

## Moving cholera vaccines ahead of the epidemic curve

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The ongoing multi-country cholera outbreaks deserve greater attention and higher prioritisation globally.<sup>1</sup> Since the early 1800s, there have been seven characterised global outbreaks of cholera. The seventh and current pandemic has been causing considerable illness effects since the early 1960s.<sup>2</sup> Most recently, floods, droughts, natural disasters, and conflicts have displaced millions of people who have restricted access to clean water and live in settings with poor sewage management and increasing disease risk, further increasing the devastating effect of cholera around the globe.<sup>3</sup> Currently, 1 billion people are at risk of contracting cholera and, concerningly, 28 countries with outbreaks in 2023, and 24 countries with active outbreaks were recorded by WHO by Sept 10, 2023 alone.<sup>4</sup> In addition, recent outbreaks have had a high case fatality rate.<sup>5</sup> The average cholera case fatality rate reported globally in 2021 was 1.9% (2.9% in Africa), a significant increase above the accepted target rate (<1%) and the highest recorded in over a decade.<sup>1,5</sup> Preliminary data suggest a similar trend for 2022 and 2023.<sup>1</sup> Cholera is an old adversary that is both preventable and treatable.<sup>5</sup> Despite widespread calls for strengthened pandemic preparedness and response, the global public health community are failing to apply lessons learned from COVID-19 to old challenges such as cholera. A key lesson learned from the COVID-19 pandemic is that early, rapid, and aggressive action is crucial in implementing public health interventions and countermeasure development.<sup>6</sup>

An effective two-dose oral regimen of cholera vaccine exists and provides immunity that lasts for approximately 3 years, but a global shortage of vaccine has exacerbated the crisis.<sup>7</sup> These shortages are not necessarily happening solely because of the global surge in cholera cases, but are also due to vaccine manufacturers' collective lack of interest in producing cholera vaccines.<sup>8</sup> The oral cholera vaccine is cheap and requires bulk sales to generate profit, which contributes to the vaccine possibly being of little commercial interest for most companies located in high-income countries. Lessons learned from COVID-19 vaccine development and production in the USA include Operation Warp Speed, a public-private partnership initiated by the US Government with the purpose of making vaccines for COVID-19 that were developed, tested, distributed, and administered in less than a year. The programme incentivised mass production of multiple vaccines and different types of vaccine technologies based on preliminary evidence, allowing for faster distribution if clinical trials showed safety and effectiveness. The plan considered that some vaccines would not prove safe or effective making the programme more costly than typical vaccine development, but that it would potentially lead to the availability of a viable vaccine several months earlier than typical

timelines. This example shows how mechanisms to incentivise vaccine producers can accelerate vaccine development and production.<sup>9,10</sup> The absence of strong leadership in engaging donors is one reason for the lack of such a mechanism for cholera vaccines. The resulting vaccine shortage led the International Coordinating Group on Vaccine Provision to suspend the standard two-dose cholera vaccine regimen in favour of a single dose to ensure greater coverage.<sup>11,12</sup> The lowered dose of the cholera vaccine is a temporary solution as data show similar efficacy in the first year and lower effectiveness over the first 4 years after vaccinations compared with normal vaccine doses.<sup>13</sup>

The 35 million available doses in 2022 have now been depleted and this crucial gap will not be filled before 2025.<sup>14</sup> As cholera has resurged, one vaccine manufacturer from a high-income country producing Comment128 [www.thelancet.com](http://www.thelancet.com) Vol 403 January 13, 2024 20% of the market share has halted production, leaving only one manufacturer to produce the global supply.<sup>14</sup> However, there are some positive developments when it comes to vaccine supply, including an increasing effort by EuBiologics in South Korea to increase its production capacity in 2024, an Indian-based manufacturer (Bharat Biotech) that is developing a new vaccine that could be available in 2025, and a South African manufacturer (Biovac) that should be able to produce oral cholera vaccine by 2027.<sup>14</sup> All these efforts offer hope for additional doses of vaccine produced and supplied locally where needed. Yet, time is of the essence and accelerated vaccine production and deployment is needed now. One of the key challenges facing the continuous stable procurement of oral cholera vaccines by Gavi, the Vaccine Alliance is the lack of predictability of vaccine supplies on a yearly basis since the vaccine is not part of the Essential Programme on Immunization and procured for stockpile and reactive intervention to emerging epidemics and outbreaks.

There is also a need for the development of vaccines that provide longer-lasting immunity and for innovative approaches such as those with probiotics and microbiome development.<sup>15</sup> Innovative incentive mechanisms such as Operation Warp Speed could incentivise more pharmaceutical companies from low-income and middle-income countries to invest in oral cholera vaccine production, to harness technology, and to rapidly stimulate the development of many different safe and effective vaccines. Technology development is also needed for targeted and effective control of cholera outbreaks, including early detection and monitoring, data analytics and prediction, remote health services, vaccination and treatment management, geographical information system mapping, water and sanitation management, public awareness, and education via digital platforms. The question remains whether science and advanced technology can do the same for cholera, a disease that has caused epidemics and pandemics for centuries, as was done for COVID-19.

The most important immediate action in response to the ongoing cholera pandemic is to save the lives of those who are infected. The Global Taskforce on Cholera Control and partners have spearheaded efforts to mobilise available tools for treatment and are advocating for greater and sustained commitment of governments to more resilient health systems and improved water sanitation and hygiene.<sup>16</sup> However, more support is urgently needed, especially in areas of poverty or conflict. The key barriers facing the Global Taskforce on Cholera Control in addition to the lack of sufficient oral cholera vaccine supplies include

insufficient funding for the implementation of multisectoral interventions, the lack of political commitment by countries to prioritise cholera control, and unexpected events increasing the risk of cholera (eg, natural disasters and conflicts).

