6 Tess BH, Granato CFH, Alves MCGP, et al. SARS-CoV-2 seroprevalence in the municipality of Sao Paulo, Brazil, ten weeks after the first reported case. *medRxiv* 2020; published online June 29. https://doi.org/10.1101/2020.06.29.20142331 (preprint).

7 Kempen JH, Abashawl A, Kinfemichael H, et al. SARS CoV-2 Serosurvey in Addis Ababa, Ethiopia. *medRxiv* 2020; published online June 23. https://doi.org/10.1101/2020.06.23.20137521 (preprint).

8 Picon RV, Carreno I, Anjos da Silva A, et al. Coronavirus disease 2019 population-based prevalence, risk factors, hospitalization, and fatality rates in southern Brazil. *Int J Infect Dis* 2020; **100:** 402–10.

9 Shakiba M, Hashemi Nazari SS, Mehrabian F, Rezvani SM, Ghasempour Z, Heidarzadeh A. Seroprevalence of COVID-19 virus infection in Guilan province, Iran. *medRxiv* 2020; published online April 26. https://doi.org/10.1101/2020.04.26.20079244 (preprint).

10 Chibwana MG, Jere KC, Kamng'ona R, et al. High SARS-CoV-2 seroprevalence in health care workers but relatively low numbers of deaths in urban Malawi. *Wellcome Open Res* 2020; **5:** 199.

11 Uyoga S, Adetifa IMO, Karanja HK, et al. Seroprevalence of anti-SARS-CoV-2 IgG antibodies in Kenyan blood donors. *medRxiv* 2020; published online July 27. https://doi.org/10.1101/2020.07.27.20162693 (preprint).

12 Diggle PJ. Estimating prevalence using an imperfect test. *Epidemiol Res Int* 2011; **2011:** 1–5.

The European Medicines Agency's EU conditional marketing authorisations for COVID-19 vaccines

Published **Online** January 13, 2021 https://doi.org/10.1016/S0140-6736(21)00085-4

Few medicines are awaited as eagerly as COVID-19 vaccines. Extraordinary efforts by scientists, regulators, and developers enabled the European Medicines Agency (EMA) to recommend the first EU conditional marketing authorisation (CMA) for the BioNTech COVID-19 mRNA vaccine (nucleoside-modified) BNT162b2 (Comirnaty)[1] some 9 months after the COVID-19 pandemic was declared. On Dec 21, 2020, the European Commission granted CMA, following the EMA's positive opinion, to BNT162b2 for active immunisation of individuals aged 16 years and older to prevent COVID-19, which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[2]

CMA is used in EU legislation for emergency situations in response to public health threats. This authorisation requires demonstration of a positive benefit–risk balance, allowing for additional post-marketing data to be provided on the condition that the company supplies these data as specific obligations within defined timelines. Specific obligations generally include clinical studies and exceptionally, in the context of emergencies, studies to provide further assurance on the pharmaceutical quality of the vaccines. The EMA's evaluation was expedited by making use of rolling reviews, specifically designed by the EMA, that allowed assessment of discrete datasets as soon as they became available. The EMA collaborated with several non-EU regulators and WHO throughout the assessment, under existing confidentiality arrangements, and has engaged with the International Coalition of Medicines Regulatory Authorities to ensure global alignment.[3]

Vaccine efficacy of BNT162b2 in the pivotal trial, which is still ongoing (NCT04368728), was high at 95% (95% CI 90·3–97·6) and the safety profile was adequate.[4] The most commonly reported adverse reactions include injection site pain, fatigue, headache, myalgia, chills, arthralgia, and pyrexia, and safety aspects are included in the EU's risk management plan.[5] Currently, the only important identified risk is anaphylaxis. Vaccine-associated enhanced disease will be monitored as a potential risk, although it is at present a theoretical concern not observed with COVID-19 vaccines. Although there might be challenges in keeping participants in placebo groups in ongoing phase 3 clinical trials, long-term safety and efficacy follow-up of trial participants, possibly for up to 24 months, is planned.[5]

Alain Jocard/Getty Images

On Jan 6, 2021, a second COVID-19 mRNA vaccine from Moderna received CMA approval in the EU after clinical trial evidence showed similar efficacy (94·1%, [89·3–96·8]) and safety[6,7] of the Moderna vaccine compared to the BNT162b2 vaccine.

