VACCINE DELIVERY RESEARCH DIGEST

**UNIVERSITY OF WASHINGTON STRATEGIC ANALYSIS,
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REPORT TO THE BILL & MELINDA GATES FOUNDATION

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1. [**The burden of recording and reporting health data in primary health care facilities in five low- and lower-middle income countries.**](#)

Siyam A, Ir P, York D, Antwi J, Amponsah F, Rambique O, et al.

ABSTRACT

BACKGROUND: Recording and reporting health data in facilities is the backbone of routine health information systems which provide data collected by health facility workers during service provision. Data is firstly collected in a register, to record patient health data and care process, and tallied into nationally designed reporting forms. While there is anecdotal evidence of large numbers of registers and reporting forms for primary health care (PHC) facilities, there are few systematic studies to document this potential burden on health workers. This multi-country study aimed to document the numbers of registers and reporting forms use at the PHC level and to estimate the time it requires for health workers to meet data demands.

METHODS: In Cambodia, Ghana, Mozambique, Nigeria and Tanzania, a desk review was conducted to document registers and reporting forms mandated at the PHC level. In each country, visits to 16 randomly selected public PHC facilities followed to assess the time spent on paper-based recording and reporting. Information was collected through self-reports of estimated time use by health workers, and observation of 1360 provider-patient interactions. Data was primarily collected in outpatient care (OPD), antenatal care (ANC), immunization (EPI), family planning (FP), HIV and Tuberculosis (TB) services.

RESULT: Cross-countries, the average number of registers was 34 (ranging between 16 and 48). Of those, 77% were verified in use and each register line had at least 20 cells to be completed per patient. The mean time spent on recording was about one-third the total consultation time for OPD, FP, ANC and EPI services combined. Cross-countries, the average number of monthly reporting forms was 35 (ranging between 19 and 52) of which 78% were verified in use. The estimated time to complete monthly reporting forms was 9…h (ranging between 4 to 15…h) per month per health worker.

CONCLUSIONS: PHC facilities are mandated to use many registers and reporting forms pausing a considerable burden to health workers. Service delivery systems are expected to vary, however an

imperative need remains to invest in international standards of facility-based registers and reporting forms, to ensure regular, comparable, quality-driven facility data collection and use.

START COMMENTARY

In this study, Siyam *et al.* describe the burden of recording and reporting health data through desk reviews, observations, and surveys of health workers in 80 public primary health care (PHC) facilities across Cambodia, Ghana, Mozambique, Nigeria, and Tanzania. This study is an important contribution as it is one of the first systematic data collection of the burden of recording and reporting in low- and middle-income countries (LMICs). Firstly, Siyam *et al.* conducted a desk review to assess requirements for recording registers and reporting forms at PHC facilities. The countries were selected by an expression of interest during WHO capacity-building workshops. In each country, the Ministry of Health (MoH) and a principal investigator from a public health institute led the study. Each countr's research team (MoH and principal investigator) randomly selected four districts and four public PHC facilities in those respective districts for data collection. Register data collected included the number of mandatory and conditional data cells to be filled for each patient. Reporting form data included the number of data cells, the mandatory data cells, and the data cells due to disaggregation. At each facility, patient load, number of health workers by occupation, and self-reported time spent on recording and reporting by health workers were collected. During a second visit to health facilities, research staff observed recording practices over two weeks in five of 16 health facilities for six services (outpatient care, antenatal care, immunization, family planning, HIV, and Tuberculosis services).

Key findings included that the mean number of registers was 34 (minimum: 16 in Ghana and maximum: 48 in Tanzania). Most registers were for reproductive, maternal, newborn, child, and adolescent health and HIV (*Figure 1*). The numbers of mandatory cells varied widely (*Figure 2*). During consultations, the Percentage of recording time spent was between 31-44% depending on the health service, with the highest percentage for immunization consultations (44%). The mean percentage of time spent across outpatient care, antenatal care, family planning, and immunization was highest in Mozambique (53%) and lowest in Cambodia (26%). When comparing self-reported data to observations, there was a tendency of staff to report longer times for recording and reporting (e.g., across outpatient care, antenatal care, family planning, and immunization services, staff reported an average of 5.9 minutes for recording whereas observations indicated an average of 3.6 minutes). In terms of reporting forms, the total number ranged from 19 in Nigeria and 52 in Mozambique. The mean number of hours needed to complete monthly reporting forms was between

10 hours in Nigeria to 65 in Tanzania per month. This study underscores the substantial burden of recording and reporting on healthcare workers across countries.

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2. [Estimation of Ethiopia's immunization coverage – 20 years of discrepancies.](#)

Pond B, Bekele A, Mounier-Jack S, Teklie H, Getachew T.

