SARS-CoV-2 variants and ending the COVID-19 pandemic

Published Online
February 11, 2021
https://doi.org/10.1016/
S0140-6736(21)00370-6

The COVID-19 pandemic has devastated health-care systems, shut down schools and communities, and plunged the world into an economic recession. While 2020 was a challenging year, 2021 looks to be difficult with the emergence of multiple variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The race to vaccinate the world will need to respond to the pathogen's constant evolution to evade immunity. What marks the path to the end of this pandemic?

2020 saw the successful development and testing of COVID-19 vaccines within timeframes not considered possible before. Two mRNA COVID-19 vaccines produced the first results, with impressive efficacy (94–95%).[1,2] A disadvantage of these two vaccines is their low temperature storage requirements. Although other COVID-19 vaccines developed to date that use viral vectors, subunit particles, or inactivated viruses have comparatively lower levels of efficacy, with estimates of 70% for ChAdOx1 nCoV-19[3] and 92% for Gam-COVID-Vac (Sputnik V)[4] adenovirus vector vaccines, they do not have the ultracold storage temperature requirements of the mRNA vaccines and are therefore easier to deliver. Data available so far for COVID-19 vaccines have shown protection only against clinical forms of infection, with the exception of recent data showing reduction in the duration of viral shedding and viral load among recipients of the ChAdOx1 nCoV-19 vaccine compared with placebo recipients, suggesting potential impact on viral transmission as well.[5]

In December, 2020, an unexpected rise in reported COVID-19 cases was attributed to the emergence of the new SARS-CoV-2 variants 501Y.V1 (B.1.1.7) in the UK and 501Y.V2 (B.1.351) in South Africa.[6,7] In South Africa, high transmission in the context of high population immunity[8] may have favoured the emergence and subsequent spread of the variant. Both variants had a mutation (N501Y) in the receptor-binding domain of the spike protein that is reported to contribute to increased transmission,[9] with estimates ranging between 40% and 70% for increased transmission.[6] The 501Y.V2 variant has two additional mutations (E484K and K417N) in the spike protein that confer a potential immune escape to antibodies.[10] In a concerning development, another set of mutations (N501Y, E484K, and K417T) in a new P.1 (501Y.V3) lineage has been identified in Manaus, Brazil.[11]

A key issue is whether COVID-19 vaccines will be able to protect against infection or disease from these new SARS-CoV-2 variants. Preliminary research suggests sera from individuals immunised with the mRNA COVID-19 vaccines neutralise a 501 mutation pseudovirion, but neutralise a 501-484-417 mutant pseudovirion to a lesser extent.[12] Moreover, preliminary clinical trial results of ChAdOx1 nCoV-19 showed 74% efficacy in the UK[3] but only 22% in South Africa,[13] whereas NVX-CoV2373, a protein-based COVID-19 vaccine, showed 89% efficacy in the UK but only 49% efficacy in South Africa, where the 501Y.V2 variant predominates.[14] Similarly, differences in vaccine efficacy in the USA and South Africa (72% *vs* 57%) were reported for the Ad26COV2.S COVID-19 vaccine.[15] More encouragingly, 85% protection against severe COVID-19 has been reported for the Ad26COV2.S vaccine in South Africa, although we do not know the precision around the estimate provided in the press release.[16] If confirmed, a vaccine strategy targeting first those at risk of severe COVID-19 might therefore still be effective even in the presence of variants.

The recent emergence of SARS-CoV-2 variants, after a period of relative viral genetic stability, is a cause for concern since multiple new escape variants could emerge in future and lead to severe epidemic rebound, as seen in South Africa. Increased viral transmission creates greater opportunities for the emergence of SARS-CoV-2 variants. Hence, the end of the pandemic is only possible when vaccines that are effective against circulating variants are distributed equitably across the world. As high-income countries race to immunise their populations within months, they leave themselves vulnerable to SARS-CoV-2 evolving in other countries to a new lineage that vaccines might not protect well against. Repeatedly formulating new vaccines may be needed to control some new SARS-CoV-2 variants. With the increase in basic reproduction number of more transmissible SARS-CoV-2 variants,[6] higher vaccine coverage will be required to achieve herd immunity, and vaccinating children might also be necessary to reach this coverage.

