A Mathematical Approach Lights up The Way to End Cholera Transmission

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In Western countries, the word cholera might sound like something belonging to the past. On the contrary, cholera still affects millions of people every year, with an estimated 120,000 deaths in 2014. The most affected area is the Bay of Bengal, where *Vibrio cholerae*, the etiologic agent of cholera, is an autochthonous resident of the Ganges river delta. Although the final solution to the epidemic is universal access to clean water, hygiene, and sanitation, oral vaccines represent a temporary solution to limit cholera cases and ultimately deaths. Although oral cholera vaccines have been proven safe and effective, their widespread use is difficult to justify economically, given the low mortality rate and incidence of the disease in most settings, even in endemic areas. However, large trials demonstrated that sufficient vaccine coverage leads to protection not only directly, but also through indirect mechanisms that benefit unvaccinated individuals. This aspect complicates attempts at cost-benefit analyses. Mathematical models are a powerful tool that can account for direct and indirect effects of vaccination campaigns.

Dr. Dobromir Dimitrov and colleagues from the Vaccine and Infectious Disease Division (VIDD), in collaboration with co-investigators from the University of Florida, published a study on *PLoS Neglected Tropical Diseases* in which they present their estimates on the effects of different strategies for vaccination against cholera in Bangladesh. "A key feature of the model is that it integrates two transmission cycles", explained Dr. Dimitrov. "It allows estimating for transmission by contact with infected individuals (short cycle transmission) or by exposure to cholera in the environment (long cycle transmission). It makes this modeling approach applicable when other diseases such as typhoid are investigated. The current version of the model reproduces well the dynamics of endemic cholera from Matlab, Bangladesh. We plan to extend the analysis to non-endemic settings in Africa using data provided by the African Cholera Surveillance Network (AFRICHOL). We are also working on evaluating the cost-effectiveness of different vaccination strategies in medium- and high-incidence states in Bangladesh to help planning for widespread cholera vaccination in Bangladesh and other countries."

To identify the best strategy, the study focused on two main aspects: age of the target population and frequency of the vaccination campaign. Given that cholera affects primarily children, the model was applied to the total population, children 1-14, and children 1-4. The study showed that vaccinating the whole population averts the greatest number and fraction of cholera cases while vaccinating children is more efficient measured by the number of vaccinations per cholera case averted.

The study also compared the effectiveness of continuous compared to campaign vaccination strategies. The administration of the vaccine in a routine, continuous strategy maintains a high level of immunity and stops transmission of cholera at about 70% coverage. In contrast, the campaign strategy every five years averts a significant fraction of cholera cases but allows outbreaks due to waning of the immune response over time and the introduction of new susceptible individuals, through new births and migratory flux.

The proposed approach, while maintaining the limits of a mathematical model, offers a solid platform to plan an effective and efficient strategy for vaccination. First, a once a year vaccination campaign would offer the same level of protection of a continuous vaccination strategy, while making its implementation more feasible. Second, while targeting the pre-school aged children could build upon pre-existing delivery programs, it would likely not suffice to eliminate cholera transmission. Finally, the provided data allow for an estimation of the cost to benefit ratio that could be used by policy makers to decide which strategy to use.

"Mathematical modeling already plays an important role in assessing the potential impact of vaccination programs and other prevention interventions taking into account the existing epidemiological and prevention context." confirmed Dr. Dimitrov. "It is a valuable tool which allows interpreting the efficacy results from completed clinical trials and translating them into realistic projections of population level effectiveness and cost-effectiveness. As a member of the HPTN Modelling Center and the Center for Statistics and Quantitative Infectious Diseases, I witness the increasing interest in utilizing math modelling analyses at different stages of the infectious disease prevention process: to inform product development, to identify optimal combination prevention, to design and conduct of large community-based clinical trials, and help generalize results. Most importantly, modeling results often provoke debates among researchers, funders and policy makers and lead to shift in thinking about optimal resource allocation."

In this case, we hope that the efforts made by Dr. Dimitrov and his co-investigators at the Fred Hutch can drive the efforts needed to eliminate cholera.

Dimitrov DT, Troeger C, Halloran ME, Longini IM, Chao DL. 2014. Comparative effectiveness of different strategies of oral cholera vaccination in bangladesh: a modeling study. PLoS Negl Trop Dis, 8(12), e3343.

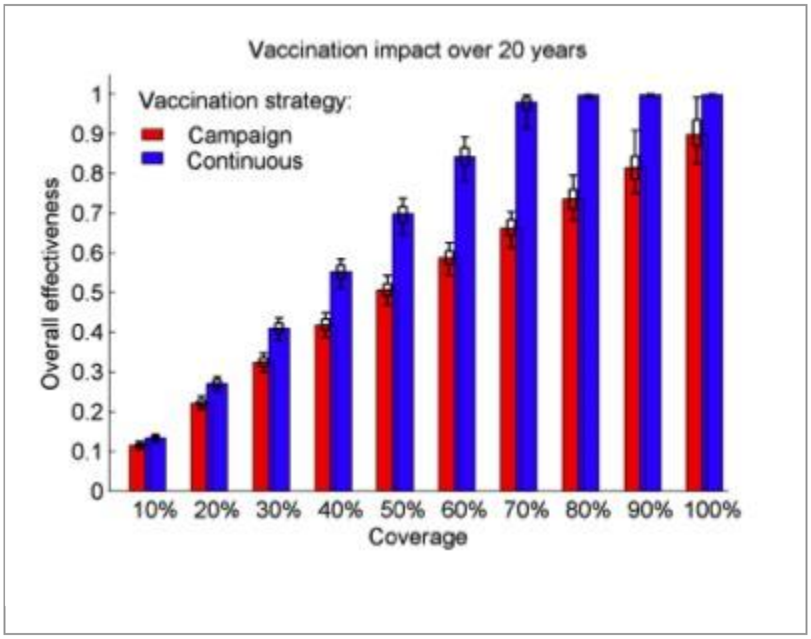

Image provided by Dr. Dobromir Dimitrov

Modeling 5-year campaign and continuous vaccination strategies for different coverage levels. The overall effectiveness is the prevented fraction of cholera cases over 20 years. The vaccine was assumed to protect for an average of 5 years and is less effective among children from ages 1 to 4 years (40% efficacy) than among older individuals (65% efficacy). The bars represent the median values, the boxes represent the interquartile range and the whiskers cover 90% of the results from 100 simulations per scenario with parameters of seasonal environmental exposure sampled from ranges based on data from Matlab, Bangladesh.