VACCINE DELIVERY RESEARCH DIGEST

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

REPORT TO THE BILL & MELINDA GATES FOUNDATION

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

MARCH 2022

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

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

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

List of Articles

1 Does Anybody Want an Injectable Rotavirus Vaccine, and Why? Understanding the Public Health Value Proposition of Next-Generation Rotavirus Vaccines.

{Abstract & START Commentary} {Full Article}

- A study exploring the public health value proposition for injectable next-generation rotavirus vaccines.

2 Projecting the cost of introducing typhoid conjugate vaccine (TCV) in the national immunization program in Malawi using a standardized costing framework.

{Abstract & START Commentary} {Full Article}

- A costing study estimating the incremental cost of typhoid conjugate vaccine introduction and recurrent delivery within the national immunization program.

3 Estimating the effect of vaccination on antimicrobial-resistant typhoid fever in 73 countries supported by Gavi: a mathematical modelling study.

{Abstract & START Commentary} {Full Article}

- A mathematical modelling study estimating the effect of vaccination on antimicrobial-resistant typhoid fever in countries supported by Gavi.

4 Cost-effectiveness of routine adolescent vaccination with an M72/AS01E-like tuberculosis vaccine in South Africa and India.

{Abstract & START Commentary} {Full Article}

- A cost-effectiveness study estimating the impact and cost-effectiveness of routine M72/AS01E tuberculosis vaccination for adolescents.

5 Coverage for pertussis vaccination during pregnancy with 4 models of vaccine delivery: a quasiexperimental, multicentre observational study.

{Abstract & START Commentary} {Full Article}

- A quasi-experimental observational study examining four models for tetanus–diphtheria–acellular pertussis vaccination for pregnant women.

6 What is the true burden of diphtheria, tetanus, pertussis and poliovirus in children aged 3-18 years in Asia? A systematic literature review.

{Abstract & START Commentary} {Full Article}

- A systematic literature review estimating the burden of diphtheria, pertussis and tetanus in children aged 3 to 18 years in Asia.

7 The last stretch: Barriers to and facilitators of full immunization among children in Nepal's Makwanpur District, results from a qualitative study.

{Abstract & START Commentary} {Full Article}

- A qualitative formative study exploring demand- and supply-side barriers and facilitators to immunization.

8 Added Value of Electronic Immunization Registries in Low- and Middle-Income Countries: Observational Case Study in Tanzania.

{Abstract & START Commentary} {Full Article}

- A qualitative/case study conceptualizing ways in which electronic immunization registries add value.

9 Global estimates of paediatric tuberculosis incidence in 2013-19: a mathematical modelling analysis.

{Abstract & START Commentary} {Full Article}

- A mathematical modelling study estimating pediatric tuberculosis incidence across 185 countries.

10 Prevalent human papillomavirus infection increases the risk of HIV acquisition in African women: advancing the argument for human papillomavirus immunization.

{Abstract & START Commentary} {Full Article}

- A case control study assessing human papillomavirus types and the risk of HIV acquisition.

Appendix

Details of Articles

1. Does Anybody Want an Injectable Rotavirus Vaccine, and Why? Understanding the Public Health Value Proposition of Next-Generation Rotavirus Vaccines.

Hausdorff W, Price J, Debellut F, Mooney J, Torkelson A, Giorgadze K, et al.

Vaccines (Basel). 2022 Mar 01;10(2).
PubMed ID: 35214608

ABSTRACT

Routine infant immunization with live, oral rotavirus vaccines (LORVs) has had a major impact on severe gastroenteritis disease. Nevertheless, in high morbidity and mortality settings rotavirus remains an important cause of disease, partly attributable to the sub-optimal clinical efficacy of LORVs in those settings. Regardless of the precise immunological mechanism(s) underlying the diminished efficacy, the introduction of injectable next-generation rotavirus vaccines (iNGRV), currently in clinical development, could offer a potent remedy. In addition to the potential for greater clinical efficacy, precisely how iNGRVs are delivered (multiple doses to young infants; alongside LORVs or as a booster; co-formulated with Diphtheria-Tetanus-Pertussis (DTP)-containing vaccines), their pricing, and their storage and cold chain characteristics could each have major implications on the resultant health outcomes, on cost-effectiveness as well as on product preferences by national stakeholders and healthcare providers. To better understand these implications, we critically assessed whether there is a compelling public health value proposition for iNGRVs based on potential (but still hypothetical) vaccine profiles. Our results suggest that the answer is highly dependent on the specific use cases and potential attributes of such novel vaccines. Notably, co-formulation of iNGRVs with similar or greater efficacy than LORVs with a DTP-containing vaccine, such as DTP-Hib-HepB, scored especially high on potential impact, cost-effectiveness, and strength of preference by national stakeholders and health care providers in lower and middle income countries.

WEB: 10.3390/vaccines10020149
IMPACT FACTOR: 4.086
CITED HALF-LIFE: 3.4

START COMMENTARY

Hausdorff *et al.* explore the public health proposition for injectable next-generation rotavirus vaccines (iNGRV). This study is importance as it can inform vaccine developers, funding bodies, and funders about the value of these hypothetical vaccines as compared to other existing interventions.

The authors focus on injectable vaccines which can avoid issues associated with oral vaccines (e.g., malnutrition, gut flora competition, intussusception). The article provides examples of several use cases of iNGRVs and compares iNGRVs to current live oral rotavirus vaccines (LORVs). The two questions guiding this value proposition study were 1) What is the potential health impact and cost-effectiveness in LMICs of different use cases of an iNGRV utilizing different assumptions for vaccine efficacy? 2) How would the different use cases affect whether national stakeholders and healthcare providers in LMICs prefer an iNGRV or the existing LORVs and how might these translate into demand forecasts for Gavi and non-Gavi countries?

