VACCINE DELIVERY RESEARCH DIGEST

**UNIVERSITY OF WASHINGTON STRATEGIC ANALYSIS,
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1. **[The current burden of Japanese encephalitis and the estimated impacts of vaccination: Combining estimates of the spatial distribution and transmission intensity of a zoonotic pathogen.](#)**

ABSTRACT

Japanese encephalitis virus (JEV) is a major cause of neurological disability in Asia and causes thousands of severe encephalitis cases and deaths each year. Although Japanese encephalitis (JE) is a WHO reportable disease, cases and deaths are significantly underreported and the true burden of the disease is not well understood in most endemic countries. Here, we first conducted a spatial analysis of the risk factors associated with JE to identify the areas suitable for sustained JEV transmission and the size of the population living in at-risk areas. We then estimated the force of infection (FOI) for JE-endemic countries from age-specific incidence data. Estimates of the susceptible population size and the current FOI were then used to estimate the JE burden from 2010 to 2019, as well as the impact of vaccination. Overall, 1,543.1 million (range: 1,292.6-2,019.9 million) people were estimated to live in areas suitable for endemic JEV transmission, which represents only 37.7% (range: 31.6-53.5%) of the over four billion people living in countries with endemic JEV transmission. Based on the baseline number of people at risk of infection, there were an estimated 56,847 (95% CI: 18,003-184,525) JE cases and 20,642 (95% CI: 2,252-77,204) deaths in 2019. Estimated incidence declined from 81,258 (95% CI: 25,437-273,640) cases and 29,520 (95% CI: 3,334-112,498) deaths in 2010, largely due to increases in vaccination coverage which have prevented an estimated 314,793 (95% CI: 94,566-1,049,645) cases and 114,946 (95% CI: 11,421-431,224) deaths over the past decade. India had the largest estimated JE burden in 2019, followed by Bangladesh and China. From 2010-2019, we estimate that vaccination had the largest absolute impact in China, with 204,734 (95% CI: 74,419-664,871) cases and 74,893 (95% CI: 8,989-286,239) deaths prevented, while Taiwan (91.2%) and Malaysia (80.1%) had the largest percent reductions in JE burden due to vaccination. Our estimates of the size of at-risk populations and current JE incidence highlight countries where increasing vaccination coverage could have the largest impact on reducing their JE burden.

START COMMENTARY

In this modelling study, Moore conduct spatial analysis of risk factors associated with Japanese encephalitis virus (JE) to estimate the susceptible population size, area at risk, force of infection (FOI), and impact of vaccination. This study makes an important contribution as JE is severely underreported, which limits understanding of the number of cases and deaths associated with various vaccination strategies. Such information on sub-national variation in risk will allow for strategic vaccination efforts in the future. Moore utilized spatial datasets of lowland rice production in Asia, waterbodies, wetlands, and soil moisture (i.e., as a proxy for water flow and surface wetness) to represent the area at risk. The susceptible population was estimated using the area at risk and population density, further refined using modeled estimates of the main JEV mosquito vector *(Culex tritaeniorhynchus*) as a cut-off (i.e., probability of occurrence ≥ 0.25). A strength of this study was the validation of at-risk areas using a literature search of all reports of JE occurrence/incidence from 2000-2019. In addition, Moore estimated the FOI for each endemic country at the national level using a literature review of academic literature reporting age-specific JE incidence data and other study-specific variables (e.g., history of JE vaccination, population size, incidence level). Based on the calculated FOE, Moore estimated the annual number of JEV infections, cases, and deaths.

Key findings included that over 1,543.1 billion people (range: 1292.6-2190.9) live in an area suitable for endemic JEV transmission, which is approximately 37.7% (range: 31.6-53.5) of the persons in countries with endemic JEV (*Table 1)*. Areas projected for be suitable for endemic JEV are presented in *Figure 1.* The FOI across all studies was an estimated 0.098 (95% range: 0.012-0.354), which translates to 9.3% annual probability of a susceptible individual living in an at-risk area being infected. The median FOE ranging from a low of 0.011 in Japan to a high of 0.286 in Indonesia. The mean number of JE cases decreased from 81,258 (95% CI: 25,437–273,640) in 2010 to 56,847 (95% CI: 18,003–184,525) in 2019. Deaths followed a similar trend, decreasing from 29,520 (95% CI: 3,334–112,498) in 2010 to 20,642 (95% CI: 2,252–77,204) in 2019 due to vaccination. Moore also estimated the number of cases and deaths in the absence of vaccination. Overall, Moore demonstrates that transmission is high in many JE-endemic countries despite recent progress due to vaccinations. This study underscores the importance of continuing and expanding JE vaccination campaigns to reduce JE morbidity and mortality.

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2. [Strengthening the immunization supply chain: A time-to-supply based approach to cold chain network optimization & extension in Madhya Pradesh.](#)

Srivastava V, Ratna M, Ray A, Shukla S, Shrivastava V, Kothari N, et al.