ABSTRACT

BACKGROUND: Coverage with the third dose of diphtheria-pertussis-tetanus-containing vaccine (DPT3) is a widely used measure of the performance of routine immunization systems. Since 2015, data reported by Ethiopia's health facilities have suggested DPT3 coverage to be greater than 95%. Yet, Demographic and Health Surveys in 2016 and 2019 found DPT3 coverage to be 53 and 61% respectively for years during this period. This case study reviews the last 20…years of administrative (based on facility data), survey and United Nations (UN) estimates of Ethiopia's nationwide immunization coverage to document long-standing discrepancies in these statistics.

METHODS: Published estimates were compiled of Ethiopia's nationwide DPT3 coverage from 1999 to 2018. These estimates come from the Joint Reporting Form submitted annually to WHO and UNICEF, a series of 8 population-based surveys and the annual reports of the WHO/UNICEF Estimates of National Immunization Coverage (WUENIC). Possible reasons for variation in survey findings were explored through secondary analysis of data from the 2012 immunization coverage survey. In addition, selected health officials involved with management of the immunization program were interviewed to obtain their perspectives on the reliability of various methods for estimation of immunization coverage.

FINDINGS: Comparison of Ethiopia's estimates for the same year from different sources shows major and persistent discrepancies between administrative, survey and WUENIC estimates. Moreover, the estimates from each of these sources have repeatedly shown erratic year-to-year fluctuations. Those who were interviewed expressed scepticism of Demographic and Health Survey (DHS) statistics. Officials of the national immunization programme have repeatedly shown a tendency to overlook all survey statistics when reporting on programme performance.

CONCLUSIONS: The present case study raises important questions, not only about the estimation methods of national and UN agencies, but about the reliability and comparability of widely trusted coverage surveys. Ethiopia provides an important example of a country where no data source provides a truly robust "gold standard" for estimation of immunization coverage. It is essential to identify and address the reasons for these discrepancies and arrive at a consensus on how to improve the reliability and acceptability of each data source and how best to "triangulate" between them.

START COMMENTARY

In this study, Pond *et al.* reports coverage of third dose of diphtheria-pertussis-tetanus-containing vaccine (DPT3) among children in Ethiopia from 8 population-based surveys and annual reports of the WHO/UNICEF Estimates of National Immunization Coverage (WUENIC) from 1999 to 2018. In addition, authors conducted qualitative interviews with Expanded Programme on Immunzation (EPI) focal persons at the national, regional, and zonal levels to understand comparative reliability of methods for estimating coverage and suggestions for improvement.

DTP3 coverage among children 12 to 23 months from 1999 to 2018 are shown in *Figure 1.* Across surveys (e.g., DHS, EPI, WUENIC), DTP3 coverage ranges from 21-66%, whereas administrative data indicate coverage levels of 40-96% and data from documents (e.g., home-based record of facility immunization register) indicate coverage of 27-63%, indicating wide variability in estimates. Overall, Pond *et al.* conclude that the reliability depends on the errors in reports of doses administered and denominator estimates. Most health officials queried reported that they regarded administrative data (i.e., Health Management Information System [HMIS]) as the most comprehensive given the granular administrative level and continuous data collection. Health officials expressed some concerns about the methods associated with DHS surveys (e.g., sampling, data collection, and language barriers). Further, the infrequent nature of DHS surveys prevented estimates from being available in a timely fashion. Strengths of this study include the mixed methods design which included quantitative indicators for comparison and qualitative interviews to corroborate quantitative findings. Another strength is the longitudinal nature, as the discrepancy between administrative and survey data varied in direction and magnitude yearly. Overall, this study underscores the importance of reliable immunization coverage estimates which are both understandable and useful for in-country immunization officials.

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3. Antimicrobial resistance in paediatric Streptococcus pneumoniae isolates amid global implementation of pneumococcal conjugate vaccines: a systematic review and meta-regression analysis.

Andrejko K, Ratnasiri B, Hausdorff W, Laxminarayan R, Lewnard J.

ABSTRACT

BACKGROUND: Pneumococcal diseases are a leading cause of morbidity and mortality among children globally, and the burden of these diseases might be worsened by antimicrobial resistance. To understand the effect of pneumococcal conjugate vaccine (PCV) deployment on antimicrobial resistance in pneumococci, we assessed the susceptibility of paediatric pneumococcal isolates to various antimicrobial drugs before and after PCV implementation.

METHODS: We did a systematic review of studies reporting antimicrobial susceptibility profiles of paediatric pneumococcal isolates between 2000 and 2020 using PubMed and the Antimicrobial Testing Leadership and Surveillance database (ATLAS; Pfizer). Population-based studies of invasive pneumococcal disease or nasopharyngeal colonisation were eligible for inclusion. As primary outcome measures, we extracted the proportions of isolates that were non-susceptible or resistant to penicillin, macrolides, sulfamethoxazole-trimethoprim, third-generation cephalosporins, and tetracycline from each study. Where available, we also extracted data on pneumococcal serotypes. We estimated changes in the proportion of isolates with reduced susceptibility or resistance to each antibiotic class using random-effects meta-regression models, adjusting for study-level and region-level heterogeneity, as well as secular trends, invasive or colonising isolate source, and countries' per-capita gross domestic product.