A robust integrated system to monitor COVID-19 vaccine safety and effectiveness in the post-approval stage will rely on specific pharmacovigilance activities run by the sponsor, the independent data collection and analysis[8] provided by the EU national competent authorities, and the joint European Centre for Disease Prevention and Control (ECDC)–EMA efforts to monitor safety and effectiveness.

Genetic variants of SARS-CoV-2 are emerging,[9,10] requiring continuous monitoring of COVID-19 vaccine performance over time. Available data suggest that BNT162b2 elicits cross-neutralising activity against genetic variants of SARS-CoV-2 that differ from the vaccine strain,[1] but further information and analyses will be needed, particularly for variants with multiple mutations, including in the receptor binding domain of the spike protein. Discussion is underway on what would be the regulatory requirements to support a change in the composition of the vaccines, addressing the need for the timely availability of such information to meet the public health demand.

Vaccines that reduce symptomatic disease have a crucial role in reducing the burden of COVID-19. However, the achievement of high vaccination coverage globally is expected to take considerable time and the ability of COVID-19 vaccines to prevent infection and transmission remains unknown.[1] In the meantime, other public health measures, such as use of face masks, physical distancing, and good respiratory and hand hygiene remain essential.

The efficacy of BNT162b2 was apparent after about 10–14 days from administration of the first dose and before the administration of the second dose 21 days afterwards (the range in the clinical study was 19–42 days).[2] Similar considerations would apply to the Moderna COVID-19 vaccine, notwithstanding the slightly different schedule with a second dose given with an interval of 28 days (dosing window allowed in the clinical study 21–42 days).[7] These findings have led some public health authorities to consider delayed administration of a second dose to maximise the numbers of people receiving the first immunisation. There are no clinical data at present that would confirm prolonged protection after a first dose beyond the intervals studied in the clinical trials, preventing the possibility for a regulatory approval of an extended dosing interval. Additionally, the levels of neutralising antibodies elicited by the first dose of these vaccines are low,[1] which would call for caution with respect to the possibility of reduced protection the longer the second dose is delayed and given the possible rapid emergence of vaccine escape genetic variants of SARS-CoV-2.

There is public health interest in understanding the interchangeability of different COVID-19 vaccines once they are approved, and, particularly, whether heterologous boosting might be suitable or even preferable. Evidence from well designed clinical trials will need to be obtained before any such approaches are put into practice. The EMA has liaised continuously with the ECDC and national immunisation technical advisory groups in the EU to explain the regulatory views on all the aspects mentioned and to stay informed about the planned vaccination strategies in different European countries.

There is an urge to start vaccination campaigns without delay but such campaigns cannot come with a lowering of the approval standards. Although the EU is expediting the scientific assessment and granting of CMAs for COVID-19 vaccines, the evaluation of marketing authorisation applications with all the necessary safeguards and controls takes longer than the review used by some countries to grant emergency use authorisations.[11] A CMA provides a controlled and robust framework to ensure that all pharmacovigilance, manufacturing controls, including batch controls for vaccines, and other post-approval obligations apply in a legally binding way and are evaluated and acted on by the EMA's scientific committees on a continuous basis. These elements ensure a high level of protection to citizens during a mass vaccination campaign. EU member states could have opted for emergency use in their own territory but have chosen a more robust, unified EU approach, with a joint assessment benefiting all member states and prioritising citizens' safety across Europe equally.

Further to the approval timelines of the new COVID-19 vaccines, roll-out of vaccination campaigns and vaccine uptake in EU member states will also depend on several factors such as limited initial vaccine supplies and effective deployment.

The approvals of the first COVID-19 vaccines in the EU are a key milestone in the response to COVID-19. The first EU marketing authorisations for COVID-19 vaccines not only offer hope to control the pandemic but also provide proof of concept for a new approach to vaccine development in response to future emerging health threats.

MC is the Chair of the EMA's COVID-19 Task Force. HE is the Chair of the EMA's Committee for Medicinal Products for Human Use. SS is the Chair of the EMA's Pharmacovigilance Risk Assessment Committee. EC is Executive Director of the EMA. We declare no other competing interests. The views expressed in this Comment are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the EMA or one of its committees or working parties.