Overall, the analyses suggest positive public health value propositions for interventions that improve the impact of rotavirus vaccination in young infants, as compared to existing LORVs with a booster at 9 or 12 months. Hausdorff *et al.* stated that an iNGRVs could potentially enhance vaccine efficacy in infants and improve coverage if formulated as part of the diphtheria, pertussis, and tetanus (DTP) vaccine. Additional theoretical advantages of iNGRVs over LORVs are presented in *Table 2* and include higher vaccine efficacy in high morbidity settings, lower cost per dose, co-administrative with LORVs, and no vaccine-induced intussusception. A notable strength of this analysis is that Hausdorff *et al.* present the clinical endpoints needed to demonstrate the advantage of iNGRVs (*Table 2)*. Detailed findings for each use case for all LMICs over 10 years starting in 2025 are presented in *Table 5.* Despite positive findings, in interviews with national stakeholders, LORVs were preferred given concerns of injection fatigue, cold chain requirements, and operational challenges. Among healthcare providers, nearly all (59 of 64) preferred LORVs due to ease of oral administration and injection reluctance. These concerns highlight the need for engagement with national stakeholders and healthcare workers to reduce vaccine-related issues if iNGRVs are developed and implemented.

Return to List of Articles

2. Projecting the cost of introducing typhoid conjugate vaccine (TCV) in the national immunization program in Malawi using a standardized costing framework.

Debellut F, Mkisi R, Masoo V, Chisema M, Mwagomba D, Mtenje M, et al.

Vaccine. 2022 Mar 10;40(12):1741-1746.
PubMed ID: 35153097

ABSTRACT

BACKGROUND: There is a substantial typhoid burden in sub-Saharan Africa, and TCV has been introduced in two African countries to date. Decision-makers in Malawi decided to introduce TCV and applied for financial support from Gavi, the Vaccine Alliance in 2020. The current plan is to introduce TCV as part of the national immunization program in late 2022. The introduction will include a nationwide campaign targeting all children aged 9.months to 15..years. Following the campaign, TCV will be provided through routine immunization at 9..months. This study aims to estimate the cost of TCV introduction and recurrent delivery as part of the national immunization program.

METHODS: This costing analysis is conducted from the government's perspective and focuses on projecting the incremental cost of TCV introduction and delivery for Malawi's existing immunization program before vaccine introduction. The study uses a costing tool developed by Levin & Morgan through a partnership between the International Vaccine Institute and the World Health Organization and leverages primary and secondary data collected through key informant interviews with representatives of the Malawi Expanded Programme on Immunization team at various levels.

RESULTS: The total financial and economic costs of TCV introduction over three years in Malawi are projected to be US$8.5 million and US$29.8 million, respectively. More than two-thirds of the total cost is made up of recurrent costs. Major cost drivers include the procurement of vaccines and injection supplies and service delivery costs. Without vaccine cost, we estimate the cost per child immunized to be substantially lower than US$1.

DISCUSSION: Findings from this analysis may be used to assess the economic implications of introducing TCV in Malawi. Major cost drivers highlighted by the analysis may also inform decision-makers in the region as they assess the value and feasibility of TCV introduction in their national immunization program.

WEB: 10.1016/j.vaccine.2022.02.016
IMPACT FACTOR: 3.143
CITED HALF-LIFE: 7.3

START COMMENTARY

In this costing study, Debellut *et al.* estimate the incremental cost of typhoid conjugate vaccine (TCV) introduction and recurrent delivery within the national immunization program. This study is important as Malawi is one of only two countries in Africa to introduce TCV and can provide critical insights on the costs to inform other countries assessing the value and feasibility. Debellut *et al.* project the introduction (start-up cost) and delivery costs (recurrent) from a government perspective. The authors conducted an activity-based costing, where each intervention activity is considered individually, and associated costs are estimated. Data for this study was obtained from the national immunization program and from six health facilities in four districts. Debellut *et al.* extrapolated these costs to each district by assuming an average cost for each activity/sub-activity.

The total financial cost of TCV introduction was estimated to be US$8.6 million and the total economic cost was estimated to be US$29.8 million. Most costs were recurrent (77.5% of financial and 86.1% of economic). Substantial financial cost drivers included the cost of vaccines and injection supplies (44.6%) followed by service delivery costs (18.2%). Detailed financial and economic costs are presented in *Table 2* and annualized costs are presented in *Table 4.* The financial cost per immunized child was $0.46 without the vaccine and $0.87 with the vaccine cost for the overall program. Estimates varied slightly for the campaign and routine immunization scenarios (*Table 3).* These small costs results (particularly delivery costs) could be attributed to the incremental approach taken in this study, which may underestimate the full costs within the routine immunization system. Overall, this study demonstrates that it is possible to introduce TCV in Malawi at a low cost.

Return to List of Articles

3. Estimating the effect of vaccination on antimicrobial-resistant typhoid fever in 73 countries supported by Gavi: a mathematical modelling study.

Birger R, Antill..n M, Bilcke J, Dolecek C, Dougan G, Pollard A, et al.

Lancet Infect Dis. 2022 Feb 06.

PubMed ID: 35123673

ABSTRACT

BACKGROUND: Multidrug resistance and fluoroquinolone non-susceptibility (FQNS) are major concerns for the epidemiology and treatment of typhoid fever. The 2018 prequalification of the first typhoid conjugate vaccine (TCV) by WHO provides an opportunity to limit the transmission and burden of antimicrobial-resistant typhoid fever.