ABSTRACT

Expansion of immunization coverage is dependent in part on delivering potent vaccines in an equitable and timely manner to immunization outreach session sites from Cold Chain Points (CCPs). When duration of travel between the last CCP and the session site (Time-to-Supply) is too long, three consequences may arise: decreased potency due to exposure to heat and freezing, beneficiary dropouts due to delayed session starts, and, increased operational costs for the Health Facility (HF) conducting the outreach sessions. Guided by the Government of India's recommendation on cold chain point expansion to ensure that all session sites are within a maximum of 60.min from the last CCP, CHAI and the State Routine Immunization Cell in the state of Madhya Pradesh collaborated to pilot a novel approach to cold chain network optimization and expansion in eight districts of Madhya Pradesh. Opportunities for realignment of remote sub-health centers (SHCs) and corresponding session sites to alternative existing CCPs or to HFs which could be converted to new CCPs were identified, and proposed using a greedy adding algorithm-based optimization which relied on health facility level geo-location data. Health facility geo-coordinates were collected through tele-calling and site visits, and a Microsoft Excel based optimization tool was developed. This exercise led to an estimated reduction in the number of remote SHCs falling beyond the permissible travel time from CCPs by 56.89 percent (132 remote sites), from 232 to 100. The 132 resolved sites include 73 sites realigned to existing CCPs, and 59 sites to be attached to 22 newly proposed CCPs. Both the network optimization approach and the institutional capacity built during this project will continue to be useful to India's immunization program. The approach is replicable and may be leveraged by developing countries facing similar challenges due to geographical, institutional, and financial constraints.

START COMMENTARY

In this study, Srivastava *et al.* developed a Microsoft Excel based algorithm-based optimization tool to determine the optimal cold chain points (CCP) network. This study is important as it provides a practical way of optimizing the immunization supply chain to ensure that vaccines maintain the

correct temperature, and that immunization outreach sessions are carried out in a timely fashion. Srivastava *et al.* proposed to allocate, expand, and optimize the CCO network with the goal of less than 60 minutes immunization sessions (referred to as "Time-to-Supply'). This guideline is based on factors related to vaccine safety/quality, health system organization, and cold chain infrastructure. Data collected for this tool included the geo-coordinates of remote immunization sites and facilities, of which travel time between locations was calculated using the Google Maps Distance Matrix API. Based on this information, sub-Health Centers (SHC) which had Time-to-Supply greater than 40 minutes were considered remote. Information on distances and remoteness was used to realign SHCs and their associated sessions based on existing CCPs within each block of a district. Lastly, for remote SHCs which could not be resolved through realignment, identification and opening of a new SHC was called for. New CCPs and SHCs attached to CCPs were identified based on maximum coverage (described in *Appendix A).*

A summary of the main results of the optimization are presented in *Table 4* and include the total number of SHCs and Time-to-Supply for each component of the optimization. Overall, Srivastava *et al.* found that of the 1,464 SHCs in 53 blocks of eight districts, 274 SHCs within 40 blocks were identified as remote. However, through validation, 42 of those were re-classified as non-remote. For the realignment step, 73 of 274 remote SHCs were recommended for realignment within their block. Lastly, 22 CCPs were recommended for setup, which six would serve 37 remote SHCs and the other 16 served 22 remote SHCs. This optimization resulted in 56.89% of SHCs being less than 40 minutes away from a CCP. Overall, this study shows a practical way to optimize limited resources to decrease travel time between CCPs and session sites, which is critical for vaccine quality, safety, and access.

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3. Modelling the spread of serotype-2 vaccine derived-poliovirus outbreak in Pakistan and Afghanistan to inform outbreak control strategies in the context of the COVID-19 pandemic.

Molodecky N, Jafari H, Safdar R, Ahmed J, Mahamud A, Bandyopadhyay A, et al.

ABSTRACT

BACKGROUND: Since July 2019, Pakistan and Afghanistan have been facing an outbreak of serotype-2 circulating vaccine derived poliovirus (cVDPV2) in addition to continued transmission of serotype-1 wild poliovirus (WPV1) and SARS-CoV-2 in 2020. Understanding the risks of cVDPV2 transmission due to pause of global vaccination efforts and the impact of potential vaccination response strategies in the current context of COVID-19 mitigation measures is critical.

METHODS: We developed a stochastic, geographically structured mathematical model of cVDPV2 transmission which captures both mucosal and humoral immunity separately and allows for reversion of serotype-2 oral polio vaccine (OPV2) virus to cVDPV2 following vaccine administration. The model includes geographic heterogeneities in vaccination coverage, population immunity and population movement. The model was fitted to historic cVDPV2 cases in Pakistan and Afghanistan between January 2010-April 2016 and July 2019-March 2020 using iterated particle filtering. The model was used to simulate spread of cVDPV2 infection from July 2019 to explore impact of various proposed vaccination responses on stopping transmission and risk of spread of reverted Sabin-2 under varying assumptions of impacts from COVID-19 lockdown measures on movement patterns as well as declines in vaccination coverage.

