VACCINE DELIVERY RESEARCH DIGEST

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

REPORT TO THE BILL & MELINDA GATES FOUNDATION

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Details of Articles

1. Using geospatial models to map zero-dose children: factors associated with zero-dose vaccination status before and after a mass measles and rubella vaccination campaign in Southern province, Zambia.

Arambepola R, Yang Y, Hutchinson K, Mwansa F, Doherty J, Bwalya F, et al.

BMJ Glob Health. 2021 Dec 31;6(12).
PubMed ID: 34969682

ABSTRACT

INTRODUCTION: Despite gains in global coverage of childhood vaccines, many children remain undervaccinated. Although mass vaccination campaigns are commonly conducted to reach these children their effectiveness is unclear. We evaluated the effectiveness of a mass vaccination campaign in reaching zero-dose children.

METHODS: We conducted a prospective study in 10 health centre catchment areas in Southern province, Zambia in November 2020. About 2 months before a national mass measles and rubella vaccination campaign conducted by the Ministry of Health, we used aerial satellite maps to identify built structures. These structures were visited and diphtheria-tetanus-pertussis (DTP) and measles zero-dose children were identified (children who had not received any DTP or measles-containing vaccines, respectively). After the campaign, households where measles zero-dose children were previously identified were targeted for mop-up vaccination and to assess if these children were vaccinated during the campaign. A Bayesian geospatial model was used to identify factors associated with zero-dose status and measles zero-dose children being reached during the campaign. We also produced fine-scale zero-dose prevalence maps and identified optimal locations for additional vaccination sites.

RESULTS: Before the vaccination campaign, 17.3% of children under 9 months were DTP zero-dose and 4.3% of children 9-60 months were measles zero-dose. Of the 461 measles zero-dose children identified before the vaccination campaign, 338 (73.3%) were vaccinated during the campaign and 118 (25.6%) were reached by a targeted mop-up activity. The presence of other children in the household, younger age, greater travel time to health facilities and living between health facility catchment areas were associated with zero-dose status. Mapping zero-dose prevalence revealed substantial heterogeneity within and between catchment areas. Several potential locations were identified for additional vaccination sites.

CONCLUSION: Fine-scale variation in zero-dose prevalence and the impact of accessibility to healthcare facilities on vaccination coverage were identified. Geospatial modelling can aid targeted vaccination activities.

WEB: 10.1136/bmjgh-2021-007479
IMPACT FACTOR: 4.280
CITED HALF-LIFE: 1.9

START COMMENTARY

In this prospective study, Arambepola *et al.* assess the effectiveness of a mass vaccination campaign targeting zero-dose children (i.e., did not receive the first dose of a vaccine by the target age). This study utilizes geospatial modelling to identify factors associated with zero-dose status among children and potential areas for additional vaccination sites. This study addresses a key gap in immunization efforts by assessing the number and distribution of zero-dose children. The study took place in 10 health facility catchment areas in Choma District in the Southern Province of Zambia. Prior to a measles and rubella mass vaccination campaign, the study team identified all built structures in the catchment areas using satellite imagery. The team created maps which were used by community volunteers to register children in each structure. Eligibility criteria included all children less than 60 months old and living in the catchment area. Health workers captured Diphtheria, Tetanus, Pertussis (DTP) and measles containing virus (MCV) status. After the vaccination campaign, all zero-dose children were revisited to see if they were vaccinated during the mass campaign. If not, they would be offered a measles and rubella dose.

A total of 13,519 children were eligible and registered for the study from 41,952 structures. Overall, 322 (17.3%) children were DTP zero-dose children, and 470 (4.3%) children 9-60 months were measles zero-dose. As part of the mass vaccination campaign and follow up, 461 of the zero dose children received measles and rubella (388 during the campaign, 118 during the home visits a week later). Univariate analyses indicated that zero-dose prevalence decreased with increased age and increased as travel time to the clinic increases (*Figure 3)*. The authors conducted a geostatic model, which showed that there was substantial variation in predicted zero-dose prevalence across the catchment area (*Figure 4*). In *Table 3*, the fitted coefficient values from the geostatistical model of the probability of a measles zero-dose child being vaccination during the campaign are presented. Overall, this study underscores the value of understanding the spatial distribution of zero-dose children to guide immunization efforts.

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2. The importance of vaccine stockpiling to respond to epidemics and remediate global supply shortages affecting immunization: strategic challenges and risks identified by manufacturers.

Jarrett S, Pagliusi S, Park R, Wilmansyah T, Jadhav S, Santana P, et al.

Vaccine X. 2021 Dec 23;9:100119.

