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Syed Arsalan Akhter Zaidi

University of Pittsburgh Medical Center, zaidi_arsalan@hotmail.com

Kainat Saleem

University of Pittsburgh Medical Center

Rahul Bollam

University of Pittsburgh Medical Center

Bushra Zaidi

Bronxcare Hospital Center

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Ethical Considerations Surrounding Vaccine Development During A Public Health Crisis

Syed Arsalan Akhter Zaidi

University of Pittsburgh Medical Center

Kainat Saleem

University of Pittsburgh Medical Center

Rahul Bollam

University of Pittsburgh Medical Center

Bushra Zaidi

Bronxcare Hospital Center

ABSTRACT

Epidemics and Pandemics have plagued humans for many centuries. In modern times, they are a cause of major healthcare expenses. The novel coronavirus pandemic of 2019-2020 spread worldwide faster than many previous pandemics. Although personal protective equipment and social distancing slowed the outbreak, the need for a vaccine emerged as an only strategy to ensure global immunization and halt the deadly outbreak. Development of a vaccine in times of a public health crisis comes replete with ethical conundrums which are often overlooked in such times. They include such things as proper informed consent, placement of a placebo in the control arm of a study, and utilization of a vulnerable population, to name a few. Discussed in this commentary are issues related to vaccine development in a pandemic situation, secondary vaccine development and conditions of equipoise.

Keywords: Vaccine; Ethics; COVID-19; EBOLA; Pandemic; Drug Development; Informed Consent; Equipoise

INTRODUCTION

Epidemics and pandemics have emerged throughout the centuries as a significant health concern. As early as the 1600s when smallpox spread in North America from European settlers to the novel coronavirus of 2019, vaccine development remains a contentious pandemic response and issue (Carlsen & Glenton, 2016; Kaur & Gupta, 2020). The 1918 Swine FLU epidemic propelled researchers to attempt to expedite the time required for research and development of vaccines and drugs for viral epidemics/pandemics. The development of a vaccine for 1918's flu epidemic was expedited and distributed within one year; however, since the process of vaccine development was in its infancy, that vaccine was not very successful (Schwartz, 2018). Beginning in the 1930s advances in research, virology, vaccine development, and clinical trials helped develop a more efficient vaccine for influenza. This led to the development of the first major flu vaccine in 1942 which contained many different influenza virus strains. The Flu epidemic of 1957 was controlled in time because there was already a vaccine developed for general flu strains. Scientists in 1957 were able to use the same background research to rapidly develop a vaccine for the H₂N₂ epidemic in 1957 (Mackenzie et al., 2012). This development curtailed the epidemic to 1.1 million deaths, while the estimate was for more than 2 million deaths. Many epidemics since then have come and been contained significantly due to rapid vaccine developments. Authors submit though, that each instance of accelerated vaccine development came with a set of ethical considerations. These included, but were not limited to, use of a placebo in trials, informed consent processes, and the time factor in development of the vaccine. In conjunction with these concerns, issues related to the continued development of a second and third vaccine after the first is FDA approved

creates an entirely new conundrum. With few exceptions, when an emergency vaccine or drug is developed, it is accompanied by unique ethical challenges. This claim was reaffirmed in the 2017 report from The National Academy of Sciences in response to the EBOLA epidemic which affirmed that substantive ethical considerations requiring human research do or should not change in emergency situations like pandemics (Busta et al., 2017; Monrad, 2020).

GENERAL ISSUES AND CONSIDERATIONS

Developmental Process and Timelines

There are various issues raised over the years about the development of vaccines and drugs as part of epidemic responses. Foremost is the time it takes to develop a vaccine to stop the outbreak. Recent examples include COVID-19 and the EBOLA epidemic which immediately preceded COVID-19. Both faced very similar issues in research and development of therapeutic agents in an expeditious manner. Authors submit that research and development of any new drug or vaccine should go through the same process as a normal drug, even if this is part of an epidemic response. Processes which should transpire in a vaccine and/or drug development are Preclinical studies are followed by INDs, trials in phases 1, 2, then 3, and eventual application for approval from FDA for use in the public. A typical vaccine development process can take anywhere between 3 to 6 years based on prior trial data and timelines (Evans et al., 2009). This process is too long when considering a high mortality epidemic such as Ebola or Covid-19. Timeline constraints influence the researchers and regulatory authorities in ways that may compromise research bioethics and regulations. Did this happen with the rapidly developed COVID vaccine?

The Dilemma of 'Complete' Informed Consent

Informed consent is one of the major foundations of Human Subject Protection in research. This process not only means giving all required information to the research participant in easy-to-understand wording, it should include risk and benefit statements and should also ensure that the participant is not under any undue influence to participate in the trial. Epidemics can make this process extremely difficult as news outlets report daily death toll daily. The news then influences the population to seek what they perceive as opportunities to improve their odds for survival (Monrad, 2020). In this scenario, when anyone is approached to participate in a clinical trial targeting the agent causing this outbreak, may it be a vaccine or drug trial, these prospect participants will be under undue influence and might not understand the benefit and risk statements completely. This raises a major ethical issue concerning such trials and treatment protocols.

