# After three years of Covid, risks to health remain

Speaking during an interview on the CBS *60 Minutes* television programme in September 2022, US President Joe Biden declared: "The pandemic is over…We still have a problem with Covid, we're still doing a lot of work on it, but the pandemic is over."

While President Biden's comments were probably just what many Americans wanted to hear, for people living in China such a notion would have seemed absurd. At the time, the country was still rigorously enforcing its "zero Covid" strategy, which relied on lockdowns rather than vaccination to control the pandemic. While this approach has been successful in the sense that the incidence of Covid-19 infection has been relatively low in China, economic and other pressures have forced the country to relax its policy, and a sharp upswing in the infection rate is expected. Wu Zunyou, chief epidemiologist at the Chinese Center for Disease Control and Prevention, was recently reported as predicting that there will be three separate waves of infection in China this winter.

Meanwhile, the official position in the EU lies somewhere between these two extremes. Speaking at a press briefing in November 2022, Steffen Thirstrup, chief medical officer at the European Medicines Agency, said that although levels of circulating virus and the incidence of Covid-19 infection in Europe were declining, the situation could yet worsen, especially if new, more virulent variants of the SARS-CoV-2 virus emerge. There is still considerable potential for the virus to spread among vulnerable populations, such as individuals with chronic medical conditions or people who have not been vaccinated. The World Health Organization's director general, Tedros Adhanom Ghebreyesus, has warned of the risk of new variants emerging in any large population not protected by vaccination, such as that in China.

So, what do the latest data show? According to the WHO, the number of new Covid-19 cases reported globally during the week 26 December 2022 to 1 January 2023 was down 22% on the previous week at more than three million, while the number of new weekly deaths was down 12% at 10,000. In the US specifically, in the week to 4 January, there were 402,525 new cases and 2,530 deaths, according to figures from the Centers for Disease Control and Prevention. Globally, over 657 million confirmed cases of Covid-19 and over 6.6 million deaths have been reported to the WHO since the beginning of the pandemic.

Professor Thirstrup's caution about the possible impact of new variants is reflected in epidemiological data published by the WHO. Six Omicron subvariants that together accounted

**Table 1. Vaccines approved for use against SARS-CoV-2 in the EU, as of December 2022**

| Vaccine | Approval | Strain | Use | Population |
|---|---|---|---|---|
| Comirnaty (BioNTech) | Full | Original strain | Primary | 6 months + |
| | | | Booster | 5 years + |
| | | Original strain + Omicron BA.1 | Booster | 12 years + |
| | | Original strain + Omicron BA.4-5 | Booster | 5 years + |
| Spikevax (Moderna) | Full | Original strain | Primary | 6 months + |
| | | | Booster | 6 years + |
| | | Original strain + Omicron BA.1 | Booster | 6 years + |
| | | Original strain + Omicron BA.4-5 | Booster | 12 years + |
| Vaxzevria (AstraZeneca) | Full | Original strain | Primary | 18 years + |
| | | | Booster | 18 years + |
| Jcovden (Janssen) | Conditional | Original strain | Primary | 18 years + |
| | | | Booster | 18 years + |
| Nuvaxovid (Novavax) | Conditional | Original strain | Primary | 12 years + |
| | | | Booster | 18 years + |
| COVID-19 Vaccine Valneva (Valneva) | Full | Original strain | Primary | 18-50 years |
| VidPrevtyn Beta (Sanofi Pasteur) | Full | Beta variant | Booster | 18 years + |

Source: EMA

for 74.4% of prevalence as of the week to 18 December 2022 are currently being monitored to track changes in prevalence and viral characteristics, although there is currently no evidence of increased severity associated with these variants compared to previous Omicron lineages.

The six variants (and their respective global prevalence) are:

- BQ.1* (44.9%), a sublineage of BA.5;
- BA.5 which has one or more of five mutations in the spike protein (10.3%);
- BA.2.75* (11.8%);
- BA.4.6* (0.6%);
- BA.2.3.20* (<0.1%); and
- XBB* (6.8%, which includes XBB.1.5).

XBB.1.5 has attracted some attention because of a rapid growth in its prevalence in the US (it accounted for 40.5% of US infections in the week to 31 December 2022, according to the CDC), together with an increased risk of immune escape and greater infectivity. It does not however appear to cause more severe disease than other Omicron variants, although its resistance to antibodies has been described as 'alarming.'

## Vaccines

Against this background, considerable progress was made during 2022 in the fight against the virus. As Marco Cavaleri, head of biological health threats and vaccines strategy at the EMA said during a press briefing in December 2022, Europe began the year with five authorised vaccines that targeted the original strain of SARS-CoV-2 and ended the year with a portfolio of seven vaccines plus four adapted vaccines that target several variants of the virus (see Table 1). In addition, the EMA has assessed data on the use of vaccines in children leading to the availability of vaccines that can be used in children aged from six months, including those with underlying conditions.

