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Differences between the three candidate COVID-19 vaccines

Christos Stylianou, Ph.D

Elena Hadjicosta, Ph.D

17-Dec-2020

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ClinBAY Ltd
182 Agias Fylaxeos street
Office 101, Kofteros Business center
3083 Limassol, Cyprus

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Introduction

During this time, everyone's focus is, without a doubt, on the three COVID-19 candidate vaccines (Pfizer-BioNTech, Moderna and AstraZeneca). Although you can easily compare the vaccines in terms of the type and characteristics, their costs, and the required timing between doses, this is not the case with their efficacy rates. These are highly influenced by the differences in the populations and the statistical approaches that were used.

In this document, we breakdown the differences between the three candidate vaccines and present some thoughts from a statistical point of view.

Differences in populations

The first reason why we cannot directly compare the three efficacy rates is due to the (unavoidable) differences in the populations.

In the *Pfizer* vaccine trial, the safety population consists of approximately 38,000 participants. The population was quite diverse with 58% between 16 and 55 years old, 42% older than 55 years old, and 18% with a non-white ethnicity. Also, across both treatment groups, around 21% had at least one comorbidity (with diabetes and pulmonary diseases being the most frequent).

In the *Moderna* vaccine trial, approximately 30,000 participants were enrolled. Similar to the Pfizer vaccine trial, the population was quite diverse with 23% over the age of 65 and 42% in the high-risk groups (for example, participants with diabetes or cardiac diseases). Also, around 37% were from the underrepresented groups in U.S. (i.e., Hispanic/Latinos, Black or African American) and approximately 25% were health-care workers.

In the *AstraZeneca* study, 23,848 participants were recruited in the four different clinical trials conducted (phase 1-2 study in UK, phase 2-3 study in UK, phase 3 in Brazil and phase

1-2 in South Africa). The population was not as diverse as in Pfizer and Moderna studies. The majority of the population (around 87% in the phase 2-3 UK study and 90% in the Brazil study) was between 18 and 55 years old. In addition, most of the participants were health-care workers (more than 70% in the phase 2-3 study in UK and more than 80% in the Brazil study). The intention to the authors understanding, was to recruit more people that are in locations or circumstances, that put them in a considerable risk of exposure to COVID-19 and thus reduce the sample size/time needed until the statistical analysis. Around 10% and 35% were from the underrepresented groups (Black, Asian, mixed) in the phase 2-3 UK study and the Brazil study, respectively. Last, approximately 25% in both aforementioned studies had at least one comorbidity (diabetes, respiratory or cardiac diseases).

Differences in primary endpoints and statistical approaches

The second reason why we cannot directly compare the efficacy rates of the three clinical trials is because of the different statistical approaches that were used to estimate them.

In epidemiology, vaccine efficacy (VE) is defined as the percentage reduction of the incidence proportion of a disease in the vaccinated group compared to the unvaccinated group. The incidence proportion is the number of new cases (within a specified time period) divided by the number of people at risk. In other words, VE is a relative risk reduction and not the “true protection rate” as this is not measurable. Different approaches for estimating the VE are used in the three clinical trials as explained below.

In the *Pfizer* vaccine trial, the final primary efficacy analysis consisted of 36,621 participants. The primary endpoint is the illness rate estimated as the COVID-19 incidence per 1000 person-years with cases confirmed at least 7 days after the second dose. The VE

is then calculated as 100% × (1-IRR), where the illness rate ratio (IRR) is the ratio of the illness rate in the vaccine group (only the first symptomatic confirmed COVID-19 case per person is counted) to the corresponding illness rate in the placebo group. The observed VE from the final analysis was 95.1% and it was evaluated using Bayesian methods. It is noted that the U.S. Food and Drug Administration has approved the Pfizer vaccine for emergency use, and also UK's Medicines and Healthcare products Regulatory Agency has granted a temporary authorization.

In the *Moderna* vaccine trial, the final primary efficacy analysis consisted of 27,817 participants. The VE is estimated as 100% × (1-HR), where HR is the hazard ratio, using a stratified Cox proportional hazard regression model. In this trial, confirmed COVID-19 cases are also symptomatic but the counting starts at least 14 days after the second dose. The observed VE from the final analysis was 94.1%.

In the *AstraZeneca* vaccine trial, the primary efficacy analysis is a pooled interim analysis of the phase 2-3 UK and Brazil studies consisted of 11,636 participants. The primary efficacy endpoint was a binary response, with a success defined as the first symptomatic confirmed COVID-19 case occurred at least 15 days after the second dose. The VE is estimated as 100% × (1-RR), where the relative risk (RR) is calculated as the ratio of the incidence of infection in the vaccine group to the corresponding ratio in the placebo group. The RR was adjusted for age and computed using a Poisson regression model with robust variance. The observed VE was 70%.

The primary efficacy analyses for the three vaccines were event-driven analyses (i.e., they analyzed the data once they reached the total number of cases needed). To the authors' understanding, the VE for the three trials is not be re-evaluated and these are considered as their final efficacy analyses. However, participants are going to be monitored for approximately 2 years to measure other endpoints, for example long-term safety, or duration of vaccine response.

Discussion

The goal of this document was to breakdown the differences between the three candidate COVID-19 vaccines in terms of the populations included in the studies and the statistical approaches used in the primary analyses, in a simple manner. Our aim was to clarify the discrepancies between the populations and how the vaccine efficacy was estimated in each trial. The authors would like to re-iterate, that any comparisons of the results from the three vaccines should be made with extreme caution and preferably avoided; no attempt at a formal comparison should be made in terms of their efficacy rates. If a comparison is needed it should be done in a shared clinical trial comparing the three vaccines in the same population with the same analyses.

One further point is that the Pfizer primary analysis was a Bayesian analysis, whereas the other two provided frequentist analyses. This means that Pfizer provided probabilities and credible intervals, whereas the other two provided p-values and confidence intervals. It is stressed that p-values are not probabilities, and confidence intervals are not credible intervals, the differences between the two methodologies are fundamental and non-comparable. The Bayesian analysis is meant to provide a probabilistic tool for decision making and it provides probability that the claim is correct. On the contrary, the frequentist approach does not work like that; it is meant to be used as a go/no-go criterion based on predefined confidence levels.

As we have seen the efficacy of the vaccines wrongly described in the press, we also wanted to provide some clarity on this endpoint. For example, if the VE is 95%, then this does not mean that the vaccine will protect 95 out of the 100 people exposed to the virus. As mentioned above, the VE is firstly a relative risk reduction (compared to the placebo group), and secondly it was measured based on symptomatic COVID-19 cases, so it does not give information about the protection against the virus but against catching the virus with symptoms. Thus, a 95% VE is a 95% reduction in the proportion of symptomatic cases in the vaccine group compared to the unvaccinated group.

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