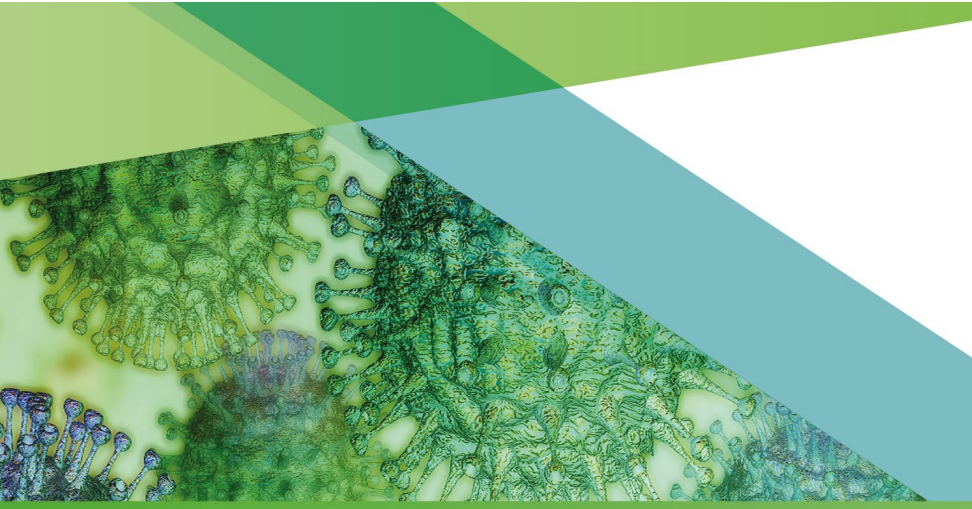


TECHNICAL REPORT

Interim public health considerations for the provision of additional COVID-19 vaccine doses

1 September 2021

Key messages

- **Providing all eligible individuals** with the recommended dose regimen should remain the current priority for COVID-19 vaccination programmes in the European Union/European Economic Area (EU/EEA).
- It is important to **distinguish between 'booster' doses for people who responded adequately to primary vaccination and additional doses for those with weakened immune systems who did not respond adequately**. Booster doses are given to vaccinated people (i.e. those who have completed a primary series of COVID-19 vaccination) to restore protection after it would have waned. On the other hand, additional doses as part of a primary vaccination series may be given to people with severely weakened immune systems, as they may not achieve an adequate level of protection from the standard primary vaccination.
- When assessing the need for possible booster doses of COVID-19 vaccine from the public health perspective, it is important to keep in mind the main objective of the vaccination strategy (i.e. preventing severe cases of COVID-19). **Vaccine effectiveness against severe disease** should preferably be chosen as the **primary outcome of interest** for assessing whether there is a clear need for a booster dose in specific groups.
- The available evidence at this time regarding 'real world' vaccine effectiveness and the duration of protection shows that all vaccines authorised in the EU/EEA are currently highly protective against COVID-19-related hospitalisation, severe disease and death, suggesting there is **no urgent need for the administration of booster doses of vaccines to fully vaccinated individuals in the general population**.
- The option of administering an **additional vaccine dose to people who may experience a limited response to the primary series of COVID-19 vaccination, such as some categories of immunocompromised individuals** (e.g. solid organ transplant recipients), **should already be considered now**. This is to be seen as an extension of the primary vaccination series for these specific groups, and not as a booster. Consideration could also be given to providing an additional dose as a precautionary measure to older frail individuals, in particular those living in closed settings (e.g. residents of long-term care facilities).
- Full **vaccination** against COVID-19 **of all** eligible family contacts and **close contacts**, including professionals providing care, **of immunocompromised and vulnerable individuals should also be considered.**
- **Close monitoring of vaccine effectiveness data and breakthrough infections**, particularly among vulnerable groups at risk of severe COVID-19 and among those living in closed settings, **should be continued, and decisions adapted accordingly**, **should a substantial decrease in effectiveness be noted in one or more population groups.**

Suggested citation: European Centre for Disease Prevention and Control. Interim public health considerations for the provision of additional COVID-19 vaccine doses, 1 September 2021. ECDC: Stockholm; 2021.

- When in contact with individuals at risk of severe disease, physical distancing (when applicable), the wearing of face masks (especially when physical distancing cannot be kept), and hand and respiratory hygiene remain pivotal measures for reducing the risk of SARS-CoV-2 transmission. These **non-pharmaceutical interventions should always complement vaccination, in particular in high-risk settings** such as long-term care facilities or hospital wards with patients at risk of severe COVID-19.
- **More solid data are needed to inform future policies on booster doses.** Knowledge gaps are particularly related to the appropriate correlate of protection to consider for the different population groups and the time from primary vaccination series until a booster dose should be given, and duration of immunity according to e.g. different age and risk groups, vaccine product, dosing interval, variant of concern (VOC), and homologous/heterologous schedule. Prospective vaccine effectiveness studies, as well as surveillance of breakthrough infections in the general population and in specific groups, are needed to answer these questions.
- **The benefits and risks of possible booster doses need to be clearly outlined and compared.** Benefits may include increased protection against severe disease, mild-to-moderate disease, post COVID-19 condition (often called 'long COVID'), SARS-CoV-2 infection, and virus transmission. Risks include possible safety concerns and public health implications (e.g. impact on vaccine confidence and uptake, global availability of vaccines).
- **Communication** about possible additional vaccine doses **should be carefully considered and delivered in a transparent, proactive, and clear way to avoid affecting vaccine confidence**. The distinction between strengthening the response to primary vaccination series, for example in immunocompromised individuals, and boosters for waning immune response or vaccine escape, should be clearly made.
- In the context of many countries outside of the EU/EEA still struggling to receive and administer enough vaccine doses to their populations, **special consideration should be given to the current global shortage of COVID-19 vaccines, which could be further worsened by the administration of booster COVID-19 vaccine doses for the general population in EU/EEA countries.**

Contents

Background and rationale

The emergence of the SARS-CoV-2 Delta (B.1.617.2) variant of concern (VOC) has caused apprehension due to its increased transmissibility and virulence, combined with some potential partial escape from the protection induced by currently available COVID-19 vaccines.