In the US, meanwhile, four vaccines have been approved or authorised for emergency use against the original strain of the virus, and two bivalent vaccines incorporating a component of the Omicron variant have been authorised for use as a booster dose (see Table 2). The US Food and Drug Administration is scheduled to hold a meeting of its Vaccines and Related Biological Products Advisory Committee (VRBPAC) on 26 January to consider whether and how the composition for primary doses of the currently available Covid-19 vaccines should be modified and how and whether the composition and schedule for booster doses should be adjusted. The meeting will be attended by representatives from the CDC and the National Institutes of Health.

## Antivirals

Progress has also been made on the development of antiviral products to treat Covid-19 infection. The first antiviral treatment of Covid-19 was Gilead Sciences Inc's Veklury (remdesivir), which was authorised for use in the EU in July 2020. Its approved indications include adults and paediatric patients (aged at least four weeks) with pneumonia requiring supplemental oxygen, and adults and paediatric patients (weighing at least 40 kg) who do not require supplemental oxygen but who are at increased risk of progressing to severe Covid-19.

In the US, Veklury was approved by the FDA in October 2020 for use in adult and paediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of Covid-19 requiring hospitalisation. The approval replaced an earlier emergency use authorisation (EUA) for the product, which was however revised to authorise the drug's use in younger hospitalised paediatric patients. The approval was later expanded to include non-hospitalised, high-risk patients.

In December 2021, the FDA issued an EUA for emergency use of Pfizer's Paxlovid for the treatment of mild-to-moderate Covid-19 in adults and paediatric patients with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe Covid-19, including hospitalisation or death. Paxlovid comprises two active substances, nirmatrelvir and ritonavir, in two different tablets. Nirmatrelvir blocks the activity of 3C-like protease, an enzyme needed by the virus to multiply, while ritonavir is a CYP3A and protease inhibitor that slows the breakdown of nirmatrelvir in the body.

In January 2022, the EMA granted a conditional marketing authorisation for Paxlovid for the treatment of Covid-19 in adults who do not require supplemental oxygen and who are at increased risk of the disease becoming severe.

Also in December 2021 the FDA issued an EUA for emergency use of Merck Sharp & Dohme LLC's Lagevrio (molnupiravir) as treatment of mild-to-moderate Covid-19 in adults with positive results of direct SARS-CoV-2 viral testing, who are at high risk for progression to severe Covid-19, including hospitalisation or death, and for whom alternative Covid-19 treatment options authorised by the FDA are not accessible or clinically appropriate. However, the results of the University of Oxford's PANORAMIC trial published in *The Lancet* in December 2022 suggested that molnupiravir did not reduce the frequency of Covid-19-associated hospitalisations or death among high-risk vaccinated adults in the community, although it did accelerate recovery among such individuals who do not progress to serious disease. A marketing authorisation application for Lagevrio has been submitted in the EU.

Other drugs that have been officially sanctioned for the treatment of Covid-19 include Kineret (anakinra, marketed by Swedish Orphan Biovitrum AB (Sobi)) and Olumiant (baricitinib, marketed by Lilly). Kineret is an immunosuppressive used in the treatment of rheumatoid arthritis and other conditions. In the EU, it is indicated for the treatment of Covid-19 in adult patients with pneumonia requiring supplemental oxygen who are at risk of progressing to severe respiratory failure. In the US, the FDA has issued an EUA for use in similar situations.

Olumiant is a Janus kinase inhibitor also used in the treatment of rheumatoid arthritis. The FDA has granted an EUA for its use in hospitalised patients aged between two and 18 years who require supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation. It is not authorised for this use in the EU.

## Monoclonal antibodies

While vaccines and antiviral products continue to be valuable in the fight against Covid-19, the situation is less clear in the case of monoclonal antibodies, with the EMA's Emergency Task Force (ETF) recently warning that monoclonal antibodies may not be effective against emerging strains of

the virus.

Four monoclonal antibody products that target the SARS-CoV-2 spike protein have been approved in the EU for the prevention and treatment of Covid-19:

- Evusheld (tixagevimab + cilgavimab, AstraZeneca AB);
- Ronapreve (casirivimab + imdevimab, Roche Registration GmbH);
- Xevudy (sotrovimab, GlaxoSmithKline Trading Services Limited); and
- Regkirona (regdanvimab, Celltrion Healthcare Hungary Kft).

These products have been shown to prevent the risk of symptomatic Covid-19 infection in the context of pre-exposure or post-exposure prophylaxis, says the ETF, and to reduce the risk of progression to severe disease, hospitalisation and death in patients with early disease not requiring supplemental oxygen and who are at an increased risk for progressing to severe disease.

