

# “COVID Vaccine” is not the excuse to delay adaptation to the “New-Normal”

With the emergence of new pandemics such as Ebola, H1N1 influenza, Zika virus, and recently SARS CoV-2, there has been a mounting pressure from Government bodies, regulators, and public on the scientific community to speed up the development of effective and safe drugs and vaccines. The panic and pressure drove several regulators to approve hydroxychloroquine for COVID-19, despite the lack of evidence for its efficacy. A recent publication highlighted the risks of such hasty decisions when hydroxychloroquine was associated with decreased survival in hospitalized patients and increased risk of ventricular arrhythmias.<sup>[1]</sup> As of now, there are more than 114 vaccines and 10 potential COVID vaccine candidates in pre-clinical and clinical evaluation.<sup>[2]</sup> We are regularly bombarded by (sometimes misleading) news of a potential COVID vaccine, which increases the stock prices of the developer and our hopes of returning back to the pre-COVID normalcy. However, it is important to be realistic, and start adapting ourselves to the “new-normal” and go ahead with or without COVID vaccine.

Mumps vaccine is considered to be the most rapid vaccine developed till now. Mumps virus was isolated in 1945<sup>[3]</sup> and the first vaccine (inactivated vaccine) came out in 1948.<sup>[4]</sup> This vaccine was not quite effective since it produced short-term immunity, and hence was discontinued in mid 1970s. The first effective mumps vaccine (Jeryllynn live attenuated) came out in 1967 and is used till date. Another excellent example of rapid response in vaccine development was experienced in 2009 when H1N1 led to the first global pandemic flu in 40 years. On April 21, CDC began working to develop a new vaccine, with the first clinical trial testing on July 22.<sup>[5]</sup> On September 15, FDA announced the approval of four H1N1 vaccines and the first doses of the same were given in USA on October 5, 2009.<sup>[5]</sup> In just a period of six months, the H1N1 vaccine progressed from clinical trial to public availability. However, we know a lot about H1N1 epidemics and characteristics than we do about COVID-19. H1N1 first emerged in 1918, disappeared in 1957, and came back in 1977.<sup>[6]</sup> The first clinical trials of influenza vaccine were conducted in mid-1930s and a working Flu vaccine was available in 1942 itself.<sup>[7]</sup> Despite a 102-year history of interaction between H1N1 and humanity, the efficacy of influenza vaccines ranges from 40% to 60% in adults.<sup>[8]</sup> SARS-CoV, belonging to the same family of viruses as COVID-19, was first reported in China and WHO had 33 candidate vaccines under development;<sup>[9]</sup> none

of these vaccines were officially licensed till date. As regards COVID-19, the scientific community has learnt about it only since the last few months.

Vaccines try to simulate the natural infection and train the immune system to defend against a specific antigen. However there are several viruses, such as RSV which do not elicit an absolute protective response from the immune system even after natural infection and hence can reinfect the host.<sup>[10]</sup> IgG antibodies are often considered to mediate long-term immunity to an antigen and peaks about 21 days after the antigen trigger.<sup>[11]</sup> In a study to evaluate the performance of ELISA and lateral flow immunoassay devices (n = 40 patients with confirmed SARS-CoV 2), IgG titers, peaking at week 3 after symptom onset, fell during the second month; it is not known whether the residual IgG levels will prevent reinfection and complications.<sup>[12]</sup> In another study, antibody titers were studied in 68 convalescent COVID patients to evaluate human antibody response to COVID-19. It was observed that the plasma neutralizing activity was low in most convalescent individuals. Plasmas collected an average of 30 days after the onset of symptoms had variable half-maximal neutralizing titers ranging from undetectable in 18% to below 1:1000 in 78%. Hence, most individuals who recover from COVID-19 without hospitalization do not contain high levels of neutralizing activity in plasma.<sup>[13]</sup>

Let us consider a scenario where we get an effective vaccine. How long will it remain valid? Viruses such as influenza virus have been known to undergo “antigenic shift” and “antigenic drift” which compromise the efficacy of existing vaccines and necessitate the development of new vaccines. A similar case can be encountered with COVID-19. The spike protein of Corona viruses not only helps in receptor binding and virus entry but also is also extremely important as an immunogen as it is the most accessible part of the viral architecture.<sup>[14]</sup> Based on the genotyping of 7818 SARS-CoV-2 genome samples collected up to May 1, 2020, mutations in diagnostic targets have been already detected.<sup>[15]</sup> Most of the vaccines under development target the spike protein of COVID-19 and a mutation in the same may result in loss of vaccine efficacy. Does it mean that there is a possibility that every few months if COVID 19 virus mutates, it needs to be incorporated in COVID-19 vaccine like we do for influenza vaccine? If yes, it would complicate the situation.

It is still important to ensure that the “effective vaccine” does no harm. Dengvaxia, the first dengue virus vaccine, is licensed in 20 endemic countries. It provides protection against severe dengue in seropositive individuals but may increase the risk for naive recipients to develop severe dengue and need for hospitalization.<sup>[16]</sup> Another important phenomenon to consider is the “antibody-dependent enhancement” of disease, as seen in Dengue Shock Syndrome and Dengue hemorrhagic shock

syndrome. “Cytokine storm” is already a recognized complication of COVID-19.<sup>[17]</sup> It is important for an “effective vaccine” not to worsen this cytokine storm.

Lastly, vaccine production is one of the most complex biological processes. Even the most basic manufacturing steps necessary to produce vaccine are difficult to execute, and this usually results in high proportion of vaccine manufacturing failures and supply shortages.<sup>[18]</sup> The manufacturing of COVID-19 vaccine will not be as simple as manufacturing of polio vaccine, and several quality controls will need to be put in place. Also advancing from small-scale manufacturing to levels required to deploy vaccine to 7 billion individuals will require substantial expertise, investment, and resources.

Even having an “effective and safe vaccine” is not an excuse to let our guards down. “Vaccinated” individuals will still need to wait for IgG to peak, and follow the social distancing norms for 3 weeks after vaccination. Viruses can still mutate and render vaccination useless. It is best not to over-rely on vaccine development and delay our adaptation to the new normal. Every level of healthcare, right from primary to tertiary care has to be involved in fighting this pandemic. As the primary care physician will see a vast majority of these patients and also interact with the general population at large, the onus is on them to spread this word and to help people adapt to the new normal until we have an effective vaccine.

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There are no conflicts of interest.

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