VACCINE DELIVERY RESEARCH DIGEST

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

REPORT TO THE BILL & MELINDA GATES FOUNDATION

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1. R&D during public health emergencies: the value(s) of trust, governance and collaboration.

Katz R, Salamanca-Buentello F, Silva D, Upshur R, Smith M.

BMJ Glob Health. 2022 Apr 01;7(3).
PubMed ID: 35346953

ABSTRACT

In January 2021, Dr Tedros Adhanom Ghebreyesus, director-general of the WHO, warned that the world was 'on the brink of a catastrophic moral failure [that] will be paid with lives and livelihoods in the world's poorest countries'. We are now past the brink. Many high-income countries have vaccinated their populations (which, in some cases, includes third and even fourth doses) and are loosening public health and social measures, while low-income and middle-income countries are struggling to secure enough supply of vaccines to administer first doses. While injustices abound in the deployment and allocation of COVID-19 vaccines, therapies and diagnostics, an area that has hitherto received inadequate ethical scrutiny concerns the upstream structures and mechanisms that govern and facilitate the research and development (R&D) associated with these novel therapies, vaccines and diagnostics. Much can be learnt by looking to past experiences with the rapid deployment of R&D in the context of public health emergencies. Yet, much of the 'learning' from past epidemics and outbreaks has largely focused on technical or technological innovations and overlooked the essential role of important normative developments; namely, the importance of fostering multiple levels of trust, strong and fair governance, and broad research collaborations. In this paper, we argue that normative lessons pertaining to the conduct of R&D during the 2014-2016 Ebola epidemic in West Africa provide important insights for how R&D ought to proceed to combat the current COVID-19 pandemic and future infectious disease threats.

WEB: 10.1136/bmjgh-2021-007873
IMPACT FACTOR: 4.280
CITED HALF-LIFE: 1.9

START COMMENTARY

In this study, Katz *et al.* discuss research and development (R&D) involved in the public health response for the West African Ebola pandemic, including the relevance of trust, governance, and collaboration. They outline the successes and setbacks which could inform ongoing and future outbreaks. A key strength of this study is the social and political context analysis, which is key to

understanding normative developments (trust, governance, and collaboration), which are understudied in discussions of R&D during outbreaks. This study provides lessons on managing the human aspects of R&D during outbreaks (rather than just the technological or scientific components, as these which are critical for success or failure of R&D.

Notable aspects of the social and political context include the legacy of colonialism leading to an initial hostility towards foreign health workers, and underlying historical distrust of Western involvement leading to hesitation or noncompliance with disease mitigating measures. Katz *et al.* describe when trust was negatively impacted as part of R&D activities during the Ebola outbreak, including through data collection and use (i.e., Westerns taking biological samples and data but not sharing it with the governments or in-country researchers). Once trust was developed, disease mitigation efforts (e.g., quarantines) and data sharing were more successful. Good governance, and specifically regulations and rapid ethics review, were key during the Ebola outbreak. This included the World Health Organization's (WHO) advisory committee on ethics, and Medecins sans Frontiers (MSF) ethical review board, and others conducting rapid ethics responses. Lastly, Katz *et al.* describe collaborations – some of which were negative interactions which embodied colonial legacies in which power and benefit was largely for high-income countries (HIC) at the expense of LMICs. One positive example of a collaboration was between Sierra Leone and the United States Centers for Disease Control (CDC), which worked together to collect data and share locations of graves with surviving family members. In Table 1, the authors present a summary of the ways that trust, governance, and collaboration are important for R&D, arose during Ebola, and are relevant for COVID-19. Overall, this article demonstrates the importance of building trust, strong governance, and collaborations to promote R&D efforts during outbreaks.

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2. COVID-19 Vaccine Acceptance among Low- and Lower-Middle-Income Countries: A Rapid Systematic Review and Meta-Analysis.

Patwary M, Alam M, Bardhan M, Disha A, Haque M, Billah S, *et al.*

Vaccines (Basel). 2022 Mar 29;10(3).

PubMed ID: 35335059

ABSTRACT

Widespread vaccination against COVID-19 is critical for controlling the pandemic. Despite the development of safe and efficacious vaccinations, low-and lower-middle income countries (LMICs) continue to encounter barriers to care owing to inequitable access and vaccine apprehension. This study aimed to summarize the available data on COVID-19 vaccine acceptance rates and factors associated with acceptance in LMICs. A comprehensive search was performed in PubMed, Scopus, and Web of Science from inception through August 2021. Quality assessments of the included studies were carried out using the eight-item Joanna Briggs Institute Critical Appraisal tool for cross-sectional studies. We performed a meta-analysis to estimate pooled acceptance rates with 95% confidence intervals (CI). A total of 36 studies met the inclusion criteria and were included in the review. A total of 83,867 respondents from 33 countries were studied. Most of the studies were conducted in India (n = 9), Egypt (n = 6), Bangladesh (n = 4), or Nigeria (n = 4). The pooled-effect size of the COVID-19 vaccine acceptance rate was 58.5% (95% CI: 46.9, 69.7, I2 = 100%, 33 studies) and the pooled vaccine hesitancy rate was 38.2% (95% CI: 27.2-49.7, I2 = 100%, 32 studies). In country-specific sub-group analyses, India showed the highest rates of vaccine acceptancy (76.7%, 95% CI: 65.8-84.9%, I2= 98%), while Egypt showed the lowest rates of vaccine acceptancy (42.6%, 95% CI: 16.6-73.5%, I2= 98%). Being male and perceiving risk of COVID-19 infection were predictors for willingness to accept the vaccine. Increasing vaccine acceptance rates in the global south should be prioritized to advance global vaccination coverage.

