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RESEARCH ARTICLE

REVISED Modeling anticipated changes in numbers of SARS-CoV-2 infections within communities due to immunization campaigns [version 2; peer review: 2 approved]

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Abstract

Background: As SARS-CoV-2 spread in early 2020, uncertainty about the scope, duration, and impact of the unfolding outbreaks caused numerous countries to interrupt many routine activities, including health services. Because immunization is an essential health service, modeling changes in SARS-CoV-2 infections among communities and health workers due to different vaccination activities was undertaken to understand the risks and to inform approaches to resume services.
Methods: Agent-based modeling examined the impact of Supplemental Immunization Activities (SIAs) delivery strategies on SARS-CoV-2 transmission in communities and health workers for six countries capturing various demographic profiles and health system performance: Angola, Ecuador, Lao PDR, Nepal, Pakistan, and Ukraine.
Results: Urban, fixed-post SIAs during periods of high SARS-CoV-2 prevalence increased infections within the community by around 28 [range:0-79] per 1000 vaccinations. House-to-house SIAs in mixed urban and rural contexts may import infections into previously naïve communities. Infections are elevated by around 60 [range:0-230] per 1000 vaccinations, but outcomes are sensitive to prevalence in health workers and SIA timing relative to peak.
Conclusions: Incremental increases in SARS-CoV-2 infection due to SIAs was small and in proportion to overall prevalence. Younger populations experience lower transmission intensity and fewer excess infections per childhood vaccine delivered. Large rural populations have lower transmission intensity but face a greater risk of introduction of SARS-CoV-2 during an SIA.

Keywords
SARS-CoV-2, agent-based modeling, vaccine delivery

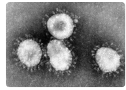This article is included in the Coronavirus (COVID-19) collection.

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Author roles: Frey K: Data Curation, Formal Analysis, Investigation, Methodology, Software, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Hagedorn B**: Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Resources, Supervision, Validation, Writing – Original Draft Preparation, Writing – Review & Editing; **McCarthy KA**: Project Administration, Resources, Supervision, Writing – Review & Editing; **Hutubessy R**: Conceptualization, Methodology, Supervision, Writing – Review & Editing; **Wang SA**: Conceptualization, Methodology, Supervision, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

How to cite this article: Frey K, Hagedorn B, McCarthy KA *et al.* **Modeling anticipated changes in numbers of SARS-CoV-2 infections within communities due to immunization campaigns [version 2; peer review: 2 approved]** Gates Open Research 2022, **6**:7 https://doi.org/10.12688/gatesopenres.13448.2

First published: 09 Feb 2022, **6**:7 https://doi.org/10.12688/gatesopenres.13448.1

Abbreviations

CMCC   COVID-19 Multi-Model Comparison Collaboration

CSSE   Center for Systems Science and Engineering

DTP3   Third dose diphtheria, tetanus toxoid, and pertussis combined vaccine

EMOD   Epidemiological MODeling software

EPI   Essential Programme on Immunization

FP   Fixed-post

GPEI   Global Polio Eradication Initiative

H2H   House-to-house

HW   Health worker

IPC   Infection prevention and control

LMIC   Low- and middle-income countries

RATR   Relative acquisition and transmission rate

SIA   Supplemental Immunization Activity

VPD   Vaccine Preventable Disease

WHO   World Health Organization

Introduction

The novel coronavirus SARS-CoV-2 spread globally and became a pandemic in early 2020. In March 2020, the WHO issued interim guidance[1] emphasizing the need to prioritize continuity of immunization services wherever they could be conducted safely and advised temporary suspension of mass vaccination campaigns based on the recommendations for physical distancing and the understanding of SARS-CoV-2 transmission. As a result of the pandemic, many countries postponed or cancelled planned SIAs in 2020 against polio[2], measles[3], cholera, yellow fever, and other VPDs[4].

SIA delay was driven by concerns over risks of SARS-CoV-2 transmission via SIAs, but there are also health risks, particularly to vulnerable populations, of delay[5]. In addition, health systems weakened by the COVID-19 pandemic are unable to keep up with day-to-day healthcare needs[6], which may leave those who are affected by non-COVID-19 illness more vulnerable to morbidity and mortality. Many countries reconsidered earlier choices to postpone SIAs, rescheduling them to occur during the ongoing pandemic[7–9]. The risks of SARS-CoV-2 transmission need to be balanced with the benefits of an SIA. To this end, the WHO published a framework to assist countries with making decisions regarding whether to implement preventive mass vaccination campaigns[10].

Routine immunization coverage has also been affected. Reductions in coverage have been documented in communities such as Karachi, Pakistan[11] and globally, the WHO reports that more than half of countries with available data had moderate or severe disruptions to immunization services[12]. The reasons are attributable to a variety of factors, including diversion of health workers to COVID-19 response, lockdowns preventing transportation or community movement, and subsequent reduction in numbers of families seeking immunization for their children, reduced numbers of immunization days in clinic, and less frequent outreach services being offered.

The purpose of the study was to estimate, using one country from each WHO region and spanning a range of COVID-19 disease burden settings, the anticipated changes in numbers of SARS-CoV-2 infections in communities due to immunization campaigns.

Methods

Example country selection

We selected six countries representing upper-middle, lower-middle, and low-income contexts; they included priority countries for the Essential Programme on Immunization (EPI) and for the Global Polio Eradication Initiative (GPEI). A country was chosen from each of the six WHO regions. We compared countries across six indicators: percentage coverage of DTP3, number of nurses per thousand total population, percentage of population under 15 years old, human development index, percentage of population living in a rural setting, and percentage of population living in a slum or informal settlement. Selected countries represent different demographics, social structure, overall economic development, and health system strength, to span the range of indicator values. Explanations of indicators, data sources, and 2019 values for other LMIC countries can be found in the *Extended data*[13].

Transmission modeling

Forecasts were generated using EMOD, an individual-based disease modeling platform[14] that has been reviewed by the COVID-19 Multi-Model Comparison Collaboration (CMCC)[15]. Additional details can be found in the *Extended data*[13]. Simulations were intended to represent SARS-CoV-2 progression in the chosen contexts and parameter values used appropriate for the respective countries.

Infections were represented by a latent period followed by an infectious period. The progression of disease within each person was stochastically variable in duration. At the end of the infectious period, the person is given total immunity from subsequent infection, as was the case early in the pandemic when these questions were being considered. Immunity is assumed to not wane over the course of the simulation. Parameters correspond to a median generation interval of about 6 days. This interval is not specified as an input parameter but

is observable in the simulation results and is a consequence of the epidemiological parameters that were input.

A total population of 1M people was used for each simulation. Each simulated person is assigned to an age cohort according to the demographics of the simulated country. Contact rates between simulated persons in the model are stratified across four routes (school, home, work, and community) and sixteen age groups (5-year age groups up to 75 years old, and one age group for those 75+ years old) using published model estimates[16], and by risk levels (low, medium, and high). Risk levels provide additional variance within age group without altering mean contact rates.

The baseline distancing scenario for each country assumes school closures, reduced work contacts, and restricted community gatherings (contact rates for school, work, and community are reduced to 0%, 50%, and 75%, respectively, from the values in 17). For all distancing policies involving a reduction in work contacts or school contacts, twenty percent of the reduced contacts were redistributed to the home route to reflect extra time spent in the home. No community contacts were redistributed to the home route.

For each country, the model was used to fit a most-likely R_0 value and case reporting rate to match reported case counts during the initial outbreak period; case count data were obtained from the COVID-19 Data Repository by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University <https://github.com/CSSEGISandData/COVID-19>[18]. Summary data are included in Table 1. Additional details on infectivity calibration can be found in the *Extended data*[13]. The indicated value for R_0 in Table 1 does not account for distancing policy and variable susceptibility with age. Contact fractions by route in Table 1 are input parameters from published model estimates[16]; the R_0 values were estimated in this study.

