The fully immunized child: Summarizing intracountry inequalities in coverage with seven routine vaccines in 195 countries and territories

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Abstract

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Introduction: Failures to achieve equal access to vaccines are inhibiting progress in boosting global vaccine coverage to meet Global Vaccine Action Plan (GVAP) and Sustainable Development Goal (SDG) targets. Past efforts to quantify the distribution of vaccines in terms of full immunization coverage have been limited in scope and comparability. In this study, we produce a complete time series of estimates of the proportion of surviving children fully immunized with seven routine childhood immunizations in 195 countries and territories.

Methods: We synthesized 563 household surveys with individual-level information on vaccination status using spatiotemporal Gaussian process regression and probability theory to quantify full immunization coverage from 2006 (the first year of rotavirus vaccine introduction) to 2017. Results were constrained to antigen-specific vaccine coverage estimates from the Global Burden of Disease (GBD) project and routine introduction data from the WHO Joint Reporting Process.

Results: In 2017, 93 countries and territories had introduced all seven key routine childhood immunizations—DTP3, MCV1, Polio3, HepB3, Hib3, PCV3, and RotaC. On a global scale and in all seven super regions, introducing more newly recommended vaccines contributed to massive gains in full immunization coverage. Latin America and the Caribbean stands out as a high achiever of full immunization coverage, with most countries including all seven vaccines in the schedule by 2017. Globally, 99 million one-year-olds remained underimmunized in 2017, representing a 21.8% decline from 2010.

Discussion: Although introductions of new vaccines and investments in vaccination programs to scale-up coverage have contributed to global improvements in immunization coverage, more than two-thirds of one-year-olds are still missing at least one key childhood vaccine. Continuing to focus on the distribution of vaccines—as opposed to antigen-specific coverage—is important for assessing GVAP and SDG goals of boosting universal access.

Introduction

Vaccinations are one of the most compelling examples of cost-effective and efficacious technologies that directly contribute to massive reductions in childhood morbidity and mortality around the world. The measles vaccine alone, for example, was forecasted to avert over 13 million deaths in just nine years,[1] and the rotavirus vaccine prevented around 28,000 deaths in children under five in just the first decade following its introduction in 2006.[2] Despite progress on a global scale, not all countries are achieving high levels of vaccination coverage.[3,4] Furthermore, disparities in access and distribution of vaccines within countries can result in significant inequalities in routine immunization with the full set of recommended childhood vaccinations.[5] Addressing such inequalities in access to vaccines is a key goal of the 2015 Sustainable Development Goals (SDG)[6] and the 2011-2020 Global Vaccine Action Plan (GVAP) Decade of Vaccines Collaboration (DoV) targets.[7,8]

Vaccines play a key role in achieving 14 of the 17 SDGs adopted by United Nations member states in 2015.[6,9] To promote Goal 3, Indicator 19 (3.b.1) calls for a measure of the percent of children receiving all immunizations—specifically: bacille Calmette-Guerin (BCG) for tuberculosis, hepatitis B, polio, diphtheria-tetanus-pertussis (DTP), Haemophilus influenza type b, Pneumococcal conjugate (PCV), rotavirus, measles, rubella, and human papilloma virus (HPV) for adolescent girls—at the "appropriate age" and by sex, age, and member country.[10] The World Health Organization's (WHO) Strategic Advisory Group of Experts (SAGE) Working Group proposed defining this indicator more precisely as a single number—the proportion of the country's target population who is vaccinated—and suggests limiting the vaccines included in the country-specific indicator to only those already part of the national schedule.[11,12] Such a composite is meant to provide a single indicator of progress that reflects the country's specific disease burden and vaccine recommendation profile, the distribution of individual access to vaccines, and the achievement of delivery systems.

The existing SDG indicator (3.b.1) as defined by the United Nations and the SAGE Working Group has several limitations. First, inherently in its design, this measure is not comparable across space and time as target populations and national schedules change to reflect shifting disease contexts and national priorities. If it is to be used as a measure of progress, the denominator must be defined in the same way across all geographies in all years of estimation. Second, in only incorporating vaccines that are included in the country's national schedule, this indicator rewards countries that are late to introduce newer vaccines, as these vaccines are the ones with typically lower antigen-specific coverage. If full vaccine coverage is to be used to allocate funding and assess progress, the UN/SAGE definition disincentivizes adding new vaccines to the schedule, as they negatively impact a country's progress score.

Other groups with individual-level information on vaccination status have estimated full coverage at small geographic and temporal scales to understand vaccine trends over time, but the methods and metrics vary substantially and are limited in both scope and application.[5,13–21] The Washington State Department of Health, for example, computed the proportion of school-aged children who completed all immunization requirements for school entry ("percent compliant") by school year since 1998.[13] This work leverages extensive data availability on schoolchildren in a relatively small geographic context. Its inclusion of vaccines based on the schedule in that year, however,

detracts from its ability to compare vaccine compliance over time: adding the second dose of varicella vaccine to the schedule in the 2008-2009 school year changed the definition of full coverage thereafter and resulted in a dip in estimates of complete coverage. Similarly, a study in Tripura, India, collected primary data on vaccination status in children aged 12 to 23 months in the Mohanpur area to quantify the proportion of fully immunized children,[14] but it only included a subset of childhood immunizations and its methods are not readily reproducible without individual-level data on a larger scale. The most extensive analysis of full vaccination coverage to date[5] quantified the proportion of children fully vaccinated in 86 low- or middle-income countries but considered a small subset of key immunizations and only explored country-years with microdata available from a Demographic and Health Survey[22] or a Multiple Indicator Cluster Survey.[23]

In this study, we constructed an indicator of full immunization coverage (FIC) in all 195 countries and territories included in the Global Burden of Disease 2017[3] from 2006 (the year of the first introduction of rotavirus vaccine in the United States)[24] to 2017. This indicator better reflects childhood protection, is relevant to all countries, is comparable over time and across all geographies, and rewards countries for introducing new vaccines to the schedule. To stabilize the numerator and denominator included in this measure of FIC, we excluded vaccines that are geography dependent (e.g. yellow fever, Japanese encephalitis, and meningitis), vaccines that can be replaced with appropriate screening or are being phased out of some country schedules (e.g. BCG), and adolescent vaccines or vaccines with highly varying country target populations and schedules (e.g. HPV). We define FIC as the proportion of children fully vaccinated with seven dose-specific childhood vaccines typically administered before age two: third-dose diphtheria-tetanus-pertussis, first-dose measles, third-dose polio, third-dose hepatitis B, third-dose Haemophilus influenzae type b, third-dose pneumococcal conjugate, and complete rotavirus (two or three doses, depending on country schedule[25]). This metric includes three of the original WHO Expanded Programme on Immunization (EPI)[26] vaccines; promotes GVAP goals of expanding existing vaccines;[8] and includes vaccinations more recently recommended by SAGE, which are important to considerations of full vaccine coverage.

