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Devising a viable global strategy to combat Cholera

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Since mid-2021, the world is facing an acute upsurge of the 7th cholera pandemic characterised by the number, size and concurrence of multiple outbreaks, the spread to areas free of cholera for decades and alarming high mortality rates. Based on the current situation and lack of vaccines and other resources, the World Health Organisation (WHO) assesses the risk at the global level as very high.

For reasons not yet fully understood, beginning in 2022 the world experienced an unprecedented surge in cholera outbreaks as characterised by the number, size and concurrence. Cholera is an acute, rapidly dehydrating diarrheal disease transmitted through water or food contaminated with the bacteria *Vibrio cholerae O1*. It is a disease of poverty, primarily affecting people living in areas without access to safe drinking water and inadequate sanitation.

The global burden of cholera is not fully known because of under-reporting, with some affected countries not reporting cases at all to avoid the stigma. One study estimates 1.3 billion people are at risk for cholera in a total of 69 endemic countries, with 2.86 million cholera cases and an estimated 95,000 deaths annually. Most of the global burden is in sub-Saharan Africa (60 per cent) and South-East Asia (29 per cent).

In January 2023, WHO declared cholera to be a grade 3 global emergency, the highest risk level. As of March, there were 24 countries reporting outbreaks, a number expected to increase as most countries are not yet in the high transmission season. The Steering Committee of the Global Task Force on Cholera Control (GTFCC) issued a statement that climate change multiplies the risk of cholera around the world, and the upsurge beginning in 2022 may be the new normal.

Unfortunately, the current global supply of vaccines is insufficient to meet the ongoing surge in outbreaks. As a result of the strained global cholera vaccine supply, in late 2022, the WHO International Coordinating Group (ICG), the body which manages emergency supplies of vaccines, temporarily suspended the standard two-dose vaccination schedule in cholera outbreaks and recommended a single dose instead. This strategy, while expanding the coverage of vaccines to a larger population, may be associated with reduced protection in young children.

Why is it so difficult to fill the gap?

An efficacious whole cell inactivated oral cholera vaccine (OCV) has been available since 2009 following development by the International Vaccine Institute (IVI) and technology transfers to Shantha Biotechnics Ltd followed by EuBiologics Co., Ltd.. Gavi, the Vaccine Alliance has supported a Global Oral Cholera Vaccine stockpile for 39 eligible nations since 2014. To date, more than 100 million doses have been delivered free of cost. Initially, the stockpile was used for emergency outbreak response, but was expanded to preventative campaigns in 2020.

In 2018, GTFCC and the WHO jointly advocated for a shift in strategy, moving vaccine supply from emergency outbreak response to routine preventive vaccine campaigns in at-risk communities to avoid the death, chaos and economic loss inevitably associated with outbreaks of a deadly disease. That year, Gavi modelled a scenario of planned preventive campaigns in at-risk countries that would generate a potential future market demand of 150 million doses per year.

Unfortunately, Shantha discontinued production of one of the two stockpiled products in 2022, leaving only a single producer, EuBiologics, capable of supplying about 36 million doses per year. In 2022, the requests for vaccine from Gavi's stockpile exceeded 70 million doses for the emergency responses alone. Current vaccine supply is insufficient to manage the ongoing surge in outbreaks, much less the imagined happy state of routine planned preventive interventions.

Historical barriers to vaccine development and commercialisation are availability of technology, regulatory hurdles, profitability, and secure demand. Are these barriers for cholera vaccines?

Technology availability: The technology and know-how to manufacture OCV is available and transferrable, with IVI conducting technology transfers with qualified manufacturers to produce biosimilars of the currently approved vaccines.

Regulatory hurdles: The second WHO-prequalified OCV, Euvichol, was licensed based on an immunological non-inferiority study to the first OCV, Shanchol. Therefore, a feasible regulatory pathway seems to exist for additional biosimilars to receive approval.

Profitability: For certain, the current OCVs are offered to Gavi as low-cost vaccines and commercial success is dependent on the low cost-high sales volume model familiar to many Developing Country Vaccine Manufacturers.

Demand: While the potential demand is forecast as large, there remains demand uncertainty. The requirements for emergency use may vary wildly from year to year. The realisation of the demand for routine planned preventive campaigns in at-risk countries is dependent on countries completing somewhat complex multi-year applications to Gavi. Several countries have completed their applications, but the vaccine has been unavailable for preventive campaigns because most of it has been deployed to emergency response. The unavailability of vaccines may itself be a disincentive for additional countries to complete applications. Improvements in demand forecasting are desperately needed to achieve a stable vaccine market.

There are at least two new entrants into the market of whole cell inactivated OCVs expected in the next few years as well as expansion of production capacity at the current supplier. Greater supply will improve the situation and, perhaps, aid a shift away from reactive responses to outbreaks and towards prevention. However, even this incremental expansion in supply seems unlikely to fill the need for cholera control and more manufacturers should consider entering the field.

The current generation of OCVs have been game changers, but they are not perfect. Protection is generally considered to be for 3-5 years, and efficacy is relatively poor in young children as compared to adults. There is room for innovation and improvement beyond biosimilars. However, the high costs and risks associated with novel vaccine development often require a high return on investment by manufacturers and investors, making vaccines targeting diseases mainly found in low- and middle-income countries unattractive.

Fortunately, there remain several philanthropies and Product Development Partners (PDPs) like IVI supporting early development of innovative new products, such as a highly thermostable oral capsule vaccine and an injected cholera conjugate vaccine (CCV). The thermostable capsule vaccine has several preferred consumer characteristics and could result in dramatically reduced delivery costs, as a result of its lightweight and compact packaging without cold chain requirements.

Under the Gavi model, countries will gradually take on co-funding of vaccines in parallel with their economic development and products that lower delivery cost may become increasingly attractive. One of the shortcomings of current OCV is reduced protection in young children. Considering the enormous global impact of bacterial conjugate vaccines on preventing bacterial diseases in infants and young children, CCV truly has the potential to be another game changer by protecting the most susceptible to disease and enabling efficient cholera prevention through routine early childhood Expanded Programme on Immunisation (EPI).

As with any new technology, there are areas of uncertainty that may cause hesitation. For instance, commercial manufacturers may wonder if innovative approaches will work as well as current products, what profitability and demand will look like in a landscape with multiple product choices, or what clinical development and regulatory strategy would be required to demonstrate a new product's safety and impact.

As has been the case with other global health products, many apparent obstacles can be overcome when commercial entities are willing to engage in multi-stakeholder partnerships with philanthropic support to bring to market safe, effective, and affordable vaccines against neglected diseases such as cholera.

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