Reduced susceptibility among children is a significant unknown. Several publications[19–24] suggest that the under-15-year-old cohort acquires and transmits SARS-CoV-2 infections at a lower rate than the general population. This model incorporates a reduction in childhood acquisition of about 55% and childhood transmission of 15%, which has a substantial impact on transmission intensity, reducing the total attack rate and slowing the speed of the outbreak. These estimates are only appropriate to the ancestral SARS-CoV-2 strain examined in this work and may not be relevant to any of the variant lineages. Details on the effect of reduced childhood susceptibility can be found in the *Extended data*[13].

Connectivity and migration between city centers, peri-urban and rural communities is also poorly documented in many LMICs. In our spatial model, we assume a single large population center, with the sizes of the other population centers (when present) distributed exponentially. These other population centers represent more rural locations and have a minimum population of 100 simulated persons (total simulation population is one million). The percentage of the population in the large population center is equal to the urban fraction of the country; urban fractions are calculated based on the rural fractions, assuming the urban and rural fractions sum to unity. A network of individual mobility between all population centers was based on the distance between and size of population centers. Modeling the outbreak of SARS-CoV-2 using this distributed community connectivity results in a slower growing and extended outbreak.

The 'urban' base case is representative of a single major population center without the network of rural locations, while the 'urban-rural' base case is representative of a major population center with surrounding rural locations. No simulations examine a rural-only setting. A rural-only setting would consist of a network of small populations without any single major center, and have outcomes dominated by the timing of disease introduction.

Individual importations often do not result in community transmission. Simulations use a low, constant rate of importation into urban centers (from an unspecified external source) to ensure that an outbreak occurs in urban locations. Rural locations do not include this external importation pressure, so rural locations are not guaranteed to experience an outbreak during a simulation. Outcomes for rural-only simulations would reflect this randomness of importations and would not be expected to provide useful insights.

Both types of base case depicted in Figure 1 are used when presenting results for this study.

In the 'urban-rural' base case, the urban fraction of the population is in the largest population center and the remainder of the population is distributed across smaller population centers. The x-axis describes the number of days post SARS-CoV-2 introduction to the community. Baseline scenarios for each country assume school closures, reduced work contacts, and restricted community gatherings.

Table 1. Baseline scenario contact rate fraction by route and estimated base reproductive number (R_0).

Country	Contact Rate Fraction by Route				R_0
	Home	School	Work	Community	
Angola	0.188	0.264	0.071	0.477	3.6
Ecuador	0.223	0.211	0.137	0.429	3.2
Lao PDR	0.195	0.222	0.067	0.516	3.0
Nepal	0.175	0.242	0.135	0.449	3.2
Pakistan	0.188	0.251	0.043	0.518	3.6
Ukraine	0.256	0.112	0.277	0.356	3.0
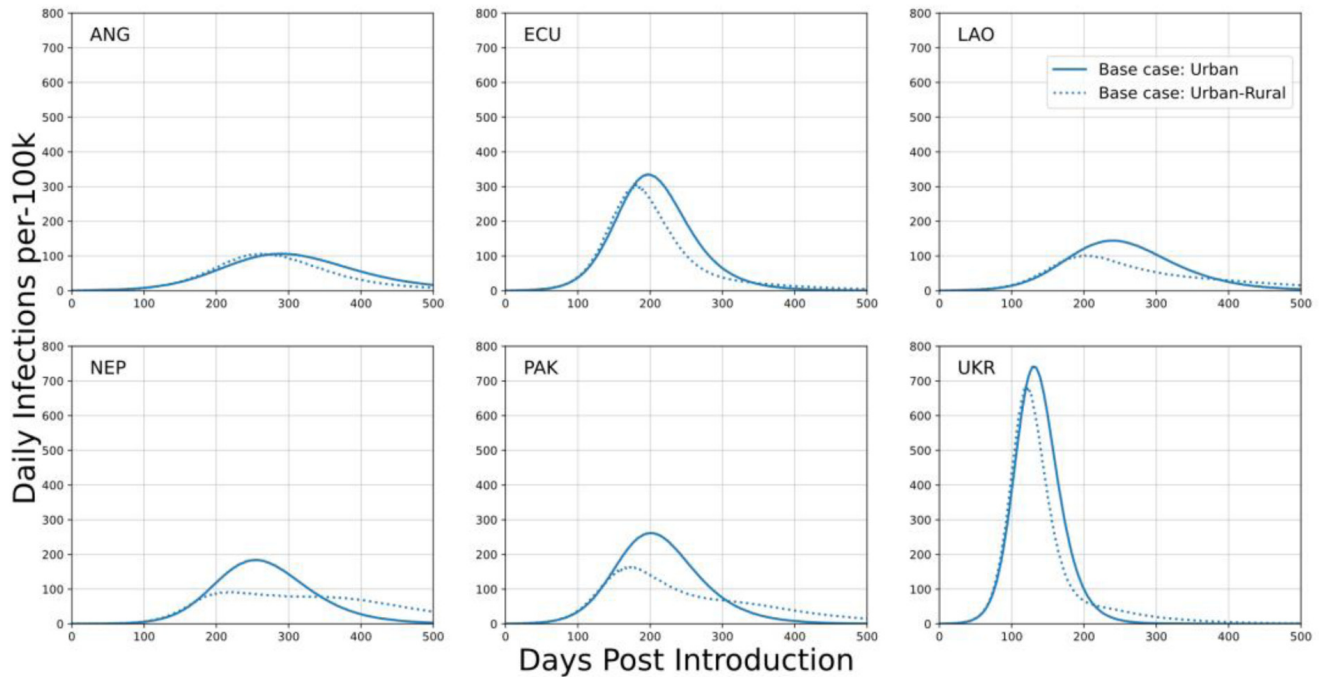
Figure 1. Daily infection trajectories per 100k population for the 'urban' base case and for the 'urban-rural' base case. In the 'urban-rural' base case, the urban fraction of the population is in the largest population center and the remainder of the population is distributed across smaller population centers. The x-axis describes the number of days post SARS-CoV-2 introduction to the community. Baseline scenarios for each country assume school closures, reduced work contacts, and restricted community gatherings.

Outcomes depicted in Figure 1 (and throughout) are trajectories of mean behavior based on ensembles of 1000 simulations. Timeseries are depicted with respect to 'days-post-introduction'; SARS-CoV-2 introduction to the community occurs at day-zero on this axis. No adaptive distancing policy is included in these scenarios. For instance, an outbreak as acute as depicted for the Ukraine setting would be expected to result in significant self-modification of behavior, which was not included or examined in this study.

These scenarios are illustrative of a wide range of potential outcomes, principally depending on the level of urbanization and shape of the population pyramid. Countries were selected as archetype contexts; the range of this variation is depicted in Figure 2 for all LMICs in the six WHO regions.

Representative country contexts examined in this study are annotated using larger markers. Size is only intended to highlight marker location.

Delivery scenarios
Base case scenarios do not attempt to quantify pre-pandemic levels of routine immunization services or reductions in those services that occurred due to social policy responses at the start of the pandemic. All the scenarios described below are incremental to the base case and the impact of each is calculated as the net difference between the delivery scenario described and this base case value.

Fixed-post (FP) SIAs were reflected in the model by adjusting the contact rates among different age cohorts for seven days, to reflect the community coming together to a central location and having some level of social interaction as well as travel. This was represented by a 50% increase in contacts within the under-5 cohort (children), a 50% increase in contacts among individuals in the 20–35-year-old cohort (their caregivers), and a 200% increase in contacts between the two groups. This scenario approximates a fixed-post SIA with a single-antigen delivered to children, during which vaccination is provided by a health worker who has brief interactions with each child and caregiver. In these scenarios, the increase in community contacts among and between the target population and their caregivers is the primary cause of additional SARS-CoV-2 infections.

