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RESEARCH ARTICLE

LITERATURE ARTICLE REVIEW ON RANDOMIZED CLINICAL TRIALS OF COVID-19 VACCINES: DO ADENOVIRUS-VECTOR VACCINES HAVE BENEFICIAL NON-SPECIFIC EFFECTS?

***Rod E. Tiassou**

MPH Student, Department of Health Sciences, Parker University Dallas, Texas

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ABSTRACT

Vaccination not only reduces the risk of short- and long-term health complications from COVID-19, but it also slows or stops the spread of the disease by preventing it from being passed onto others that are at high-risk for severe COVID-19 illness, like grandparents or daycare staff with underlying medical conditions. The pace of the COVID-19 vaccine development process is unprecedented and is challenging the traditional paradigm of vaccinology science. The main pressure comes from the pandemic situation, but what makes it possible is a complex set of factors and innovative environments built overtime, which this manuscript aims to review.The development of COVID-19 vaccines has been one of the most significant scientific achievements in recent history. Since the outbreak of the pandemic, researchers worldwide have been working tirelessly to develop safe and effective vaccines to protect against the virus. The vaccines have been developed using innovative technologies, such as mRNA, and have undergone extensive clinical trials to ensure their safety and efficacy.

INTRODUCTION

The coronavirus disease (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in over 192 million cases and 4.1 million deaths as of July 22, 2021 (JHUM, 2021). This pandemic has brought along a massive burden in morbidity and mortality in the healthcare systems. Despite the implementation of strong public health measures, there have been devasting effects in other sectors such as our economy. The emergence of such a severe and acute pandemic prompted a collaborative effort worldwide to tackle the virus, which included public health protection measures such as isolation, social distancing, handwashing, mask-wearing, intermittent lockdowns, and vaccinations(JHUM, 2021). The development of the coronavirus disease (COVID-19) vaccine was a significant breakthrough in ways to solve this huge issue that the world had never seenin the century. Various research studies have been conducted to identify how the virus works and ways to manage COVID, including the efficacy of the vaccines (Sobieszczyk *et al.,* 2022). However, there is limited data on how these measures work for the immunocompromised, despite the grave impact of these virulent strains in this population (Park *et al.,* 2023). Therefore, researchers suggest a need for an alternative or more personalized approach to providing adequate protection against COVID-19.

Corresponding author: *Rod E. Tiassou,
MPH Student, Department of Health Sciences, Parker University Dallas, Texas.

There is no widely available therapy for coronavirus disease (COVID-19). Paxlovid tablets, co-packaged for oral use, are approved for the treatment of mild-to-moderate coronavirus disease (COVID-19) in adults and pediatric patients, with positive outcomes, especially in those at substantial risk for progression to severe COVID-19 (Mahase, 2021). However, this drug is not widely available. According to current knowledge, vaccinating the general population is the only way to avert severe forms of disease and death globally (Sheikh *et al.,* 2021). Vaccines currently available on the market proved to be effective against hospitalization and death for all SARS-CoV-2 variants up to the Delta. Research shows that if the COVID-19 vaccine is 80% effective, the coverage must be at least 75% in the general population to achieve herd immunity and control the pandemic (Bartsch *et al.,* 2020).

MATERIALS AND METHODS

Vaccines present the body's immune system with certain proteins from the virus called antigens, which activate the immune response to generate antibodies that protect against the disease. It is one of the most important ways of fighting infectious diseases, such as COVID-19. The type of research design used by researchers to develop the COVID-19 vaccine was a Randomized Clinical Trial. The two major Randomized Clinical Trials of mRNA vaccines that were performed were produced by Pfizer and Moderna and included 74,193 adults (>16 or >18 years of age) (37,110 vaccinated; 37,083

