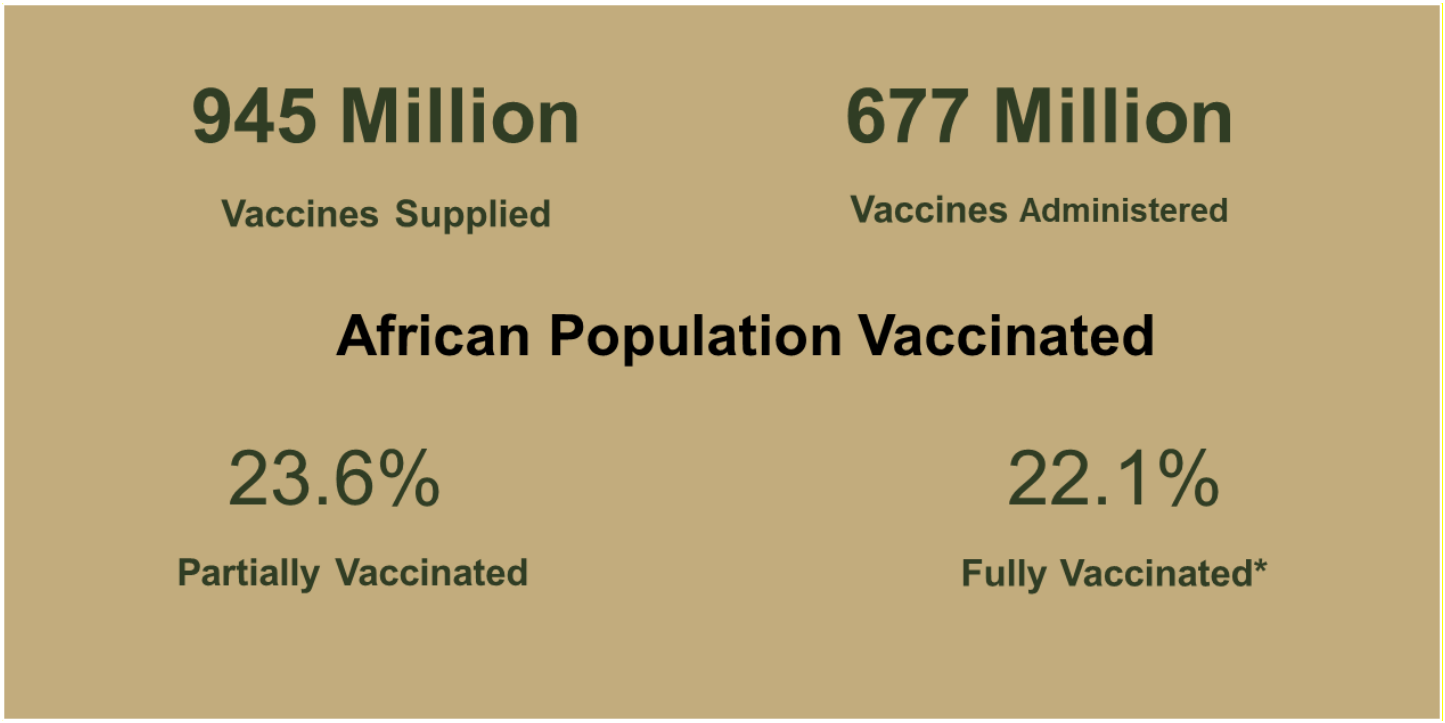
COVID-19 Scientific and Public Health Policy Update[1] (31 August 2022)

This bi-weekly brief details the latest developments in scientific knowledge and public health policy from around the world as well as updates to the COVID-19-related guidance from Africa CDC, WHO and other public health agencies. This brief complements the Weekly Outbreak Brief and other documents on COVID-19 and the actions that the African Union/Africa CDC and WHO/AFRO are taking to help African Union Member States. Contents are ***not intended to serve as recommendations*** *from the African Union-Africa CDC or WHO/AFRO; rather, the brief serves as a summary of the scientific information available in the public space to Member States. The outbreak is evolving rapidly and the nature of this information will continue to change. We will provide regular updates to ensure Member States are informed of the most critical developments on the science and public health best practices related to COVID-19.*

A. Trending Topics

Status of Vaccines in Africa



*Received two doses of a two-dose COVID-19 vaccine series or one dose of the Johnson & Johnson vaccine
https://africacdc.org/COVID-19-vaccination/
Updated 31 August 2022

Note:

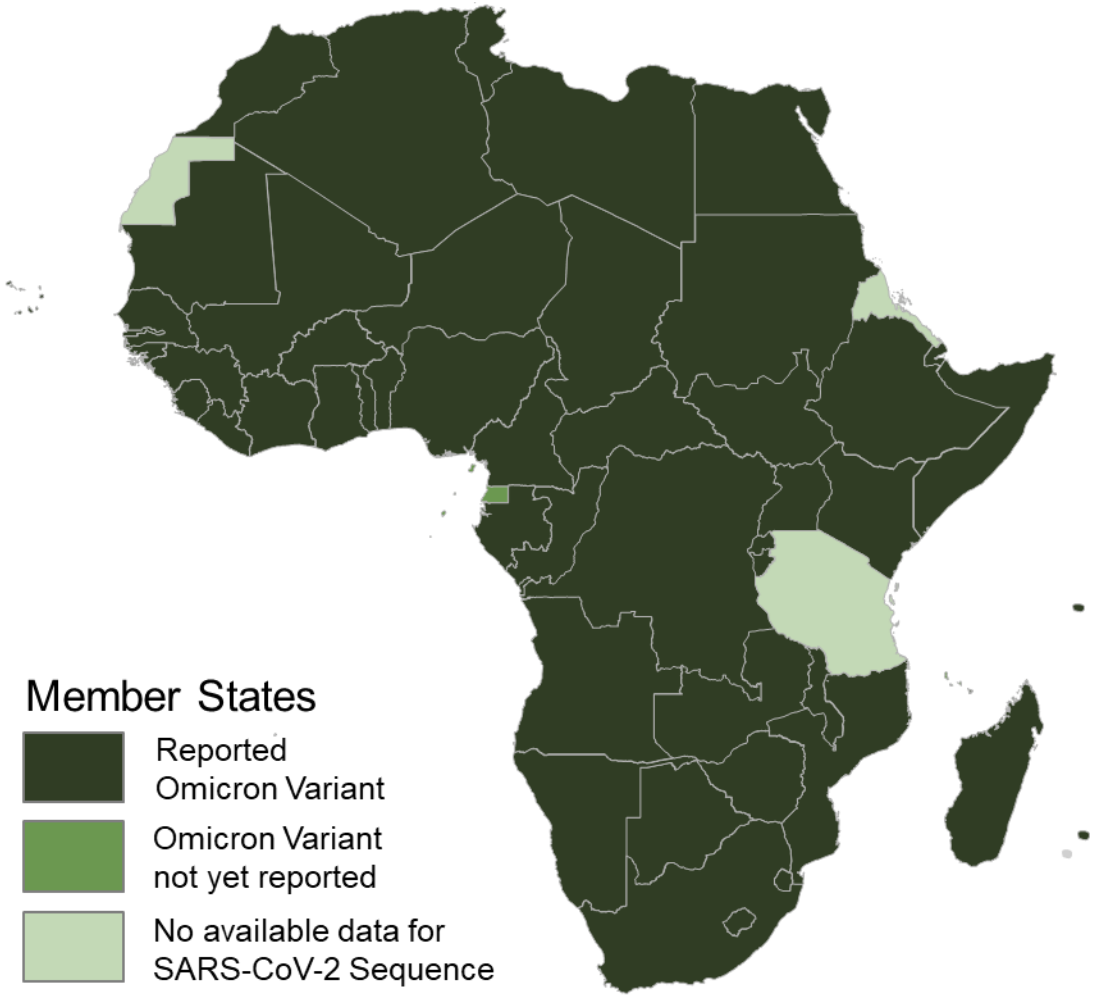
I. There is a reduction in figures (vaccines supplied) reported previously due to data cleaning.