House-to-house (H2H) SIAs were reflected in the model by adjusting the interaction rates between health workers and the general population, to reflect the process by which a vaccinator moves from one house to the next administering vaccinations. No changes were made to general community
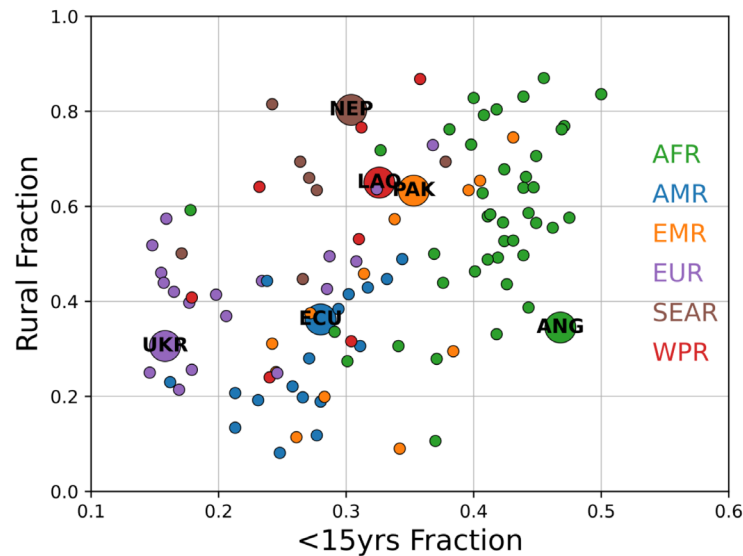
Figure 2. Variation in population fraction younger than 15yrs and rural population fraction in low- and middle-income countries for all six WHO regions. Representative country contexts examined in this study are annotated using larger markers. Size is only intended to highlight marker location..

contacts rates with each other. This implies that the children and their caregiverscontinue to abide by general distancing practices and no additional travel would be required.

To reflect house-to-house SIAs in mixed urban-rural scenarios, health workers were moved from the urban center to smaller communities. For these scenarios, vaccination outreach incorporates many more occurrences of long-distance travel than are present in the baseline mobility structure. In these house-to-house SIAs in rural locations, the potential for health workers to unintentionally introduce SARS-CoV-2 into communities not currently undergoing transmission is the primary cause of additional infections, which then cascade to further infections in the community.

In a typical measles SIA, a vaccinator is expected to deliver between 100–150 vaccinations per day in urban settings and 75–100 per day in more rural areas[25]. All scenario results report SARS-CoV-2 infections using a per-population basis (e.g., per-100k). Outcomes for fixed-post SIAs incorporate a fractional increase in the number of contacts among the target population and care givers, which accounts for the difference in target population sizes between the contexts. Outcomes for house-to-house SIAs account for the difference in target population sizes by scaling the number of health workers used by the size of the target population. SIA durations and frequency were not varied based on context; however, variations in timing independent of context were examined for sensitivity purposes.

Routine outreach was implemented similarly to a fixed-post SIA, with both children and adults experiencing a 20% increase

in intra-community contact rates. However, in the case of outreach, the health worker was expected to interact with both adults and children, since outreach events are intended to serve a wider population. They are also held periodically and consistently; for these purposes we assumed three days per month for a period of three months, with a cumulative 15% of the target population receiving health services.

Sensitivity analyses

Timing of the vaccination delivery, including scenarios where the delivery occurred prior to peak, near the peak, or after the peak of the SARS-CoV-2 outbreak, was examined as part of the sensitivity analysis.

Impact of infections within health worker populations were varied by simultaneously adjusting the acquisition and transmission rates of health workers; these variations were intended to represent the application of infection prevention and control (IPC) measures. Modifications affected both 1) the acquisition of SARS-CoV2 by the health worker if susceptible and 2) the transmission of SARS-CoV-2 by the health worker if infectious. Levels examined include relative acquisition and transmission rates (RATRs) of 20x, 15x, 10x, 5x, and 1x; levels are for health workers with respect to non-health worker individuals of similar ages. Effectively, these RATRs imply that healthcare workers are always at or above the level of risk of the general population. It is likely HW acquisition and transmission is asymmetric; onward transmission may be more strongly moderated than acquisition based on factors both controllable by health workers (e.g., mask wearing) and structural (e.g., occupational risk). Symmetry has been assumed in this model for simplicity.

The health worker cohort persists for the entire duration of the simulation, the RATRs in this cohort do not change during the vaccine delivery scenarios. Health workers are re-allocated to COVID-19 related tasks (SIAs) during task implementation periods but are assumed to be involved in other health-related activities during other periods. Health worker contact patterns did not follow the age structured matrix used for other groups, see additional file 1 for details. Relative acquisition and transmission rates should be interpreted as an input that controls the overall attack rate of the HW cohort; they capture the aggregate effect of IPC measures and do not correspond to or attempt to quantify the effect of any specific implementation of IPC (e.g., mask wearing or distancing).

Results
Routine outreach and fixed-post scenarios
Time to peak SARS-CoV-2 incidence varied by country. For comparability across contexts, vaccination events were timed with respect to time to peak SARS-CoV-2 incidence for the urban setting. These timings can be found in the *Extended data*[13]. Routine outreach scenarios did not result in outcomes different from the base case in either the urban only or the urban-rural settings. Mean trajectories were reproduced to within available precision.

Urban, fixed-post SIAs were implemented with respect to the time of SARS-CoV-2 peak incidence. Scenarios examined implementation of a single event 45 days before, 15 days before, 15 days after, or 45 days after peak incidence. Simulated outcomes in Figure 3 implemented each fixed-post SIA independently.

Impact of relative acquisition/transmission rates in health workers on transmission
Relative acquisition and transmission rates in health workers affect both the overall epidemic for the general population and the attack rate among health workers themselves. The 10x rate in health workers slightly reduces the time to peak incidence for the epidemic relative to the 1x rate, although this change tends to be small. Health workers are a small fraction of the total population (0.1%), but their contacts with vulnerable populations tend to give this cohort an outsized impact for its total size. In scenarios where health workers acquire and transmit infections at the 1x rate, the overall attack rate among health workers is reduced by between 40 to 63 percentage points, compared to scenarios where health workers acquire at the 10x rate (see Table 2).

