VACCINE DELIVERY RESEARCH DIGEST

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REPORT TO THE BILL & MELINDA GATES FOUNDATION

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1.   [Health spending and vaccination coverage in low-income countries](#)

Castillo-Zunino F, Keskinocak P, Nazzal D, Freeman MC.

ABSTRACT

INTRODUCTION: Routine immunisation is a cost-effective way to save lives and protect people from disease. Some low-income countries (LIC) achieved remarkable success in childhood immunisation. Yet, previous studies comparing the relationship between economic growth and health spending with vaccination coverage have been limited. We investigated these relationships among LIC to understand what financial changes lead to childhood immunisation changes.

METHODS: We identified which financial indicators were significant predictors of vaccination coverage in LIC by fitting regression models for several vaccines, controlling for population density, land area and female years of education. We then identified LIC with high vaccination coverage (LIC+) and compared their economic and health spending trends with other LIC (LIC−) and lower-middle income countries. We used cross-country multi-year regressions with mixed-effects to test financial indicators' rate of change. We conducted statistical tests to verify if financial trends of LIC+ were significantly different from LIC−.

RESULTS: During 2014–2018, gross domestic product per capita ($p=0.67$–0.95, range given by tests with different vaccines), total/private health spending per capita ($p=0.57$–0.97, $p=0.32$–0.57) and aggregated development assistance for health (DAH) per capita ($p=0.38$–0.86) were not significant predictors of vaccination coverage in LIC. Government health spending per capita ($p=0.022$–0.073) and total/government spending per birth on routine immunisation vaccines ($p=0.0007$–0.029, $p=0.016$–0.052) were significant positive predictors of vaccination coverage. From 2000 to 2016, LIC+ increased government health spending per capita by US$0.30 per year, while LIC− decreased by US$0.16 (significant difference, $p<0.0001$). From 2006 to 2017, LIC+ increased government spending per birth on routine immunisation vaccines by US$0.22 per year, while LIC− increased by US$0.10 ($p<0.0093$).

CONCLUSION: Vaccination coverage success of some LIC was not explained by economic development, total health spending nor aggregated DAH. Vaccination coverage success of LIC+ was

associated with increasing government health spending particularly in routine immunisation vaccines.

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IMPACT FACTOR: 4.29
CITED HALF-LIFE: 1.9

START COMMENTARY

Castillo-Zunino *et al.* conducted a study to evaluate the association between health spending and vaccination coverage in low income countries. This study fills a gap in the literature assessing the relationship between economic growth and health spending with vaccination coverage. They fit regressions with fixed and mixed effects to compare low-income countries (LICs) in terms of income, health spending, and vaccine spending both per capita and per live birth. Further, they conducted sub-group analyses for countries with high vaccination coverage (referred to as LIC+) compared to other LICs (referred to as LIC-). Lastly, they investigated time-varying differences in financial indicators. Castillo-Zunino *et al.* utilized data sources from WHO, UNICEF, the World Bank, the UNDP, and IHME.

Results showed that increased government health spending per capita was significantly associated with higher vaccination coverage. Other financial indicators, including GDP/GNI per capita, total/private health spending per capita, and development assistance for health were not significant predictors of vaccination coverage in LICs. A summary of cross-section fixed-effects regression models is shown in Table 1. When considering the high vaccination coverage versus low countries, LIC+ increased spending by $0.30 per capita whereas LIC- decreased spending by $0.16 (p<0.0001). A summary of financial indicators rate of change in country groups is shown in Table 3. Castillo-Zunino *et al.* conclude that differences in vaccination coverage cannot be explained by the countries' economic development, total health spending, or development assistance. Government health spending and spending per birth on routine immunization were however found to be positive predictors of vaccine coverage. This may indicate that spending needs to be invested into vaccination efforts rather than depending on broad improvements in economic indicators.

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2. [An Implementation Research Approach to Re-orient Health Supply Chains Toward an Equity Agenda in the COVID-19 Era](#)

Frisch MF, Scott KW, Binagwaho A

ABSTRACT

The Covid-19 pandemic has exposed critical inequities in global healthcare supply chains and the need for these systems to be analyzed and reoriented with an equity lens. Implementation research methodology can guide the use of evidence-based interventions to re-orient health supply chains towards equity and optimize health outcomes. Using this approach, private and public sector entities can adapt their strategies to focus not just on efficiency and cost savings but ensuring that vulnerable populations have access to essential medications, vaccines, and supplies. Findings can inform regulations that address supply chain inequities at the global level, strengthen existing systems to fill structural gaps at the national level, and address contextual challenges at the subnational level. This methodology can help account for historical practices from prior health initiatives, identify contemporary barriers and facilitators for positive change, and have applicability to the Covid-19 pandemic and ongoing vaccine distribution efforts. An implementation research approach is critical in equipping health supply chains with a path for more resilient and equitable distribution of necessary supplies, vaccines, and delivery of care.