FINDINGS: From 4910 studies screened for inclusion, we extracted data from 559 studies on 312,783 paediatric isolates. Susceptibility of isolates varied substantially across regions both before and after implementation of any PCV product. On average across all regions, we estimated significant absolute reductions in the proportions of pneumococci showing non-susceptibility to penicillin (11.5%, 95% CI 8.6-14.4), sulfamethoxazole-trimethoprim (9.7%, 4.3-15.2), and third-generation cephalosporins (7.5%, 3.1-11.9), over the 10 years after implementation of any PCV product, and absolute reductions in the proportions of pneumococci resistant to penicillin (7.3%, 5.3-9.4), sulfamethoxazole-trimethoprim (16.0%, 11.0-21.2), third-generation cephalosporins (4.5%, 0.3-8.7), macrolides (3.6%, 0.7-6.6) and tetracycline (2.0%, 0.3-3.7). We did not find evidence of changes in the proportion of isolates non-susceptible to macrolides or tetracycline after PCV implementation. Observed changes in penicillin non-susceptibility were driven, in part, by

replacement of vaccine-targeted serotypes with non-vaccine serotypes that were less likely to be non-susceptible.

INTERPRETATION: Implementation of PCVs has reduced the proportion of circulating pneumococci resistant to first-line antibiotic treatments for pneumonia. This effect merits consideration in assessments of vaccine impact and investments in coverage improvements.

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START COMMENTARY

In this systematic review and meta-regression analysis, Andrejko *et al.* review studies reporting antimicrobial susceptibility profiles before and after pneumococcal conjugate vaccine (PCV) implementation. This analysis makes an important contribution to the literature as it synthesizes findings from 559 studies across 104 countries to understand changes of over time in susceptibility, which is critical for informing future PCV roll outs. Andrejko *et al.* summed isolates for each drug class, geography, isolate source (i.e., carriage or invasive pneumococcal disease [IPD]) and vaccine exposure (i.e., PCV-exposed and PCV-naïve) to understand the regional prevalence of non-susceptibility and resistance to penicillin, the differences in susceptibility of circulating pneumococci before and after PCV implementation, and changes in microbial resistance prevalence over time among serotypes exposed to vaccine-driven population immunity and not contained in PCV.

Key findings across studies found positive impacts of PCV implementation, including reductions in prevalence of non-susceptibility and resistance to penicillin, sulfamethoxazole-trimethoprim, and third generation cephalosporins. The authors note small reductions in the prevalence of resistance to tetracycline and macrolides, but these trends do not hold for prevalence of non-susceptibility. After adjusting for study-, country- and regional confounders, findings demonstrate that PCVs have improved antimicrobial susceptibility of circulating pneumococci, which means that resistance to common drugs for treatment of pneumonia is reduced. This finding is importance as it further supports that PCV reduces morbidity and mortality by allowing for simpler treatment for pediatric pneumonia. Notable limitations include the limited studies in low-income countries, which could limit the understanding of susceptibility in these settings or regions, and the exclusion of studies focused on isolates of select serotypes, which may have affected the study size and findings.

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4. Modelling the relative benefits of using the measles vaccine outside cold chain for outbreak response.

Azam J, Saitta B, Bonner K, Ferrari M, Pulliam J.

ABSTRACT

INTRODUCTION: Rapid outbreak response vaccination is a strategy for measles control and elimination. Measles vaccines must be stored and transported within a specified temperature range, but this can present significant challenges when targeting remote populations. Measles vaccine licensure for delivery outside cold chain (OCC) could provide more vaccine transport/storage space without ice packs, and a solution to shorten response times. However, due to vaccine safety and wastage considerations, the OCC strategy will require other operational changes, potentially including the use of 1-dose (monodose) instead of 10-dose vials, requiring larger transport/storage equipment currently achieved with 10-dose vials. These trade-offs require quantitative comparisons of vaccine delivery options to evaluate their relative benefits.

METHODS: We developed a modelling framework combining elements of the vaccine supply chain - cold chain, vial, team, and transport equipment types - with a measles transmission dynamics model to compare vaccine delivery options. We compared 10 strategies resulting from combinations of the vaccine supply elements and grouped into three main classes: OCC, partial cold chain (PCC), and full cold chain (FCC). For each strategy, we explored a campaign with 20 teams sequentially targeting 5 locations with 100,000 individuals each. We characterised the time needed to freeze ice packs and complete the campaign (campaign duration), vaccination coverage, and cases averted, assuming a fixed pre-deployment delay before campaign commencement. We performed sensitivity analyses of the pre-deployment delay, population sizes, and two team allocation schemes.

RESULTS: The OCC, PCC, and FCC strategies achieve campaign durations of 50, 51, and 52.days, respectively. Nine of the ten strategies can achieve a vaccination coverage of 80%, and OCC averts the most cases.

DISCUSSION: The OCC strategy, therefore, presents improved operational and epidemiological outcomes relative to current practice and the other options considered.