Simulations are focused on disease transmission, and do not address the morbidity or mortality effects that may arise from a depletion of health workers availability due to COVID-19, which was documented in West Africa after the Ebola outbreak of 2014[26]. The impact of health worker infections on the progress of the overall epidemic in an urban setting is low or negligible for most contexts.
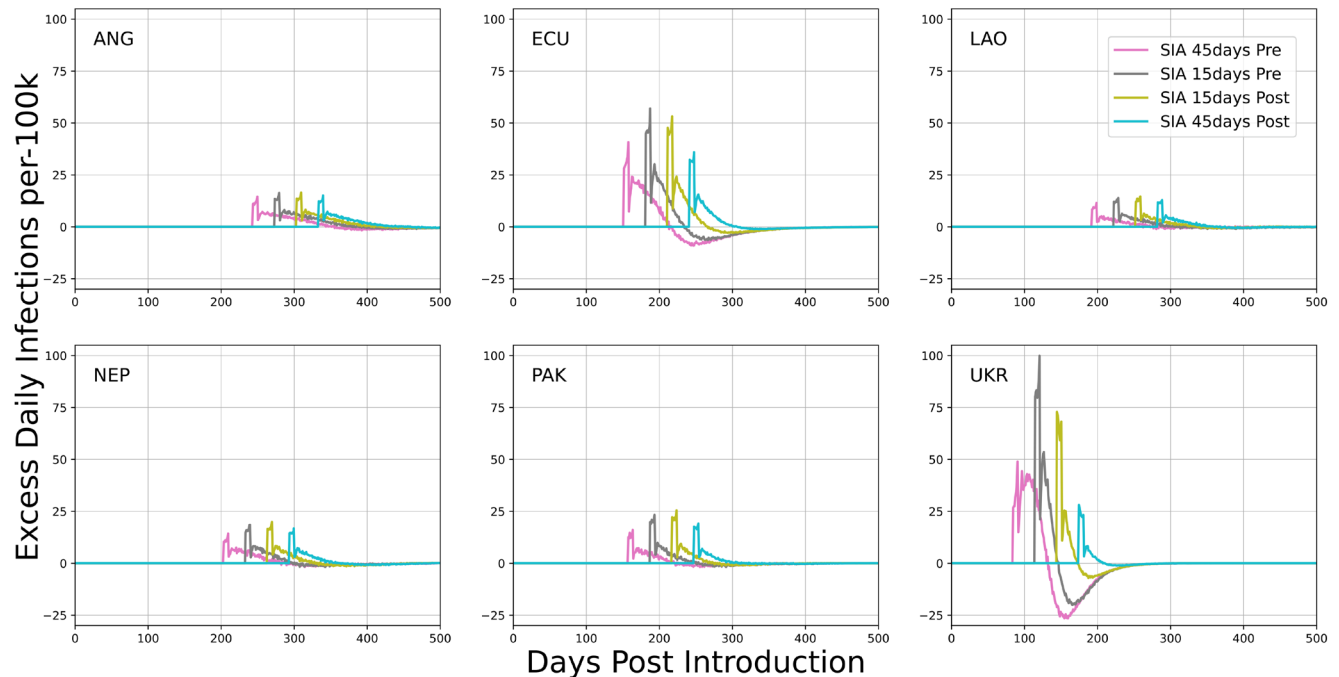
Figure 3. Mean excess daily SARS-CoV-2 infections per 100k individuals in each country examining fixed-post SIAs in urban simulations. Scheduling of SIAs is with respect to the time of peak incidence. The x-axis describes the number of days post SARS-CoV-2 introduction to the community.

Table 2. Overall SARS-CoV-2 attack rate among health workers (HW) for the two-year period of simulation when varying the relative acquisition/transmission rate (RATR) for the health worker cohort.

Country	Attack Rate (%) in Heath Workers for the Urban Setting				
	HW RATR 20x	HW RATR 15x	HW RATR 10x	HW RATR 5x	HW RATR 1x
Angola	91	86	75	51	13
Ecuador	99	99	97	86	34
Lao PDR	81	75	63	42	11
Nepal	83	80	77	65	24
Pakistan	88	83	71	48	13
Ukraine	99	99	99	98	59

Acquisition and transmission rates in the health worker cohort are inputs, and overall attack rates for health workers are strongly influenced by those inputs. Contact rates and patterns occurring outside of vaccination activities represent continuing healthcare activities undertaken by health workers. Results presented in Table 2 are the mean attack rates for health workers and in-part reflect the overall force of infection during the epidemic.

House-to-house scenarios

House-to-house SIAs in urban environments that occur around peak SARS-CoV-2 incidence did not have a measurable impact on infection rates. In these scenarios, health worker contact patterns and rates were reconfigured for the period of the SIA, but this reconfiguration did not result in an elevated number of infections. Ongoing transmission in the urban environment was the primary driver of infections in these house-to-house simulations. It is likely that the vaccination activities did cause additional SARS-CoV-2 infections, but not at a level that was distinguishable from expected base case transmission levels.

An important juxtaposition of this outcome is for house-to-house SIAs in mixed urban and rural environments. For the mixed urban-rural environments, urban health workers were used to systematically visit rural locations for vaccination activities. In these simulations, the SIA was again timed to coincide with peak urban incidence. This delivery method can introduce the virus to locations not experiencing community transmission at the time of the SIA; it is also sensitive to infections among health workers.

Figure 4 depicts the expected increases in infection rates due to such an SIA. Both the level of prevalence and degree of urbanization were contributing factors to the increase in infection rates. Low levels of urbanization corresponded to a greater number of potentially naïve communities at the time

of the SIA; higher prevalence at the time of the SIA increased the likelihood of a HW being infected at the time of the SIA and potentially being the cause of a new introduction.

Reducing infections in health workers can mitigate the risk of introduction to naïve communities. Adjusting SIA timing so that it occurs a month or more away from peak incidence also reduced the risk of introductions. Outcomes for these simulations suggest elevated risk only when current prevalence is high and HWs have a greater probability of being infected than the general community. In a high connectivity environment, the increased number of infections associated with an SIA is in proportion to the increased contact rate during the SIA, while with intermediate connectivity (i.e., urban-rural), there is a possibility of non-linear effects.

Summary

Statistics for urban, fixed-post SIA and rural, house-to-house SIA implementation are summarized in Table 3 and represent the main results of this study. Excess infections due to fixed-post SIAs were largely insensitive to relative acquisition and transmission risk of health workers. Marginal increases in infections in these scenarios were driven by increased community mixing at fixed-posts and not specific interactions with health workers, like how large gatherings for other purposes would be expected to increase transmission.

All fixed-post scenarios include zero excess infections as a potential outcome. These null results suggest that while the infection rate increases for the duration of the SIA, the overall attack rate for the epidemic is not always substantially affected.

Outcomes for each country demonstrate that marginal increases in infection tend to be small and in proportion to overall prevalence. Angola, Ecuador, and Ukraine are mostly urban
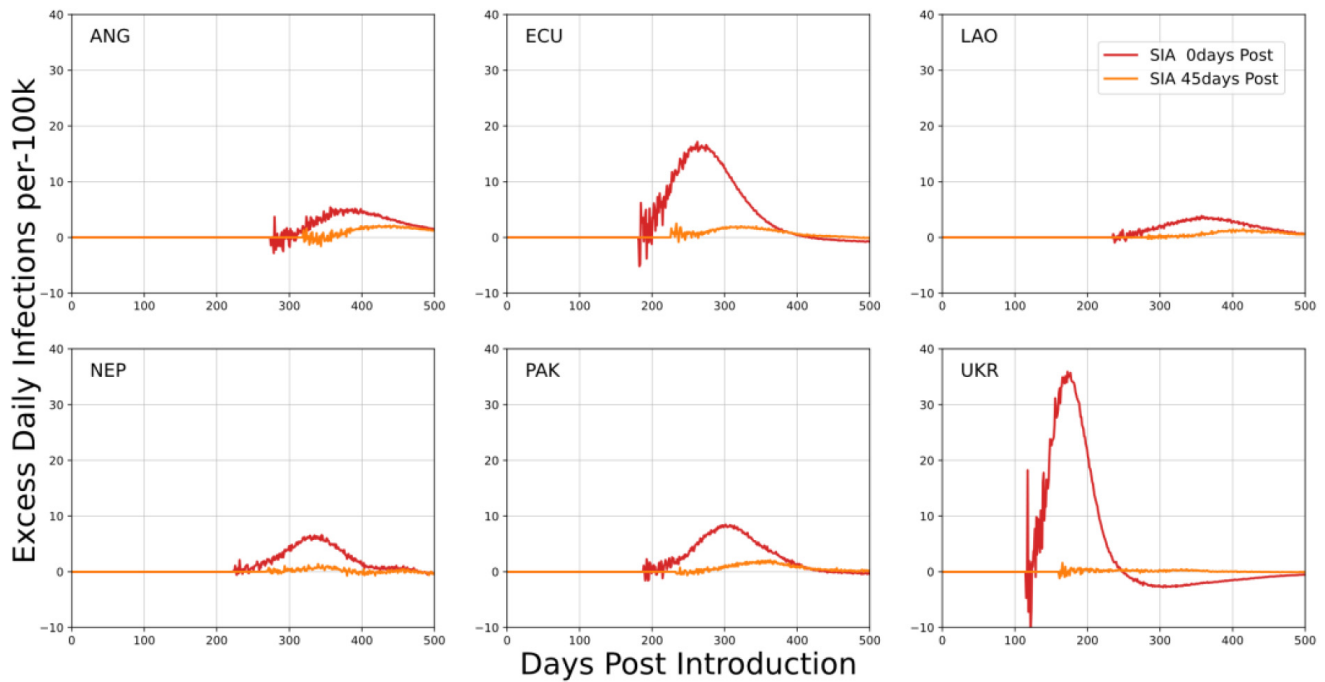
Figure 4. Mean excess daily SARS-CoV-2 infections per 100k individuals in each country examining house-to-house SIAs in mixed urban-rural simulations. Scheduling of SIAs is with respect to the time of peak incidence. The x-axis describes the number of days post SARS-CoV-2 introduction to the community.

