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Significant flaws in the Pfizer COVID-19 vaccine trial

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The global Covid-19 pandemic has not only led to a harsh medical reality, more so in some countries than others, but has also devastated the economies of multiple parts of the world. It is therefore not surprising that a rush to develop vaccines for the disease has engulfed the world. Pfizer was the first to complete a (shortened) phase 2/3 trial, the results of which were reported in the New England Journal of Medicine [1]. Unfortunately, this article reveals significant flaws in the conduction, analysis and reporting of the data and departs significantly from the usually high standards of this prestigious journal.

In fact, to the best of our knowledge it is unprecedented that the corresponding author of this paper is an employee of the sponsoring company. This immediately casts a long shadow on the objectivity of reporting in the paper and the editorial decision to publish it [2]. Indeed, a careful reading of the work reveals multiple problems.

First, the efficacy of the vaccine in preventing the spreading of the virus and reducing infectivity, which is the most important factor in its ability to ameliorate the devastating effects of the pandemic, was not tested. Quite surprisingly, the effect of vaccination on overall number of virus-shedding individuals was not assessed, even though it is established that a significant fraction of the infected population capable of transmitting the disease are asymptomatic [3]. Only a very narrow endpoint, of patients who meet both being symptomatic and having a positive PCR test was chosen. This does not take into account the significant inaccuracies of the PCR test [4]. In fact, even the large group of patients with symptoms compatible with Covid-19 but PCR-negative (not mentioned in the paper but reported in the Pfizer FDA briefing document (https://www.fda.gov/media/144245/download), with very minor differences between the vaccine and placebo groups) was ignored. Thus, we are presented in this paper with a seemingly very impressive relative efficacy of 95%, which in fact gives us no information regarding absolute risk (https://blogs.bmj.com/bmj/2020/11/26/peter-doshi-pfizer-and-modernas-95-effective-vaccines-lets-be-cautious-and-first-see-the-full-data/), nor infectivity of the patients and very limited data regarding clinically significant end-points of severe disease, ICU admission or mortality. There is also no data regarding immunological studies in the various groups of patients. This data was only provided on a very small group of young and healthy patients in the phase I paper [5]. This is important not only for efficacy, but also for assessment of the risk of unintended immunological sequelae. One cannot assume, based on such a small and selected group of patients, that there will be a good titer of virus-neutralizing antibodies and a favorable Th1/Th2 response in elderly patients or those with comorbidities known to have an effect on immune function.

The adverse effect section of the paper conspicuously lacks any laboratory studies, which is surprising based on the fact that in the phase I group there were abnormalities of blood counts [5]. It is also known that mRNA vaccines can be transferred to the liver [6], thus one would expect that all blood chemistries including liver and renal function tests would be evaluated to ensure that indeed there is no risk of end-organ damage.

Understandably, the brief period of this clinical trial, two months, was an outcome of the general urgency caused by the pandemic. However, to conclude that “Safety over a median of 2 months was similar to that of other viral vaccines” is highly misleading. The mRNA vaccine technology is novel and as opposed to other vaccines, involves the transfection of cells with genetic material , and only phase I studies of such vaccines have been reported prior to this work. One significant and recognized risk of the expression of a foreign protein on self-cells is the induction of severe auto-immune reactions [7].

Since there is no information on the distribution of the vaccine in different cell types and organs following intramuscular injection (in contrast, for example, to another vaccine candidate, for which such detailed information has been published [6]), it is very difficult to assess the relevant risk. Certainly, a very short follow-up period does not provide a long enough time window to conclude that the risk for auto-immune reactions does not exist. The paper totally ignores this aspect.

The paper only briefly mentions the highly recognized risk of vaccine-mediated disease enhancement, which the authors are fully aware. They wave this risk off as "theoretical", and assess it to be unlikely based on data from 10 patients over a very short period of time. Clearly, this significant risk should have been much more fully addressed.

Finally, the fast pace of the publication of this work has led to multiple inaccuracies. For example, it is unclear how two patients in the vaccine group who, as reported in the FDA briefing document (https://www.fda.gov/media/144245/download), were hospitalized with respiratory symptoms and findings in imaging studies, are not reported in the paper as severe adverse events. Also, there is an unexplained discrepancy between the number of patients with AIDS that are reported as participating in the study and the number of such patients for whom there is available safety data (only one). This is very important, as the inclusion of a significant number of HIV-positive patients purportedly alleviates the concerns of the potential risks in this patient population. These risks stem from with the significant immune dysregulation in these patients, as well as the potential reverse transcriptase activity that could inadvertently lead to the unwanted incorporation of the genetic material of the vaccine into the genome.

In Summary, the way in which the data is presented in the paper creates a false sense of security regarding the efficacy and safety of the mRNA vaccine. This is extremely concerning, as the publication of this paper is important in promoting the rapid approval of the vaccine in numerous countries. We believe that due to the enormous effect the results of this trial have on the entire population world-wide, steps should be urgently taken to clarify all those issues. …

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