

# Vaccination strategies for epidemic cholera in Haiti with implications for the developing world

Dennis L. Chao<sup>a</sup>, M. Elizabeth Halloran<sup>a,b</sup>, and Ira M. Longini, Jr.<sup>a,b,1</sup>

<sup>a</sup>Center for Statistics and Quantitative Infectious Diseases, Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, WA 98109; and <sup>b</sup>Department of Biostatistics, School of Public Health, University of Washington, Seattle, WA 98195

Edited by G. Balakrish Nair, National Institute of Cholera and Enteric Diseases, Kolkata, India, and approved March 16, 2011 (received for review February 9, 2011)

In October 2010, a virulent South Asian strain of El Tor cholera began to spread in Haiti. Interventions have included treatment of cases and improved sanitation. Use of cholera vaccines would likely have further reduced morbidity and mortality, but such vaccines are in short supply and little is known about effective vaccination strategies for epidemic cholera. We use a mathematical cholera transmission model to assess different vaccination strategies. With limited vaccine quantities, concentrating vaccine in high-risk areas is always most efficient. We show that targeting one million doses of vaccine to areas with high exposure to *Vibrio cholerae*, enough for two doses for 5% of the population, would reduce the number of cases by 11%. The same strategy with enough vaccine for 30% of the population with modest hygienic improvement could reduce cases by 55% and save 3,320 lives. For epidemic cholera, we recommend a large mobile stockpile of enough vaccine to cover 30% of a country's population to be reactively targeted to populations at high risk of exposure.

infectious diseases | simulation modeling

After an absence of over 100 y, cholera has returned to Haiti (1, 2). By February 14, 2011, 234,303 cholera cases and 4,533 deaths were reported (3). Cholera is a waterborne disease that affects at least 3–5 million people annually, mostly in the developing world (4). The most recent example of Haiti shows that areas that have not seen cholera in decades can be vulnerable under the combination of poverty, lack of or destruction of infrastructure, weather, and natural disasters, conditions in which cholera thrives (4–8).

The cholera vaccine is safe, effective, and inexpensive but not widely used (9–11). Currently, two killed oral cholera vaccines could be made available. Dukoral is registered for use with the World Health Organization but is relatively expensive, whereas Shanchol (Shantha Biotechnics) is not yet registered but would be significantly cheaper and easier to administer than Dukoral (Crucell). It is believed that about one million doses of both vaccines together could be made available within the coming year. Most people would require two doses and small children would possibly require three doses to get optimal protection. So far, there has been reluctance to use the limited supplies of vaccine in Haiti because of the lack of a good strategy, logistical problems, and uncertainty about the size of the available supply (12). The benefits of cholera vaccination in emergency situations need to be weighed against that of other programs (11, 13–15). Through the use of a mathematical cholera transmission model (Fig. 1, *Materials and Methods*, and *SI Appendix*), we investigate various feasible vaccination strategies that could be effective in Haiti as well as other locations experiencing epidemic cholera.

## Results

**Cholera Epidemic in Haiti.** Simulated cholera epidemics begin with massive contamination of *Vibrio cholerae* on October 9, 2010, in the Artibonite River in the St. Marc, Petite Rivière d'Artibonite, Verrettes, and Mirebalais communes, where the first cholera cases were detected. Because the source and nature of the in-

roduction of cholera to the region is not known, we did not model any events earlier than the first reported outbreaks along the Artibonite. We assume that these outbreaks were sparked by *V. cholerae* in the river at least 10 d before the first reported large outbreaks, but the cause of this contamination is beyond the scope of this study. In this baseline simulated scenario, 302,000 cumulative cases occur by the end of 6 mo (Table 1). We did not attempt to replicate the exact course of the epidemic, which was exacerbated by natural and political events, such as Hurricane Tomas, national elections, and possibly, uneven reporting rates that lie outside the scope of the model. However, the simulated departmental curves capture major features of the epidemic dynamics, including the initial sharp spike of cases in Artibonite in late October, the large wave of cases in Nord in November and Port-au-Prince in December, and the late arrival of the epidemic in the more remote departments of Grand-Anse and Nippes (Fig. 2 and *Movie S1*).

We selected parameter values to be consistent with this broad pattern of epidemic spread. Significant departures from our parameter choices result in dynamics that do not match reported data from the epidemic. The timing of the regional epidemic, particularly in departments distant from Artibonite, was sensitive to parameters relevant to travel of individuals and the propagation of *V. cholerae* down rivers (*SI Appendix*, Figs. S10–S12). The magnitude of the epidemic peaks was sensitive to parameters relevant to transmission and the natural history of cholera (*SI Appendix*, Figs. S8, S9, S14, and S15) but less sensitive to within-household transmission of cholera (*SI Appendix*, Fig. S13).