Table 3. Expected excess SARS-CoV-2 infections and infections-per-vaccination, under varying scenarios of relative acquisition and transmission risk (RATR) for health workers (HW) when SIA is undertaken at time of peak COVID-19 incidence. Bracketed ranges span mean outcomes for the six countries.

Delivery method	HW RATR	Excess community infections per 100k total population		Excess community infections per 1k vaccinations	
Fixed-post SIA: urban	20x	310	[0, 550]	27	[0, 75]
	15x	310	[0, 610]	28	[0, 78]
	10x	250	[0, 530]	23	[0, 76]
	5x	230	[0, 560]	22	[0, 77]
	1x	300	[0, 590]	28	[0, 79]
House-to-house SIA: urban-rural	20x	400	[0, 970]	64	[0, 140]
	15x	680	[0, 950]	67	[0, 170]
	10x	520	[0, 1300]	60	[0, 230]
	5x	460	[0, 810]	54	[0, 135]
	1x	120	[0, 410]	17	[0, 75]

with progressively older populations, and baseline transmission intensity increases with mean population age. Pakistan, the Lao PDR, and Nepal are mostly rural, and decreasing mean urban population fraction tends to reduce the severity of initial outbreak along with prolonging the overall duration of outbreak.

Summary statistics in Table 3 are based on the mean outcomes for the scenarios examined in this study, which are biased toward larger excess values because SIA implementation was timed to occur around peak incidence. Countries are expected to demonstrate significant sub-national heterogeneity in epidemic trajectories due to regionally differing times of first introduction. Nationally implemented SIAs would be expected to sample multiple different locations along the trajectories described in this study, resulting in fewer excess infections than in Table 3.

Discussion

This study helps decision makers in LMICs in understanding the risk-benefit tradeoff of proceeding with immunization services during the pandemic through stylized modeled simulations. There is potentially a large asymmetry in suspending SIAs for diseases like measles and polio: minor increases in SARS-CoV-2 infections averted, but consequently large increases in other vaccine preventable diseases. The modeling approach presented here is a general one and applicable to other emergent infections of pandemic potential, although great care would be necessary selecting pathogen appropriate inputs. SARS-CoV-2 transmission is less intense in young populations, which strongly influences these outcomes.

All these scenarios focus on the increase in SARS-CoV-2 infections to health workers and the community due to vaccination activities, and do not describe the COVID-19 disease burden specifically. While the benefits of vaccination accrue primarily to vaccine recipients (here, the <5yr cohort), the COVID-19 burden will fall most heavily on the aged (>50yr cohort)[17]. Balancing this asymmetry between risks and benefits across age cohorts is not addressed in this study; the primary outcome is estimating the plausible range of incremental SARS-CoV-2 infections due to SIAs.

Routine outreach scenarios would be expected to lead to some number of additional infections because of the model structure that represents them as an increase in total contacts during the outbreak. The rate of contacts present in the base case as typical behavior makes this increase sufficiently low as to be not distinguishable from zero.

Urban, fixed-post SIAs tended to have a low impact on the ongoing epidemic. Average outcomes were about 20 to 30 additional SARS-CoV-2 infections per 1000 vaccinations. This quantity is biased upward because scenarios examined were in proximity to epidemic peak, which is not an outcome that would be expected to occur during implementation of a nationwide SIA. The model does not include a responsive mechanism for individual behavior with respect to total prevalence and it is likely individuals would self-modify behavior to mitigate acute peaks of the sort represented here. Values are appropriately interpreted as a conservative / high estimate of what would be observed in practice. Additionally, overall attack rates for the entire epidemic were not strongly affected by this SIA implementation. In several scenarios, the change in attack rate was not significantly different from zero even though the rate of infections during the SIA period

was elevated. This outcome suggests that infections during the SIA were displacing infections that likely would have occurred later, marginally accelerating the epidemic but not affecting its outcome. This tendency to accelerate the epidemic was most pronounced for interventions occurring before peak incidence. For all fixed-post implementations, excess infections were strongly correlated with prevalence at the time of implementation.

Outcomes describing single-antigen vaccinations are likely extensible to multi-antigen SIAs. Multi-antigen SIAs would be characterized by longer periods of interaction between the health worker and individual receiving vaccination, and an elevated probability of transmission during that interaction. A much larger consideration is the probability that a participant in that interaction is infectious, which is a consequence of prevalence and IPC measures at the time of the intervention.

House-to-house SIAs in mixed urban-rural contexts have the potential to import infections to previously naïve communities. This risk is a consequence of using health workers from urban locations that may be infectious at the time of the SIA.

Reducing prevalence among HWs largely eliminates the scenario where communities (such as rural or semi-isolated populations) will see the first introduction of virus during a SIA. Prevalence also strongly affects the importation risk because of the likelihood that a health worker may be exposed prior to rural travel. Marginal increases in infections in these scenarios represented an increase in mean epidemic attack rate and not an acceleration of the outbreak. Increased mobility correlated with greater importation risk; local vaccination staff should be used wherever possible. In all scenarios, attack rates in health worker populations emphasize the need for protection.

Increased infection experienced by health workers was not examined as a primary outcome in this study. Scenarios examined the potential effects on community infection rates because of varying levels of prevalence among health workers, but not the effect of the SIAs themselves on infections in health workers. Additional work in this area is needed.

Urbanization and age-structure metrics depicted in Figure 2 are the primary covariates examined for this study, and extensions of these results to other countries based on those dimensions provide the greatest inferential power. However, in all simulations the incremental infection due to vaccination activities was small and in proportion to overall prevalence. Urbanization and age structure can help inform expected levels of prevalence of SARS-CoV-2 during an outbreak, but those prevalence levels themselves are the most important guide for SIA implementation; forecasts on the timescale required for SIA planning are not currently achievable. Outcomes in Table 3 should guide expectations for increased infections with respect to peak prevalence, and those measures used to inform the decision on proceeding with a SIA.

Data availability

Underlying data

Open Science Framework: Modeling anticipated changes in numbers of SARS-CoV-2 infections within communities due to immunization campaigns, https://doi.org/10.17605/OSF.IO/C3DXR[13].

This project contains the simulation data.

Summary data generated or analyzed during this study are included in the article.

Extended data

Open Science Framework: Modeling anticipated changes in numbers of SARS-CoV-2 infections within communities due to immunization campaigns, https://doi.org/10.17605/OSF.IO/C3DXR[13].

This project contains the following extended data:

- Detailed methods for the epidemiological model.
- Detailed methods for country specific parameters.
- Scenario results and confidence intervals.
- Country-level index values.
- Sensitivity to latent period.
- Time to peck incidence.
- Uncertainty analysis
- Outcomes for multiple fixed-post SIAs.
- Outcomes for routine outreach.
- Outcomes in absolute terms.
- Interpretation of RATR

Data are available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0).