RESULTS: Simulated monthly incidence of cVDPV2 from the best-fit model demonstrated general spatio-temporal alignment with observed cVDPV2 cases. The model predicted substantial spread of cVDPV2 infection, with widespread transmission through 2020 in the absence of any vaccination activities. Vaccination responses were predicted to substantially reduce transmission and case burden, with a greater impact from earlier responses and those with larger geographic scope. While the greatest risk of seeding reverted Sabin-2 was predicted in areas targeted with OPV2, subsequent spread was greatest in areas with no or delayed response. The proposed vaccination strategy demonstrated ability to stop the cVDPV2 outbreak (with low risk of reverted Sabin-2 spread) by February 2021.

CONCLUSION: Outbreak response vaccination campaigns against cVDPV2 will be challenging throughout the COVID-19 pandemic but must be implemented urgently when feasible to stop transmission of cVDPV2.

START COMMENTARY

In this analysis, Molodecky *et al.* develop a mathematical model of serotype-2 circulating vaccine derived poliovirus (cVDPV2) to understand the risk of transmission due to COVID-19 related immunization disruptions. This study is important as highlights the importance of immunization activities during public health crises. Poliomyelitis cases were identified through sequencing stool samples of all-cause Acute Flaccid Paralysis (AFP) from January 1, 2010 to March 1, 2020. Molodecky *et al.* developed a spatiotemporal stochastic model of poliovirus transmission for <36 month old children based on the standard susceptibility-exposed-infected-recovered (SEIR) compartmental framework with special considerations for cVDPV2 infections. The model includes routine and supplementary immunization activities (SIAs). Two key strengths of this study are 1) the model was fitted to historic daily incidence of cVDPV2 and modified for forward simulation based on withdrawal of oral polio virus 2 (OPV2) in April 2016 and 2) the model simulated the spread of the cVDPV2 outbreak that originated in Diamir, Pakistan. This, along with model assumptions related to operational challenges of SIAs ensured that it more accurately represented the risk of cVDPV2 transmission.

Molodeckey *et al.* report that between January 2010 to June 2016, 87 cVDPV2 cases and 18 cVDPV2 cases were reported in Pakistan and Afghanistan, respectively. The July 2019 outbreak originating in Diamir resulted in 59 cases. Since March 1 2020, another 44 total cases have been reported. Routine immunization coverage ranged from a 34% to 94%. Assuming no vaccination response since March 2020, the model predicted that the outbreak started in Diamir, Pakistan would spread rapidly and result in >400 infections in 24% (IQR: 22-25) of districts in Afghanistan and 44% (44-46) districts in Pakistan (shown in *Figure 2). Figure 4* shows the impact of different vaccination strategies and population movement on poliovirus transmission. These results indicate that the proposed vaccination response could interrupt transmission in Pakistan and Afghanistan by early 2021, highlighting the need for an urgent response during the COVID-19 pandemic.

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4. Challenges of evaluating and modelling vaccination in emerging infectious diseases.

Madewell Z, Dean N, Berlin J, Coplan P, Davis K, Struchiner C, et al.

ABSTRACT

Outbreaks of emerging pathogens pose unique methodological and practical challenges for the design, implementation, and evaluation of vaccine efficacy trials. Lessons learned from COVID-19 highlight the need for innovative and flexible study design and application to quickly identify promising candidate vaccines. Trial design strategies should be tailored to the dynamics of the specific pathogen, location of the outbreak, and vaccine prototypes, within the regional socioeconomic constraints. Mathematical and statistical models can assist investigators in designing infectious disease clinical trials. We introduce key challenges for planning, evaluating, and modelling vaccine efficacy trials for emerging pathogens.

START COMMENTARY

In this review, Madewell *et al.* present the unique challenges of vaccine efficacy trials for emerging infectious diseases. This commentary is impactful as it demonstrates that the typical vaccine development and approval process (which typically takes 10-15 years) is not useful for disease outbreaks. Delays between understanding the pathogen (e.g., viral reservoirs, transmission routes), the incidence and duration, and vaccine characteristics (e.g., optimal dosage, side effects) can allow for a pathogen to spread globally. The authors describe the importance of emergency use authorization in streamlining the regulatory process. However, this process does not address issues post-approval, such as mass production, access, cold chain capacity, and vaccine hesitancy related to a fast approval process. Other challenges include unpredictable incidence and waning transmission. Some challenges are related specifically to conducting trials, including how to quickly implement them, collect data frequently, maintain a placebo arm, and analyze results (including evaluating effects on infectiousness, estimating indirect, total, and overall effects). Further, there is a critical need to continuously evaluate a vaccine effectiveness and efficacy with an evolving pathogen. A couple of recommendations to address these challenges include considering alternate study designs (e.g., cross over studies, non-inferiority trials) and preparing protocols and ethical

review documents for studies before outbreaks occur to reduce delays. Overall, Madewell *et al.* summarize challenges and how they may be overcome in innovative vaccine trial designs.