WEB: 10.3390/vaccines10030427

IMPACT FACTOR: 4.086

CITED HALF-LIFE: 3.4

START COMMENTARY

In this systematic review and meta-analysis, Patwary *et al.* report pooled COVID-19 acceptance rates across low- and lower-middle income countries. This study is importance as vaccine hesitancy is a huge global issue negatively impacting efforts to control COVID-19, yet no studies to date have conducted a systematic review and meta-analysis of vaccine acceptance and hesitancy rates and associated factors for LMICs. Eligibility criteria included studies with no restriction on study population; descriptive/observational studies with a cross sectional, longitudinal, or experimental

study; taking place in a low to low-middle income country defined as gross national income of USD 4,095 or less; peer reviewed and published in English between 2020-2021. Patwary *et al.* conducted an assessment of study quality using the Joanna Briggs Institute (JBI) tool.

Table 1 describes characteristics of the included studies, including the country, study design, target population, sample size, reported vaccine acceptance percentage and factors associated with vaccine acceptance. In total, 33 studies were included in the meta-analysis. The estimated COVID-19 vaccination acceptance rate across LMICs was 58.5% (95% CI: 46.90-69.70%). Figure 2 shows a forest plot of vaccine acceptance rates. In country-specific sub-group analyses, the highest pooled acceptance rate was in India, followed by Nigeria (Figure 4), whereas the highest hesitancy rates were shown in Egypt followed by Pakistan (Figure 5). When evaluating factors associated with vaccine acceptance rates (including sex, residence, marital status, education, occupation, chronic disease stat, healthcare worker status, taking vaccine previously, and perceived risk), only being male (OR 1.2 across 17 studies) and perceived risk of COVID-19 (R:2.4 across 3 studies) were significantly associated with vaccine acceptance. The quality assessment indicated that all studies were high-quality observational studies. In conclusion, this study demonstrates the wide variation in acceptance and hesitancy, which should be considered in vaccine implementation efforts.

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3. Building the Momentum for A Stronger Pharmaceutical System in Africa.

Ussai S, Chillotti C, Stochino E, Deidda A, Ambu G, Anania L, *et al.*

Int J Environ Res Public Health. 2022 Mar 31;19(6).
PubMed ID: 35328999

ABSTRACT

Despite impressive progress, nearly two billion people worldwide have no access to essential medicines. The COVID-19 pandemic revealed Africa's vulnerability due to its reliance on imports for most vaccines, medicines, and other health product needs. The vaccine manufacturing is complex and requires massive financial investments, with global, regional, and national regulatory structures introducing consistent and urgent reforms to assure the quality and safety of medicines. In 2020, there were approximately 600 pharmaceutical manufacturers in Africa, 80% of which were concentrated in eight countries: Egypt, Algeria, Morocco, Tunisia, Nigeria, Ghana, Kenya, and South Africa. Only 4 countries had more than 50 manufacturers, while 22 countries had no local production. Out of the 600, around 25% were multinational companies. Africa is equally affected by modest scaled capacities substantially engaging in packaging and labelling, and occasionally fill and finish steps, facing criticalities in terms of solvent domestic markets. This article discusses the challenges in the development of a local pharmaceutical manufacturing in Africa and reflects on the importance of the momentum for strengthening the local medical production capacity in the continent as a critical opportunity for advancing universal health coverage (UHC).

WEB: 10.3390/ijerph19063313
IMPACT FACTOR: 2.007
CITED HALF-LIFE: 5.8

START COMMENTARY

In this article, Ussai *et al.* describe challenges related to local pharmaceutical manufacturing in Africa. This summary is important, as it provides key statistics to understand the state of the pharmaceutical manufacturing industry and highlights challenges and opportunities for improving capacity. In 2020, there were an estimated 600 pharmaceutical manufacturers across all 55 countries in Africa. However, these are not equally distributed; 80% of manufacturers are in eight countries whereas there is no local production in 22 countries. Despite the limited production of pharmaceuticals, country-level COVID-19 vaccine production has been prioritized through several initiatives (e.g., European commission one-billion-euro package for vaccines, medicines, and health products, Russian Direct Investment Fund Morocco to produce Russian vaccine, Aspen Pharmacare producing Johnson & Johnson Vaccine in South Africa; Rwanda and BioNTech signing an

agreement to make first mRNA vaccine manufacturing facility). Ussai *et al.* also note that most vaccines in Africa are imported from Europe (51.5%) followed by India (19.3%) due to weak regulatory and supply chain environments and restricted access to finance. Other challenges such as Intellectual Properties (IP) regulation have become relevant during COVID-19 given calls to allow for flexibility around trade secrets and protection given the public health emergency. However, such flexibility has not been granted. Similarly, Ussai *et al.* note issues related to quality assurance and fraud, which is often ensured by a Stringent Regulatory Authority (SRA) which are rare in Africa. Subsequently, an estimated 1 in 10 products from LMICs are considered substandard. Ussai *et al.* conclude by stating that COVID-19 has provided an opportunity to expedite local production and strengthening regional and national regulatory systems.

