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Perspective

Vaccines for neglected tropical diseases: Learnings from COVID-19

The fiftieth anniversary of the Expanded Programme on Immunization (EPI) is an occasion to celebrate. To celebrate the 154 million lives saved from vaccine preventable disease, and also for creation of a vaccine delivery system in every country of the world that is able to reach around 85 per cent of children[1]. Starting from six, the EPI today delivers more than 13 vaccines across the life course globally[2]. When launched, the EPI addressed immunization for children alone; however, the addition of new vaccines has increased the beneficiaries to include older children, adolescents, and adults. This programme has evolved into what is now commonly known as the Essential Programme on Immunization. The latest vaccine to be added is COVID-19 for adults[3].

The COVID-19 pandemic had the fastest response, regulatory emergency authorization and roll out in vaccine history. There is still much to learn about how the vaccines were developed at 'pandemic speed' and converted into vaccinations for every country in the world that asked for it. This may be helpful in the development and deployment of vaccines for other health conditions. It offers a glimmer of hope for the vaccines for neglected tropical diseases (NTDs).

The NTDs are a mixed bag of ailments caused by bacteria, viruses, fungi, parasites, and toxins. They are known to be associated with devastating social, health, and economic consequences. Currently, World Health Organization (WHO) recognizes 21 diseases as NTDs[4]. These are mostly prevalent among the poor and neglected communities, particularly in tropical areas.

The WHO's 2021–2030 roadmap for NTDs *inter alia* targets for a 90 per cent reduction in individuals needing interventions against NTDs; and a 75 per cent reduction in the disability-adjusted life years (DALYs) related to NTDs[5]. For some countries, effective interventions including vaccines exist but are largely underutilized, while for others, either vaccine development is needed or the vaccine use needs to be expanded for meeting global targets on control and elimination[6].

For the soil transmitted helminths, the main stay for control and treatment has been drugs. As the patients do not develop immunity to the infection, the medicines must be taken repeatedly year after year to prevent re-infection[7]. However, several such treatments suffer from shortcomings including toxicity, drug resistance, and limited efficacy in context to the various parasitic stages. In such situations drugs alone will be insufficient to interrupt the transmission. Vaccines offer hope[6].

The NTDs like dengue and chikungunya have been receiving global attention and funding as these have epidemic potential. For example, chikungunya is part of the portfolio of Coalition for Epidemic Preparedness Innovation (CEPI) for vaccine development[8], and one of the three vaccines it supported in late stage development has been approved by the US Food and Drug Administration, and the European Medicines Agency[9]. Similarly, there are currently two licensed dengue vaccines, and a third one is in clinical development late stage[10].

In 2023, the global market for dengue vaccine was evaluated at US$ 589 million and this is projected to go up to US$ 1.6 billion by 2030[11], Similarly, the global market for chikungunya vaccine is expected to grow from US$ 264 million in 2022 to around US$ 625 million by the year 2032[12]. Given the market size it is no surprise that there is considerable interest in their vaccine development. But such is not the case with most of the other NTDs. Some examples of other NTDs being targeted by human vaccines include, hook worm, visceral and cutaneous leishmaniasis, leprosy, onchocerciasis, rabies, schistosomiasis, trachoma, and yellow fever[13,14].

Challenges in development of vaccines for NTDs

Developing vaccines for NTD's have several challenges[13,14] including: (*i*) many organisms causing NTDs have complex structure/life cycle making identification of protective antigens difficult for inclusion in the vaccine; (*ii*) most low- and middle-income countries (LMICs) which are hosts to NTDs,

barring a few, also have limited capacity to invest in research and development (R&D) for vaccines and have poor access to modern technology. Finding donors for vaccine development for NTDs has not been successful at all times;(*iii*) uncertain market does not assure vaccine sales. Due to this there is little incentive for multinational companies to invest in them. Furthermore, a challenging regulatory pathway to market authorization is a deterrent. Overall the market for NTD vaccines is likely to be limited; and (*iv*) the Governments of LMICs are believed to be the major buyers for the vaccines for NTDs, but their poor public health infrastructure is likely to pose a significant challenge for receiving and delivering them.

Lessons learnt from the COVID-19 vaccine experience

De-risking vaccine development to encourage vaccine manufacturers: Tens of billions of dollars were provided for COVID-19 vaccine research and development[15]. Governments and other agencies (like the World Bank, CEPI) signed advance purchase agreements / advance market commitments (AMC) for their purchase. Gavi set up the COVAX Advance Market Commitment (AMC92) to enable the 92 LMICs to access the COVID-19 vaccines[16]. A similar approach which incentivizes vaccine makers to produce the needed vaccines without the fear of market failure will be necessary for NTD vaccines as well.

Use of new technology: All 183 COVID-19 candidate vaccines developed on 11 platforms were in various phases of clinical development and 119 were in pre-clinical stage as of March 30, 2023[17]. It was possible to develop, viral-vectored mRNA as well as whole inactivated virus vaccines rapidly compared to other technologies, such as live attenuated and subunit vaccines, since each required extensive manufacturing and process development[18]. It was essential to try different approaches as one did not know which one would be successful. For instance, a replication-competent vesicular stomatitis based approach was successful for Ebola virus, but not for COVID-19[19].