placeboes), among whom there were 61 deaths (31 vaccine recipients, 30 placebo recipients) (Thomas *et al.,* 2021). These vaccines were not associated with lower overall mortality, the overall Rate Ratio being 1.03 (0.63–1.71) (Benn *et al.,* 2023). In the third Randomized Clinical Trial of the mRNA vaccine, from Cure Vac, six reported eight deaths in the vaccine group and six in the placebo group, suggesting a similar trend as in the other two mRNA trials (Benn *et al.,* 2023). However, the deaths in the CureVac Randomized Clinical Trial were not reported by cause of death, and since the vaccine has now been withdrawn due to low vaccine efficacy, it has not been included. Discovery Phase of any new vaccine like the COVID-19 vaccine.Before any vaccine testing or development begins, scientists study the structure of a virus and how it causes disease in the body. This allows them to identify potential ways of creating an effective vaccine. This process usually takes several years. Nevertheless, modern technology allowed the genetic makeup of COVID-19 to be shared with researchers worldwide just a few weeks after the first case of the virus (Heinz, 2021). Once scientists select the type of vaccine that looks the most promising, the vaccine is then created in the lab.

Pre-Clinical Testing: Scientists study the COVID-19 vaccine, looking at the safety and efficacy of the vaccine in animals before moving to testing in humans in laboratory settings.

Clinical Trials: If enough research supports a vaccine candidate, it can then be evaluated using clinical trials involving people. These clinical trials, done in three phases, are tightly regulated by the FDA. In the case of the COVID-19 vaccine, all three phases were planned simultaneously to prevent delays if a vaccine candidate was proven effective. But usually, each phase is planned after the previous one is completed since companies do not want to put time and money behind a vaccine if it will not be successful. This may result in one- to two-year gaps between clinical trial phases (Heinz, 2021).

Phase 1 Clinical Trial: A study of usually less than one hundred people was designed to determine if the COVID-19 vaccine is safe, the best dosage, and if there are any serious side effects.

Phase 2 Clinical Trial: A larger study with a few hundred volunteers focuses on how well the COVID-19 vaccine works. These studies also continue to investigate its safety and side effects.

Phase 3 Clinical Trial: An even more extensive study, often including thousands of volunteers, allows scientists to compare people who receive the COVID-19 vaccine to those who did not (a placebo). They can better determine if the vaccine is safe and effective in a larger population of individuals. Volunteers are randomly selected to receive either the vaccine or an alternative "control" medication. The control medication is usually a placebo or another vaccine like the polio vaccine that is already Food and Drug Administration-approved (Hallas, 2021).

FDA Review of Clinical Trials: The Food and Drug Administration looks for evidence that the vaccine is effective and does no harm, then approves it for public use. If a vaccine is not proven safe, has significant side effects, or does not show efficacy, the vaccine is not distributed to the public. The development of the COVID-19 vaccine went through the same process and was approved by Food and Drug Administration for emergency first a later confirm its effectiveness against most COVID-19 variants, especially mRNA vaccines, produced by Pfizer and Moderna.

RESULTS AND DISCUSSION

Recently, mass vaccination has proved essential to dealing with pandemics like COVID-19. Nevertheless, the effectiveness of a vaccine depends on the number of people willing to take it and one approach to encouraging uptake is to publish information about safety and effectiveness. But confirmation bias research in other domains suggests that people may evaluate this information through the lens of their existing beliefs (Malthouse, 2023). The differences between the study populations in the Randomized Clinical Trials of the two vaccine types could have biased the comparison as different disease patterns and levels of care could have influenced the measured effect of the vaccines on overall mortality. A slightly larger proportion of the participants from the adenovirus Randomized Clinical Trials may have been from middle- and low-income countries (Benn *et al.,* 2023). More individuals were infected with COVID-19 in the mRNA Randomized Clinical Trials than in the adenovirus-vector vaccine Randomized Clinical Trials. However, there were more COVID-19 deaths in the adenovirus-vector Randomized Clinical Trials (El Sahly, *et al*. 2021). Therefore, participants in the mRNA Randomized Clinical Trials may have had access to better health care during COVID-19 infection, and this may have reduced the impact of mRNA vaccination on overall mortality. According to (Falsey *et al.,* 2021),There was a higher proportion of accidents in the adenovirus-vector vaccine Randomized Clinical Trials, and when accidents were excluded, the contrast between mRNA and adenovirus-vector vaccines became more pronounced. Cardiovascular deaths were more common in the mRNA Randomized Clinical Trials (Falsey *et al.,* 2021). Participants in these trials may have had more co-morbidities or more events because they had longer follow-ups. However, the effect of COVID-19 vaccines on cardiovascular events differed, beneficial for the adenovirus-vector vaccines but not for the mRNA vaccines. The lack of impact of mRNA vaccines on cardiovascular morbidity is supported by a recent epidemiological survey in France (Jabagi *et al.,* 2022). The differences in mortality patterns in the Randomized Clinical Trials of the mRNA and the adenovirus-vector vaccines can explain the apparent contrast in overall mortality effects between the two types of vaccines.