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4. Nepal measles outbreak response immunization during COVID-19: A risk-based intervention strategy.

Bose A, Rai P, Gupta B, Pradhan R, Lacoul M, Shakya S, et al.

Vaccine. 2022 Mar 29.

PubMed ID: 35300872

ABSTRACT

In 2020, National Immunization Programme (NIP) of Nepal implemented a measles outbreak response immunization (ORI) campaign, which was additional to an ongoing preventive measles-rubella SIA campaign. Both campaigns were implemented during ongoing COVID-19 transmission. By April, 220 measles cases and two deaths were confirmed from eight districts of Nepal. The NIP triangulated information from surveillance (measles and COVID-19), measles immunization performance and immunity profile, programme capacities and community engagement and applied a logical decision-making framework to the collated data to inform 'Go/No-Go' decisions for ORI interventions. This was reviewed by the National Immunization Advisory Committee (NIAC) for endorsement. Outbreak response with non-selective immunization (ORI), vitamin-A administration and case management were implemented in affected municipalities of four districts, while in the remaining districts outbreak response without ORI were undertaken. The structure and iterative application of this logical framework has been described. ORI was implemented without interrupting the ongoing measles-rubella vaccination campaign which had targeted children from 9 to 59.months of age. The age group for ORI was same as SIA in one sub-district area, while for the other three sub-district areas it was from 6 months to 15 years of age. More than 32,000 persons (97% coverage) were vaccinated in ORI response. Overall measles incidence decreased by 98% after ORI. The daily incidence rate of measles was 94 times higher (95% confidence interval: 36.11 - 347.62) before the ORI compared to two weeks after ORI until year end. Close attention to surveillance and other data to inform actions and seamless collaboration between NIP and core immunization partners (WHO, UNICEF), with guidance from NIAC were key elements in successful implementation. This was an example of feasible application of the global framework for implementation of a mass vaccination campaign during COVID-19 through application of a simple decision-making logical framework.

WEB: 10.1016/j.vaccine.2022.02.057

IMPACT FACTOR: 3.143

CITED HALF-LIFE: 7.3

START COMMENTARY

In this study, Bose *et al.* describe the use of a measles outbreak response immunization (ORI) campaign alongside a preventive measles-rubella (MR) supplementary immunization campaign (SIA) and during the ongoing COVID-19 pandemic. This study is important as it describes how a risk-based ORI is implemented, including the rationale, application of policy guidelines, and a systematic decision-making process, which can provide guidance for other disease outbreaks and contexts. For background, Bose *et al.* describe that the MR campaign took place in two phases for 9–59 month-olds in the first half of 2020. However, during this time, the vaccine preventable disease (VPD) surveillance program observed an increased incidence in measles cases among children five years or older. Bose *et al.* also provide information on the measles response mechanisms and decision framework. The framework includes six dimensions to aid the decision to conduct, withhold, or defer the program, including: 1) program mandate for ORI; 2) direct epidemiological risk of measles transmission; 3) competing epidemiological risks of COVID-19 transmission; 4) community demand and ownership of ORI; 5) operational feasibility; 6) local program capacity for ORI.

Key findings included that there were 11 laboratory confirmed measles outbreaks in eight districts of Nepal, and that 78% (172 of 220) of cases were above the age group targeted by the MR SIA. Underserved communities accounted for 95% of cases. *Table 1* shows confirmed measles outbreaks by age group and vaccination status. *Figure 1* is a map of Nepal which shows both confirmed measles outbreaks and COVID-19 cases between January 1 to April 30, 2020. To decide if an ORI should be implemented, the logical framework was implemented. *Table 2* shows the logical framework decision matrix, which includes direct risks (e.g., sporadic and outbreak measles cases, risk of contiguous spread) and indirect risk (e.g., COVID-19 cases), community demand, local capacity, and decision for ORI. In total, six municipalities within four districts received ORI, which was shown to reduce measles cases by 98% (*Table 4* and *Figure 2*). Daily incidence was significantly reduced in each district independently at 95% level of confidence. This study shows how outbreak response can be implemented in a systematic and timely manner, which could be utilized in future outbreaks in Nepal and beyond.

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5. Differential health impact of intervention programs for time-varying disease risk: a measles vaccination modeling study.

Portnoy A, Hsieh Y, Abbas K, Klepac P, Santos H, Brenzel L, *et al.*

BMC Med. 2022 Mar 23;20(1):113.