START COMMENTARY

In this commentary, Frisch *et al.* call for an analysis of supply chains in the wake of inequities illuminated by the Covid-19 pandemic. Specifically, they state that an implementation research framework can help identify supply chain issues and strategies to address those issues. This commentary is impactful as it suggests means of improving the inequalities associated with Covid-19. The implementation research framework focuses on studying and addressing contextual factors relevant for the that need to be addressed when implementation of evidence-based interventions to improve health. Relatedly, the framework focuses on implementation strategies, approaches used for successful implementation of evidence-based interventions, and implementation outcomes, the results of implementation of evidence-based interventions (e.g., acceptability, appropriateness, sustainability). Frisch *et al.* also note a limitation of this framework—that this approach requires high

levels of engagement from stakeholders, implementation science researchers, and supply chain experts, which may not be possible given the ongoing crisis.

Frisch *et al.* describe a prior example of the use of implementation research methods to a prior supply chain challenge to provide universal access to antiretrovirals (ARVs) for HIV in LMICs which included the identification of barriers at the national and sub-national level. National barriers included issues with forecasting demand and weaknesses with national logistics whereas sub-national barriers included examples such as last mile ARV delivery and storage. Authors state that this same approach can be used for Covid-19 vaccine delivery and ensure greater access and equity global.

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3. [Evaluating the potential economic and health impact of rotavirus vaccination in 63 middle-income countries not eligible for Gavi funding: a modelling study](#)

Debellut F, Clark A, Pecenka C, Tate J, Baral R, *et al.*

ABSTRACT

BACKGROUND: Middle-income countries (MICs) that are not eligible for funding from Gavi, the Vaccine Alliance, have been slow to adopt rotavirus vaccines. Few studies have evaluated the cost-effectiveness and benefit-risk of rotavirus vaccination in these settings. We aimed to assess the potential economic and health impact of rotavirus vaccination in 63 MICs not eligible for funding from Gavi.

METHODS: In this modelling study, we estimated the cost-effectiveness and benefit-risk of rotavirus vaccination in 63 MICs not eligible to Gavi funding. We used an Excel-based proportionate outcomes model with a finely disaggregated age structure to estimate the number of rotavirus gastroenteritis cases, clinic visits, hospitalisations, and deaths averted by vaccination in children younger than 5 years over a 10-year period. We calculated cost-effectiveness ratios (costs per disability-adjusted life-years averted compared with no vaccination) and benefit-risk ratios (number of hospitalisations due to rotavirus gastroenteritis averted per excess hospitalisations due to intussusception). We evaluated three alternative vaccines available globally (Rotarix, Rotavac, and Rotasiil) and used information from vaccine manufacturers regarding anticipated vaccine prices. We ran deterministic and probabilistic uncertainty analyses.

FINDINGS: Over the period 2020-29, rotavirus vaccines could avert 77 million (95% uncertainty interval [UI] 51-103) cases of rotavirus gastroenteritis and 21 million (12-36) clinic visits, 3 million (1·4-5·6) hospitalisations, and 37 900 (25 900-55 900) deaths due to rotavirus gastroenteritis in 63 MICs not eligible for Gavi support. From a government perspective, rotavirus vaccination would be cost-effective in 48 (77%) of 62 MICs considered. The benefit-risk ratio for hospitalisations prevented versus those potentially caused by vaccination exceeded 250:1 in all countries.

INTERPRETATION: In most MICs not eligible for Gavi funding, rotavirus vaccination has high probability to be cost-effective with a favourable benefit-risk profile. Policy makers should consider this new evidence when making or revisiting decisions on the use of rotavirus vaccines in their respective countries.

