TITLE: **Testing vaccines in the time of Covid: The changing landscape**

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A recent review by a WHO Expert Committee (1), made the case as to why placebo-controlled trials of Covid-19 vaccines should continue. They argued that there is a need to obtain the following information: assessment of shorter and longer-term safety data; duration of immunity; the impact of waning immunity on protection and possible vaccine enhanced disease from SARS-CoV 2; protection against clinically severe disease; and the association between degree of protection and age of recipient as well as co-existing conditions. The emergence of new variations of the virus (UK, South Africa, Brazil, etc.) call for additional vaccine studies. This information should be collected on both older and newer vaccines.

Whenever a new disease emerges, there are ethical dilemmas regarding the testing of vaccines, new drugs, and new methods of care. The disease has yet to be fully described, treatments may be unknown, and the epidemiology is being defined in real time. Baseline data is limited. The gold standard of study design remains the randomized placebo-control study. In early stages of discovery there is no standard therapy or vaccine(s) so the use of placebo is justifiable. This has certainly been the case with Covid-19.

Trials dealing with therapeutics have focused on testing established drugs for other purposes rather than on the development of new products. For vaccines the story has been different. The new biology has vastly accelerated the development and testing of new vaccines within a time frame that has been nothing short of remarkable. From the time that the genome was released by Chinese scientists in January 2020 until the first vaccine was developed took only 10 weeks. Research methods developed over many years created platforms for vaccine development as soon as the novel virus was characterized.

The first vaccines were produced by Moderna and BioNTech (who partnered with Pfizer), both using the mRNA technology. Phase 3 trials for each, comparing the vaccine to placebo,(with a combined total of 75,000 subjects) were completed in October and November 2020 and the vaccines were approved for Emergency Use by the US FDA in December. A number of other vaccine candidates using other technologies were also being tested in Phase 1,2, 3 studies and applications have been submitted for approval to the US FDA as well as other national governmental agencies. These include the following: Johnson and Johnson; Novavax; Oxford-AstraZeneca (Covishield); Sputnick V (Russia); Sinopharm and Sinovac (China); and Covaxin (India).

The continued development and testing of vaccines has led to ethical dilemmas which include the following: 1) Should the control group receive a vaccine or placebo in future vaccine studies?; 2) What information should vaccinees or control groups receive prior to the study regarding study design and access to a vaccine if it shown to be effective; 3) Is it appropriate to continue blinded follow up of placebo recipients in existing trials and should trial sponsors be obligated to unblind treatment assignments for participants who desire to obtain a vaccine?

If an effective vaccine is licensed should all future vaccine candidates be compared to this vaccine? How is effective defined and who makes this determination? The WHO? A national scientific body? What if the comparative vaccine is not available in the country where a trial is being undertaken? This could occur because of cost or the ability to maintain conditions to ensure vaccine viability, such as storing a vaccine in the subzero temperatures required by the Pfizer/BioNTech vaccine? A vaccine requiring only one dose and/or can be stored at room temperature, would make it far attractive to LMICs. Should this vaccine be compared only with a similar product meeting these criteria?

Since the statement from the WHO Expert Committee was developed in early November and first published in early December, much has changed. A number of effective vaccines (70-95% against infection) have been licensed under Emergency Use or Compassionate Use provisions. One or more of these vaccines are now potentially available anywhere in the world, even if supplies may be limited. Public health recommendations have been published by the WHO as well as many national public health authorities. As noted, early on in the pandemic there were no effective vaccines so the use of a placebo comparator was justified. But new and emerging diseases are like a flowing river. The information is constantly changing; the ethical parameters must change as well. At this moment it seems difficult to justify the use of a placebo during a vaccine trial. Assuming participants in a study will be fully informed that an effective vaccine is available, why would anyone choose to be in a placebo group? From this time forward vaccine studies will have to be designed as randomized non-inferiority trials. This will certainly increase duration and expense. Though mortality is primarily in those over 60 (and in certain other high-risk groups), morbidity and mortality still occur in younger age groups so the age of the participants should not factor into this decision. The risk in not negligible. Some might argue that in testing a vaccine against a new variant of SARS-CoV 2 the use of a placebo in the control group would be justified; but some first-generation vaccines appear to be effective in preventing severe disease from new strains which may be more infectious.

Study participants must be given all relevant information as to the effectiveness of the product being tested, possible side effects, compensation should adverse conditions occur, and the ability to withdraw at any time without prejudice. Should a vaccine prove to be effective, volunteers should be told and be allowed to choose as to whether to have the test vaccine or another proven product. The informed consent document should be clear on these issues and understood by the participant (a quiz to determine understanding could be given). All effort should be made to follow up cases and controls for the very reasons stated by the committee.

What information should be available to trial participants after the study has been completed? Is it fair or ethical to not inform a trial participant what vaccine they have received in the trial? If it is possible that vaccines based on different approaches might interfere with each other shouldn’t a person be made aware of this? As of now there are no studies on whether vaccines interact with each other (2). If the participant wishes to use a vaccine other than the first vaccine (or placebo), they should have the data on which to make an informed choice. As an example, Moderna unblinded its trial and informed participants if they were in the placebo arm, giving them the option to obtain the vaccine. Long-term comparison of vaccine to placebo was no longer possible, but there was the opportunity to increase safety data and obtain long-term information on efficiency.

Public health authorities are rightly concerned that many will refuse the vaccine. This is referred to as vaccine hesitancy. The hesitancy will put many individuals at risk of infection and could limit over all immunity in the population. Many reasons are given for vaccine hesitancy including religious beliefs, politics, false news reports (part of the infodemic landscape) and misunderstanding of both individual and community risk. A principal reason for hesitancy is a lack of trust in government, science, and public health authorities. It is critical, therefore, that pharmaceutical companies, drug regulation agencies, government, and the public health community develop and nurture trust. If the public feels information is withheld and study participants are not being fully informed, trust will be damaged and no amount of data will be able to overcome this mistrust, especially in the short run. Plummeting rates of measles vaccination and increased measles cases followed the dengue vaccine controversy in the Philippines (3). The research community should ensure that quality ethical science be conducted, in the testing of new vaccines and that information is clear and transparent, if these vaccines are to find their way into the arms of the public.

**References:**

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