

# VACCINE DELIVERY RESEARCH DIGEST

UNIVERSITY OF WASHINGTON STRATEGIC ANALYSIS,  
RESEARCH & TRAINING (START) CENTER

REPORT TO THE BILL & MELINDA GATES FOUNDATION

PRODUCED BY: MESIC, A. & SHARMA, M.

SEPTEMBER 2021

*Want the Vaccine Delivery Research Digest delivered directly to your inbox?*

Subscribe on the Digest website: <http://uwstartcenter.org/publication-digests/vaccine-digest>



**START  
CENTER**

STRATEGIC ANALYSIS,  
RESEARCH & TRAINING CENTER  
Department of Global Health | University of Washington

# List of Articles

- 1 Differences in Pneumococcal and Haemophilus influenzae Natural Antibody Development in Papua New Guinean Children in the First Year of Life.  
{[Abstract & START Commentary](#)} {[Full Article](#)}
  - A cohort study demonstrating natural antibody development against pneumococcal proteins and non-typeable *Haemophilus influenzae* of 101 children 1, 4, 9, 10, 23, and 24 months of age in Papua New Guinea.
- 2 Protection by vaccination of children against typhoid fever with a Vi-tetanus toxoid conjugate vaccine in urban Bangladesh: a cluster-randomised trial.  
{[Abstract & START Commentary](#)} {[Full Article](#)}
  - A cluster-randomized trial assessing the total and overall protection of Vi-tetanus toxoid conjugate vaccine against blood-culture confirmed typhoid in Dhaka, Bangladesh.
- 3 30 years of polio campaigns in Ethiopia, India and Nigeria: the impacts of campaign design on vaccine hesitancy and health worker motivation.  
{[Abstract & START Commentary](#)} {[Full Article](#)}
  - A qualitative study utilizing data to construct a causal loop diagram of interactions between mass polio vaccination campaigns and government health systems in Ethiopia, India, and Nigeria.
- 4 Every Child on the Map: A Theory of Change Framework for Improving Childhood Immunization Coverage and Equity Using Geospatial Data and Technologies.  
{[Abstract & START Commentary](#)} {[Full Article](#)}
  - A study presenting a theory of change for the use of geospatial technology to improve immunization outcomes in low- and middle-income countries.
- 5 Introducing rotavirus vaccine in eight sub-Saharan African countries: a cost-benefit analysis.  
{[Abstract & START Commentary](#)} {[Full Article](#)}
  - A cost-benefit analysis comparing the costs and health outcomes associated with four rotavirus vaccines (Rotarix, Rotateq, Rotavac, and Rotasiil) in the Central African Republic, Chad, Comoros, Equatorial Guinea, Gabon, Guinea, Somalia, and South Sudan.
- 6 Estimating global and regional disruptions to routine childhood vaccine coverage during the COVID-19 pandemic in 2020: a modelling study.

[{Abstract & START Commentary}](#) [{Full Article}](#)

- A modelling study estimating disruptions in vaccine coverage due to the COVID-19 pandemic in 2020 globally and by Global Burden of Disease super-region.

7 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.

[{Abstract & START Commentary}](#) [{Full Article}](#)

- A modelling study reporting on routine vaccine coverage over time on a global, regional, and national level by vaccine.

8 Delivery channels and socioeconomic inequalities in coverage of reproductive, maternal, newborn, and child health interventions: analysis of 36 cross-sectional surveys in low-income and middle-income countries.

[{Abstract & START Commentary}](#) [{Full Article}](#)

- A cross-sectional study describing the association between wealth-related inequalities and coverage of 20 reproductive, maternal, newborn, and child health interventions in 26 LMICs.

9 Realising the broader value of vaccines in the UK.

[{Abstract & START Commentary}](#) [{Full Article}](#)

- A multiple-methods study proposing a framework for broader value assessment of vaccines.

10 Disregarding the restrictive vial-opening policy for BCG vaccine in Guinea-Bissau: impact and cost-effectiveness for tuberculosis mortality and all-cause mortality in children aged 0-4 years

[{Abstract & START Commentary}](#) [{Full Article}](#)

- A modelling study estimating the absolute and percentage change in TB and all-cause deaths in children 0-4 years of age with the current BCG vaccine restrictive opening policy and a non-restrictive opening policy in Guinea-Bissau.

[Appendix](#)

# Details of Articles

## 1. [Differences in Pneumococcal and Haemophilus influenzae Natural Antibody Development in Papua New Guinean Children in the First Year of Life.](#)

Martinovich K, Rahman T, de Gier C, Seppanen E, Orami T, Granland C, et al.

*Front Immunol.* 2021 Aug 28;12:725244.

PubMed ID: 34447389

### ABSTRACT

**BACKGROUND:** Development of vaccines to prevent disease and death from *Streptococcus pneumoniae*, and nontypeable *Haemophilus influenzae* (NTHi), the main pathogens that cause otitis media, pneumonia, meningitis and sepsis, are a global priority. Children living in low and lower-middle income settings are at the highest risk of contracting and dying from these diseases. Improved vaccines with broader coverage are required. Data on the natural development of antibodies to putative vaccine antigens, especially in high-risk settings, can inform the rational selection of the best antigens for vaccine development.

**METHODS:** Serum IgG titres to four pneumococcal proteins (PspA1, PspA2, CbpA, and Ply) and five NTHi antigens (P4, P6, OMP26, rsPilA and ChimV4) were measured in sera collected from 101 Papua New Guinean children at 1, 4, 9, 10, 23 and 24 months of age using multiplexed bead-based immunoassays. Carriage density of *S. pneumoniae* and *H. influenzae* were assessed by quantitative PCR on genomic DNA extracted from nasopharyngeal swabs using species-specific primers and probes. All data were log-transformed for analysis using Student's unpaired t-tests with geometric mean titre (GMT) or density (GMD) calculated with 95% confidence intervals (CI).

**RESULTS:** Serum-pneumococcal protein-specific IgG titres followed a "U" shaped pattern, with a decrease in presumably maternally-derived IgG titres between 1 and 4 months of age and returning to similar levels as those measured at 1 month of age by 24 months of age. In contrast, NTHi protein-specific IgG titres steadily increased with age. There was no correlation between antibody titres and carriage density for either pathogen.

**CONCLUSION:** This longitudinal study indicates that the waning of maternally-derived antibodies that is usually observed in infants, after infants does not occur for NTHi antigens in Papua New Guinean infants. Whether NTHi antigen IgG can be transferred maternally remains to be determined. Vaccines that are designed to specifically increase the presence of protective NTHi antibodies in the first few months of life may be most effective in reducing NTHi disease.

