Editorial

COVID-19 vaccines & pandemic

The story of COVID-19 pandemic continues unabated for almost a year and a half with numerous unexpected twists and turns due to emerging waves and variants. The pandemic has hit the world severely. India has also been hit badly, especially in the second wave of the pandemic. As on May 31, 2021, India has contributed 28.2 million cases and 0.34 million deaths to a global tally of 171 million cases and about 3.7 million deaths. In absolute numbers, the United States of America is the country with the greatest number of cases and mortality, followed by India. The impact of the pandemic on several smaller and developing countries such as Bangladesh, Bhutan, Sri Lanka, Pakistan, Thailand and Vietnam, has been subdued, uneven in causing morbidity and mortality and less consequential.

Are vaccines effective in containing pandemic?

Initially, the countries which had state-of-the-art health services found it difficult to cope in preventing infections, managing cases and reducing deaths. Most resource-rich countries could however, swiftly put together their act and tame the virus – at least for the present. They achieved this through primarily vaccinating large populations and promoting COVID appropriate behaviour and vaccines. Israel, the United Kingdom and the USA have significantly reduced transmission and resultant morbidity and mortality using the time-tested and effective tool of vaccination. Perhaps, Israel is the best example, where during the massive third wave, it delivered more than 10 million doses within four months, thus immunizing around five million people with two doses of mRNA vaccine given 21 days apart. These vaccines included almost 88 per cent of people aged 50 yr or older. According to Centers for Disease Control and Prevention (CDC), the USA has vaccinated almost 63.4 per cent of its adult population with at least one dose of COVID-19 vaccine. The UK has achieved one-dose vaccination of more than 68 million people, of whom 28 million have received both the doses. Bhutan despite being a small country but with a good healthcare delivery system, could immunize 94 per cent of its adult population within two weeks in April 2021.

The unmistaken message from these countries to the entire world is to accelerate immunization of eligible population before the pandemic assumes another monstrous dimension. This is the biggest challenge being faced by the developing countries with limited access to quality vaccines. Taming the pandemic globally will not be possible until significant vaccination coverage is assured in all the countries. A variety of vaccines are now available and another large set of vaccines is soon to be added to the global arsenal.

Current landscape of vaccines against COVID-19

Unprecedented global efforts continue in development and ascertaining efficacy and safety of numerous vaccine candidates against COVID-19. According to the WHO, of the 287 vaccine candidates, 185 are still in preclinical stage, while 97 have progressed to various phases of clinical trials. Nine vaccines have obtained Emergency Use Authorization (EUA) from respective national regulatory authorities (Figure).

EUA is an emergency response to a serious public health emergency that allows use of medical countermeasures including vaccines even in the presence of inadequate comprehensive data which are sufficiently indicative with benefits outweighing risk. It is because of EUA that we have several licensed vaccines.

Salient characteristics of COVID-19 vaccines

Most of the vaccines are likely to become available soon. COVID-19 vaccines have a two-dose regimen...
except the one produced by Johnson and Johnson which has a one-dose regimen and the upcoming DNA vaccine (Zydus Cadila) which will have a three-dose regimen. Intramuscular administration is the preferred route of administration, while intranasal and intradermal vaccines are also expected soon. The cold chain requirements for most of these vaccines (with notable exception of mRNA vaccines) match with those of existing facilities for childhood vaccines i.e., 2-6°C.

For most of the COVID-19 vaccines in current use, the efficacy (or relative risk reduction) varies between 67 and 95 per cent. The whole-virion inactivated vaccine developed in India (Bharat Biotech International Limited and the Indian Council of Medical Research) shows 81 per cent efficacy. Gam-COVID-Vac, another vaccine available in India (developed in Russia with two different types of adenoviruses), has been shown to have an efficacy of 91.6 per cent (95% confidence interval 85.6-95.2). This vaccine uses two serotypes of adenoviruses as vectors (Ad25 and Ad5). This design is intended to overcome the pre-existing immunity that may develop to adenoviruses. The next-generation vaccines are likely to have improved efficacy to respond effectively to global demand of quality vaccine which are needed in huge numbers. For individual protection of all residents of the planet with a two-dose vaccine, around 16 billion doses are needed, of which as of May 31, 2021, 835 million doses have been administered, 20 per cent of which has been given to Indians. To achieve herd immunity by vaccinating 70-80 persons of global population, around 11-12 billion doses of vaccines need to be produced. Given the rapid strides being made in scaling up of vaccine production, it is expected that the world would be able to surpass this requirement by the end of 2022. The challenge shall be in equitable and ethical distribution of these vaccines. As of March 2021, 70 per cent of 8.6 billion doses of COVID-19 vaccines were secured by high-income countries. This does not augur well for containing pandemic.