START COMMENTARY

In this modeling study, Debellut *et al.* estimate the cost-effectiveness and benefit-risk of three oral rotavirus vaccination in 63 middle-income countries (MICs) that are not eligible for Gavi funding. This article is impactful as it assesses rotavirus economic outcomes for countries which do not have international support from Gavi and have been slow in adopting the vaccines when compared to low income countries. By providing estimates of the public health and economic impact, the authors provide evidence to aide decision makers in MICs. Author estimated the burden of non-severe rotavirus gastroenteritis (RVGE), non-severe and severe RVGE clinic visits, severe RBGE cases, severe RVGE hospitalizations, and deaths. To estimate vaccine coverage, authors used country-specific coverage rates of diphtheria-tetanus-pertussis as a proxy for rotavirus vaccine coverage. Vaccine efficacy data was drawn from a pooled analysis of all randomized trials on oral rotavirus vaccines, stratified by under 5 mortality and dose. Costs were estimated from a recent study published in 2020 on inpatient and outpatient diarrhea costs from a government and societal perspective. The main study outcome was the incremental cost effectiveness (ICER), expressed in US dollars per DALY averted with the threshold of 0.5 times the per capita gross domestic product (GDP) to determine cost effectiveness.

Key findings included that the use of rotavirus vaccine could potentially avert 77 million cases, 21 million visits, and 3 million hospitalizations across MICs from 2020-2019. In 48 countries (77%) rotavirus vaccination was associated with an ICER of 0.5 times their GDP, which the authors considered to be cost-effective. Nearly half (n=21) of these countries are not yet using rotavirus vaccines. Key strengths of this analysis include the consideration of elevated intussusception risk in the ICERs, which was calculated as the number of admissions due to rotavirus averted per excess intussusception hospital admission and the inclusion of a probabilistic sensitivity analysis. Limitations include the lack of indirect benefits (i.e., herd immunity) and that there was equal dose-specific efficacy, regardless of the product used. Debellut *et al.* conclude that these vaccinations might provide good value for money at current prices.

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4. Effects of engaging communities in decision-making and action through traditional and religious leaders on vaccination coverage in Cross River State, Nigeria: A cluster-randomised control trial

Oyo-Ita A, Bosch-Capblanch X, Ross A, Oku A, Esu E,

ABSTRACT

BACKGROUND: Vaccination coverage levels fall short of the Global Vaccine and Action Plan 90% target in low- and middle- income countries (LMICs). Having identified traditional and religious leaders (TRLs) as potential public health change agents, this study aimed at assessing the effect of training them to support routine immunisation for the purpose of improving uptake of childhood vaccines in Cross River State, Nigeria.

METHODS: A cluster-randomised controlled study was conducted between 2016 and 2019. Of the 18 Local Government Areas (LGA) in Cross River State, eight (four urban and four rural LGAs) were randomized into the intervention and control study arms. A multi-component intervention involving the training of traditional and religious leaders was implemented in the four intervention LGAs. Baseline, midline and endline surveys collected information on children aged 0-23 months. The effect of the intervention on outcomes including the proportion fully up-to-date with vaccination, timely vaccination for pentavalent and measles vaccines, and pentavalent 1-3 dropout rates were estimated using logistic regression models using random effects to account for the clustered data.

RESULTS: A total of 2598 children at baseline, 2570 at midline, and 2550 at endline were included. The intervention was effective in increasing the proportion with at least one vaccine (OR 12.13 95% CI 6.03-24.41 $p<0.001$). However, there was no evidence of an impact on the proportion of children up-to-date with vaccination ($p = 0.69$). It was effective in improving timeliness of Pentavalent 3 (OR 1.55; 95% CI: 1.14, 2.12; $p = 0.005$) and Measles (OR 2.81; 96% CI: 1.93-4.1; $p<0.001$) vaccination. The odds of completing Pentavalent vaccination increased (OR = 1.66 95% CI: 1.08,2.55).

CONCLUSION: Informal training to enhance the traditional and religious leaders' knowledge of vaccination and their leadership role can empower them to be good influencers for childhood vaccination. They constitute untapped resources in the community to boost routine immunisation. Pan African Clinical Trial Registry (PACTR) PACTR202008784222254.

START COMMENTARY

In this randomized controlled trial, Oyo-Ita *et al.* evaluate the effect of engaging with communities through traditional and religious leaders on vaccination coverage of children 0-23 months of age. Eight Local Government Areas (LGAs) were randomized to either the intervention or control arms. The primary outcome was vaccination coverage. Secondary outcomes included the dropout rate for Pentavalent 3 vaccine, the timing of Pentavalent and measles vaccination, the morbidity and mortality of vaccine-preventable diseases, preventive clinic service utilization, changes in the processes and perceptions of actors, and intervention cost-effectiveness. The intervention took place between May 2017 to November 2018 and consisted of several components including traditional and religious (TRL) training, health worker training, community engagement, and strengthening of the ward development committee. The baseline, midline, and endline were conducted in December 2016, February 2018, and January 2019, respectively.

