Vaccines in the time of cholera

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Cholera, an acute watery diarrheal disease caused by *Vibrio cholerae* 01 and, less commonly, by *V. cholerae* 0139, is a major global public health problem in developing countries, causing an estimated 100,000 deaths per year and resulting in major microeconomic and macroeconomic losses. Cholera in developing countries is often described as occurring in two epidemiological forms: epidemic and endemic (1). Although these terms represent extremes at ends of a continuum, the terms are conceptually useful.

Epidemiological Patterns and Control of Cholera

Epidemic cholera occurs unpredictably against a background of no or little natural immunity in the populations at risk. Often arriving in the wake of humanitarian emergencies, epidemic cholera tends to affect children and adults equally. The recent epidemic of cholera in Haiti provides a good example (2). Endemic cholera occurs recurrently in a predictable pattern in time and space, and this recurrent pattern confers natural immunity to cholera in affected populations. Because adults have greater levels of immunity than children, children are affected with higher incidence rates and with greater clinical severity. Many populations in the Ganges Delta experience endemic cholera (3). There are numerous examples between these extremes, as illustrated by major surges of cholera observed after floods and other natural disasters in Bangladesh.

The mainstays of control of cholera consist of provision of clean water and adequate sanitation, appropriate rehydration therapy of cholera patients, and antibiotics for severely affected patients. Conventional parenteral whole-cell vaccines against cholera were abandoned as public health tools decades ago because of poor levels of protection and unacceptable side effects (4). Licensed newer generation vaccines are given orally and consist either of killed cholera *Vibrio* whole cells, with or without a nonpathogenic fragment of cholera toxin, or of live genetically attenuated organisms (5). Both live and killed oral vaccines have been proven safe and protective, and killed oral vaccines have been shown to protect both children and adults against cholera for at least 2 y (6–8). Nevertheless, oral vaccines have been little used for the control of endemic and epidemic cholera, and they have been deployed mostly as vaccines for travelers.

Interest in using oral vaccines for the control of cholera has increased in recent years, as reflected in a recently strengthened recommendation by the World Health Organization (WHO) for the preemptive use of oral cholera vaccines to control endemic cholera and for consideration of reactive use of these vaccines in cholera epidemics (9). In part, this interest reflects the safety and protective capacity of oral vaccines and, in the case of a killed oral vaccine produced in India, the low cost of the vaccine. The case for introducing oral cholera vaccines as routine public health tools has also been strengthened by an apparent increase in the magnitude, severity, and duration of recently reported epidemics, such as those observed in Angola, Zimbabwe, Vietnam, and Haiti, perhaps related to the widespread emergence of the modified genetic forms of *V. cholerae* 01 El Tor biotype that produce classical biotype cholera toxin (10).

Nevertheless, the use of oral cholera vaccines continues to fuel vigorous debates in the public health community, especially regarding reactive use of the vaccines for control of reported epidemics. Opponents of deploying these vaccines have argued that the use of the vaccines in such settings is often not logistically and programmatically feasible, and that it is expected to add little to traditional nonvaccine measures. Moreover, the global supply of killed oral cholera vaccine is quite limited, currently at about 2 million doses, and it has been questioned what impact this small number of doses would have. It is against the background of this controversy that two articles in PNAS, each reporting on the results of models projecting the hypothetical impact of using killed oral cholera vaccines in recent massive cholera epidemics, add important information (11, 12). Each article focuses on a cholera epidemic in which oral cholera vaccines were not used but the decision not to vaccinate was hotly debated.

Modeling of the Use of Oral Vaccines

Central to both articles is the estimation of the intensity of transmission of cholera during an epidemic, estimated in models as the parameter Ro. Ro, or the basic reproduction number, is the number of secondary infections caused by introduction of an infected person into a fully susceptible population (13). Ro can be estimated in a variety of ways. One utilized by both papers is to use a dynamic transmission model parameterized to reflect the underlying mechanisms of transmission and calibrated to the caseload observed during the epidemic.

A Ro $\geq$1 describes transmission that will be sustained or increased, whereas lower values portend the extinction of an epidemic. High values for Ro denote infections with shorter generation times and more explosive epidemics. Ro can also be used to estimate the proportion of the population that must be immune to extinguish an epidemic and, correspondingly, the proportion of a population that must be vaccinated to accomplish this task. Epidemics with lower values for Ro are more amenable to control with a vaccine that can impede transmission.

Importantly, Ro is not invariant for a given pathogen and may be influenced by a multitude of factors that influence transmission, including demographic, behavioral, cultural, and socioeconomic characteristics of a population, as well as environmental variables. Thus, Ro may be heterogeneous for an outbreak of cholera within a single country, and this heterogeneity should be accounted for when using models to project the impact of using cholera vaccines.