As a result, the need to administer an additional dose of COVID-19 vaccine to people has been discussed in several European Union (EU)/European Economic Area (EEA) countries, with some considering additional vaccine doses for specific population groups this autumn. This is a complex and dynamic evaluation that needs to take into account several dimensions and potential implications. The assessment of the need for additional doses involves the regulatory authorities, such as the European Medicines Agency (EMA), which assess the balance of risks and benefits to individuals; national immunisation technical advisory groups (NITAGs), which assess, in addition, the population-level impacts and programmatic considerations; and national public health authorities, which are responsible for the vaccination programmes. Currently, COVID-19 vaccines in the EU/EEA are primarily procured through the European Commission's procurement process, with some countries having separate national procurements for nationally authorised vaccines.

There is a need for a continued review of the spread and characteristics of the circulating VOCs and of variants of interest (VOIs), of the evidence of duration of immunity following vaccination and natural infection, and of vaccine effectiveness against symptomatic disease caused by VOCs (e.g., the Delta VOC), to support this complex assessment and better understand potential public health needs for additional vaccine doses and their implications.

Scope of this document

This document aims to provide the target audience with interim public health considerations for the provision of additional COVID-19 vaccine doses. The most recent evidence regarding vaccine effectiveness against symptomatic and asymptomatic infection due to the circulating variants and regarding duration of immunity will be briefly summarised. Considerations around the implementation of additional COVID-19 vaccine doses will also be discussed. This document does not aim to provide recommendations about the administration of additional doses of COVID-19 vaccines but summarises the current evidence and outlines options for consideration by public health authorities.

Target audience

The target audiences for this document are the European Commission, the Health Security Committee (HSC), the EU/EEA National Immunisation Technical Advisory Groups (NITAGs)' collaboration, and national public health institutes and ministries of health in the EU/EEA, as well as public health experts and decision-makers at national and subnational levels.

Epidemiological situation

Epidemiological trends

As of week 33 (ending 22 August 2021), the overall 14-day case notification rate for COVID-19 in the EU/EEA was 204.3 per 100 000 population (country range: 7.0-602.6). This rate has been stable for three weeks, with increasing trends observed in 16 countries. The 14-day case notification rate in people aged 65 years or older for the EU/EEA, based on data reported by 24 countries, was 82.8 per 100 000 population (country range: 6.0-191.9), and this pooled rate has been stable for two weeks. Increasing trends were observed in 15 countries. Overall hospital admissions due to COVID-19 have been stable for four weeks. The intensive care unit (ICU) admission rate for the EU/EEA, based on data reported by 13 countries, was 1.0 per 100 000 (country range: 0.1-2.0) population, and this pooled rate has been stable for two weeks. The 14-day COVID-19 death rate has increased to 9.6 deaths per million population compared with 7.4 deaths the previous week [1].

To date, the highest notification rates have been reported among younger age groups. However, increases in cases in older age groups, as well as increases in COVID-19 hospitalisation indicators, have also been observed in several countries. While milder cases of COVID-19 have also been seen in vaccinated individuals, albeit at a lower extent, the majority of hospitalisations are currently occurring among unvaccinated individuals [2-5].

The high number of reported cases observed in the current weeks is expected to continue given the ongoing increase in the occurrence of the Delta VOC, which has now become dominant in the EU/EEA.