Key findings included that the intervention had no effect on improving full coverage of vaccination in children (RR 1.03, 95% CI 0.83–1.28) but did increased the odds of a child having at least one vaccine at the final survey (OR: 12.13; 95% CI 6.03–24.41) and the odds of having timely Pentavalent 1 (OR 1.96; 95% CI 1.53–2.53), and timely Pentavalent 3 (OR 1.55; 95% CI: 1.14–2.12). Although this study did not find an impact on improving full coverage among young children, it did show several other positive outcomes including a reduction of unvaccinated children, indicating that community engagement with traditional and religious leaders may be a worthwhile approach in future vaccination efforts.

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5. [Impact and cost-effectiveness of potential interventions against infant respiratory syncytial virus (RSV) in 131 low-income and middle-income countries using a static cohort model](#)

Baral R, Higgins D, Regan K, Pecenka C.

BMJ Open. 2021 Apr 24;11(4):e046563.

PubMed ID: 33895717

ABSTRACT

OBJECTIVES: Interventions to prevent childhood respiratory syncytial virus (RSV) disease are limited and costly. New interventions are in advanced stages of development and could be available soon. This study aims to evaluate the potential impact and cost-effectiveness of two interventions to prevent childhood RSV-a maternal vaccine and a monoclonal antibody (mAb).

DESIGN: Using a static population-based cohort model, we evaluate impact and cost-effectiveness of RSV interventions, from a health systems perspective. The assumed baseline efficacy and duration of protection were higher for the mAb (60%-70% efficacy, protection 6 months) compared with the maternal vaccine (40%-60% efficacy, protection 3 months). Both interventions were evaluated at US$3 and US$5 per dose for Gavi and non-Gavi countries, respectively. A range of input values were considered to explore uncertainty.

SETTINGS: 131 low-income and middle-income countries.

PARTICIPANTS: Pregnant women and live birth cohorts.

INTERVENTIONS: Maternal vaccine given to pregnant women and mAb given to young infants. Primary and secondary outcome measures: Disability-adjusted life years averted, severe ase averted, deaths averted, incremental cost effectiveness ratios.

RESULTS: Under baseline assumptions, maternal vaccine and mAbs were projected to avert 25% and 55% of RSV-related deaths among infants younger than 6 months of age, respectively. The average incremental cost-effectiveness ratio per disability-adjusted life year averted was US$1342 (range US$800-US$1866) for maternal RSV vaccine and US$431 (range US$167-US$692) for mAbs. At a 50% gross domestic product per capita threshold, maternal vaccine and mAbs were cost-effective in 60 and 118 countries, respectively.

CONCLUSIONS: Both interventions are projected to be impactful and cost-effective in many countries, a finding that would be enhanced if country-specific Gavi cofinancing to eligible countries

were included. mAbs, with assumed higher efficacy and duration of protection, are expected to be more cost-effective than RSV maternal vaccines at similar prices. Final product characteristics will influence this finding.

START COMMENTARY

In this study, Baral *et al.* provide estimates on the potential impact and cost-effectiveness of maternal vaccines and monoclonal antibodies for respiratory syncytial virus (RSV) prevention across 131 low- and middle-income (LMIC) countries. This article is important as it provides estimates on the potential impact of RSV intervention candidates which may be introduced in the next few years. The study evaluated the impact of a single dose RSV maternal vaccine given at 24-36 weeks of gestation, and of a single-dose monoclonal antibodies (mAb) given to infants at birth, compared to no intervention. The analysis used a 10 year time horizon (from 2030-2039) and assumed nationwide introduction in 2030 from a health systems perspective. Model outcomes included c cases averted, severe cases averted, hospitalisations averted, deaths averted, disability-adjusted life years (DALYs) averted and the incremental cost per DALY averted. The cost-effectiveness threshold was 0.5 gross domestic product (GDP). Key model inputs including intervention characteristics, disease burden, hospital admissions are summarized in Table 1. Baral *et al.* also conducted one-way sensitivity analyses by varying parameters including efficacy, duration of protection, coverage, and price.

Results projected that the occurrence of nearly 42 million non-severe and 15.28 million severe cases of RSV globally over the 10-year period and 11.48 million hospitalizations and 504,963 deaths among children younger than 6 months. A maternal vaccine was projected to avert 17% of severe RSV cases and 25% of RSV-related deaths among young infants globally. An RSV mAb was projected to 55% of RSV deaths of young infants. The average annual cost of vaccination programs for all countries was estimated to be about $546.43 million for the maternal vaccine and $538.40 million for mAb. The ICER per DALY averted was approximately $1342 for the maternal vaccine and $431 for mAb. Estimates vary slightly depending on Gavi-eligibility. Overall, authors find that RSV interventions would potentially be cost-effective across all countries. However, it is important to note that this analysis depends on many assumptions, particularly for interventions which are still in development and may ultimately have different product characteristics.