METHODS: We combined output from mathematical models of typhoid transmission with estimates of antimicrobial resistance from meta-analyses to predict the burden of antimicrobial-resistant typhoid fever across 73 lower-income countries eligible for support from Gavi, the Vaccine Alliance. We considered FQNS and multidrug resistance separately. The effect of vaccination was predicted on the basis of forecasts of vaccine coverage. We explored how the potential effect of vaccination on the prevalence of antimicrobial resistance varied depending on key model parameters.

FINDINGS: The introduction of routine immunisation with TCV at age 9 months with a catch-up campaign up to age 15 years was predicted to avert 46-74% of all typhoid fever cases in 73 countries eligible for Gavi support. Vaccination was predicted to reduce the relative prevalence of antimicrobial-resistant typhoid fever by 16% (95% prediction interval [PI] 0-49). TCV introduction with a catch-up campaign was predicted to avert 42..5 million (95% PI 24..8-62..8 million) cases and 506…000 (95% PI 187…000-1..9 million) deaths caused by FQNS typhoid fever, and 21..2 million (95% PI 16..4-26..5 million) cases and 342…000 (95% PI 135…000-1..5 million) deaths from multidrug-resistant typhoid fever over 10 years following introduction.

INTERPRETATION: Our results indicate the benefits of prioritising TCV introduction for countries with a high avertable burden of antimicrobial-resistant typhoid fever.

FUNDING: The Bill & Melinda Gates Foundation.

WEB: 10.1016/S1473-3099(21)00627-7

IMPACT FACTOR: 24.446

CITED HALF-LIFE: 4.7

START COMMENTARY

In this mathematical modelling study, Birger *et al.* estimate the effect of vaccination on antimicrobial-resistant typhoid fever in countries supported by Gavi. This study is important as antimicrobial resistance for typhoid fever is a substantial public health threat which vaccination with typhoid conjugate vaccine (TCV) could help avert. Outcomes included in this study are the total number of cases of typhoid, the number of drug-resistance typhoid cases, deaths, and Disability-Adjusted Life Years (DALYs) averted for 73 countries that are eligible for Gavi support. The authors utilized a transmission dynamic model that incorporated age-specific vaccination. Input parameters impacting the effect of vaccination on drug resistant cases are presented in *Table 1.*

An estimated 66.7 million (95% Probability Interval [PI]: 48.1-88.3 million) cases of typhoid fever would be averted over 10 years with routine use of TCV with catch up campaigns up to age 15. This would also avert a predicted 42.5 million (95% PI: 24.8-62.9 million) of fluoroquinolone non-susceptibility (FQNS) cases and 21.2 million (95% PI: 16.4-26.5 million) multidrug resistance cases over 10 years. Detailed findings on the predicted number of antimicrobial-resistance typhoid cases, deaths, and DALYs by country are presented in *Table 3.* Overall, two-thirds of the morbidity (cases, DALYs) and mortality (deaths) could be averted through TCV introduction. One notable limitation of this study is the limited data for the prevalence of FQNS and multidrug resistance. Although some country-specific estimates were established, several countries were missing data or had outdated (e.g., 10-year-old) data. However, Birger *et al.* made assumptions using region-specific data and utilize several statistical methods to address this limitation. This study provides predictions of the effect of vaccination on reducing the burden of typhoid fever and antimicrobial-resistant typhoid fever.

Return to List of Articles

4. Cost-effectiveness of routine adolescent vaccination with an M72/AS01E-like tuberculosis vaccine in South Africa and India.

Harris R, Quaife M, Weerasuriya C, Gomez G, Sumner T, Bozzani F, et al.

Nat Commun. 2022 Feb 15;13(1):602.
PubMed ID: 35105879

ABSTRACT

The M72/AS01E tuberculosis vaccine showed 50% (95%CI: 2-74%) efficacy in a phase 2B trial in preventing active pulmonary tuberculosis disease, but potential cost-effectiveness of adolescent immunisation is unknown. We estimated the impact and cost-effectiveness of six scenarios of routine adolescent M72/AS01E-like vaccination in South Africa and India. All scenarios suggested an M72/AS01E-like vaccine would be highly (94-100%) cost-effective in South Africa compared to a cost-effectiveness threshold of $2480/disability-adjusted life-year (DALY) averted. For India, a prevention of disease vaccine, effective irrespective of recipient's M. tuberculosis infection status at time of administration, was also highly likely (92-100%) cost-effective at a threshold of $264/DALY averted; however, a prevention of disease vaccine, effective only if the recipient was already infected, had 0-6% probability of cost-effectiveness. In both settings, vaccinating 50% of 18 year-olds was similarly cost-effective to vaccinating 80% of 15 year-olds, and more cost-effective than vaccinating 80% of 10 year-olds. Vaccine trials should include adolescents to ensure vaccines can be delivered to this efficient-to-target population.

WEB: 10.1038/s41467-022-28234-7
IMPACT FACTOR: 14.919
CITED HALF-LIFE: 3.7

START COMMENTARY

In this cost-effectiveness study, Harris *et al.* estimate the impact and cost-effectiveness of six scenarios of routine M72/AS01E tuberculosis vaccination for adolescents in South Africa and India from 2025 to 2050. This article is important as the vaccine candidate, M72/AS01E has shown promise (50% efficacious in preventing pulmonary tuberculosis [95% Confidence Interval [CI]: 2-84%] among 18 to 50-year-olds). However, the epidemiological impact and cost-effectiveness of this potential vaccine is unknown. Harris *et al.* estimated the cost-effectiveness of routine immunization of adolescents, which could potentially be a more feasible and cost-effective approach than mass immunization campaigns. In this analysis, an age-structured compartmental dynamic *M. tuberculosis* model was utilized. Detailed characteristics about the modelled M72/AS01E-like vaccine is included in *Table 2.* One strength of this analysis is that it assessed the effectiveness among people irrespective of their infectious status (e.g., both pre- and post-infection efficacy) and among those

that were infected (post-infection efficacy). Another key strength of this analysis is that authors considered both costs to the health system and to patients.