START COMMENTARY

In this modelling study, Azam *et al.* develop a framework for the vaccine supply change to compare 10 strategies of vaccine supply elements, including strategies outside of cold chain (OCC), with partial cold chain (PCC), and with full cold chain (FCC). This article is impactful as it compares benefits of vaccine delivery options which may be particularly useful in the context of rapid measles outbreaks when cold chain may not be readily available. The modelling framework includes supply chain inputs (i.e., near/far population size, number of freezers) and epidemiological inputs (i.e., vaccine efficacy, initially immune population) to determine intermediate outputs (i.e., commencement delay, campaign start days), and final outputs (i.e., campaign duration, vaccination coverage, cases averted) (Figure 1). The 10 vaccination strategies are described in *Table S3* in the *Supplementary Material* and include strategies with 10-dose vials, 1-dose vials, and variations in cold chain. Additionally, sensitivity analyses were conducted to assess the impact of different near (e.g., urban) and far (e.g., rural) populations and team allocation schemes, and to explore the impact of pre-deployment delays on cases averted.

Key findings included that all strategies except mono-dose FCC achieved 80% vaccine coverage. There was a similar duration of? 80% coverage across strategies (OCC: 50 days, PCC: 51 days, and FCC: 52 days). OCC strategies averted the most cases, followed by the PCC strategies (*Figure 4).* In sensitivity analyses, the proportional team allocation scheme (i.e., team sizes proportional to the population) led to higher or equal vaccination coverage when compared to the equal team (i.e., team sizes were equal irrespective of population size). In terms of pre-deployment delays, the OCC strategies averted the most cases when there was a short delay. The number of cases that could be potentially averted decrease substantially between strategies with longer delays. Overall, authors conclude OCC strategies can result in shorter campaigns with high vaccine coverage and more cases averted. However, results are sensitive to pre-deployment delays. Key strengths of this study include the inclusion of two types of vials (1-dose and 10-dose) and variations in cold chain in the strategies and assessment of population size, team allocation scheme, and pre-deployment delay in the sensitivity analyses. Overall, this study underscores the potential benefits of using OCC campaigns in the context of measles outbreaks to reduce campaign time, increase coverage, and avert measles cases which should be considered in future outbreaks.

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5. Subnational inequalities in diphtheria-tetanus-pertussis immunization in 24 countries in the African Region.

Kirkby K, Bergen N, Schlotheuber A, Sodha S, Danovaro-Holliday M, Hosseinpoor A.

ABSTRACT

OBJECTIVE: To analyse subnational inequality in diphtheria-tetanus-pertussis (DTP) immunization dropout in 24 African countries using administrative data on receipt of the first and third vaccine doses (DTP1 and DTP3, respectively) collected by the Joint Reporting Process of the World Health Organization and the United Nations Children's Fund.

METHODS: Districts in each country were grouped into quintiles according to the proportion of children who dropped out between DTP1 and DTP3 (i.e., the dropout rate). We used six summary measures to quantify inequalities in dropout rates between districts and compared rates with national dropout rates and DTP1 and DTP3 immunization coverage.

FINDINGS: The median dropout rate across countries was 2.4% in quintiles with the lowest rate and 14.6% in quintiles with the highest rate. In eight countries, the difference between the highest and lowest quintiles was 14.9 percentage points or more. In most countries, underperforming districts in the quintile with the highest rate tended to lag disproportionately behind the others. This divergence was not evident from looking only at national dropout rates. Countries with the largest inequalities in absolute subnational dropout rate tended to have lower estimated national DTP1 and DTP3 immunization coverage.

CONCLUSION: There were marked inequalities in DTP immunization dropout rates between districts in most countries studied. Monitoring dropout at the subnational level could help guide immunization interventions that address inequalities in underserved areas, thereby improving overall DTP3 coverage. The quality of administrative data should be improved to ensure accurate and timely assessment of geographical inequalities in immunization.

START COMMENTARY

Kirkby *et al.* analyze subnational inequality in diphtheria-tetanus-pertussis (DTP) immunization dropout in 24 African countries. This study is important as it quantifies immunization coverage

inequalities, which are often concealed in national estimates. Administrative data on DTP1 and DTP3 from 2018 was collected from districts for the Joint Reporting Process of the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF). DTP1-DTP3 dropout rate was described as a percentage (calculated as the difference between the number of third and first doses divided by the number of first doses x 100). Kirkby *et al.* divided districts into quintiles according to their dropout rate to be able to compare across countries (quintile 1 being the highest dropout and quintile 5 being the lowest). In total, six measures of inequality were calculated, including the absolute difference, the relative difference, the weighted mean difference from the mean, the weighted index of disparity, and the population attributable fraction (*Table 2).*

Key results indicated variation in dropout percentages across countries (a high of 22.6% in South Sudan and a low of 3.5% in Burkina Faso). In addition to variation in the national dropout rate, there was substantial variation within countries (e.g., in Ethiopia, the highest district drop out was 57% and the lowest was 0%). Five countries (Central African Republic, Angola, Mauritania, South Sudan, and Mali) had large subnational inequality, defined as a 20 percentage point or more difference between quintiles 1 and 5 (*Figure 3).* A notable strength of this study inclusion of various summary measures of dropout rates, which allow for a full understanding of inequality within countries. One such measure includes the population attributable fraction, which summarizes the improvement that could be achieved with reduction/elimination of inequality within countries. Overall, this study demonstrates that national estimates of coverage and drop-out are not sufficient to understanding inequality in countries. By targeting districts with the highest drop out rates in countries, there would be substantial improvements in national coverage and preventable disease and death in these 24 countries, and others facing similar challenges.