Funding should be made available for near-patient rapid diagnosis to help hospitals and communities know when cholera is present and a threat and for environmental surveillance with genomic analysis to unveil sources of cholera and permit source control by targeted water sanitation and hygiene interventions. There is an urgent need for a fundraising initiative for cholera control and vaccination programmes. WHO has released in total about US\$10 million for cholera response efforts in 2022–23, yet in September, 2022, UNICEF reported a cholera funding gap of \$11.4 million in Syria alone.<sup>14</sup> Leadership of WHO to engage funders for financial commitments is crucial, as is stronger engagement by national governments. Ethiopia, for example, is attempting to engage bilateral support and South Korea is providing Korean-produced cholera vaccines to many countries via bilateral channels. Specialised agencies, such as the UN High Commissioner for Refugees and the International Organization for Migration should be engaged in cholera control and treatment among refugees and non-state groups.

As has been learned from the global response to COVID-19, there is rightly great concern about being prepared for a new, emergent infectious threat, often referred to as “disease X”;<sup>16</sup> however, our focus should not only be on the possible next pandemic, but crucially also on the current pandemic of cholera that is spreading around the globe. In the context of current challenges, the global community should act quickly to mitigate the growing effect of cholera illness and death by anticipating the effects of accelerating climate change on susceptible communities, responding effectively to humanitarian disasters and mass migration, and supporting health systems and public health measures to diagnose, treat, and vaccinate against cholera.

### **Conflict of interest statement**

LB declares an appointment at the non-profit organisation Right to Care. All authors are members of the Strategic and Technical Advisory Group on Infectious Hazards with Pandemic and Epidemic Potential (STAG-IH) that provides independent advice to WHO. We declare no competing interests.

### **References**

- 1 Thomson F. Responding to the global cholera pandemic. *Bull World Health Organ* 2023; 101: 234–35.
- 2 Hu D, Liu B, Feng L, et al. Origins of the current seventh cholera pandemic. *Proc Natl Acad Sci USA* 2016; 113: E7730–39.
- 3 Tarnas MC, Karah N, Almhawish N, Aladhan I, Alobaid R, Abbara A. Politicization of water, humanitarian response, and health in Syria as a contributor to the ongoing cholera outbreak. *Int J Infect Dis* 2023; 131: 115–18.

- 4 WHO. New analysis confirms world seeing an upsurge of cholera. Sept 22, 2023. <https://www.who.int/news/item/22-09-2023-new-analysis-confirms-world-seeing-an-upsurge-of-cholera> (accessed Sept 30, 2023).
- 5 WHO. Multi-country outbreak of cholera, external situation report #5. Aug 4, 2023. <https://www.who.int/publications/m/item/multi-country-outbreak-of-cholera--external-situation-report--5---4-august-2023> (accessed Sept 5, 2023).
- 6 WHO. Call for urgent and collective action to fight cholera. May 19, 2023. <https://www.who.int/publications/m/item/call-for-urgent-and-collective-action-to-fight-cholera> (accessed June 10, 2023).
- 7 WHO. Cholera vaccines: WHO position paper—August 2017. Aug 25, 2017. <https://apps.who.int/iris/bitstream/handle/10665/258764/WER9234-477-498.pdf?sequence=1> (accessed Sept 1, 2023).
- 8 Odevall L, Hong D, Digilio L, et al. The Euvichol story—development and licensure of a safe, effective and affordable oral cholera vaccine through global public private partnerships. *Vaccine* 2018; 36: 6606–14.
- 9 Serchen J, Cline K, Mathew S, Hilden D; Health and Public Policy Committee of the American College of Physicians. Preparing for future pandemics and public health emergencies: an American College of Physicians policy position paper. *Ann Intern Med* 2023; 176: 1240–44.
- 10 Fauci AS, Folkers GK. Pandemic preparedness and response: lessons from COVID-19. *J Infect Dis* 2023; 228: 422–25.
- 11 WHO. Shortage of cholera vaccines leads to temporary suspension of two-dose strategy, as cases rise worldwide. Oct 19, 2022. <https://www.who.int/news/item/19-10-2022-shortage-of-cholera-vaccines-leads-to-temporary-suspension-of-two-dose-strategy--as-cases-rise-worldwide> (accessed Sept 10, 2023).
- 12 Taylor L. Cholera: WHO rations vaccines to preserve stocks amid rising outbreaks. *BMJ* 2022; 379: o2528.
- 13 Franke MF, Ternier R, Jerome JG, Matias WR, Harris JB, Ivers LC. Long-term effectiveness of one and two doses of a killed, bivalent, whole-cell oral cholera vaccine in Haiti: an extended case-control study. *Lancet Glob Health* 2018; 6: e1028–35.
- 14 Feinmann J. Cholera makes a comeback amid calls to boost vaccine production. *BMJ* 2023; 380: 636.
- 15 Satchell KJF. Engineered bacteria for cholera prophylaxis. *Cell Host Microbe* 2018; 24: 192–94.
- 16 WHO. Global strategic preparedness, readiness, and response plan for cholera. May 19, 2023. [https://cdn.who.int/media/docs/default-source/documents/emergencies/global-cholera-sprp-v7-2023-05-19\\_cleared.pdf?sfvrsn=7b5f7ced\\_1&download=true](https://cdn.who.int/media/docs/default-source/documents/emergencies/global-cholera-sprp-v7-2023-05-19_cleared.pdf?sfvrsn=7b5f7ced_1&download=true) (accessed Sept 1, 2023).