II. Africa CDC has changed the denominator of the calculation for percentage fully vaccinated from 2020 population to 2022 population estimates (UNFPA) to give accurate projections from effective population size (Ne) perspectives. The resulting effect is that there will be a slight reduction in fully vaccinated coverage percentages of member states and the continent at large.

[1] This update compiled for use by African Union Member States and is developed collaboratively by the African Union-Africa CDC and World Health Organization - Regional Office for Africa. **This is a preliminary summary of information and does not represent policy decisions, recommendations, or final conclusions of the African Union- Africa CDC or WHO/AFRO**.

Variants of Concern (VOC)

The Omicron variant (B.1.1.529), first reported in South Africa on 24th November 2021, has spread to 198 countries/territories/areas worldwide. As of 31 August 2022, 51 (92.7%) of the 55 Member States in Africa have reported this variant. For more information visit https://africacdc.org/institutes/africa-pathogen-genomics-initiative/.



Updated 31 August 2022

B. New guidelines and resources

Since 17 August 2022,

- Africa CDC[2] has published new guidance and resources on:
  - Africa CDC – Mastercard Foundation: Saving Lives and Livelihoods Newsletter, August 2022
  - Outbreak Brief 136: Coronavirus Disease 2019 (COVID-19) Pandemic

- U.S. CDC[3] has published new guidance and resources on:
  - Selected Adverse Events Reported after COVID-19 Vaccination
  - Print Resources
  - Novavax COVID-19, Adjuvanted Vaccine: Overview and Safety

[2] Africa CDC: Africa Centres for Disease Control and Prevention
[3] U.S. CDC: United States Centres for Disease Control and Prevention

- Safety Monitoring of Pfizer-BioNTech COVID-19 Vaccine Booster Doses Among Children Aged 5–11 Years — United States, May 17–July 31, 2022

- WHO[4] has published new guidance and resources on:
  - Progress on WASH in health care facilities 2000-2021: Special focus on WASH and infection prevention and control (IPC)
  - Promising practices and lessons learnt in the South-East Asia Region in accessing medical oxygen during the COVID-19 pandemic
  - Interim recommendations for use of the Valneva VLA2001 vaccine against COVID-19
  - Background document on the Valneva VLA2001 vaccine against COVID-19
  - Good practice statement on the use of second booster doses for COVID-19 vaccines
  - Interim recommendations for use of the Pfizer–BioNTech COVID-19 vaccine, BNT162b2, under Emergency Use Listing
  - Interim recommendations for use of the Moderna mRNA-1273 vaccine against COVID-19

- U.S. FDA[5] has issued press releases on:
  - On 26 August, FDA provided additional guidance to help prescribers evaluate potential drug interactions when using Paxlovid therapy for COVID-19
  - On 26 August, FDA removed N95 Respirators from medical device shortage list, signalling sufficient supply
  - On 19 August, FDA Authorised the emergency use of Novavax COVID-19 Vaccine in individuals 12 through 17 years of age
  - As of 30 August, 439 tests and sample collection devices are authorised by the FDA under emergency use authorisations (EUAs)

- ECDC[6] has issued new resources on:
  - Long-term qualitative scenarios and considerations of their implications for preparedness and response to the COVID-19 pandemic in the EU/EEA
  - Generic protocol for COVID-19 vaccine effectiveness studies at long-term care facilities in the EU/EEA

- UKHSA[7] has issued new guidance and press releases on:
  - Using the NHS COVID Pass to demonstrate COVID-19 status
  - National protocol for Spikevax® bivalent Original/Omicron COVID-19 vaccine
  - COVID-19: managing healthcare staff with symptoms of a respiratory infection
  - Preventing and controlling outbreaks of COVID-19 in prisons and places of detention
  - COVID-19: testing during periods of low prevalence

C. Scientific updates

Basic Science

- This study in Egypt describes the genomic epidemiology of SARS-CoV-2 up to July 2021 using a subset of 976 high-quality genomes analysed together with a representative set of global sequences within a phylogenetic framework. A single lineage, C.36, introduced early in the pandemic was responsible for most of the cases in Egypt. Furthermore, to remain dominant in the face of mounting immunity from

[4] WHO: World Health Organization
[5] U.S. FDA: United States Food and Drug Administration
[6] ECDC: European Centre for Disease Prevention and Control
[7] UKHSA: United Kingdom Health Security Agency

previous infections and vaccinations, this lineage acquired several mutations known to confer an adaptive advantage. These results highlight the value of continuous genomic surveillance in regions where VOCs are not predominant and the need for enforcement of public health measures to prevent expansion of the existing lineages.

- This cohort study in Singapore assessed the dynamics of neutralising antibodies in children and adolescents up to 16 months after SARS-CoV-2 infection. The study involved 126 participants (aged 0 to 16 years) with SARS-CoV-2 infection confirmed by polymerase chain reaction test from February 2020 to September 2021. Peak neutralising antibody levels were reached at a median of 84% approximately 1 to 3 months after infection. Neutralising antibody levels remained reasonably high with a median of 69.8% at 9 to 13 months after infection. In the adjusted analysis, neutralising antibody levels by post-infection time were not associated with patient characteristics, such as sex and symptom status. However, during the acute phase of infection (<1 month), neutralising antibody levels were highest in those younger than 5 years (71.6%; 95% CI, 58.5%-84.6%) and lowest in the 12 to 16 years group (49.9%; 95% CI, 41.3%-58.6%). Neutralising antibodies in participants younger than 5 years remained little changed in the point estimates up to 16 months after infection.
- This study in Brazil spatially quantified the immune and structural cells in exudative, intermediate, and advanced diffuse alveolar damage (DAD) patterns in fatal COVID-19 through multiplex immunohistochemistry. The study involved 18 adult patients who died between March and April 2020 due to COVID-19. Spatial DAD progression was associated with expansion of immune cells, macrophages, CD8+ T cells, fibroblasts, and (lymph) angiogenesis. Viral load correlated positively with exudative DAD and negatively with disease/hospital length. In all cases, enteric bacteria were isolated, and *Candida parapsilosis* in eight cases. Cytokines correlated mainly with macrophages and CD8+T cells. Pro-coagulation and acute repair were enriched pathways in exudative DAD whereas intermediate/advanced DAD had a molecular profile of elevated humoral and innate immune responses and extracellular matrix production. These complex features have important implications for disease management and the development of novel treatments.
- This modelling study in the United States sheds light on the pathogenesis of severe COVID-19 by focusing on cells that trigger inflammation through molecular patterns: infected cells carrying pathogen-associated molecular patterns (PAMPs) and damaged cells producing damage-associated molecular patterns (DAMPs). The former signals the presence of pathogens while the latter signals danger such as hypoxia or lack of nutrients. Analyses show that SARS-CoV-2 infections can lead to a self-perpetuating feedback loop between DAMP expressing cells and inflammation, identifying the inability to quickly clear PAMPs and DAMPs as the main contributor to hyperinflammation. The model explains clinical findings and reveal conditions that can increase the likelihood of desired clinical outcome from treatment administration. In particular, the analysis suggest that antivirals need to be administered early during infection to have an impact on disease severity. The simplicity of the model and its high level of consistency with clinical findings motivate its use for the formulation of new treatment strategies.