PubMed ID: 34934942

ABSTRACT

While stockpiling vaccines adds another layer of complexity to vaccine manufacturing, it constitutes a crucial component of comprehensive disease preparedness and control strategies in public health management. Stockpiling provides the ability to immediately respond to epidemics, disease outbreaks, vaccine shortages or stock-outs at local, regional or global levels. Some stockpiles are static, not shipped until an emergency occurs; other stockpiles are rotating with vaccines used in on-going routine immunization programmes. Programmatic use indicates which vaccines to stockpile, the nature of the stockpile and the amount of vaccine to be held at any time. For immediate shipment, fully released product must be stockpiled with the challenge of monitoring remaining shelf-life requirements and the potential risk of expiry. Existing stockpiles are managed and financed globally under the purview of international organizations in the global immunization community, except for buffer stocks held by manufacturers for short periods. The added challenges to manufacturers of stockpiling vaccines, including storage, human resources and other related costs including vaccine destruction when no longer useable, needs to be recognized. This is all the more so with the likelihood of vaccine stockpiling becoming more prominent with changing disease patterns due to climate change and population movements, as well as the significant investment in the research and development of new epidemic prevention vaccines. While vaccine stockpiles managed and financed globally provide rapid response to country requests, more attention is needed in the future to ways that vaccine stockpiling can be brought under the direct purview of individual countries or regional groupings.

WEB: 10.1016/j.jvacx.2021.100119

IMPACT FACTOR: N/A

CITED HALF-LIFE: N/A

START COMMENTARY

Jarrett *et al.* summarize findings from the Developing Countries Vaccine Manufacturers' Network (DCVMN) working group, which was established to understand challenges and successes related to establishing best practices for maintaining consistent vaccine supplies in LMICs. This study summarizes discussions among 52 manufacturers with global stockpiling experiences from the

DCVMN. This work makes an important contribution in summarizing the key issues related to stockpiling, which is critical in situations where the fast deployment of vaccines is required without advanced planning (e.g., during outbreaks). Without stockpiles, there is a risk of vaccine stock-outs and disruptions in routine and supplementary immunization activities. Discussions took place on March 2021 and were led by five expert manufacturers on cholera, meningitis, polio, and yellow fever. Discussions focused on both rotating stockpiles, those that are continuously replenished to a certain number of doses and used for emergency (outbreak) and non-emergency immunizations, and static stockpiles, which are replenished after being deployed to outbreaks to keep the volume constant.

Challenges identified included constraints with supplies due to the demand for complex vaccines (e.g., those with combination formulae or those require specific manufacturing procedures), pricing challenges (i.e., manufacturers exiting from low-profit products), and administrative burdens (i.e., documentation, licensure, and other procedure requirements). Manufacturers also noted that other issues such as batch failure and transport delays could also affect stockpiles. Four cases studies are presented, including a rotating cholera vaccine emergency stockpile in Korea, a rotating yellow fever emergency stockpile in Brazil, a rotating meningococcal A conjugate vaccine stockpile in India, and a static emergency oral poliovirus vaccine stockpile in Indonesia. Jarrett *et al.* highlight the risks to manufactures, including product loss due to shelf-life, additional requirements for investments in infrastructure, and financial risks. The authors conclude that in order for manufacturers of stockpiles to meet global needs, three key areas should be addressed: 1) a greater understanding of the full investment by manufacturers (e.g., cold chain, personnel); 2) an establishment of adequate financing measures, and 3) an agreement on lowering shelf-life requirements of vaccines in stockpiles.

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3. Bias, Precision and Timeliness of Historical (Background) Rate Comparison Methods for Vaccine Safety Monitoring: An Empirical Multi-Database Analysis.

Li X, Lai L, Ostropolets A, Arshad F, Tan E, Casajust P, et al.

Front Pharmacol. 2021 Dec 15;12:773875.

PubMed ID: 34899334

ABSTRACT

Using real-world data and past vaccination data, we conducted a large-scale experiment to quantify bias, precision and timeliness of different study designs to estimate historical background (expected) compared to post-vaccination (observed) rates of safety events for several vaccines. We used negative (not causally related) and positive control outcomes. The latter were synthetically generated true safety signals with incident rate ratios ranging from 1.5 to 4. Observed vs. expected analysis using within-database historical background rates is a sensitive but unspecific method for the identification of potential vaccine safety signals. Despite good discrimination, most analyses showed a tendency to overestimate risks, with 20%-100% type 1 error, but low (0% to 20%) type 2 error in the large databases included in our study. Efforts to improve the comparability of background and post-vaccine rates, including age-sex adjustment and anchoring background rates around a visit, reduced type 1 error and improved precision but residual systematic error persisted. Additionally, empirical calibration dramatically reduced type 1 to nominal but came at the cost of increasing type 2 error.

