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LETTER TO THE EDITOR:

COVID-19 VACCINE DEVELOPMENTS AND CONSIDERATIONS FOR APPRAISAL OF THE EVIDENCE

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Dear Editor

The infectious SARS-CoV-2 (Coronavirus Disease 2019: COVID-19) has caused significant impact globally and necessitates a rapid response to curb the COVID-19 pandemic. This includes development of vaccines over compressed timelines, which requires international collaboration to increase the understanding of viral genomics, structural biology as well as explore new vaccine platforms [1]. This includes DNA- and RNA-based vaccines, which are appealing during this infectious crisis, as synthetic processes to manufacture them are relatively quick without the need for culture or fermentation. Trials involving these platforms have progressed, despite the fact that there are no approved RNA vaccines to date.

This fervent activity for COVID-19 diagnostics, vaccines and therapeutics is also accompanied by an outpour of scientific publications, resulting in the World Health Organisation (WHO) and major journals cataloguing COVID-19 related research into collections and databases [2]. The urgency of sharing such scientific information has also led researchers to publish pre-print manuscripts in servers such as medRxiv without peer review. For clinicians and policy makers, the challenge is to be able to critically appraise this overwhelming deluge of information to decide on benefits and risks of treatment. In this letter, several considerations for appraisal of the literature on the COVID-19 vaccines are discussed.

Firstly, there are several types of candidate vaccines for COVID-19, the major ones being live attenuated virus, recombinant viral vector, inactivated virus, protein subunit, virus-like particles and nucleic acid. Each platform has their own strengths and weaknesses; for example, live-attenuated tends to create a

stronger immune response, but would not be suitable for immunocompromised patients [3].

When reviewing the evidence from vaccine trials, it is important to determine generalisability of findings to the target population. Exclusion criteria of studies should be reviewed, particularly in terms of age, ethnicity and medical comorbidities. Outcome measures should also be scrutinized; is the outcome based on levels of neutralising antibodies, or does the vaccine reduce the risk of acquiring infection, symptoms of infection, or rate of viral shedding and infectivity? Trials may occasionally be discontinued early if there is evidence of a difference between treatment and control groups during the pre-specified interim analysis. When this occurs, a longer duration of follow-up monitoring is necessary for evaluation of long-term safety.

Immunogenicity:

Phases I and II trials aim to identify the appropriate dose-range on healthy volunteers and offers preliminary data for efficacy and side effects. The evidence from these trials compares participant serum levels of neutralising antibodies compared with convalescent serum levels from recovered Covid-19 patients, assuming these titres would meet minimum requirements for immunogenicity. However, the absolute antibody level required and whether these equates to real world protection from infection remains unknown, thus the need to await Phase III trial outcomes. These titres may also not be comparable between studies due to lack of assay standardization, hence we are unable to compare efficacy between vaccines. Information regarding the duration of immunogenicity and durability of response is also not currently available so it remains unclear whether these vaccines require repeat doses in the future.

Changes to the immune system with age also mean that the response to vaccines in older people should be assessed separately. Immunosenescence leads to defects in the innate and adaptive immune response, thus vaccine responses tend to be weaker and decline earlier. Thus, improved vaccination strategies, adjuvants and vaccines specifically targeting the aged immune system may be required [4].

The coronavirus genome is also prone to mutations or genetic drift, which may affect immune recognition. For example, the 23403A>G variant in spike protein B-cell epitope is found in European countries such as Netherlands and France, but not in China. It is crucial to ensure that vaccines will provide an international breadth of coverage for different virus strains caused by mutations [5].

Reactogenicity:

Safety data for COVID-19 vaccines are lacking, which necessitates active surveillance and follow-up of vaccine recipients, particularly as mass vaccination programmes may occur to resolve the pandemic. Specific sub-groups

should also be evaluated to determine the risk and benefit of vaccination, particularly the elderly, those with chronic illnesses, and people with allergies and intolerances.

While there is only limited data available, any information suggestive of possible safety issues should be highlighted for monitoring. This includes animal studies, particularly in non-human primates, which demonstrate vaccine responses close to humans. For example, vaccine-associated enhanced disease (VAED) may occur where an immune response to a vaccine causes a higher risk of adverse outcomes upon infection compared to infections without prior vaccination. Concerns of VAED risk for COVID-vaccines should be raised if pre-clinical studies show a high levels of binding antibodies, low levels of neutralising antibodies, low affinity antibodies, dominant T-helper 2 T-cell responses, increased post-challenge inflammatory responses, enhanced lung pathology or unexpected extra-pulmonary lesions. These markers should be evaluated in Phase I and II trials as well [6].

Overall, there is much information updated almost daily regarding the Covid-19 vaccine developments, yet insufficient data to make absolute informed decisions to choose between the different types. There is much to learn and catch-up regarding what we hope to be the savior against this pandemic.

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