In another Randomized Clinical trial, researchers discovered several challenges and potential biases that were related to when conducting vaccine effectiveness studies on observational data. According to (Ostropolets *et al*,2021), first, we observed that outcome definitions are prone to measurement error, which has not been studied thoroughly. The specifics of data capture and billing processes were associated with some patients having assigned COVID-19 diagnosis codes for billing for tests rather than as an indicator of active disease (Ostropolets *et al.,* 2021). Another reason for assigning the code was the COVID-19 sequela, where the actual date of COVID-19 infection could have been anywhere

from 6 months to a couple of weeks in the past. Consequently, index data misclassification can be present in other healthcare institutions and should be scrutinized to make valid inferences. In addition, the overall mortality effects of the two vaccine types have only been evaluated in observational studies(Palinkas *et al.,* 2022). Beneficial effects on overall mortality of AstraZeneca and Gam-COVID-Vac, albeit not Johnson & Johnson adenovirus-vector vaccines, in comparison with Pfizer and Moderna mRNA vaccines were seen in a Hungarian observational study (Palinkas *et al.,* 2022). Beneficial effects on overall mortality were reported in an observational study from Buenos Aires in Argentina, which used non-mRNA vaccines (Macchia *et al.,* 2021). In contrast to the Randomized Clinical Trials of mRNA vaccines, an observational study from the Center for Disease Control reported lower rates of non-COVID-19 mortality among mRNA-vaccinated individuals (Xu *et al.,* 2021). However, these observational studies have numerous sources of bias, including healthy vaccine bias, and merely underscore that Randomized Clinical Trials are needed to assess the association between vaccination and overall health. In addition to all the factors cited above, there are also determinants of vaccine hesitancy that were specific to the COVID-19 scenario, such as distrust in the rapid development of vaccines, considering the vaccine more dangerous than COVID-19 or considering COVID-19 as harmless, believing oneself to be already immunized, and doubt about the provenience of the vaccine. Because the development of COVID-19 vaccines was quick, people felt that there was a higher risk of this vaccination in comparison to previous ones, and do notknow about its benefits and costs on individuals. According to (Benn *et al.,* 2023), the literature on COVID-19 underlined a direct relationship between the perception of the risk of being infected and the propensity to get vaccinated. This factor can cause the level of hesitancy to rise six-fold in people who are confident that they will not be infected(Benn *et al.,* 2023). According to the socio-cognitive model proposed by (Eberhardt *et al*, 2021), people are more likely to engage in protective behavior when they believe that not acting poses a risk to themselves and that protective behavior reduces the threat (Eberhardt *et al*, 2021). Now that there are mass-vaccination programs with COVID-19 vaccines are underway, data on their effects on non-COVID-19 mortality must be collected with no bias. As COVID-19 mortality comes under better control due to herd immunity and increasing vaccination coverage, the impact on non-COVID-19 mortality becomes particularly important from a public health perspective point of view. Thus, epidemiologists continue to investigate, and surveillance is in place to better control this virus and implement a new policy to avoid a future spread.

On the other hand, the opportunity for conducting large-scale Randomized Control Trials of vaccines has passed once the vaccines were introduced to the general population. To throw light on the potential differences in non-specific effects between vaccine types, an obvious way forward would be to conduct RCTs comparing the mRNA vaccines and adenovirus-vector vaccines for their effect on COVID-19 mortality, as well as non-COVID-19 mortality (Park *et al.,* 2023). Even though the effects such as positive and negative within the group of adenovirus-vector vaccines would turn out to be more heterogeneous with longer follow-up, more studies should be conducted, and it seems clear that the overall health effects of the Johnson & Johnson and AstraZeneca vaccines must be evaluated against the leading mRNA vaccines. In addition, future trials of new COVID-19 vaccines should be compelled to report overall mortality data by cause, sex, and age with accuracy without bias.