WEB: 10.3389/fphar.2021.773875

IMPACT FACTOR: 5.811

CITED HALF-LIFE: 2.8

START COMMENTARY

Li *et al.* quantify the bias, precision, and timeliness of different study designs in estimating historical background (expected) to post-vaccination (observed) rates of safety events for vaccines. This study makes an important contribution as it assesses the reliability of measures used to understand post-marketing safety of vaccines. Cohort studies with a historical comparison are typically used to measure the incidence of adverse events following immunization. This method is subject to limitations, including temporal and geographical variations in historical comparisons which may affect how the historical and observed populations can be compared. Data utilized for this study was from the Optum and IBM MarketScan databases (IBM MarketScan Commercial Claims and Encounters, IBM MarketScan Multi-state Medicaid, IBM MarketScan Medicare Supplemental Beneficiaries), two databases of electronic health records and administrative health claims. The use of several databases is a key strength of this work. Vaccines included were the H1N1 vaccine,

different types of seasonal flu vaccine, varicella-zoster vaccines, and HPV 9-valent recombinant vaccine. Post-vaccination rates were collected for 1-9 months after H1N1 and flue, and for 1-12 months for varicella-zoster and HPV. For the background rates, the general population rates were obtained for the same period before these vaccines. Rates were adjusted for confounders to produce age-sex adjusted rates, visit-anchored rates, and visit and age-sex adjusted rates. Li *et al.* include both negative control outcomes (i.e., those without any plausible link to the vaccines) and positive control outcomes (i.e., those that may have a plausible relation to the vaccines). This is a key strength of this analysis.

Results showed a was low type 2 error (i.e., positive control outcomes being missed), ranging from 0-10%. Type 1 errors (i.e., the proportion of negative control outcomes identified as safety signals) were higher, ranging from 30-100% depending on the vaccine and database. Adjustments based on age-sex and background rates reduced error by 50%. Most background rate comparisons showed that potential safety signals could be observed in the first few months after vaccines, although some of these associations may have been exaggerated in these months. Overall, Li *et al.* conclude that comparability of background and post-vaccine rates could be improved by including adjustments for age, sex, and background rates.

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4. Feasibility of using infant testing during immunization to estimate HIV mother-to-child-transmission rates in Zambia.

Simbaya J, Funjika P, Moonga A, Mwale J, Kankasa C.

BMC Infect Dis. 2021 Dec 13;21(1):1239.

PubMed ID: 34886792

ABSTRACT

BACKGROUND: This study piloted the feasibility of infant testing in immunization services as a strategy for estimating MTCT rates among the population of HIV exposed infants at national and subnational levels in Zambia.

METHODS: The study recruited a cross-sectional nationally representative sample of 8042 caregiver-baby pairs in 38 high volume immunization sites in 7 towns across 3 provinces of Zambia. All mothers who brought their children below the age of one year for immunization at the study facilities were invited to participate in the study. All consenting mothers were interviewed and blood drawn from their babies for; rapid HIV antibody test to determine exposure and DNA PCR test for samples of all HIV-exposed babies to determine HIV infection.

RESULTS: Of 8042 recruited caregiver-baby pairs, 1409 (17.5%) babies were HIV-exposed. Approximately 90.2% of all mothers of HIV exposed infants reported that they attended ANC visits more than two times and facility based deliveries stood at 91.6%. Exclusive breastfeeding among HIV exposed infants reduced with increase in age of infant; it was highest at 6 weeks (82.2%) followed by 10 weeks (74.0%) and 14 weeks (58.2%). MTCT rates were relatively lower than what was reported before in subnational studies and stood at 4.7% among Penta 1 seekers, 2.8% among Penta 2 seekers, 2.1% among Penta 3 seekers and 5.0% among Measles vaccination seekers. The overall MTCT rate stood at 3.8%. About 48.1% of HIV positive babies were male compared to 51.9% females. Babies of mothers below the age of 25 years accounted for..almost half (51.9%) of all HIV infected babies in the study. Reported exclusive breastfeeding among HIV positive babies was 77.8% for Penta 1 seekers, 75.0% for Penta 2 seekers and 100% for Penta 3 seekers.

CONCLUSIONS: The study succeeded in estimating the MTCT rates using infant testing in immunization services, thereby demonstrating that it is feasible to use routine infant testing in immunization services as a strategy for estimating MTCT rates among the population of HIV-exposed infants in countries with high HIV burden and immunization coverage.

WEB: 10.1186/s12879-021-06892-0

IMPACT FACTOR: 2.688

CITED HALF-LIFE: 7.2

START COMMENTARY

In this cross-sectional pilot study, Simbaya *et al.* assess the feasibility of estimating HIV mother-to-child transmission (MTCT) rates during routine infant immunization in Zambia. This study is important as measuring MTCT is a challenge in Zambia and other low-and middle-income countries (LMICs). Often, data is unavailable, incomplete, inaccurate, and/or not timely. This study explores an opportunity to test infants while they are receiving other routine services, which may provide critical data on MTCT that can inform prevention and treatment efforts. Mothers and infants (under 12 months of age) were recruited from 38 health facilities across Copperbelt, Lusaka, and Southern provinces while seeking immunization for Penta vaccine 1 to 3 and measles vaccine for 9 month old infants.