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6. [Reducing dengue fever cases at the lowest budget: a constrained optimization approach applied to Thailand](#)

Knerer G, Currie CSM, Brailsford SC.

ABSTRACT

BACKGROUND: With the challenges that dengue fever (DF) presents to healthcare systems and societies, public health officials must determine where best to allocate scarce resources and restricted budgets. Constrained optimization (CO) helps to address some of the acknowledged limitations of conventional health economic analyses and has typically been used to identify the optimal allocation of resources across interventions subject to a variety of constraints.

METHODS: A dynamic transmission model was developed to predict the number of dengue cases in Thailand at steady state. A CO was then applied to identify the optimal combination of interventions (release of Wolbachia-infected mosquitoes and paediatric vaccination) within the constraints of a fixed budget, set no higher than cost estimates of the current vector control programme, to minimize the number of dengue cases and disability-adjusted life years (DALYs) lost. Epidemiological, cost, and effectiveness data were informed by national data and the research literature. The time horizon was 10 years. Scenario analyses examined different disease management and intervention costs, budget constraints, vaccine efficacy, and optimization time horizon.

RESULTS: Under base-case budget constraints, the optimal coverage of the two interventions to minimize dengue incidence was predicted to be nearly equal (Wolbachia 50%; paediatric vaccination 49%) with corresponding coverages under lower bound (Wolbachia 54%; paediatric vaccination 10%) and upper bound (Wolbachia 67%; paediatric vaccination 100%) budget ceilings. Scenario analyses indicated that the most impactful situations related to the costs of Wolbachia and paediatric vaccination with decreases/ increases in costs of interventions demonstrating a direct correlation with coverage (increases/ decreases) of the respective control strategies under examination.

CONCLUSIONS: Determining the best investment strategy for dengue control requires the identification of the optimal mix of interventions to implement in order to maximize public health outcomes, often under fixed budget constraints. A CO model was developed with the objective of minimizing dengue cases (and DALYs lost) over a 10-year time horizon, within the constraints of the estimated budgets for vector control in the absence of vaccination and Wolbachia. The model provides a tool for developing estimates of optimal coverage of combined dengue control strategies that minimize dengue burden at the lowest budget.

START COMMENTARY

In this modelling study, Knerer *et al.* describe a constrained optimization (CO) to identify the optimal allocation of resources comparing pediatric vaccination and *Wolbachia*-infected mosquitoes for dengue fever prevention in Thailand. In this analysis, a dynamic transmission model was used to project the incident number of dengue fever cases, and disability-adjusted life years lost for a 10 year time horizon for both vaccination and *Wolbachia* release.

The model predicts 7 million symptomatic dengue cases and 67,381 DALYs would occur over 10 years and the total disease costs would be $338 million. In an unconstrained case, the projected optimal coverage for *Wolbachia* and pediatric vaccination (100% of each intervention) would reduce 6 million dengue cases and 58,000 DALYs for $679 million over 10 years. Vaccination costs accounted for $351 million and *Wolbachia* would cost $274 million. In Table 3, Knerer *et al.* present the optimal mix of the two interventions with budget constraints, whereas Figure 1 provides a visual of the two interventions against budget constraints. A key strength of this analysis is that scenario analyses were conducted on several input parameters to test the robustness of the findings and determine the most important influential parameters.

There are some notable limitations of this analysis. Firstly, there was no consideration for population age structure or dengue serotype. Additionally, non-medically attended cases were not included, which leads to an underestimate of costs. Relatedly, economic costs (e.g., lost productivity time or wages) were not considered, so benefits may be underestimated. Despite these limitations, this article provides estimates for optimal coverage of combined dengue control strategies which can guide policymaking and budget decisions in Thailand and elsewhere.

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7. [Nigeria experience on the use of polio assets for the 2017/18 measles vaccination campaign follow-up](#)

Oteri AJ, Adamu U, Dieng B, Bawa S, Terna N,

ABSTRACT

BACKGROUND: The global polio eradication initiative has made giant stride by achieving a 99% reduction in Wild poliovirus (WPV) cases, with Nigeria on the verge of being declared polio-free following over 36 months without a WPV. The initiative has provided multiple resources, assets and lessons learnt that could be transitioned to other public health challenges, including improving the quality and vaccination coverage of measles campaigns in order to reduce the incidences of measles in Nigeria. We documented the polio legacy and assets used to support the national measles campaign in 2017/2018.