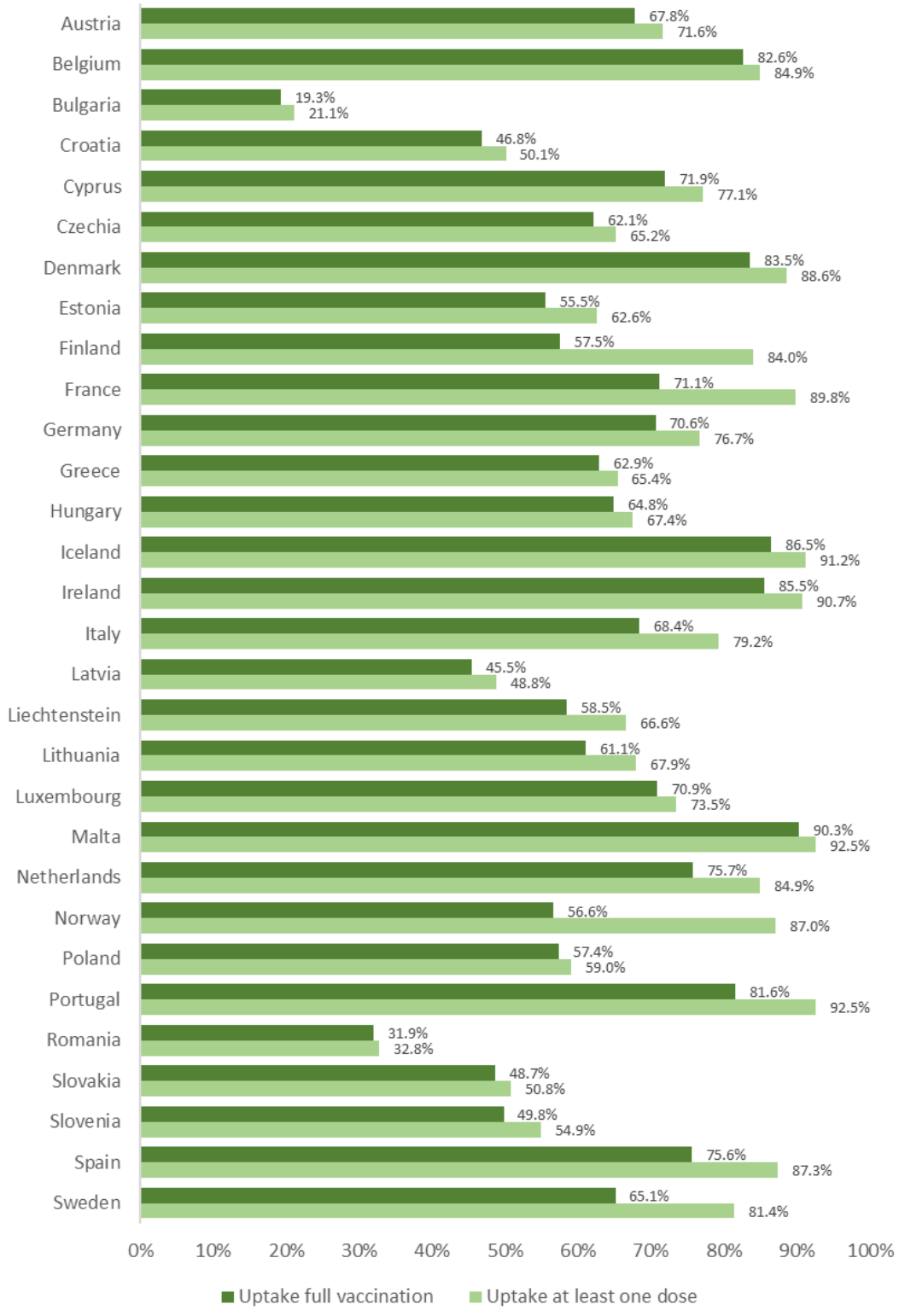
Vaccine roll-out

As of 22 August 2021 (week 33, 2021), over 520 million vaccine doses have been administered in the EU/EEA. Since the start of the COVID-19 vaccine deployment in December 2020, the cumulative vaccine uptake in the adult population (aged 18 years and older) in the EU/EEA has reached 75.6% for at least one vaccine dose (range 21.1-92.5%) and 66.7% for the full vaccination course (range 19.3-90.3%) (30 reporting countries) [6].

The cumulative vaccine uptake is higher in target groups that have been prioritised since the beginning of the vaccine rollout, in particular the elderly and healthcare workers (HCWs). In people aged 80 years and above, the median vaccine uptake among EU/EEA countries is 86.5% (range 19.7-100%) for at least one dose, and 84.8% (range 18.2-100%) for the full vaccination course (27 countries reporting). Fifteen countries have already administered the full vaccination course to more than 80% of the population aged 80 years and above [7]. Nevertheless, the progress in the rollout is unequal across EU/EEA countries (Figure 1), and approximately 38 million people have not yet completed their primary vaccination course.

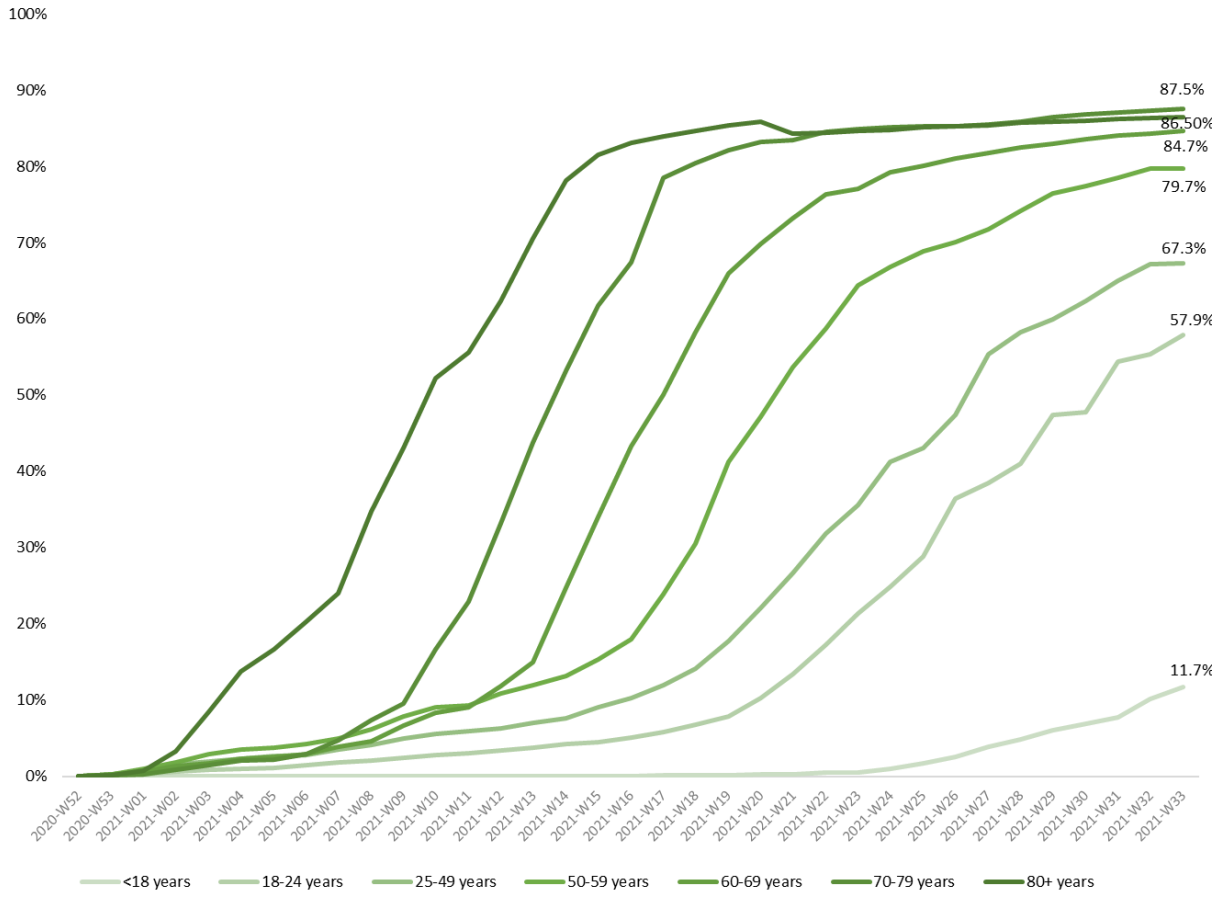
As vaccine uptake has increased in priority groups (the elderly, residents in long-term care facilities, healthcare workers, etc.), countries have progressively expanded the rollout to include younger age groups, in some cases to the entire population including children aged 12 years and above. Figure 2 presents the median weekly cumulative uptake of full vaccination by age group among EU/EEA countries.