Vaccination of special population groups

Apart from adults, there are special groups that require vaccination against COVID-19. These are children, pregnant women and people who have recently recovered from COVID-19. Although the disease in children is mild and invokes a good immune response, epidemiologically, this population is important for curtailing transmission of virus. The apprehensions that COVID-19 vaccines in children may interfere with the routine childhood vaccination need to be dispelled. The trials need to have similar criteria as in adults to understand efficacy and safety of COVID-19 vaccines as well as study interference with other childhood vaccines. Pfizer has published its data with 100 per cent efficacy of its mRNA vaccine in children of 12-16 yr of age. This vaccine has already been given to >600,000 children in the USA. Trials with all other vaccines in children of varying age groups are underway and their outcomes shall determine the policy guidance for vaccinating children with COVID-19 vaccines.

Pregnant women who if infected with SARS-CoV-2 are likely to develop a severe form of infection. If vaccinated, these women should respond with immune response which matches that of non-pregnant women. Another advantage is of transmission of immunity to newborns. Clearly, additional studies are required.
yet global recommendations are now favouring vaccination of this subpopulation.18

People who have recovered from COVID-19 should also be administered vaccine.19 A gap of three months is being generally recommended after clinical recovery from COVID-19, administration of monoclonal antibody or convalescent plasma20.

**Interval between two doses of vaccines**

The vaccination schedule for the various COVID-19 vaccines is mainly determined by the results of the clinical trials. Determination of ideal interval also requires understanding of local or anticipated epidemiology, the immune response in targeted beneficiaries and deployment challenges in the country. In India, BBV152 has been consistently delivered with a four-week interval, while there have been changes in the regimen for ChAdOx1 nCoV-19 based upon further field studies.21 Ideally, India should plan its own studies with different intervals between the two doses to arrive at the best regimen in the Indian context.

There is virtually no contraindication to vaccinating the eligible population. There is sufficient scientific evidence available now that anyone with a history of allergy or anaphylaxis to any substance other than COVID-19 vaccine or any of its components should not be refused COVID vaccine.22 Anaphylaxis with ChAdOx1 nCoV-19 has been rarely seen in India and almost never with BBV152. In the USA, the anaphylaxis rate with mRNA vaccines is 1:200,000 with Pfizer mRNA vaccine and 1:360,000 with Moderna mRNA vaccines.22 Other mild-to-moderate adverse events following immunization (AEFI) are having the same pattern in almost all the vaccines.

**Blood clot concerns and breakthrough infections post vaccination**

Vaccine-induced immune thrombocytopenia (VIIT) is typical and characteristic AEFI following ChAdOx1 nCoV-19 vaccine.23,24 It includes cerebral venous sinus thrombosis, portal vein thrombosis and sometimes arterial thrombosis. VIIT is associated with low platelet count and high D-dimer value, occurs predominantly in younger females in the age group of 30-50 yrs and is manifested between 5-24 days following vaccination. Patients usually have positive antibodies to platelet factor 4, but whether that is the cause is yet to be confirmed.24 In India with its limited AEFI surveillance, the number of such complications seems to be comparable to non-vaccinated populations, but in the UK, the numbers are increasing.23 Several recommendations have been made in Europe to avoid administering ChAdOx1 nCoV-19 vaccine to vulnerable age groups of 30-40 yr.