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5. [Strategies for vaccine-product innovation: Creating an enabling environment for product development to uptake in low- and middle-income countries.](#)

Giersing B, Shah N, Kristensen D, Amorij J, Kahn A, Gandrup-Marino K, et al.

ABSTRACT

Vaccine-product innovations that address barriers to immunization are urgently needed to achieve equitable vaccine coverage, as articulated in the new Immunization Agenda 2030 and the Gavi 5.0 strategy. In 2020, the Vaccine Innovation Prioritisation Strategy (VIPS) prioritized three innovations, namely microarray patches (MAPs), heat-stable and controlled-temperature chain (CTC) enabled liquid vaccine formulations and barcodes on primary packaging. These innovations were prioritized based on the priority immunization barriers that they may help overcome in resource constrained contexts, as well as by considering their potential impact on health, coverage and equity, safety, economic costs and their technical readiness and commercial feasibility. VIPS is now working to accelerate the development and lay the foundation for future uptake of the three priority vaccine-product innovations, with the long term-goal to ensure equitable vaccine coverage and increased impact of vaccines in low- and middle- income countries. To inform our strategic planning, we analyzed four commercially available vaccine product-innovations and conducted interviews with individuals from 17 immunization organizations, and/or independent immunization experts. The findings are synthesized into an 'innovation conundrum' that describes the challenges encountered in developing vaccine-product innovations and a vaccine-product innovation 'theory of change', which highlights actions that should be undertaken in parallel to product development to incentivize sustainable investment and prepare the pathway for uptake and impact.

START COMMENTARY

In this review, Giersing *et al.* describe vaccine production innovation through four case studies and interviews with 17 immunization partner stakeholders. This study is important as it describes the urgent need for innovative vaccines which address context-specific barriers to immunization. It describes priority innovations (i.e., microarray patches [MAPs], heat-stable and controlled-temperature chain [CTC], and barcodes on packaging), case studies including challenges and

drivers of success, and lessons learned. The four case studies include Auto-disable (AD) syringes (*Box 1),* a Uniject compact prefilled AD device (*Box 2)*, a disposable syringe jet injector (*Box 3),* and heat-sensitive vaccine vial monitors (*Box 4).* The authors identified several characteristics related to successful development and uptake of the innovations in the case studies, including the articulation of a clear public health need, simple solutions which are appealing for investment, financing for all stages of development, broad applicability (i.e., the innovation can be used for several vaccines), and lower cost products (which are considered less risky). Giersing *et al.* also describe challenges (coined 'the Innovation Conundrum') (*Figure 2).* Root causes of these challenges include a lack of alignment across different types of stakeholders, a lack of clear articulation of value for countries, funders, and manufacturers, and an insufficient understanding of country needs, priorities, and preferences. One strength of this article is that the authors present recommendations for three outcomes that can create a vaccine-production innovation environment. The three outcomes are: 1) clarity on country perspectives and priorities; 2) an aligned partnership and sustained resources; and 3) de-risked investments for vaccine manufacturers and innovation developers. These outcomes are presented as part of a detailed theory of change in *Figure 3.* These insights are critical to transform vaccine-productive innovation environments to improve vaccine coverage and equity.

6. [Drought and child vaccination coverage in 22 countries in sub-Saharan Africa: A retrospective analysis of national survey data from 2011 to 2019.](#)

Nagata J, Epstein A, Ganson K, Benmarhnia T, Weiser S.

ABSTRACT

BACKGROUND: Extreme weather events, including droughts, are expected to increase in parts of sub-Saharan Africa and are associated with a number of poor health outcomes; however, to the best of our knowledge, the link between drought and childhood vaccination remains unknown. The objective of this study was to evaluate the relationship between drought and vaccination coverage.

METHODS AND FINDINGS: We investigated the association between drought and vaccination coverage using a retrospective analysis of Demographic and Health Surveys data in 22 sub-Saharan African countries among 137,379 children (50.4% male) born from 2011 to 2019. Drought was defined as an established binary variable of annual rainfall less than or equal to the 15th percentile relative to the 29 previous years, using data from Climate Hazards Group InfraRed Precipitation with Station (CHIRPS) data. We evaluated the association between drought at the date of birth and receipt of bacillus Calmette-Gu.rin (BCG), diphtheria-pertussis-tetanus (DPT), and polio vaccinations, and the association between drought at 12 months of age and receipt of measles vaccination. We specified logistic regression models with survey fixed effects and standard errors clustered at the enumeration area level, adjusting for child-, mother-, and household-level covariates and estimated marginal risk differences (RDs). The prevalence of drought at date of birth in the sample was 11.8%. Vaccination rates for each vaccination ranged from 70.6% (for 3 doses of the polio vaccine) to 86.0% (for BCG vaccination); however, only 57.6% of children 12 months and older received all recommended doses of BCG, DPT, polio, and measles vaccinations. In adjusted models, drought at date of birth was negatively associated with BCG vaccination (marginal RD = -1.5; 95% CI -2.2, -0.9), DPT vaccination (marginal RD = -1.4; 95% CI -2.2, -0.5), and polio vaccination (marginal RD = -1.3; 95% CI -2.3, -0.3). Drought at 12 months was negatively associated with measles vaccination (marginal RD = -1.9; 95% CI -2.8, -0.9). We found a dose-response relationship between drought and DPT and polio vaccinations, with the strongest associations closest to the timing of drought. Limitations include some heterogeneity in findings across countries.