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6. Human papillomavirus (HPV) vaccine introduction in Sikkim state: Best practices from the first statewide multiple-age cohort HPV vaccine introduction in India-2018-2019.

Ahmed D, VanderEnde K, Harvey P, Bhatnagar P, Kaur N, Roy S, et al.

ABSTRACT

BACKGROUND: Cervical cancer is a leading cause of cancer-associated mortality among women in India, with 96,922 new cases and 60,078 deaths each year, almost one-fifth of the global burden. In 2018, Sikkim state in India introduced human papillomavirus (HPV) vaccine for 9-13-year-old girls, primarily through school-based vaccination, targeting approximately 25,000 girls. We documented the program's decision-making and implementation processes.

METHODS: We conducted a post-introduction evaluation in 2019, concurrent with the second dose campaign, by interviewing key stakeholders (state, district, and local level), reviewing planning documents, and observing cold chain sites in two purposefully-sampled community areas in each of the four districts of Sikkim. Using standard questionnaires, we interviewed health and education officials, school personnel, health workers, community leaders, and age-eligible girls on program decision-making, planning, training, vaccine delivery, logistics, and communication.

RESULTS: We conducted 279 interviews and 29 observations in eight community areas across four districts of Sikkim. Based on reported administrative data, Sikkim achieved >95% HPV vaccination coverage among targeted girls for both doses via two campaigns; no severe adverse events were reported. HPV vaccination was well accepted by all stakeholders; minimal refusal was reported. Factors identified for successful vaccine introduction included strong political commitment, statewide mandatory school enrollment, collaboration between health and education departments at all levels, and robust social mobilization strategies.

CONCLUSIONS: Sikkim successfully introduced the HPV vaccine to multiple-age cohorts of girls via school-based vaccination, demonstrating a model that could be replicated in other regions in India or similar low- and middle-income country settings.

START COMMENTARY

In this evaluation study, Ahmed *et al.* conducted stakeholder interviews, desk reviews of planning documents, and observations of cold chain and waste management facilities to evaluate human papilloma virus (HPV) vaccine introduction activities in Sikkim state. This evaluation is important as Sikkim state was the first state in India to introduce state-wide HPV vaccine targeting multiple cohorts of girls and can serve as an example for future implementations across other states in India. The evaluation took place in all four districts in Sikkim state, including two health facilities and two schools included from each district. The authors conducted 279 interviews and 29 observations (*Table 1).*

The HPV program resulted in over 95% vaccine coverage for the first dose and over 90% for the second dose among eligible girls in Sikkim state. High rates were attributed to strong partnerships between schools and health facilities. Health workers interviewed (n=24), 92% reported high satisfaction with training, and 96% received written materials about HPV vaccination. Training gaps included inconsistent refresher training of health workers and teachers during the training. HPV vaccination was highly acceptable among health and education stakeholders which may have been a result of intense advocacy and sensitization efforts. Most targeted girls, (79%, 157 or 199) were able to identify benefits of HPV vaccination. Despite positive communication/advocacy findings, gaps included the lack of a structured communication plan or tailored messaging at the health facility and district level. Although health workers put in intensive effort to ensure girls came back for second doses, there were some missed opportunities for vaccination including that girls who missed the first round were not able to receive the first dose during the second round. The evaluation team observed 17 cold chain points which all had functioning equipment and very low vaccination wastage rates (<0.05% in both campaigns). One key strength of this analysis is the purposeful selection of a high- and low-performing health center in each district and different types of schools, both of which offered unique experiences and insights related to HPV vaccination. In conclusion, Sikkim state demonstrated that it is feasible to introduce HPV vaccine to multiple-cohorts of girls statewide, which should be replicated in other states, and similar settings to reduce the burden of cervical cancer.

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7. [Cost of vaccine delivery strategies in low- and middle-income countries during the COVID-19 pandemic.](#)

Banks C, Portnoy A, Moi F, Boonstoppel L, Brenzel L, Resch S.

ABSTRACT

BACKGROUND: The COVID-19 pandemic has disrupted immunization services critical to the prevention of vaccine-preventable diseases in many low- and middle- income countries around the world. These services will need to be modified in order to minimize COVID-19 transmission and ensure the safety of health workers and the community. Additional budget will be required to implement these modifications that ensure safe delivery.