Breakthrough infection following vaccination is a matter of great emerging concern. It has the potential of harming vaccination programme. Two major reasons for breakthrough infection are exposure to the virus before the vaccines mount the expected protective response efficacy of vaccines ranging between 65 and 92 per cent and the ability of the virus to escape immune response through its variants. The USA has fully vaccinated more than 100 million people, 0.01 per cent of these developed diseases and 160 died.25 The Israel study also shows breakthrough infections and mortality higher than that in the USA27 though both countries used mRNA vaccine. Vaccines however, reduce risk of hospitalizations due to severe COVID-19 and death.27

**Variants of SARS-CoV-2**

Variants of SARS-CoV-2 are assuming threatening proportions in causing disease, death and escaping immune response generated by the vaccines.28 The WHO has classified these into variants of interest, variants of concern and variants of high consequences based upon several characteristics without attaching name of any country with the origin of the variants (Table).28,29 Of all variants of concern, the delta variant is being detected in several locations and linked with severe disease and higher mortality vis-a-vis other variants. The delta variant is believed to be causing higher hospitalizations in the UK.30 Obviously, these and several other new variants that are likely to emerge shall become major obstacles in the future in containing pandemic and reducing mortality. Significant work is being done on variants of concern and it is likely that these may impact the epidemiology of disease and technology advances achieved with vaccines till date.

**National policy and plan to mitigate pandemic**

The nationwide vaccination shall require strong harmonized political commitment, sustained funding, effective programme implementation, multi-sectoral coordination and acceptance by the communities. The countries must provide right information to the communities to ensure positive behaviour and acceptance of technologies. Vaccine hesitancy is a huge issue that is attributable to lack of trust and faith in vaccination, infodemics, inadequate access,
breakthrough infections, etc. There is an urgent need to convert vaccine hesitancy to vaccine eagerness.

There are several developing countries that do not have access to vaccines and/or resources to procure and administer them to their eligible populations. The global community is trying to address these challenges through a multi-sectoral global platform called COVAX which is a part of Access to COVID-19 Tools accelerator coordinated by Global Vaccine Alliance (GAVI), Coalition for Epidemic Preparedness Innovations, WHO, UNICEF and others. It aims to meet at least 20 per cent of vaccine requirements of developing countries with or without payment. Till May 31, 2021, more than 78 million doses of vaccines have been shipped by COVAX to 129 countries.

Conclusions

COVID-19 vaccinations combined with COVID-19 appropriate behaviour are the most effective tools for individual protection and pandemic containment. Despite rapid development of the vaccines, their access and efficacy remain limited. Second-generation vaccines with improved efficacy and safety are urgently needed. Vaccinating the targeted number of beneficiaries shall be a daunting task for any government and SARS-CoV-2 variants are likely to play an important obstructive role in the context of vaccine hesitancy. Extensive risk communications and continued efforts to win public confidence in the vaccine must persist. Surveillance is also critical. As of now, COVID-19 vaccines have shown tremendous success in the USA, UK and Israel. A similar triumph in rest of the world is immediately called for to see the end of the pandemic.

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References

1. Worldometers: Available from: https://www.worldometers.info/coronavirus/?fbclid=IwAR35ZFiRZJ8yBCwazX2Nk7YjJZOLDQiZSA_MsJAfdK74s8f2a_Dgx4IVk#countries, accessed on May 30, 2021.
2. Leshem E, Wilder-Smith A. COVID-19 vaccine impact in Israel and a way out of the pandemic. Lancet 2021; 397: 1783-5.
3. UK Government. Vaccinations in United Kingdom. Available from: https://coronavirus.data.gov.uk/details/vaccinations, accessed on May 31, 2021.
4. Centres for Disease Control and Prevention. COVID Data Tracker. Available from: https://covid.cdc.gov/covid-data-tracker/#vaccinations, accessed on May 30, 2021.
5. Dorji T, Tamang ST. Bhutan’s experience with COVID-19 vaccination in 2021. BMJ Glob Health 2021; 6: e005977.
6. World Health Organization. COVID-19 Vaccine Tracker and Landscape. Available from: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines, accessed on May 31, 2021.
7. US Food and Drug Administration. Emergency Use Authorization. Available from: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization, accessed on May 29, 2021.

8. Oliiaro P, Torreele E, Vaillant M. COVID-19 vaccine efficacy and effectiveness—the elephant (not) in the room. Available from: https://www.thelancet.com/action/showPdf?pii=S2666-5247%2821%2900069-0, accessed on May 28, 2021.

9. Indian Council of Medical Research. Phase 3 clinical trial of COVAXIN, developed by ICMR & Bharat Biotech, shows 81% efficacy. Available from: https://www.icmr.gov.in/pdf/press_release_files/Press_Release_ICMR_03_March_2021.pdf, accessed on May 31, 2021.

