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COVER STORY

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Covid

Vaccine Trials

How comparing Apples with Apples has gone wrong

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Covid 19

with its high infection rate, choked the health care systems around the world. It severely impacted the economies of almost all the countries. Many developed and developing countries had actively partaken in the vaccine race. Medical science teams worldwide had successfully come up with vaccines within a short span, which is an impossible feat a few decades back. The vaccine's effectiveness is typically tested in multiple phases, and it enters its first phase only after it is proven harmless on animals.

The initial phase involves a small group of participants, typically less than 100, administered with the vaccine in small quantities. They will be monitored to determine whether the vaccine is safe, tolerable, and causes any side effects. In Phase-2, the number of volunteers would be in hundreds. Medical teams would determine the dosage of vaccine required to trigger the immune response during this phase.

Phase-3 trial is the macro version of the first two trials, the number of volunteers would be in thousands, and the volunteers are from different geographies to capture the demographic variability. The experiment should be randomized controlled where the volunteers on whom the experiment is conducted are split into two groups, vaccine and placebo. The assignment into these groups should be completely random, and the entire experiment should be conducted under similar conditions. The vaccine group receives the vaccine, and Placebo groups won't receive the vaccine.

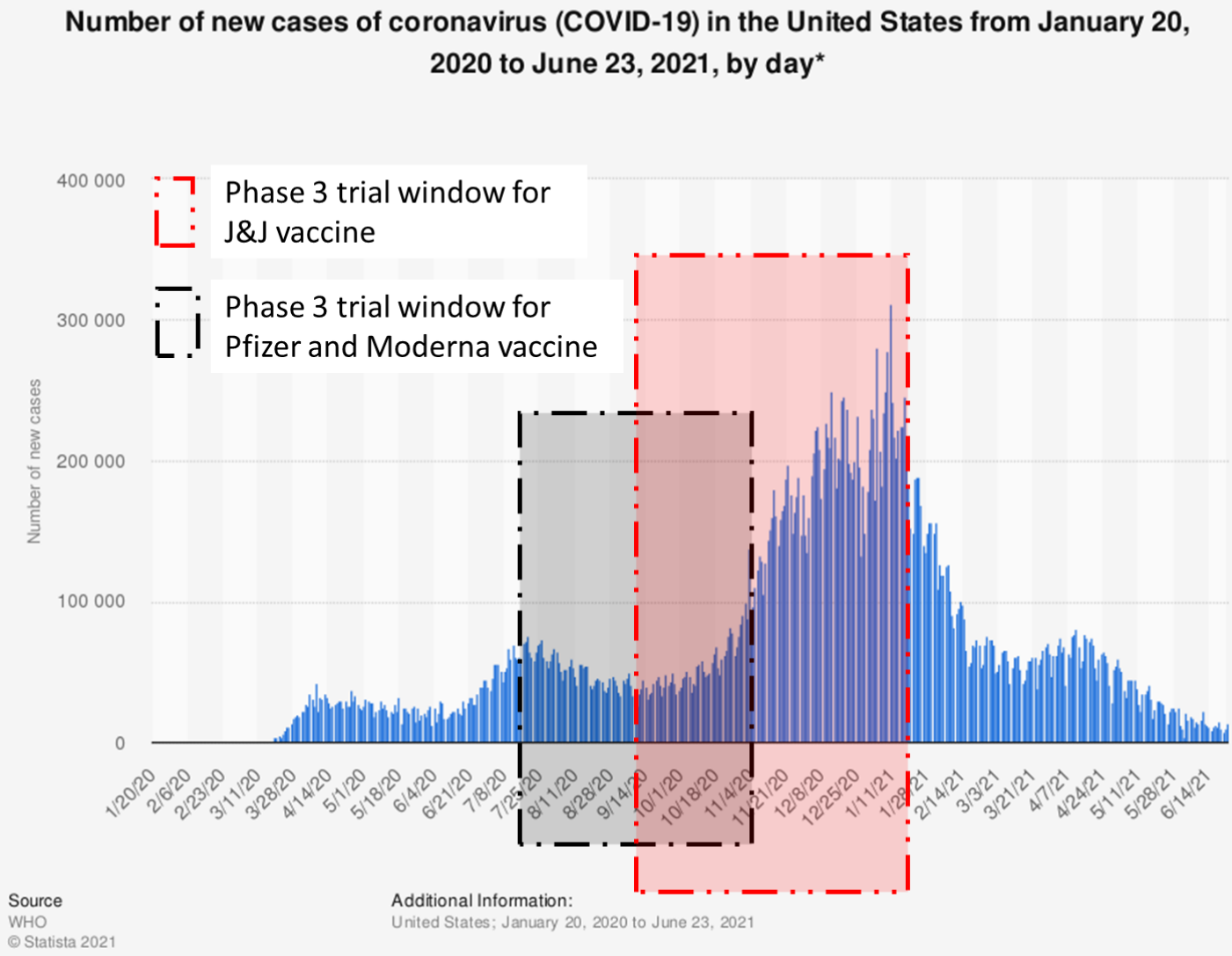
The experiment should be double-blinded, i.e., both volunteers themselves and doctors treating them don't know whether they belong to the vaccine group or placebo group. A Double-blinded experiment ensures that there is no bias from the doctor and puts the placebo groups under the impression that they are receiving the vaccine. By comparing these two groups, we can get to know whether the vaccine has any impact on curing a particular disease.

