Vos T, Lim SS, Abbafati C, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet* 2020; **396**: 1204–22. doi: https://doi.org/10.1016/S0140-6736(20)30925-9.

13 Zheng P, Barber R, Sorensen RJD, Murray CJL, Aravkin AY. Trimmed Constrained Mixed Effects Models: Formulations and Algorithms. *J Comput Graph Stat* 2021; **2021**: 1–13.

14 Murray CJL, Aravkin AY, Zheng P, et al. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet* 2020; **396**: 1223–49. doi: https://doi.org/10.1016/S0140-6736(20)30752-2.

15 UNICEF, WHO. WHO and UNICEF Year of Introductions for Selected Vaccines Database 2019. July 15, 2020. https://immunizationdata.who.int/listing.html?topic=vaccine-intro (accessed July 15, 2020).

16 Micah A, Ikilezi G, Bachmeier SD, et al. Estimating total spending by source of funding on vaccines, delivery, routine and supplementary activities for immunisation activities in low- and middle-income countries, 2000-2017. *The Lancet*. [In Review.]

17 Sorensen R, Causey K, Haeuser E, Mosser JF. Hierarchical Bayesian spline cascades, with two applications to vaccine coverage. 2021; published online Feb 17.

18 Causey K, Fullman N, Sorensen RJD, et al. Estimating global and regional disruptions to routine childhood vaccine coverage during the COVID-19 pandemic in 2020: a modelling study. *The Lancet* [In Review].

19 Sadoh AE, Nwaneri DU, Ogboghodo BC, Sadoh WE. Effect of introduction of pentavalent vaccine as replacement for Diphtheria–Tetanus–Pertussis and Hepatitis B vaccines on vaccination uptake in a health facility in Nigeria. *Vaccine* 2016; **34**: 2722–8.

20 Tricarico S, McNeil HC, Cleary DW, *et al.* Pneumococcal conjugate vaccine implementation in middle-income countries. *Pneumonia* 2017; **9**: 6.

21 Masresha BG, Luce R, Okeibunor J, Shibeshi ME, Kamadjeu R, Fall A. Introduction of the Second Dose of Measles Containing Vaccine in the Childhood Vaccination Programs Within the WHO Africa Region – Lessons Learnt. *J Immunol Sci* 2018; **Suppl**: 113–21.

22 de Figueiredo A, Simas C, Karafillakis E, Paterson P, Larson HJ. Mapping global trends in vaccine confidence and investigating barriers to vaccine uptake: a large-scale retrospective temporal modelling study. *The Lancet* 2020; **396**: 898–908.

23 Lahariya C. 'Health system approach' for improving immunization program performance. *J Fam Med Prim Care* 2015; **4**: 487.

24 Harris RC, Chen Y, Côte P, *et al.* Impact of COVID-19 on routine immunisation in South-East Asia and Western Pacific: Disruptions and solutions. *Lancet Reg Health - West Pac* 2021; **10**: 100140.

25 Yuk-Chiu Yip J. Healthcare resource allocation in the COVID-19 pandemic: Ethical considerations from the perspective of distributive justice within public health. *Public Health Pract Oxf Engl* 2021; **2**: 100111.

26 de Oliveira LH, Trumbo SP, Matus CR, Sanwogou NJ, Toscano CM. 2016. Pneumococcal conjugate vaccine introduction in Latin America and the Caribbean: progress and lessons learned, Expert Review of Vaccines, 15:10, 1295-1304, DOI: 10.1586/14760584.2016.1166961.

27 de Oliveira LH, Danovaro-Holliday MC, Matus CR, Andrus JK. Rotavirus vaccine introduction in the Americas: progress and lessons learned. *Expert Rev Vaccines* 2008; **7**: 345–53.

28 Chard AN, Gacic-Dobo M, Diallo MS, Sodha SV, Wallace AS. Routine Vaccination Coverage — Worldwide, 2019. *MMWR Morb Mortal Wkly Rep* 2020; **69**: 1706–10.