10. Jones I, Roy P. Sputnik V COVID-19 vaccine candidate appears safe and effective. Lancet 2021; 397: 642-3.

11. Barouch DH, Kik SV, Weaverling GJ, Dilan R, King SL, Maxfield LF, et al. International seroepidemiology of adenovirus serotypes 5, 26, 35, and 48 in pediatric and adult populations. Vaccine 2011; 29: 5203-9.

12. Our World in Data. Available from: https://ourworldindata.org/covid-vaccinations?country=IND, accessed on May 31, 2021.

13. Irwin A. What it will take to vaccinate the world against COVID-19. Nature 2021; 592: 176-8.

14. Callaway E. COVID vaccines and kids: five questions as trials begin. Nature 2021; 592 : 670-1.

15. Frenck RW Jr., Klein NP, Kitchin N, Gurtman A, Absalon J, Lockhart S, et al. Safety, immunogenicity, and efficacy of the BNT162b2 COVID-19 vaccine in adolescents. N Engl J Med 2021. doi: 10.1056/NEJMoa2107456.

16. Press briefing by white house COVID-19 response team and public health officials. Available from: https://www.whitehouse.gov/briefing-room/press-briefings/2021/05/18/press-briefing-by-white-house-covid-19-response-team-and-public-health-officials-37/, accessed on May 31, 2021.

17. Gray KJ, Bordt EA, Atyeo C, Deriso E, Akinwunmi B, Young N, et al. Coronavirus disease 2019 vaccine response in pregnant and lactating women: A cohort study. Am J Obstet Gynecol 2021. doi: https://doi.org/10.1016/j.ajog.2021.03.023.

18. Centres for Disease Control and Prevention. COVID-19 Vaccine While Pregnant or Breast Feeding. Available from: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/pregnancy.html, accessed on May 29, 2021.

19. World Health Organization. Getting the COVID-19 Vaccine. Available from: https://www.who.int/news-room/feature-stories/detail/getting-the-covid-19-vaccine#, accessed on May 31, 2021.

20. Centres for Disease Control and Prevention. Frequently Asked Questions on COVID-19 vaccination. Available from: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/faq.html, accessed on May 31, 2021.

21. Voysey M, Costa Clemens SA, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: A pooled analysis of four randomised trials. Lancet 2021; 397 : 881-91.

22. Turner PJ, Ansotegui IJ, Campbell DE, Cardona V, Ebisawa M, El-Gamal Y, et al. COVID-19 vaccine-associated anaphylaxis: A statement of the World Allergy Organization Anaphylaxis Committee. World Allergy Organ J 2021; 14 : 100517.

23. Cines DB, Bussel JB. SARS-CoV-2 vaccine-induced immune thrombotic thrombocytopenia. N Engl J Med 2021; 384 : 2254-6.

24. European Pharmaceutical Review. Vaccine-induced prothrombotic immune thrombocytopenia: pathogenetic and epidemiological issues of concern. Available from: https://www.europeanpharmaceuticalreview.com/article/152978/vaccine-induced-prothrombotic-immune-thrombocytopenia-pathogenetic-and-epidemiological-issues-of-concern/, accessed on May 30, 2021.

25. Oliiaro P, Torreele E, Vaillant M. COVID-19 vaccine efficacy and effectiveness – The elephant (not) in the room. Lancet Microbe 2021; 2 : E279-80.

26. Centres for Disease Control and Prevention. COVID-19 Vaccine breakthrough infections reported to CDC - United States, January 1-April 30, 2021. Available from: https://www.cdc.gov/mmwr/volumes/70/wr/mm7021e3.htm, accessed on May 29, 2021.

27. Haas EJ, Angulo FJ, McLaughlin JM, Anis E, Singer SR, Khan F, et al. Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: An observational study using national surveillance data. Lancet 2021; 397 : 1819-29.

28. World Health Organization. Tracking SARS CoV Variants. Available from: https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/, accessed on May 31, 2021.

29. World Health Organization. International Health Regulations (2005) Third Edition. Available from: https://www.who.int/publications/i/item/9789241580496, accessed on May 30, 2021.

30. Public Health England. Variants: Distribution of case data. Available from: https://www.gov.uk/government/publications/covid-19-variants-genomically-confirmed-case-numbers/variants-distribution-of-case-data-3-june-2021, accessed on May 29, 2021.

31. Covax Facility. Available from: https://www.gavi.org/covax-facility, accessed on May 31, 2021.