METHODS: Using a simple modeling analysis, we estimated the additional resource requirements associated with modifications to supplementary immunization activities (campaigns) and routine immunization services via fixed sites and outreach in 2020 US dollars. We considered the following four categories of costs: (1) personal protective equipment (PPE) & infection prevention and control (IPC) measures for immunization sessions; (2) physical distancing and screening during immunization sessions; (3) delivery strategy changes, such as changes in session sizes and frequency; and (4) other operational cost increases, including additional social mobilization, training, and hazard pay to compensate health workers.

RESULTS: We found that implementing a range of measures to protect health workers and communities from COVID-19 transmission could result in a per-facility start-up cost of $466-799 for routine fixed-site delivery and $12-220 for routine outreach delivery, and $12-108 per immunization campaign site. A recurrent monthly cost of $137-1,024 for fixed-site delivery and $152-848 for outreach delivery per facility could be incurred, and a $0.32-0.85 increase in the cost per dose during campaigns.

CONCLUSIONS: By illustrating potential cost implications of providing immunization services through a range of strategies in a safe manner, these estimates can provide a benchmark for program managers and policy makers on the additional budget required. These findings can help country practitioners and global development partners planning the continuation of immunization services in the context of COVID-19.

START COMMENTARY

In this modelling study, Banks *et al.* explore the costs of four programmatic adaptions to supplementary immunization activities and routine immunization during the COVID-19 pandemic. This study is important as COVID-19 has disrupted immunization services globally, and additional efforts and resources will be required to minimize transmission among health workers and communities. Cost data were obtained from the Immunization Delivery Cost Catalogue (IDCC). Scenarios evaluated included: routine delivery at low volume facilities, routine delivery at high-volume facilities, and campaigns, each with a low-intensity and high-intensity scenario. The high-intensity scenario follows country policies and practices for immunization services during COVID-19 and the Ebola pandemic. Costs are presented as one-time investments, monthly costs while the pandemic is ongoing, per-dose, for types of delivery (routine, fixed-site, and outreach delivery), and at the facility level. The four cost categories included 1) personal protective equipment (PPE) and infection, prevention, and control (IPC) supplies, 2) additional staff and supplies to conduct screening and ensure physical distancing, 3) changes in daily targets, session sizes, and frequency for routine outreach and campaign delivery, and 4) operational cost components associated with COVID-19 (e.g., higher mean training costs, increased communication about routine immunization).

Overall, implementing measures to reduce the risk of COVID-19 transmission to health workers and communities resulted in a per-facility start-up cost of $466-799 for routine fixed sites, $12-220 for outreach delivery, and $12-108 per campaign site. Recurrent monthly costs ranged from $137-1,024 for fixed sites per facility and $152-848 for outreach delivery per facility. Banks *et al.* estimated a $0.32-0.85 increased costs per dose during immunization campaigns. To provide a real world example, a case study was presented for Tanzania utilizing recent survey data and the aforementioned assumptions. Overall, by including the adaptions to routine immunization, there would be an incremental annual cost increase of $19-123 million, depending on the scenario. Limitations of this study include a potential overestimation of PPE/IPC measures and associated costs and uncertainty around costs for staffing, hazard pay during outbreaks, and social mobilization. Overall, this study provides data which can guide resource mobilization for routine immunization during the ongoing COVID-19 outbreak.

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8. [Cost-effectiveness of infant respiratory syncytial virus preventive interventions in Mali: A modeling study to inform policy and investment decisions.](#)

Laufer R, Driscoll A, Baral R, Buchwald A, Campbell J, Coulibaly F, et al.

ABSTRACT

IMPORTANCE: Low- and middle-income countries have a high burden of respiratory syncytial virus lower respiratory tract infections. A monoclonal antibody administered monthly is licensed to prevent these infections, but it is cost-prohibitive for most low- and middle-income countries. Long-acting monoclonal antibodies and maternal vaccines against respiratory syncytial virus are under development.

OBJECTIVE: We estimated the likelihood of respiratory syncytial virus preventive interventions (current monoclonal antibody, long-acting monoclonal antibody, and maternal vaccine) being cost-effective in Mali.

DESIGN: We modeled age-specific and season-specific risks of respiratory syncytial virus lower respiratory tract infections within monthly cohorts of infants from birth to six months. We parameterized with respiratory syncytial virus data from Malian cohort studies, as well as product efficacy from clinical trials. Integrating parameter uncertainty, we simulated health and economic outcomes for status quo without prevention, intra-seasonal monthly administration of licensed monoclonal antibody, pre-seasonal birth dose administration of a long-acting monoclonal antibody, and maternal vaccination. We then calculated the incremental cost-effectiveness ratio of each intervention compared to status quo from the perspectives of the government, donor, and society.

RESULTS: At a price of $3 per dose and from the societal perspective, current monoclonal antibody, long-acting monoclonal antibody, and maternal vaccine would have incremental cost-effectiveness ratios of $4280 (95% CI $1892 to $122,434), $1656 (95% CI $734 to $9091), and $8020 (95% CI $3501 to $47,047) per disability-adjusted life-year averted, respectively.