CONCLUSIONS: In this study, we observed that drought was associated with lower odds of completion of childhood BCG, DPT, and polio vaccinations. These findings indicate that drought may hinder vaccination coverage, one of the most important interventions to prevent infections among children. This work adds to a growing body of literature suggesting that health programs should consider impacts of severe weather in their programming.

START COMMENTARY

In this retrospective study, national survey data from 22 countries in Africa was combined with historical rainfall data from 2011 to 2019 to estimate the association between drought and childhood vaccination completion. This study is impactful as extreme weather events, such as droughts, are expected to increase in sub-Saharan Africa and are linked to poor health outcomes. However, the association between droughts and childhood immunization has not been studied. Immunization data was obtained from vaccination cards and mothers' report during Demographic and Health Surveys (DHS) and included Bacillus Calmette-Guerin (BCG), Diphtheria-Pertussis-Tetanus (DPT), polio, and measles vaccines (doses and ages of children included are described in *Table 1)*. Droughts were determined using Climate Hazards Group InfraRed Precipitation with Station (CHIRPS) data. Drought was defined as annual precipitation in the 12 months prior to the exposure time point equal or lower than 15% of the historical record in the past 30 years, a cut off is based on previous literature. Two strengths of this analysis is that the authors explored whether findings were sensitive to this definition by analyzing rainfall as a continuous measure and using values closer to 0 as more severe drought, Additionally, the authors used historical (30-year) data rather than absolute rainfall which can be unreliable. Covariates included sociodemographic variables for the child and mother (e.g., sex, birth order, education, marital status).

In total, 137,379 children were included in the analysis. Vaccination rates were lowest for polio (70.7%) and highest for BCG (86.1%). Drought at birth was lowest in Guinea (0.7% of births) and highest in South Africa (32.1% of births) (*Figure 1*). After controlling for covariates, drought at birth was significantly associated with decreased likelihood of vaccination (-1.5 percentage points for BCG, 95% CI: −2.2, −0.9); -1.4 percentage points for DPT, 95% CI: -2.3, -0.5, and -1.3 percentage points for polio, 95% CI -2.3, -0.3) compared to children born at dates without drought. For drought at 12 months, the trend was similarly statistically significant for measles (-1.9 percentage points) compared to children at 12 months without drought. Similar associations were shown between drought at birth/at 12 months and full vaccination, although these varied by country (*Figure 2).* Overall, this study shows that droughts can impact childhood vaccination coverage, indicating that extreme weather should be considered in immunization programming.

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7. Implications of armed conflict for maternal and child health: A regression analysis of data from 181 countries for 2000-2019.

Jawad M, Hone T, Vamos E, Cetorelli V, Millett C.

ABSTRACT

BACKGROUND: Armed conflicts have major indirect health impacts in addition to the direct harms from violence. They create enduring political instability, destabilise health systems, and foster negative socioeconomic and environmental conditions-all of which constrain efforts to reduce maternal and child mortality. The detrimental impacts of conflict on global maternal and child health are not robustly quantified. This study assesses the association between conflict and maternal and child health globally.

METHODS AND FINDINGS: Data for 181 countries (2000-2019) from the Uppsala Conflict Data Program and World Bank were analysed using panel regression models. Primary outcomes were maternal, under-5, infant, and neonatal mortality rates. Secondary outcomes were delivery by a skilled birth attendant and diphtheria, pertussis, and tetanus (DPT) and measles vaccination coverage. Models were adjusted for 10 confounders, country and year fixed effects, and conflict lagged by 1 year. Further lagged associations up to 10 years post-conflict were tested. The number of excess deaths due to conflict was estimated. Out of 3,718 country-year observations, 522 (14.0%) had minor conflicts and 148 (4.0%) had wars. In adjusted models, conflicts classified as wars were associated with an increase in maternal mortality of 36.9 maternal deaths per 100,000 live births (95% CI 1.9-72.0; 0.3 million excess deaths [95% CI 0.2 million-0.4 million] over the study period), an increase in infant mortality of 2.8 per 1,000 live births (95% CI 0.1-5.5; 2.0 million excess deaths [95% CI 1.6 million-2.5 million]), a decrease in DPT vaccination coverage of 4.9% (95% CI 1.5%-8.3%), and a decrease in measles vaccination coverage of 7.3% (95% CI 2.7%-11.8%). The long-term impacts of war were demonstrated by associated increases in maternal mortality observed for up to 7 years, in under-5 mortality for 3-5 years, in infant mortality for up to 8 years, in DPT vaccination coverage for up to 3 years, and in measles vaccination coverage for up to 2 years. No evidence of association between armed conflict and neonatal mortality or delivery by a skilled birth attendant was found. Study limitations include the ecological study design, which may mask sub-national variation in conflict intensity, and the quality of the underlying data.