Vaccines

- This population-based cross-sectional study in Cameroon assessed the impact of government efforts to reduce COVID-19 vaccine hesitancy (VH) and identified the key risk factors driving hesitancy. The study involved 6732 participants across 10 regions of Cameroon from February to April 2022. A total of 4352 responders (64.6%) hesitated to take a COVID-19 vaccine. The risk factors associated with VH were living in an urban setting (OR: 1.3, 95% CI: 1.1–1.5); being a female (OR: 1.5, 95% CI: 1.3–1.7); jobless or a student (OR: 1.1, 95% CI: 0.89–1.4), and working in the education sector (OR: 1.1, 95% CI: 0.87–1.3); being a politician/policy maker/administrator (OR: 2.2, 95% CI: 1.6–3.1) and being an engineer or technician (OR: 3.6, 95% CI: 2.7–4.8) was associated with COVID-19 VH. This was also true for people with medium income (OR: 1.6, 95% CI: 1.4–1.9), those that had no education or only studied to the primary school level (OR: 2.7, 95% CI: 2.0–3.6), and had secondary/high school/professional training (OR: 1.2, 95% CI = 1.1–1.4). The most frequently chosen reasons were; “Confusing information/scare-mongering on social media (n = 1244, 28.8%)”, “Lack of detailed

evidence-based information on vaccines (n = 812, 18.8%)", "Local/traditional remedies are available (n = 784, 18.1%)" and "Concerns about the reliability or source of vaccines (n = 536, 12.4%)".

- This animal model study in the United States assessed the utility of replication in a vaccine by comparing replication-defective adenovirus (RD-Ad) and replicating single-cycle adenovirus (SC-Ad) vaccines that express the SARS-CoV-2 spike protein. SC-Ad produced 100 times more spike protein than RD-Ad and generated significantly higher antibodies against the spike protein than RD-Ad after single immunisation of Ad-permissive hamsters. SC-Ad–generated antibodies climbed over 14 weeks after single immunisation and persisted for more than 10 months. When the hamsters were challenged 10.5 months after single immunisation, a single intranasal or intramuscular immunisation with SC-Ad-Spike reduced SARS-CoV-2 viral loads and damage in the lungs and preserved body weight better than vaccination with RD-Ad-Spike. Their results demonstrate the utility of harnessing replication in vaccines to amplify protection against infectious diseases.

Diagnostics

- This cross-sectional study in the United States characterised the ability of school-aged children to self-collect nasal swabs for SARS-CoV-2 testing compared with collection by health care workers. The study involved 196 symptomatic children and adolescents aged 4 to 14 years old across the Children's Healthcare of Atlanta system from July to August 2021. Children and adolescents were given instructional material consisting of a short instructional video and a handout with written and visual steps for self-swab collection. Of the 196 participants, 87 (44.4%) tested positive for SARS-CoV-2 and 105 (53.6%) tested negative by both self- and health care worker–collected swabs. Two children tested positive by self- or health care worker–collected swab alone; 1 child had an invalid health care worker swab. Compared with health care worker–collected swabs, self-collected swabs had 97.8% (95% CI, 94.7%-100.0%) and 98.1% (95% CI, 95.6%-100.0%) positive and negative percent agreement, respectively, and SARS-CoV-2 Ct values did not differ significantly between groups (mean [SD] Ct, self-swab: 26.7 [5.4] vs health care worker swab: 26.3 [6.0]; p = 0.65).
- This study in the United States assessed the analytical and clinical accuracy of 2 rapid diagnostic tests for detecting SARS-CoV-2 (SCoV-2 Ag *Detect* Rapid Self-Test [InBios International Inc] and BinaxNOW COVID-19 Ag Card [Abbott Laboratories] during 3 phases of variants. The study involved 802 participants (>18 years) who reported onset of COVID-19–like symptoms in King County, Washington, from February 2021 to January 2022, during pre-Delta, Delta, and Omicron phases of SARS-CoV-2 infection. No significant differences were found in the analytical limit of detection or clinical diagnostic accuracy of rapid antigen testing across SARS-CoV-2 variants. The estimated limit of detection for both rapid nucleocapsid antigen tests was at or below a 50% tissue culture infectious dose of 62.5, and the positive percent agreement of the SCoV-2 Ag *Detect* Rapid Self-Test ranged from 81.2% (95% CI, 69.5%-89.9%) to 90.7% (95% CI, 77.9%-97.4%) across the 3 phases of variants. The diagnostic sensitivity increased for nasal swabs with a lower cycle threshold by RT-PCR, which correlates with a higher viral load. These findings suggest that home-based rapid antigen testing programs may be an important intervention to reduce global SARS-CoV-2 transmission.
- This study in the United States used computational protein modelling tools to suggest molecular beacon architectures that function as conformational switches for high-sensitivity detection of the SARS-CoV-2 spike protein receptor binding domain (S-RBD). Integrating these beacons on a miniaturized total internal reflection fluorescence (mini-TIRF) microscope, the authors detect the S-RBD and pseudotyped SARS-CoV-2 with limits of detection in the femtomolar range. They envision that their mini-TIRF platform could serve as a robust platform for point-of-care diagnostics for SARS-CoV-2 and future emergent viral threats.

Care and Treatment

- This retrospective cohort study in the United Kingdom assessed the relationship between ambulatory COVID-19 and short-term (30-day) risk of venous thromboembolism (VTE). The study also assessed the clinical and genetic risk factors for post–COVID-19 VTE. The study involved 18,818 outpatients

with COVID-19 and 93,179 propensity score–matched noninfected participants between March 2020 and September 2021. COVID-19 was associated with an increased risk of VTE in 30 days (incidence rate of 50.99 and 2.37 per 1000 person-years for infected and uninfected people, respectively; HR, 21.42; 95% CI, 12.63-36.31). However, risk was substantially attenuated among the fully vaccinated (HR, 5.95; 95% CI, 1.82-19.5; interaction p = 0.02). In patients with COVID-19, older age, male sex, and obesity were independently associated with higher risk, with adjusted HRs of 1.87 (95% CI, 1.50-2.33) per 10 years, 1.69 (95% CI, 1.30-2.19), and 1.83 (95% CI, 1.28-2.61), respectively. Further, inherited thrombophilia was associated with an HR of 2.05 (95% CI, 1.15-3.66) for post–COVID-19 VTE. These findings may reinforce the need for vaccination, inform VTE risk stratification, and call for targeted VTE prophylaxis strategies for unvaccinated outpatients with COVID-19.