A total of 8,289 caregiver-infant pairs consented for the interview and 8,042 consented for HIV testing. HIV infant testing response was nearly identical across provinces (Copperbelt: 98.6%, Southern: 97.0%, and Lusaka: 96.0%) (*Table 1)*. Most mothers were less than 25 years old (47.1%), married (81.6%), had secondary education (62.1%) and were unemployed (67.2%). In terms of HIV infant exposure (HEI), 17.5% of infants were exposed, of whom slightly more were male (55.9%). *Table 2* describes infant HEI by primary caregiver demographics including age, marital status, education, and employment. When calculating adjusted odds ratios, the lowest exposure rates were shown in mothers that were married, with education levels above primary, and with current enrollment in college. Of the 1,409 total exposed infants, 1,389 were tested. Tests indicated MTCT rates of 4.7% at six weeks, 2.8% at 10 weeks, 2.1% at 14 weeks, and 5.0% at 9 months. Overall, these results indicate that is it feasible to test infants for HIV during routine immunization services for several vaccines (Penta 1-3, measles) and geographies. By estimating MTCT rates for infants below 12 months, services to prevent and treat MTCT can be developed and implemented.

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5. Examination of scenarios introducing rubella vaccine in the Democratic Republic of the Congo.

Cheng A, Frey K, Mwamba G, McCarthy K, Hoff N, Rimoin A.

Vaccine X. 2021 Dec 03;9:100127.

PubMed ID: 34849482

ABSTRACT

BACKGROUND: Rubella vaccine has yet to be introduced into the national immunization schedule of the Democratic Republic of the Congo (DRC); the current burden of congenital rubella syndrome (CRS) is unknown and likely to be high. An important consideration prior to introducing rubella containing vaccine (RCV) is the potential inverse relationship between RCV coverage and CRS incidence. Increasing RCV coverage will also increase in the average age of infection. Cumulative infections across all age groups will decrease, but the number of infections in age groups vulnerable to CRS may increase.

METHODS: Rubella transmission dynamics in the DRC were simulated using a stochastic agent-based model of transmission. Input parameter values for known properties, demographic variables, and interventions were fixed; infectivity was inferred from seropositivity profiles in survey data.

RESULTS: Our simulations of RCV introduction for the DRC demonstrate that an increase in CRS burden is unlikely. Continued endemic transmission is only plausible when routine immunization coverage is less than 40% and follow-up supplemental immunization activities have poor coverage for decades.

CONCLUSION: Increased vaccination coverage tends to increase the annual variability of CRS burden. Simulations examining low vaccination coverage and high mean CRS burden are outbreak prone, with multiple years of reduced burden followed by acute outbreaks. These outcomes contrast simulations with no vaccination coverage and high mean CRS burden, which have more consistent burden from year to year.

WEB: 10.1016/j.jvacx.2021.100127

IMPACT FACTOR: N/A

CITED HALF-LIFE: N/A

START COMMENTARY

In this modelling study, Cheng *et al.* consider several scenarios of congenital rubella syndrome (CRS) transmission after introduction of rubella containing vaccine (RCV) using an agent-based model in the Democratic Republic of Congo (DRC). This study can help project the expected

public health impact of incorporating RCV into the national immunization plan in DRC. Data for the model was obtained from the 2013-2014 Demographic Health Survey (DHS) and dried blood spots (DBS) tested for HIV, measles, mumps, rubella, varicella, tetanus, malaria, and polio. The model utilized for this analysis was the Generic branch of EMOD, a stochastic agent-based model of transmission which includes fixed input parameters (infectious period, birth rate, and existing interventions) as well as a consideration for seropositivity to determine the infectivity (i.e., the basic reproductive number, R0). Burden was forecasted for a three-decade period (from 2021-2050) for each province in DRC. The introduction of RCV was simulated as a catch-up supplementary immunization activity (SIA) targeting children between 9 months to adolescents under 15 years with existing routine immunization rates (i.e., 50% coverage in DRC).

Key findings indicated that R0 ranged from 3 to 8 across provinces. One province, Mai Ndombe was bimodal, indicating it had two transmission patterns of endemic and outbreak. Mean estimates for CRS were between 0.1-1.6 per thousand births across provinces for an estimated 3,600 cases annually. With the RCV introduction, the median annual burden decreased substantially to near 0. Mean annual burden did not decrease for all provinces but did change distribution. *Figure 5* demonstrates the change in CRS rates over 30 years with varying vaccine coverage (0-100%). Overall, this modelling study demonstrates the transmission impacts of introduction RCV with SIAs.
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6. World Health Organization Expert Working Group: Recommendations for assessing morbidity associated with enteric pathogens.