Assuming a coverage of 80% among 10-year-olds and 15-year-olds and 50% among 18-year-olds, the M72/AS01E vaccine would lead to substantial decreases in incidence rates in 2050. Key findings included that a vaccine with both pre- and post-infection efficacy had a greater impact on incidence rates in 2050, than a vaccine with only post-infection efficacy. In South Africa, it was determined that there was 94-100% probability that any adolescent routine immunization with M72/AS01E would be cost-effective (both pre/post-infection, and post-infection only). In contrast, results from India showed that routine vaccination with a pre- and post-infection vaccine was cost-effective from the health system perspective (92-100% probability of cost-effectiveness). However, the post-infection only vaccine was not shown to be cost-effective (0-6% probability) utilizing standard cut offs for cost-effectiveness in country. One notable finding was that the cost-effectiveness results did not change with higher vaccine delivery costs. Overall, this study highlights the need for continued investment and development of M72/AS01E and similar vaccines given promising cost-effectiveness findings.

Return to List of Articles

5. Coverage for pertussis vaccination during pregnancy with 4 models of vaccine delivery: a quasiexperimental, multicentre observational study.

Li Y, Brousseau N, Guay M, Dub.. ., Laghdir Z, Boucoiran I, et al.

CMAJ Open. 2022 Feb 28;10(1):E56-E63.
PubMed ID: 35105682

ABSTRACT

BACKGROUND: Vaccination of pregnant people with a vaccine containing acellular pertussis (tetanus-diphtheria-acellular pertussis [Tdap]) has been recommended in Canada since 2018, and the evaluation of delivery models for efficient maternal Tdap administration is a priority for the Quebec Ministry of Health. We implemented 3 vaccine delivery models, in addition to the existing standard of practice model, and compared the vaccine coverage achieved by the 4 models in Quebec.

METHODS: In this quasiexperimental, multicentre observational study, we recruited pregnant people at less than 21 weeks' gestation in 4 Quebec regions from April to October 2019. We compared 4 vaccine delivery models: local community service centres (centre local de services communautaires [CLSCs], baseline), family medicine groups (FMGs), obstetrics clinic and the oral glucose challenge test (OGCT). In addition to the CLSCs, 3 FMGs, 1 obstetric clinic and a hospital-based OGCT screening program participated. We determined vaccination status from a self-reported questionnaire, the Quebec Immunization Registry or medical charts. We compared model-specific (for participants recruited to a model and subsequently vaccinated within that model) and overall vaccine coverage (considering all vaccine delivery pathways) and used logistic regression to adjust for sociodemographic variables.

RESULTS: Overall, 946 of 1000 recruited pregnant people were eligible for analyses. Vaccination via the FMGs achieved the highest model-specific vaccine coverage (67.8%, 95% confidence interval [CI] 60.5%-74.4%), but coverage was not significantly different from the CLSCs (63.8%, 95% CI 57.6%-69.6%). For overall vaccine coverage, the FMG (86.5%, 95% CI 80.6%-90.9%) and obstetrics models (85.9%, 95% CI 80.9%-89.7%) achieved significantly higher vaccine coverage than the CLSCs (66.3%, 95% CI 60.1%-71.9%). The OGCT model did not improve overall vaccine coverage (61.8%, 95% CI 56.1%-67.2%).

INTERPRETATION: Compared with CLSCs, overall vaccine coverage was higher when Tdap was offered in FMGs or an obstetrics clinic providing prenatal care. Health professionals involved in pregnancy follow-up recommending and offering the vaccine may be a key factor in optimizing vaccine coverage.

WEB: 10.9778/cmajo.20210011
IMPACT FACTOR: N/A
CITED HALF-LIFE: N/A

START COMMENTARY

In this quasi-experimental observational study, four models of vaccine delivery for tetanus–diphtheria–acellular pertussis (Tdap) among pregnant women in four Quebec regions were assessed. Participants included pregnancy women less than 21 weeks' gestation. The four delivery models included at local community service centers (the standard of care), family medicine groups, obstetrics clinics, and during an oral glucose challenge test. Outcomes included model-specific vaccine coverage and overall vaccine coverage. Model-specific vaccine coverage was defined as the proportion of people who received Tdap vaccination according to the specific vaccine delivery pathway, out of the total number of people eligible for each model. A key strength of this analysis is the inclusion of both measures, which can provide important insights into the best model for future resource allocation and use.

The study population (n=946) comprised of women largely born in Canada (71.2%), Francophone (79.8%), with university-level education (52.4%), and in their first pregnancy (43.5%). Li *et al.* used multivariable logistic regression to estimate the adjusted odds of vaccine for each model. Covariates included in the model were sociodemographic factors such as maternal age, country of birth, education, language, and number of previous children. For the standard of care, model-specific coverage was 63.6% and overall vaccine coverage was 66.3%. Higher overall coverage was achieved by the family medicine group model (86.5%) and obstetrics models (85.9%). However, model-specific vaccine coverage was similar for the standard of care and the family medicine group. Similarly, offering the vaccine during gestational diabetes did not show improvements in model-specific or overall vaccination coverage. This study shows the potential of improving Tdap coverage by targeting vaccination efforts through healthcare workers involved with routine pregnancy visits.

Return to List of Articles

6. What is the true burden of diphtheria, tetanus, pertussis and poliovirus in children aged 3-18 years in Asia? A systematic literature review.