Figure 1. Cumulative uptake (%) of at least one vaccine dose and full vaccination among adults (18+ years) in EU/EEA countries



Source: TESSy (data from 30 countries, as of 22 August 2021).

Figure 2. Median cumulative uptake (%) of full vaccination by age group in EU/EEA countries



Source: TESSy (data from 27 countries, as of 22 August 2021).

Distribution of variants of concern and variants of interest

As of 15 August 2021, the following variants are listed as of concern for EU/EEA: B.1.1.7 (Alpha, first detected in the United Kingdom (UK)); B.1.1.7+E484K (first detected in UK); B.1.351 (Beta, first detected in South Africa); P.1 (Gamma, first detected in Brazil); and B.1.617.2 (Delta, first detected in India) [8].

The median (range) of the VOCs reported in all samples sequenced from the 16 EU/EEA countries with sufficient level of sampling and a valid denominator was 96.8% (29.4–99.4%) for Delta, 0.7% (0.3–65.1%) for Alpha, 0.1% (0.0–0.8%) for Gamma, 0.0% (0.0–0.8%) for Beta, and 0.0% (0.0–0.1%) for B.1.1.7+E484K.

The median (range) of the VOIs reported in all samples sequenced in this period for the 16 EU/EEA countries with sufficient level of sampling and a valid denominator was 0.0% (0.0–1.0%) for B.1.621, 0.0% (0.0–0.1%) for B.1.525 (Eta), and 0.0% (0.0–0.0%) for C.37 (Lambda). The Delta VOC is the most common variant in EU/EEA countries, and the proportion is still increasing in the majority of countries. Among the countries that reported an adequate sequencing volume, Delta now accounts for at least 95% of all sequenced viruses in in 11 countries (Austria, Belgium, Denmark, Estonia, Germany, Italy, the Netherlands, Portugal, Slovenia, Spain, and Sweden). The proportion of Alpha VOC has been decreasing in the majority of EU/EEA countries. Community transmission and outbreaks due to the Beta and the Gamma VOCs are reported, but there is no clear overall increasing trend for these variants according to the available data in the European Surveillance System (TESSy) and the GISAID EpiCoV database. For this reason, Delta is currently by far the most relevant variant to consider when planning for possible additional vaccine doses.

Variant characteristics and evidence for impact on transmissibility, immunity and severity

ECDC regularly assesses new evidence on variants detected through epidemic intelligence, rules-based genomic variant screening, and other scientific sources. Currently, five variants designated as VOCs by ECDC are under

surveillance in the EU/EEA and around the world: Alpha, B.1.1.7+E484K, Beta, Gamma, and Delta VOCs. Another six SARS-CoV-2 variants are considered as VOI by ECDC, and additional variants are being monitored [8].

Variants of concern

For the VOCs, clear evidence is available indicating a significant impact on transmissibility, severity and/or immunity that is likely to have an impact on the epidemiological situation in the EU/EEA, as well as immunity following vaccination and on vaccine effectiveness.

Delta VOC is currently the most common variant in EU/EEA countries and the proportion is still increasing. The spread of the Delta VOC should be considered when planning for possible additional vaccine doses. Additional information on the characteristics of the other VOCs is provided in the Annex.

Delta

The Delta VOC is associated with increased transmissibility and virulence compared to other previous variants [9], causing more severe illness in unvaccinated people. Patients infected with the Delta VOC were more likely to be hospitalised than patients infected with Alpha or non-VOC SARS-CoV-2 lineages [10,11]. A comparison of secondary attack rates (including in households) of the Alpha and the Delta infections showed that the Delta VOC has higher rates of secondary attack compared to Alpha. However, these data were not yet corrected for vaccination status [12]. A recent study from China characterises a transmission chain originating from one individual infected with Delta. The results showed that the viral loads of the Delta VOC infections were on average ~1 000 greater compared to A/B lineage infections during the initial epidemic wave in China in early 2020, suggesting potentially faster viral replication and greater infectiousness. Furthermore, the results showed that the time interval from the exposure to a positive PCR test in the quarantined population was on average about six days in 2020, prior to the emergence of the Delta VOC, while it was four days in the Delta VOC cases in 2021. However, this study is not conclusive, as case numbers for 2021 were small and sampling may have occurred earlier in the course of disease during this outbreak compared to sampling in 2020 [13]. Several studies provide emerging evidence that vaccine effectiveness against infection with the Delta VOC is reduced compared to infection with Alpha VOC. Vaccine effectiveness against severe, critical or fatal disease still remains high after full vaccination [10,14]. However, vaccine breakthrough infections can occur, and preliminary evidence suggests that fully vaccinated people becoming infected with the Delta VOC can have high viral loads, although declining more rapidly than in unvaccinated individuals [15].