Hasso-Agopsowicz M, Lopman B, Lanata C, Rogawski McQuade E, Kang G, Prudden H, et al.
Vaccine. 2021 Dec 14;39(52):7521-7525.
PubMed ID: 34838322

ABSTRACT

BACKGROUND: Diarrhoeal infections are one of the leading causes of child's mortality and morbidity. Vaccines against *Shigella,* enterotoxigenic *E. coli (*ETEC), *norovirus* and invasive non-typhoidal *Salmonella* are in clinical development, however, their full value in terms of short and long-term health and socio-economic burden needs to be evaluated and communicated, to rationalise investment in vaccine development, and deployment. While estimates of mortality of enteric infections exist, the long-term morbidity estimates are scarce and have not been systematically collected.

METHODS: The World Health Organization (WHO) has convened a Burden of Enteric Diseases Morbidity Working Group (BoED MWG) who identified key workstreams needed to characterise the morbidity burden of enteric infections. The group also identified four criteria for the prioritisation of pathogens of which impact on long-term morbidity needs to be assessed.

RESULTS: The BoED MWG suggested to identify and analyse the individual level data from historical datasets to estimate the impact of enteric infections and confounders on long-term morbidity, including growth faltering and cognitive impairment in children (workstream 1); to conduct a systematic review of evidence on the association of aetiology specific diarrhoea with short- and long- term impact on growth, including stunting, and possibly cognitive impairment in children, while accounting for potential confounders (workstream 2); and to conduct a systematic review of evidence on the association of aetiology specific diarrhoea with short- and long- term impact on health outcomes in adults. The experts prioritised four pathogens for this work: *Campylobacter jejuni, ETEC (LT or ST), norovirus (G1 or G2),* and *Shigella (dysenteriae, flexneri, sonnei).*

CONCLUSIONS: The proposed work will contribute to improving the understanding of the impact of enteric pathogens on long-term morbidity. The timing of this work is critical as all four pathogens have vaccine candidates in the clinical pipeline and decisions about investments in development, manufacturing or vaccine procurement and use are expected to be made soon.

WEB: 10.1016/j.vaccine.2021.11.033
IMPACT FACTOR: 3.143
CITED HALF-LIFE: 7.3

START COMMENTARY

Hasso-Agopsowicz *et al.* present recommendations from the World Health Organization (WHO) Burden of Enteric Diseases Morbidity Working Group (BoED MWG) to evaluate the morbidity burden of enteric infections. These recommendations are critical as the long-term burden in terms of health and socio-economic risks are not well understood but are required to assess the potential impact of enteric pathogen vaccines, which are currently in development. Overall, the BoED MWG agreed that the short- and long-term morbidity of enteric pathogens is poorly understood, and therefore cannot be applied to assess the actual value of enteric pathogen vaccines. As such, they propose a series of workstreams to better understand the short- and long-term morbidity.

Workstream 1 is to identify and analyze individual-level data from historical datasets to understand the long-term morbidity of growth faltering and cognitive impairment. Workstream 2 is to conduct a systematic review on the aetiology-specific diarrhoea with short- and long-term impact on growth (stunting, cognitive impairment). Workstream 2 is to conduct a systematic review of aetiology specific diarrhoea on the health outcomes of adults. In *Table 1*, Hasso-Agopsowicz *et al.* present a selection of 17 relevant pathogens, including whether they are in clinical development, feasible to develop into a vaccine, show any evidence of impacts on growth or infections, or show that non-diarrhoeal infections impact growth/cognition. This chart, along with the recommendations about how to select pathogens for assessment using a standardized approach can be useful for those interested in contributing to workstreams. The BoED MWG recommend four pathogens that are of priority to assess: *Campylobacter jejuni, ETEC (LT or ST), norovirus* (G1 or G2), and *Shigella (dysenteriae, flexneri, sonnei).* Overall, the recommendations presented provide guidance to researchers interested in contributing to an understanding of the morbidity of enteric pathogens to inform vaccine development, manufacturing, and distribution efforts in the future.

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7. Pneumococcal carriage among children in low and lower-middle-income countries: A systematic review.

Tvedskov E, Hovmand N, Benfield T, Tinggaard M.

Int J Infect Dis. 2022 Jan 11;115:1-7.

PubMed ID: 34800691

ABSTRACT

OBJECTIVES: Streptococcus pneumoniae is one of the most important causes of diseases leading to child mortality, especially in low- and lower-middle-income countries. This review aims to describe the prevalence of carriage of *S. pneumoniae* and the impact of vaccination among children aged under five years in low- and lower-middle-income countries since 2012.

METHOD: The study is a systematic review of the literature. Relevant publications were searched in PubMed and screened systematically for information on the prevalence of carriage of S. pneumoniae among children aged under five years. 149 publications were identified, and 20 were included in the review.

RESULTS: The prevalence of *S. pneumoniae* ranged between 26.7% - 90.7%. The prevalence of vaccine-type carriage ranged between 4.4% - 57.6% but generally decreased in countries after the introduction of PCV, with a reduction of 15.6% - 65.7%. Half of the post- pneumococcal conjugate vaccine (PCV) studies reported a vaccine-type carriage rate below 15%.

