Considerations for Vaccine Efficacy Trials Targeting Emerging Infectious Diseases

While the scale and global impact of the COVID-19 pandemic was unprecedented, its origins as an emerging infectious disease (EID) was not – what lessons must be learned to prevent future other EIDs developing into disasters on a similar scale?

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Emerging infectious diseases pose a global public health risk. Without prompt containment and control, local outbreaks of an EID can snowball into a global pandemic. SARS-CoV-2 has been a particularly disastrous EID. However, the COVID-19 pandemic was neither unprecedented nor unexpected. Anthropogenic factors, including globalisation, urbanisation, and antimicrobial misuse, have increased the frequency of EID outbreaks (1). Managing these outbreaks will be a primary public health concern for the foreseeable future.

Vaccines are the most reliable way to diffuse the risk of an EID (2). They have been instrumental in the eradication of smallpox, and in the control of diseases including polio, measles, and influenza (3). Most recently, vaccines have proven pivotal to the control of the COVID-19 pandemic (4). The speed of COVID-19 vaccine development – just under a year – was unprecedented. In comparison, the traditional vaccine development timeline is 5-10 years; much too long for vaccination to be used as a containment strategy for an EID, unless a previously developed vaccine is already able to combat it (for example, monkeypox can be combatted with the vaccine originally developed for smallpox) (2).

One reason for lengthy vaccine development timelines is the difficulty establishing efficacy. While vaccine candidates can be developed and tested in the absence of an outbreak, efficacy trials must be conducted in a population where there is active transmission of the target disease. For diseases that are emergent, rather than endemic, when and where an outbreak will occur is difficult to predict. Moreover, initiation of a clinical trial must happen before an identified outbreak wanes, while there are still enough individuals at risk of infection for the trial to have statistical power.

This article will review outbreak surveillance infrastructure and clinical design strategies that have helped vaccine efficacy trials be responsive and adaptable enough to combat emerging infectious diseases, and will discuss how these strategies could be implemented to control or prevent future pandemics.

Disease Surveillance and Reporting

Without robust surveillance and reporting for a target disease, vaccine development can be impeded by an inability to select appropriate sites or enrol enough target patients to establish efficacy. A prime illustration of this is respiratory syncytial virus (RSV) vaccine development. RSV is a respiratory disease that can cause severe outbreaks in livestock and humans. But these outbreaks are seasonal, brief, and difficult to predict or identify. In a single area, an RSV outbreak may occur once every decade and last only a few months. When outbreaks occur, they are difficult to identify because the disease has non-specific symptoms and is difficult to diagnose. Despite successful RSV vaccine

development for livestock in the 1950s, human vaccines have been in development for decades. In March 2022, the FDA granted breakthrough therapy designation for a human RSV vaccine, but no vaccine has yet achieved approval. A recent report by the World Health Organization (WHO) identified an early outbreak detection system as an essential, but missing, element of the RSV vaccine development effort (5).

One promising initiative for early outbreak detection and disease surveillance is wastewater monitoring. This method may be especially useful for diseases such as RSV where clinical surveillance is challenging, but the tracking of outbreaks is required to initiate public health response. Wastewater concentrations may allow insight into when infection rates begin to rise and may be especially useful for identifying unusual season trends in diseases (6). Recent research validating the wastewater monitoring method for RSV, COVID-19 and antimicrobial resistance suggests that the method may be effective for cost-effective, population-wide surveillance of a variety of diseases (6, 7, 8).

> *Unreliable and decentralised data proved a major challenge during vaccine development for COVID-19*

Another vital component of disease surveillance infrastructure is smart data reporting. Epidemiological information gathered by surveillance systems must be reported so that it can be readily accessed, interpreted, aggregated, and acted upon. Unreliable and decentralised data proved a major challenge during vaccine development for COVID-19. Efforts to centralise and standardise data and its accessibility, and modernise the US's outdated public health data system, include the recent launch of the Centers for Disease Control and Prevention's Center for Forecasting and Outbreak Analytics (9). Other pre-existing successful surveillance and reporting programmes include the WHO's Global Influenza Surveillance and Response System, and the Global Initiative on Sharing All Influenza Data (2).

While centralised data reporting is important, it relies on effective surveillance and reporting at the local level. In fact, local and regional systems of data reporting can be sufficiently informative for site selection and implementation of vaccine efficacy trials. Examples of effective surveillance and reporting at the local level include efforts by the African Centre of Excellence for Genomics of Infectious Diseases to identify and characterise viral pathogens in samples from patients with high fevers who have tested negative

for common regional diseases. This surveillance led to the identification of a yellow fever outbreak in 2017 (10).

Adaptive Trial Design

To respond rapidly and responsively to disease outbreak information, vaccine efficacy trials must employ adaptive trial designs. One way to achieve this adaptivity is with patient enrolment strategies that respond to disease surveillance information, as is the case in ring vaccination. In these trials, the 'ring' of contacts surrounding an identified case are enrolled in the clinical trial. This population is likely to experience a higher incidence rate than the general population, allowing for smaller sample sizes. One challenge associated with ring vaccination is that it may require the addition of sites, which may not be optimal for vaccine study. Rather than training staff at each new site, these trials may employ a team that travels to enrol new participants (11).

Ring vaccination was effectively employed during the development of the Ebola vaccine, and may have potential for vaccine efficacy trials against other EIDs where the vaccine evokes a quick immune response and the disease spreads relatively slowly through contact networks. For more rapidly spreading diseases, a broader contact network may be necessary, or a trial may adopt an alternative strategy where patients are enrolled at sites, but are not vaccinated until sufficient disease transmission is detected proximate to the site (11).

Core protocols offer another promising strategy for EID vaccine trials. Core protocols, also known as master protocols, allow a trial to investigate multiple therapies or multiple diseases in a single study. Recently, core protocols have been developed for the investigation of a vaccine over the course of multiple outbreaks. This has major advantages over traditional methods since it prevents trial failure, due to insufficient data and the premature release of data from underpowered studies, which can make it difficult to develop definitive evidence of a vaccine's efficacy or safety (12).

In combination with robust surveillance and reporting, implementing responsive enrolment strategies into a core protocol could be an especially promising clinical trial design for vaccines targeting EIDs. Of course, there are many additional factors before and after a vaccine efficacy trial that will inform the success of vaccination strategies to combat future pandemics. This includes the public's trust of vaccines, which is not only crucial for vaccination of populations once a vaccine has been developed and approved, but also essential for clinical trial enrolment and retention. Additionally, a comprehensive vaccine development and distribution strategy must include sufficient funding and a distribution program that is more equitable and accessible to populations regardless of income. This collaborative and strategic effort in vaccine development will be challenging, but it is an essential long-term investment for global public health.

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