**CLINICAL TRIAL REGISTRATION:** <https://clinicaltrials.gov/>, identifier NCT01619462.

**WEB:** [10.3389/fimmu.2021.725244](https://doi.org/10.3389/fimmu.2021.725244)

**IMPACT FACTOR:** 7.561

**CITED HALF-LIFE:** 2.7

## START COMMENTARY

In this cohort study, Martinovich *et al.* demonstrate natural antibody development against four pneumococcal proteins (PspA1, PspA2, CbpA, and Ply) and five nontypeable *Haemophilus influenzae* (NTHi) antigens (P4, P6, OMP26, rsPilA and ChimV4) from 101 children at age 1, 4, 9, 10, 23, and 24 months in Papua New Guinea. This study is important as it provides data on the natural development of antibodies in a country with one of the highest rates of respiratory infections in the world. This data can be used for the selection of antigens for future vaccine development efforts. Serum and nasopharyngeal swab samples were collected from children as part of a larger clinical trial assessing the safety and immunogenicity of 10-valent and 13-valent pneumococcal conjugate vaccines (PCV) and 23-valent pneumococcal polysaccharide vaccine (PPV23) booster. Quantitative PCR was used for detection of *S. pneumoniae* and *H. influenzae* carriage density. Two multiplexed bead-based immunoassays assessed protein-specific IgG against the pneumococcal proteins PspA1, PspA2, CbpA, Ply (ST306) and NTHi antigens PD, P4, P6. Data was log-transformed to normalize prior to running Student's unpaired T-tests. Martinovich *et al.* reported geometric mean titre (GMT) or density (GMD) and conducted linear regressions to study relationships between pneumococcal density or NTHi density and IgG.

Key findings included that 58% (n=55) of children received PCV10 and 50% (n=46) received PCV13 at months 1, 2, and 3 as part of the clinical trial. The proportion of children who received a dose of PPV23 was similar (PCV10 group: 60%, PCV13 group: 58.7%). GMTs of serum IgG were comparable between the two groups for all pneumococcal and NTHi antigens except for anti-CbpA IgG, which was shown to be statistically significantly lower in the PCV13 group at 10 months. Martinovich *et al.* also reviewed compared children that received PPV23 at 9 months compared to those that did not and found significantly higher increases in P4-specific IgG levels for those that did receive the booster (p=0.015). All children were combined in analyses assessing titre trends, which showed that natural serum IgG titers waned in the early months of life (4-9 months) and returned back to baseline by 24 months (shown in *Figure 1*). Serum IgG titers to NTHi antigens showed a different trend, with significant increases from 1 to 4 month, and an increasing trend up to 24 months (although not statistically significant) (*Figure 2*). Nearly all children were colonized with pneumococcus (93% by 24 months) and *H. influenzae* (100% by 24 months). Overall, the study found differences in antibody development to pneumococcal proteins and NTHi antigens despite similar colonization levels in the first years of life of children in Papua New Guinea.

[Return to List of Articles](#)

## 2. [Protection by vaccination of children against typhoid fever with a Vi-tetanus toxoid conjugate vaccine in urban Bangladesh: a cluster-randomised trial.](#)

Qadri F, Khanam F, Liu X, Theiss-Nyland K, Biswas P, Bhuiyan A, et al.

*Lancet.* 2021 Sep 01;398(10301):675-684.

PubMed ID: 34384540

### ABSTRACT

**BACKGROUND:** Typhoid fever remains a major cause of morbidity and mortality in low-income and middle-income countries. Vi-tetanus toxoid conjugate vaccine (Vi-TT) is recommended by WHO for implementation in high-burden countries, but there is little evidence about its ability to protect against clinical typhoid in such settings.

**METHODS:** We did a participant-masked and observer-masked cluster-randomised trial preceded by a safety pilot phase in an urban endemic setting in Dhaka, Bangladesh. 150 clusters, each with approximately 1350 residents, were randomly assigned (1:1) to either Vi-TT or SA 14-14-2 Japanese encephalitis (JE) vaccine. Children aged 9 months to less than 16 years were invited via parent or guardian to receive a single, parenteral dose of vaccine according to their cluster of residence. The study population was followed for an average of 17.1 months. Total and overall protection by Vi-TT against blood culture-confirmed typhoid were the primary endpoints assessed in the intention-to-treat population of vaccinees or all residents in the clusters. A subset of approximately 4800 participants was assessed with active surveillance for adverse events. The trial is registered at [www.isrctn.com](http://www.isrctn.com), ISRCTN11643110.

**FINDINGS:** 41,344 children were vaccinated in April-May 2018, with another 20,412 children vaccinated at catch-up vaccination campaigns between September and December 2018, and April and May 2019. The incidence of typhoid fever (cases per 100,000 person-years) was 635 in JE vaccinees and 96 in Vi-TT vaccinees (total Vi-TT protection 85%; 97.5% CI 76 to 91,  $p < 0.0001$ ). Total vaccine protection was consistent in different age groups, including children vaccinated at ages under 2 years (81%; 95% CI 39 to 94,  $p = 0.0052$ ). The incidence was 213 among all residents in the JE clusters and 93 in the Vi-TT clusters (overall Vi-TT protection 57%; 97.5% CI 43 to 68,  $p < 0.0001$ ). We did not observe significant indirect vaccine protection by Vi-TT (19%; 95% CI -12 to 41,  $p = 0.20$ ). The vaccines were well tolerated, and no serious adverse events judged to be vaccine-related were observed.

**INTERPRETATION:** Vi-TT provided protection against typhoid fever to children vaccinated between 9 months and less than 16 years. Longer-term follow-up will be needed to assess the duration of protection and the need for booster doses.

**FUNDING:** The study was funded by the Bill & Melinda Gates Foundation.

**WEB:** [10.1016/S0140-6736\(21\)01124-7](https://doi.org/10.1016/S0140-6736(21)01124-7)

**IMPACT FACTOR:** 60.390

**CITED HALF-LIFE:** 8.6

## START COMMENTARY

In this cluster randomized trial, Qadri *et al.* assess the total and overall protection of Vi-tetanus toxoid conjugate vaccine (Vi-TT) against blood-culture confirmed typhoid in Dhaka, Bangladesh. Prior studies have focused only on immunological endpoints, were conducted in non-endemic settings, and not powered to evaluate clinical protection of children and herd protection. This study makes a critical contribution to the literature as it is the first to study the direct and indirect impact of Vi-TT on clinical typhoid in a typhoid-endemic population.

The authors conducted a participant-masked and observer-masked trial with 1:1 random assignment to either Vi-TT or SA 14-14-2 Japanese encephalitis (JE) vaccine with 150 clusters. The primary analyses assessed total vaccine protection by Vi-TT against typhoid, and overall vaccine protection (defined as protection of an entire population by vaccination including the direct effect, i.e., those who were vaccinated, and the indirect effect, i.e., those who benefited from the vaccination). The secondary analyses conducted included vaccine safety, immune responses, indirect vaccine protection, and total protection against paratyphoid fever. Outcomes were assessed among the entire populations of the clusters at 18-months of follow up. The authors estimated vaccine protection by calculating the incidence of disease in the Vi-TT group compared to the SA-14-14-2 group one day after vaccination. Given the dynamic population, overall vaccine protection was calculated by comparing the incidence of disease among all residents in the Vi-TT clusters compared to the SA 14-14-2 clusters, starting after the day of residence in each cluster. Inter-group comparisons were conducted using chi-squared tests for categorical data and Student's t-tests for quantitative data. Mixed-effects Poisson regression models with a random intercept were fit to estimate the incidence rate ratio (IRR) for each cluster.