- This retrospective cohort study in the United States assessed the incidence and clinical features of post-acute sequelae of SARS-CoV-2 infection (PASC) in children. The study involved 659,286 participants (<21 years) across 9 children's hospitals between March 2020 and October 2021. A total of 59 893 (9.1%) tested positive for SARS-CoV-2. The most common syndromic, systemic, and medication features were loss of taste or smell (adjusted hazard ratio [aHR], 1.96; 95% CI, 1.16-3.32), myocarditis (aHR, 3.10; 95% CI, 1.94-4.96), and cough and cold preparations (aHR, 1.52; 95% CI, 1.18-1.96), respectively. The incidence of at least 1 systemic, syndromic, or medication feature of PASC was 41.9% (95% CI, 41.4-42.4) among viral test–positive children vs 38.2% (95% CI, 38.1-38.4) among viral test–negative children, with an incidence proportion difference of 3.7% (95% CI, 3.2-4.2). A higher strength of association for PASC was identified in those cared for in the intensive care unit during the acute illness phase, children younger than 5 years, and individuals with complex chronic conditions.
- This secondary analysis of a randomised clinical trial in Canada assessed the risk of kidney or hepatic toxic effects with remdesivir administration in patients with impaired kidney function. The study involved 1281 patients of which 59 had a baseline estimated glomerular filtration rate (eGFR) of less than 30 mL/min/1.73 m^2. Remdesivir was administered intravenously with a loading dose of 200 mg on day 1, followed by daily 100-mg doses for 9 days or until discharge. There were no significant differences in key outcomes between groups. Adjustment for sex and baseline eGFR did not change mortality outcomes (odds ratio, 0.74; 95% CI, 0.23-2.40). Analysis of covariance for change in eGFR showed no significant difference between groups. For patients with eGFR less than 60 mL/min/1.73 m^2 (n = 248) at randomisation, there was no significant difference between those receiving remdesivir (n = 122) or standard care (n = 126) in hospital mortality (35.2% vs 42.1%; p= 0.26), new mechanical ventilation (10.6% vs 15.7%; p = 0.27), or new dialysis (6.2% vs 5.0%; p = 0.70). These findings suggest that remdesivir can be safely administered in patients with kidney dysfunction, balancing possible risks and benefits.
- This retrospective cohort study in Israel assessed the effectiveness of nirmatrelvir in preventing severe COVID-19 outcomes during the omicron surge. The study involved 3902 patients who received nirmatrelvir between January and March 2022. Among patients 65 years of age or older, the rate of hospitalisation due to COVID-19 was 14.7 cases per 100,000 person-days among treated patients as compared with 58.9 cases per 100,000 person-days among untreated patients (adjusted hazard ratio, 0.27; 95% CI, 0.15 to 0.49). The adjusted hazard ratio for death due to COVID-19 was 0.21 (95% CI, 0.05 to 0.82). Among patients 40 to 64 years of age, the rate of hospitalisation due to COVID-19 was 15.2 cases per 100,000 person-days among treated patients and 15.8 cases per 100,000 person-days among untreated patients (adjusted hazard ratio, 0.74; 95% CI, 0.35 to 1.58). The adjusted hazard ratio for death due to COVID-19 was 1.32 (95% CI, 0.16 to 10.75).
- This phase 3, double-blind, randomised, placebo-controlled trial in the United States assessed the effectiveness of three repurposed drugs (metformin, ivermectin, and fluvoxamine) in preventing serious SARS-CoV-2 infection in non-hospitalised adults. The study involved 1,431 patients who had been enrolled within 3 days after a confirmed diagnosis of infection and less than 7 days after the onset of symptoms. The primary composite end point was hypoxemia (≤93% oxygen saturation on home oximetry), emergency department visit, hospitalisation, or death. The adjusted odds ratio for a primary event was 0.84 (95% CI, 0.66 to 1.09; p=0.19) with metformin, 1.05 (95% CI, 0.76 to 1.45; p=0.78) with ivermectin, and 0.94 (95% CI, 0.66 to 1.36; p=0.75) with fluvoxamine. In prespecified secondary

analyses, the adjusted odds ratio for emergency department visit, hospitalisation, or death was 0.58 (95% CI, 0.35 to 0.94) with metformin, 1.39 (95% CI, 0.72 to 2.69) with ivermectin, and 1.17 (95% CI, 0.57 to 2.40) with fluvoxamine. The adjusted odds ratio for hospitalisation or death was 0.47 (95% CI, 0.20 to 1.11) with metformin, 0.73 (95% CI, 0.19 to 2.77) with ivermectin, and 1.11 (95% CI, 0.33 to 3.76) with fluvoxamine. None of the three medications that were evaluated prevented the occurrence of hypoxemia, an emergency department visit, hospitalisation, or death associated with COVID-19.

- This multicentre prospective cohort study in the Netherlands assessed trajectories of physical recovery and levels of physical function reached in hospitalised patients for COVID-19 within different care pathways. The study involved 582 patients who had been discharged from hospital between March 2020 and June 2021 across 10 centres. Follow up visits were performed at 3-, 6-, and 12-months post-hospital discharge and included assessment of cardiorespiratory fitness (6 min walk test [6MWT], 1 min sit-to-stand test [1MSTST]), muscle strength (maximum handgrip strength [HGS]) and mobility (de Morton Mobility Index [DEMMI]). The authors followed patients across 4 different rehabilitation settings: no rehabilitation (No-rehab, 19.6% [114/582]), community-based rehabilitation (Com-rehab, 54.1% [315/582]), medical rehabilitation (Med-rehab, 13.7% [80/582]), and rehabilitation in a skilled nursing facility (SNF-rehab, 12.5% [73/582]). Overall, outcomes in 6MWT (14.9 meters [95% CI 7.4 to 22.4]), 1MSTST (2.2 repetitions [1.5 to 2.8]), and HGS (3.5 kg [2.9 to 4.0]) improved significantly (p<0.001) from 3 to 6 months and only HGS from 6 to 12 months (2.5 kg [1.8 to 3.1]; p<0.001). DEMMI scores did not significantly improve over time. At 3 months, percentage of normative values reached in 1MSTST differed significantly (p<0.001) across care pathways, with largest impairments in Med- and SNF-rehab groups. At 12 months these differences were no longer significant, reaching, overall, 90.5% on 6MWD, 75.4% on 1MSTST, and 106.9% on HGS. These findings indicate the importance of rehabilitation.