Using routine statistics on reported cases of cholera, Mukandavire and colleagues (11) estimate the Ro for the massive country-wide cholera epidemic in Zimbabwe that occurred in 2008–2009, with nearly 100,000 reported cases and over 4,000 deaths. Estimates of Ro varied between the country's 10 provinces, but within a relatively modest range from just over 1–2.72. The greatest contribution to Ro in this setting was human-to-human transmission, either directly or indirectly via contamination of food or water. This is not surprising, because Zimbabwe is a landlocked country that lacks the major estuarine reservoirs for cholera seen in many cholera-endemic settings. The authors project that these estimates of Ro are consistent with the notion that future cholera epidemics are likely and that these epidemics could be prevented with mass immunization with killed oral cholera vaccine at relatively modest levels of vaccine uptake (13–81%, depending on the setting). Although these projections of potential vaccine impact are not based on detailed analyses of vaccine introduction strategies and they do not account for concomitant nonvaccine interventions to control cholera, they provide notional evidence that because of the absence of estuarine reservoirs, mass immunization might eliminate cholera from this country, which suffered

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from cholera yearly between 1998 and the time of the modeled outbreak.

Chao and colleagues (12) take the proposition of using killed oral cholera vaccine a step further, with a detailed analysis of the hypothetical impacts of several realistic introduction strategies for oral cholera vaccines had they been deployed in the major epidemic of cholera in Haiti that began in October 2010. To date, this epidemic has caused more than 250,000 cases and 4,500 deaths. The epidemic in Haiti was very explosive, probably reflecting the absence of preexisting population immunity to cholera, which had not occurred in Haiti in over a century; the crowded and unhygienic living conditions, which were worsened by an earthquake and a hurricane; and the existence of rivers to augment transmission. Using an individual, agent-based, dynamic transmission model that attempted to capture the geographical complexity of the Haiti epidemic through use of both ecological and individual-level variables, this analysis estimates the average country-wide Ro for the epidemic to be 2.6. However, there was a major heterogeneity of transmission, depending on the proximity of one's residence to a river, with local reproduction numbers of 10.0 for populations living along rivers and 0.8 for other persons. Because most cases arose in these very high transmission areas, the herd protective effects of vaccination were projected to be minimal.

The analysis revisits what might have happened in Haiti had immunization with a killed oral cholera vaccine been undertaken preemptively before the epidemic, which is typically thought of as a best-case scenario in terms of vaccine impact, or reactively beginning 21 d after the first reported cases, a scenario that might be possible with a well-functioning global cholera vaccine stockpile. In circumstances in which quantities of available vaccine are sufficient to cover less than 50% of the entire population, a reactive vaccination strategy preferentially targeting populations residing along major rivers, which were considered high risk, was projected to have a greater impact than random preemptive vaccination of the same percentage of the general population. At all levels of vaccine coverage for reactive vaccination strategies, targeted vaccination of high-risk populations was projected to have a greater impact than either random mass immunization of the general population or ring vaccination of small subpopulations in which cases were being reported. Importantly, the models projected that improvement of personal hygiene would add substantially to the impact of vaccination.

The analysis of Chao et al. (12) suggests that a relatively small supply of cholera vaccine could have been efficiently deployed, with substantial impact, if it had been targeted to high-risk populations shortly after the epidemic began. The analysis may have overestimated the value of targeted reactive vaccination of high-risk populations, because high-risk populations were identified with the benefit of hindsight. On the other hand, the analysis is conservative in that it considers only a several-month time horizon, thereby excluding the impact that vaccination would have over the long term if cholera continues to occur in Haiti (14). Also, in agreement with other recently published models of cholera in Haiti, the analysis of Chao et al. (12) predicts that use of oral cholera vaccine will complement improvements in water and sanitation in the prevention of cholera (15, 16). Although the analysis does not consider the use of antibiotic therapy of cholera patients, another analysis of the Haiti cholera epidemic suggests that this may also have an impact on transmission, as predicted by the known efficacy of appropriate antibiotics in reducing the duration of illness and fecal excretion of *V. cholerae* 01 in patients who have cholera (15). In aggregate, these findings suggest that the public health community has multiple valuable and complementary tools, including vaccination, in its armamentarium to control cholera, none of which is fully adequate on its own, and that all tools at our disposal should be used in these epidemics.

Future Needs

It must be recognized, however, that these mathematical models, no matter how sophisticated, are simplifications of reality, rely on many assumptions, and are calibrated against routinely reported cholera surveillance data whose accuracy may at times be suspect. Thus, although the models provide important guidance about the potential of cholera vaccines in settings like Zimbabwe and Haiti, they are not a substitute for careful analysis of the costs, feasibility, and impact of cholera vaccine actually deployed under realistic public health conditions. Studies of this sort, which are especially sparse for reactive cholera vaccination (17, 18), constitute a high priority (9). However, deployment of cholera vaccines and study of vaccines thus deployed will be rhetorical if the current status quo of limited oral cholera vaccine production and the absence of a well-coordinated global mechanism for efficient vaccine distribution continue. For a vaccine such as killed oral cholera vaccine, which has a very small commercial market, ensuring that vaccine will be produced and available when needed will require that the public sector provide purchase guarantees to vaccine companies. An attractive short-term solution for such a guaranteed purchase, as well as for coordinated and efficient provision of vaccine to affected populations, is a global cholera vaccine stockpile analogous to stockpiles that have been successfully used for yellow fever and meningitis vaccines (19). Such a stockpile has been proposed and even recommended over a decade ago by a group of experts convened by the WHO, but it has never been implemented (20). The time for such a stockpile has clearly come.

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