Immunizations were conducted at baseline (April 15-May 15, 2018) and approximately every six months. The study population was followed for an average of 17.1 months. Total protection by Vi-TT was estimated to be 85% (97.5% Confidence Interval [CI] 92-147,  $p < 0.0001$ ) and overall protection was 57% (97.5% CI 43-68,  $p < 0.0001$ ). However, indirect protection was 19% and non-statistically significant. Most common vaccine-related side effects noted included fever, feeling unwell, diarrhea, and pain at the injection site. Serious adverse events were significantly higher in the SA-14-14-2 group, although unrelated to the receipt of the vaccines. There were significantly more deaths in the Vi-TT group (25 vs. 13  $p < 0.073$ ), eight were due to trauma or drowning. One



limitation of this study is that it deviated from the statistical analyses proposed in the study protocol: the authors initially proposed targeting the inner 80% of the population in each geography and following the population for 24 months. However, the COVID-19 pandemic restricted study activities, so instead, the full population was analyzed after 18 months. However, this study provides evidence on the safety, immunogenicity, and effectiveness of Vi-TT. This study supports suggestions that Vi-TT could be effectively incorporated into Expanded Programmes on Immunisation (EPIs).

[Return to List of Articles](#)

### 3. [30 years of polio campaigns in Ethiopia, India and Nigeria: the impacts of campaign design on vaccine hesitancy and health worker motivation.](#)

Neel A, Closser S, Villanueva C, Majumdar P, Gupta S, Krugman D, et al.

*BMJ Glob Health.* 2021 Aug 05;6(8).

PubMed ID: 34344665

## ABSTRACT

**INTRODUCTION:** The debate over the impact of vertical programmes, including mass vaccination, on health systems is long-standing and often polarised. Studies have assessed the effects of a given vertical health programme on a health system separately from the goals of the vertical programme itself. Further, these health system effects are often categorised as either positive or negative. Yet health systems are in fact complex, dynamic and tightly linked. Relationships between elements of the system determine programme and system-level outcomes over time.

**METHODS:** We constructed a causal loop diagram of the interactions between mass polio vaccination campaigns and government health systems in Ethiopia, India and Nigeria, working inductively from two qualitative datasets. The first dataset was 175 interviews conducted with policymakers, officials and frontline staff in these countries in 2011-2012. The second was 101 interviews conducted with similar groups in 2019, focusing on lessons learnt from polio eradication.

**RESULTS:** Pursuing high coverage in polio campaigns, without considering the dynamic impacts of campaigns on health systems, cost campaign coverage gains over time in weaker health systems with many campaigns. Over time, the systems effects of frequent campaigns, delivered through parallel structures, led to a loss of frontline worker motivation, and an increase in vaccine hesitancy in recipient populations. Co-delivery of interventions helped to mitigate these negative effects. In stronger health systems with fewer campaigns, these issues did not arise.

**CONCLUSION:** It benefits vertical programmes to reduce the construction of parallel systems and pursue co-delivery of interventions where possible, and to consider the workflow of frontline staff. Ultimately, for health campaign designs to be effective, they must make sense for those delivering and receiving campaign interventions, and must take into account the complex, adaptive nature of the health systems in which they operate .

**WEB:** [10.1136/bmjgh-2021-006002](https://doi.org/10.1136/bmjgh-2021-006002)

**IMPACT FACTOR:** 4.280

**CITED HALF-LIFE:** 1.9

## START COMMENTARY

Neel *et al.* analyzed qualitative data from two studies to construct a causal loop diagram of interactions between mass polio vaccination campaigns and government health systems in Ethiopia, India, and Nigeria: 1) The Polio Eradication Impacts Study, conducted in 2011–2012, and 2) The Synthesis and Translation of Research and Innovations from Polio Eradication (STRIPE) study, conducted in 2019. This article is impactful as it applies a complex adaptive systems (CAS) approach to study the relationship between polio campaigns conducted by the Global Polio Eradication Initiative (GPEI) and broader health systems. By applying this approach, less apparent connections and dynamics can be identified to better understand the positive and negative impacts of vertical programs such as mass vaccination campaigns on the health system. Based on interviews (described in *Table 1*) in the three countries, a causal loop diagram (CLD) was constructed. Each country has had a substantial number of polio campaign activities, providing important information on the relationships between mass campaigns and health systems.

The CLD, (*Figure 1*), describes interactions between the polio campaigns and health systems at the policy, frontline health worker, and community level. On the policy level, the polio program impacted outcomes through 1) parallelism (e.g., constructing parallel systems for polio vaccination rather than relying on routine immunization) and 2) pushing health systems to focus on global agenda. Regarding parallelism, although strengthening existing systems such as routine immunization or sanitation programs are a key component on GPEI, these were not an area of focus. However, in some settings, polio resources were used for health system strengthening including diagnosis, surveillance, and education. On the frontline health worker level, motivation of frontline staff was critical to campaign OPV coverage. Across all three countries, polio program fatigue was noted and often driven by high campaign frequency. Other issues reported included the duplication of effort and a lack of convergence between the polio program and other programs (e.g., HIV/AIDS, leprosy). In southern Nigeria and South India, rational workloads, and co-delivery improved workloads for staff. On a community level, trust in the polio campaigns was related to a community's trust in the broader health system. Polio refusals or hesitancy were related to frequent campaigns and demands for other services. This article is important as the CAS approach shows pathways and interactions that would be less typically be less apparent, which inform the authors' recommendations: 1) programs should not focus on a single disease, 2) health worker burden and fatigue should be considered, 3) programs which target issues which are not a community's priority will face challenges; 4) and campaigns should be designed and implemented taking into account context, interconnectedness, and path dependency.

[Return to List of Articles](#)

## 4. [Every Child on the Map: A Theory of Change Framework for Improving Childhood Immunization Coverage and Equity Using Geospatial Data and Technologies.](#)

Chaney S, Mechael P, Thu N, Diallo M, Gachen C.

*J Med Internet Res.* 2021 Aug 25;23(8):e29759.

PubMed ID: 34342584

### ABSTRACT

The effective use of geospatial data and technologies to collect, manage, analyze, model, and visualize geographic data has great potential to improve data-driven decision-making for immunization programs. This article presents a theory of change for the use of geospatial technologies for immunization programming—a framework to illustrate the ways in which geospatial data and technologies can contribute to improved immunization outcomes and have a positive impact on childhood immunization coverage rates in low- and middle-income countries. The theory of change is the result of a review of the state of the evidence and literature; consultation with implementers, donors, and immunization and geospatial technology experts; and a review of country-level implementation experiences. The framework illustrates how the effective use of geospatial data and technologies can help immunization programs realize improvements in the number of children immunized by producing reliable estimates of target populations, identifying chronically missed settlements and locations with the highest number of zero-dose and under-immunized children, and guiding immunization managers with solutions to optimize resource distribution and location of health services. Through these direct effects on service delivery, geospatial data and technologies can contribute to the strengthening of the overall health system with equity in immunization coverage. Recent implementation of integrated geospatial data and technologies for the immunization program in Myanmar demonstrate the process that countries may experience on the path to achieving lasting systematic improvements. The theory of change presented here may serve as a guide for country program managers, implementers, donors, and other stakeholders to better understand how geospatial tools can support immunization programs and facilitate integrated service planning and equitable delivery through the unifying role of geography and geospatial data.