PubMed ID: 35260139

ABSTRACT

BACKGROUND: Dynamic modeling is commonly used to evaluate direct and indirect effects of interventions on infectious disease incidence. The risk of secondary outcomes (e.g., death) attributable to infection may depend on the underlying disease incidence targeted by the intervention. Consequently, the impact of interventions (e.g., the difference in vaccination and no-vaccination scenarios) on secondary outcomes may not be proportional to the reduction in disease incidence. Here, we illustrate the estimation of the impact of vaccination on measles mortality, where case fatality ratios (CFRs) are a function of dynamically changing measles incidence.

METHODS: We used a previously published model of measles CFR that depends on incidence and vaccine coverage to illustrate the effects of (1) assuming higher CFR in “no-vaccination” scenarios, (2) time-varying CFRs over the past, and (3) time-varying CFRs in future projections on measles impact estimation. We used modeled CFRs in alternative scenarios to estimate measles deaths from 2000 to 2030 in 112 low- and middle-income countries using two models of measles transmission: Pennsylvania State University (PSU) and DynaMICE. We evaluated how different assumptions on future vaccine coverage, measles incidence, and CFR levels in “no-vaccination” scenarios affect the estimation of future deaths averted by measles vaccination.

RESULTS: Across 2000-2030, when CFRs are separately estimated for the “no-vaccination” scenario, the measles deaths averted estimated by PSU increased from 85.8% with constant CFRs to 86.8% with CFRs varying 2000-2018 and then held constant or 85.9% with CFRs varying across the entire time period and by DynaMICE changed from 92.0 to 92.4% or 91.9% in the same scenarios, respectively. By aligning both the “vaccination” and “no-vaccination” scenarios with time-variant measles CFR estimates, as opposed to assuming constant CFRs, the number of deaths averted in the vaccination scenarios was larger in historical years and lower in future years.

CONCLUSIONS: To assess the consequences of health interventions, impact estimates should consider the effect of “no-intervention” scenario assumptions on model parameters, such as measles CFR, in order to project estimated impact for alternative scenarios according to intervention strategies and investment decisions.

WEB: 10.1186/s12916-022-02242-2
IMPACT FACTOR: 6.782
CITED HALF-LIFE: 5.2

START COMMENTARY

In this mathematical modelling analysis, Portnoy *et al.* illustrate the impact of interventions on measles mortality using dynamic modelling which accounts for underlying disease incidence targeted by the intervention across 112 low- and middle-income countries. This study is important as it offers a methodological innovation which models CFR dynamically to address the dependence of case-fatality ratio (CFR) on incidence and other health system characteristics and calculates impact with a consideration for a no vaccination scenario. In this model, CFR is either time-varying or time invariant. Analytic scenarios are shown in *Table 1.* Two models of measles transmission (Pennsylvania State University [PSU] and DynaMICE) were used.

Time invariant CFRs were 2.1% for children under five and 1% for children 5 years of age or older. Time-varying CFRs were 2.3-6.3% in 2000 and 0.4-3.1% in the year 2030. *Appendix 1* shows the estimated CFRs from 2000 to 2030 by under-five mortality rate and region. *Table 2* shows the measles deaths averted due to vaccination across 112 countries from 2000 to 2030 assuming a constant CFR and percent reduction compared to no vaccination for both models (PSU and DynaMICE) whereas *Figure 1* visually demonstrates the results. *Table 3* shows the number of deaths averted assuming a time-varying case fatality ratio. Overall, Portnoy *et al.* show the importance of considering the measles incidence and vaccination presence in understanding the impact of vaccines on mortality across LMICs.

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6. WHO-led consensus statement on vaccine delivery costing: process, methods, and findings.

Levin A, Boonstoppel L, Brenzel L, Griffiths U, Hutubessy R, Jit M, *et al.*

BMC Med. 2022 Mar 23;20(1):88.

PubMed ID: 35255920

ABSTRACT

BACKGROUND: Differences in definitions and methodological approaches have hindered comparison and synthesis of economic evaluation results across multiple health domains, including immunization. At the request of the World Health Organization's (WHO) Immunization and Vaccines-related Implementation Research Advisory Committee (IVIR-AC), WHO convened an ad hoc Vaccine Delivery Costing Working Group, comprising experts from eight organizations working in immunization costing, to address a lack of standardization and gaps in definitions and methodological guidance. The aim of the Working Group was to develop a consensus statement harmonizing terminology and principles and to formulate recommendations for vaccine delivery costing for decision making. This paper discusses the process, findings of the review, and recommendations in the Consensus Statement.

METHODS: The Working Group conducted several interviews, teleconferences, and one in-person meeting to identify groups working in vaccine delivery costing as well as existing guidance documents and costing tools, focusing on those for low- and middle-income country settings. They then reviewed the costing aims, perspectives, terms, methods, and principles in these documents. Consensus statement principles were drafted to align with the Global Health Cost Consortium costing guide as an agreed normative reference, and consensus definitions were drafted to reflect the predominant view across the documents reviewed.

RESULTS: The Working Group identified four major workstreams on vaccine delivery costing as well as nine guidance documents and eleven costing tools for immunization costing. They found that some terms and principles were commonly defined while others were specific to individual workstreams. Based on these findings and extensive consultation, recommendations to harmonize differences in terminology and principles were made.