CONCLUSION: Vaccine-type-carriage has decreased in most countries with the introduction of PCV. Still, coverage is only moderate, and carriage rates of S. pneumoniae vary significantly between countries. Continuous monitoring of carriage is needed to evaluate the effect of the further introduction of PCV10 and PCV13.

WEB: 10.1016/j.ijid.2021.11.021
IMPACT FACTOR: 3.202
CITED HALF-LIFE: 5.3

START COMMENTARY

In this systematic review, Signe Filtenborg Tvedskov *et al.* describe the prevalence of *S. pneumoniae* carriage among children under five years in LMICs since 2012 and the impact of the pneumococcal conjugate vaccine (PCV). This review can provide important information to LMICs that have not added PCV into national immunization programs. Inclusion criteria included studies on *Streptococcus Pneumoniae* vaccine-type (VT) carriage prevalence among children aged 5 years and

younger in LMICs. For countries which have introduced PCV10 or PCV13, the change in VT carriage after introduction was also assessed.

Of 149 publications identified, 37 were selected after title/abstract review. Of these, 20 were ultimately included in the review. Studies took place in several countries including The Gambia, Mozambique, Haiti, Morocco, Kenya, Ghana, Tanzania, Pakistan, Lao People's Democratic Republic, Nigeria, Cambodia, India, Bhutan, Vietnam, and Egypt and were published between 2012 and 2020. Most (18) studies were cross-sectional. Only 2 of 20 studies from Vietnam and Egypt had not introduced PCV. Key results indicated that carriage rates of all serotypes ranged from 26.7-90.5% in pre-PCV studies. Detailed findings for each study are shown in *Table 1*. One strength of this review it includes 9 studies which were carried out before PCV introduction which represent baseline VT carriage rates. Among six studies which reported pre- and post-PCV introduction rates, all reported an increase in non-vaccine (NVT) serotypes (from a range 14-53.1% to a range of 21.1-74.1% after) and a decrease in VT carriage (a range of -15.6 to -65.7 % after). Details regarding carriage rates pre- and post-introduction are summarized in *Table 2*. Overall, this study demonstrates the high VT carriage rates in LMICs and that these rates decrease after PCV introduction, underscoring the urgency for LMICs to include this vaccine in national immunization programs.

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8. Insights from modelling malaria vaccines for policy decisions: the focus on RTS,S.

Galactionova K, Smith T, Penny M.

Malar J. 2021 Dec 03;20(1):439.
PubMed ID: 34794430

ABSTRACT

Mathematical models are increasingly used to inform decisions throughout product development pathways from pre-clinical studies to country implementation of novel health interventions. This review illustrates the utility of simulation approaches by reviewing the literature on malaria vaccine modelling, with a focus on its link to the development of policy guidance for the first licensed product, RTS,S/AS01. The main contributions of modelling studies have been in inferring the mechanism of action and efficacy profile of RTS,S; to predicting the public health impact; and economic modelling mainly comprising cost-effectiveness analysis. The value of both product-specific and generic modelling of vaccines is highlighted.

WEB: 10.1186/s12936-021-03973-y
IMPACT FACTOR: 2.631
CITED HALF-LIFE: 5.6

START COMMENTARY

In this review article, Galactionova *et al.* describe the utility of simulation approaches for malaria modelling with a focus on the recently licensed malaria vaccine, RTS,S/AS01. This review makes an important contribution as it describes the critical role of modelling studies in informing policy decisions for malaria vaccines. Authors describe the history of modelling vaccines, which began as early as 1950s with models focused on reducing the morbidity and mortality, whereas most are now focused on elimination.

Galactionova *et al.* describe several categories of malaria vaccine models, including models that focus on the mechanism of action, the efficacy profile, and the economics of the vaccine. Models for the mechanism of action and efficacy are parameterized using the transmission rate from mosquitoes to humans and aim to understand efficacy against infection and the decay of efficacy over time. Some of these models are developed using data from the vaccine trials (e.g., aggregated 3-monthly phase 3 trial incidence data was used in the OpenMalaria, EMOD GTK, and GSK model) whereas other models use hypothetical efficacy profiles and deployment modalities. These models will often focus on determining efficacy requirements to meet certain targets (i.e., prevalence reduction or elimination).

Utilizing the RTS,S/AS01 efficacy profile, a model was built to develop the public health impact and inform the WHO guidance on deployment of the vaccine. Model results indicated that among populations of children 2-10 years of age with prevalence between 10-65%, a high coverage (68%) of long-lasting insecticidal nets, and moderate treatment coverage (45%), four doses would avert a median of 116,480 cases (range: 31,450-160,410) and 484 deaths (189–859) deaths per 100,000 fully-vaccinated children over 15 years. Most economic models of malaria vaccines have conducted cost-effectiveness analyses and budget impact analyses, with few focusing on macroeconomic modelling. The primary focus of these models is to determine if the RTS,S vaccine should be introduced in a country alongside other prevention and treatment strategies. Overall, this review summarizes the value of modelling for existing and future malaria vaccines to guide decision-making for RTS,S roll out.