METHODS: We documented the integration of the measles campaign coordination with the Polio Emergency Operation Centre (EOC) at national and state levels for planning and implementing the measles SIA. Specific polio strategies and assets, such as the EOC incident command framework and facilities, human resource surge capacity, polio GIS resource These strategies were adapted and adopted for the MVC implementation overcome challenges and improve vaccination coverage. We evaluated the performance through a set process and outcome indicators.

RESULTS: All the 36 states and Federal Capital Territory used the structure and resources in Nigeria and provided counterpart financing for the MVC 2017/ 2018. The 11 polio high-risk states deployed the use of GIS for microplanning process, while daily call-in data were tracked in 99.7% of the LGAs and 70,846 reports were submitted real-time by supervisors using Open data kit (ODK). The national coverage achieved was 87.5% by the post-campaign survey with 65% of states reporting higher coverage in 2018 compared to 2015.

CONCLUSION: Polio eradication assets and lessons learned can be applied to measles elimination efforts as the eradication and elimination efforts have similar strategies and programme implementation infrastructure needs. Leveraging these strategies and resources to support MVC planning and implementation resulted in more realistic planning, improved accountability and availability of human and fiscal resources. This approach may have resulted in better MVC outcomes and contributed to Nigeria's efforts in measles control and elimination.

START COMMENTARY

Oteri *et al.* report on process and outcome indicators related to the transfer of polio legacy and assets to the national measles campaign in Nigeria. Given the substantial progress that Nigeria has made in eliminating polio, procedures were established to ensure that polio immunization campaign assets would be available to assist in achieving other public health goals (e.g., measles immunization). Figure 1 shows the polio eradication initiative coordinating mechanisms on the national, state, local government area (LGA), and ward level.

In terms of the collaboration between polio emergency operation centres (EOCs) and the National Measles Technical Coordinating Committee, the authors provide examples of transfer of assets and utilization of approaches from polio to measles efforts. The summary of polio assets and best practices are described in depth in the text and in Table 1 and include sharing of facilities, establishment of working groups, and updating of field guidelines and standard operating procedures. Another key feature of this study was the presentation of prior supplementary immunization activity challenges, innovations applied to overcome them, and subsequent measles vaccination campaign improvements. In the post-measles vaccination coverage survey, five of 36 states achieved the target 95% coverage, compared to only one state in 2015 (before the polio/measles transfer of assets and approaches). Overall, Oteri *et al.* report high levels of readiness, higher levels of coverage, and indicators of improvements of quality of vaccination microplanning (i.e., with the use of GIS). This study is impactful it shows the value of leveraging existing assets and lessons learned from polio campaigns to improve measles vaccination campaign planning and implementation.

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8. [Heterologous protection against malaria by a simple chemoattenuated PfSPZ vaccine regimen in a randomized trial](#)

Sulyok Z, Fendel R, Eder B, Lorenz FR, Kc N

ABSTRACT

Immunization with Plasmodium falciparum (Pf) sporozoites under chemoprophylaxis (PfSPZ-CVac) is the most efficacious approach to malaria vaccination. Implementation is hampered by a complex chemoprophylaxis regimen and missing evidence for efficacy against heterologous infection. We report the results of a double-blinded, randomized, placebo-controlled trial of a simplified, condensed immunization regimen in malaria-naive volunteers (EudraCT-Nr: 2018-004523-36). Participants are immunized by direct venous inoculation of 1.1×10^5 aseptic, purified, cryopreserved PfSPZ (PfSPZ Challenge) of the PfNF54 strain or normal saline (placebo) on days 1, 6 and 29, with simultaneous oral administration of 10 mg/kg chloroquine base. Primary endpoints are vaccine efficacy tested by controlled human malaria infection (CHMI) using the highly divergent, heterologous strain Pf7G8 and safety. Twelve weeks following immunization, 10/13 participants in the vaccine group are sterilely protected against heterologous CHMI, while (5/5) participants receiving placebo develop parasitemia (risk difference: 77%, p = 0.004, Boschloo's test). Immunization is well tolerated with self-limiting grade 1-2 headaches, pyrexia and fatigue that diminish with each vaccination. Immunization induces 18-fold higher anti-Pf circumsporozoite protein (PfCSP) antibody levels in protected than in unprotected vaccinees (p = 0.028). In addition anti-PfMSP2 antibodies are strongly protection-associated by protein microarray assessment. This PfSPZ-CVac regimen is highly efficacious, simple, safe, well tolerated and highly immunogenic.