Acknowledgements

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Open Peer Review

Current Peer Review Status: ✓ ✓

Version 2

Reviewer Report 17 October 2022

✓ **Sylvia K. Ofori** [ID]

Department of Biostatistics, Epidemiology and Environmental Health Sciences, Jiann-Ping Hsu College of Public Health, Georgia Southern University, Statesboro, GA, USA

The authors have adequately addressed my comments.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Infectious disease epidemiology and modeling

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 04 October 2022

✓ **Sabina Marchetti** [ID]

Bank of Italy, Rome, Italy

I appreciate the responses and integrations provided by the authors. All main comments were fairly addressed.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Mathematical modeling of infectious diseases; Statistics

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

- -

Version 1

Reviewer Report 05 August 2022

?

Sylvia K. Ofori 🆔

Department of Biostatistics, Epidemiology and Environmental Health Sciences, Jiann-Ping Hsu College of Public Health, Georgia Southern University, Statesboro, GA, USA

Summary:
The study uses agent-based modeling to assess the impact of different vaccination programs, specifically Supplementary Immunization Activities (SIA) on COVID-19 in urban, rural-urban jurisdictions and healthcare workers who travel to vaccinate vulnerable children. The authors focused on countries in each of the six WHO regions; Angola, Ecuador, Lao PDR, Nepal, Pakistan, and Ukraine. Adequate background on the impact of the COVID-19 pandemic on SIA and Routine Immunizations was provided by the authors. The study concluded that fixed-post SIAs in urban regions during high SARS-CoV-2 prevalence were associated with an increase in cases.

General comments:
- The authors referred readers multiple times to the extended data for certain details (I am assuming this may be due to the word limit). Important details on the epidemiological model are needed in the main text as it is difficult for the reader to appreciate what the authors set out to do.

- The conclusion of the study and recommendations for practice are not clear and do not fully support the objectives of the study (especially for the selected countries, and the implications for other LMICs). I am not sure why the authors highlighted the selection of countries from each of the WHO regions in the analysis as there seem to be no comparisons in the narrative of the results. Also, the objective in the abstract states that the authors conducted the study to inform approaches to resume services, however, the conclusions do not adequately highlight the recommended approaches.

- What were some of the limitations of the model used based on assumptions made by the authors? Any recommendations for future researchers to consider addressing these limitations?

- In the discussion section of the paper, the authors suggested that the role of HW in

transmission could be avoided when local HW in rural regions was responsible for administering the vaccines. Did the authors consider exploring a scenario of using only local HW for the house-to-house immunizations and how that could have affected the outcome? Aside from the use of local vaccination staff where possible, are there any practical recommendations to lower the importation risk from HWs?

Minor comments:
- In the abstract, is there any reason the authors highlighted results for urban regions and healthcare workers in the results, but the conclusion focused on something else?

- The results for the countries included in the study could also have been highlighted in the results section.

- Some acronyms are not included in the abbreviation list.

- How were countries in each of the six WHO regions selected? Were there any specific criteria, was it random or arbitrary? This is not clear in the main text as the authors only mentioned that a country was selected from each region.

- Any reason for specifically redistributing 20% of reduced contacts to the home route? Was the percentage varied in an uncertainty analysis?

- In the methods, rural-only networks were not considered. Although the authors explained what that network would look like, an explanation as to why this was excluded was not given.

- The circles in figure 2 seem to suggest that the selected countries have a larger proportion of persons <15 years and a rural population.

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Not applicable

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: I am an intern for a pharmaceutical company. I confirm that this potential conflict of interest did not affect my ability to write an objective and unbiased review of the article.

Reviewer Expertise: Infectious disease epidemiology and modeling

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 17 Sep 2022
Kurt Frey, Bill & Melinda Gates Foundation, Seattle, USA

Reviewer 2

Authors' Response
Thank you for your time and consideration in reviewing this manuscript. It is greatly appreciated. All feedback has been reproduced below with a detailed reply to each point (indicated using an italic font).

Reviewer - Summary
The study uses agent-based modeling to assess the impact of different vaccination programs, specifically Supplementary Immunization Activities (SIA) on COVID-19 in urban, rural-urban jurisdictions and healthcare workers who travel to vaccinate vulnerable children. The authors focused on countries in each of the six WHO regions; Angola, Ecuador, Lao PDR, Nepal, Pakistan, and Ukraine. Adequate background on the impact of the COVID-19 pandemic on SIA and Routine Immunizations was provided by the authors. The study concluded that fixed-post SIAs in urban regions during high SARS-CoV-2 prevalence were associated with an increase in cases.

Reviewer - Comments
1. The authors referred readers multiple times to the extended data for certain details (I am assuming this may be due to the word limit). Important details on the epidemiological model are needed in the main text as it is difficult for the reader to appreciate what the authors set out to do.

This article was originally drafted to respect a 3000-word limit, but there is no restriction on article length at Gates Open Research. More details for the epidemiological model from appendix 1 have been added to the Methods section of the article.

2. The conclusion of the study and recommendations for practice are not clear and do not fully support the objectives of the study (especially for the selected countries, and the implications for other LMICs). I am not sure why the authors highlighted the selection of countries from each of the WHO regions in the analysis as there seem to be no comparisons in the narrative of the results. Also, the objective in the abstract states that the authors conducted the study to inform approaches to resume services, however, the conclusions do not adequately highlight the recommended approaches.

One country was selected from each WHO region to demonstrate that the approach to estimating impact was general to a wide variety of countries. Individual countries were used as examples so that parameter combinations (e.g., age distributions and urbanization) were representative of specific places, in order to inform global guidance. Precise recommendations to modeled countries were not provided because the authors did not have direct familiarity with country-specific policies.

The goal of this study was to evaluate the potential range of impact SIAs could have on the novel coronavirus pandemic, and to provide quantitative evidence for in-country decision makers when they were weighing the relative health impacts of suspending SIAs for diseases like measles and polio vs. SARS-CoV-2 risks. We found that SIAs caused modest increases in SARS-CoV-2 infections, which can then be compared to impacts on SIAs' impacts on other vaccine preventable diseases.

Additional emphasis has been added to the discussion section to assist decision makers, but it is not possible to specifically advocate that SIAs not be suspended, given that this paper is focused strictly on quantifying SARS-CoV-2 and does not model other diseases at the same time. This choice was an intentional one because the range of potential comparators is wide and too much to cover in a single paper.

3. What were some of the limitations of the model used based on assumptions made by the authors? Any recommendations for future researchers to consider addressing these limitations?

This model was developed and implemented in May 2020; it assumed re-infection did not occur and ignored the potential for immune evasion through variant strains. Those were reasonable assumptions based on the observed epidemiology at the time, but the pandemic has evolved since then. An updated model would need to account for waning immunity and differences in variant serotypes, although that effect may be minor. For the purposes of infection, recent variant behavior (e.g., Omicron) could be represented as a novel strain encountering a semi-naïve population, partially mitigated by vaccination and previous exposures.

Connecting SARS-CoV-2 infections and COVID-19 burden is also a model limitation. The benefits of SIAs are primarily accrued by children under the age of 5, while the consequences of increased transmission intensity are borne in large part by older populations.

These limitations are discussed in the manuscript.

4. In the discussion section of the paper, the authors suggested that the role of HW in transmission could be avoided when local HW in rural regions was responsible for administering the vaccines. Did the authors consider exploring a scenario of using only local HW for the house-to-house immunizations and how that could have affected the outcome? Aside from the use of local vaccination staff where possible, are there any practical recommendations to lower the importation risk from HWs?

Scenarios utilizing local HWs were indistinguishable from the base case; no statistically significant increases in infection were identified. Those outcomes (and other effectively null results) were not

included in the manuscript to focus on scenarios that resulted in non-zero burden increases.