Food and Drug Administration (FDA) agency of USA has initially approved three vaccines for Covid treatment: Pfizer, Moderna, and Johnson and Johnson(J&J). Pfizer is the first-ever covid vaccine to receive FDA approval on December 11th, 2020, followed by Moderna after a week. Both vaccines are mRNA-based and administered in two doses. The former claimed efficacy of 95%, and the latter claimed 94.1%. Johnson and Johnson (J&J vaccine) is the third vaccine that got its approval from FDA on February 27^{th,} 2021. Unlike the previous two vaccines, it is a single shot carrier vaccine that uses a different approach than the mRNA vaccine to provide immunity. This vaccine claimed an overall efficacy of 72% in the USA and 66% worldwide. The general perception towards these vaccines going purely by their efficacies is that the J&J vaccine is comparatively less effective than Pfizer and Moderna. There are lot more things that have to be deliberated before comparing these vaccines.

The general public has a misapprehension about the efficacy of the vaccine claimed over trials in translating it into the actual scenario. The vaccine efficacy can be calculated as:

$$Vaccine\ Efficacy = 1 - \frac{Attack\ rate\ of\ vaccinated\ group}{Attack\ rate\ of\ placebo\ group}$$

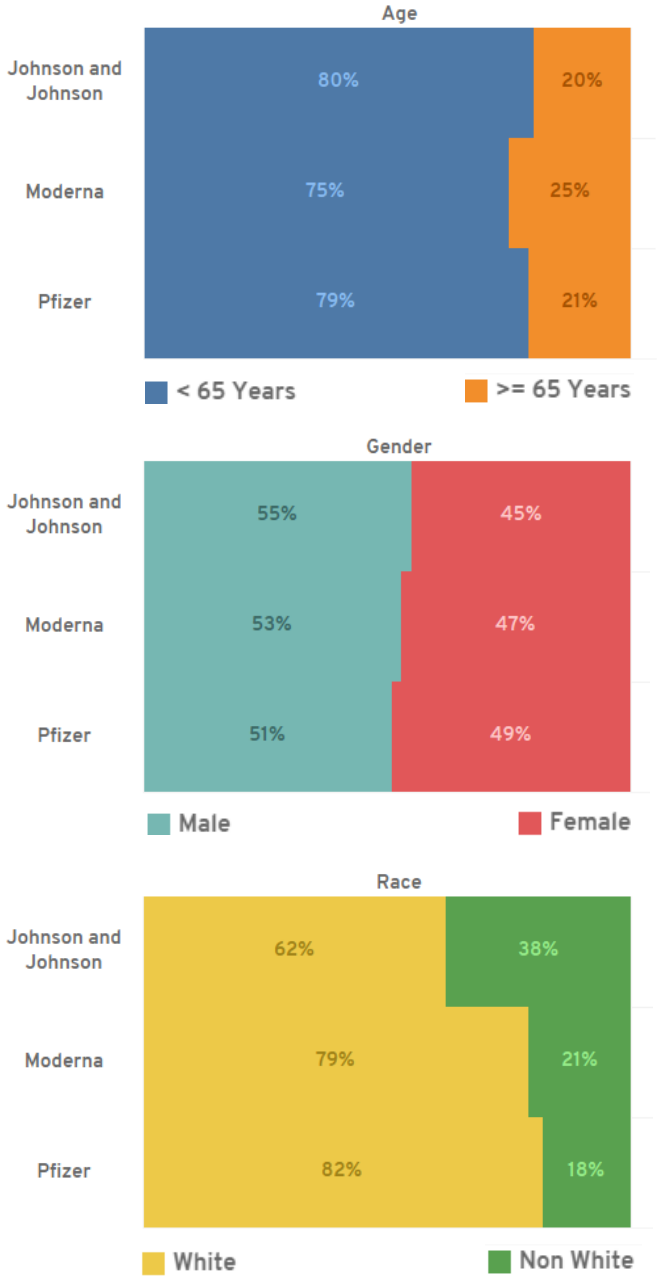
The attack rate of a group is the ratio of the number of people infected with the disease to the total number of people in that group. The ratio of attack rates i.e., the ratio of probabilities of getting infected in the vaccinated group to the placebo group is called Relative risk.



Vaccine trial windows and daily Covid19 cases in the USA

Let's say the claimed efficacy of the vaccine is 95%; this means the relative risk of vaccinated to placebo group is 0.05. This indicates the risk of infection in the vaccinated group is 20 times less compared to the unvaccinated group. This should not be mistaken to 95% of those who got vaccinated will be resistant to the infection. The question is whether the efficacy is a rightful metric to compare the vaccines? Absolutely yes, provided if the vaccines have had their trials at the same time and with a similar volunteer pool. Vaccine efficacy does depend on the time of trials and volunteer pool.