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9. Inclusion of Additional Unintended Consequences in Economic Evaluation: A Systematic Review of Immunization and Tuberculosis Cost-Effectiveness Analyses.

Nymark L, Miller A, Vassall A.

Pharmacoecon Open. 2021 Nov 24;5(4):587-603.

PubMed ID: 33948928

ABSTRACT

OBJECTIVE: Our objective was to review economic evaluations of immunization and tuberculosis to determine the extent to which additional unintended consequences were taken into account in the analysis and to describe the methodological approaches used to estimate these, where possible.

METHODS: We sourced the vaccine economic evaluations from a previous systematic review by Nymark *et al.* (2009-2015) and searched PubMed/MEDLINE and Embase from 2015 to 2019 using the same search strategy. For tuberculosis economic evaluations, we extracted studies from 2009 to 2019 that were published in a previous review by Siapka *et al.* We followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance. Studies were classified according to the categories and subcategories (e.g., herd immunity, non-specific effects, and labor productivity) defined in a framework identifying additional unintended consequences by Nymark and Vassall. Where possible, methods for estimating the additional unintended consequences categories and subcategories were described. We evaluated the reporting quality of included studies according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) extraction guideline.

RESULTS: We identified 177 vaccine cost-effectiveness analyses (CEAs) between 2009 and 2019 that met the inclusion criteria. Of these, 98 included unintended consequences. Of the total 98 CEAs, overall health consequence categories were included 73 times; biological categories: herd immunity 43 times; pathogen response: resistance 15 times; and cross-protection 15 times. For health consequences pertaining to the supply-side (health systems) categories, side effects were included five times. On the nonhealth demand side (intrahousehold), labor productivity was included 60 times. We identified 29 tuberculosis CEAs from 2009 to 2019 that met the inclusion criteria. Of these, six articles included labor productivity, four included indirect transmission effects, and one included resistance. Between 2009 and 2019, only 34% of tuberculosis CEAs included additional unintended consequences, compared with 55% of vaccine CEAs.

CONCLUSIONS: The inclusion of additional unintended consequences in economic evaluations of immunization and tuberculosis continues to be limited. Additional unintended consequences of economic benefits, such as those examined in this review and especially those that occur outside

the health system, offer valuable information to analysts. Further work on appropriate ways to value these additional unintended consequences is still warranted.

WEB: 10.1007/s41669-021-00269-4
IMPACT FACTOR: N/A
CITED HALF-LIFE: 2.2

START COMMENTARY

In this systematic review, Solvar Nymark *et al.* describe if and how unintended consequences are captured in tuberculosis and immunization economic analyses. This study makes an important contribution as indirect health and non-health effects are often excluded from analyses, although it is critical to understand these effects when conducting a cost-effectiveness analysis (CEA) and determining the costs and benefits of a health intervention. Solvar Nymark *et al.* propose a framework for identifying and characterizing additional unintended consequences, defined as the additional costs and effects beyond the direct health impact, shown in *Figure 1*. Examples of health consequences include biological outcomes such as indirect protection and resistance, demand outcomes such as changes in health service consumption, and supply outcomes such as scientific spill overs. Examples of non-health consequences include demand side changes in labour productivity and seeking of informal care and supply side outcomes such as the supply of public services and change in provider behaviour. This study combined two prior searches from two separate vaccine and tuberculosis systematic reviews. Studies were eligible if they were published from January 2009 to December 2019, written in English, based in a LMIC, and conducted an economic evaluation of tuberculosis treatment or vaccines.

Overall, Solvar Nymark *et al.* included 177 vaccine CEAs and 29 tuberculosis CEAs. The summary of each CEA and additional unintended consequences are shown in *Table 1*. Approximately 55% (98) of vaccine CEAs included at least one unintended consequence. Most (41%) were biological outcomes such as resistance and herd immunity, followed by labor productivity (34%). Of the 29 tuberculosis CEAs, 10 included unintended consequences, including 14% which considered transmission and 3% which included resistance. Among non-health outcomes, 21% identified labor productivity. In addition, the authors describe the methods that were utilized to estimate the effects (e.g., mathematical equations, dynamic transmission models). Overall, this study demonstrates that indirect health and non-health outcomes are not consistently included in the CEAs on vaccines and tuberculosis treatment. Further study is warranted to determine if similar trends exist for other interventions across disease areas.

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10. Application of the Geographic Information System (GIS) in immunisation service delivery; its use in the 2017/2018 measles vaccination campaign in Nigeria.