Utilization of personal protective equipment (PPE) and other non-pharmaceutical interventions is expected to significantly lower importation risk due to an infected HW. Previous versions of the manuscript included a presentation of Relative Acquisition / Transmission Rates (RATR)s in HWs that was focused on the use of PPE as a method for reducing HW infection; although that description was omitted due to concerns of imprecise estimates of the effect of PPE on transmission risk. Careful use of PPE could potentially reduce HW risk below that experienced by the public (i.e., RATR values <1.0), although those scenarios were not considered.

Reviewer - Other minor comments

1. In the abstract, is there any reason the authors highlighted results for urban regions and healthcare workers in the results, but the conclusion focused on something else?

The original abstract was formatted to respect a 200-word maximum, but there is no restriction on abstract length at Gates Open Research.

Additional emphasis on the SIA scenarios has been added to the Conclusions subsection of the abstract.

2. The results for the countries included in the study could also have been highlighted in the results section.

Trends in country specific outcomes have been added to the Results section.

3. Some acronyms are not included in the abbreviation list.

All abbreviations have been added to the Abbreviations section.

4. How were countries in each of the six WHO regions selected? Were there any specific criteria, was it random or arbitrary? This is not clear in the main text as the authors only mentioned that a country was selected from each region.

Appendix 4 in Additional File 1 lists country-level indices for all lower- or middle-income countries with a population of greater than one million. All listed countries were considered for use as representative contexts. Countries were selected to span the range of key indicator values and based on the expertise of our WHO co-authors.

To clarify this, the Example Country Selection subsection under Methods has been amended to describe how countries were selected to span the range of indicators.

5. Any reason for specifically redistributing 20% of reduced contacts to the home route? Was the percentage varied in an uncertainty analysis?

Using 20% for redistribution of contacts was a choice made based on assumptions of the effect of behavior modification and was not varied as part of an uncertainty analysis.

6. In the methods, rural-only networks were not considered. Although the authors explained what that network would look like, an explanation as to why this was excluded was not given.

Rural only networks were not considered because individual importations often do not result in community transmission. Forcing importation of virus to a rural community causes behavior analogous to miniature urban environments.

Description added to the text.

7. The circles in figure 2 seem to suggest that the selected countries have a larger proportion of persons <15 years and a rural population.

We apologize for the confusion. We have noted in the text that size is only intended to highlight countries of interest and their locations.

Competing Interests: No competing interests were disclosed.

Reviewer Report 24 June 2022

https://doi.org/10.21956/gatesopenres.14705.r32200

? **Sabina Marchetti** (iD)

Bank of Italy, Rome, Italy

The paper provides insights on the trade-off between preventive and routine immunization activities against a number of diseases and SARS-CoV-2 transmission induced by mass vaccination campaigns. Changes in the number of infections derived from individual-based transmission model scenarios with simplified spatial networks providing a stylised representation of plain urban and urban-rural dynamics. The analysis considers one representative low-medium income country for each WHO regions, namely Angola, Ecuador, Lao PDR, Nepal, Pakistan and Ukraine.

Comments:

1. Albeit the authors refer readers to Extended data (and to "additional file 1", that I could not find..?) for details on the model characteristics, the paper may benefit from high-level descriptions or examples on the main trajectories entailed by the individual-based model. For instance, I found hard to grasp any details on the paths and specificities of health workers within the developed framework, even though the authors underline their key role in SARS-CoV-2 transmission from urban to rural areas for their analysis and policy relevance. Moreover, it should be clarified to

which extent the pandemic affects health workers: are they re-allocated to, for instance, COVID-19 related tasks, or do they suspend their activity due to infection? To what extent does the model account for asymptomatic individuals?

2. Overall, I found difficult to appreciate the policy relevance of the work, due to a number of reasons that expose its soundness to several weaknesses. In detail, if the takeaway message was "policy makers should suspend all SIAs until the peak is over", it ought to be put in connection with insights on how this would reflect on the different diseases addressed by SIAs. This would enable a comprehensive analysis of the trade-off between SARS-CoV-2 transmission and deployment of SIAs.

I am under the impression (but I might be wrong and therefore would require clarification by the authors in the text) that the main "policy takeaway messages" rely on a set of assumptions that are hard to validate and prevent straightforward generalisation to any LMIC. For instance, the discussion might support the goodness of suspending SIAs until after the (ascertained) end of the peak, to protect (mainly the elderly?) from SARS-CoV-2. Throughout, SIAs would address (primarily) children who are assumed (but not proved for the ancestral strain of the virus, nor unequivocally for ensuing variants) to be less at risk. Even so, how do the authors compare the quality of life of a non-immunised child via SIA and that of an adult hospitalised due to SARS-CoV-2 infection (i.e. are the authors accounting for medium and long term implications while advising policy makers)? As a comprehensive analysis of the general burden of disease would be out of the scope of the paper, I recommend the authors lay down all caveats so as to clarify the limitations and key assumptions of their framework.

Along this line, authors might discuss the implications of the absence of a mechanism underlying individual behaviour. While the authors acknowledge self-induced behavioural dynamics plays a key role in outbreaks (in the Methods: Transmission Modelling subsection), their relevance close to a pandemic peak and the documented asymmetry in responsiveness between urban and rural populations might affect the depicted scenarios (e.g., Li *et al*., 2021[1]).

Other minor comments:

1. The paper is full with acronyms that are known to many readers or can be drawn from the context. However, authors ought to explicate and/or include them in the abbreviation list. They include - I might have missed others - VPDs, DTP3, EMOD (in this case the citation might be referred to the acronym), LIMC, HW.

2. The sentence in the Introduction "The WHO […] advised temporary suspension of mass vaccination campaigns based on the recommendations for physical distancing and the understanding of SARS-CoV-2 transmission" seemingly suggests distribution of available vaccines against COVID-19 was suspended upon WHO recommendation whereas it should be clarified it refers to those against diseases different from COVID-19.

2. In the Introduction, add reference to "WHO regions", to help the reader.

3. In the Methods, authors should specify the literature and empirical analyses suggesting children cohorts are characterised by lower susceptibility and transmissibility rates primarily refer to the original strains of the virus, whereas the same cannot be ascertained for successive

variants.

4. Figure 2: Specify size is only intended to highlight annotated dots.

5. Figure 3: Clarify infection from what in the caption and extend limits of the y-axis, to enable full representation of the curves for Ukraine.

6. Figure 3/Figure 4: Not sure about what authors are pointing out here: "allowing health workers to administrate SIA within a pandemic peak should be avoided"? How does this compare to "keep some random individuals moving within and between areas at some point around the peak" from the model standpoint? As a further (low-level) observation, annotation of the SARS-CoV-2 incidence peaks on all panels might help the reader.

References

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Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

No

If applicable, is the statistical analysis and its interpretation appropriate?

Not applicable

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Mathematical modeling of infectious diseases; Statistics

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 17 Sep 2022

Kurt Frey, Bill & Melinda Gates Foundation, Seattle, USA

Authors' Response
Thank you for your time and consideration in reviewing this manuscript. It is greatly appreciated. All feedback has been reproduced below with a detailed reply to each point (indicated using italic font).

Reviewer - Summary
The paper provides insights on the trade-off between preventive and routine immunization activities against a number of diseases and SARS-CoV-2 transmission induced by mass vaccination campaigns. Changes in the number of infections derived from individual-based transmission model scenarios with simplified spatial networks providing a stylised representation of plain urban and urban-rural dynamics. The analysis considers one representative low-medium income country for each WHO regions, namely Angola, Ecuador, Lao PDR, Nepal, Pakistan and Ukraine.