Methods

We define full vaccination coverage as the proportion of children in the target population vaccinated with all of the following seven vaccines: third-dose diphtheria-tetanus-pertussis (DTP), first-dose measles (MCV1), third-dose polio (Polio3), third-dose hepatitis B (HepB3), third-dose Haemophilus influenzae type b (Hib3), third-dose pneumococcal conjugate vaccine (PCV3), and rotavirus vaccine ("complete" coverage with two or three doses, depending on country schedule;[25] RotaC). This metric is a single indicator of progress that, despite differences in country schedules, is comparable across all geographies and years of estimation by including all seven vaccines even if they have not been introduced in the national schedule; if no child is receiving one of these critical vaccines, no child is fully vaccinated. Full immunization coverage can be expressed as the joint probability of vaccination:

$$FIC = P(DTP3 \ \& \ MCV1 \ \& \ Polio3 \ \& \ HepB3 \ \& \ Hib3 \ \& \ PCV3 \ \& \ RotaC).$$

Conditional probabilities of vaccination status

We identified all data sources that were tagged with vaccine keywords in the Global Health Data Exchange (GHDx),[27] had individual-level information on vaccination status, and collected data between 1980 and 2018. Our overall dataset was comprised of 618 household surveys, including 269 Demographic and Health Surveys (DHS),[22] 167 Multiple Indicator Cluster Surveys (MICS),[23] 24 Reproductive Health Surveys (RHS),[28] 11 Living Standards Measurement Study (LSMS) surveys,[29] and 147 other smaller survey series and country-specific surveys. These data sources capture information on vaccination status by antigen and dose from vaccine cards and maternal recall. We considered a child to be vaccinated with a certain number of doses of an antigen if the survey recorded either a date from the child's vaccine card or, in the absence of a vaccine card, an affirmative response from the mother.

A child was included in in the analysis if they were between 12 months (i.e. at least as old as the first full year following the target age range for most vaccines) and five years of age. The first cohort of one-year-olds was excluded if the country-specific vaccine schedule for MCV1 (as of 2017[25]) was later than 12 months. Irrespective of schedule, each child's vaccination status was assigned to the child's year of birth. This definition aligned with the WHO's 2018 Joint Reporting Process[25] definition of administrative coverage, avoided including children who had not completed the full schedule, and allowed us to utilize coverage data across several birth cohorts within the same survey. All data were tabulated to survey-, geography-, year- and antigen-specific estimates from weighted unit record data, taking into account survey design.

Only 44 of the 618 data sources provided information on all seven components of FIC (Table 1). With very limited data on all seven vaccines at the individual level for every country-year of interest, we can approximate FIC by leveraging information from (1) conditional probabilities as calculated from unit record data on vaccination status from household surveys that include even a subset of vaccines and (2) antigen- and dose-specific estimates (marginal probabilities) of vaccine coverage.

Table 1: Available individual-level data by count of household surveys and unique countries covered.

Probability	**Surveys**	**Countries covered**
P(DTP3 & MCV1 & Polio3 & HepB3 & Hib3 & PCV3 & RotaC)	44	30
P(DTP3)	592	116
P(MCV1)	580	116
P(Polio3)	581	116
P(DTP3 & MCV1 & Polio3)	558	116
P(HepB3)	310	107
P(HepB3 | DTP3 & MCV1 & Polio3)	304	106
P(Hib3)	200	89
P(DTP3 & MCV1 & Polio3 & HepB3 & Hib3 & PCV3 & RotaC)	44	30
P(DTP3)	592	116

First, we used probability theory—namely, Bayes' Rule on the relationship between marginal and conditional probabilities,[30,31] given that the marginal distributions of vaccine coverage are not statistically independent—to split the full joint probability into the product of several smaller probabilities. At its simplest, and adding vaccines approximately sequentially by introduction, FIC can be expressed as:

$$
\begin{aligned}
&P(DTP3 \,\&\, MCV1 \,\&\, Polio3 \,\&\, HepB3 \,\&\, Hib3 \,\&\, PCV3 \,\&\, RotaC) = \\
&P(DTP3) * \\
&P(MCV1 \mid DTP3) * \\
&P(Polio3 \mid MCV1 \,\&\, DTP3) * \\
&P(HepB3 \mid Polio3 \,\&\, MCV1 \,\&\, DTP3) * \\
&P(Hib3 \mid HepB3 \,\&\, Polio3 \,\&\, MCV1 \,\&\, DTP3) * \\
&P(PCV3 \mid Hib3 \,\&\, HepB3 \,\&\, Polio3 \,\&\, MCV1 \,\&\, DTP3) * \\
&P(Rotavirus \mid PCV3 \,\&\, Hib3 \,\&\, HepB3 \,\&\, Polio3 \,\&\, MCV1 \,\&\, DTP3),
\end{aligned}
$$

where each probability can be computed at the survey level as the proportion of children with non-missing information on vaccination status who meet the conditions. $P(HepB3 \mid DTP3 \,\&\, MCV1 \,\&\, Polio3)$, for example, represents the proportion of children vaccinated with at least DTP3, MCV1, and Polio3 who were also vaccinated with at least three doses of HepB. All available data on each probability can then be synthesized in a statistical framework (see below) before taking the product to estimate FIC.