Variants of interest

For VOIs, evidence is available on genomic properties, epidemiological evidence or in-vitro evidence that could imply a significant impact on transmissibility, severity and/or immunity, realistically having an impact on the epidemiological situation in the EU/EEA. However, the evidence is still preliminary or is associated with major uncertainty.

Recently, several outbreaks caused by the two, VOIs Lambda and B.1.621, were reported in the EU/EEA. Evidence indicating an impact of these variants on immunity following vaccination and on vaccine effectiveness is increasing.

Lambda

The Lambda variant was first detected in Peru and classified as a VOI based on its high circulation rates in South American countries and the presence of critical mutations in the receptor binding domain of the spike protein. These mutations may contribute to its increased transmissibility and could result in susceptibility to re-infection or a reduction in protection provided by current vaccines [8]. In a study performed in Chile, researchers used plasma samples from healthcare workers who received a two-dose scheme of the inactivated virus vaccine CoronaVac and performed a pseudotyped virus neutralisation assay. The results showed that neutralisation was decreased by 3.05-fold for the Lambda VOI compared to the wild type (lineage A). Based on these results, the authors suggest an increased infectivity for the Lambda VOI and immune escape from neutralising antibodies elicited by CoronaVac [16]. Similar results were presented in another study in which the authors demonstrated a higher infectivity with viral vectors pseudotyped with the Lambda spike protein. Furthermore, the authors showed that the virus was neutralised with a 2.3-3.3-fold decrease by convalescent sera and mRNA-vaccine-elicited antibodies. However, the virus was neutralised well by a therapeutic monoclonal antibody cocktail [17]. The findings of increased transmissibility and/or reduced neutralisation of Lambda by vaccine-induced antisera were confirmed by other *in vitro* studies from Japan and the United States (US) [18,19]. Of note, all these studies were published as preprints and need to be interpreted with caution.

B.1.621

The B.1.621 variant was first identified in Colombia and is currently listed as a VOI by ECDC and WHO [8,20]. No WHO label is currently assigned for this VOI. B.1.621 was detected in several countries in South and Central America, the US, but also in several European countries (Austria, Belgium, Denmark, Finland, France, Germany, Ireland, Italy, Luxembourg, Portugal, Spain, the Netherlands, the UK, etc.) [21,22]. Genomic and evolutionary characterisation of B.1.621 shows several substitutions in the spike protein [21], among them the mutations R346K, E484K, and P681H, which have been reported to show reduced neutralisation by antibodies [23-25]. Scientific studies describing the characteristics of B.1.621 are limited, but preliminary pseudovirus neutralisation

data from the UK indicate that sera from vaccinees show decreased ability to neutralise the B.1.621 VOI compared to the first wave virus and the Alpha VOC, with a magnitude of change similar to the Beta VOC. Furthermore, sera from individuals who have been infected with the Delta VOC do not have strong neutralising activity against either the Beta VOC or the B.1.621 VOI [22]. In a study investigating a cluster of B.1.621 VOI infections in Italy, the virus was isolated from a patient sample to perform a neutralisation assay with human sera collected from 37 individuals between 10 and 20 days after the administration of the second dose of Comirnaty. All sera efficiently neutralised the B.1.621 VOI isolate, suggesting that this VOI is not a concern for vaccine efficacy [26]. The data have to be interpreted with caution, as case numbers were small and further studies are needed.

Vaccine effectiveness: update of the evidence

Vaccine effectiveness against SARS-CoV-2 infection by severity (mild/moderate disease, severe disease, hospitalisation, death) and variants of concern

The overview of COVID-19 vaccine effectiveness in this section of the report is largely based on:

- A living systematic review of COVID-19 vaccine effectiveness studies conducted by the International Vaccine Access Center at John Hopkins Bloomberg School of Public Health and the WHO [27,28]. Results from relevant observational studies are published on a weekly basis [29], including forest plots by vaccine product, disease outcome, and VOC [30], with the latest update provided on 12 August 2021.
- The McMaster University Health Forum COVID-END Evidence Network to support Decision-making living evidence synthesis on efficacy and effectiveness of available COVID-19 vaccines for variants of concern #6 version 15: 11 August 2021 [31].
- ECDC has also analysed evidence of vaccine effectiveness comparing partial vaccination to full vaccination in a recently published technical report [32].

Based on the evidence from the above sources, overall, vaccine effectiveness from EU-authorised vaccines, including Comirnaty, Spikevax and Vaxzevria, show strong protection against symptomatic disease, severe disease, hospitalisation and death following a full vaccination course in the general population, in residents of long-term care facilities (LTCFs) and in older adults. The majority of studies were conducted on the wild-type SARS-CoV-2 or when the Alpha VOC was the predominant variant in circulation. The evidence shows that full vaccination with COVID-19 vaccines is effective against SARS-CoV-2 infection caused by wild-type SARS-CoV-2 in the general population, with vaccine effectiveness estimates in general ranging between 80 to 90% [33]. The vaccines have been shown to have lowered effectiveness against infection by the Beta VOC but have remained effective against infection by the Alpha VOC. In studies from various countries, there is some emerging evidence of reduced effectiveness against infection and mild-to-moderate disease with the Delta VOC compared to the Alpha VOC, however effectiveness against severe disease and death seems to be maintained at a high level for the moment.