**WEB:** [10.2196/29759](https://doi.org/10.2196/29759)

**IMPACT FACTOR:** 5.034

**CITED HALF-LIFE:** 4.8

### START COMMENTARY

In this article, Chaney *et al.* present a theory of change for the use of geospatial technology to improve immunization outcomes in low- and middle-income countries (LMICs). This study is

important as it reviews the latest literature to develop a theory of change showing how geospatial technologies could optimize routine immunization program design, implementation, and monitoring to improve immunization coverage. Further, it can guide future planning and investments into geospatial technology for immunization programs. The theory of change (*Figure 1*) includes enablers (e.g., information system government, human and financial resources), foundations (e.g., health system mapping, population estimation), inputs (e.g., production of digital maps, optimization of resource distribution), which lead to outputs (e.g., identification of zero-dose/under-immunized children, improved service delivery), which lead to outcomes (e.g. more children immunization, improved quality), which then lead to impact (e.g., => 80% children fully immunized, equitably across geography, culture, and socioeconomic factors).

The study noted three main areas where geospatial data and technologies could have an impact: 1) increase the number of children immunized through improved target setting, 2) optimize immunization resource distribution and location of services, and 3) improve the quality, timeliness, and perception of immunization services with equity in coverage between communities. For example, spatially accurate maps could be developed to plan outreach activities, especially for settlements often missed through tradition microplanning efforts. Further, immunization resources (i.e., number of vaccinators and vaccines are needed, and locations to send them) could be optimized using geospatial data. In addition, the authors present results from a case study in Myanmar which utilized geospatial technologies to determine a geo-references master list of facilities, settlements, and health area boundaries. This map allowed health workers to include overlooked populations in immunization micro plans and improve target population estimates. Overall, this study demonstrates how effective geospatial data and technology can improve data-driven decision-making, optimize the deployment of immunization services, and increase equity, underscoring the need to consider the use of geospatial technology in LMICs.

[Return to List of Articles](#)

## 5. [Introducing rotavirus vaccine in eight sub-Saharan African countries: a cost-benefit analysis.](#)

Okafor C, Ekwunife O.

*Lancet Glob Health.* 2021 Aug 23;9(8):e1088-e1100.

PubMed ID: 3429796134297947

### ABSTRACT

**BACKGROUND:** Stimulated by the economic challenges faced by many sub-Saharan African countries and the changes in the rotavirus burden across these countries, this study aimed to inform the decision of health policy makers of eight sub-Saharan countries, who are yet to introduce the rotavirus vaccine as of Dec 31, 2020, on the health economic consequences of the introduction of the vaccine in terms of the costs and benefits.

**METHODS:** We did a cost-benefit analysis using a simulation-based decision-analytic model for children aged younger than 1 year, who were followed up to 259 weeks, in the Central African Republic, Chad, Comoros, Equatorial Guinea, Gabon, Guinea, Somalia, and South Sudan. Data were collected and analysed between Jan 13, 2020, and Dec 11, 2020. Cost-effectiveness analysis and budget impact analysis were done as secondary analyses. Four rotavirus vaccinations (Rotarix, Rotateq, Rotavac, and Rotasiil) were compared with no vaccination. The primary outcome was disability-adjusted life-years averted, converted to monetary terms. The secondary outcomes include rotavirus gastroenteritis averted, and rotavirus vaccine-associated intussusception. The primary economic evaluation measure was the benefit-cost ratio (BCR).

**FINDINGS:** For the modelling period, Jan 1, 2021, to Dec 31, 2030, we found that the benefits of introducing the rotavirus vaccine outweighed the costs in all eight countries, with Chad and the Central African Republic having the highest BCR of 19.42 and 11.36, respectively. Guinea had the lowest BCR of 3.26 amongst the Gavi-eligible countries. Equatorial Guinea and Gabon had a narrow BCR of 1.86 and 2.06, respectively. Rotarix was the optimal choice for all the Gavi-eligible countries; Rotasiil and Rotavac were the optimal choices for Equatorial Guinea and Gabon, respectively.

**INTERPRETATION:** Introducing the rotavirus vaccine in all eight countries, but with caution in Equatorial Guinea and Gabon, would be worthwhile. With the narrow BCR for Equatorial Guinea and Gabon, cautious, pragmatic, and stringent measures need to be employed to ensure optimal health benefits and cost minimisation of the vaccine introduction. The final decision to introduce the rotavirus vaccine should be preceded by comparing its BCR to the BCRs of other health-care projects.

**FUNDING:** Copenhagen Consensus Center and the Bill & Melinda Gates Foundation.

**WEB:** [10.1016/S2214-109X\(21\)00220-5](https://doi.org/10.1016/S2214-109X(21)00220-5)

**IMPACT FACTOR:** 21.597

**CITED HALF-LIFE:** 3.1

## START COMMENTARY

In this cost-benefit analysis, Okafor *et al.* compare the costs and health outcomes associated with four rotavirus vaccines (Rotarix, Rotateq, Rotavac, and Rotasiil) in the Central African Republic, Chad, Comoros, Equatorial Guinea, Gabon, Guinea, Somalia, and South Sudan. This article adds value as it evaluates the economic implications of rotavirus introduction in eight Gavi-eligible countries which have not yet introduced the vaccine to determine whether vaccination is an efficient use of resources. Further, this analysis estimates benefit-cost ratios (BCRs) which can be used to compare rotavirus introduction to other healthcare programs in each country. The authors constructed a Markov model which included four states: well, moderate diarrhea, severe diarrhea, and death. Transition probabilities were determined from prior literature, including a systematic review, and the Institute for Health Metrics and Evaluation (IHME) 2019 reports for each country. This model estimated the number of moderate and severe rotavirus cases and deaths for each country. The authors assumed that moderate rotavirus gastroenteritis would be treated in an outpatient setting and severe would be managed inpatient. Detailed information on input parameters are shown in *Table 1* and *Table 2*. The primary outcome of interest was disability-adjusted life years (DALYs) averted. Secondary outcomes included cases averted, and rotavirus vaccine-associated intussusception. In addition to a cost-benefit analysis, authors conducted a cost-effectiveness and budget impact analysis.