29 United Nations Children's Fund (UNICEF), World Health Organization (WHO). WHO/UNICEF Progress and Challenges with Achieving Universal Immunization Coverage Report 2019. Geneva, Switzerland: World Health Organization (WHO), 2020.

30 Glass RI. Priority setting for the introduction of rotavirus vaccine: What evidence was essential? *BioMed Central Ltd.*, 2018 DOI:10.1186/s12962-018-0126-7.

31 Facts and figures. https://www.gavi.org/programmes-impact/our-impact/facts-and-figures (accessed June 17, 2021).

Figures and tables

Figure 1. Scale-up ratios by vaccine and years of introduction.
Lines capture scale-up ratios by estimated vaccine. Plot A shows the aggregate scale-up trends within the first five years of introduction for each vaccine, whereas Plot B shows the aggregate scale-up trends for all years of introduction for each vaccine within the estimated time series (1980-2019). The dashed line denotes 95% scale-up. HepB3=Hepatitis B vaccine, third-dose. Hib3=*Haemophilus influenzae* type b, third dose. MCV2=measles-containing vaccine, second-dose. PCV3=pneumococcal conjugate vaccine, third-dose. RCV1=rubella-containing vaccine, first-dose. RotaC=completed rotavirus series.

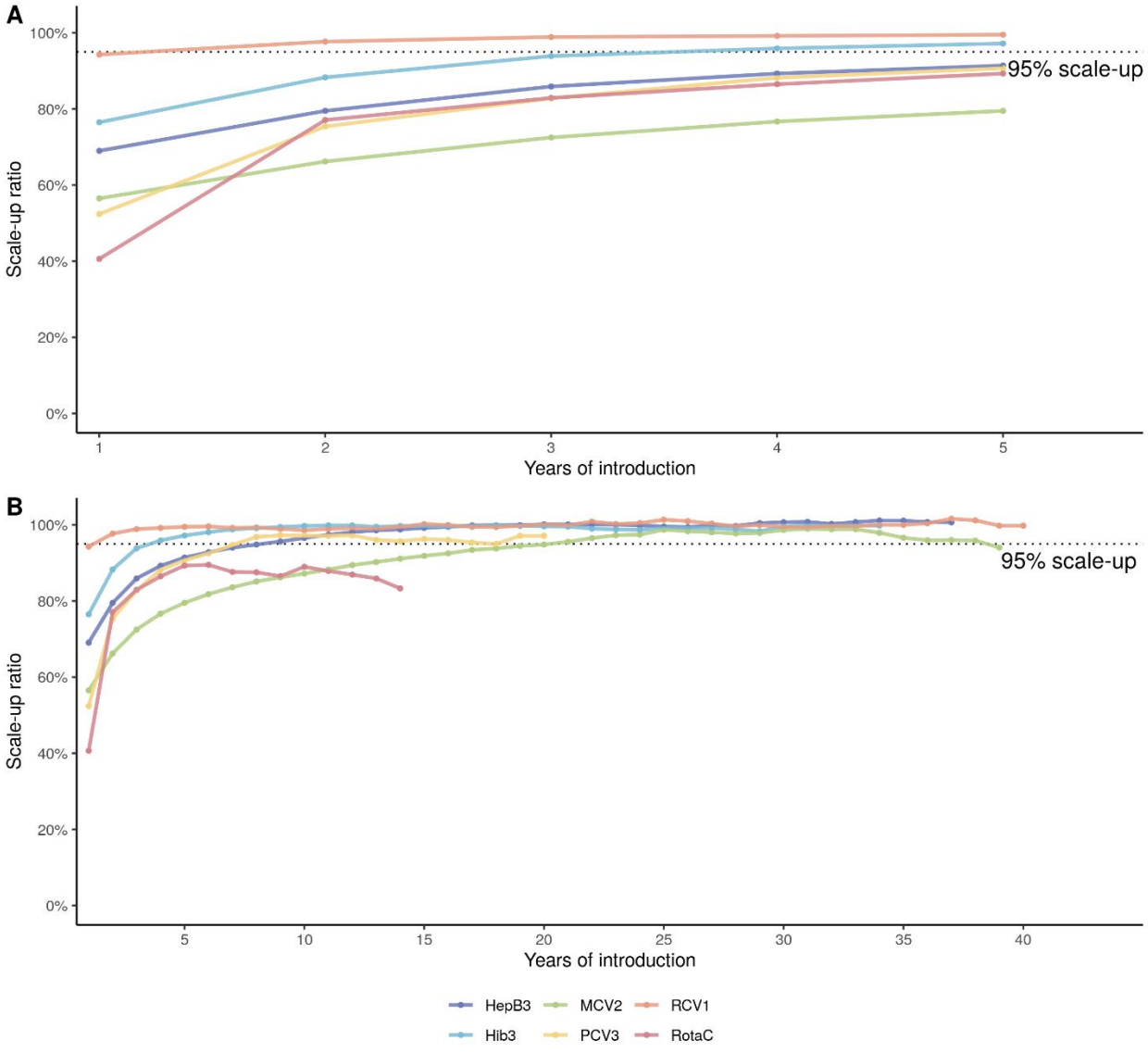

Figure 2. DTP-based vaccine scale-ups using DTP1 and DTP3.
Lines show vaccine scale-up for newer vaccines delivered on the same schedule as the DTP series. Lines of scale-up are colored based on use of DTP1 or DTP3 as the reference scale-up denominator. DTP1=diphtheria-tetanus-pertussis, first-dose. DTP3=diphtheria-tetanus-pertussis, third-dose. HepB3=Hepatitis B vaccine, third-dose. Hib3=*Haemophilus influenzae* type b, third dose. PCV3=pneumococcal conjugate vaccine, third-dose. RotaC=completed rotavirus series.