Although a direct application of Bayes' Rule in this way would allow for the use of data sources administered across a larger time series even if they only include information on some vaccines, it would require us to exclude surveys with crucial information on RotaC if they did not also contain information on PCV3, for example, which still leaves the conditional probabilities containing more recently recommended vaccines with small data availability. Instead, to further increase our input data and reduce the number of computations from seven to five, we based our estimate of FIC on three basic vaccinations that were part of the original Expanded Programme on Immunization (EPI) schedule.[26] Approximating Bayes' Rule above, we computed the joint probability of DTP3, MCV1, and Polio3 vaccination and four conditional probability indicators, each of which is grounded on the joint probability of vaccination with DTP3, MCV1, and Polio3. This method allowed us to maximize our data inputs because nearly all identified survey data with unit record information (558 unique surveys covering 116 countries; Table 1) included information on at least these three basic vaccinations. With this approach, we computed five probabilities from survey data:

$$
\begin{aligned}
&P(DTP3 \,\&\, MCV1 \,\&\, Polio3), && \textit{Probability 1} \\
&P(HepB3 \mid DTP3 \,\&\, MCV1 \,\&\, Polio3), && \textit{Probability 2a} \\
&P(Hib3 \mid DTP3 \,\&\, MCV1 \,\&\, Polio3), && \textit{Probability 2b} \\
&P(PCV3 \mid DTP3 \,\&\, MCV1 \,\&\, Polio3), \text{ and} && \textit{Probability 2c} \\
&P(RotaC \mid DTP3 \,\&\, MCV1 \,\&\, Polio3), && \textit{Probability 2d}
\end{aligned}
$$

which were synthesized (described below) and then multiplied to estimate FIC.

Applying Bayes' Rule to get from the original seven to the final five probabilities of interest, the abridged conditional probabilities required us to make three assumptions about the relationships between Hib3, PCV3, and RotaC coverage and other vaccines, namely:

$$P(Hib3 \mid DTP3 \,\&\, MCV1 \,\&\, Polio3) \qquad \textit{Assumption 2b}$$
$$\sim P(Hib3 \mid HepB3 \,\&\, Polio3 \,\&\, MCV1 \,\&\, DTP3),$$
$$P(PCV3 \mid DTP3 \,\&\, MCV1 \,\&\, Polio3) \qquad \textit{Assumption 2c}$$
$$\sim P(PCV3 \mid Hib3 \,\&\, HepB3 \,\&\, Polio3 \,\&\, MCV1 \,\&\, DTP3), \text{ and}$$
$$P(RotaC \mid DTP3 \,\&\, MCV1 \,\&\, Polio3) \qquad \textit{Assumption 2d}$$
$$\sim P(RotaC \mid PCV3 \,\&\, Hib3 \,\&\, HepB3 \,\&\, Polio3 \,\&\, MCV1 \,\&\, DTP3).$$

We tested these three assumptions in surveys with data on all component antigens and found that the modeled probabilities we calculated were highly correlated with the true probabilities they were meant to approximate (R_{2b}=0.94; R_{2c}=1.00; R_{2d}=0.97). These simplifications result in a slight systematic underestimation of probabilities *2b*, *2c*, and *2d*, which we adjust for when constructing the full joint probability of FIC.

After calculating probabilties *1*, *2a*, *2b*, *2c*, and *2d* at the survey level, we estimated a complete time series of our data using a statistical framework. We used a spatiotemporal Gaussian process regression (ST-GPR) to capture temporal variation in the distribution of vaccines, synthesize point estimates from our input data, and derive a complete time series in all 195 countries and territories for each of these five probabilities. This method has been used extensively in other time-series analyses including the Global Burden of Disease (GBD) and related studies[3,32–36] to leverage all available data sources, use data that is nearby in space and time to make predictions in geography-years with fewer surveys, and account for uncertainty. We defined our prior (stage one) model as:

$$logit(P_{c,t}) = \beta_0 + \beta_1 X_{c,t} + \alpha_c + \gamma_{R[c]} + \omega_{SR[c]} + \varepsilon_{c,t},$$

where $P_{c,t}$ is the probability of vaccination that is being modeled (i.e. probabilties *1*, *2a*, *2b*, *2c*, and *2d*) for country, c, and year, t; $X_{c,t}$ is value of the predictive covariate (here, the marginal probability of vaccination, the Healthcare Access and Quality Index,[36] and/or an estimate of conflict mortality) for country, c, and year, t; and α_c, $\gamma_{R[c]}$, and $\omega_{SR[c]}$ are country, region, and super-region random intercepts, respectively.

Random draws of 1,000 samples were obtained from each modeled probability by country and year. Ninety-five percent uncertainty intervals (UI) were calculated by taking the ordinal 2.5th and 97.5th draws from the sample distribution.

Antigen- and dose-specific vaccine coverage

We used estimates of coverage of antigen- and dose-specific vaccines from the Global Burden of Disease project[3] to inform our estimates of full vaccine coverage. These estimates provided a full time series of coverage from 1980 through 2017 in all 195 countries in a comprehensive statistical framework and leveraged information from not only household surveys with individual-level data, but also survey report tabulations, literature data, and bias-corrected administrative data collected through the World Health Organization's Joint Reporting Process.[25]

Constructing the joint distribution

We estimated the full joint distribution,

$$P(DTP3 \,\&\, MCV1 \,\&\, Polio3 \,\&\, HepB3 \,\&\, Hib3 \,\&\, PCV3 \,\&\, RotaC),$$

as the product of the joint probability of vaccination with DTP3, MCV1 and Polio3 (*Probability 1*) and modeled estimates of the four conditional probabilities (*2a*, *2b*, *2c*, and *2d*) in a step-wise approach. In this step, we accounted for the slight systematic underestimation in probabilities *2b*, *2c*, and *2d* compared to assumptions *2b*, *2c*, and *2d* by applying a global correction factor. First, we computed the mean relationship between each of the modeled and true probabilities across all available surveys using linear regression:

$$Assumption_{p,s,t} = \beta_0 + \beta_1 Probability_{p,s,t},$$

where $Assumption_{p,s,t}$ is the "true" conditional probability for probability, p, survey, s, and year, t, and $Probability_{p,s,t}$ is the conditional probability grounded in DTP3, MCV1, and Polio3 conditionality for probability, p, survey, s, and year, t. We multiplied the global correction factors, β_1, by their respective conditional probabilities (*2b*, *2c*, and *2d*) in the step-wise multiplication of all five probabilities:

$$\begin{aligned}
&P(DTP3 \,\&\, MCV1 \,\&\, Polio3) * \\
&P(HepB3 \mid DTP3 \,\&\, MCV1 \,\&\, Polio3) * \\
&P(Hib3 \mid DTP3 \,\&\, MCV1 \,\&\, Polio3) * \beta_{1,2b} * \\
&P(PCV3 \mid DTP3 \,\&\, MCV1 \,\&\, Polio3) * \beta_{1,2c} * \\
&P(RotaC \mid DTP3 \,\&\, MCV1 \,\&\, Polio3) * \beta_{1,2d},
\end{aligned}$$

where β_1 is the linear regression coefficient of the assumption regressions for probabilities *2b*, *2c*, and *2d*, respectively.