Rotarix had the lowest cost followed by Rotavac in seven of the eight countries. The Rotarix cost per child ranged between US\$1.52 in Somalia to \$3.27 in Comoros. DALYs averted were optimal for Rotarix, followed by Rotavac for all countries. The highest DALYs averted were in Chad, and the lowest observed were in Guinea. Overall, the economic impact ranged from US\$172,107 in Equatorial Guinea to US\$2,104,677 in Somalia for ten years. For rotavirus vaccine-associated intussusception and death, Equatorial Guinea was the lowest (335 cases and one death) and Chad was the highest (5,738 cases and 594 deaths). For all of the countries, Rotarix offered the highest BCR followed by Rotavac. Rotasiil offered the highest for Guinea and Rotavac for Gabon. In all countries, Rotarix, Rotavac, and Rotasiil were cost-effective. A key strength of this study is the cost estimation for vaccines comprised of not only the cost of the vaccine, but also vaccine wastage costs, and international handling/freight for each vaccination scenario. Delivery costs included personnel and logistics (e.g., cold chain, buildings). In conclusion, this analysis supports the introduction of rotavirus vaccines across eight sub-Saharan African countries.

[Return to List of Articles](#)

## 6. [Estimating global and regional disruptions to routine childhood vaccine coverage during the COVID-19 pandemic in 2020: a modelling study.](#)

Causey K, Fullman N, Sorensen R, Galles N, Zheng P, Aravkin A, et al.

*Lancet.* 2021 Aug 26;398(10299):522-534.

PubMed ID: 34273292

### ABSTRACT

**BACKGROUND:** The COVID-19 pandemic and efforts to reduce SARS-CoV-2 transmission substantially affected health services worldwide. To better understand the impact of the pandemic on childhood routine immunisation, we estimated disruptions in vaccine coverage associated with the pandemic in 2020, globally and by Global Burden of Disease (GBD) super-region.

**METHODS:** For this analysis we used a two-step hierarchical random spline modelling approach to estimate global and regional disruptions to routine immunisation using administrative data and reports from electronic immunisation systems, with mobility data as a model input. Paired with estimates of vaccine coverage expected in the absence of COVID-19, which were derived from vaccine coverage models from GBD 2020, Release 1 (GBD 2020 R1), we estimated the number of children who missed routinely delivered doses of the third-dose diphtheria-tetanus-pertussis (DTP3) vaccine and first-dose measles-containing vaccine (MCV1) in 2020.

**FINDINGS:** Globally, in 2020, estimated vaccine coverage was 76.7% (95% uncertainty interval 74.3-78.6) for DTP3 and 78.9% (74.8-81.9) for MCV1, representing relative reductions of 7.7% (6.0-10.1) for DTP3 and 7.9% (5.2-11.7) for MCV1, compared to expected doses delivered in the absence of the COVID-19 pandemic. From January to December, 2020, we estimated that 30.0 million (27.6-33.1) children missed doses of DTP3 and 27.2 million (23.4-32.5) children missed MCV1 doses. Compared to expected gaps in coverage for eligible children in 2020, these estimates represented an additional 8.5 million (6.5-11.6) children not routinely vaccinated with DTP3 and an additional 8.9 million (5.7-13.7) children not routinely vaccinated with MCV1 attributable to the COVID-19 pandemic. Globally, monthly disruptions were highest in April, 2020, across all GBD super-regions, with 4.6 million (4.0-5.4) children missing doses of DTP3 and 4.4 million (3.7-5.2) children missing doses of MCV1. Every GBD super-region saw reductions in vaccine coverage in March and April, with the most severe annual impacts in north Africa and the Middle East, south Asia, and Latin America and the Caribbean. We estimated the lowest annual reductions in vaccine delivery in sub-Saharan Africa, where disruptions remained minimal throughout the year. For some super-regions, including southeast Asia, east Asia, and Oceania for both DTP3 and MCV1, the high-income super-region for DTP3, and south Asia for MCV1, estimates suggest that monthly doses were delivered at or above expected levels during the second half of 2020.



**INTERPRETATION:** Routine immunisation services faced stark challenges in 2020, with the COVID-19 pandemic causing the most widespread and largest global disruption in recent history. Although the latest coverage trajectories point towards recovery in some regions, a combination of lagging catch-up immunisation services, continued SARS-CoV-2 transmission, and persistent gaps in vaccine coverage before the pandemic still left millions of children under-vaccinated or unvaccinated against preventable diseases at the end of 2020, and these gaps are likely to extend throughout 2021. Strengthening routine immunisation data systems and efforts to target resources and outreach will be essential to minimise the risk of vaccine-preventable disease outbreaks, reach children who missed routine vaccine doses during the pandemic, and accelerate progress towards higher and more equitable vaccination coverage over the next decade.

**FUNDING:** Bill & Melinda Gates Foundation.

**WEB:** [10.1016/S0140-6736\(21\)01337-4](https://doi.org/10.1016/S0140-6736(21)01337-4)

**IMPACT FACTOR:** 60.390

**CITED HALF-LIFE:** 8.6

## START COMMENTARY

In this modelling study, Causey *et al.* estimate disruptions in vaccine coverage due to the COVID-19 pandemic in 2020 globally and by Global Burden of Disease (GBD) super-region. The main outcome of interest was monthly disruptions in the administration of the diphtheria-tetanus-pertussis third dose (DTP3) and measles-containing vaccine (MCV1). The authors estimated expected DTP3 and MCV1 coverage in the absence of a pandemic, which was compared to observed data. This study makes an important contribution to the literature as it quantifies the disruptions of routine immunization services due to COVID-19 and can inform decision-making on recovery and health system strengthening for future disease outbreaks. Data utilized for this study included country-reported data on DTP3 and MCV1 monthly doses, supplemented by electronic medical records and registries and human mobility measures. Time-varying changes in human mobility reflect how movement and behavior changed during the pandemic compared to pre-pandemic and can serve as a proxy measure for societal disruptions. Causey *et al.* included mobility as an average percentage reduction (ranging from 0-1, 0 indicating no reduction in mobility, 1 indicating a 100% decrease in mobility). The analysis included two steps. First, the average relationships between cumulative disruptions in mobility and vaccine coverage were modeled. Second, residual variation in disruption by month was modelled, to account for trends not explained by mobility.

Key findings included that DTP3 estimates were 7.7% (95% Uncertainty Interval [UI]: 6.0-10.1) lower than expected and MCV1 were 7.9% (95% UI: 5.2-11.7) lower than expected. The most

severe disruptions occurred in April 2020 with slight improvements from May to December 2020. Asia had the largest acute decline, whereas the Middle East and North Africa had less acute declines but rather a slow, plateauing recovery. Detailed trends by region are shown in *Figure 3* for both DTP3 and MCV1. Overall, about 30 million (95% UI: 27.6-33.1) eligible children missed DTP3 and 27.2 million (95% CI 23.4-32.5) missed MCV1 (shown in *Figure 4*). A key strength of this study include the estimation of immunization disruptions regionally and globally, whereas most prior studies have focused on a limited geography or population. There are a few notable limitations, including that administrative records may not have captured all doses given (e.g., may have missed supplemental immunization activities) and mobility is an imprecise and imperfect measure of the impact of COVID-19 across countries. However, this study provides evidence on the importance of sustaining vaccine services during outbreaks, which can inform future preparedness efforts.

[Return to List of Articles](#)

## 7. [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.](#)

GBD 2020, Release 1, Vaccine Coverage Collaborators.

*Lancet.* 2021 August 7;398(10299):503-521.

