Editorial

SARS-CoV-2 Variants and Vaccine Boosters

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Similar to the mythical king *Raavan* in the *Ramayana,* the SARS-CoV-2 is generating new variants. Hundreds of variants and multiple variants of concern (VOC) have emerged globally following the initial strain first reported from China. VOCs are defined as mutations conferring increased infectivity, virulence, or relative capacity for immunological escape.[1] In the first year of the pandemic, five major VOCs were reported- ancestral, alpha, beta, gamma, and delta. The latest in the series is omicron, sixth and the most mutated VOC that is predicted to spread like wildfire across the globe.[2,3,4] Variants emerge due to multiple reasons, the most important being prolonged virus residence in the host (immunocompromised humans) that provide time for virus to multiplicate and change the amino-acid sequences to suit the virus sustenance and development.[3]

VACCINES AND WANING IMMUNITY

Multiple strategies have been employed to control the epidemic starting from public health measures such as population health education and test-trace-isolation strategy; and non-pharmacological interventions including universal masking, hand hygiene, and physical distancing.[5] Other strategies included early aggressive case-management with monoclonal antibodies (Sotrovimab, etc.) and a (failed) strategy of virus elimination using pharmacotherapy. Vaccines have emerged as a viable strategy and multiple vaccines that generate virus protein specific antibodies are currently available (Table).[6] Vaccine development has proceeded at a very fast pace and, thanks to the scientists involved, we currently have very effective and safe vaccines available.[1]

Early in the course of vaccine efficacy studies, it was identified that duration of protection starts to wane after 5-6 months following second dose of the mRNA vaccines, with a slightly longer time period after the attenuated virus vaccines.[7] Two-dose vaccine efficacy studies also reported persisting neutralizing antibodies for the ancestral and alpha VOCs for 6-9 months with concomitant reduction in efficacy against prevention of severe disease and hospitalization. Efficacy against the delta virus was for a much shorter duration (Figure 1). An increase in the disease severity was noted following this period. Accordingly, many countries in Europe and North America recommended the third dose of the vaccine, also known as booster dose, 6 months following the second. This restored vaccine efficacy in prevention of severe disease and deaths to 90%.[3,4] More than 100 countries have now recommended the third dose of the vaccine to be taken at 6-9 months after the second dose.[8] India is not one of them.

CURRENT VARIANTS AND BOOSTER EFFICACY

Two main SARS-CoV-2 VOCs are currently fueling the Covid-19 pandemic across the globe- delta and omicron.[3,4] The delta variant swept across India in the first half of 2021

Table: Commonly available Covid-19 vaccines

Vaccine Name	Generic Name	Technology	Availability in India
Pfizer-BioNTech	BNT162b2	Recombinant mRNA	No
Moderna	mRNA-1273	Recombinant mRNA	No
University of Oxford-AstraZeneca	AZD1222	Adenovirus viral vector	Yes
Bharat Biotech	BBV123	Inactivated virus vaccine	Yes
Sinopharm	BBIBP-CorV	Inactivated virus vaccine	No
Johnson & Johnson	Ad26.CoV2.S	Adenovirus vector vaccine	No
Sputnik	Sputnik-V	Adenovirus viral vector	Yes
Novavax	NVX-CoV2373	Adjuvant spike protein vaccine	No

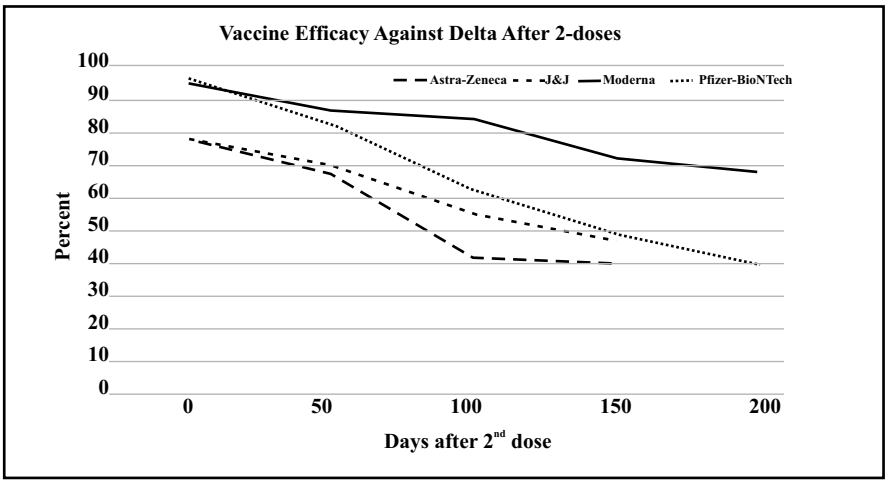

Figure 1: Waning immunity against delta VOC after the second dose of different vaccines.[7]

and led to unmeasurable deaths and despair because of its high transmissibility and case-fatality.[9] Our study at Jaipur reported that the in-hospital deaths among hospitalized delta variant patients were 1.7-1.9 times more than the previous variants.[10] This is similar to data from other centers in the country and elsewhere.[3] Recent studies indicate that omicron variant has transmissibility that is 2-3 times more than the delta with similar rates of hospitalization and deaths.[3,4] If true, this could lead to greater disease and deaths by the omicron variant as compared to the previous ones.[4] Studies have also reported that neutralization of omicron was undetectable in most double vaccinated individuals 3-4 months after mRNA vaccines.[11] On the other hand, recent reports have shown up to 100-fold increase in neutralization activity versus omicron after 3rd dose of vaccine.[12] Clearly there is a case to support third dose of the vaccine in all individuals, especially the vulnerable. Whether the third dose is the same as the first two or requires a mix-and-match approach needs further studies in the context of omicron. COV-BOOST, a randomized trial in the UK, has reported that combining mRNA vaccines with adenoviral vaccines provide better and longer lasting immunity in context of the booster vaccination.[13]

RECOMMENDATION

Many states, including Rajasthan, have requested the central government to permit the third dose (booster) vaccination for at-risk elderly, multimorbid individuals, and health care workers and have requested additional supply of vaccine doses.[14] This decision has been apparently delayed due to vaccine equity issues (providing two doses to all) and lack of large randomized controlled trial scientific evidence as highlighted in recent reports.[1] The third dose of vaccine has already demonstrated benefit in reducing the growth of omicron epidemic in epidemiological studies and serological studies in European countries.[15] It has been argued that the time to act is now and delaying the booster rollout can fuel the next wave of the epidemic.[15] We posit that not providing the third dose of vaccine (boosters) to the susceptible is a form of vaccine inequity. Studies have shown that elderly and the multimorbid are a neglected segment of society similar to underprivileged children who suffer from pediatric vaccine inequity in many parts of the globe. The elderly and multimorbid are also a fertile ground for emergence of new VOCs and unless we vaccinate this group of our population, the mythical *Raavan* shall keep on producing new heads. Waiting for the *Brahmastra* (pan-coronavirus or pan-sarbecovirus vaccines)[13] shall only lead to more disease, deaths, and socioeconomic catastrophe. As a clinician, and given the evidence of benefit, I would strongly recommend booster shots for all the susceptible. It is high time that policy makers worldwide recommend this strategy.

Post-script: Since submission of the Editorial on 24th December 2021, Government of India has approved protective (third) dose of vaccination to all healthcare workers and vulnerable elderly.

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