START COMMENTARY

In this randomized control trial, Sulyok *et al.* report findings on the effectiveness of immunization with *Plasmodium falciparum* (Pf) sporozoites under chemoprophylaxis (PfSPZCVac). The primary outcome of interest is vaccine efficacy, which is testing using a controlled human malaria infection (CHMI) with the Pf7G8 strain. The study initially enrolled 21 participants but one dropped out due to a medical abnormality. In total, 20 were randomized and 18 participants received all three immunizations. Two other participants withdrew after the second immunization and received treatment.

Overall, 7 of 13 participants in the intervention group had detectable parasitemia. In terms of vaccine efficacy, after 12 weeks, 10 of 13 intervention participants were protected (measured by infection with Pf7G8). Twelve weeks following immunization, 10/13 participants in the vaccine group are sterilely protected against heterologous CHMI, while (5/5) participants receiving placebo develop parasitemia (risk difference: 77%, p = 0.004, Boschloo's test) whereas none in the placebo group were protected after CHMI. In terms of safety, there were no related serious adverse events during the immunization phase. Common reported side effects included headache, dizziness, and fatigue which occurred often in the intervention than placebo group. Other related grade 1 and 2 adverse events are described in Table 2. This study makes an important contribution to the literature as it demonstrates vaccine efficacy against a heterologous strain of Pf parasite indicating high level and cross-strain protection which is tolerable and safe, indicating that further studies with larger study populations should be conducted for PfSPZ-CVac.

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9. [Domestic dog demographics and estimates of canine vaccination coverage in a rural area of Zambia for the elimination of rabies](#)

Kaneko C, Omori R, Sasaki M, Kataoka-Nakamura C, Simulundu E

ABSTRACT

BACKGROUND: An estimated 75% or more of the human rabies cases in Africa occur in rural settings, which underscores the importance of rabies control in these areas. Understanding dog demographics can help design strategies for rabies control and plan and conduct canine mass vaccination campaigns effectively in African countries.

METHODOLOGY/PRINCIPAL FINDINGS: A cross-sectional survey was conducted to investigate domestic dog demographics in Kalambabakali, in the rural Mazabuka District of Zambia. The population of ownerless dogs and the total achievable vaccination coverage among the total dog population was estimated using the capture-recapture-based Bayesian model by conducting a canine mass vaccination campaign. This study revealed that 29% of the domestic dog population was under one year old, and 57.7% of those were under three months old and thus were not eligible for the canine rabies vaccination in Zambia. The population growth was estimated at 15% per annum based on the cross-sectional household survey. The population of ownerless dogs was estimated to be small, with an ownerless-to-owned-dog ratio of 0.01-0.06 in the target zones. The achieved overall vaccination coverage from the first mass vaccination was estimated 19.8-51.6%. This low coverage was principally attributed to the owners' lack of information, unavailability, and dog-handling difficulties. The follow-up mass vaccination campaign achieved an overall coverage of 54.8-76.2%.

CONCLUSIONS/SIGNIFICANCE: This paper indicates the potential for controlling canine rabies through mass vaccination in rural Zambia. Rabies education and responsible dog ownership are required to achieve high and sustainable vaccination coverage. Our findings also propose including puppies below three months old in the target population for rabies vaccination and emphasize that securing an annual enforcement of canine mass vaccination that reaches 70% coverage in the dog population is necessary to maintain protective herd immunity.

START COMMENTARY

In this cross-sectional study, Kaneko *et al.* describe domestic dog demographics in a rural district of Zambia. This study makes an important contribution to the literature as it explores dog demographics in a rural setting, where most human rabies cases occur. This information is critical for rabies control strategies. Two canine mass rabies vaccination campaigns and a survey were conducted. Kaneko *et al.* aimed to estimate the ownerless dog population, investigate demographics of domestic dogs, conduct mass vaccination campaigns, estimate coverage obtained in the campaigns, and reveal owner's knowledge, attitude, and practices related to rabies control.