CONCLUSIONS AND RELEVANCE: In Mali, long-acting monoclonal antibody is likely to be cost-effective from both the government and donor perspectives at $3 per dose. Maternal vaccine would need higher efficacy over that measured by a recent trial in order to be considered cost-effective.

START COMMENTARY

In this modelling study, Laufer *et al.* estimate the cost-effectiveness of infant respiratory syncytial virus (RSV) prevention interventions in Mali. Interventions evaluated include: current monoclonal antibody, long-action monoclonal antibody, and maternal vaccine. This study is important as preventative treatments for RSV are in in advanced development, indicating a need to estimate the potential health and economic impacts of implementation for LMICs. The model includes four scenarios: 1) status quo without the intervention; 2) intra-seasonal infant prophylaxis with monthly doses of short-acting monoclonal antibodies (short-acting mAb); 3) pre-seasonal infant prophylaxis with a single birth dose of long-action monoclonal antibody (long-acting mAb), and 4) year-round, single dose maternal vaccination. *Table 1* summarizes the various input parameters (e.g., demographic, economic, RSV intervention, etc.). For health outcomes, Laufer *et al.* projected the number of RSV-LRTI cases, hospitalizations, Disability Adjusted Life-Years (DALYs) and deaths per birth cohort. In addition, the authors estimated budget impact and cost-effectiveness. Laufer *et al.* conducted a sensitivity analysis to determine which parameters have the greatest influence on the results and a secondary analysis to understand the impact of changes in model structure and assumptions, described in *Table 2*.

Overall, the cost effectiveness per DALY averted was $4,280 for short-acting mAb would be, $1,656 for long-acting mAb would be, and $8,020 for maternal vaccine. *Figure 1* depicts intervention coverage, cost per dose, donor willingness to pay, and government willingness to pay across scenarios. In sensitivity analyses, the most influential parameter was inpatient case fatality rate. In sensitivity analyses, providing maternal vaccines to pregnant women during pre-seasonal campaigns decreased to 5,354 (95% CI: $2,351-31,523). Overall, findings indicate that long-acting mAb may provide better value compared to short-acting mAb and maternal vaccine. The annual budget impact of including long-acting mAb to the immunization program would result in a 0.21% increase in the overall 2017 health budget. This indicates that long-acting mAb, and other future interventions may cost-effective in Mali and other LMICs.

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9. Immunogenicity and Safety of a Tetravalent Dengue Vaccine Administered Concomitantly or Sequentially With Tdap Vaccine: Randomized Phase IIIb Trial in Healthy Participants 9-60 Years of Age in the Philippines.

Santos J, Montellano M, Solante R, Perreras N, Meyer S, Toh M, et al.

ABSTRACT

BACKGROUND: Incorporating dengue vaccination into existing childhood vaccination programs could increase vaccine coverage. This study assessed the safety and immunogenicity of concomitant versus sequential administration of the combined tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccine and the tetravalent dengue vaccine (CYD-TDV).

METHODS: This phase IIIb, randomized, open-label, multicenter study was conducted in the Philippines in individuals 9-…60 years of age (NCT02992418). Participants were to receive 3 CYD-TDV doses 6 months apart, the first dose administered either concomitantly or sequentially (28 days post-Tdap). Antibody levels were measured at baseline and 28 days post-first doses of Tdap vaccine and CYD-TDV, using enzyme-linked immunosorbent assay (pertussis, tetanus), micrometabolic inhibition test-toxin neutralization assay (diphtheria) and plaque reduction neutralization test (dengue). Immunogenicity was assessed for all participants, and statistical analysis reported for baseline dengue seropositive participants. Safety was assessed throughout.

RESULTS: Among 688 randomized participants, 629 (91.4%) were baseline dengue seropositive (concomitant group, n = 314 and sequential group, n = 315). After the first dose, non-inferiority of immune responses between concomitant and sequential vaccination was achieved; between-group geometric mean antibody concentration ratios were close to 1 for anti-PT, anti-FHA, anti-PRN and anti-FIM, between-group differences in percent achieving seroprotection (titers 0.1 IU/mL) were 0.26% (diphtheria) and 0.66% (tetanus), and between-group geometric mean antibody titer ratios were close to 1 for dengue serotypes 1-4. Safety profiles in both study groups were comparable.

CONCLUSIONS: CYD-TDV and Tdap vaccine administered concomitantly or sequentially in baseline dengue seropositive participants elicited comparable immunogenicity and safety profiles.

START COMMENTARY

In this randomized controlled trial, Santos *et al.* assess the safety and immunogenicity of concomitant versus sequential administration of combined tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccine and the tetravalent dengue vaccine (CYD-TDV). This study is important as dengue is responsible for substantial morbidity in dengue-endemic countries, but vaccine coverage is limited. A potential method of efficiently introducing new vaccines to immunization schedules includes co-administration, which is being considered in future school-based dengue vaccination programs for those 9 and above in the Philippines. Participates (9–≤60 years of age) who had received 3 or 4 previous doses of DTaP were randomized 1:1 with center and age stratification to receive either sequential administration (Tdap then CYD-TDV 28 days later), or both concomitantly. Immunogenicity assessments including measuring neutralizing antibody titers for the 4 dengue serotypes and antibody levels against pertussis antigens (PT, FHA, PRN, and FIM).