Also in this step, we constrained FIC to not exceed the marginal distributions of antigen-specific coverage. For example, $P(DTP3 \,\&\, MCV1 \,\&\, Polio3)$ cannot be greater than the minimum probability of vaccination for DTP3, MCV1, or Polio3, and $P(DTP3 \,\&\, MCV1 \,\&\, Polio3) * P(HepB3 \mid DTP3 \,\&\, MCV1 \,\&\, Polio3)$ cannot be greater than $P(HepB3)$. This constraint on full coverage by antigen- and dose-specific vaccination coverage allowed us to leverage information from administrative data and report tabulations from the marginal distribution estimates of vaccine coverage, given that only individual-level data can be used as inputs for the conditional probability models. This approach also allowed us to indirectly confirm that full coverage was constrained to zero if not all antigens had yet been introduced to the country's routine schedule.

Uncertainty was propagated by performing each multiplication and marginal distribution constraint step at the 1,000 draw level.

Model validation

We tested the utility of our metric of FIC by comparing it to two other indicators of immunization coverage, including (1) the joint probability of full vaccination coverage assuming complete independence of DTP3, MCV1, Polio3, HepB3, Hib3, PCV3, and RotaC (i.e. the product of antigen-specific coverage estimates) and (2) the lowest antigen-specific coverage in that country and year which, by definition, must be greater than or equal to FIC. Fit was assessed using root mean square error (RMSE),

$$RMSE_{FIC} = \sqrt{\frac{\sum_{i=1}^{N}(FIC_i - data_i)^2}{N}},$$

and mean absolute error (MAE),

$$MAE_{FIC} = \frac{\sum_{i=1}^{N} |FIC_i - data_i|}{N},$$

where FIC is the indicator of full immunization coverage, for N data points where individual-level survey data on all antigens in the joint probability were available.

We assessed our model using five-fold out-of-sample cross validation on the base joint probability model $P(DTP3 \,\&\, MCV1 \,\&\, Polio3)$, each conditional probability, and our final FIC indicator constructed from these five components.

We also compared our metric to past and current SDG full coverage indicators (i.e. the geometric mean of antigen-specific coverage[37] and the arithmetic mean of antigen-specific coverage[3]), but neither came close to predicting FIC and both were excluded from the final analysis.

Denominators

We used country- and year-specific population estimates of one-year-olds from the Global Burden of Disease 2017 study[38] as denominators to produce population-weighted aggregates in proportion and count space.

Secondary analysis: Second-dose measles

Only 53 country-years of individual-level data in 29 countries were available for the second dose of the measles vaccine (MCV2). These data were not extensive enough to allow for inclusion in a statistical model as specified above. In order to address this limitation, we performed a secondary analysis exploring the relationships between MCV2 vaccination status and other antigens. We tested the collinearity of antigens in surveys with information on MCV2 vaccination status in addition to the seven components of the full coverage indicator by computing variance inflation factors (VIF) for each predictor of FIC. We also tested the utility of predictors of the conditional probability $P(MCV2 \mid DTP3 \,\&\, MCV1 \,\&\, Polio3)$ by exploring the variation in probability across surveys and by analyzing coefficients from a linear regression model with the marginal distribution of MCV2 coverage as a predictor,

$$P(MCV2 \mid DTP3 \,\&\, MCV1 \,\&\, Polio3)_{c,t} = \beta_0 + \beta_1 MCV2_{c,t},$$

where $P(MCV2 \mid DTP3 \,\&\, MCV1 \,\&\, Polio3)_{c,t}$ is the survey-level conditional probability data for country, c, and year, t, and $MCV2_{c,t}$ is the country, c, and year, t, estimate of second-dose measles coverage.

Results

Globally, 36 million children (26.6% of one-year-olds; 95% UI 23.9-29.3%) were fully immunized in 2017, a 21.8% (95% UI 19.2-24.3%) improvement from 2010 in the number of children not fully vaccinated. Grouping countries into seven "super regions" by geographic proximity and level of development, countries in Latin America and the Caribbean outperformed their peers to achieve 61.8% (95% UI 58.1-64.6%) FIC by 2017 (Figure 1). This trend is largely driven by the timely introduction of newer vaccines into the routine immunization schedules of countries in Latin America relative to other super regions. By 2010, 11 countries (34%) in Latin America and the Caribbean had introduced all seven vaccines, compared to six (18%) high- income countries; three