CONCLUSIONS: Use of standardized principles and definitions outlined in the Consensus Statement within the immunization delivery costing community of practice can facilitate interpretation of economic evidence by global, regional, and national decision makers. Improving methodological alignment and clarity in program costing of health services such as immunization is important to support evidence-based policies and optimal resource allocation. On the other hand, this review and Consensus Statement development process revealed the limitations of our ability to harmonize given

that study designs will vary depending upon the policy question that is being addressed and the country context.

WEB: 10.1186/s12916-022-02278-4
IMPACT FACTOR: 6.782
CITED HALF-LIFE: 5.2

START COMMENTARY

In this article, Levin *et al.* aimed to discuss the process, review findings, and recommendations from the WHO Vaccine Delivery Costing Working Group, which included experts from eight organizations conducting immunization costing. This study is important as it addresses gaps in standardization, definitions, and methods for vaccine delivery costing for decision-making. Methods included conducting interviews to identify groups and guiding documents on vaccine costing for LMICs. A landscape analysis of documents were used to draft consensus statement principles. *Figure 1* shows a complete timeline of the consultation process.

As a result of interviews and document review, four workstreams on vaccine delivery costing were identified including 1) retrospective routine immunization cross-sectional costing, 2) retrospective single-vaccine costing, 3) new vaccine introduction cost projection, and 4) national immunization program cost projection (shown in *Figure 2* along with guiding documents/tools). Levin *et al.* describe each workstream with examples in the article. *Table 1* list guiding documents on vaccine delivery costing identified and reviewed by the working group including which organization developed the document, guidelines, publication year, target intervention, purposes, and relevant workstreams whereas *Table 2* shows comparisons of costing terms definitions from the aforementioned documents. From this review and summary, gaps were identified. Some notable gaps were that documents did not describe how methods were affected by the choice of perspective (i.e., payer perspective, or donor perspective) or if economic costs of existing capital (i.e., equipment or building space) or vaccine costs should be included. The detailed review showed that documents do not always include definitions of costing terms. As such, the working group recommended definitions of costing terms (i.e., vaccine delivery costs, vaccine cost, economic cost, capital cost). Similarly, the working group recommend several (16) costing principles. For example, one principle is that the perspective of the cost estimation should be stated and explained. This study provides urgently needed standardization in terminology, implementation, and principles in vaccine delivery costing.

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7. WHO guidance on COVID-19 vaccine trial designs in the context of authorized COVID-19 vaccines and expanding global access: Ethical considerations.

Singh J, Kochhar S, Wolff J, Atuire C, Bhan A, Emanuel E, *et al.*

Vaccine. 2022 Mar 31;40(14):2140-2149.

PubMed ID: 35248422

ABSTRACT

While the degree of COVID-19 vaccine accessibility and uptake varies at both national and global levels, increasing vaccination coverage raises questions regarding the standard of prevention that ought to apply to different settings where COVID-19 vaccine trials are hosted. A WHO Expert Group has developed guidance on the ethical implications of conducting placebo-controlled trials in the context of expanding global COVID-19 vaccine coverage. The guidance also considers alternative trial designs to placebo controlled trials in the context of prototype vaccines, modified vaccines, and next generation vaccines.

WEB: 10.1016/j.vaccine.2022.02.038

IMPACT FACTOR: 3.143

CITED HALF-LIFE: 7.3

START COMMENTARY

In this review article, Singh *et al.* summarize expert guidance on the ethical implications of conducting placebo-controlled trials in the context of the COVID-19 pandemic. Further, they describe alternative study deigns for prototype vaccines, modified vaccines, and next generation vaccines. This review raises an important question about how to justify the use of placebos given increasing levels of COVID-19 vaccination coverage around the world. Singh *et al.* present prior expert panel determinations on the use of placebos to discuss the suitability of applying this existing guidance during the ongoing pandemic. The authors highlight three questions to demonstrate that existing guidance is not sufficient for the current situation: (1) what constitutes an establish effective intervention? 2) what constitutes a best proven intervention?; and 3) when is a placebo-control COVID-19 trial clearly unacceptable?).

Singh *et al.* describe scenarios where placebo control designs are appropriate for COVID-19. For example, randomized, double-blind parallel group placebo-controlled trials are ethical for groups which the vaccines are not yet authorized (e.g., children), or for booster-trials if the booster has not yet been authorized. Randomized, double-blind placebo control crossover trials could be suitable if all placebo participants are able to ultimately receive the vaccine (i.e., either through the study or if it became authorized during the trial). Adaptive designs may have some benefits, including that they

can prospectively plan modifications to one or more aspects of the design, such as determining that placebo is no longer appropriate if there is persuasive evidence of efficacy and safety of another vaccine. Singh *et al.* also summarize how appropriateness may vary depending on what type of vaccine is being tested (i.e., prototype vaccine, modified, or next generation). Specific ethical recommendations for prototype vaccines include that participants should be informed that they are eligible to receive authorize vaccines at any point in the trial, and trials should be modified as local programmatic eligibility changes. Alternative designs include active control trials (i.e., comparing a new vaccine to an existing one), inactive control (i.e., using a vaccine licensed for another condition unrelated to the condition in the study so participants receive some benefit), synthetic or external controls (i.e., utilizing real world data from sources or evaluations of historical clinical trials). For modified vaccine trial, it may be appropriate to use immunobridging (i.e., a scientific approach inferring effectiveness by comparing immune responses under different conditions) or historical controls. For next generation vaccines (i.e., those covering several serotypes or using alternative routines of administration), it will be challenging to justify placebo controls, prompting the need for clinical disease endpoint studies, human challenge studies, and non-efficacy studies. Overall, this study provides guidance on ethical considerations for vaccine trials, which can inform the planning and execution of future studies.