CONCLUSIONS: Our analysis indicates that armed conflict is associated with substantial and persistent excess maternal and child deaths globally, and with reductions in key measures that indicate reduced availability of organised healthcare. These findings highlight the importance of

protecting women and children from the indirect harms of conflict, including those relating to health system deterioration and worsening socioeconomic conditions.

START COMMENTARY

In this longitudinal study, Jawad *et al.* explore the indirect impacts of armed conflict on maternal and child health globally. This study makes a critical contribution as there is limited evidence on the maternal and child population impacts of armed conflict. This study determines the number of excess maternal and child deaths attributed to armed conflict. Further, Jawad *et al.* considered longer term impacts (i.e., lagged associations for up to 10 years post-conflict), which have similarly been understudied globally. Conflict data was obtained from the Uppsala Conflict Data Program Georeferenced Event Dataset (UCDP EGC). Conflict events are defined as "the use of armed force by an organized actor against another organized actor or civilians, resulting in at least one death for that location and time." Health outcomes, including maternal, under-5, infant, and neonatal mortality, delivery by a skilled birth attendant, and vaccine coverage of DTP and measles among 12-23 month old children were obtained from the UN Maternal Mortality Estimation Inter-Agency Group and the UN Inter-Agency Group for Child Mortality Estimation. Covariates included measures to capture changes in wealth, the pollical system, demographics, population education, and ciliate-related factors. One limitation is that conflict duration was not taken into account.

Armed conflict was present in 18% of the observation period (i.e., 670 of the 3,718 country-year observations), most were minor conflict (77.9%). In adjusted analyses, conflict was associated with an average absolute increase in maternal mortality of 22.5 per 100,000 (95% CI 1.7–43.2), with higher absolute increases in conflicts classified as wars (36.9 per 100,000), which resulted in an excess 0.3 million maternal deaths. Although mean under-5 and neonatal mortality were higher in conflict-affected areas, these results were not significant in adjusted analyses. In adjusted regression models, conflicts classified as wars were associated with an increase of 2.8 infant deaths per 1,000 live births (95% CI 0.1-5.9), leading an estimated 2 million excess infant deaths. Armed conflict was shown to be associated with a reduction in measles vaccination (2.6%, 95% CI: 0.2%-5.0) and war was associated with 4.9% and 7.3% reduction in DTP and measles, respectively. Many of these negative results persist for years (7 years for maternal mortality and 8 years for infant mortality).

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8. [Microplanning for designing vaccination campaigns in low-resource settings: A geospatial artificial intelligence-based framework.](#)

Augusto Hernandes Rocha T, Grapiuna de Almeida D, Shankar Kozhumam A, Cristina da Silva N, B.rbara Abreu Fonseca Thomaz E, Christine de Sousa Queiroz R, et al.

ABSTRACT

Existing campaign-based healthcare delivery programs used for immunization often fall short of established health coverage targets due to a lack of accurate estimates for population size and location. A microplan, an integrated set of detailed planning components, can be used to identify this information to support programs such as equitable vaccination efforts. Here, we presents a series of steps necessary to create an artificial intelligence-based framework for automated microplanning, and our pilot implementation of this analysis tool across 29 countries of the Americas. Further, we describe our processes for generating a conceptual framework, creating customized catchment areas, and estimating up-to-date populations to support microplanning for health campaigns. Through our application of the present framework, we found that 68 million individuals across the 29 countries are within 5.km of a health facility. The number of health facilities analyzed ranged from 2 in Peru to 789 in Argentina, while the total population within 5.km ranged from 1,233 in Peru to 15,304,439 in Mexico. Our results demonstrate the feasibility of using this methodological framework to support the development of customized microplans for health campaigns using open-source data in multiple countries. The pandemic is demanding an improved capacity to generate successful, efficient immunization campaigns; we believe that the steps described here can increase the automation of microplans in low resource settings.

START COMMENTARY

In this study, Rocha *et al.* present steps for automated geographic information system and artificial intelligence (GeoAI) microplanning immunization programs, which could help to identify target populations. This purpose of these methodological steps are to accurately estimate up-to-date target populations and their locations using open-source databases. Rocha *et al.* demonstrate this process across 29 American countries. Population and settlement distributions can be layered with spatial covariates to develop gridded population datasets. A detailed description of the datasets used are described in *Table 1.* Health facility locations can be obtained from OpenStreetMap and

Healthsites.io, although these may be limited in some geographies. Based on population, health facility, and the transportation network, customized catchment areas for each facility can be built. Once the populations are identified, a microplan which consists of resource estimation, cold-chain logistics, operations, supervision, recording and reporting tools, and a monitoring framework can be developed. Of the 29 countries assessed, the number of people within five kilometers (km) of a health facility ranged from 1,233 in Peru to 15,304,439 in Mexico. Considering this five km distance, it is possible to cover 68 million people across the 29 countries. The results of spatial analyses of facilities are presented in *Figure 2.* Strengths of this study include the use of advanced technologies (GIS, AI, and data mining) and publicly-available data, which makes these steps generalizable to other countries. The authors provide an ArcGIS toolbox which runs all of the describe analytical steps. This study demonstrates the feasibility of using GeoAI microplanning to improve access to vaccines.