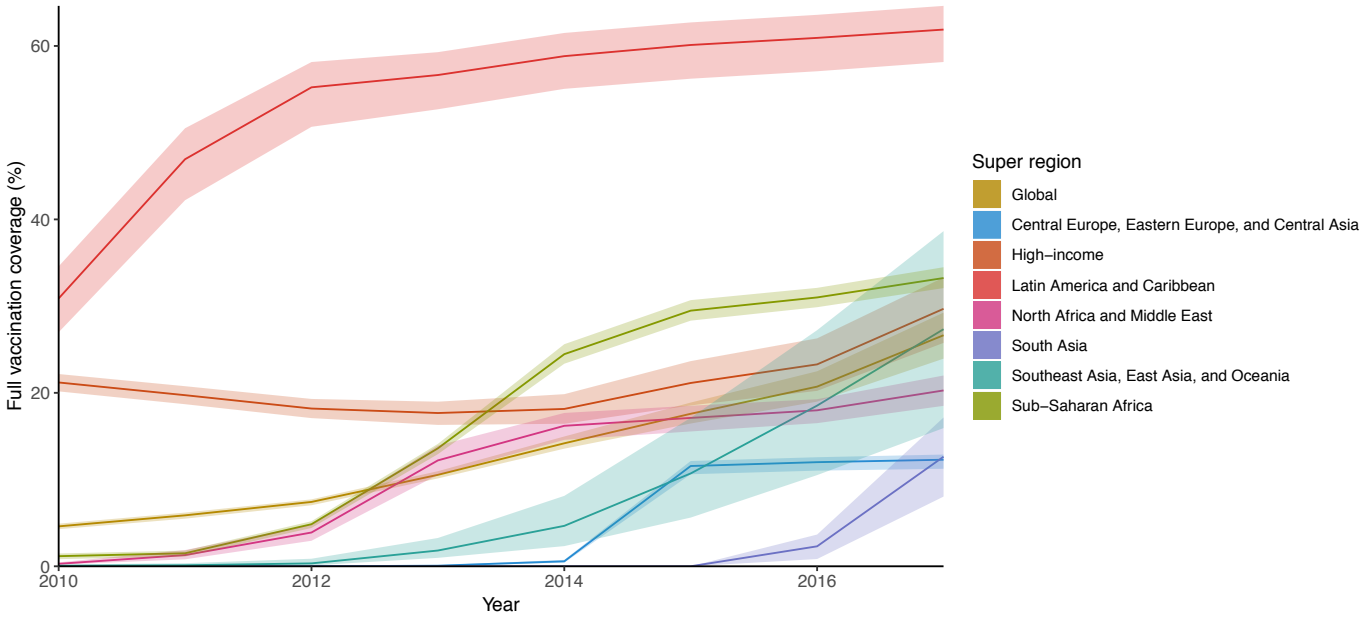

Figure 1: Super-region trends in FIC from 2010 to 2017.

in North Africa and the Middle East (11%); and zero in Central Europe, Eastern Europe, and Central Asia. By 2017, 56% of countries in Latin America and the Caribbean included all seven vaccines in their routine schedules, representing nearly all (94%) of the super region's under-one population.

In 2017, 93 countries and territories included DTP3, MCV1, Polio3, HepB3, Hib3, PCV3, and RotaC—all seven components of FIC—in their national routine immunization schedules. Among these countries, the proportion of children who received all seven vaccines ranged from 0.7% (95% UI 0.2-2.1%) in Ireland, which introduced rotavirus in 2016 and, by 2017, had not scaled up coverage to meet other antigens, to 92.1% (95% UI 88.1-95.2%) in Nicaragua, which had all seven vaccines introduced since 2010 and boasted high coverage across all antigens in 2017 (Supplementary Table S1, Figure 2B). Geographies with all seven vaccines introduced for at least a decade prior to 2017 achieved full vaccination coverage of at least 40.0% (95% UI 27.2-49.9%; U.S. Virgin Islands), median 51.5% (95% UI 28.8-69.2%; Luxembourg), and at most 68.7% (95% UI 41.5-86.5; Belgium) of children in the target population in 2017 (Supplementary Table S1).

The probabilities of vaccination with HepB3, Hib3, PCV3, and RotaC conditional upon vaccination with DTP3, MCV1, and Polio3 tended to increase over time following introduction (Figure 3). All indicators had statistically significant exponentiated univariate logistic model coefficients, which can be interpreted as odds ratios (HepB3 β=1.10, Hib3 β=1.33, PCV3 β=1.74, and RotaC β=1.80). The full coverage indicator was mildly inversely associated with the calendar year of the last introduction in countries with all seven antigens introduced by 2017 (R=-2.24, p=0.01). Countries that underperformed relative to the time since last introduction had low antigen-specific coverage for at least one vaccine. For example, the United States introduced