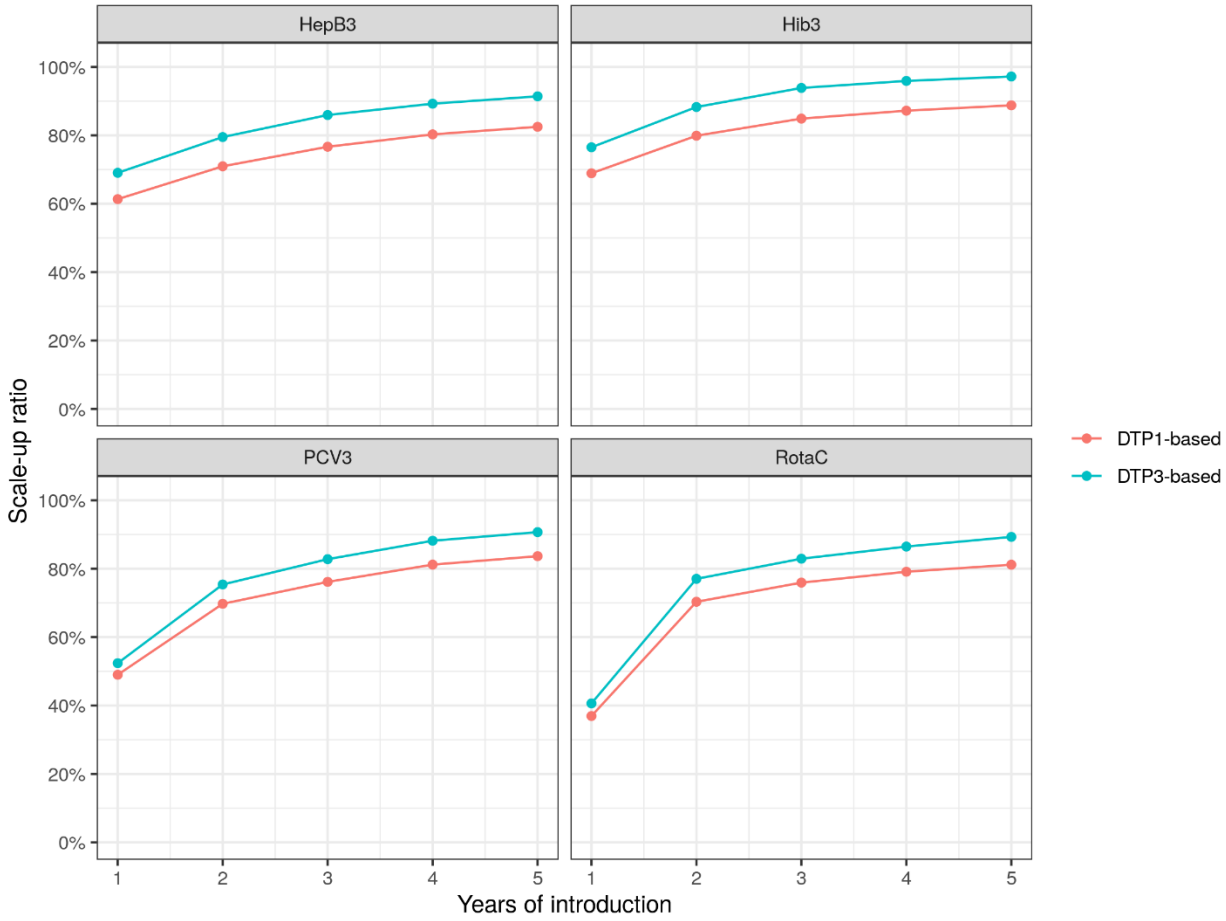

Figure 3. Relationship between vaccine scale-up and national government spending.
The solid blue line represents the relationship between vaccine scale-up ratios and national government dollars spent per capita by immunization funding category estimated by local regression (LOESS). Gray shading represents 95% confidence interval of the modeled estimate. Displayed points show vaccine scale-up and amount of government spending in the year of vaccine introduction scaled by the under-1 year national target population size.