**Table 2. Vaccines approved for use against SARS-CoV-2 in the US, as of December 2022**

| Vaccine | Approval | Strain | Use | Population |
|---|---|---|---|---|
| Pfizer-BioNTech COVID-19 Vaccine | BLA | Original strain | Primary | 12 years + |
| | EUA | Original strain | Primary | 6 months + |
| Pfizer-BioNTech COVID-19 Vaccine, Bivalent | EUA | Original strain + Omicron BA.4-5 | Booster | 6 months + |
| Moderna COVID-19 Vaccine | BLA | Original strain | Primary | 18 years + |
| | EUA | Original strain | Primary | 12 years + |
| | EUA | Original strain | Primary | 6 months + |
| Moderna COVID-19 Vaccine, Bivalent | EUA | Original strain + Omicron BA.4-5 | Booster | 6 months + |
| Janssen COVID-19 Vaccine | EUA | Original strain | Primary | 18 years + |
| | | Original strain | Booster | 18 years + |
| Novavax COVID-19 Vaccine, Adjuvanted | EUA | Original strain | Primary | 12 years + |
| | | Original strain | Booster | 18 years + |

Source: FDA. BLA = Biologics License Application. EUA = Emergency Use Authorization.
Note: Pfizer-BioNTech COVID-19 Vaccine is marketed as Comirnaty for the prevention of Covid-19 in individuals 12 years of age and older. Moderna COVID-19 Vaccine is marketed as Spikevax for the prevention of Covid-19 in individuals 18 years of age and older.

However, in a statement issued on 9 December 2022, the ETF said that recent laboratory studies had shown that monoclonal antibodies that target the spike protein of SARS-CoV-2 are poorly effective at neutralising Omicron strains BA.4.6, BA.2.75.2, XBB, BQ.1 and BQ1.1 (the latter two variants were expected to become the dominant strains in the EU by the end of 2022). Because the precise relationship between viral susceptibility *in vitro* and serum concentration of the monoclonal antibodies *in vivo* is not fully understood, it is not possible to predict the extent, if any, to which clinical efficacy of these monoclonal antibodies might be affected by the reduced *in vitro* neutralisation activity, the ETF said. Furthermore, there are no clinical trial data available to determine whether clinical efficacy is modified. Healthcare professionals were therefore advised to consider alternative antiviral treatment options, which are expected to retain their antiviral activity against the emerging variants of concern.

In the US, AstraZeneca's Evusheld is authorised for emergency use for preventing Covid-19 in adults and children not currently infected with SARS-CoV-2 but who are severely immune compromised or for whom vaccination is not recommended. Eli Lilly & Co's bebtelovimab is authorised for the emergency treatment of mild-to-moderate Covid-19 in patients aged 12 years and older who are at high-risk for progression to severe Covid-19. Three other monoclonal antibody products have been granted EUAs, but are not currently authorised because of the high frequency of circulating SARS-CoV-2 variants that are not susceptible to them: GlaxoSmithKline Plc's sotrovimab, Lilly's bamlanivimab + etesevimab, and Regeneron Pharmaceuticals Inc's REGEN-COV (casirivimab + imdevimab).

One further monoclonal antibody-based product authorised for the treatment of certain patients with Covid-19 is Roche's tocilizumab, marketed in the US as Actemra and in the EU as RoActemra. It acts as by blocking the interleukin-6 receptor, thereby reducing the inflammation associated with the exaggerated immune response sometimes seen in Covid-19 patients. It is not affected by the guidance concerning anti-spike protein monoclonal antibodies.

It is clear that, although enormous progress has been made in dealing with Covid-19, and despite President Biden's comments in September, the pandemic is not over yet. Perhaps the area of greatest concern is the situation in China, where the relaxation of public health restrictions has been predicted to lead to a rapid rise in cases, although official figures do not so far reflect this. While some commentators have suggested that this rapid rise will lead to population immunity being reached very quickly, others have warned that it would create ideal conditions for the emergence of new and possible more virulent strains of the virus. However, the WHO's Technical Advisory Group on Virus Evolution (TAG-VE) said on 4 January 2023 that no new variant or mutation of known significance had so far been identified in genomic data released by the Chinese Center for Disease Control and Prevention.

Another area of concern is post-Covid syndrome, also known as long Covid. Symptoms of this vary, but may include fatigue, fever, not being able to think clearly ('brain fog') and respiratory symptoms including difficulty breathing, shortness of breath and cough. Although a great deal of research is underway, there is currently no specific treatment for post-Covid syndrome, although there is evidence that prior vaccination reduces the risk of developing the syndrome.

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