The emergence of new SARS-CoV-2 variants calls for a number of important measures (panel). First, fewer new

***Panel:* Priorities to address new SARS-CoV-2 variants**

- Continue to suppress and push to eliminate SARS-CoV-2 while rolling out COVID-19 vaccines
- Improve surveillance of SARS-CoV-2 variants through global sequencing and sharing of variant-specific PCR primers
- Create a central repository of samples of sera and cells from individuals with past infection or past immunisation with available COVID-19 vaccines for seroneutralisation and cellular immunity functional testing against newly discovered variants
- Produce COVID-19 vaccines reactively and adapt them to newly emerging lineages
- Ensure global access, availability, and affordability of COVID-19 vaccines to ensure no countries are left behind

infections means less viral replication, which, in turn, lowers the risk of new variants. This situation can only be achieved by a combination of non-pharmaceutical interventions and scale-up of vaccines, both being important, until population immunity is achieved. Aiming for a COVID-19 elimination strategy is the preferred option in this context.

Second, for surveillance of the circulation of SARS-CoV-2 variants, sharing of variant-specific PCR primers could help to monitor their spread, particularly in resource-limited countries. In addition, every country should include genomic sequencing of SARS-CoV-2 variants in their plans. For resource-limited countries, support from WHO, the Africa Centres for Disease Control and Prevention, and other partner institutions will be necessary to help develop expertise and capacity as well as strengthen health systems. All genetic sequences should be posted on international platforms such as GISAID for shared analyses. Infections in people who were previously infected or vaccinated should be carefully examined for escape variants.

For **GISAID** see https://www.gisaid.org

Third, a central repository of samples of sera and cells from individuals with past infection or past immunisation with available COVID-19 vaccines should be established for seroneutralisation and cellular immunity functional testing against newly discovered variants. This repository could release regular advisories to provide guidance on a minimum set of epitopes to be included in new COVID-19 vaccines.

Fourth, the production of COVID-19 vaccines should be reactive and adapted to newly emerging lineages. This flexibility is likely to be easier to achieve with the new COVID-19 vaccine technologies currently being deployed and based on nucleic acids (mRNA vaccines or viral vector vaccines).[17]

Finally, vaccines need to be available, affordable, and accessible at a global scale. Several high-income countries have purchased vaccine doses, sometimes close to nine doses per person,[18] while WHO has called for greater equity and stronger support for the COVAX initiative and its mandate of equitable vaccine access, especially for resource-limited countries. Of note is an initiative of the African Union to independently purchase and distribute COVID-19 vaccines to countries over the continent to supplement the COVAX programme.[19] Whether vaccine delivery should be prioritised to countries with high SARS-CoV-2 prevalence and continued transmission—eg, South Africa, Brazil, Mexico, or India—to prevent further emergence of new variants has to be considered.

This pandemic is a reminder to high-income countries that infectious diseases have a tremendous impact on economies and lives, and rapid development and implementation of effective vaccines against these diseases should remain priorities globally. Global cooperation to ensure equity and responsiveness to local contexts is essential on the difficult path ahead to ending the COVID-19 pandemic.

AF and BL are members of the French COVID-19 Scientific Council. AF, BA, and MPK are members of the French COVID-19 Vaccine Strategy Committee. MPK is Chair of the French COVID-19 Vaccine Committee and Chair of the COVAX Independent Product Group. SSAK is Co-Chair of the South African Ministerial Advisory Committee on COVID-19. DS is a member of the Scottish COVID-19 Advisory Group and the UK Cabinet Office COVID-19 Advisory Group. We declare no other competing interests.

**Arnaud Fontanet, Brigitte Autran, Bruno Lina, Marie Paule Kieny, Salim S Abdool Karim, Devi Sridhar*
fontanet@pasteur.fr

Institut Pasteur, Emerging Diseases Epidemiology Unit, Paris 75015, France (AF); Conservatoire National des Arts et Métiers, PACRI Unit, Paris, France (AF); Sorbonne-Université, Paris, France (BA); UMR-S Inserm/UPMC 1135, CIMI-Paris (Centre de Recherches Immunité Maladies Infectieuses), Paris, France (BA); CNR des Virus des Infections Respiratoires, Institut des Agents Infectieux, Hospices Civils de Lyon (BL); Virpath, Centre International de Recherche en Infectiologie, Université de Lyon, Inserm U1111, CNRS UMR5308, École Normale Supérieure de Lyon, UCBL, Lyon, France (BL); Inserm, Paris, France (MPK); Centre for the AIDS Programme of Research in South Africa (CAPRISA), Durban, South Africa (SSAK); Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY, USA (SSAK); Usher Institute of Population Health Sciences and Informatics, Edinburgh Medical School, University of Edinburgh, Edinburgh, UK (DS)

1 Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med* 2021; **384:** 403–16.
2 Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med* 2020; **383:** 2603–15.
3 Voysey M, Costa Clemens SA, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet* 2020; **397:** 99–111.