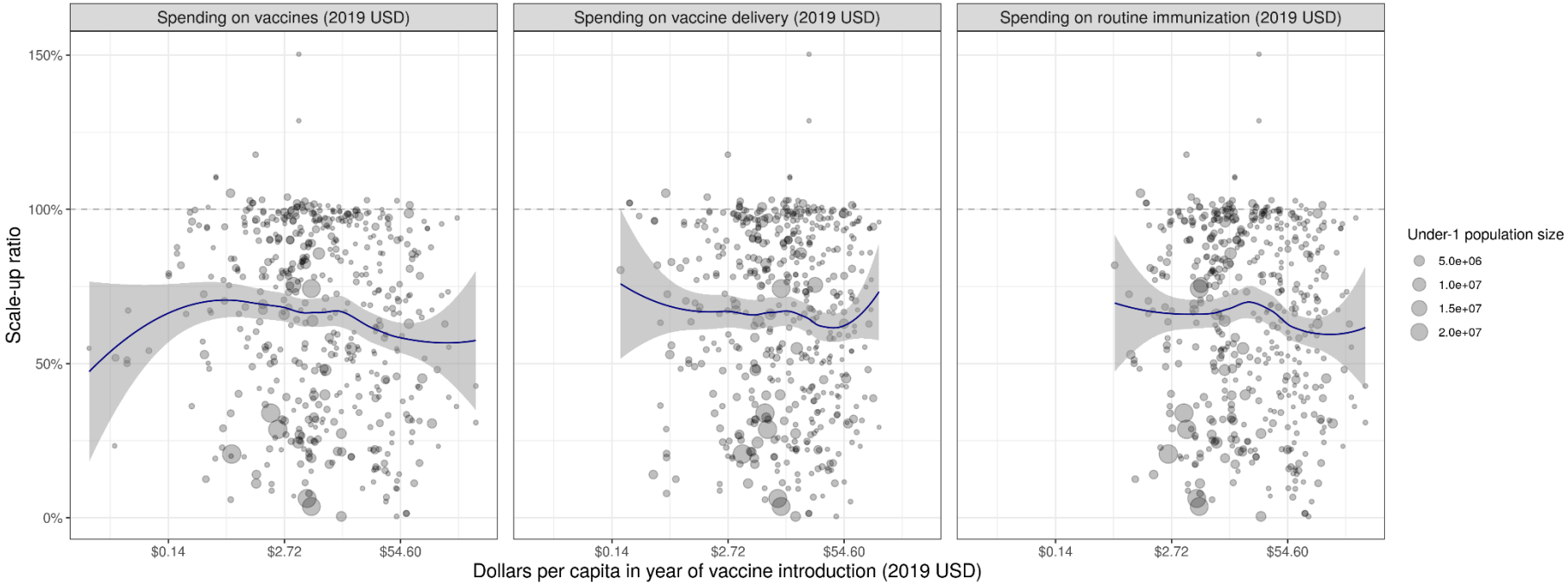

Figure 4. Scale-up ratios by vaccine and Gavi support classification.
Lines represent country scale-up patterns by vaccine for the first five years of introduction grouped by classifications of national Gavi support (Current, Past, or Never). Solid black lines represent the average scale-up observed among all countries per Gavi support classification by vaccine. Dashed black lines represent the first year scale-up ratios met or exceeded 95% scale-up by vaccine and Gavi support classification. HepB3=Hepatitis B vaccine, third-dose. Hib3=*Haemophilus influenzae* type b, third dose. MCV2=measles-containing vaccine, second-dose. PCV3=pneumococcal conjugate vaccine, third-dose. RCV1=rubella-containing vaccine, first-dose. RotaC=completed rotavirus series. Current=current receipt of Gavi support. Past=previous receipt of Gavi support. Never=No current or previous receipt of Gavi support.