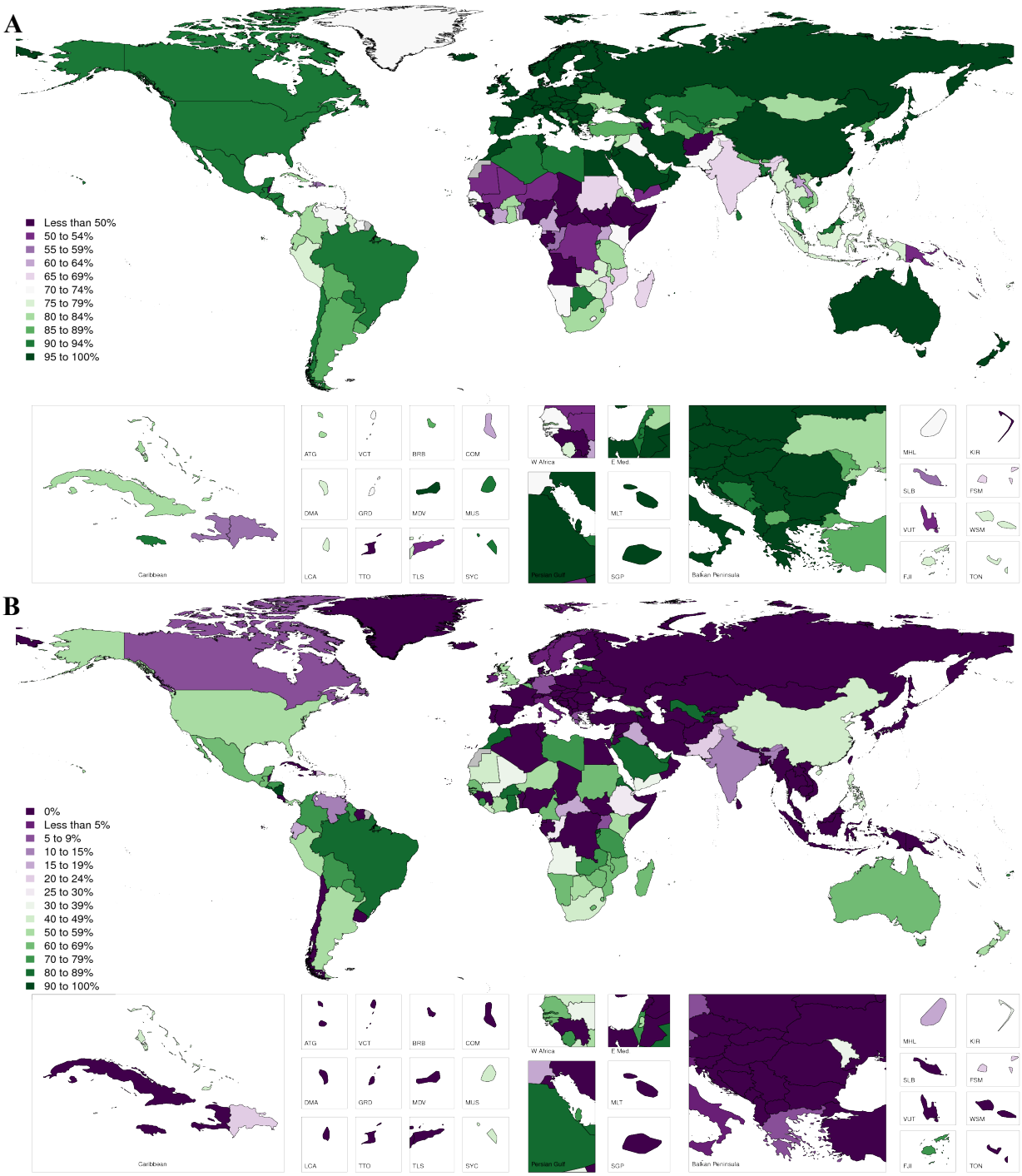

Figure 2: (A) Percent of children vaccinated with DTP3, MCV1, and Polio3, by country, in 2017. (B) Percent of fully vaccinated children in 2017; countries in the deepest purple shade had not introduced all seven vaccines (DTP3, MCV1, Polio3, HepB3, Hib3, PCV3, and RotaC (i.e. 0% FIC) by 2017.

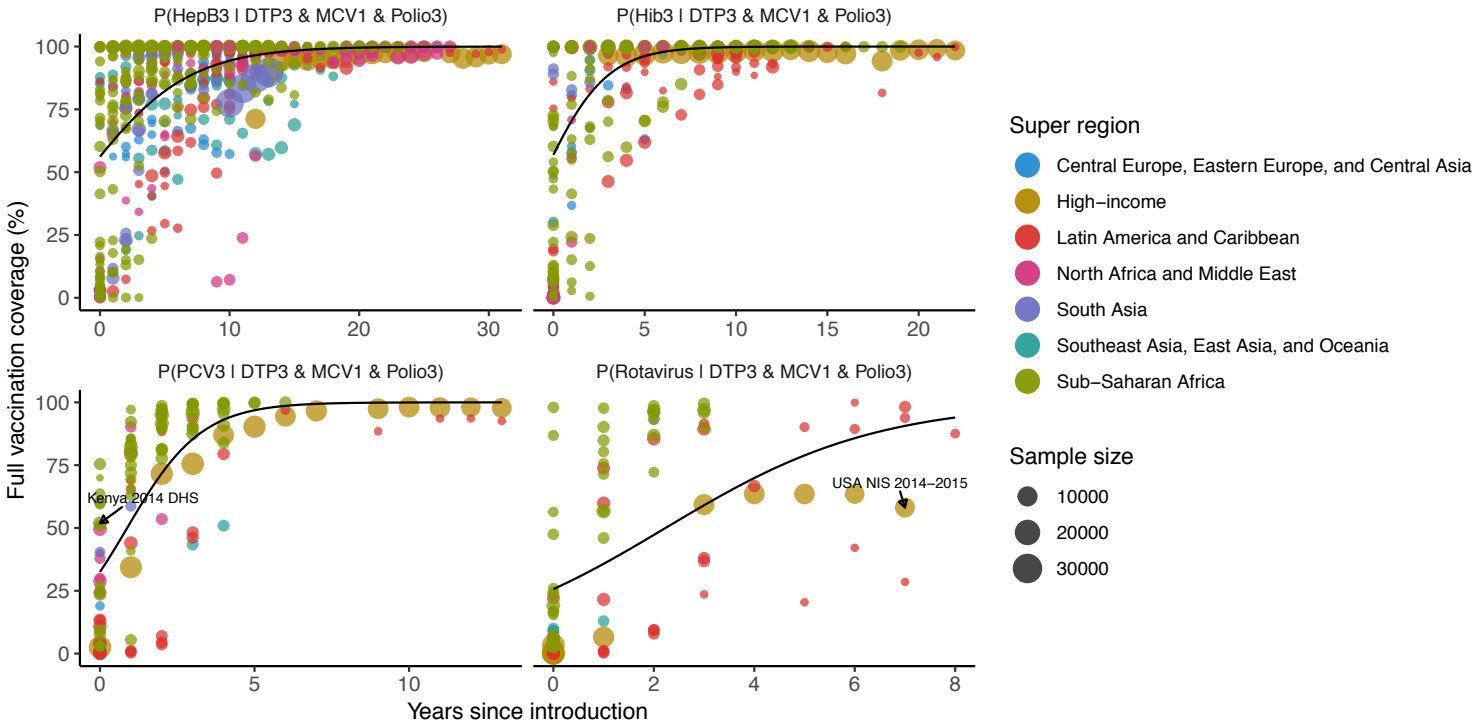

Figure 3: The probability of vaccination with HepB3, Hib3, PCV3, and RotaC vaccines conditional upon vaccination with DTP3, MCV1, and Polio3 increases with time since introduction in the routine schedule.

the rotavirus vaccine in 2006, but data from the 2013-2014 National Immunization Survey (NIS)[39] show that rotavirus vaccine coverage was only 54.6% among the 2012 birth cohort (Figure 3). Countries with high full coverage relative to the time since last introduction maintained high vaccine coverage in already introduced vaccines and rapidly scaled up coverage of newly introduced vaccines. Kenya, for example, scaled up PCV coverage rapidly after introduction in 2011; the 2014 DHS[40] indicated PCV3 coverage of 51.9% in the first year of rollout (Figure 3).

At the individual level, vaccination status of one antigen was often not predictive of the others (Table 2). Compared to more established vaccine like DTP3, Polio3, and MCV1, vaccines that were introduced more recently, such as rotavirus and PCV, were less correlated with other antigens even in countries that had all seven vaccines introduced into the national routine schedule by the year of data collection.

Table 2: Correlation matrix of vaccination status with seven dose-specific antigens from pooled unit record data of children under five years with information on all vaccines.