Epidemiology

- This prospective cohort study in South Africa assessed the prevalence of and risk factors for post COVID-19 condition (PCC) among hospitalised individuals. The study involved 3094 patients who were hospitalised between December 2020 and August 2021. At 3 months of follow-up, 66.7% (1249/1873) participants reported new or persistent COVID-19-related symptoms, compared with 82.1% (1978/2410) at 1 month after hospital discharge. The most common symptoms reported at 3 months were fatigue (50.3%), shortness of breath (23.4%), confusion or lack of concentration (17.5%), headaches (13.8%), and problems seeing or blurred vision (10.1%). On multivariable analysis, the factors associated with persistent symptoms after acute COVID-19 were being female (adjusted incident rate ratio 1.20, 95% CI 1.04–1.38) and admission to an intensive care unit (1.17, 1.01–1.37).
- This repeated cross-sectional study in the United States assessed whether analysis of new-born dried blood spot (DBS) samples could be used to monitor SARS-CoV-2 seroprevalence (nucleocapsid [N] and spike [S] IgG antibodies) in infants and individuals giving birth. The study involved analysis of DBS samples from 415,293 infants in New York between 1 November 2019 and 30 November 2021. From February through November 2021, S seroprevalence was strongly correlated with cumulative vaccinations in each New York State region and in the state overall (r_S = 0.92-1.00, p ≤ 0.001). S and N seroprevalences were significantly lower in new-borns with very low birth weight (720 [14.8%] for S and 138 [2.8%] for N, p < 0.001) and low birth weight (5,160 [19.3%] for S and 1,233 [4.6%] for N, p = 0.009) compared with new-borns with normal birth weight (77,116 [20.1%] for S and 19,872 [5.2%] for N). Lower N and higher S seroprevalences were observed in multiple births (odds ratio [OR], 0.84; 95% CI, 0.75-0.94; for N and OR, 1.24; 95% CI, 1.18-1.31; for S) vs single births and for maternal age older than 30 years (OR, 0.87; 95% CI, 0.80-0.94; for N and OR, 1.17; 95% CI, 1.11-1.23; for S) vs younger than 20 years. These findings suggest that antibody testing of new born DBS samples is an effective way to conduct large-scale monitoring of SARS-CoV-2 seroprevalence among individuals recently giving birth.
- This systematic review and meta-analysis assessed the incubation period of COVID-19 and the incubation periods of COVID-19 caused by different SARS-CoV-2 variants. The review involved 142 studies with 8112 patients. The pooled incubation period was 6.57 days (95% CI, 6.26-6.88) and

ranged from 1.80 to 18.87 days. The mean incubation period of COVID-19 was 5.00 days (95% CI, 4.94-5.06 days) for cases caused by the Alpha variant, 4.50 days (95% CI, 1.83-7.17 days) for the Beta variant, 4.41 days (95% CI, 3.76-5.05 days) for the Delta variant, and 3.42 days (95% CI, 2.88-3.96 days) for the Omicron variant. The mean incubation was 7.43 days (95% CI, 5.75-9.11 days) among older patients (ie, aged over 60 years old), 8.82 days (95% CI, 8.19-9.45 days) among infected children (ages 18 years or younger), 6.99 days (95% CI, 6.07-7.92 days) among patients with non-severe illness, and 6.69 days (95% CI, 4.53-8.85 days) among patients with severe illness. These results suggest that with the evolution of mutant strains, the incubation period of COVID-19 decreased gradually from Alpha variant to Omicron variant.

- This retrospective time-series analysis in Kenya assessed the effect of the COVID-19 pandemic on essential health-care services. The study examined changes in 17 indicators across four periods: the pre-pandemic period (from January, 2018 to February, 2020), two pandemic periods (from March to November 2020, and February to October, 2021), and the period during the COVID-19-associated health-care workers' strike (from December, 2020 to January, 2021). The onset of the pandemic was associated with statistically significant decreases in: outpatient visits (28.7%; 95% CI 16.0–43.5%), cervical cancer screening (49.8%; 20.6–57.9%), number of HIV tests conducted (45.3%; 23.9–63.0%), patients tested for malaria (31.9%; 16.7–46.7%), number of notified tuberculosis cases (26.6%; 14.7–45.1%), hypertension cases (10.4%; 6.0–39.4%), vitamin A supplements (8.7%; 7.9–10.5%), and three doses of the diphtheria, tetanus toxoid, and pertussis vaccine administered (0.9%; 0.5–1.3%). Pneumonia cases reduced by 50.6% (31.3–67.3%), diarrhoea by 39.7% (24.8–62.7%), and children attending welfare clinics by 39.6% (23.5–47.1%). Cases of sexual violence increased by 8.0% (4.3–25.0%). Skilled deliveries, antenatal care, people with HIV infection newly started on antiretroviral therapy, confirmed cases of malaria, and diabetes cases detected were not significantly affected negatively. Although most of the health indicators began to recover during the pandemic, the health-care workers' strike resulted in nearly all indicators falling to numbers lower than those observed at the onset or during the pre-strike pandemic period.

Infection Prevention & Control

- This cross-sectional study in 3 Southeast Asian jurisdictions assessed the COVID-19 vaccine willingness among health care workers (HCWs). The study involved 3396 doctors and nurses in Hong Kong, Nepal and Vietnam. The prevalence rate of willingness to take the COVID-19 vaccine was highest in Nepal (95.4% [313 of 328]), followed by Vietnam (90.6% [212 of 234]), and lowest in Hong Kong (54.4% [1542 of 2834]). Doctors were more willing to take COVID-19 vaccination than nurses (odds ratio, 5.28; 95% CI, 3.96-7.04). Older age (odds ratios, 1.39-3.70), male gender (odds ratio, 1.41; 95% CI, 1.11-1.75), higher educational level (odds ratio, 1.48; 95% CI, 1.17-1.87), and having seasonal influenza vaccination uptake history (odds ratio, 2.15; 95% CI, 1.82-2.54) were found to be associated with increased willingness. Choice of vaccination brand with adequate information, immunity passport, time off from work for vaccination and subsidy for travel to inconvenient vaccination centres were considered as strategies to enhance vaccine willingness.
- This multicentre phase 2/3 randomised clinical trial in the United States assessed the safety, antiviral, and clinical efficacy of bamlanivimab. Non-hospitalised adults were randomised 1:1 within 10 days of COVID-19 symptoms to bamlanivimab or blinded-placebo in two dose-cohorts (7000 mg, n = 94; 700 mg, n = 223). No differences in bamlanivimab vs placebo were observed in the primary outcomes: proportion with undetectable nasopharyngeal SARS-CoV-2 RNA at days 3, 7, 14, 21, and 28 (risk ratio = 0.82–1.05 for 7000 mg [p(overall) = 0.88] and 0.81–1.21 for 700 mg [p(overall) = 0.49]), time to symptom improvement (median 21 vs 18.5 days [p = 0.97], 7000 mg; 24 vs 20.5 days [p = 0.08], 700 mg), or grade 3+ adverse events. However, bamlanivimab was associated with lower day 3 nasopharyngeal viral levels and faster reductions in inflammatory markers and viral decay by modelling. This study provides evidence of faster reductions in nasopharyngeal SARS-CoV-2 RNA levels but not shorter symptom durations in non-hospitalised adults with early variants of SARS-CoV-2.
- This study in Canada investigated the effect of antimicrobial photodynamic therapy with methylene blue (MB-aPDT) to inactivate human betacoronavirus OC43 and SARS-CoV-2 in vitro and in a proof-of-

principle COVID-19 clinical trial. The study assessed the practicality, technical feasibility, and short-term efficacy of the method. aPDT yielded inactivation of up to 6-Logs in vitro, as measured by RT-qPCR and infectivity assay. From a photo-physics perspective, the in vitro results suggest that the response is not dependent on the virus itself, motivating potential use of aPDT for local destruction of SARS-CoV-2 and its variants. In the clinical trial the authors observed variable effects on viral RNA in nasal-swab samples as assessed by RT-qPCR attributed to aPDT-induced RNA fragmentation causing falsely-elevated counts. However, the viral infectivity in clinical nares swabs was reduced in 90% of samples and undetectable in 70% of samples. Their results show that MB-aPDT is a safe, easily delivered and effective front-line technique that can reduce local SARS-CoV-2 viral load.