**Case for Vaccination.** We examined prevaccination strategies in which vaccination occurs well before the epidemic starts and reactive vaccination strategies in which vaccination begins after the epidemic has started. The results show that randomly prevaccinating a fraction of the population well before the epidemic begins can reduce the number of cases roughly in proportion to the number of individuals vaccinated and delay the epidemic peak (Fig. 3 *A* and *B* and Table 1). We measure the overall effectiveness of a vaccination strategy by the percentage of cases averted with respect to the baseline simulations in which vaccines were not used (16). To achieve 50% overall effectiveness, vaccine coverage of more than 50% of the population would be required.

**Reactive Vaccination Strategies.** We present results for three different reactive vaccination strategies: reactive mass vaccination, reactive ring vaccination, and reactive high-exposure vaccination.

Author contributions: D.L.C., M.E.H., and I.M.L. designed research; D.L.C., M.E.H., and I.M.L. performed research; D.L.C. contributed new reagents/analytic tools; D.L.C., M.E.H., and I.M.L. analyzed data; and D.L.C., M.E.H., and I.M.L. wrote the paper.

The authors declare no conflict of interest.

This article is a PNAS Direct Submission.

Freely available online through the PNAS open access option.

<sup>1</sup>To whom correspondence should be addressed. E-mail: longini@scharp.org.

This article contains supporting information online at [www.pnas.org/lookup/suppl/doi:10.1073/pnas.1102149108/-DCSupplemental](http://www.pnas.org/lookup/suppl/doi:10.1073/pnas.1102149108/-DCSupplemental).







Maintenance of a cholera stockpile for emergency use could be coordinated with production of cholera vaccine for general use in endemic areas (22). The two current killed oral cholera vaccines, Dukoral and Shanchol, have shelf lives of 3 and 2 y, respectively (11). If continuous production of these vaccines could be achieved, then the stockpiled vaccine that is not used within 2 y could be cycled out for routine vaccination in endemic areas. Because both vaccines can be made relatively cheaply, current cost of about \$5 US for Dukoral and \$1.50 US for Shanchol (11), an international investment case could be made to support production and distribution of these vaccines (4, 6). Vaccine distribution could be coordinated through global and regional public health organizations such as the World Health Organization and Pan American Health Organization. For endemic cholera, the routine biannual vaccination of 50–70% of at-risk populations would virtually eliminate cholera transmission from those regions (22). The rapid and repeated use of cholera vaccine could greatly reduce the burden of this disease in the developing world.

## Materials and Methods

The form of the mathematical model is an individual-based stochastic model. A detailed description of the model is in *SI Appendix*. The model uses a synthetic population to represent the 9.5 million people of Haiti. The model incorporates population density data at a 1 km<sup>2</sup> resolution and the locations of major rivers and highways (Fig. 1A). Susceptible people in the model can become infected by contact with *V. cholerae* in their local environment (Fig. 1B) or their households (Fig. 1C). After infected, people undergo a 1- to 5-d latent period, after which they become infectious (22). Twenty percent of infectious people are symptomatic and shed 10 times

more *V. cholerae* into their local environments than asymptomatic individuals. We include a hyperinfectious state of freshly shed cholera that causes a burst of community-wide transmission (26). If an infectious individual lives or works near a river, that individual will also shed *V. cholerae* into the river, which transports *V. cholerae* downstream (Fig. 1B). People are placed into communities of ~500, and these communities are spatially organized according to LandScan data, which estimates the population density at a 30° × 30° resolution (~1 km<sup>2</sup>; <http://www.ornl.gov/sci/landscan/>, accessed November 11, 2010). Some people travel daily to nearby communities, where they can be exposed to or shed *V. cholerae*. People can also occasionally make long-distance trips within the country, with a higher probability if travel is along major highways.

In the simulation, people may be vaccinated, and it is assumed that vaccine reaches maximum efficacy after 3 wk (*SI Appendix*, Fig. S1); at this point, vaccinated infected people are 64% less likely to become symptomatic,  $VE_p = 0.64$  (27), and 50% less infectious than infected unvaccinated people,  $VE_i = 0.50$  (22). Vaccine provides some but less protection before 3 wk post-vaccination. It is possible that vaccine also reduces the probability of infection given exposure to an infected source,  $VE_s$ . However, there are no estimates of this vaccine effect, because clinical disease with confirmed infection was the primary outcome from cholera vaccine trials. *SI Appendix* has further discussion of this point. The vaccination campaign may be accompanied by a hygiene awareness campaign, which lowers exposure to *V. cholerae* from the environment and the household by 10% or 30%.

**ACKNOWLEDGMENTS.** We thank Jon Sugimoto for geographic information system data assistance and both Robyn Fisher and Lara Petusky Coger for their insights about Haiti. This work was partially supported by the National Institute of General Medical Sciences Models of Infectious Disease Agent Study Grant U01-GM070749 and the National Institutes of Health Grant R01-A139129.

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