	DTP3	*MCV1*	*Polio3*	*HepB3*	*Hib3*	*PCV3*	*RotaC*
DTP3	1						
MCV1	0.644	1					
Polio3	0.746	0.606	1				
HepB3	0.838	0.587	0.678	1			
Hib3	0.890	0.611	0.706	0.836	1		
PCV3	0.504	0.392	0.435	0.502	0.512	1	
RotaC	0.225	0.186	0.156	0.241	0.238	0.284	1

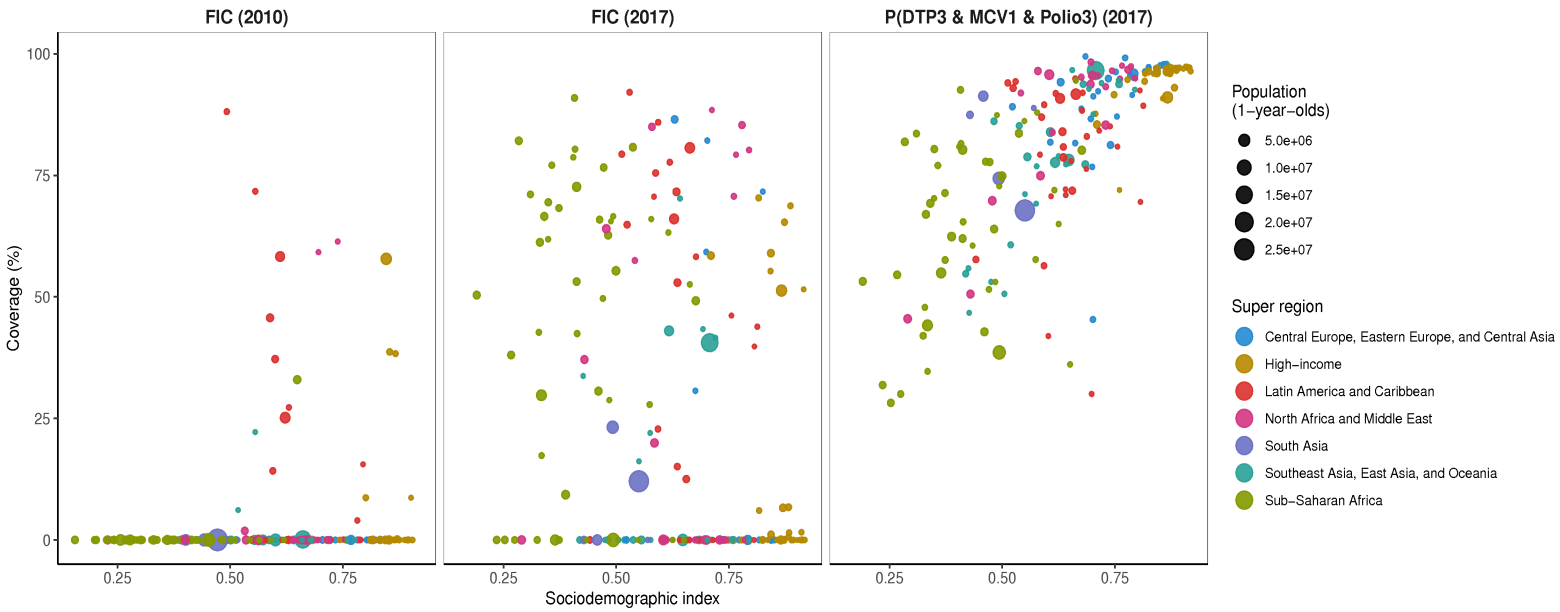

Figure 4: FIC versus the sociodemographic index (SDI). While countries with higher SDI tended to include all seven components of FIC in their routine schedule earlier than countries with lower SDI, SDI was not predictive of FIC by 2017 (R^2=0.07). In contrast, the joint probability of vaccination with DTP3, MCV1, and Polio3 was mildly associated with SDI in 2017 (R^2=0.49).

When comparing estimates of FIC to the socio-demographic index (SDI), expected variation between indicators by level of development[32] did not hold (Figure 4). While countries with higher SDI (e.g. countries in the high-income and Latin America super regions) tended to include all seven components of FIC in their routine schedule earlier than countries with lower SDI, SDI was not predictive of overall FIC by 2017 (linear model R^2=0.07). Only one country in Sub-Saharan Africa (South Africa) had introduced all seven vaccines in 2010, but that number increased to 35 (76% of countries) in 2017. These introductions led to Sub-Saharan Africa overtaking high-income countries overall in terms of FIC during this time period (Figure 1). In contrast, the joint probability of vaccination with DTP3, MCV1, and Polio3 (Figure 2A) was mildly associated with SDI (linear model R^2=0.49; Figure 4).

In an out-of-sample cross-validation analysis, our indicator performed better than the lowest survey-level estimate of antigen-specific coverage in terms of MAE and RMSE on nearly all tests (Figure 5). With all metrics, our model outperformed the joint probability of full coverage assuming complete independence of the marginal distributions.

In our secondary analysis, we found that second-dose measles coverage was the least correlated to a child's vaccination status with other antigens; its variance inflation factor was 1.02, compared to the second smallest, 1.12 (RotaC), and the largest, 3.37 (DTP3). Its association to the three base vaccines was highly variable (Supplementary Figure S1). In addition, the marginal distribution of MCV2 coverage was not predictive of the conditional probability of MCV2 given vaccination with DTP3, MCV1, and Polio3 (adjusted R^2=0.051).