Nicholson L, Adkins E, Karyanti M, Ong-Lim A, Shenoy B, Huoi C, et al.

Int J Infect Dis. 2022 Mar 03;117:116-129.
PubMed ID: 35077880

ABSTRACT

OBJECTIVES: In recent years, outbreaks and a rising incidence of diphtheria, tetanus, and pertussis have occurred in Asia, particularly in older children.

METHODS: A systematic search of MEDLINE and Embase was conducted from January 2000 to October 2020 to identify the epidemiology of diphtheria, tetanus, pertussis, and poliomyelitis in children and adolescents (aged 3-18 years) in Asia. The results were then related to vaccination schedules, booster coverage rates, pertussis source of infection, and booster immunogenicity, as identified by a pragmatic review. The International Prospective Register of Systematic Reviews (PROSPERO) registration: #CRD42020222445.

RESULTS: A total of 35 studies were included in this review. Limited data were reported on the epidemiology of diphtheria, tetanus, pertussis, and poliomyelitis. Data from studies reporting the incidence of diphtheria and pertussis exemplify the shift in epidemiology to older children/adolescents. Seroprevalence data suggest that immunity to pertussis and diphtheria is below the level of herd immunity in several Asian countries in this population.

CONCLUSION: The true burden of diphtheria, pertussis, and tetanus in children aged 3-18 years in Asia is unknown because of weak or absent nationwide surveillance systems. The available evidence highlights the inadequacies in immunity, either by gaps in a recommendation or suboptimal booster coverage, supporting the public health need for booster vaccinations in this population.

WEB: 10.1016/j.ijid.2022.01.045
IMPACT FACTOR: 3.202
CITED HALF-LIFE: 5.3

START COMMENTARY

In this systematic literature review, Nicholson *et al.* attempt to estimate the exact burden of diphtheria, pertussis and tetanus in children aged 3 to 18 years in Asia. Despite effective vaccines, there is still a burden of vaccine-preventable diseases such as diphtheria, pertussis, and tetanus. The exact burden is unknown and likely underestimated, underscoring a need for a systematic review to assess the epidemiology, burden, and mortality rate of diphtheria, pertussis, tetanus, and

polio among children in Asia. Inclusion criteria for the systematic review included: 1) observational studies (e.g., cohort, cross-sectional, etc.); 2) in any language; 3) from year 2000 and later; 4) reporting incidence, prevalence, or mortality of diphtheria, pertussis, tetanus, wild-polio virus (WPV), vaccine-associated paralytic polio (VAPP), and vaccine-derived poliovirus (VDPV). A risk of bias and quality assessment were conducted as part of this systematic review (described in detail in *Supplementary File S1).*

Of 1,967 total studies identified, 35 were ultimately included in the qualitative synthesis. Included studies took place in Japan (n=7), India (n=7), South Korea (n=5), Indonesia (n=4), Taiwan (n=4), Thailand (n=4), Singapore (n=2), Pakistan (n=1), and Asia broadly (n=1). Detailed information about each study is presented in *Table 1.* One key strength of this study is that it presents the epidemiology and the seroprevalence and antibody titers reported in studies. In terms of seroprevalence, the diphtheria seroprevalence varied widely by study and location (e.g., greater than 95% in Singapore compared to 24.9% among 9 to 17-year-olds and 39.1% among 5 to 8 year-olds in India). *Table 3* presents diphtheria seroprevalence and antibody titers in the six studies which reported it. Tetanus seroprotective levels were consistently higher (between 84.3-100%) (*Table 5).* Among participants aged 4-10, pertussis seroprevalence levels for anti-PT IgG ranged between 25.0%−73.0% and 74.8%−91.1% for anti-FHA IgG. Seroprevalence levels were high (>90%) for all types of polio (*Table 9*). Despite these findings on seroprevalence, there was a dearth of robust data to assess the effectiveness of immunization campaigns, largely due to the lack of public health surveillance systems. However, with the limited data, it is evident that there is a need for increased boosters among older children to improve the coverage and seroprevalence rates among children 3 to 18 years of age in Asia.

Return to List of Articles

7. The last stretch: Barriers to and facilitators of full immunization among children in Nepal's Makwanpur District, results from a qualitative study.

Paul A, Nepal S, Upreti K, Lohani J, Rimal R.

PLoS One. 2022 Feb 16;17(1):e0261905.
PubMed ID: 35061723

ABSTRACT

BACKGROUND: Approximately 35% of Nepal's children have not received all recommended vaccines, and barriers to immunization exist on both the demand- (i.e., access, affordability, acceptance) and supply- (i.e., logistics, infrastructure) sides.

OBJECTIVE: This article describes a formative study to understand the barriers to and facilitators of immunization in Makwanpur, Nepal from both the demand- and supply-sides.

METHODS: Through in-depth interviews, key informant interviews, and focus group discussions (N = 76), we assessed knowledge, attitudes, and experiences with immunization; social norms related to immunization; perceptions of local health facilities; and descriptions of client-provider relationships. Data were analyzed using an iterative, grounded theory approach.

RESULTS: Three major themes emerged, including positive demand of vaccines, lack of mutual trust between service seekers and service providers, and internal and external motivators of vaccine supply. On the demand-side, caregivers reported high levels of immunization-related awareness, knowledge, and acceptance, largely perceived to be due to a generational shift. On the supply-side, providers expressed passion for their work despite lack of support from local authorities and a desire for more training. Between caregivers and providers, lack of mutual trust emerged as a prominent barrier, revealing a cycle of positive service bias.