Existing Products and Repurposing

Another commonly seen scenario in epidemics occurs when drugs already approved for treatment are subjected to new clinical trials for the later outbreak. In this case, two ethical questions come to play. First, is there a need for clinical trials if the safety profile has already been established? The second is the dilemma of holding a possible beneficial treatment from the control arm. As an example, Remdesivir, which was initially developed for use against the EBOLA virus in 2017 by Gilead Pharmaceuticals, was repurposed during the COVID-19 epidemic, and given to patients with coronavirus after emergency use authorization was granted by FDA (Pardo et al., 2020). This drug is an anti-viral with promising results from very small trials conducted against coronavirus. That data was used before it was approved for use in patients with coronavirus, but before this, it had large trials against the EBOLA virus with a very good safety profile. Once such a safety profile is established, concerns are raised if it is ethical to withhold treatment from the control arm during a deadly outbreak. The argument for this pertained to risks of Remdesivir in patients suffering from multiple systems organ failure as was seen in severe COVID-19. These same risks were not present in patients with EBOLA.

Are Secondary Vaccine Trials Ethical?

In 2017 a vaccine was developed for EBOLA by Merck which held promising phase-3 results. It was approved by FDA for use in the general population. While the vaccine was in the initial phases of development, other pharmaceutical companies like Johnson and Johnson were also working on development of an EBOLA vaccine. After the approval of Merck's vaccine, ethical issues arose regarding the necessity of continuance of other vaccine trials. To continue would mean delegating the approved vaccine only to participants of the that trial. (Miles, n.d.). To clarify, patients who were enrolled in the vaccine trial by Johnson & Johnson vaccine for EBOLA would not be eligible to receive the approved vaccine by Merck. They became ineligible as recipients in both the experimental as well as the control arm. Stated simply, they were now at greater risk for potential infection if exposed to EBOLA. As was just witnessed, the same ethical conundrum was played out when Pfizer's vaccine became FDA approved while other companies such as Sanofi who had not begun phase-3 trials for their vaccines (Thomas, n.d.). Participants in the other clinical trials were exempt from the Pfizer's FDA approved vaccine.

The three main considerations in the above scenarios all center on the second vaccine's control group of the clinical trial. Recall that enrolling patients in the control group for the second vaccine trial possibly meant withholding beneficial treatment that is already approved by FDA. Secondly, control groups with no immunization could accelerate the spread of outbreaks (Nuismer et al., 2018). Thirdly, withholding beneficial treatments have historically affected vulnerable populations more than the general population (Monrad, 2020). That's why the clinical research for vaccine development should only be conducted under conditions of Equipoise; meaning, clinical trials should be beneficial for more than the approved drug. There should be enforced general population written guidelines from highly recognized and approved regulatory authorities in population vaccine administration (Fries & Krishnan, 2004; Hausman, 2020).

Potential Justifications for a Secondary Vaccine Trial

The most important argument justifying the development of the second vaccine during an outbreak, or an epidemic is when the second product is promising higher efficacy data in the early phases of development or is in a formulation that might be more accessible and easier to administer to the general population. In the case of COVID-19, Pfizer's vaccine for coronavirus needed to be stored in a temperature of -70 degrees F. This is a really difficult task for under-developed countries (Haq et al., 2020; Madewell et al., 2020). Vaccine candidates by Sanofi and Johnson & Johnson did not require such extreme temperatures for storage and were easier to administer. In addition, efficiency data shown were comparable to Pfizer.

Economical and Logistical Issues

Other factors which come into play during drug development in an epidemic are logistics and economics. When billions of people are being impacted and millions of doses of a vaccine are needed, it is logistically impossible to confine the production of an drug antidote to one company (Haq et al., 2020; Monrad, 2020). This factor supports the research and development of vaccines by different companies simultaneously, so that although with slight differences in efficacy of their products, at least most of the population will be able to get the vaccine in a considerably shorter span.

CONCLUSION

Epidemics and pandemics are egregious health emergencies which seem to be accelerating in frequency and intensity. These create a tremendous global economic toll. Discussed in this commentary were ethical issues associated with the worldwide demand to stop the pandemic as quickly as possible by any means necessary. While few would argue that standardized procedures to ensure adequacy of informed

consent, equity in representative population selection, and attention to all three phases of clinical trials were abbreviated and, in some cases, dismissed, the fact remains that the pandemic was halted within the parameters of the emergency use protocols used. Perhaps lessons learned amidst honest exploratory and debriefing sessions will reposition us for the next pandemic. May scientists submit that it is not if, but when. Be ye also ready.

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