The comparative effectiveness of the different COVID vaccines: where do we stand?

La eficacia comparada de las vacunas COVID: ¿dónde estamos?

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Approved COVID-19 vaccines for human use in the European Union

A total of three vaccines have been approved by the European Medicines Agency (EMA) for human use to date. The Pfizer/BioNTech vaccine Comirnaty was approved by the EMA Committee for Medicinal Products for Human Use (CHMP) on the 21st of December 2020, and rolled out in many member states within a week from approval. Similarly, and only a few days later, Moderna's vaccine was approved on 6th of January 2021. More recently, the Oxford-AstraZeneca Chadox1nCoV-19 vaccine was approved on 29th of January 2021. The two former are mRNA vaccines, whilst the last is based on a modified chimpanzee adenovirus.

I welcome the interest of general media and the public on the clinical trial data on COVID-19 vaccine efficacy, and am hopeful that this will lead to greater acceptance by the public. However,I am also surprised by the lack of rigor with which many (including eminent scientists) discuss the comparative efficacy of these vaccines.

Phase 3 trials of clinical efficacy: what do we know and what is yet to be confirmed

Numerous randomised controlled trials have been conducted, and some are still ongoing, on the efficacy of different candidate COVID-19 vaccines. Preliminary findings from the pivotal trial that led to the approval of Comirnaty have been published[1], and suggest a 95% efficacy against COVID-19, with no effect modification by age, sex, race, body mass index or baseline comorbidity. This phase 3 trial was an observer-blinded, placebo-controlled, randomised clinical trial conducted in people 16 years of age or older in 4 countries: United States (76.7% of participants), Argentina (15.3%), Brazil (6.1%) and South Africa (2.0%). A total of 45,548 people were included and randomized to the active vaccine or a placebo, both administered in the form of two doses 3 weeks apart.

Efficacy data for the Moderna vaccine have also been published[2]. In the study by Baden LR *et al,* a total of 30,420 participants were randomly assigned to either the experimental vaccine or a placebo, again in an observer-blinded randomised controlled trial. The study was conducted entirely in the United States, and targeted for recruitment people at high risk of COVID-19 infection. Vaccine assignment was stratified based on age and estimated risk of Covid-19 complications using specific criteria provided by the Centre for Disease Control (CDC)[3].

The efficacy data for the AstraZeneca Chadox1 vaccine are based on a pooled analysis of 4 randomised controlled trials, reported in two different publications in December 2020[4] and February 2021[5]. The studies were conducted in the UK, Brazil, and South Africa, and include a mixture of placebo-controlled and studies where a meningitis vaccine inactive against COVID-19 was used as a control arm. In addition, one of the UK studies included a group that had a low dose of the vaccine with the first injection. The latest published pooled estimate of vaccine efficacy is 66.7%, lower (63.1%) in the standard dosage, and higher

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(80.7%) in the low dose-standard dose regimen. Reports from the EMA and other regulators have highlighted a low proportion of elderly people in these trials[6], leading to national restrictions in the use of this vaccine to those aged <65 or even <55 years old in some EU countries.

Sources of heterogeneity in vaccine efficacy trials

As detailed above, many differences exist in the design, geographical area, and period when the COVID-19 vaccine efficacy trials were conducted. The choice of design includes important considerations regarding comparator arms, blinding, and sampling. Differences in these remainan obvious caveat that precludes the comparison of effect estimates between these trials.

Important known differences are, as detailed above:

- The choice of comparator arm: some of the trials have been placebo-controlled whilst others have used an alternative vaccine (against meningitis) as an active control. Such differences can result in differences in the meaning of the estimated safety and efficacy, as illustrated The impact of choice of control arm has been illustrated by the differences in effect observed in two large randomised controlled trials of remdesivir: from an almost 30% reduction in mortality in a placebo-controlled study[7] to no effect on any of the primary outcomes (including mortality) in the WHO-sponsored pragmatic SOLIDARITY trial[8].
- Blinding: different blinding strategies have been used in different trials, potentially leading to different levels of concealment of treatment allocation, also illustrated by the example mentioned above.
- Sampling has also differed between trials, with some stratifying by specific features to maximise representativeness or to accelerate completion of the trial by recruiting populations at high risk of SARS-CoV-2 infection and/or COVID-19 disease severity. This is an additional source of confusion for the comparison between trial results, and even more so in the presence or suspicion of treatment effect heterogeneity.

In addition to the three above, the time and geographical area when studies were conducted are two major sources of difficulty for the comparison between trial findings. Time and geography combined are major drivers of the occurrence of events. E.g. while the UK had a relatively low incidence of COVID-19 in the summer of 2020, countries like Brazil or the US had much higher levels of community transmission. These differences can result in different levels of ascertainment, screening and other strategies, and therefore lead to the recognition and diagnosis of different levels of COVID-19 severity amongst trial participants.

In parallel, the appearance of new variants of concern can also be responsible for differential detection of COVID-19, and for different levels of public health restrictions, all resulting in heterogeneity in community transmission and potentially in severity[9]. Even more worryingly, some early data suggest that some of these variants of concern might reduce vaccine efficacy[10]. The coincidence (or not) of geography and time when trials were conducted, andthe variants represented at that time in the participating regions is therefore a key consideration that must be taken into account before trial estimates can be compared[11].

Conclusions: can we tell which vaccine is more efficacious?

It is important that we learn on the comparative effectiveness and safety of COVID-19 vaccines. We must investigate their potentially differential effects on different populations, including those under-represented in all trials to date, eg pregnant women or children. For now, all the limitations above should preclude the ascertainment that one vaccine is more or less effective than others. It will probably take time before the community can undertake the necessary head-to-head trials comparing two active vaccines. Until then, we should say clearly what we know: all approved vaccines are (at the time of approval) known to be efficacious against COVID-19, and very efficacious at preventing severe COVID-19. But we must also disclose what we are still in the process of investigating: 1. what is the duration of the vaccine-conferred immunity? 2. what are their effects (both benefits and potentially harm) in those not recruited or under-represented in the conducted randomised clinical trials, and 3.what is the comparative effectiveness (or safety) of the approved vaccines.

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