Comparison of 2021 VIMC cholera models

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The purpose of this report is to describe differences in the 2021 VIMC cholera model runs submitted by Johns Hopkins University (JHU) and International Vaccine Institute (IVI). Modeling results varied due to differences in underlying cholera incidence rate data, incidence rate projection assumptions, their approach to targeting vaccination campaigns, and vaccine effectiveness assumptions.

# Cholera incidence rate estimates

## Baseline incidence data in sub-Saharan Africa

Both teams relied on published gridded mean annual incidence rate estimates for 35 countries of sub-Saharan Africa: Angola, Burundi, Benin, Burkina Faso, Central African Republic, Côte d'Ivoire, Cameroon, the Democratic Republic of the Congo, Republic of the Congo, Ethiopia, Ghana, Guinea, Guinea-Bissau, Kenya, Liberia, Madagascar, Mali, Mozambique, Mauritania, Malawi, Namibia, Niger, Nigeria, Rwanda, Senegal, Sierra Leone, Somalia, South Sudan, Chad, Togo, Tanzania, Uganda, South Africa, Zambia, and Zimbabwe (Lessler et al. 2018). These estimates were derived from a spatial Bayesian modeling framework that downscales suspected cholera case observations to the 20 km by 20 km grid. The original source data varied by country and time and included public reports such as the UNICEF cholera platform, ProMed, published literature, and confidential sources such as situation reports, outbreak reports, and line lists from Ministries of Health and WHO. The primary model output from this source was a 20 km by 20 km raster of 1000 posterior samples of the mean annual incidence rate of suspected cholera from 2010 to 2016.

The IVI team aggregated the mean of the posterior samples of these gridded estimates into a single incidence rate estimate for each country. They then assumed that country-level incidence rate was a lognormal random variable where the mean was the country-level incidence rate estimate from the model output and the standard deviation was 1.5 times the mean, which was derived from the mean of coefficient of variation in the number of cholera available at Global Health Observatory. In contrast, the JHU model relied on the “raw” gridded posterior samples from the published paper, and the variation in the posterior samples is a source of variability in the modeled output.

## Baseline incidence data outside Africa

For the 10 remaining countries (Afghanistan, Algeria, Haiti, Iran, Iraq, Nepal, Pakistan, Philippines, Thailand, and Yemen), the teams took slightly different approaches. For all countries except Haiti, India, and Bangladesh, the IVI team used country-level annual case counts reported in the WHO Global Health Observatory (GHO) database (World Health Organization, n.d.). For Haiti, the IVI team used 2016-2020 case counts provided by Haiti’s Ministère de la Santé Publique et de la Population (MSPP) (République d’Haiti, n.d.). The IVI team applied the incidence rate measured in Kolkata, India as the country-level incidence rates in both India and Bangladesh.

For all countries except India and Bangladesh, the JHU team used country-level case counts reported in the annual cholera reports published by the WHO Weekly Epidemiological Record (WER). It should be noted that the GHO data and WER reports are derived from the same source, but GHO stopped updating this data table after 2017 (the last year of reported data was in 2016), while the WER continues to post annual cholera reports (JHU included data through 2020); there may also be minor differences if corrections were made in GHO after WER reports were published. For Bangladesh, the JHU team used unpublished 5 km by 5 km gridded posterior samples of the cholera incidence rate; these estimates were derived from a Bayesian hierarchical model similar to that in (Lessler et al. 2018) using 2014-2018 acute watery diarrhea (AWD) cases from hospital-based surveillance in all 64 districts of Bangladesh and culture-confirmed *V. cholerae* cases obtained from systematic sampling of AWD patients at 22 sentinel hospital sites comprising a national enteric disease surveillance system. The JHU team assumed that India had the same country-level incidence rate as the Bangladesh model estimates; the variability in country-level incidence across posterior estimates from the Bangladesh model was preserved in the estimates applied to India.

## Incidence projection assumptions

Acknowledging that the cholera incidence rate is unlikely to remain constant over a period of 101 years (from 2000 to 2100), both teams used time-varying trends to project baseline incidence rates into the future.

The IVI team used the data on the relative risk of people who have or don’t have access to improved water, sanitation, and hygiene (WASH) and the temporal trend of WASH over the period of 2000-2100. The calculation assumed that the country-level incidence arises from two distinct sub-populations that have or don’t have access to improved WASH. While the incidence rate for each sub-population remains constant, the proportions change over time (i.e., the sub-population with access to improved WASH increases over time in general), which changes the overall incidence rate. A saturating exponential function was fitted to model the WASH trend data from WHO UNICEF Joint Monitoring Program.