General population

Twenty-three studies from a range of different countries and vaccines, included in the living systematic review of vaccine effectiveness, reported mean vaccine effectiveness estimates against symptomatic disease after complete vaccination (≥7 days post final dose) that ranged from approximately 82 to 97% for Comirnaty; 89 to 99% for Spikevax and 78% for Vaxzevria. Vaccine effectiveness estimates from seven studies against severe disease after complete vaccination (≥7 days post final dose) ranged from approximately 92 to 100% for Comirnaty and 90 to 96% for Spikevax. Vaccine effectiveness estimates from 25 studies against hospitalisation after complete vaccination (≥7 days post final dose) ranged from approximately 87 to 99% for Comirnaty; 90 to 91% for Spikevax; 89 to 100% for pooled analysis of mRNA vaccine data (Comirnaty and Spikevax) and 95% for pooled analysis of Comirnaty, Spikevax and Vaxzevria. Vaccine effectiveness estimates against death from nine studies after complete vaccination (≥7 days post final dose) ranged from approximately 91 to 98% for Comirnaty and 99 to 100% for pooled analysis of mRNA vaccine data (Comirnaty and Spikevax) [30].

These studies covered vaccine effectiveness data for different VOC and were carried out at different time points in different contexts.

Studies with variant-specific estimates

Beta VOC

A test-negative case control study from Qatar showed vaccine effectiveness estimates against severe, critical or fatal disease caused by the Beta VOC in the general population estimated at 100% (74-100) [34].

Alpha VOC

Studies assessing vaccine effectiveness following complete vaccination against symptomatic infection caused by the Alpha VOC in the general adult population from Canada [35] and the UK [36] show estimates ranging from 89 to 94% for Comirnaty, approximately 92% for Spikevax, and 75% for Vaxzevria.

Vaccine effectiveness estimates against severe disease or hospitalisation caused by the Alpha VOC from studies conducted in the general population in Qatar [34] measuring severe/fatal disease, in Canada [35] on hospitalisation or death, in the UK [37] and the US [38] on hospitalisation, range from approximately 95 to 100% following two doses of Comirnaty, 94% for Spikevax, 86% for Vaxzevria, and 92.8% from pooled analysis from mRNA vaccines data (Comirnaty and Spikevax).

Vaccine effectiveness against infection, symptomatic infection, severe disease and hospitalisation caused by the Delta VOC

With the increasing spread of the Delta VOC which is fast becoming the dominant variant in most EU/EEA countries, studies on vaccine effectiveness against the Delta VOC are crucial to determine the potential need for booster doses. There are continuously emerging data on the level of protection that full vaccination with the COVID-19 vaccines provide against infection, symptomatic infection, severe disease, and hospitalisation due to the Delta VOC.

Studies of Delta VOC: specific estimates

A test-negative case-control study conducted by Sheik et al. in the general population in Scotland between 1 April and 6 June 2021 showed that the effect of the full vaccination course of Comirnaty or Vaxzevria on infection with the Alpha VOC appeared to be higher when compared to the Delta VOC. They showed 92% (95% CI: 90-93) protection following two doses of Comirnaty against the Alpha VOC compared to 79% (95% CI: 75-82) against the Delta VOC and 73% protection (95% CI: 66-78) against the Alpha VOC, and 60% (95% CI: 53-66) against the Delta VOC following two doses of Vaxzevria [10].

A test-negative case control study from Qatar in those over 12 years old assessed the effectiveness of Comirnaty and Spikevax against infection with the Delta VOC, with 2 175 cases with confirmed Delta VOC infection and matched controls. They found that vaccine effectiveness against SARS-CoV-2 infection, symptomatic or asymptomatic, was 64.2% (95% CI: 38.1-80.1) following ≥14 days after the first dose, but only 53.5% (95% CI: 43.9-61.4) following ≥14 days after the second dose of Comirnaty. In comparison, effectiveness estimates following ≥14 days of one dose of Spikevax were 79% (95% CI: 58.9-90.1) and 84.8% following two doses. Effectiveness against severe, critical, or fatal disease due to the Delta VOC remained high at 89.7% (95% CI: 61-98.1) following the second dose with Comirnaty, and 100.0% (95% CI: 41.2-100.0) for Spikevax. In earlier studies in the same population in Qatar, vaccine effectiveness following two doses of Comirnaty against the Alpha VOC was estimated at 89.5%. The authors suggest that this may reflect some waning of Comirnaty protection over time, it may be the normalisation of behaviour of those that are fully vaccinated, or it could be related to immune escape by the Delta VOC [14].

A test-negative case control study in Ontario, Canada, with 421 073 participants from the general population found 87% (95% CI: 64-95) vaccine effectiveness against symptomatic disease from the Delta VOC following complete vaccination (≥7 days post final dose) with Comirnaty and 78% (95% CI: 65-86) effectiveness against hospitalisation due to the Delta VOC after two doses of Comirnaty (≥7 days post final dose) [35].

A test-negative case-control study from England in the general population with 19,109 cases and 171 834 controls found estimates of vaccine effectiveness against symptomatic disease caused by the Delta VOC of 88.0% (95% CI: 85.3-90.1) following two doses of Comirnaty and 67.0% (95% CI: 61.3-71.8) effectiveness following two doses with Vaxzevria [36].

There is evidence of high vaccine effectiveness against hospitalisation caused by the Delta VOC from a test-negative case-control study in England in patients seeking emergency care services with subsequent hospitalisation, which found 96% (95% CI: 86-99) effectiveness following two doses of Comirnaty (≥ 14 days post final dose) and 92% (95% CI: 75-97) following two doses of Vaxzevria (14+ days post final dose). These vaccine effectiveness estimates are similar to the estimates found against hospitalisation caused by the Alpha VOC [37].

A study from England using the REal-time Assessment of Community Transmission-1 (REACT-1) analysed prevalence trends and their drivers using RT-PCR swab-positivity data from round 12 (between 20 May and 7 June 2021) and round 13 (between 24 June and 12 July 2021) estimated vaccine effectiveness against infection based on self-reported vaccine status. They found estimated vaccine effectiveness against infection in round 12 of 64% (95% CI: 11-85) and against symptomatic infection as 83% (95% CI: 19-97) compared to an estimated effectiveness against infection of 49% (95% CI: 22-67) and against symptomatic infection of 59% (95% CI: 23-78) in round 13 (estimates were not provided by vaccine product) [39].