PubMed ID: 34273291

### ABSTRACT

**BACKGROUND:** Measuring routine childhood vaccination is crucial to inform global vaccine policies and programme implementation, and to track progress towards targets set by the Global Vaccine Action Plan (GVAP) and Immunization Agenda 2030. Robust estimates of routine vaccine coverage are needed to identify past successes and persistent vulnerabilities. Drawing from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2020, Release 1, we did a systematic analysis of global, regional, and national vaccine coverage trends using a statistical framework, by vaccine and over time.

**METHODS:** For this analysis we collated 55,326 country-specific, cohort-specific, year-specific, vaccine-specific, and dose-specific observations of routine childhood vaccination coverage between 1980 and 2019. Using spatiotemporal Gaussian process regression, we produced location-specific and year-specific estimates of 11 routine childhood vaccine coverage indicators for 204 countries and territories from 1980 to 2019, adjusting for biases in country-reported data and reflecting reported stockouts and supply disruptions. We analysed global and regional trends in coverage and numbers of zero-dose children (defined as those who never received a diphtheria-tetanus-pertussis [DTP] vaccine dose), progress towards GVAP targets, and the relationship between vaccine coverage and sociodemographic development.

**FINDINGS:** By 2019, global coverage of third-dose DTP (DTP3; 81.6% [95% uncertainty interval 80.4-82.7]) more than doubled from levels estimated in 1980 (39.9% [37.5-42.1]), as did global coverage of the first-dose measles-containing vaccine (MCV1; from 38.5% [35.4-41.3] in 1980 to 83.6% [82.3-84.8] in 2019). Third-dose polio vaccine (Pol3) coverage also increased, from 42.6% (41.4-44.1) in 1980 to 79.8% (78.4-81.1) in 2019, and global coverage of newer vaccines increased rapidly between 2000 and 2019. The global number of zero-dose children fell by nearly 75% between 1980 and 2019, from 56.8 million (52.6-60.9) to 14.5 million (13.4-15.9). However, over the past decade, global vaccine coverage broadly plateaued; 94 countries and territories recorded decreasing DTP3 coverage since 2010. Only 11 countries and territories were estimated to have reached the national GVAP target of at least 90% coverage for all assessed vaccines in 2019.

**INTERPRETATION:** After achieving large gains in childhood vaccine coverage worldwide, in much of the world this progress was stalled or reversed from 2010 to 2019. These findings underscore the importance of revisiting routine immunisation strategies and programmatic approaches, recentring service delivery around equity and underserved populations. Strengthening vaccine data and monitoring systems is crucial to these pursuits, now and through to 2030, to ensure that all children have access to, and can benefit from, lifesaving vaccines.

**FUNDING:** Bill & Melinda Gates Foundation.

**WEB:** [10.1016/S0140-6736\(21\)00984-3](https://doi.org/10.1016/S0140-6736(21)00984-3)

**IMPACT FACTOR:** 60.390

**CITED HALF-LIFE:** 8.6

## START COMMENTARY

In the following modelling study, the GBD 2020 team and Vaccine Coverage Collaborators report on routine vaccine coverage over time on a global, regional, and national level by vaccine. This study is important as it estimates vaccine coverage from 1980 to 2019, including time- and location-varying adjustments which may address reporting bias, discrepant data sources, and uncertainty in other vaccine coverage studies. Assessing trends and progress towards the Global Vaccine Action Plan (GVAP) 2020 goal of 90% of coverage for child vaccines are critical for informing vaccination programs, policies, and investments. Vaccine coverage was defined as the proportion of children who received at least the stated vaccine dose through a routine immunization program (i.e., not a campaign). In total, the GBD team used 975 unique sources, representing 55,326 country-cohort-year-vaccine-dose-specific datapoints for children aged 12-59 months. The GBD 2020 team and collaborators used country-specific vaccine schedules and introduction years to calculate age-cohort-specific coverage. Covariates included in the coverage model were Healthcare Access and Quality (HAQ) index, GBD estimates from conflict and terrorism per capita, and country-reported stockouts or other disruptions (indicated by discontinuities in administrative data). In addition to coverage estimates, three additional analyses were conducted including an analysis of vaccine coverage and sociodemographic development, progress towards the GVAP 2020 target, and the number of zero dose children.

There are substantial increases in global vaccine coverage by vaccine from 1980-2019, as demonstrated in *Figure 1*. However, progress on three vaccines (DTP3, MCV1, and Pol3) decreased or stalled in many locations between 2010-2019. An estimated 94 countries have recorded decreasing DTP3 coverage. Trends show that newer vaccines introduced in the 2000s (HepB, Hib, MCV2, PCV, RCV, and RotaC) began to approach coverage similar to well-established vaccines. The sub-Saharan African region had the lowest proportion of 90% mean coverage in 2019 (*Figure*

3). Only 11 countries reached 90% or higher mean coverage across all nine vaccines. There were positive associations between higher Socio-demographic index (SDI) and coverage, although the relationship was not linear (*Figure 4*). Lastly, authors estimated that the number of zero-dose children fell 75% (from 56.8 million in 1980 to 14.5 million in 2019), indicating substantial gains in vaccine coverage. Overall, this study provides important data on global, regional, and national coverage across vaccines and years which underscore the need to continue programs, investments, and policies to increase vaccination coverage.

[Return to List of Articles](#)

8. [Delivery channels and socioeconomic inequalities in coverage of reproductive, maternal, newborn, and child health interventions: analysis of 36 cross-sectional surveys in low-income and middle-income countries.](#)

Leventhal D, Crochemore-Silva I, VIDALETTI L, Armenta-Paulino N, Barros A, Victora C.

*Lancet Glob Health.* 2021 Aug 23;398(10299):503-521.

PubMed ID: 3427329134273296

## ABSTRACT

**BACKGROUND:** Global reports have described inequalities in coverage of reproductive, maternal, newborn, and child health (RMNCH) interventions, but little is known about how socioeconomic inequality in intervention coverage varies across multiple low-income and middle-income countries (LMICs). We aimed to assess the association between wealth-related inequalities in coverage of RMNCH interventions.

**METHODS:** In this cross-sectional study, we identified publicly available Demographic Health Surveys and Multiple Indicator Cluster Surveys from LMICs containing information on household characteristics, reproductive health, women's and children's health, nutrition, and mortality. We identified the most recent survey from the period 2010-19 for 36 countries that contained data for our preselected set of 18 RMNCH interventions. 21 countries also had information on two common malaria interventions. We classified interventions into four groups according to their predominant delivery channels: health facility based, community based, environmental, and culturally driven (including breastfeeding practices). Within each country, we derived wealth quintiles from information on household asset indices. We studied two summary measures of within-country wealth-related inequality: absolute inequalities (akin to coverage differences among children from wealthy and poor households) using the slope index of inequality (SII), and relative inequalities (akin to the ratio of coverage levels for wealthy and poor children) using the concentration index (CIX). Pro-poor inequalities are present when intervention coverage decreased with increasing household wealth, and pro-rich inequalities are present when intervention coverage increased as household wealth increased.