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8. Impact of catch-up human papillomavirus vaccination on cervical cancer incidence in Kenya: A mathematical modeling evaluation of HPV vaccination strategies in the context of moderate HIV prevalence.

Liu G, Mugo N, Bayer C, Rao D, Onono M, Mgodi N, et al.

EClinicalMedicine. 2022 Mar 05;45:101306.

PubMed ID: 35243272

ABSTRACT

BACKGROUND: Cervical cancer incidence is high in Kenya due to HIV and limited access to cancer prevention services. Human papillomavirus (HPV) has been shown to increase HIV acquisition; however, the potential impact of HPV vaccination on HIV is unknown. We modeled the health impact of HPV vaccination in the context of the HIV epidemiology in Kenya.

METHODS: Using a validated compartmental transmission model of HIV and HPV set in Kenya, we evaluated five scenarios of nonavalent HPV vaccination: single-age-vaccination of 10-year-old girls at 90% coverage; multi-age-cohort (MAC) vaccination of 10-14-year-old girls at 90% coverage; MAC plus moderate-coverage (50%) catch-up vaccination of 15-24-year-old women; MAC plus high-coverage (80%) catch-up of 15-24-year-old women; and MAC plus catch-up of 15-44-year-old women at 80% coverage (HPV-FASTER). We compared cervical cancer incidence, HIV prevalence, and cumulative cervical cancer and HIV cases averted after 50 years to a baseline scenario without vaccination. In all scenarios, we assumed the UNAIDS 90-90-90 goal for HIV treatment is attained by 2030.

FINDINGS: In 2021, model-estimated cervical cancer incidence is 44/100,000 and HIV prevalence among women is 6.5%. In 2070, projected cancer incidence declines to 27/100,000 and HIV prevalence reaches 0.3% without vaccination. With single-age-vaccination, cancer incidence in 2070 is reduced by 68%, averting 64,529 cumulative cancer cases. MAC vaccination reduces cancer incidence by 75%, averting 206,115 cancer cases. Moderate and high-coverage catch-up and HPV-FASTER reduce cancer incidence by 80%, 82%, and 84%, averting 254,930, 278,690, and 326,968 cancer cases, respectively. In all scenarios, HIV prevalence in 2070 is reduced by a relative 8-11%, with 15,609-34,981 HIV cases averted after 50 years.

INTERPRETATION: HPV vaccination can substantially reduce cervical cancer incidence in Kenya in the next 50 years, particularly if women up to age 24 are vaccinated. HIV treatment scale-up can also alleviate cervical cancer burden. However, HPV vaccination has modest additional impact on HIV when antiretroviral therapy coverage is high.

FUNDING: National Institutes of Health, Bill and Melinda Gates Foundation.

WEB: 10.1016/j.eclinm.2022.101306
IMPACT FACTOR: N/A
CITED HALF-LIFE: N/A

START COMMENTARY

In this mathematical modeling analysis, Liu *et al.* project the health impact of HPV vaccination in the context of HIV epidemiology in Kenya. Cervical cancer disproportionately affects women in low- and middle-income countries (LMICs) and is the leading cancer among women due to low coverage of screening and human papillomavirus vaccine (HPV) and high HIV prevalence. Liu *et al.* utilize a previously published compartmental dynamic model of heterosexual HPV and HIV transmission to simulate demographic dynamics, HIV and HPV infections and progressions, and interactions between the two. Six scenarios are modeled: 1) no vaccination; 2) single-age-cohort vaccination (i.e., 90% of girls vaccinated by age 10); 3) multi-age cohort (MAC) vaccination (i.e., girls 10-14 are vaccinated with 90% coverage); 4) MAC plus moderate-coverage catch up (i.e., women aged 15-24 at 50% coverage); 5) MAC plus high coverage catch up (i.e., women aged 15-24 at 90% coverage); 6) HPV FASTER, a strategy with MAC and one year of vaccination for women aged 15-44 at 80% coverage. Outcomes included annual age-standardized cervical cancer incidence rates from 2021-2070, cumulative number of cervical cancer cases averted 30 and 50 years after vaccine introduction relative to no vaccination, yearly relative percent reductions in HIV prevalence compared to no vaccination, and cumulative number of HIV cases averted 30 and 50 years after vaccination.