Non-pharmaceutical interventions, social distancing

- This qualitative study in Côte d'Ivoire explored people's experience with and perceptions of the COVID-19 pandemic. The authors conducted 24 focus group discussions and 29 in-depth interviews with members of the general population and health providers in November 2021. The analysis explored barriers and facilitators to seven recommended prevention behaviours with a particular focus on response efficacy, self-efficacy, and social norms. The authors found these constructs to be salient for participants who generally felt that the behaviours were useful for preventing COVID-19 but were difficult to practice for a variety of reasons. The perception that COVID-19 prevention behaviours were anti-social emerged as a key theme. Behaviour change interventions must reframe the recommended behaviours as pro-social, while making them very easy to practice by removing social and structural barriers such as the expense or inaccessibility of masks and hand sanitizer.
- This modelling study in Japan developed a data-driven computational framework to compute the population-level risk and the burden of different isolation guidelines with rapid antigen tests (i.e., lateral flow tests). Their results show that when the detection limit is higher than the infectiousness threshold values, additional consecutive negative results are needed to ascertain infectiousness status. Further, rapid antigen tests should be designed to have lower detection limits than infectiousness threshold values to minimize the length of prolonged isolation

D. Clinical Trials Updates

Key updates:

Vaccine trials:

- On 30 August 2022, Moderna announced the Therapeutic Goods Administration (TGA) in Australia has granted provisional approval for its Omicron-containing bivalent booster vaccine, mRNA-1273.214 (Spikevax Bivalent Original/Omicron) as a booster dose for active immunisation to prevent COVID-19 in individuals 18 years of age and older. Spikevax Bivalent Original/Omicron is a next-generation bivalent vaccine that contains 25 µg of mRNA-1273 (Spikevax) and 25-µg of a vaccine candidate targeting the Omicron variant of concern (BA.1). The decision from the TGA based on clinical trial data from a phase 2/3 trial, in which mRNA-1273.214 met all primary endpoints, including superior neutralising antibody response against Omicron (BA.1) when compared to a 50-µg booster dose of mRNA-1273 in previously uninfected participants. A booster dose of mRNA-1273.214 increased neutralising geometric mean titres (GMT) against Omicron approximately 8-fold above baseline levels. In addition, mRNA-1273.214 elicited potent neutralising antibody responses against the Omicron subvariants BA.4 and BA.5 compared to the currently Authorised booster (mRNA-1273) regardless of prior infection status or age. mRNA-1273.214's reactogenicity and safety profile is consistent with the currently Authorised Spikevax (mRNA-1273) booster. Clinical trial registration #: (NCT05249829).
- On 29 August 2022, Moderna announced Swissmedic has granted temporary Authorisation for the use of Moderna's Omicron-targeting bivalent booster vaccine, Spikevax Bivalent Original/Omicron (mRNA-1273.214) for active immunisation to prevent COVID 19 for individuals aged 18 years and older. Spikevax Bivalent Original/Omicron is a next-generation bivalent vaccine that contains 25 µg of mRNA-1273 (Spikevax) and 25 µg of a vaccine candidate targeting the Omicron variant of concern (BA.1). The decision from Swissmedic is based on clinical trial data from a Phase 2/3 trial, in which mRNA-

1273.214 met all primary endpoints, including superior neutralising antibody response against Omicron (BA.1) when compared to the currently Authorised 50 µg booster dose of Spikevax (mRNA-1273) in previously uninfected participants. A booster dose of Spikevax Bivalent Original/Omicron (mRNA-1273.214) increased neutralising geometric mean titres (GMT) against Omicron approximately 8-fold above baseline levels. In addition, Spikevax Bivalent Original/Omicron (mRNA-1273.214) elicited higher neutralising antibody titres against the Omicron subvariants BA.4 and BA.5 when compared to Spikevax (mRNA-1273) regardless of prior infection status or age, including in those aged 65 and older. mRNA-1273.214 was generally well tolerated, with a reactogenicity and safety profile consistent with the currently Authorised booster. Clinical trial registration #: (NCT05249829).

- On 26 August 2022, Novavax announced that the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom (UK) has granted expanded Conditional Marketing Authorisation (CMA) for Nuvaxovid (NVX-CoV2373) COVID-19 vaccine for active immunisation to prevent COVID-19 in adolescents aged 12 through 17. The expanded CMA was based on data from the ongoing paediatric expansion of the Phase 3 PREVENT-19 trial of 2,247 adolescents aged 12 through 17 years across 73 sites in the U.S., to evaluate the safety, effectiveness (immunogenicity), and efficacy of Nuvaxovid. In the paediatric expansion, Nuvaxovid achieved its primary effectiveness endpoint and demonstrated 80% clinical efficacy overall at a time when the Delta variant was the predominant circulating SARS-CoV-2 strain in the U.S. Preliminary safety data from the paediatric expansion showed the vaccine to be generally well-tolerated. Serious and severe adverse events were low in number and balanced between vaccine and placebo groups, and not considered related to the vaccine. Clinical trial registration #: (NCT04611802).
- On 26 August 2022, Pfizer and BioNTech announced they have completed a submission to the European Medicines Agency (EMA) for a booster dose of an Omicron BA.4/BA.5-adapted bivalent COVID-19 vaccine for individuals 12 years of age and older. The bivalent vaccine contains 15-µg of mRNA encoding the wild-type spike-protein of SARS-CoV-2, which is present in COMIRNATY (the original Pfizer-BioNTech COVID-19 Vaccine) and 15-µg of mRNA encoding the spike protein of the Omicron BA.4/BA.5 variants. All other components of the vaccine remain unchanged. Pre-clinical data showed a booster dose of Pfizer and BioNTech's Omicron BA.4/BA.5-adapted bivalent vaccine generated a strong neutralising antibody response against Omicron BA.1, BA.2 and BA.4/BA.5 variants, as well as the original wild-type strain. In addition to the pre-clinical, quality and manufacturing data for the Omicron BA.4/BA.5 adapted bivalent vaccine, the submission is supported by safety, tolerability and immunogenicity data from a Phase 2/3 trial of a 30-µg booster dose of their Omicron BA.1-adapted bivalent vaccine, which combines 15-µg of mRNA encoding the wild-type spike protein of SARS-CoV-2 with 15-µg of mRNA encoding the spike protein of the Omicron BA.1 variant. Clinical trial registration #: (NCT04816643).
- On 23 August 2022, Moderna announced has completed submission of BA.4/BA.5 Omicron-targeting bivalent COVID-19 booster vaccine, mRNA-1273.222 to the U.S. Food and Drug Administration (FDA) for emergency use Authorisation. The application is for a 50 µg booster dose for adults 18 years of age and older, and is based on preclinical data as well as clinical trial data available for the BA.1 Omicron-targeting bivalent booster candidate and mRNA-1273.214. mRNA-1273.222 targets both the original strain of SARS-CoV-2 as well as the BA.4/BA.5 subvariants of the Omicron strain. The application is based on preclinical data for mRNA-1273.222 as well as clinical trial data from a Phase 2/3 studying mRNA-1273.214, a bivalent booster vaccine targeting the Omicron BA.1 subvariant. In the study, mRNA-1273.214 met all primary endpoints, including superior neutralising antibody response against Omicron (BA.1) when compared to a 50µg booster dose of mRNA-1273 in previously uninfected participants, as well as potent neutralising antibody responses against the Omicron subvariants BA.4 and BA.5 compared to the currently Authorised booster (mRNA-1273) regardless of prior infection status or age. Clinical trial registration #: (NCT05249829).
- On 23 August 2022, Pfizer and BioNTech announced updated efficacy results from a Phase 2/3 trial evaluating a three 3-µg dose series of the Pfizer-BioNTech COVID-19 Vaccine in children 6 months through 4 years of age, reinforcing previously reported interim vaccine efficacy data. Participants in the study received either the Pfizer-BioNTech COVID-19 Vaccine (3-µg) as a three-dose series or placebo (2:1 randomisation). Vaccine efficacy, a secondary endpoint in the trial, was 73.2% (2-sided 95% CI:

43.8%, 87.6%) among children 6 months through 4 years of age without evidence of prior COVID-19 infection. This analysis was based on 13 cases in the Pfizer-BioNTech COVID-19 Vaccine group (n=794) and 21 cases in the placebo group (n=351) diagnosed from March to June 2022. Consistent with the time period when the cases occurred, sequencing of viral RNA from illness visit nasal swabs indicated that observed cases were primarily caused by Omicron BA.2. These results confirm that three 3-µg doses of Pfizer-BioNTech COVID-19 vaccine provide young children with a high level of protection at a time when the Omicron BA.2 strain was highly prevalent with a favourable safety profile. Clinical trial registration #: (NCT04816643).

- On 22 August 2022, Pfizer and BioNTech announced they have completed a submission to the U.S. Food and Drug Administration (FDA) requesting Emergency Use Authorisation (EUA) of a booster dose of an Omicron BA.4/BA.5-adapted bivalent COVID-19 vaccine for individuals 12 years of age and older. The bivalent vaccine contains mRNA encoding the original SARS-CoV-2 spike protein and Omicron BA.4/BA.5 variant spike protein. Pre-clinical data showed a booster dose of Pfizer and BioNTech's Omicron BA.4/BA.5-adapted bivalent vaccine generated a strong neutralising antibody response against Omicron BA.1, BA.2 and BA.4/BA.5 variants, as well as the original wild-type strain. A clinical study investigating the safety, tolerability and immunogenicity of the Omicron BA.4/BA.5-adapted bivalent vaccine in individuals 12 years of age and older is ongoing. Clinical trial registration #: (NCT04955626).
- On 22 August 2022, Novavax reported the U.S. Centers for Disease Control and Prevention (CDC) recommended expanding the use of Novavax COVID-19 Vaccine, Adjuvanted (NVX-CoV2373) as a two-dose primary series for active immunisation to prevent coronavirus disease 2019 caused by the severe acute respiratory syndrome coronavirus 2 to adolescents aged 12 through 17. The recommendation follows the emergency use Authorisation (EUA) granted for use in adolescents aged 12 through 17 by the U.S. Food and Drug Administration on August 19, 2022, and the EUA granted for adults aged 18 and older on July 13, 2022. The CDC previously recommended use of the vaccine in adults aged 18 and older.
- On 19 August 2022, Novavax announced the Novavax COVID-19 Vaccine, Adjuvanted (NVX-CoV2373) has received expanded emergency use Authorisation (EUA) from the U.S. Food and Drug Administration (FDA) to provide a two-dose primary series for active immunisation to prevent COVID-19in adolescents aged 12 through 17. The decision was based on data from the ongoing paediatric expansion of the Phase 3 PREVENT-19 trial of 2,247 adolescents aged 12 through 17 years across 75 sites in the U.S., to evaluate the safety and effectiveness of the Novavax COVID-19 Vaccine, Adjuvanted. In paediatric expansion, the vaccine achieved its primary efficacy endpoint with clinical efficacy of 78.29% (95% CI: 37.55%, 92.45%) overall at a time when the Delta variant was the predominant circulating SARS-CoV-2 strain in the U.S. The efficacy analysis was supported by assessment of antibody titres that were shown to be higher in adolescents than in young adults. Safety data from the paediatric expansion showed the vaccine to be generally well-tolerated. Serious and severe adverse reactions (AR) were low in number and balanced between vaccine and placebo groups, and not considered related to the vaccine. Clinical trial registration #: (NCT04611802).
- On 18 August 2022, Novavax announced that New Zealand's Medsafe has granted expanded provisional approval for Nuvaxovid (NVX-CoV2373) COVID-19 vaccine for active immunisation to prevent COVID-19 in adolescents aged 12 through 17. The provisional approval was based on data from the ongoing paediatric expansion of the Phase 3 PREVENT-19 trial of 2,247 adolescents aged 12 through 17 years across 73 sites in the U.S., to evaluate the safety, effectiveness (immunogenicity), and efficacy of Nuvaxovid. In the paediatric expansion, Nuvaxovid achieved its primary effectiveness endpoint and demonstrated 80% clinical efficacy overall at a time when the Delta variant was the predominant circulating SARS-CoV-2 strain in the U.S. Preliminary safety data from the paediatric expansion showed the vaccine to be generally well-tolerated. Serious and severe adverse events were low in number and balanced between vaccine and placebo groups, and not considered related to the vaccine. Clinical trial registration #: (NCT04611802).
- On 18 August 2022, the WHO Strategic Advisory Group of Experts on Immunisation (SAGE) provided interim policy recommendations for the usage of Valneva's Covid-19 vaccine, VLA2001. According to the recommendations, two 0.5ml intramuscular doses of the vaccine are intended to be given as part

of the initial dosing regimen. The second dose should be given a minimum of 28 days following the first shot. The vaccine is said to be safe and effective for all people aged 18 to 50 years. With limited data available on the Valneva vaccine's immunogenicity in people aged 50 years and older, it is not advised for usage in this age group. A second booster dose is advised for people at increased risk of severe disease. After primary vaccination with an mRNA vaccine, the Valneva vaccine cannot be used as a heterologous booster. This vaccine could be used for heterologous boosting following the completion of the initial series with Astrazeneca's ChAdOx1-S vaccine.

- On 17 August 2022, Novavax announced that New Zealand's Medsafe has granted expanded provisional approval for Nuvaxovid (NVX-CoV2373) COVID-19 vaccine for active immunisation to prevent COVID-19 as a heterologous and homologous booster dose in adults aged 18 and older. The request was supported by data from Novavax' Phase 2 trial conducted in Australia, from a separate Phase 2 trial conducted in South Africa, and from the UK-sponsored COV-BOOST trial. As part of the Novavax-sponsored Phase 2 trials, a single booster dose of Nuvaxovid was administered to healthy adult participants approximately six months after their primary two-dose vaccination series of Nuvaxovid. The third dose produced increased immune responses comparable to or exceeding levels associated with protection in Phase 3 clinical trials. In the COV-BOOST trial, Nuvaxovid induced a significant antibody response when used as a heterologous third booster dose. Safety reporting of reactogenicity events showed an increasing incidence across all three doses of Nuvaxovid, reflecting the increased immunogenicity seen with a third dose. Medically attended adverse events, potentially immune-mediated medical conditions, and severe adverse events occurred infrequently following the booster dose and were balanced between vaccine and placebo groups. Clinical trial registration #: (NCT05372588).