**FINDINGS:** Across the 36 LMICs included in our analyses, coverage of most interventions had pro-rich patterns in most countries, except for two breastfeeding indicators that mostly had higher coverage among poor women, children and households than wealthy women, children, and households. Environmental interventions were the most unequal, particularly use of clean fuels, which had median levels of SII of 48.8 (8.6-85.7) and CIX of 67.0 (45.0-85.8). Interventions primarily delivered in health facilities—namely institutional childbirth (median SII 46.7 [23.1-63.3] and CIX 11.4 [4.5-23.4]) and antenatal care (median SII 26.7 [17.0-47.2] and CIX 10.0 [4.2-17.1])—also usually had pro-rich patterns. By comparison, primarily community-based interventions, including those against

malaria, were more equitably distributed-eg, oral rehydration therapy (median SII 9.4 [2.9-19.0] and CIX 3.4 [1.3-25.0]) and polio immunisation (SII 12.1 [2.3-25.0] and CIX 3.1 [0.5-7.1]). Differences across the four types of delivery channels in terms of both inequality indices were significant (SII  $p=0.0052$ ; CIX  $p=0.0048$ ).

**INTERPRETATION:** Interventions that are often delivered at community level are usually more equitably distributed than those primarily delivered in fixed facilities or those that require changes in the home environment. Policy makers need to learn from community delivery channels to promote more equitable access to all RMNCH interventions.

**FUNDING:** Bill & Melinda Gates Foundation and Wellcome Trust.

**TRANSLATIONS:** For the French, Portuguese and Spanish translations of the abstract see Supplementary Materials section.

**WEB:** [10.1016/S2214-109X\(21\)00204-7](https://doi.org/10.1016/S2214-109X(21)00204-7)

**IMPACT FACTOR:** 21.597

**CITED HALF-LIFE:** 3.1

## START COMMENTARY

In this cross-sectional study, Leventhal *et al.* describe the association between wealth-related inequalities and coverage of 20 reproductive, maternal, newborn, and child health (RMNCH) interventions in 26 LMICs. This study not only summarizes the magnitude of socioeconomic inequality in coverage of RMNCH interventions but also expands the concept of delivery channels to four types (environmental, health facility-based, community-based, and culturally-driven) to frame the understanding of inequalities in LMICs. Data utilized included Demographic Health Surveys (DHS) and the Multiple Indicator Cluster Surveys (MICS). The authors used 18 widely accepted indicators for intervention coverage, and two malaria related indicators. The intervention coverage describe essential interventions such as family planning, institutional childbirth, and prenatal and postnatal care. Inequality was measured using two summary indices, including the slope index of inequality (SII) and the concentration index (CIX). SII is measured from -100 to 100 with positive values indicating higher coverage among the wealthy and negative values indicating higher coverage among the poor. The CIX describes the distance between an observed distribution and total equality.

Leventhal *et al.* describe median coverage of the 20 indicators in *Figure 1*. The highest coverage was shown for continued breastfeeding at 12-15 months, birth registration, childhood immunization, and institutional birth. However, dietary diversity, antimalarial treatment, clean fuels,

and piped water had low coverage (below 25%). *Figure 2* describes median values for SII and CIZ in coverage of the 20 indicators, with different colors indicating the four delivery channels. Overall, there were significant variations in the magnitude of inequalities across the four categories of delivery channels. Environmental interventions were the most significantly unequal based on both SII and CIX (p value = 0.0002 and p=0.0018, respectively). Facility-based interventions showed significant pro-wealthy patterns whereas community based interventions were more equal. Continued breastfeeding had pro-poor absolute inequality. The authors conducted a sensitivity analysis using all available data from 2010 for 103 countries, and observed the same patterns shown in the main analyses. Overall, the authors conclude that there are pro-rich inequalities for most indicators, although the magnitude varies based on delivery channel, underscoring the need to consider and design approaches which utilize varying delivery channels (namely community-based) to reduce health inequalities across LMICs.

[Return to List of Articles](#)



## 9. [Realising the broader value of vaccines in the UK.](#)

Brassel S, Neri M, O'Neill P, Steuten L.

*Vaccine X*. 2021 May 18;9(8):e11101-e11109.

PubMed ID: 340511803429794834416207

### ABSTRACT

Many health technology assessment (HTA) agencies limit their assessments of vaccines to the health benefits for the vaccinated individual, the costs associated with vaccine administration and the disease avoided. However, because the value of vaccines tends to accrue to a large extent beyond the vaccinated individual, they are systematically undervalued in many current HTA processes. This is also the case in the UK, where the Joint Committee on Vaccination and Immunisation (JCVI) is in charge of assessing preventative vaccines, while therapeutic vaccines fall in the realm of the National Institute for Clinical Excellence (NICE). To contribute to a forward-looking perspective, we designed a framework to capture the broader value of vaccination. We reviewed the current state of the global vaccines pipeline and selected seven preventative and three therapeutic vaccines that are likely to enter the UK market within five years. We assessed on which value elements the selected vaccines would potentially generate value, and compared those against the novel broader value framework. A review of the current value elements considered by the JCVI and NICE allowed identifying the critical gaps between potential value generation and value recognition. To our knowledge, this is the first time that the broader value of vaccination has been pro-actively assessed for pipeline vaccinations. Our findings show that the existing narrow evaluation frameworks are likely to systematically undervalue the value of potential future vaccines coming to the UK market. This is particularly relevant, where their impact on AMR and other health interventions, and on the productivity of the workforce is of concern. Recommendations to overcome this include an explicit and more consistent inclusion of, and data collection on, the impact of vaccines on AMR and other health interventions by JCVI and NICE; the consideration of a societal perspective and the fiscal impact of vaccines to societies.

**WEB:** [10.1016/j.jvacx.2021.100096](https://doi.org/10.1016/j.jvacx.2021.100096)

**IMPACT FACTOR:** 0.52

**CITED HALF-LIFE:** n/a

### START COMMENTARY

In this multiple-methods study, Brassel *et al.* propose a framework for broader value assessment of vaccines. This study provides an innovative approach for expanding health benefits of vaccination beyond the vaccinated individual, costs associated with the vaccine, and disease

avoided to an approach focused on capturing the broader value of vaccinations. This is important given that health technology assessments (HTA) systematically undervalue potential future vaccines, and underestimate the benefits on herd-immunity, antimicrobial resistance, and other health interventions. Methods utilized in this study included a literature review to identify existing frameworks, a review of the vaccine pipeline in the UK, a qualitative analysis on elements which a vaccine may affect, and a gap analysis to compare existing frameworks to the elements identified. Eight experts reviewed the results of each component of the study.