Discuss the concept of generalization of results in a sample population to the target population relating to the COVID-19 vaccine: According to (Borden *et al.,* 2018), the focus of applied research is different from that of basic research. Although you may still work from a theory when formulating your hypothesis, your primary goal is to generate information that can be applied directly to a real-world problem (Borden *et al.,* 2018). In thisRandomized Clinical Trialwith the longest possible blinded follow-up, mRNA vaccines did not affect overall mortality despite protecting against some COVID-19 deaths. In contrast, the adenovirus-vector vaccines were associated with lower overall mortality. The adenovirus-vector vaccines were further associated with a lower risk of dying from the causes of death that would represent non-specific effects of vaccines, the “non-accident, non-COVID-19” deaths (Sadoff *et al.,* 2022). According to this study, both types of vaccines protected against COVID-19 death; however, they had differential effects on overall mortality. When compared with the mRNA Randomized Clinical Trials, the Rate Ratio for overall mortality was lower in the adenovirus Randomized Clinical Trials, with a rate-ratio of 0.36 (0.16–0.82) (0.37 (0.19–0.70)/1.03 (0.63–1.71)) (Benn *et al.,* 2023). The two groups of vaccines also differed concerning “non-accident, non-COVID-19 mortality” (test of homogeneity, $p = 0.027$). The impact differed most strongly for cardiovascular deaths ($p = 0.002$). Compared with the mRNA vaccines, both Johnson&Johnson ($p = 0.016$) and AstraZeneca ($p = 0.14$) tended to have lower overall mortality (Benn *et al.,* 2023).

There is a limitation to the estimation of overall mortality during the COVID-19 pandemic like the cohorts studied. Most of the volunteers participating in the trials were adult individuals in general good health, resulting in low COVID-19 and overall mortality (Benn *et al.,* 2023). In a real-life situation in which the COVID-19 vaccines are administered to highly vulnerable populations with high COVID-19-related mortality, significant reductions in overall mortality are expected, also for mRNA vaccines. However, the intriguing differences in the effects on non-accident, non-COVID-19 mortality are likely to persist and should be investigated in future studies (Benn *et al.,* 2023). These results suggest that adenovirus-vector vaccines compared with placebo have beneficial non-specific effects, reducing the risk of non-COVID-19 diseases. The most compelling cause of non-COVID-19 death was cardiovascular disease, against which the data for the current Randomized Clinical Trials suggest that the adenovirus-vector vaccines provide at least some protection (Sobieszczyk *et al.,* 2022). In addition, the number of deaths in these Randomized Clinical Trials was limited, and chance could therefore have played a role in these findings. However, the internally consistent effects and the significant difference in effect sizes between the two vaccine types speak against “chance” as the main explanation(Klein, 2012). Since there are well-established sex and age differences in the immune system, it is important to report and analyze data by sex and age group. This was not possible for the present study since the Randomized Clinical Trials only reported deaths by

randomization allocation, not by sex and age. The vaccine-related factors and effectiveness were the respondents' main reasons to believe that this virus is human-caused and that the vaccine was made to hurt or harm them. People hoped to confirm their willingness to vaccinate by extending the test time and ensuring the safety and effectiveness of the vaccine (Karlsson *et al.,* 2021). From the perspective of individual factors, older people should be a priority group for vaccination, but they did not show a greater desire to be vaccinated than younger people. Considering individual societal attributes, people who were currently vaccinated against seasonal influenza are more likely to receive the COVID-19 vaccine, which is related to the perception of, and trust in, the vaccine among this population. A Finnishproposed that people's intention toward vaccination can be predicted by their perception of the risks around vaccine safety (Karlsson *et al.,* 2021). The group with high confidence in the effectiveness and safety of vaccines had a lower probability of negative vaccine attitudes than the group with quiet confidence. The mortality reduction associated with adenovirus-vector vaccines appears difficult to understand if the expectation is that vaccines only protect against death from the target disease (Klein, 2012). Therefore, it is necessary to consider a non-specific effect, and their immunological basis that has been established for several other vaccines. According to (Benn *et al.,* 2020), non-specific effects of vaccines have been observed to differ between live-attenuated vaccines and non-live vaccines; live vaccines have been associated with reduced all-cause mortality while this has not been seen for non-live vaccines (Benn *et al.,* 2020).

