

How can investing in technology transfers help build a sustainable manufacturing ecosystem? An example from cholera

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“New manufacturers with greater geographical diversity for oral cholera vaccine are required”

VIEWPOINT

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THE CHOLERA PANDEMIC

The world is currently facing an upsurge of the seventh cholera pandemic, with

Zambia being the latest country to report unprecedented outbreaks with more than 12,000 cases and 467 deaths already in 2024 [1]. Cholera is an acute diarrheal disease that

spreads rapidly throughout communities faced with inadequate access to safe water and basic sanitation, with the greatest burden occurring in Africa and Asia [1]. This burden has been compounded in recent years by an intensification of the climate crisis, conflicts, political instability, and humanitarian emergencies [2]. Whilst long-term disease control will rely on access to safe water and sanitation, vaccination is key to immediate control.

In 2013, the WHO created a global stockpile of oral cholera vaccine (OCV) [3]. Since then, demand for vaccines has grown, with Gavi estimating the average annual demand between 2023 and 2030 to be approximately 85 million doses [4]. The stockpile originally included Shanchol™ (Shantha Biotechnics) and Euvichol-Plus® (EuBiologics Co., Ltd), however Shantha Biotechnics ended production and distribution of Shanchol™ at the end of 2023 [5]. This left EuBiologics as the sole manufacturer of cholera vaccines. As outbreaks continue to rise and with new manufacturing capabilities taking years to build, a worrying and increasing mismatch between supply and demand is projected. As a short-term solution, in 2022 the International Coordinating Group (ICG; the body that allocates OCV), switched from a two-dose to a one-dose OCV strategy for outbreak response campaigns [6].

A year later, the one-dose strategy still prevails. In 2023, all 36 million OCV doses manufactured were delivered in one-dose reactive campaigns, with a remaining estimated 70 million annual dose gap [7]. New manufacturers with greater geographical diversity for OCV are required, but the question the world was faced with was ‘how can supply be rapidly increased?’

WHAT ACTION IS BEING TAKEN?

Whilst cholera outbreaks were increasing, the world’s attention was on the recovery from COVID-19 and preparation for future outbreaks, with equity at the heart of many of these discussions. Significant political

attention led to the African Union and Africa Centres for Disease Control and Prevention launching the ‘Partnerships for African Vaccine Manufacturing’ (PAVM) in 2021. The goal was to strengthen the African vaccine manufacturing ecosystem, with the ambition of locally manufacturing 60% of Africa’s routine immunization needs by 2040 [8].

In response, Wellcome commissioned a report in 2023 to better understand the perspectives of African manufacturers on the challenges to scaling up vaccine-manufacturing capacity and capabilities. The three main challenges (beyond market-access prerequisites) that were highlighted for support were [9]:

1. **Access to finance:** provision of specialized and cost-effective funding options with extended repayment periods;
2. **Talent:** provision of assistance to support African manufacturers in acquiring practical experience through secondments with seasoned manufacturers and facilitation of international experts in local manufacturing operations;
3. **Transfer of technology:** funding and collaboration with African manufacturers to facilitate the transfer of technology, enabling capacity development so these manufacturers become viable candidates for private partnerships.

Global discussions on increasing manufacturing capability and technology transfers have centered around mRNA vaccines, with multiple new initiatives (e.g., WHO mRNA hub, BioNtech/CEPI) [10,11]. The unanswered question is how to sustain these new initiatives. With the exception of COVID vaccines (where demand is waning), there are no vaccines licensed on an mRNA background. For manufacturers to build a sustainable business there needs to be a clear demand for the vaccine.

Gavi published a white paper in November 2022 highlighting a clear supply need for certain vaccines in their portfolio

and signaling possible market demand that would be attractive for manufacturers. This included cholera, measles-rubella, yellow fever, Ebola, and malaria vaccines [12]. Given that the African continent has the largest cholera burden, but that no cholera vaccines are manufactured on the continent, this emulates the exact vaccine equity that the PAVM was initiated to address.

A STEP CLOSER TO SUSTAINABILITY AND INCREASED OCV SUPPLY

Technology transfers are not straightforward—they can fail at many different stages and take significant time (e.g., the transfer of Hib vaccine to Fiocruz from GSK took 8 years) [9]. This is often a barrier to bringing a new platform, vaccine, or part of the process into a manufacturing organization, and where philanthropy is often called on to contribute. In November 2022, with funding from the Gates Foundation and Wellcome Trust, the International Vaccine Institute (IVI) entered into a technology transfer agreement with Biovac to manufacture OCV-s (simplified OCV) in Africa, with the long-term goal of WHO pre-qualification [13]. Whilst there are many barriers to face before this transfer starts to alleviate the strained stockpile, it is a start towards developing a diversified OCV manufacturing ecosystem.

The technology transfer brings with it the opportunity to build talent and expertise in the African continent by transferring know-how to Biovac, as well as the capabilities to develop and manufacture drug substance. OCV-s has a clearly defined regulatory pathway to licensure; the South African Health Products Regulatory Authority can build expertise in overseeing and regulating the manufacture of clinical trial products and building an ecosystem capacity beyond Biovac within South Africa.

The Global Task Force for Cholera Control (GTFCC) was endorsed by the World Health Assembly in 2018 to reduce cholera deaths by 90% and eliminate local transmission in at least 20 countries by 2030 [14,15]. Alongside a reliable, geographically diversified supply, other evidence gaps such as effective prediction of local outbreaks and increasing cholera incidence are critical to enable effective cholera control. This type of holistic approach is needed to connect research on transmission, vaccine duration and effectiveness, water, sanitation, and hygiene, together with policymakers at a global, regional, and national levels. These ambitious goals merit a concerted global effort to improve the reactive and unsustainable cholera control options many countries require today alongside cholera control in the future through preventative OCV campaigns.

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BIOGRAPHIES

JEANETTE HAYES is a Research Manager in the Vaccines team which sits within the Infectious Disease Health Challenge area at Wellcome. She joined Wellcome at the beginning of 2023 and has been involved in managing a portfolio of projects that largely focus on cholera, ranging from early product development for new cholera vaccines to later stage vaccine effectiveness studies generating new evidence required for policy decisions. Before joining Wellcome, she worked in public health in an evidence and intelligence team for a local council in the UK, carrying out data analysis which was used to help guide local health policy decisions. Prior to working Jeanette studied infectious diseases for 4 years at the University of Edinburgh before completing her masters at the London School of Hygiene and Tropical Medicine.

CHARLOTTE WELLER is Head of Prevention in the Infectious Diseases Area at Wellcome. Since 2016, she has led a team to develop new and improved vaccines and antibodies, gaining a better understanding of protective immunity and strengthening the connection between research and decision makers. Charlotte joined Wellcome in 2014 and led the funding response to the Ebola epidemic of 2014 to 2015 and managed the epidemics research activities. Charlotte was involved in founding CEPI and currently chairs CEPI Investors Council and contributes to a number of national and international advisory committees in vaccines and epidemics. Before joining Wellcome Charlotte gained over 16 years of research experience in both academic and pharmaceutical environments, ranging from host pathogen interactions to cellular and molecular immunology. Including leading target identification and validation in the respiratory disease area at Novartis. Prior to this, Charlotte investigated cell localization and function in health, respiratory disease and parasite infections as a postdoctoral fellow at Imperial College London. She holds a PhD in Immunology at Imperial College London.

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