Reviewer - Comments
1. Albeit the authors refer readers to Extended data (and to "additional file 1", that I could not find..?) for details on the model characteristics, the paper may benefit from high-level descriptions or examples on the main trajectories entailed by the individual-based model. For instance, I found hard to grasp any details on the paths and specificities of health workers within the developed framework, even though the authors underline their key role in SARS-CoV-2 transmission from urban to rural areas for their analysis and policy relevance. Moreover, it should be clarified to which extent the pandemic affects health workers: are they re-allocated to, for instance, COVID-19 related tasks, or do they suspend their activity due to infection? To what extent does the model account for asymptomatic individuals?

An OSF registry for v01 of the submitted manuscript is located at https://osf.io/c3dxr*; a direct link to the additional file 1 is* https://osf.io/c3dxr/files/osfstorage/61f5eeeb026ee60528b502ab*.*

This article was originally drafted to respect a 3000-word limit, but there is no restriction on article length at Gates Open Research. More details for the epidemiological model have been added from appendix 1 to the methods section of the article.

In these simulations, health workers are re-allocated to COVID-19 related tasks (SIAs) during task implementation periods but are assumed to be involved in other health-related activities during other periods. A health worker is assumed to be always at or above baseline risk for infection by SARS-CoV-2, as indicated by their relative acquisition/transmission rate (RATR) for a given simulation. Health workers are assumed to self-isolate (given symptoms) at the same rate as non-health workers. This has been clarified in the methods section of the manuscript.

For all infections, latent and infectious periods are drawn from appropriate distributions for all simulated individuals, including healthcare workers. All infections have a pre-symptomatic phase, although only about 10% of infections will be totally asymptomatic (totally asymptotic infections are those with infectious periods less than the difference between latent and incubation periods); this outcome occurs because of the epidemiological assumptions about latency and incubation and is not an input to the model, so is not described in the assumptions.

2. Overall, I found difficult to appreciate the policy relevance of the work, due to a number of reasons that expose its soundness to several weaknesses. In detail, if the takeaway message was "policy makers should suspend all SIAs until the peak is over", it ought to be put in connection with insights on how this would reflect on the different diseases addressed by SIAs. This would enable a comprehensive analysis of the trade-off between SARS-CoV-2 transmission and deployment of SIAs.

This work was <u>not</u> intended as advocacy for suspending SIAs and the results show the opposite. At the time of the investigation (May – Aug 2020), many SIAs were being suspended, and it was the intent of the authors to provide modeling to quantify the SARS-CoV-2 impact if these campaigns were to be run instead. The results are in direct support of continuing and/or resuming SIAs. Specifically, estimates of marginal increases in SARS-CoV-2 infection rates if an SIA were to occur at or around peak SARS-CoV-2 incidence (a plausible worst-case scenario) are low.

It wasn't possible to couple this model with averted burden estimates for the various diseases targeted by SIAs, so the conclusions intentionally avoided specific guidance on SIA implementation decisions and leaves the comparison and decisions about trade-offs to in-country policy makers.

I am under the impression (but I might be wrong and therefore would require clarification by the authors in the text) that the main "policy takeaway messages" rely on a set of assumptions that are hard to validate and prevent straightforward generalisation to any LMIC. For instance, the discussion might support the goodness of suspending SIAs until after the (ascertained) end of the peak, to protect (mainly the elderly?) from SARS-CoV-2. Throughout, SIAs would address (primarily) children who are assumed (but not proved for the ancestral strain of the virus, nor unequivocally for ensuing variants) to be less at risk. Even so, how do the authors compare the quality of life of a non-immunised child via SIA and that of an adult hospitalised due to SARS-CoV-2 infection (i.e. are the authors accounting for medium and long term implications while advising policy makers)? As a comprehensive analysis of the general burden of disease would be out of the scope of the paper, I recommend the authors lay down all caveats so as to clarify the limitations and key assumptions of their framework.

We have intentionally limited the discussion to SARS-CoV-2 infections and do not address COVID-19 burden for the exact reasons expressed by the reviewer. All interventions modeled were targeted to children (<5yrs old), while COVID-19 burden is concentrated in the elderly and other populations with co-morbidities, making the direct comparison of 'health value' difficult.

Additional emphasis on this limitation has been added to the discussion section.

Along this line, authors might discuss the implications of the absence of a mechanism underlying individual behaviour. While the authors acknowledge self-induced behavioural dynamics plays a key role in outbreaks (in the Methods: Transmission Modelling subsection), their relevance close to a pandemic peak and the documented asymmetry in responsiveness between urban and rural
populations might affect the depicted scenarios (e.g., Li et al., 20211).

The heterogeneity described in the Li et al. reference is an examination of the overdispersion of transmission (relative to Poisson statistics) observed in urban and rural areas. Specifically, that "the average reproductive number (R) and k [the dispersion parameter] did not [differ between urban and rural areas]." The heterogeneity in this manuscript incorporates uniform reproductive numbers and dispersion parameters, as described by Li et al., along with structural differences to represent the contact pattern variation between urban and rural settings.

Additional discussion on the absence of an underlying mechanism for individual behavior has been added.

Reviewer - Other minor comments
1. The paper is full with acronyms that are known to many readers or can be drawn from the context. However, authors ought to explicate and/or include them in the abbreviation list. They include - I might have missed others - VPDs, DTP3, EMOD (in this case the citation might be referred to the acronym), LIMC, HW.

Thank you for the list. All abbreviations have been added to the Abbreviations section.

2. The sentence in the Introduction "The WHO [...] advised temporary suspension of mass vaccination campaigns based on the recommendations for physical distancing and the understanding of SARS-CoV-2 transmission" seemingly suggests distribution of available vaccines against COVID-19 was suspended upon WHO recommendation whereas it should be clarified it refers to those against diseases different from COVID-19.

This guidance was issued in early 2020, before availability of a safe and effective vaccine against COVID-19. The text has been clarified that the guidance does not pertain to COVID vaccination.

3. In the Introduction, add reference to "WHO regions", to help the reader.

Noted in the text.

4. In the Methods, authors should specify the literature and empirical analyses suggesting children cohorts are characterized by lower susceptibility and transmissibility rates primarily refer to the original strains of the virus, whereas the same cannot be ascertained for successive variants.

Thank you for this point. We have clarified in the methods section that these estimates are only appropriate for the ancestral strain of SARS-CoV-2 and not the variant lineages.

5. Figure 2: Specify size is only intended to highlight annotated dots.

Thank you, we have noted this in the text.

6. Figure 3: Clarify infection from what in the caption and extend limits of the y-axis, to enable full representation of the curves for Ukraine.

We have clarified the captions for figures 3 and 4 to indicate that these values are for SARS-CoV-2

infections. We have also re-scaled the y-axis in Figure 3 per the reviewer's suggestion.

7. Figure 3/Figure 4: Not sure about what authors are pointing out here: "allowing health workers to administrate SIA within a pandemic peak should be avoided"? How does this compare to "keep some random individuals moving within and between areas at some point around the peak" from the model standpoint? As a further (low-level) observation, annotation of the SARS-CoV-2 incidence peaks on all panels might help the reader.

The contrast between figures 3 and 4 was intended to highlight the differences between administering an SIA in a well-mixed (i.e., urban) environment and an environment with intermediate connectivity (i.e., urban-rural). In a high connectivity environment, the increased number of infections associated with an SIA is in proportion to the increased contact rate during the SIA, while with intermediate connectivity, there is a possibility of non-linear effects.

The implementation of house-to-house vaccination was implemented as a random (contact forming) walk among the target (<5yr old) population by health workers (individuals potentially at elevated risk of being infected/infectious). The intent of the study was to quantify the marginal increase in infections attributable to this activity.

Time of peak incidence is noted in Table A7-1. We did not include it in the figure to avoid overcrowding the image.

Competing Interests: No competing interests were disclosed.