Marco Cavaleri, Harald Enzmann, Sabine Straus, Emer Cooke
marco.cavaleri@ema.europa.eu

European Medicines Agency, 1083 HS Amsterdam, Netherlands (MC, HE, SS, EM); Federal Institute for Drugs and Medical Devices, European Union and International Affairs, Bonn, Germany (HE); Medicines Evaluation Board, Utrecht, Netherlands (SS)

1 European Medicines Agency. Comirnaty assessment report. Dec 21, 2020. https://www.ema.europa.eu/en/documents/assessment-report/comirnaty-epar-public-assessment-report_en.pdf (accessed Jan 8, 2021).
2 European Medicines Agency. Comirnaty EU product information. 2020. https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf (accessed Jan 8, 2021).
3 International Coalition of Medicines Regulatory Authorities. ICMRA statement on clinical trials. June 24, 2020. http://icmra.info/drupal/news/statement_on_clinical_trials (accessed Jan 8, 2021).
4 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.
5 European Medicines Agency. Comirnaty risk management plan. Dec 21, 2020. https://www.ema.europa.eu/en/documents/rmp/comirnaty-epar-risk-management-plan_en.pdf (accessed Jan 8, 2021).
6 European Medicines Agency. EMA recommends COVID-19 vaccine Moderna for authorisation in the EU. Jan 6, 2021. https://www.ema.europa.eu/en/news/ema-recommends-covid-19-vaccine-moderna-authorisation-eu (accessed Jan 8, 2021).
7 European Medicines Agency. COVID-19 Moderna vaccine EU product Information 2021. https://www.ema.europa.eu/en/documents/product-information/covid-19-vaccine-moderna-product-information_en.pdf (accessed Jan 8, 2021).
8 European Medicines Agency. Pharmacovigilance plan for COVID-19 vaccines. 2020. https://www.ema.europa.eu/en/documents/other/pharmacovigilance-plan-eu-regulatory-network-covid-19-vaccines_en.pdf (accessed Jan 8, 2021).
9 European Centre for Disease Prevention and Control. Threat assessment brief on SARS-CoV-2 variant in United Kingdom. Dec 20, 2020. https://www.ecdc.europa.eu/en/publications-data/threat-assessment-brief-rapid-increase-sars-cov-2-variant-united-kingdom (accessed Jan 8, 2021).
10 European Centre for Disease Prevention and Control. Risk related to spread of new SARSCoV-2 variants of concern in the EU/EEA. Dec 29, 2020. https://www.ecdc.europa.eu/sites/default/files/documents/COVID-19-risk-related-to-spread-of-new-SARS-CoV-2-variants-EU-EEA.pdf (accessed Jan 8, 2021).
11 European Commission Regulation (EC) No 507/2006 of 29 March 2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council. https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/reg_2006_507/reg_2006_507_en.pdf (accessed Jan 8, 2021).

COVID-19 vaccines and women's security

Published **Online**
December 22, 2020
https://doi.org/10.1016/S0140-6736(20)32727-6

Pandemics such as COVID-19 are gendered with regard to who is infected, who dies, who provides care, who is secured against violence and economic change, and who leads and makes decisions.[1] Vaccines are no different and there is a need to address male bias in vaccine development to make women safe from deadly diseases.[2] For example, clinical trials that are not done in both men and women can raise adverse outcomes during implementation due to sex-based differences in immunological response.[3] The excitement and awe at the speed of COVID-19 vaccine development and delivery needs to be attentive to the social and political dynamics in which the vaccine is delivered—women's work and their security are at the heart of this.

The delivery and facilitation of COVID-19 vaccines will disproportionately depend on the unpaid labour of women. Vaccine uptake partly depends on the free labour of women within the household, impacting women's economic and personal security. Unpaid labour will generally fall to women as parents or family carers; women will typically have the responsibility for arranging when and how children and wider family members, such as older relatives, get immunised. This process is likely to be more onerous with vaccines requiring two doses, such as the Pfizer–BioNTech, Moderna, and Oxford–AstraZeneca options.[4–6] This effort to practically access

Carl Recine/Reuters