CONCLUSIONS: We identified mutual trust as a key pathway toward reaching full immunization coverage in Nepal and we recommend future interventions adopt an approach which focuses on removing social barriers (i.e., distrust) and structural barriers (i.e., opening hours, neglected infrastructure) to immunization.

WEB: 10.1371/journal.pone.0261905
IMPACT FACTOR: 2.740
CITED HALF-LIFE: 5.6

START COMMENTARY

In this qualitative formative study, Paul *et al.* explore demand- and supply-side barriers and facilitators to immunization in Makwanpur, Nepal. The authors conducted key informant interviews, in-depth interviews, and focus group discussions (N=76). The study included mothers who were residents of the health facility catchment area and those that worked for or volunteered at the health facility. The key informant interview guide included items related to immunization coverage in the ward, communication between caregivers and healthcare providers, the health facility environment, and discussions on workload. The in-depth interview guide focused on family's experiences with vaccination and family involvement in the child's health. The focus group discussions assessed the perception of the health facilities, characteristics of an ideal health facility, and communication between caregivers/healthcare workers.

Demand-side facilitators to immunization included a high demand for vaccines, a desire among women to protect their children, a positive generational shift toward immunization, awareness and knowledge of immunization, and positive norms regarding immunization. Demand-side barriers included misconceptions (type not specified*)* and negative attitudes towards the immunization. Negative attitudes may have been more common historically, which was illustrated in experiences described by older participants (i.e., "we never went, why would you want to go"). In terms of supply-side facilitators, participants described national priorities and policies relating to immunization, pride and satisfaction among health providers, messaging from the government, and Palikas (i.e., administrative divisions) implementing local immunization programs. Barriers noted were limited support from Palikas, uncomfortable health facilities, and a lack of staff training. In addition to the noted barriers and facilitators, participants noted a lack of mutual trust between health workers and patients, which could contribute to gaps in immunization coverage. Specifically, themes focused on power imbalances, poor quality of care, perceived micro-aggressions (i.e., by health workers towards clients), and client non-compliance/positive service bias (i.e., healthcare workers treating clients who comply better than those who do not comply). Based on these findings, Paul *et al.* recommend the following: 1) immunization interventions should focus on facilitating people's desires to immunize their children; 2) health communication messages focus on addressing misperceptions about the prevalence of vaccine coverage?; 3) healthcare workers require support from Palikas in order to remain motivated; 4) the health system needs to address the positivity bias through catch up campaigns; 5) a need to build trust in the system which could be achieved through health workers showing greater respect when patients visit health clinics and the inclusion of marginalized populations.

Return to List of Articles

8. Added Value of Electronic Immunization Registries in Low- and Middle-Income Countries: Observational Case Study in Tanzania.

Secor A, Mtenga H, Richard J, Bulula N, Ferriss E, Rathod M, et al.

JMIR Public Health Surveill. 2022 Feb 16;8(1):e32455.

PubMed ID: 35060919

ABSTRACT

BACKGROUND: There is growing interest and investment in electronic immunization registries (EIRs) in low- and middle-income countries. EIRs provide ready access to patient- and aggregate-level service delivery data that can be used to improve patient care, identify spatiotemporal trends in vaccination coverage and dropout, inform resource allocation and program operations, and target quality improvement measures. The Government of Tanzania introduced the Tanzania Immunization Registry (TImR) in 2017, and the system has since been rolled out in 3736 facilities in 15 regions.

OBJECTIVE: The aims of this study are to conceptualize the additional ways in which EIRs can add value to immunization programs (beyond measuring vaccine coverage) and assess the potential value-add using EIR data from Tanzania as a case study.

METHODS: This study comprised 2 sequential phases. First, a comprehensive list of ways EIRs can potentially add value to immunization programs was developed through stakeholder interviews. Second, the added value was evaluated using descriptive and regression analyses of TImR data for a prioritized subset of program needs.

RESULTS: The analysis areas prioritized through stakeholder interviews were population movement, missed opportunities for vaccination (MOVs), continuum of care, and continuous quality improvement. The included TImR data comprised 958,870 visits for 559,542 patients from 2359 health facilities. Our analyses revealed that few patients sought care outside their assigned facility (44,733/810,568, 5.52% of applicable visits); however, this varied by region; facility urbanicity, type, ownership, patient volume, and duration of TImR system use; density of facilities in the immediate area; and patient age. Analyses further showed that MOVs were highest among children aged <12 months (215,576/831,018, 25.94% of visits included an MOV and were applicable visits); however, there were few significant differences based on other individual or facility characteristics. Nearly half (133,337/294,464, 45.28%) of the children aged 12 to 35 months were fully vaccinated or had received all doses except measles-containing vaccine-1 of the 14-dose under-12-month schedule (ie, through measles-containing vaccine-1), and facility and patient characteristics associated with dropout varied by vaccine. The continuous quality improvement analysis showed that most quality issues (eg, MOVs) were concentrated in <10% of facilities, indicating the potential for EIRs to target quality improvement efforts.

CONCLUSIONS: EIRs have the potential to add value to immunization stakeholders at all levels of the health system. Individual-level electronic data can enable new analyses to understand service delivery or care-seeking patterns, potential risk factors for underimmunization, and where challenges occur. However, to achieve this potential, country programs need to leverage and strengthen the capacity to collect, analyze, interpret, and act on the data. As EIRs are introduced and scaled in low- and middle-income countries, implementers and researchers should continue to share real-world examples and build an evidence base for how EIRs can add value to immunization programs, particularly for innovative uses.