By 2050, cervical cancer incidence is projected to decrease by 23% for the single-age cohort scenario, 33% for the MAC scenario, 45% for the MAC and moderate catch up, and 51% for the MAC and high coverage, when compared to no vaccination. The HPV-FASTER strategy demonstrated the biggest reduction (62%, 98,783 cases [interquartile range: 77,219-114,567). For the scenarios for 2070, the incidence reductions ranged from 68% for single-age-cohort to 84% for HPV FASTER. For HIV, the prevalence reductions are modest (5.4% reduction among men and women by 2050). However, cumulatively, between 7,596 [IQR: 5,018-12,627) cases of HIV would be averted for the single-age-cohort to a high of 23,626 (IQR: 15,811-37,286) for HPV-FASTER. The impact of HPV vaccination on cervical cancer incidence rates and incidence rate ratios are shown in *Figure 3.* One notable limitation of this study are the simplified assumptions (i.e., around constant sexual behavior patterns and vaccine coverage). However, Liu *et al.* reported interquartile ranges to reflect uncertainty in the results. Overall, the results demonstrate that cervical cancer burden can be dramatically reduced with HPV vaccination, underscoring the need for scale up of routine and catch-up HPV vaccination campaigns.

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9. Tracking Demographic Movements and Immunization Status to Improve Children's Access to Immunization: Field-Based Randomized Controlled Trial.

Ateudjieu J, Tchio-Nighie K, Goura A, Ndinakie M, Dieffi Tchifou M, Amada L, *et al.*

JMIR Public Health Surveill. 2022 Mar 18;8(3):e32213.

PubMed ID: 35230249

ABSTRACT

BACKGROUND: Countries' Expanded Program on Immunization (EPI) contribute to the reduction of mortality and morbidity, but access to these vaccines remains limited in most low-income countries.

OBJECTIVE: We aim to assess whether involving community volunteers (CVs) to track children's vaccination status and demographic movements and using recorded data to plan catch-up immunization sessions can improve children's vaccination timeliness, completeness, and coverage.

METHODS: This was a field-based randomized controlled trial and communities of the Foumban health district in West Cameroon were allocated to intervention or control groups. In the intervention group, a CV per community was trained to visit households monthly for a year to assess and record in a register, details of EPI-targeted children, their demographic movements and immunization status. The scanned recorded pages were sent to the health center immunization team through WhatsApp and used to organize monthly community catch-up immunization sessions. In the control group, EPI vaccination sessions were routinely conducted. Surveys were conducted at 6 and 12 months from the beginning of the intervention in both study groups to assess and compare immunization timeliness, coverage, and completeness.

RESULTS: Overall, 30 buildings per cluster were surveyed at midline and endline. Of the 633 and 729 visited households in the intervention group at midline and endline, 630 (99.5%) and 718 (98.4%), respectively, consented to participate. In the control group, 507 and 651 households were visited and 505 (99.6%) and 636 (97.7%), respectively, consented to participate. At 12 months intervention, the month one timeliness of bacille Calmette-Guerin (BCG) vaccine did not increase in the intervention group compared with the control group for the age groups 0-11 months (adjusted odds ratio [aOR] 1.1, 95% CI 0.7-1.8) and 0-59 months (aOR 1.1, 95% CI 0.9-1.4), and significantly increased for the first-year BCG vaccine administration for the age group 0-23 months (aOR 1.5, 95% CI 1.1-2.2). The coverage of diphtheria-pertussis-tetanus and hepatitis B+Hemophilus influenzae type B (DPT-Hi…+Hb) dose 3 (aOR 2.0, 95% CI 1.5-2.7) and of DPT-Hi+Hb dose 1 (aOR 1.8, 95% CI 1.4-2.4) vaccines increased significantly in the intervention group compared with the control group in the age groups 12-59 months and 12-23 months, respectively. Specific (DPT-Hi+Hb dose 1 to DPT-Hi+Hb dose 3: aOR 1.9, 95% CI 1.4-2.6) and general (BCG to measles: aOR 1.5,

95% CI 1.1-2.1) vaccine completeness increased significantly in the intervention group compared with the control group.

CONCLUSIONS: Findings support that involving CVs to track children's vaccination status and demographic movements and using recorded data to plan catch-up immunization sessions improve children's vaccination timeliness, completeness, and coverage. This strategy should be adopted to improve access to vaccination for EPI target populations and the consistency verified in other contexts.

TRIAL REGISTRATION: Pan African Clinical Trials Registry PACTR201808527428720; https://pactr.samrc.ac.za/TrialDisplay.aspx?TrialID=3548.

WEB: 10.2196/32213
IMPACT FACTOR: 2.577
CITED HALF-LIFE: 3.1

START COMMENTARY

In this cluster-randomized controlled trial, Ateudjieu *et al.* assess the impact of involving community volunteers to track children's vaccination status and demographic movements to plan catch-up immunization campaigns to improve timeliness, completeness, and coverage in Cameroon. The rationale for the study is that prior supervision activities indicated immunization coverage was negatively impacted by short- and long-term travel (i.e., periodic trips and constant travel by nomads) and newborns not coming into contact with the health system if they are born in nomadic communities. However, such factors are not taken into account when planning immunization activities. As such, an intervention was developed in which community volunteers (CVs) were trained to record and register all children aged 0-59 months and their demographic movements (previous and next months) and use this information to implement monthly immunization sessions. Foumban district was selected for the study as it is inhabited by seminomadic people and had been affected by outbreaks of vaccine-preventable disease in each of the past five years. Clusters were defined as communities, and randomization was stratified according to setting (urban or rural), the importance of yearly population movements, distance to health facility, and the occurrence of vaccine-preventable diseases. Participants included all children aged 0-59 months living in select clusters. The primary outcome was documented children's immunization timeliness (proportion of children aged <5 years with documented BCG vaccine in first month of life).