Oteri J, Idi Hussaini M, Bawa S, Ibizugbe S, Lambo K, Mogekwu F, et al.

Vaccine. 2021 Nov 15;39 Suppl 3:C29-C37.
PubMed ID: 33478790

ABSTRACT

BACKGROUND: As global effort is made towards measles elimination, the use of innovative technology to enhance planning for the campaign has become critical. GIS technology has been applied to track polio vaccination activities in Nigeria with encouraging outcomes. Despite numerous measles vaccination campaigns after the first catch up campaign in 2005, sub-optimal outcomes of previous measles supplemental immunization activities necessitated the use of innovative ideas to achieve better outcomes especially when planning for the 2017/2018 measles vaccination campaign. This led to the application of the use of the GIS technology for the Northern states in 2017/2018 campaign. This study is a report of what was achieved with the use of the GIS in the 2017/2018 measles vaccination campaign in Nigeria.

METHODS: GIS generated ward maps were used for the microplanning processes for the 2017/2018 measles vaccination campaign. These ward maps had estimates of the target population by settlements, the number and location of vaccination posts ensuring that a vaccination post is sited within one-kilometer radius of a settlement, and the number of teams needed to support the vaccination campaign as well as the catchment area and daily implementation plans. The ward microplans were verified by checking for accuracy and consistency of the target population, settlements, number of teams, vaccination posts and daily implementation work plans using a standard checklist. The ward maps were deployed into use for the measles vaccination campaign after the state team driven validation and verification by the National team (Government and Partners) RESULTS: The Northern states that applied the GIS technology had a closer operational target population to that on the verified microplan than those of the non-GIS technology states. Greater than 90% of the ward maps had all that is expected in the maps - i.e settlements, target populations, and vaccination posts captured, except Kaduna, Katsina and Adamawa states. Of all enumeration areas sampled during the post-campaign survey in states with GIS ward maps, none had a zero-vaccination coverage of the surveyed children, with the exception of one in Borno state that had security issues. In the post campaign coverage survey, the percentage of responses that gave vaccination post being too far as a reason for non-vaccination of children in the Northern zones that used GIS generated ward maps was less than half the rate seen in the southern zones where the GIS microplanning was not used.

CONCLUSION: The use of GIS-generated wards maps improved the quality of ward micro plans and optimized the placement of vaccination posts, resulting in a significant reduction in zero-dose clusters found during the post campaign coverage survey.

WEB: 10.1016/j.vaccine.2021.01.021
IMPACT FACTOR: 3.143
CITED HALF-LIFE: 7.3

START COMMENTARY

In this observational study, Oteri *et al.* describe how geographic information system (GIS) technology was utilized in microplanning efforts for a measles vaccination campaign in the Northern states of Nigeria. This study is important as it highlights the strengths of using GIS technology to improve coverage of immunization activities. All 36 states in Nigeria were involved in the 2017/2018 measles campaign which targeted children aged 9-59 months. Of these, half used GIS generated operational target populations (Northern states of Adamawa, Bauchi, Borno, Jigawa, Kaduna, Kano, Katsina, Sokoto, Yobe and Zamfara) whereas the others (the Southern states) used estimates from a household micro census. GIS-generated ward maps were built using data from the polio program in Nigeria from 2013-2016 and from satellite imagery. Settlements were identified and then combined with population grids to estimate the population in each settlement and the corresponding optimal number and locations of vaccination posts and human resources for each settlement. Details on each target population are presented in *Table 1a* and distributions of teams and vaccination posts are shown in *Table 3*.

When comparing the GIS-generated estimates for target population to the walk-through census, the operational target populations had lower percent variation (8.2% in GIS states vs. 19.6% in other). Oteri *et al.* found greater than 90% validation in 7 of the 10 states that used GIS for microplanning. This validation step is a key strength of this analysis. None of the states which used GIS microplanning had any enumeration areas with 0% vaccination coverage. Another notable finding was that vaccination post being too far away was noted as a reason for non-vaccination more often among the states not using GIS in their microplanning (1.87% in southern states vs. 0.7% in northern). There was an overall increase in coverage compared to the prior campaign in 2015/2016 (shown in *Figure 3b*). However, in 3 of the 10 study states, three saw a decline in coverage (*Figure 3a*). One limitation of this study is the lack of a true control. Although the results were compared to the results of the Southern states, it is not evident if states are comparable to one another, which limits the conclusions that can be drawn from this analysis. Overall, this study demonstrates that GIS technology is feasible to use to improve microplans for immunization activities to improve coverage and reduce the number of missed children.

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Appendix

The literature search for the January Vaccine Delivery Research Digest was conducted on January 2, 2022. We searched English language articles indexed by the US National Library of Medicine and published between November 15, 2021 and December 14, 2021. The search resulted in 643 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]) (“2021/11/15”[PDAT] : “2021/12/14”[PDAT]))