Therapeutics trials:

- On 29 August 2022, Kinarus announced the first patient has been dosed in the Phase 2 KINFAST trial, a multicentre placebo-controlled trial evaluating KIN001 in mild or moderate COVID-19 patients in an outpatient setting. The trial will enrol patients at clinical trial sites in Switzerland and Germany. KIN001 is an orally administered combination of two drugs that have demonstrated synergistic antiviral and anti-inflammatory activity, as well as ability to reduce tissue fibrosis. In contrast to other antivirals and monoclonal antibody therapies, which target SARS-Cov2 directly, KIN001 targets human host cell pathways required for SARS-Cov2 viral replication, blocking the virus' ability to replicate and reducing potential for the emergence of escape mutants. Recent data demonstrating KIN001's strong antiviral efficacy and equal potency against the original SARS-CoV-2 strain and variants of concern (VOC), including delta and omicron. KINFAST Phase 2 study is expected to enrol approximately 400 non-hospitalised patients with confirmed mild to moderate symptoms and confirmed SARS-CoV-2 infection with an interim assessment after enrolling about 140 patients. Patients will be randomised within 5 days of symptom onset. The primary endpoint is the time to recovery, based on the daily symptoms' evaluation by the patient. Other efficacy endpoints will include number of patients requiring hospitalisation for COVID-19, as well as the total burden of symptoms (severity and duration), as assessed by the patient.
- On 22 August 2022, Ascletis announced the China National Medical Products Administration (NMPA) has approved the Investigational New Drug (IND) application of ASC10, an oral inhibitor drug candidate targeting RNA-dependent RNA polymerase (RdRp) for COVID-19. ASC10 is an oral double prodrug which has a new and differentiated chemical structure from the single prodrug molnupiravir. After oral administration, both ASC10 and molnupiravir are rapidly and completely converted in vivo into the same active metabolite ASC10-A, also known as β-D-N4-hydroxycytidine (NHC). ASC10 oral tablet formulation for the clinical study was developed with in-house proprietary technology of Ascletis. In the SARS-CoV-2 infected mouse models, ASC10 at 240 mg/kg twice daily led to a 4.0 log reduction in viral titre in lungs, equivalent to molnupiravir at 500 mg/kg twice daily. Preclinical studies demonstrated that ASC10-A has potent cellular antiviral activity against Omicron variant (EC50 = 0.3 μM), Delta variant (EC50 = 0.5 μM) and wildtype virus (EC50 = 0.7 μM). It also suggested that there were no drug-drug interactions between ASC10 and other common medicines. Clinical trial registration #: (NCT04345276).

- On 22 August 2022, Tonix announced the first participant was enrolled in the Phase 2 PREVAIL study of TNX-102 SL as a potential treatment for a subset of patients with Long COVID syndrome (Long COVID) whose symptoms overlap with fibromyalgia. Long COVID is known officially as Post-Acute Sequelae of COVID-19 (PASC). The Phase 2 PREVAIL study is 14-week double-blind, randomised, multicentre, placebo-controlled study to evaluate the efficacy and safety of TNX-102 SL taken daily at bedtime in patients with multi-site pain associated with post-acute sequelae of SARS-COV-2 infection (PASC). TNX-102 SL is a patented sublingual tablet formulation of cyclobenzaprine hydrochloride which provides rapid transmucosal absorption and reduced production of a long half-life active metabolite, norcyclobenzaprine, due to bypass of first-pass hepatic metabolism. The trial is being conducted at approximately 30 sites in the U.S. and is expected to enrol approximately 470 patients (235 per arm) who will be randomised in a 1:1 ratio to treatment with TNX-102 SL or placebo tablets. The primary efficacy endpoint will be changed from baseline in the weekly average of daily self-reported worst pain intensity scores at the Week 14 endpoint. Key secondary efficacy endpoints include change from baseline in self-reported scores for sleep disturbance, fatigue and cognitive function. Clinical trial registration #: (NCT05472090).
- On 19 August 2022, Moleculin reported preliminary results from the third cohort of the first-in-human Phase 1a, randomised, double-blind, placebo-controlled, overlapping SAD and MAD study to investigate the effects of WP1122 administered as an oral solution in healthy human volunteers. This cohort consisted of 10 subjects dosed with 32 mg/kg or placebo in the dose escalation trial evaluating the safety and pharmacokinetics (PK) of WP1122 in healthy volunteers in the United Kingdom (UK). Based on the overall results in Cohort 3, the Safety Review Committee (SRC) for the study deemed the third single ascending dose (SAD) cohort dose safe and well-tolerated, allowing the fourth SAD Cohort with a dose escalation to 64 mg/kg to begin. Additionally, dosing of WP1122 in the multiple ascending dose (MAD) cohorts will commence at a total daily dose of 32 mg/kg, which has been shown to be safe in the single dose cohort. WP1122 was developed as a 2-deoxy-D-glucose (2-DG) prodrug to provide a more favourable pharmacological profile and was found to have greater potency than 2-DG alone in preclinical models where tumour cells require higher glycolytic activity than normal cells. WP1122 has also been shown to have a greater antiviral effect than 2-DG against SARS-CoV-2 in MRC-5 cells in culture. Clinical trial registration #: (NCT05195723).
- On 19 August 2022, Sorrento announced the China National Medical Products Administration (NMPA) clearance of a Phase I study of its oral main viral protease (Mpro) inhibitor, STI-1558, in subjects with COVID-19 in a MAD study in China. STI-1558 has been well tolerated with only a few related transient and mild adverse events. The STI-1558 Pharmacokinetics profile confirms is readily absorbed by humans with high bioavailability and no need for ritonavir, a potent cytochrome P450 3A4 inhibitor, to block metabolic clearance in order to maintain effective blood levels. In the double blind and placebo-controlled MAD study, a total of 56 patients with mild or no symptoms will be enrolled into three dose cohorts (active: placebo, 3:1), 300 mg BID (n=8), 600 mg BID (n=24) and 800 mg BID (n=24). In addition to evaluation of the safety and tolerability, the viral load in patients will be examined to assess the antiviral activity of STI-1558 treatment in subjects with COVID-19 in comparison with placebo treatment. This will allow an evaluation of the safety, tolerability and efficacy of STI-1558 as a standalone treatment without ritonavir as a booster.
- On 18 August 2022, CureVac announced the start of a Phase 1 study of the modified COVID-19 mRNA vaccine candidate CV0501, administered as a booster dose to previous COVID-19 vaccination. CV0501 is CureVac's first COVID-19 vaccine candidate applying chemically modified mRNA based on CureVac's advanced second-generation mRNA backbone. CV0501 encodes for the prefusion stabilized full-length spike protein of the SARS-CoV-2 Omicron variant and is formulated within lipid nanoparticles (LNPs). As for all vaccines candidates applying the second-generation mRNA backbone, CV0501 was designed with specifically optimized non-coding regions to exhibit improved mRNA translation for increased and extended protein expression compared to the first-generation mRNA backbone. The CV0501 study follows the start of a Phase 1 study that evaluates an unmodified second-generation COVID-19 vaccine candidate CV2CoV, encoding for the original virus variant. The comprehensive approach to evaluate both an unmodified and a modified, second-generation vaccine candidate against COVID-19 is expected to identify the best-performing candidate for later-stage

clinical development. In line with this approach, data from both studies are expected to be reported as a combined data set.

Immunotherapies trials:

- None

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