A total of 64 communities were randomized. One limitation of this study is the exclusion of 16 of 80 eligible communities due to inaccessibility throughout the year. This limits generalizability to these remote communities, which may have worse immunization outcomes given limited accessibility to services. *Table 1* presents baseline characteristics for the intervention and control arm. There were

some differences between groups, such as intervention group having fewer (n=3) mainly seminomadic populations compared to the control group (n=5), although this was not statistically significant. Vaccination coverage did not differ by study arm at baseline. At midline (12 months intervention), the primary outcome (timeliness defined as the proportion of children with BCG in the first month) did not significantly increase due to the intervention compared to the control group aged 0-11 months (adjusted odds ratio [aOR]: 1.1, 95% CI 0.7-1.8) or 0-59 months (aOR: 1.1, 9% CI 0.9-1.4). There were some notable positive findings, including significant increases in first year timeliness of BCG vaccines and increased coverage of three vaccines: diphtheria-pertussis-tetanus and hepatitis B and Hemophilus influenzae type B dose (1 and 3) in the intervention group compared to the control group. Given these improvements, it demonstrates the potential of a CV intervention to reduce missed vaccines in Cameroon.

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10. Innovations in vaccine delivery: increasing access, coverage, and equity and lessons learnt from measles and rubella elimination.

Goodson J, Rota P.

Drug Deliv Transl Res. 2022 Apr 08;12(5):959-967.

PubMed ID: 35211868

ABSTRACT

Disease eradication and elimination programs drive innovations based on progress toward measurable objectives, evaluations of new strategies and methods, programmatic experiences, and lessons learned from the field. Following progress toward global measles elimination, reducing measles mortality, and increasing introductions of.measles and rubella vaccines to national programs, the measles and rubella immunization program has faced setbacks in recent years. Currently available vaccine delivery methods have complicated logistics and drawbacks that create barriers to vaccination; innovations for easier, more efficient, and safer vaccine delivery are needed. Progress can be accelerated by new technologies like microarray patches (MAPs) that are now widely recognized as a potential new tool for enhancing global immunizations efforts. Clinical trials of measles-rubella vaccine MAPs have begun, and several other vaccine MAPs are in the pre-clinical development pathway. MAPs could significantly contribute to Immunization Agenda 2030 priorities, including reaching zero-dose children; increasing vaccine access, demand, coverage, and equity; and achieving measles and rubella elimination. With strong partnerships between public health agencies and biotechnology companies, translational novel vaccine delivery systems can be developed to help solve public health problems and achieve global health priorities.

WEB: 10.1007/s13346-022-01130-9

IMPACT FACTOR: N/A

CITED HALF-LIFE: N/A

START COMMENTARY

In this review article, Goodson and Rota describe how innovations such as vaccine microarray patches (MAPs) can accelerate progress in global measles and rubella immunization efforts. The authors describe historical advances in reducing vaccine-preventable diseases through developments such as disease surveillance systems to guide immunization efforts for smallpox, polio, measles, and rubella, the use of the bifurcated needle during mass vaccination campaigns, expansion of cold chain capabilities, and ring vaccination strategies to contain outbreaks. Despite advances, authors note that global progress has slowed, demonstrated in *Figure 1*¸ which shows increasing trends in the number of vaccine-preventable deaths since 2017. Some of these challenges are related to vaccine limitations. For measles and rubella vaccination, there are

substantial difficulties related to the handling and maintenance of continuous cold chain requirements, shortages of trained medical professionals, specific required materials (i.e., a reconstitution diluent, hypodermic needle, and subcutaneous injection), and multidose vials leading to wastage (i.e., must be discarded after 6 hours). Given these limitations, innovations focused on aerosolized, intranasal, and subcutaneous delivery using small adhesive patches have been tested. Goodson and Rota highlight the advantages of measles-rubella MAPs, including thermostability (which means less dependence on cold chain), ease of administration (i.e., no reconstitution is required), less waste (i.e., needles are not used), and small packaging (i.e., fewer cold chain storage requirements). MAPs could be particularly useful for mass campaigns and routine outreach services, which are highly affected by logistic and cold chain challenges. For MAPs to actively contribute to global elimination goals, there is a need for studies evaluating safety and immunogenicity and future investments into manufacturing.

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Appendix

The literature search for the April 2022 Vaccine Delivery Research Digest was conducted on March 28, 2022. We searched English language articles indexed by the US National Library of Medicine and published between February 15, 2022 and March 14, 2022. The search resulted in 598 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]) (“2022/02/15”[PDAT] : “2022/03/14”[PDAT]))