Key results indicated non-inferiority of the humoral response to pertussis antigens with concomitant versus sequential administration. Similarly, non-inferiority of the responses to each of the dengue serotypes for concomitant versus sequential was demonstrated. Baseline titers were similar across groups, and geometric mean titers increased similarly across groups regardless of mode of administration. A non-inferior immune response was also demonstrated for the concomitant administration in the dengue-seropositive group. Detailed findings by antigens and serotypes are shown in *Table 2.* Injection site reactions and solicited systematic reactions were similar across arms for all participants and dengue seropositive participants (*Table 3).* Overall, 2.4% of participants in the concomitant group reported a serious adverse event compared to 3.2% in the sequential group. This study demonstrates promising findings that it may be feasible and safe to co-administer CYD-TDV and Tdap.

10. [Introducing Rotavirus Vaccination in Nigeria: Economic Evaluation and Implications.](#)

Okafor C.

ABSTRACT

BACKGROUND: As Nigeria prepares to introduce a rotavirus vaccine, the Gavi board has approved the extension of the transition period for the country until 2028. The current position of the country on Gavi's funding profile calls for a pragmatic step in planning and implementation so that sustainability at the fully self-financing phase will be feasible.

OBJECTIVE: This study aimed to inform the decisions of the country's health policymakers on the costs, benefits, and implications of the introduction of rotavirus vaccine.

METHODS: This study was an economic evaluation using a simulation-based Markov model. It compared four approaches: 'no vaccination' and vaccination with ROTARIX, ROTAVAC, or ROTASIIL. Ten cohorts from the year 2021 to 2030 were used in the analysis. Primary measures were the benefit-cost ratio (BCR) and the incremental cost-effectiveness ratio (ICER). Future costs and outcomes were discounted to 2019 values.

RESULTS: The adjusted vaccine cost of ROTARIX was the highest, followed by ROTAVAC and ROTASIIL, whereas the immunization delivery cost was in the reverse order. All the vaccines were very cost effective, with ROTARIX being the optimal choice for the 10-year period, having a BCR of 27 and an ICER of $US100 (95% confidence interval [CI] 71-130)/disability-adjusted life-year averted. Adopting ROTARIX was the optimal choice from 2021 to 2027, whereas ROTAVAC was optimal from 2028 to 2030. The net budget impact of the programme was $US76.9 million for the 10-year period. The opportunity cost of a late introduction was about $US8 million per annum from 2021 to 2028.

CONCLUSIONS: The rotavirus vaccine ROTARIX should be implemented in Nigeria at the earliest opportunity. A switch to ROTAVAC should be considered from the year 2028. Cost-minimization measures are imperative to ensure the sustainability of the programme after the transition out of Gavi support.

START COMMENTARY

In this economic analysis, Okafor use a Markov model to compare four approaches of rotavirus vaccination in Nigeria: 1) no vaccination; 2) vaccination with ROTARIX, or ROTAVAC, or ROTASIIL for ten cohorts from the year 2021-2030. This study is important as it is likely that Gavi's support in Nigeria will be ended soon, requiring Nigeria to determine if it will be possible to implement and sustain the rotavirus vaccine through self-financing. The model estimated number of moderate and severe rotavirus (RVGE) cases, number of deaths, and accumulated deaths over 5 years. Model parameters included birth rate, population, vaccine effectiveness, vaccine wastage, price, co-financing share, and start-up vaccination costs (*Table 1).* Okafor *et al.* estimated costs from the payer and societal levels.

Overall, the adjusted mean cost of full immunization per child is highest for ROTARIX ($2.66), compared to ROTAVAC ($2.03) and ROTASIIL ($1.89). Mean immunization delivery cost is lowest for ROTARIX ($2.14) compared to ROTAVAC ($2.82) and ROTASIIL ($3.14). The number of fully vaccinated children are very similar across vaccines. The cases of moderate and severe RVGE averted are highest for ROTARIX. The budget impact is lowest for ROTARIX. The benefit-cost ratio, including cost per DALY averted per vaccinated child, health sector cost averted per vaccinated child, and total benefit (as quantified by cases and deaths) is highest for ROTARIX. Overall, results indicates that ROTARIX may provide the best value for money in Nigeria. One of the key strengths of this analysis was the inclusion of a univariate sensitivity analysis, which evaluated the impact of vaccine wastage. Okafor assessed a scenario of a 50% reduction in wastage to determine if this affected the optimal vaccine choice. It was shown that ROTAVAC might be a most cost-effective after 7 years, if wastage was reduced. Overall, this study underscores the importance of rotavirus introduction in Nigeria.

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Appendix

The literature search for the October 2021 Vaccine Delivery Research Digest was conducted on September 27, 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 545 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]))