To capture a broader range of uncertainty, the JHU team considered four incidence rate projection settings; two dimensions each with two options were crossed to create four total settings. Fifty simulations were run for each setting. One dimension considered the secular time trend for baseline incidence rates: constant baseline incidence over time or time-varying trend applied to baseline incidence estimates. The time-varying trend was fit as a Poisson regression model of cases reported in WER annual cholera reports with country random effects. The fit was then projected from 2000 to 2100 assuming constant model coefficients.

The second dimension of incidence rate projection settings in the JHU model considered variability due to sporadic cholera outbreaks in second-level administrative units (often, districts) – with outbreak-type variability in baseline incidence in 21 African countries (Benin, Côte D’Ivoire, Cameroon, Chad, DR Congo, Republic of the Congo, Ethiopia, Ghana, Guinea, Guinea-Bissau, Kenya, Mali, Malawi, Namibia, Niger, Nigeria, Sierra Leone, Somalia, South Sudan, Tanzania, Zambia, Zimbabwe) versus without outbreak-type variability in baseline incidence. From a dataset of district-level outbreaks in these 21 countries (Zheng et al. 2022), we derived annual district-level outbreak probabilities, annualized outbreak-year incidence rates, and non-outbreak-year incidence rates. For each simulation with the outbreak setting, the model used stochastic random draws to determine whether a given district had an outbreak in a modeled year (according to its outbreak probability) and how the baseline incidence rate should be adjusted (according to a randomly selected outbreak-year or non-outbreak-year incidence rate, as appropriate).

# Targeting vaccination campaigns

The IVI team assumed that vaccine was distributed across the country homogeneously and all vaccinated individuals were fully vaccinated.

In contrast, the JHU team targeted vaccination campaigns by district (second-level administrative unit) within a country. Districts were targeted in descending order according to their cholera-affected population size, which was calculated as the product of the annual population and baseline mean annual incidence rate in the district (Lessler et al. 2018). District boundaries were derived from GADM shapefiles (“GADM Maps and Data,” n.d.). All vaccinated individuals received two doses (i.e., were fully vaccinated) and the same district could not be targeted more than once every three years.

# Direct vaccine effects

The IVI team modeled an “all-or-nothing” vaccine, which means that a fraction (*VE*) of vaccine recipients is completely protected from infection. The fraction *VE* represented vaccine efficacy and is modeled as a function of time (i.e., year post-vaccination). The *VE* at year *t* post-vaccination was determined based on the meta-analyses of seven trials (with 695 patients with cholera) and six observational studies (217 patients with cholera) (Bi et al. 2017). The team used the two-dose efficacy broken down by year post-vaccination (1-4 years). The vaccine efficacy was assumed to be 56% (95% CI 42–66), 59% (49–67), 39% (95% CI 13 to 57), and 26% (–46 to 63) in the first, second, third, and the fourth year after vaccination, respectively. They also assumed that the vaccine efficacy decreased to zero after five years to reflect the decreasing trend.

The JHU team assumed that the targeted district fully vaccinated (two doses) 80% of the population. Using the same meta-analysis data (Bi et al. 2017), the JHU team fit a log-linear decay function to 2-dose vaccine efficacy such that initial vaccine efficacy was assumed to be 60%, 52%, 43%, 32%, 20%, and 0% after 1, 2, 3, 4, 5, and over 5 years post-vaccination (Lee et al. 2019).

# Indirect vaccine effects

Both teams included indirect effects of vaccination in their modeling approaches. In the IVI model, the magnitude of indirect effect for a given vaccine coverage was based on the cluster-randomized clinical trials in Matlab, Bangladesh (Ali et al. 2005) and Kolkaka, India (Ali et al. 2013). These data provide incidence rates of unvaccinated people in the vaccination coverage clusters. Indirect vaccine efficacy was calculated as a relative reduction in the incidence rate and applied to country-level coverage. The IVI team fitted a logistic function where indirect vaccine efficacy was regressed against the effective vaccine coverage of the cluster, which was defined as the product of vaccine efficacy and vaccination coverage.

The JHU team derived estimates of indirect vaccine effects from the same two studies (Ali et al. 2005, 2013). As described elsewhere (Lee et al. 2019), these data were fit to a logistic function to estimate the relative reduction in incidence among unvaccinated individuals due to vaccination coverage in their neighborhoods; estimates were applied to each 5 km by 5 km grid cell according to its vaccination coverage.

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