This Randomized Clinical Trial revealed that the AstraZeneca vaccine showed that monocyte frequency and count were increased up to 3 months after vaccination compared with their pre-vaccine levels (Benn *et al.,* 2023). Because the role of Monocytes is to exhibit enhanced antigen presentation functions and had an increased capacity to produce key cytokines and chemokines in response to unrelated stimuli. Therefore, the vaccine induces trained immunity, and a reduced risk of infections would be anticipated to lead to a lower risk of overall mortality, including a lower risk of cardiovascular deaths(Eberhardt *et al.,* 2021). The trained immunity induced by adenovector vaccines and the enhanced inflammation after mRNA vaccines could help explain their contrasting effects on overall mortality, including cardiovascular deaths. It should be noted that the trained immunity phenotype induced by endogenous mediators might be linked to the development of atherosclerosis (Eberhardt *et al.,* 2021). As a result, more studies with longer follow-ups than just a few months would be important to determine the net or right effect of these vaccines again the COVID-19 virus. In general, how researchers have reached the point of doing Randomized Clinical Trials for the COVID-19 vaccine? How do researchers get ideas to make COVID-19 vaccine? COVID-19 vaccine researchers get this idea from dialogues and observations in which they realize a challenge and recognize a new path for solving it. Therefore, it is crucial to create a space in which challenges are discussed openly and without fear, stimulating innovative solutions. Ideas come from experience and previous knowledge or facts about this object of knowledge, although this knowledge is always filtered through the perspective of one or more theories (Krieger, 2011). Epidemiology studies the distribution and determinants of disease in human populations, and epidemiological ideas arise from observing and thinking about populations. Unsystematic Observation is one of the most potent sources of research ideas in curiosity about the causes or determinants of commonplace, everyday behavior (Borden *et al.,* 2018). This idea involves a researcher simply observing behavior without looking for anything or using any specific type of methodology. Systematic Observation of behavior is another powerful source of research ideas (Borden *et al.,* 2018). It is a highly structured method of observational research that occurs through the structured observation and coding of a research phenomenon. According to Borden *et al*, theories can provide ideas for research in two ways. First, theories allow you to predict what should happen under conditions not previously observed (Borden *et al.,* 2018). The theory was made for the COVID-19 vaccine about the origin of the disease, the cause, the type of the virus, the transmission mode, the spread, and the human body's reaction to the virus. Now, the hypothesis was developed to be evaluated with Randomized Clinical Trials for vaccine efficacy. Then, researchers apply the finding to the entire population. Thus, applied research according to Borden *et al.,* is problem oriented whereas basic research is aimed at building basic knowledge about phenomena (Borden *et al.,* 2018). It is to identify solutions to specific problems or find answers to questions. Overall, it is a solution-based research method. An example of this would be a researcher tasked with finding ways to increase COVID-19 efficacy in all people.

CONCLUSION

Efforts to promote vaccination and reduce vaccine hesitancy, and continued public precautions and care when visiting hospitals should be encouraged. Further research is crucial to identify and establish appropriate measures, alongside active engagement from the government, healthcare, and the public to continue to protect both the immunosuppressed and immunocompetent population. For this global pandemic to end, people must be vaccinated as quickly as possible until herd immunity can be achieved (Bartsch *et al.,* 2020). One aspect of achieving this, in the face of vaccine hesitancy, is to address the lack of community understanding of how vaccines work, the risks, and the factors that keep this area of research volatile and distribution policies ever-changing. In addition, it is important to remain cautious about the information being released and to trust accredited sources and experts, rather than the aberrant rumors being spread through social media (Yap *et al.,* 2021). Nonetheless, the COVID-19 vaccines have shown to be highly promising, and we recommend everyone eligible to take the vaccine at the correct dosing interval when they are given the chance as this would potentiate a positive trend toward pandemic resolution.These next-generation immunizations have never been tried at such a large scale before. However, there is evidence that these processes are safe and effective, with a reduced risk of the side effects generated by previous types of vaccines such as live attenuated or deactivated whole-virus vaccines.

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