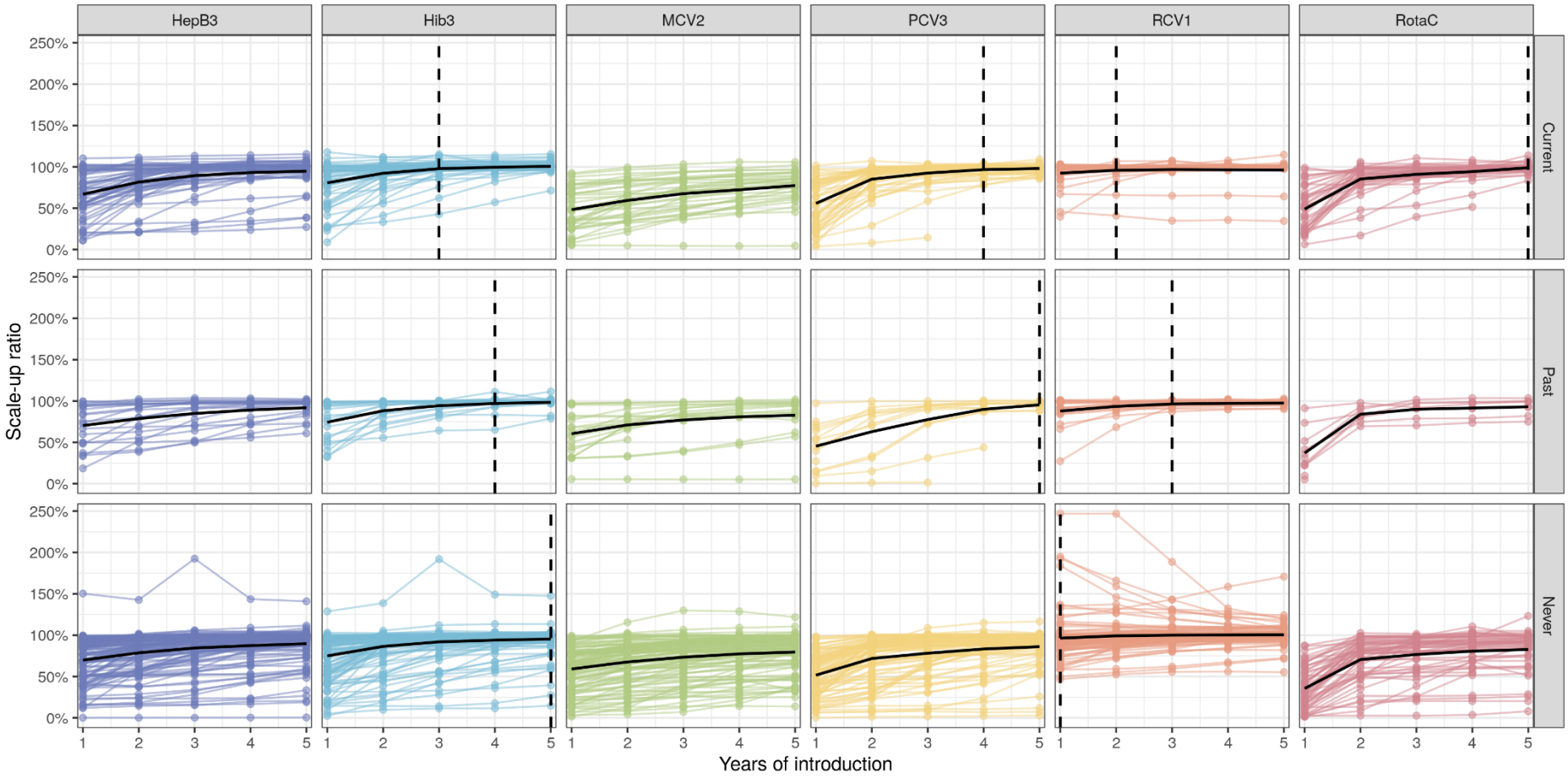

Table 1. Tabulation of national vaccine introductions by 2019.
HepB3=Hepatitis B vaccine, third-dose. Hib3=*Haemophilus influenzae* type b, third dose. MCV2=measles-containing vaccine, second-dose. PCV3=pneumococcal conjugate vaccine, third-dose. RCV1=rubella-containing vaccine, first-dose. RotaC=completed rotavirus series.

	# countries introduced (2019) N = 204
HepB3	196 (96.1%)
Hib3	198 (97.1%)
MCV2	174 (85.3%)
PCV3	155 (76.0%)
RCV1	157 (77.0%)
RotaC	111 (54.4%)
Any	**204 (100%)**
All	**78 (38.2%)**

Supplementary results

Table S1. Covariate betas associated with reference vaccine coverage in global model.
Tabulated betas describe the magnitude of the coefficient on reference EPI coverage used in the global "stage 1" MR-BRT coverage models. For HepB3, Hib3, PCV3, and RotaC models, β1 is the coefficient on DTP3 coverage; for MCV2 and RCV1 models, β1 is the coefficient on MCV1 coverage. EPI=Expanded Programme on Immunization. MR-BRT= meta-regression – Bayesian, regularised, trimmed. DTP3=diphtheria-tetanus-pertussis, third-dose. MCV1=measles-containing vaccine, first-dose. HepB3=Hepatitis B vaccine, third-dose. Hib3=*Haemophilus influenzae* type b, third dose. MCV2=measles-containing vaccine, second-dose. PCV3=pneumococcal conjugate vaccine, third-dose. RCV1=rubella-containing vaccine, first-dose. RotaC=completed rotavirus series.

	β1
HepB3	0.799
Hib3	0.853
MCV2	0.487
PCV3	0.475
RCV1	0.354
RotaC	-0.209