WEB: 10.2196/32455
IMPACT FACTOR: 4.112
CITED HALF-LIFE: 1.5

START COMMENTARY

In this study, Secor *et al.* conceptualize the ways in which electronic immunization registries (EIRs) can add value to immunization programs beyond measuring vaccine coverage. This study is important as it provides an overview of other ways that EIRs may be useful, particularly in setting where immunization coverage is already high. Further, the authors assess the feasibility and potential value add with Tanzania as a case study. There were two primary phases of the program: 1) stakeholder interview with 40 participants (Gavi Secretariat, partners, and country representatives) to develop a conceptual framework based on barriers to national immunization programs and ways that EIRs can add value; 2) a case study using data from Tanzania's EIR which evaluated the impact of dose timeliness, urbanicity, stockouts, and age on the outcomes of missed opportunities for vaccination, vaccine dropout, assigned facility and non-assigned visits.

Several barriers and corresponding ways that EIRs can provide value are presented in *Textbox 1.* Barriers include a lack of understanding about what drives immunization demand, overly complex processes, and microplanning challenges. Potential EIR-based solutions include that the data can identify un- or under-immunized children and drivers of vaccination status, streamline data capture, and capture more accurate, timely, and complete denominators to inform microplanning. The case study sample included 2,444,803 vaccine doses over 958,870 visits and 559,542 patients. Detailed patient and facility characteristics are presented in *Table 2.* One key aspect of this analysis was the exploration of population movement (care seeking at alternative, non-assigned facilities). Overall, 94.48% of visits were at the assigned facility whereas other were at non-assigned facilities within 5 km (1.82%), at non-assigned facilities outside of 5 km but within same district (1.51%), or outside of the district but within the same region (0.36%). Detailed results are shown in *Figure 1-2* and *Table 3.* Predictors were significantly associated with the outcome of given visit to a non-assigned facility were being a child assigned to a public facility, facilities with a longer duration of

EIR use, and facilities in areas with higher health facility density. Visits with missed opportunities for vaccination by vaccine type and patient/facility characteristics are presented in *Table 5.* When evaluating reasons (i.e., reasons listed by the provider in the EIR), which was about 54.26% of the data, the primary reason was facility stock out (52.48%). In regression models (*Table 7),* age group and time with EIR at the facility were significantly less likely to report missed opportunities for vaccination. Secor *et al.* also explored the continuum of care in terms of immunization coverage, vaccine drop out, immunization typologies, and visit dropout. Lastly, they consider continuous quality improvement (*Table 11*). This case study demonstrates the utility of EIRs.

Return to List of Articles

9. Global estimates of paediatric tuberculosis incidence in 2013-19: a mathematical modelling analysis.

Yerramsetti S, Cohen T, Atun R, Menzies N.

Lancet Glob Health. 2022 Feb 16;10(2):e207-e215.

PubMed ID: 3489551734895518

ABSTRACT

BACKGROUND: Many children who develop tuberculosis are thought to be missed by diagnostic and reporting systems. We aimed to estimate paediatric tuberculosis incidence and underreporting between 2013 and 2019 in countries representing more than 99% of the global tuberculosis burden.

METHODS: We developed a mathematical model of paediatric tuberculosis natural history, accounting for key mechanisms and risk factors for infectious exposure (HIV, malnutrition, and BCG non-vaccination), the probability of infection given exposure, and progression to disease among infected individuals. We extracted paediatric population estimates from UN Population Division data, and we used WHO estimates for adult tuberculosis incidence rates. We parameterised this model for 185 countries and calibrated it using data from countries with stronger case detection and reporting systems. Using this model, we estimated trends in paediatric incidence, and the proportion of these cases that are diagnosed and reported (case detection ratio [CDR]) for each country, age group, and year.

FINDINGS: For 2019, we estimated 997,500 (95% credible interval [CrI] 868,700-1,163,100) incident tuberculosis cases among children, with 481,000 cases (398,400-587,400) among those aged 0-4 years and 516,500 cases (442,900-608,000) among those aged 5-14 years. The paediatric CDR was estimated to be lower in children aged 0-4 years (41%, 95% CrI 34-50) than in those aged 5-14 years (63%, 53-75) and varied widely between countries. Estimated CDRs increased substantially over the study period, from 18% (15-20) in 2013 to 53% (45-60) in 2019, with improvements concentrated in the Eastern Mediterranean, South-East Asia, and Western Pacific regions. Over the study period, global incidence was estimated to have declined slowly at an average annual rate of 1.52% (1.42-1.66).

INTERPRETATION: Paediatric tuberculosis causes substantial morbidity and mortality, and these data indicate that cases (and, thus, probably associated mortality) are currently substantially underreported. These findings reinforce the need to ensure prompt diagnosis and care for children developing tuberculosis, strengthen reporting systems, and invest in research to develop more accurate and easy-to-use diagnostics for paediatric tuberculosis in high-burden settings.

FUNDING: National Institutes of Health.

WEB: 10.1016/S2214-109X(21)00462-9
IMPACT FACTOR: 21.597
CITED HALF-LIFE: 3.1

START COMMENTARY

In this mathematical modelling study, Yerramsetti *et al.* estimate pediatric tuberculosis (TB) incidence from 2013 to 2019 across 185 countries which account for 99% of the global burden. This study makes an important contribution as it utilizes a novel mathematical model which accounts for undernutrition, a key risk factor for TB in high-risk settings. Data inputs for the model included population size, age-stratified TB incidence rates, prevalence of pediatric HIV, undernutrition, energy malnutrition, and pediatric antiretroviral therapy, BCG vaccination coverage, and number of contacts. Further details on inputs are provided in *Appendix 1.* Outcomes included the pediatric tuberculosis incidence for age groups of 0-4 years and 5-14 years from 2013 to 2019. Notable strengths of this analysis are the inclusion of a sensitivity analysis to test the robustness of the analysis to alternative assumptions (i.e., changes in individual parameters), the inclusion of uncertainty intervals, and the comparison with other incidence estimates such as WHO and the Institute for Health Metrics and Evaluation.

