Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

COVID-19 vaccines: A race against time

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Introduction

Less than one year after the declaration of COVID-19 as a pandemic disease by the Word Health Organization (WHO), the collaboration of the global scientific community has put on track no less than 308 vaccine candidates, among which 16 are currently in Phase III trials [1]. At the time of writing, the Pfizer-BioNTec, Moderna and Janssen vaccines have received an emergency use authorisation by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). EMA has also granted a conditional marketing authorisation for the Oxford-AstraZeneca vaccine. First real life data from nationwide vaccination campaigns are becoming available and show that vaccines could help preventing hospitalisations and controlling the epidemic, as reported in Israel [2]. But recently, new SARS-CoV-2 lineages called B.1.1.7 (corresponding to the 501Y.V1 variant), B.1.351 (501Y.V2 variant) and B.1.1.28/P.1 (501Y.V3 variant) respectively emerged in the United Kingdom (UK), South Africa and Brazil, and represent a challenge for current vaccines with preliminary results showing variable levels of cross-reaction depending on the viral strain [3]. How much vaccines will be able to protect against infection due to these SARS-CoV-2 variants or to future emerging variants is still uncertain, and comparing estimates of their respective efficacy is a delicate challenge [4]. Herein we briefly present the main vaccines in use around the world and discuss the challenges still ahead in 2021.

BNT162b2 mRNA COVID-19 vaccine (BioNTech-Pfizer)

The BioNTech-Pfizer vaccine is a lipid nanoparticle-formulated, nucleoside modified mRNA vaccine encoding full-length S protein. Its efficacy was first assessed in a double blind, randomised phase III trial across Argentina, Brazil, South Africa and USA, in which 43,548 participants were randomised to receive two 30 μg doses of BNT162b2 vaccine 21 days apart or placebo [5]. Protection occurred as early as the second week after the first vaccine administration, with an increase of protection against COVID-19 up to 95% after the second administration. The vaccine is reactogenic, but the side effects remained acceptable in all populations studied with a short-term safety profile characterised by mild to moderate pain at the injection site, fatigue and headache lasting less than 48 h. No grade 4 adverse side effects were observed. Data for people over 75 were scarce in this trial and absent for children, pregnant women or immunocompromised patients. Efficacy was measured only in symptomatic patients, with no evidence of a potential effect against viral shedding. Data in a nationwide mass vaccination setting from Israel suggests that the effectiveness of the vaccine is consistent with that of the randomised trial [6].

mRNA-1273 COVID-19 vaccine (NIAID – Moderna)

This lipid nanoparticle encapsulated mRNA vaccine encodes pre fusion S protein. In a Phase III randomised, placebo-controlled trial conducted in 99 centres across the United States, in which persons at high risk for SARS-CoV-2 infection or its complications received two intramuscular doses or placebo 28 days apart, the vaccine showed 94.1% efficacy at preventing COVID-19 illness, including severe disease, at least 14 days after the second injection [7]. Hypersensitivity reactions were reported in 1.5% and 1.1% of participants respectively in the vaccine and placebo groups with three Bell's palsy in the vaccine group and 1 in the placebo group.

AZD1222 COVID-19 vaccine (Oxford University- AstraZeneca)

The Oxford-AstraZeneca vaccine is based on a replication-deficient simian adenovirus (ChAdOx1) vector containing codon-optimised S protein. Efficacy data from a blinded, randomised, controlled trial across UK and Brazil, in which the control group received meningococcal vaccination (ACYW), showed a AZD1222 vaccine efficacy in the standard dose scheme (two standard doses, 28 days apart) of 62.1%, but a 90% efficacy in the low dose scheme (one low dose followed by a standard dose, 28 days apart) [8]. Immunocompromised volunteers were not included in the trial and few elderly participants (over 65) were represented, leading to a debate on the population for the EMA conditional marketing authorisation. At the time of writing, some European countries have temporarily suspended its use as a precautionary measure based on reports of rare blood clotting disorders in persons who had received this vaccine. However, WHO and EMA consider that

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Table 1
Characteristics known to date of the three main variant lineages of SARS-CoV-2.

	B.1.1.7	B.1.351	B.1.1.28/P.1
Corresponding variant	501Y.V1	501Y.V2	501Y.V3
Country of emergence	United Kingdom	South Africa	Brazil
Key mutations	N501Y	N501Y E484K K417N	N501Y E484K K417T
Transmissibility	40–90% increased [11,12]	No data	No data
Risk of mortality	Hazard ratio 1.64 (95% CI 1.32–2.04) [18]	No data	No data
Vaccine efficacy	AZD1222: similar efficacy compared to canonical non B.1.1.7 lineage [19] BNT162b2: efficacy in real life in Israel [6]	AZD1222: 22% efficacy [17] Ad26.COV2.S: up to 85% efficacy [10]	No data

the benefits of the AZD1222 vaccine outweigh its risks and thus recommends that vaccinations continue [9].