In terms of value frameworks for vaccines, the authors note that literature typically includes both narrow and broad value elements of vaccines, but only the former is included in HTAs. The authors present four categories of value (*Table 1*), including health effects (i.e., the impact of vaccines on the vaccinated individuals and their caregivers); productivity effects (i.e., the impact on productivity of the individual and their caregivers); the health system and community (i.e., the impact on the unvaccinated population), and the health system economic effect. Brassel *et al.* identified 782 vaccine products in the pipeline. Of these, 10 in phase III were selected to explore value elements qualitatively. Of these, six are expected to have community and health system effects. Six of seven vaccines are likely to have value in terms of transmission whereas four are likely to have value in preventing antimicrobial resistance. Breast cancer is presented as an example of a therapeutic vaccine and *Escherichia Coli* is presented as a example of a preventative vaccine. Lastly, as part of the gap analysis, Brassel *et al.* note that areas that are consistently likely to be excluded from the Joint Committee on Vaccination and Immunisation/National Institute for Clinical Excellence across disease areas include antimicrobial resistance and enablement value (i.e. to improve the cost-effectiveness of other non-vaccine interventions). One limitation of this study is the generalizability; it only includes effects which are likely relevant for a high income setting, and excluded effects such as fertility, consumption, and security which may be important effects for vaccine valuation in LMICs. In conclusion, this study summarizes the importance of quantifying the benefits of vaccines fully to understand the true value to societies.

[Return to List of Articles](#)

## 10. [Disregarding the restrictive vial-opening policy for BCG vaccine in Guinea-Bissau: impact and cost-effectiveness for tuberculosis mortality and all-cause mortality in children aged 0-4 years](https://doi.org/10.1136/bmjgh-2021-006127)

Thysen SM, Fisker AB, Byberg S, Aaby P, Roy P, White R, Griffiths U, Harris RC

*BMJ Global Health*. 2021 Aug;6(8):e006127.

PubMed ID: 34344667

### ABSTRACT

**OBJECTIVE:** BCG vaccination is frequently delayed in low-income countries. Restrictive vial-opening policies, where a vial of BCG vaccine is not opened for few children, are a major reason for delay. During delays, children are unprotected against tuberculosis (TB) and deprived of non-specific effects of BCG. We assessed the potential effect and cost-effectiveness of disregarding the restrictive vial-opening policy, on TB and all-cause mortality, in children aged 0-4 years in Guinea-Bissau.

**METHODS:** Using static mathematical models, we estimated the absolute and percentage change in TB and all-cause deaths, in children aged 0-4 years, between the current BCG vaccine restrictive-opening policy scenario, and a non-restrictive policy scenario where all children were vaccinated in the first health-facility contact. Incremental cost-effectiveness was estimated by integration of vaccine and treatment costs.

**FINDINGS:** Disregarding the restrictive BCG vial-opening policy was estimated to reduce TB deaths by 11.0% (95% uncertainty range (UR):0.5%-28.8%), corresponding to 4 (UR:0-15) TB deaths averted per birth cohort in Guinea-Bissau, resulting in incremental cost-effectiveness of US\$ 911 per discounted life-year gained (LYG) (UR:145-9142). For all-cause deaths, the estimated reduction was 8.1% (UR: 3.3%-12.7%) corresponding to 392 (UR:158-624) fewer all-cause deaths and an incremental cost-effectiveness of US\$ 9 (UR:5-23) per discounted LYG.

**CONCLUSIONS:** Disregarding the restrictive BCG vial-opening policy was associated with reductions in TB deaths and all-cause deaths and low cost-effectiveness ratios. Our results suggest that it would be cost-effective to disregard the restrictive vial-opening policy. Other settings with similar practice are also likely to gain from disregarding this policy.

**WEB:** [10.1136/bmjgh-2021-006127](https://doi.org/10.1136/bmjgh-2021-006127)

**IMPACT FACTOR:** 4.280

**CITED HALF-LIFE:** 1.9

## START COMMENTARY

In this modelling study, Thysen *et al.* estimate the absolute and percentage change in TB and all-cause deaths in children 0-4 years of age with the current BCG vaccine restrictive opening policy and a non-restrictive opening policy in Guinea-Bissau. This analysis is important as one of the key delays to BCG vaccinations in LMICs are that vials will not be opened unless 10-12 children are present, and no studies to date have assessed the impact of increasing timeliness on all-cause mortality, economic outcomes, or overall impact on the national level. Two models were developed for the analysis: one for all-cause deaths and one for TB deaths. Data inputs and assumptions are listed in *Table 1*. One assumption of note is leaky vaccine efficacy, rather than complete protection against all-cause mortality. A key strength of this study was the performance of a probabilistic uncertainty analysis for each parameter in the models.

In total, disregarding the restrictive vial opening policy was estimated to reduce TB deaths, admissions, and cases by 11% (95% UR: 0.5-28.8%). An estimated 4 deaths (UR: 0-10) were averted per birth cohort in the first 5 years of life. The vial policy would reduce all-cause mortality by 8.1% (UR: 3.3-12.7%). In terms of costs and cost effectiveness, both models showed that the vial-policy change would result in higher vaccination costs and lower household costs. For all-cause effects of BCG, the number of discounted life-years gained (LYG) were 10,605 (UR: 4,279-16,896) for an ICER of US\$9 (UR: 5-23) per discounted LYG. Some limitations of note include those out-of-pocket costs for treatment were not included, which likely underestimated the costs. In addition, estimates for prevalence and mortality may be underestimated. However, given the sensitivity analyses, these limitations should not be a major concern. Overall, this study shows that disregarding the restrictive vial-opening policy would result in large reductions in all-cause deaths and small reductions in TB-deaths, indicating that this policy should be considered for implementation broadly.

[Return to List of Articles](#)

# Appendix

The literature search for the September 2021 Vaccine Delivery Research Digest was conducted on August 30, 2021. We searched English language articles indexed by the US National Library of Medicine and published between August 15, 2021, and September 14, 2021. The search resulted in 576 items.

## SEARCH TERMS

(((((vaccine[tiab] OR vaccines[tiab] OR vaccination[tiab] OR immunization[tiab] OR immunisation[tiab] OR vaccine[mesh] OR immunization[mesh]) AND (logistics[tiab] OR supply[tiab] OR “supply chain”[tiab] OR implementation[tiab] OR expenditures[tiab] OR financing[tiab] OR economics[tiab] OR “Cost effectiveness”[tiab] OR coverage[tiab] OR attitudes[tiab] OR belief[tiab] OR beliefs[tiab] OR refusal[tiab] OR “Procurement”[tiab] OR timeliness[tiab] OR systems[tiab])) OR (“vaccine delivery”[tiab])) NOT (“in vitro”[tiab] OR “immune response”[tiab] OR gene[tiab] OR chemistry[tiab] OR genotox\*[tiab] OR sequencing[tiab] OR nanoparticle\*[tiab] OR bacteriophage[tiab] OR exome[tiab] OR exogenous[tiab] OR electropor\*[tiab] OR “systems biology”[tiab] OR “animal model”[tiab] OR cattle[tiab] OR sheep[tiab] OR goat[tiab] OR rat[tiab] OR pig[tiab] OR mice[tiab] OR mouse[tiab] OR murine[tiab] OR porcine[tiab] OR ovine[tiab] OR rodent[tiab] OR fish[tiab])) AND (English[LA]) (“2021/08/15”[PDAT] : “2021/09/14”[PDAT]))