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9. Vaccine complacency and dose distribution inequities limit the benefits of seasonal influenza vaccination, despite a positive trend in use.

Palache A, Rockman S, Taylor B, Akcay M, Billington J, Barbosa P.

ABSTRACT

Sustainable demand for seasonal influenza vaccines is a component of national security strategies for pandemic preparedness. However, the ongoing COVID-19 pandemic has revealed many weaknesses in the capacity of countries to design and execute sustainable vaccination programs. An influenza pandemic remains a global threat and yet there is no global monitoring system for assessing progress towards influenza vaccination coverage targets. The International Federation of Pharmaceutical Manufacturers and Associations' (IFPMA) Influenza Vaccine Supply International Task Force (IVS) developed a survey method in 2008 to estimate seasonal influenza vaccination coverage rates, which in turn serves as a crude estimate of pandemic preparedness. It provides evidence to guide expanded efforts for pandemic preparedness, specifically for increasing COVID-19 vaccine immunization levels. Furthermore, the results presented herein serve as a proxy for assessing the state of pandemic preparedness at a global and regional level. This paper adds data from 2018 and 2019 to the previous analyses. The current data show an upward or stable global trend in seasonal influenza vaccine dose distributed per 1,000 population with a 7% increase between 2017 and 2018 and 6% increase between 2018 and 2019. However, considerable regional inequities in access to vaccine persist. Three regions, Africa, the Middle-east, and Southeast Asia together account for 50% of the global population but only 6% of distributed seasonal influenza vaccine doses. This is an important finding in the context of the ongoing COVID-19 pandemic, as distribution of influenza vaccine doses in many ways reflects access to COVID-19 vaccines. Moreover, improving seasonal vaccine uptake rates is critical for optimizing the annual benefits by reducing the huge annual influenza-associated societal burdens and by providing protection to vulnerable individuals against serious complications from seasonal influenza infections.

START COMMENTARY

This study presents seasonal influenza vaccine distribution data from 2018 and 2019 from the International Federation of Pharmaceutical Manufacturers and Associations' (IFPMA) Influenza Vaccine Supply International Task Force to understand pandemic preparedness on a regional and

global level. This data was combined with prior IFPMA IVS' surveys from 2004-2017. Surveys cover 90% of all influenza vaccine manufacturers, who are based in 13 countries. Parameters included to assess changes in the distribution of seasonal influenza vaccines were: 1) the number of countries in which influenza vaccines were distributed; 2) absolute number of seasonal influenza vaccine doses distributed; 3) number of doses distributed to each country per 1,000 persons; and 4) annual number of countries with doses distributed to ≥15.9% of the population rate (termed 'the hurdle rate'). Population sizes of countries were also considered in the analyses.

Findings included that the number of countries distributing seasonal influenza vaccines increased from 108 in 2004 to 134 in 2019. Similarly, 262 million doses were distributed in 2004 compared to 531 million in 2019. Despite this upward trend, recent years (from 2014 to 2019) have seen a 0.3% decline in doses distributed. In 2004, only 16 countries had distributed doses over the hurdle rate compared to 31 in 2019. An estimated 41 influenza doses per 1,000 population were distributed in 2004 compared to 70 per 1,000 in 2019, indicating modest growth. *Figure 2* depicts the variation in five-year averages of the number of doses of seasonal influenza vaccines by WHO region and *Figure 3* shows the percentage vaccine distribution per population in WHO region in 2019. This study shows the positive trends in seasonal influenza vaccine distribution, while noting the global inequities (e.g., that 50% of the global population has access to 6% of the global share of doses), which is important information for future programs and polices aimed at increasing access to seasonal influenza vaccines.

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10. [Short message service (SMS) reminders for childhood immunisation in low-income and middle-income countries: a systematic review and meta-analysis.](#)

Eze P, Lawani L, Acharya Y.

ABSTRACT

INTRODUCTION: Childhood vaccine delivery services in the low- and middle-income countries (LMIC) are struggling to reach every child with lifesaving vaccines. Short message service (SMS) reminders have demonstrated positive impact on a number of attrition-prone healthcare delivery services. We aimed to evaluate the effectiveness of SMS reminders in improving immunisation coverage and timeliness in LMICs.