A study based on a large community-based survey of randomly selected households across the UK found that full vaccination with either Comirnaty or Vaxzevria was still effective against new infections from the Delta VOC, with vaccine effectiveness of 80% (95% CI: 77-83) and 67% (95% CI: 62-71), respectively, but effectiveness was reduced compared to the Alpha VOC. They found that a single dose of Spikevax has similar or greater effectiveness against the Delta VOC as single doses of Comirnaty and Vaxzevria. The results also suggest that the effectiveness of two doses of Comirnaty declines faster compared with two doses of Vaxzevria, but after four or five months the effectiveness of the two vaccines would be similar, although the long-term effects would need to be studied further. The authors also found that two doses of either Comirnaty or Vaxzevria provided as least the same level of protection against infection as previous natural COVID-19 infection and that people who had been vaccinated after natural infection had even more protection against laboratory-confirmed infection than vaccinated individuals who had not been naturally infected before [40].

Studies from the period when Delta VOC was predominant

In a retrospective cohort study in 77 607 adults in Minnesota, US comparing effectiveness of Comirnaty to Spikevax from January to July 2021 during which either the Alpha or Delta VOCs was highly prevalent (with the Delta VOC prevalence increasing from 0.7% in May to over 70% in July), the authors found high vaccine effectiveness of both vaccines against hospitalisations: Spikevax 91.6% (95% CI: 81-97) compared to Comirnaty 85% (95% CI: 73-93) [41]. The study found, however that in July the effectiveness against infection was substantially lower for Spikevax at 76% (95% CI: 58-87) and even lower for Comirnaty at 42% (95% CI: 13-62). The study found that individuals vaccinated with Spikevax were about half as likely to experience breakthrough infections as individuals vaccinated with Comirnaty [41].

A study by Rosenberg et al. in New York, US, using state-wide immunisation, laboratory testing, and hospitalisation databases looked at rates of new laboratory-confirmed COVID-19 cases and hospitalisations by vaccination status among those who received the Comirnaty, Spikevax or Vaxzevria vaccines. During the period from 3 May to 25 July 2021, the vaccine effectiveness against new COVID-19 cases declined from 91.7% to 79.8%; yet the vaccine effectiveness against hospitalisation remained quite stable, ranging from 91.9% to 95.3%. The noted decline in vaccine effectiveness against new COVID-19 cases coincides with an increase from <2% to >80% of the Delta VOC in the US region and relaxation of NPIs [3].

A study from the US, with 21 hospitals in 18 states, evaluated the duration of mRNA vaccine (Comirnaty and Spikevax) effectiveness in individuals aged ≥18 years against hospitalisation from COVID-19 during 11 March - 14 July 2021. Effectiveness against hospitalisation from COVID-19, including groups at higher risk for severe COVID-19, was sustained over the surveillance period, at 86% (95% CI: 82-88) overall. The sustained vaccine effectiveness estimates were unchanging among subgroups at highest risk for severe outcomes from COVID-19, including older adults, adults with three or more chronic medical conditions, and those with immunocompromising conditions (although vaccine effectiveness was lower for those with immunocompromised conditions (63% (95% CI: 44-76) compared to those without immunocompromising conditions (90% (95% CI: 87-92)) but was sustained over time in both populations). The Delta VOC-specific vaccine effectiveness was not assessed in the study but the authors state that estimates were similar during June-July when there was higher circulation of the Delta VOC compared with March-May when Alpha was the predominant VOC [42].

The Danish public health institute has published an official communication of an analysis of data from 2,000 breakthrough infections between 1 March to 3 August 2021 including the period when the Delta VOC has become predominant in Denmark. They found a high vaccine effectiveness against infection due to the Delta VOC following two doses (14 days post second dose) of Comirnaty (78.8% (95% CI: 77.2-80.4), Spikevax (88.1% (95% CI: 83.6-91.4). However, the vaccine effectiveness estimates were slightly lower than against the Alpha VOC. They also found high vaccine effectiveness against hospitalisations due to the Delta VOC of 85.6% (95% CI: 80.4-89.5) and 97.0% (95% CI: 78.8-99.6), respectively for Comirnaty and Spikevax, although the majority of patients hospitalised during the period when Delta VOC was dominant were much younger than during the period when Alpha variant was dominant [43].

A study from Israel used the Israel Central Bureau of Statistics and the Ministry of Health database of all residents of the country who became fully vaccinated before 1 June 2021 (n=9 395 923) (unvaccinated, vaccinated and previously infected individuals) to estimate vaccine effectiveness of full vaccination from Comirnaty (seven days post second dose) against documented SARS-CoV-2 infection and severe COVID-19 in different age groups, adjusted for week of infection, past PCR testing, demographic group, and sex. They estimated that the vaccine effectiveness against infection for people aged 60 years or older decreases from 73% (95% CI: 66-78) for those who became fully vaccinated in the second half of March to 57% (95% CI: 52-62) for those who became fully vaccinated during the second half of January. A similar decrease in vaccine protection is shown for the other age groups. There was also a decrease in the protection of the Comirnaty against severe disease for the 60+ age group from 91% (95% CI: 85-95) to 86% (95% CI: 82-90) between those vaccinated four months before the study to those vaccinated six months before the study. For the age group 40-59 years, the corresponding vaccine effectiveness was decreased from 98% (95% CI: 94-99) to 94% (95% CI: 87-97). The study authors point out that data on unvaccinated individuals were not directly available and some individuals who were not vaccinated may differ in important characteristics, which could result in biased estimates. In addition, the vaccination policies in Israel differ to other countries, as Israel used only one vaccine (Comirnaty) and had a three-week interval between the two doses. The current analysis also used data from July 2021, a time when, for the majority of the Israeli population, at least five months passed from the second dose to the outbreak of the Delta variant. The study authors conclude that the vaccine seems to be highly effective even after six months compared to the unvaccinated population, but its effectiveness is significantly lower than it was closer to the vaccination date [44].