4 Logunov DY, Dolzhikova IV, Shcheblyaokov DV, et al. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVIC-19 vaccine: an interim analysis of a randomized controlled phase 3 trial in Russia. *Lancet* 2021; published online Feb 2. https://doi.org/10.1016/S0140-6736(21)00234-8.

5 Emary KRW, Golubchik T, Aley PK, et al. Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 VOC 202012/01 (B.1.1.7). *SSRN* 2021; published online Feb 4. https://dx.doi.org/10.2139/ssrn.3779160.

6 Volz E, Mishra S, Chand M, et al. Transmission of SARS-CoV-2 lineage B.1.1.7 in England: insights from linking epidemiological and genetic data. *medRxiv* 2021; published online Jan 4. https://doi.org/10.1101/2020.12.30.20249034 (preprint).

7 Tegally H, Wilkinson E, Giovanetti M, et al. Emergence and rapid spread of a new severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) lineage with multiple spike mutations in South Africa. *MedRxiv* 2020; published online Dec 22. https://doi.org/10.1101/2020.12.21.20248640 (preprint).

8 Hsiao M, Davies MA, Kalk E, et al. SARS-CoV-2 seroprevalence in the Cape Town Metropolitan sub-districts after the peak of infections. *NICD COVID-19 Special Public Health Surveill Bull* 2020; **18:** 1–9.

9 Gu H, Chen Q, Yang G, et al. Adaptation of SARS-CoV-2 in BALB/c mice for testing vaccine efficacy. *Science* 2020; **369:** 1603–07.

10 Wibmer CK, Ayres F, Hermanus T, et al. SARS-CoV-2 501Y.V2 escapes neutralization by South African COVID-19 donor plasma. *bioRxiv* 2021; published online Jan 19. https://doi.org/10.1101/2021.01.18.427166 (preprint).

11 Faria NR, Claro IM, Candido D, et al. Genomic characterisation of an emergent SARS-CoV-2 lineage in Manaus: preliminary findings. *Virological*, January, 2021. https://virological.org/t/genomic-characterisation-of-an-emergent-sars-cov-2-lineage-in-manaus-preliminary-findings/586 (accessed Feb 8, 2021).

12 Wang Z, Schmidt F, Weisblum Y, et al. mRNA vaccine-elicited antibodies to SARS-CoV-2 and circulating variants. *bioRxiv* 2021; published online Jan 30. https://doi.org/10.1101/2021.01.15.426911 (preprint).

13 Cohen J. South Africa suspends use of AstraZeneca's COVID-19 vaccine after it fails to clearly stop virus variant. *Science* 2021; published online Feb 8. https://doi.org/10.1126/science.abg9559.

14 Wadman M, Cohen J. Novavax vaccine delivers 89% efficacy against COVID-19 in U.K.—but is less potent in South Africa. *Science* 2021; published online Jan 28. https://doi.org/10.1126/science.abg8101.

15 Cohen J. One-dose of COVID-19 vaccine offers solid protection against severe disease. *Science* 2021; published online Jan 29. https://doi.org/10.1126/science.abg7115.

16 Johnson & Johnson. Johnson & Johnson announces single-shot Janssen COVID-19 vaccine candidate met primary endpoints in interim analysis of its phase 3 ENSEMBLE trial 2021. Jan 29, 2021. https://www.jnj.com/johnson-johnson-announces-single-shot-janssen-covid-19-vaccine-candidate-met-primary-endpoints-in-interim-analysis-of-its-phase-3-ensemble-trial (accessed Feb 9, 2021).

17 Muik A, Wallisch AK, Sänger B, et al. Neutralization of SARS-CoV-2 lineage B.1.1.7 pseudovirus by BNT162b2 vaccine-elicited human sera. *Science* 2021; published online Jan 29. https://doi.org/10.1126/science.abg6105.

18 Mullard A. How COVID vaccines are being divided up around the world. *Nature* 2020; published online Nov 30. https://doi.org/10.1038/d41586-020-03370-6.

19 Africa News. African Union secures 400 million vaccine doses. Jan 28, 2021. https://www.africanews.com/2021/01/28/african-union-secures-additional-400-million-vaccine-doses/ (accessed Feb 9, 2021).