The Phase-3 trials of Pfizer and Moderna were conducted from the end of July 2020 to mid of November 2020. For Johnson and Johnson vaccine, it was conducted from late September 2020 to the end of January 2021. From the figure, it is visible that the vaccine trials of Pfizer and Moderna have started when the daily cases are reducing, whereas for the J&J vaccine, the trials have taken place when the daily cases are increasing until towards the maximum peak. The average daily cases during the trials of the former two vaccines are less compared to the latter, i.e., J&J Vaccine.



Volunteer pools for the three vaccines

The volunteer pool used for the Johnson & Johnson vaccine trial is significantly diverse compared to that of Pfizer and Moderna. Moreover, Pfizer and Moderna vaccines are tested far before the emergence of troublesome variants. Therefore, it is not sure how well these vaccines perform on the new variants. On the other hand, J&J was conducting its vaccine trials during the period of new variants.

The three vaccines cannot be compared based on efficacies as they had their trials at different times of pandemic, used dissimilar protocols, and tested on different pools of people across the world. Here the important metric is the number of hospitalizations, which all three vaccines could equivalently reduce. The efficacies can be directly compared only when there is a head-to-head clinical trial. In the USA, J&J has witnessed a decline in demand for their vaccines. The number of people who opted for Pfizer and Moderna is 11 times more than the number of people who opted for the J&J vaccine. The possible reason is majorly due to the inherent number bias among the people, comparing the vaccines purely through efficacy score.