Yerramsetti *et al.* estimate a total of 997,500 (95% Credible Interval [Crl] 868,700-1,163,100) across 185 countries in 2019, presented in *Table 1.* The study indicated global incidence is declining slowly at an average rate of 1.52% (1.42-1.66). Over the study period (2013-2019), the case detection rate (CDR) increased substantially. Countries within Africa had the lowest average CDRs (*Figure 2*). In addition to global estimates, the authors assessed incidence and case notifications for 30 countries with the highest burden (shown in *Table 2*). Countries differed substantially with levels of diagnosing and reporting (i.e., from 0% of reported cases of percentage of estimated incidence in the Democratic Republic of Congo to 100% in Russia). The global and regional estimates of pediatric tuberculosis incidence attributable to the risk factors of HIV, malnutrition, BCG non-vaccination, and all three risk factors combined are presented in *Table 3.* Incidence estimates in this analysis are similar to prior models, all of which differ from WHO reports of TB, highlighting issues of global underreporting.

Return to List of Articles

10. Prevalent human papillomavirus infection increases the risk of HIV acquisition in African women: advancing the argument for human papillomavirus immunization.

Liu G, Mugo N, Brown E, Mgodi N, Chirenje Z, Marrazzo J, et al.

AIDS. 2022 Feb 02;36(2):257-265.

PubMed ID: 34172672

ABSTRACT

OBJECTIVE: Vaccine-preventable human papillomavirus (HPV) infection is common, especially in sub-Saharan Africa where HIV risk is also high. However, unlike other sexually transmitted infections (STIs), HPV's role in HIV acquisition is unclear. We evaluated this relationship using data from MTN-003, a clinical trial of HIV chemoprophylaxis among cisgender women in sub-Saharan Africa.

DESIGN: A case-control study.

METHODS: We matched 138 women who acquired HIV (cases) to 412 HIV-negative controls. Cervicovaginal swabs collected within 6 months before HIV seroconversion were tested for HPV DNA. We estimated the associations between carcinogenic (high-risk) and low-risk HPV types and types targeted by HPV vaccines and HIV acquisition, using conditional logistic regression models adjusted for time-varying sexual behaviors and other STIs.

RESULTS: Mean age was 23 (.4) years. Any, high-risk and low-risk HPV was detected in 84, 74 and 66% of cases, and 65, 55 and 48% of controls. Infection with at least two HPV types was common in cases (67%) and controls (49%), as was infection with nonavalent vaccine-targeted types (60 and 42%). HIV acquisition increased with any [adjusted odds ratio (aOR) 2.5, 95% confidence interval (95% CI) 1.3-4.7], high-risk (aOR 2.6, 95% CI 1.5-4.6) and low-risk (aOR 1.8, 95% CI 1.1-2.9) HPV. Each additional type detected increased HIV risk by 20% (aOR 1.2, 95% CI 1.1-1.4). HIV acquisition was associated with HPV types targeted by the nonavalent (aOR 2.1, 95% CI 1.3-3.6) and quadrivalent vaccines (aOR 1.9, 95% CI 1.1-3.2).

CONCLUSION: HPV infection is associated with HIV acquisition in sub-Saharan African women. In addition to preventing HPV-associated cancers, increasing HPV vaccination coverage could potentially reduce HIV incidence.

WEB: 10.1097/QAD.0000000000003004

IMPACT FACTOR: 4.177

CITED HALF-LIFE: 8.4

START COMMENTARY

In this case-control study, Liu *et al.* estimate associations between carcinogenic (high-risk) and low-risk HPV types and types targeted by human papillomavirus (HPV) vaccines and HIV acquisition. This study makes an important contribution as it explores a notable research gap in understanding the association with HPV and HIV acquisition. This study was conducted within a larger multi-center randomized placebo-controlled trial in South Africa, Uganda, and Zimbabwe. Trial participants were non-pregnant, contracepting, women living with HIV. Criteria for the case control analysis was 1) having a stored cervical cancer or vaginal swab specimen available for testing and 2) cervical cancer or vaginal swab collection between one to six months before HIV seroconversion. One strength of this analysis is the consideration of HPV infection in several ways including infection with any type, infection with any of the high-risk types, infection with any of the low-risk types, and infection with any high-risk type other than HPV 16 and 18.

Table 2 shows the demographic characteristics and sexual behaviors of cases and controls at enrollment and during follow up. Another notable strength of this analysis was the inclusion of time-varying sexual behaviors (presented in *Table 2*). Overall, authors found a high prevalence of HPV in the study sample (84% of cases, and 65% of controls, $p<0.001$). High risk HPV was also common 74% among cases and 55% among controls, $p<0.001$). *Table 3* presents the crude and adjusted associations between HPV types detected and HIV acquisition. In adjusted analysis, women with any HPV infection had 2.6 times higher risk of HIV seroconversion compared to women without any HPV infection. The risk of HIV seroconversion increased with the number of HPV types detected (illustrated in *Figure 1*). In conclusion, Liu *et al.* show that infection with any HPV type, including high risk or low risk, may increase the risk of HIV acquisition, highlighting the need for increased efforts for HPV vaccination in high-risk HIV settings.

Return to List of Articles

Appendix

The literature search for the March 2022 Vaccine Delivery Research Digest was conducted on February 28, 2022. We searched English language articles indexed by the US National Library of Medicine and published between January 15, 2021 and February 14, 2021. The search resulted in 628 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]) (“2022/01/15”[PDAT] : “2022/02/14”[PDAT]))