Overall, the study visited 510 households, of which 333 owned at least one dog. In total, the survey covered 3,882 people and 876 dogs. Most households owned dogs for guarding (98.2%). During the first vaccination campaign, 392 dogs were vaccinated. During the second, 300 dogs were vaccination. Detailed estimates for the vaccination coverage in owned and overall dog populations are shown in Table 4. During the first campaign, 152 of 333 dog-owning households participated. The most common reason (32.0%) for non-participation was that the owner was not informed about the campaign. Many dog owners (75.4% reported being knowledgeable about rabies. However, most of those owners (70.5%) were not able to list rabies symptoms in humans, indicating a discrepancy in knowledge. Kaneko *et al.* found that population of ownerless dogs was estimated to be very low, indicating that rabies control through mass vaccinations of canines is feasible in this setting. Overall, this study provides critical insight into dog demographics and key issues to address during future canine rabies campaigns.

Return to List of Articles

10. The mortality effects of disregarding the strategy to save doses of measles vaccine: a cluster-randomised trial in Guinea-Bissau

Byberg S, Aaby P, Rodrigues A, Stabell Benn C, Fisker AB.

ABSTRACT

INTRODUCTION: Measles vaccine (MV) may improve health beyond measles protection. To avoid wastage from multi-dose vials, children in Guinea-Bissau are only measles vaccinated when aged 9-11 months and when six or more children are present. We assessed health impacts of providing MV to all measles-unvaccinated children 9-35 months.

METHODS: We cluster-randomised 182 village clusters under demographic surveillance in rural Guinea-Bissau to an 'MV-for-all-policy' arm where we offered MV regardless of age and number of children present at our bi-annual village visits, or a 'Restrictive-MV-policy' arm where we followed national policy. Measles-unvaccinated children aged 9-35 months were eligible for enrolment and followed to 5 years of age. In intention-to-treat analyses, we compared mortality using Cox regression analyses with age as underlying timescale. The primary analysis was for children aged 12-35 months at eligibility assessment. Interactions with several background factors were explored.

RESULTS: Between 2011 and 2016, we followed 2778 children in the primary analysis. MV coverage by 3 years was 97% among children eligible for enrolment under the MV-for-all-policy, and 48% under the Restrictive-MV-policy. Mortality was 59% lower than anticipated and did not differ by trial arm (MV-for-all-policy: 45/1405: Restrictive-MV-policy: 44/1373; HR: 0.95 (95% CI 0.64 to 1.43)). The effect of MV-for-all changed over time: The HR was 0.53 (95% CI 0.27 to 1.07) during the first 1½ years of enrolment but 1.47 (95% CI 0.87 to 2.50) later (p=0.02, test of interaction). Explorative analyses indicated that the temporal change may be related to interactions with other childhood interventions.

CONCLUSION: The MV-for-all-policy increased MV coverage but had no overall effect on overall mortality.

WEB: 10.1136/bmjgh-2020-004328
IMPACT FACTOR: 4.280
CITED HALF-LIFE: 1.9

START COMMENTARY

In this cluster-randomized control trial, Byberg *et al.* report results from a randomized trial which aimed to provide measles vaccine to all unvaccinated children 9-35 months without consideration for vaccine wastage. This is different from the status quo, in which children are only vaccinated when 9-11 months old and when six or more children are present to avoid wasting doses in the multi-dose vials. Overall, 182 clusters were randomized to the measles-vaccination (MV) for all arm (intervention) or the restrictive measles vaccination policy arm (control). The study achieved balance between groups in terms of age, sex, maternal age, maternal school, prior vaccinations, and socioeconomic status indicators. The main outcome was mortality. Other outcomes assessed included hospital admissions, nutritional status, and MV coverage.

Byberg *et al.* found higher MV coverage in the intervention compared to control sites; MV coverage was 96% in the intervention compared to 85% in the restrictive policy clusters. However, there was no statistically significant association between the MV intervention and mortality (Hazard ratio [HR]: 0.95, 95% CI: 0.64 to 1.43) in the intent-to-treat, per-protocol, or community-level analyses. Similarly, there was no difference in hospital admission rates or mid upper-arm circumference between the intervention and control. A strength of this study was analysis of interactions with other interventions such as vaccine campaigns that may have affected the mortality rate. When dividing the follow-up time into before and after the campaigns, Byberg *et al.* found a statistically significant difference in the mortality rate among children aged 12-35 months. the authors concluded that providing MV for all children resulted in a higher MV coverage. However, many children remained measles unvaccinated by 3 years of age, indicating that MV should be provided to all children, rather than a specific age range or for a minimum group of children.

Appendix

The literature search for the June 2021 Vaccine Delivery Research Digest was conducted on May 23, 2021 We searched English language articles indexed by the US National Library of Medicine and published between April 15, 2021 and May 14, 2021. The search resulted in 484 results.

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]) ("2021/04/15"[PDAT] : "2021/05/14"[PDAT]))