Ad26.COV2.S Covid-19 vaccine (Beth Israel Deaconness Medical Center-Janssen Pharmaceutical Companies)

This single-shot recombinant adenovirus vaccine (Ad26) incorporates SARS-CoV-2 full stabilised S protein. First data regarding vaccine efficacy has been made public by the means of press release. A first interim analysis 28 days after a one-dose vaccination showed 66% efficacy at preventing moderate to severe COVID-19 with a 85% efficacy in preventing severe disease [10]. As the FDA did in February, EMA has granted an Emergency Use Authorisation on March 11 for this vaccine, which is the last conditional approval to date for COVID-19 vaccines.

Challenges ahead

Neutralisation of viral variants

Variant lineages of SARS-CoV-2 have been increasing around the world (Table 1). The N501Y mutation, which is present in the three main variants (UK, South African, Brazilian), modifies the receptor-binding domain of the S protein and may lead to 40 to 90% increased transmission [11,12]. The 501Y.V2 and 501Y.V3 variants have another mutation, E484K, in the S protein that may confer a potential immune escape to antibodies [13]. Moreover, Public Health England (PHE) announced in February 2021 that 11 samples of the B.1.1.7 variant harboured the E484K [14]. In vitro, the largely preserved neutralisation of pseudo viruses bearing the B.1.1.7 spike by BNT162b2-immune sera makes it unlikely that the UK variant virus will escape BNT162b2-mediated protection [15]. However, sera from individuals immunised with the mRNA COVID-19 vaccines seems to have significantly less neutralising activity against pseudovirions combining the N501Y and E484K mutations [16]. AZD1222 COVID-19 vaccine showed only 22% efficacy in South Africa where the 501Y.V2 variant predominates [17], whereas 85% protection against severe COVID-19 has been reported in South Africa for the Ad26COV2.S vaccine (press release) [10].

Reduction of asymptomatic infections and transmission

Data available for COVID-19 vaccines have mainly shown protection against symptomatic infections including severe COVID-19. However, preliminary data suggested that the Moderna vaccine could decrease asymptomatic infection by two-thirds as compared to the placebo, although the numbers were small and the design of the study not adapted for this analysis. Recent data with the AZD1222 vaccine also showed reduction in the duration of viral shedding and viral load among participants receiving it compared with placebo recipients [19]. This may suggest an impact on viral transmission but these data must be confirmed by further studies designed for the analysis of vaccine efficacy on asymptomatic infection and transmission.

Optimisation of vaccine schedules

Uncertainty persists on the most effective vaccine schedules, both individually and collectively. Some countries such as the USA have chosen to scrupulously comply with the regimens of the Phase III trials, while others such as the United Kingdom have recommended delaying the second dose in order to quickly increase the number of people who have had at least one dose of the vaccines. Likewise, it is not yet established which is the best vaccination schedule for patients who have already been infected. It now seems that one dose of vaccine is sufficient, given at least 6 months after the infection but this may need to change with the diffusion of variants. Generally, it is unlikely that one vaccine will solve the COVID-19 crisis. We can already imagine regional adaptations of vaccines or even cocktails of different SARS-CoV-2 strains to produce an immune response to several variants at the same time. Many other questions are still awaiting answers such as the duration of protection provided by the vaccines, the relative effectiveness of the humoral and cellular immunity they induce, their effect in older populations, children, pregnant women or immunocompromised patients.

Societal challenges

Finally, societal and global challenges must be met. There can be no global control of the pandemic without greater equity in the supply of vaccines, which are currently almost entirely purchased by the richest countries. In addition, vaccine hesitancy seems stronger than ever in the face of these rapidly developed vaccines in the context of a prolonged pandemic. It is now essential to create the conditions for a constructive dialogue between doctors, researchers and citizens in order to deliver reliable and constantly updated information on these vaccines. The "infodemic" of fake news can only be countered with transparent and honest medical information that succeeds in restoring faith in medicine. This challenge of medical communication aimed at the general public is probably one of the main challenges of modern science and medicine.

Conclusion

Among the positive consequences of this crisis, the COVID-19 pandemic has enabled the successful rollout of RNA vaccines that are safe, quick to develop and can adapt quickly to genetic sequence changes such as the ones present in variants. The place of other vaccine platforms remains of course intact and it is only by increasing the number of effective and well-tolerated vaccines that we can hope to see the light at the end of the tunnel. Indeed, as the

COVID-19 epidemic continues to ravage the world, we are hanging on the ruthless race between vaccine development and SARS-CoV-2 mutations.

Declaration of interest

None declared.

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