Hence, multiple approaches are needed to develop vaccines for NTDs because of their complexity and the need for low-cost vaccines.

Tech-transfer and improving manufacturing capacity in LMICs: One of the important lessons learnt from COVID-19 is the need to diversify production of safe and efficacious health products including vaccines and expand their local production, especially in LMICs. The WHO has committed to facilitate mRNA technology transfer to six African countries (Nigeria, Kenya, Egypt, Senegal, Tunisia and South Africa)[20].

Tech-transfer alone will not translate into improving access unless the vaccine manufacturers' capacity is also increased. Multiple high-level regional efforts, such as the Partnership for African Vaccine Manufacturing (PAVM), are now underway to increase the manufacturing capacity in LMICs.[21] For example, in 2022, Moderna announced that it would build a USD 500 million plant in Kenya in order to manufacture 0.5 billion doses of COVID-19 vaccine annually. BioNTech is also building facilities in Rwanda, Senegal and South Africa. Gavi too has committed up to USD 1 billion[21]. Innovations, for example, adenovirus, mRNA, and particle vaccines, along with the ability to produce these at large scale and at low-cost hold much promise for improving access and may prove to be helpful for vaccines for NTDs.

Capacity strengthening of the National Regulatory Authorities (NRA): Given the uncertainty of the market for low-cost NTD vaccines and lack of incentives, chances are that a vaccine for a NTD will be produced in a LMIC rather than by a multinational. Currently, vaccines produced in LMICs are required to go through either a WHO pre-qualification process or a stringent regulator to obtain global distribution authorization. Presently all the stringent NRAs are located in HICs and have experience of global health threats but may have little or no experience about a vaccine for NTDs[19]. It is important to strengthen the capacity of some of the NRAs in LMICs from being a well-functioning stable, and integrated regulatory system (Maturity level 3 – ML 3) to an advanced level of operational performance and with continuous improvement (ML 4), at the level of stringent NRA[19,22]. This will not only ensure the safety, efficacy, and quality of vaccines manufactured in LMICs but also permit a vaccine approved by an ML-4 NRA to be considered for global distribution by the WHO.

Speeding up regulatory reviews: Some regulatory agencies around the globe that received COVID-19 vaccine trial data used a 'rolling review' concept. These data were submitted and reviewed as and when these became available, without waiting for the full report at the end of the trial. European Medicines Agency was able to provide decisions between 17 and 36 days, against a maximum timeline of 210 active days[23]. It is

hoped that rolling reviews would be institutionalized and become available as a regulatory tool in a non-pandemic situation where the 'pandemic urgency' may be lacking, including vaccines for NTDs.

Ensuring no one gets left behind: The purpose of creating the COVID-19 Vaccine Global Access (COVAX) was to accelerate the development as well as manufacture of COVID-19 vaccines while ensuring fair and equitable access for every country in the world. COVAX was envisioned as an end-to-end coordination mechanism for a gamut of activities. It delivered nearly two billion vaccine doses to 146 economies and assisted lower-income economies to achieve two-dose coverage (57%), compared to the global average (67%)[24].

Ghana was one of the first countries to receive a vaccine consignment from the COVAX. It was also the first country in Africa to use drones for distributing COVID-19 vaccines in difficult-to-reach areas within the country while maintaining the cold chain requirements[25]. Pilots in countries like Ghana were followed up by intense trials in India using drones to deliver healthcare products in different terrains including Telangana, and the difficult Himalayan region of Arunachal Pradesh[26]. A study funded by Indian Council of Medical Research further established their utility across diverse climatic, operational and geographical conditions, especially in the harsh terrain of Manipur and Nagaland in Northeast India[27]. By successfully providing last-mile delivery of vaccines in remote and hard-to-reach areas, the hope that drones bring in securing equitable quick access to vaccines is particularly relevant in the context of the NTDs.

Vaccine hesitancy: An umbrella review on COVID-19 vaccine hesitancy across diverse populations and regions indicate a pooled vaccine hesitancy of 32 per cent (95% CI: 0.25-0.39) in general population globally. If this is happening for a pandemic disease, the naysayers are likely to be much more for endemic diseases. Widespread dissemination of misinformation and anti-vaccine propaganda and disinformation is common across the African countries and LMICs in Asia[28]. This challenge could limit the progress and uptake of vaccines being developed for NTDs.

Over the past two years several of these lessons learnt for pandemic preparedness have been translated into actions. Notably the transfer of technology for mRNA platform, and capacity building for vaccine manufacturers for COVID-19 vaccines, especially in Africa has been disappointing. Some investments have been paused / halted and losses written off, as there was no demand for COVID-19 vaccines. The lesson is that these set of activities need to be complemented by demand generation for the vaccines. To have better vaccine manufacturing facilities in the country / region, the countries should be willing to pay higher prices for in-country made vaccines compared to the similar vaccine made by large companies and sold at lesser costs[21].

The rapid development and approval of six vaccines for COVID-19 in a record time has heralded a new era and sets the bar high. This approach may be helpful in the development and deployment of vaccines for other health conditions like neglected tropical diseases. The way has been paved for others to follow. At the same time, one needs to recognize that the conditions favourable for rapid COVID-19 vaccine development were unique and may not be replicable for vaccines for NTDs.

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