METHODS: PubMed, Embase, Scopus, Cochrane CENTRAL, CINAHL, CNKI, PsycINFO and Web of Science including grey literatures and Google Scholar were systematically searched for randomised controlled trials (RCTs) and non-RCTs that evaluated the effect of SMS reminders on childhood immunisation and timeliness in LMICs. Risk of bias was assessed using the Cochrane Risk of Bias 2.0 assessment tool for RCTs and Cochrane Risk of Bias in Non-randomised Studies of Interventions tool for non-RCTs. Meta-analysis was conducted using random-effects models to generate pooled estimates of risk ratio (RR).

RESULTS: 18 studies, 13 RCTs and 5 non-RCTs involving 32, 712 infants (17,135 in intervention groups and 15, 577 in control groups) from 11 LMICs met inclusion criteria. Pooled estimates showed that SMS reminders significantly improved childhood immunisation coverage (RR=1.16; 95% CI: 1.10 to 1.21; I2=90.4%). Meta-analysis of 12 included studies involving 25, 257 infants showed that SMS reminders significantly improved timely receipt of childhood vaccines (RR=1.21; 95% CI: 1.12 to 1.30; I2=87.3%). Subgroup analysis showed that SMS reminders are significantly more effective in raising childhood immunisation coverage in lower middle-income and low-income countries than in upper middle-income countries (p<0.001) and sending more than two SMS reminders significantly improves timely receipt of childhood vaccines than one or two SMS reminders (p=0.040).

CONCLUSION: Current evidence from LMICs, although with significant heterogeneity, suggests that SMS reminders can contribute to achieving high and timely childhood immunisation coverage.

PROSPERO REGISTRATION NUMBER: CRD42021225843.

START COMMENTARY

In this systematic review and meta-analysis, Eze *et al.* assess the association between short message service (SMS) reminders and childhood immunization coverage. This study is impactful as it quantifies the impact of SMS reminders, which are widely used interventions to improve health outcomes. Inclusion criteria for studies were 1) population including mothers of children <24 months of age; 2) interventions which provided messages related to childhood immunization; 3) a comparison group of usual care (i.e., standard reminders at the health center, written appointments); 4) effectiveness determined by DTP-3, Penta-3, or overall childhood immunization uptake and/or timeliness; and 5) a randomized or non-RCT interventional study.

In total, 18 studied met inclusion criteria. Most (n=13) were RCTs and peer reviewed and published (n=17). The studies represented 32,712 infants in the intervention groups and 15,557 in the control groups across 11 countries. The risk of bias assessment found that 6 of 13 RCTs had a low risk of bias, 5 had some concerns of bias, and 2 had a high risk of bias. However, 4 of 5 non-RCTs were deemed to have serious/critical risk of bias. Of the 18 studies, 12 showed that SMS reminders significantly improved immunization coverage in the intervention group compared to the control. Similar results were shown in the meta-analysis (RR: 1.16, 95% CI: 1.10-1.21). Eze *et al.* performed subgroup analyses which showed substantial differences in effect size based on the country's income and the study's quality. Outcomes for each individual study are described in detail in *Table 1.* Of studies which assessed timeliness (n=12), 10 showed significant improvement in timely receipt of vaccines compared to the comparison group. Overall, despite differences in quality of studies, the magnitudes and direction of associations between SMS reminders and immunization outcomes demonstrate strong evidence. SMS reminders should be used for future vaccine efforts, particularly in LMICs where phones are ubiquitous and vaccine coverage rates are low.

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Appendix

The literature search for the November 2021 Vaccine Delivery Research Digest was conducted on October 27, 2021. We searched English language articles indexed by the US National Library of Medicine and published between September 15, 2021, and October 14, 2021. The search resulted in 622 items.

SEARCH TERMS

(((((vaccine[tiab] OR vaccines[tiab] OR vaccination[tiab] OR immunization[tiab] OR immunisation[tiab] OR vaccine[mesh] OR immunization[mesh]) AND (logistics[tiab] OR supply[tiab] OR "supply chain"[tiab] OR implementation[tiab] OR expenditures[tiab] OR financing[tiab] OR economics[tiab] OR "Cost effectiveness"[tiab] OR coverage[tiab] OR attitudes[tiab] OR belief[tiab] OR beliefs[tiab] OR refusal[tiab] OR "Procurement"[tiab] OR timeliness[tiab] OR systems[tiab])) OR ("vaccine delivery"[tiab])) NOT ("in vitro"[tiab] OR "immune response"[tiab] OR gene[tiab] OR chemistry[tiab] OR genotox*[tiab] OR sequencing[tiab] OR nanoparticle*[tiab] OR bacteriophage[tiab] OR exome[tiab] OR exogenous[tiab] OR electropor*[tiab] OR "systems biology"[tiab] OR "animal model"[tiab] OR cattle[tiab] OR sheep[tiab] OR goat[tiab] OR rat[tiab] OR pig[tiab] OR mice[tiab] OR mouse[tiab] OR murine[tiab] OR porcine[tiab] OR ovine[tiab] OR rodent[tiab] OR fish[tiab])) AND (English[LA]) ("2021/09/15"[PDAT] : "2021/10/14"[PDAT]))