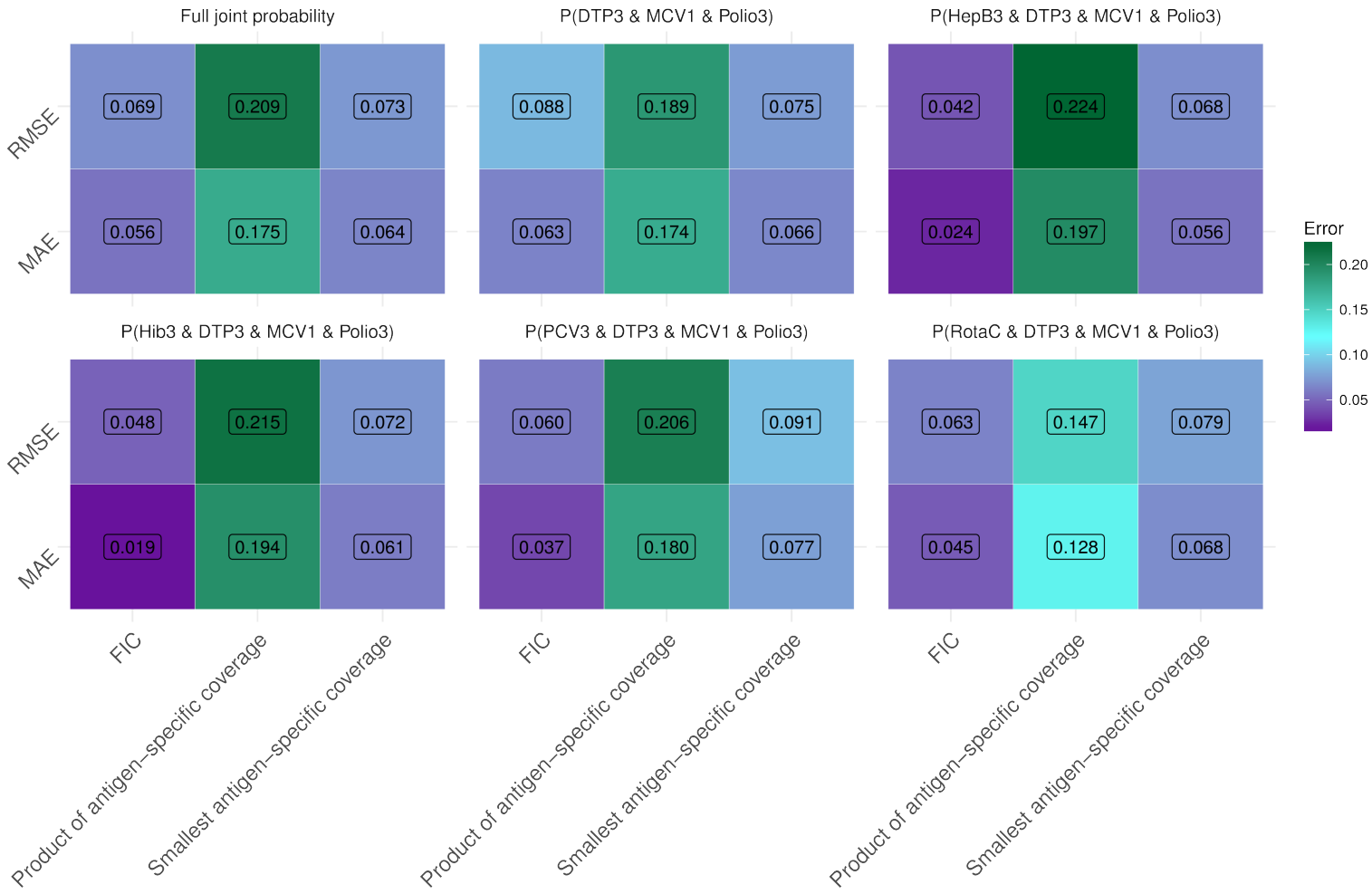

Figure 5: Out-of-sample model validation of our indicator of FIC (an estimate of the joint probability of full coverage), the product of survey-level antigen-specific coverage (the joint probability of full coverage assuming complete independence of the marginal distributions) and the smallest survey-level estimate of antigen-specific coverage (the highest survey-level value of FIC). We compared these indicators in terms of root mean square error (RMSE) and mean absolute error (MAE). Our indicator performed better than the product of antigen-specific coverage on all metrics, and better than the smallest antigen-specific coverage in nearly all comparisons.

Discussion

Many countries have made substantial progress in fully immunizing children with seven key vaccines since 2010. Latin America, in particular, stands out as a high achiever of equitable vaccination coverage, a phenomenon also seen across other indicators of maternal and child health.[41] Developing countries are outperforming high-income countries by quickly scaling up newly introduced vaccines to achieve comparably high FIC for their level of development. Overall, gains on the global scale have been largely driven by countries introducing more vaccines into their routine immunization schedules, but FIC has also been boosted by increasing antigen-specific coverage and more uniformly distributing vaccines across target populations. Even with this

progress, a large proportion of children globally are still missing at least one potentially life-saving vaccine. Improving FIC in contexts where many children are being left out requires the infrastructure to introduce newly recommended vaccines as well as scale up coverage of these antigens in a timely manner.

There are several limitations to this study. First, our restriction to data sources with unit record data limited our pool of available data to a relatively small sample for a global analysis. However, by using all relevant data from the Global Health Data Exchange,[27] our dataset likely represents a significant portion of applicable nationally representative data that exist. Second, we were unable to adjust for biases implicit in household survey data like maternal recall bias, catch-up doses administered after 24 months of age, differential mortality by vaccination status, and private market or campaign doses. Furthermore, these available data did not enable us to directly measure FIC, instead requiring us to make several assumptions about the relationships between conditional probabilities of vaccination in order to approximate the joint probability of FIC. However, observed within-survey variation in the conditional probabilities of vaccination status was minimal and we applied a correction factor to reduce the downward bias that accompanied inflating these denominators.

Our analysis suggests that, while our seven-component FIC is an important metric of inequalities in a country's vaccination program, the second dose of the measles vaccine is an important additional predictor of full vaccination coverage in children. Given the great variation in introduction status, country schedules, coverage across space and time, and relationships to vaccination status with other antigens, MCV2 is an important indicator to consider in future analyses. Without appropriate data, we could neither directly include it in our indicator nor approximate it with other predictors. A focus on data, particularly by expanding existing household survey data collection efforts, could enable future FIC analyses to include MCV2, HPV, and other important, globally-relevant vaccines.

While antigen-specific vaccine coverage remains high in some countries, especially for the well-established vaccines like measles, diphtheria-tetanus-pertussis, and polio, reporting aggregate-level estimates of vaccine coverage by antigen masks local inequities in vaccine distribution and access. Our efforts to summarize the distribution of childhood vaccines tells a different story about global progress in strengthening immunization services to achieve SDG Goal 3. More recently developed vaccines are poorly correlated with established vaccines as well as with each other but are, arguably, equally important to reducing childhood infections.[42–45] Assessments of the success of vaccination programs and routine administration infrastructures, therefore, should continue to take into account the relationships between high coverage antigens and the scale-up of new vaccines. These intracountry variations in coverage are importantly encompassed in the Global Vaccine Action Plan aim to achieve universal access to immunizations by 2020.[7] Today, our measure suggests that we are still a long way from achieving that goal.

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