Vaccine effectiveness against symptomatic infection by risk group (residents of long-term care facilities, older adults, immunocompromised individuals)

Residents of long-term care facilities

Studies from Denmark, France, Spain and the UK on vaccine effectiveness following a full vaccination course in residents of LTCFs when wild-type or the Alpha VOC was predominant show that COVID-19 vaccines were protecting against symptomatic infection, in particular there was evidence of high vaccine effectiveness against severe disease in this risk group, although slightly lower when compared with estimates from the general population [45]. Estimates ranged from approximately 75 to 97% effectiveness against hospitalisations following two doses of Comirnaty [48,49], with 88% for pooled analysis for mRNA vaccine data (Comirnaty and Spikevax) [48] and 89 to 98% effectiveness against death following two doses of Comirnaty (≥7 days post final dose) [48,49] with 97% with pooled analysis from Comirnaty and Spikevax [48]. Estimates from studies on vaccine effectiveness against SARS-CoV-2 infection in LTCF residents ranged from 53 to 66% following full vaccination with Comirnaty and 71 to 81% following full vaccination with Comirnaty or Spikevax [48,50-53].

Beta VOC

A retrospective cohort study of vaccine effectiveness against hospitalisations caused by the Beta VOC in 378 LTCF residents in eastern France conducted between January and May 2021 [52] estimated 49% (95% CI: 14-69) against infection and 86% (95% CI: 67-94) vaccine effectiveness against hospitalisation and death after two doses of Comirnaty (≥7 days post final dose).

Gamma VOC

In a Gamma VOC outbreak in a single LTCF in Canada, Ontario in 60 residents and 83 staff the vaccine effectiveness against severe disease in residents was calculated as 78.6% (95% CI: 47.9-91.2) after two doses of Comirnaty or Spikevax (≥14 days post final dose) [53].

Delta VOC

A study from the US using weekly data reported by nursing homes to CDC during the period soon after vaccine introduction (1 March to 9 May 2021) compared to the time during the Delta VOC predominance (21 June to 1 August 2021) found that two doses of Comirnaty or Spikevax were 74.7% (95% CI: 70.0-78.8) effective against SARS-CoV-2 infection in nursing home residents during March to May based on reports from 3,862 facilities, which then declined significantly to 53.1% (95% CI: 49.1-56.7) during June-July based on reports from 14 917 facilities. Vaccine effectiveness estimates during the intermediate period (May-June 2021) were lower than those during the pre-Delta period but were not significantly different [54].

As yet, there are no vaccine effectiveness studies published with the Delta VOC-specific estimates against severe disease or hospitalisations in LTCF residents.

Older adults

Several vaccine effectiveness studies in older adults from various countries, including a study from Brazil on the Gamma VOC, and studies with the Alpha VOC as the dominant variant at the time of the studies from Denmark, Finland, the UK, the US, Israel and a multi-country study, showed strong protection against symptomatic infection and severe disease (hospitalisation) following complete vaccination (≥7 days post final dose) in older adults.

Alpha VOC

In people 60 years of age and older estimates against symptomatic infection when the Alpha VOC was the dominant variant ranged from 76 to 90% following two doses of Comirnaty [57-59] and 89% (95% CI: 78-94) following two doses of Vaxzevria [55]. Vaccine effectiveness estimates in people over 60 years of age against hospitalisation ranged from approximately 87 to 93% following two doses of Comirnaty [48,60] and 94% with pooled analysis from both Vaxzevria and Spikevax [59].

Vaccine effectiveness against symptomatic disease following two doses of Comirnaty in individuals 80 years and over in the UK was 88% (95% CI: 84-90) [60]. Vaccine effectiveness against hospitalisation following two doses of Comirnaty in those 80 years and over, from studies from the UK and Israel, ranged from approximately 75 to 93% [27,32,63-65].

Gamma VOC

In a test-negative study in Sao Paulo, Brazil with 61 164 participants over the age of 60 years, the vaccine effectiveness was 77.9% (95% CI: 69.2-84.2) against symptomatic infection caused by the Gamma VOC, 87.6% (95% CI: 78.2-92.9) against hospitalisation and 93.6% (95% CI: 81.9-97.7) against death following two doses of Vaxzevria [63].

Immunocompromised individuals

There are currently limited data on COVID-19 vaccine effectiveness in people who are immunocompromised. Based on the current evidence from Israel, the US and Qatar, it has been shown that vaccine effectiveness against infection and hospitalisation following full vaccination with the Comirnaty and Spikevax vaccines in certain groups of immunocompromised individuals was reduced when compared to non-immunocompromised individuals.

A retrospective cohort study comprised of 14 697 fully vaccinated patients who received an mRNA vaccine (Comirnaty or Spikevax) by Khan et al. showed that vaccine effectiveness against SARS-CoV-2 infection was 80% among individuals with inflammatory bowel disease on immunosuppressive medication [64].

Chemaitelly et al conducted a retrospective cohort study to assess mRNA (Comirnaty or Spikevax) vaccine effectiveness among kidney transplant recipients (n = 782) registered with the national public healthcare provider in Qatar. This cohort study estimated vaccine effectiveness against SARS-CoV-2 infection at 46.6% (95% CI: 0.0-73.7) ≥14 days after the second dose, 66.0% (95% CI: 21.3-85.3) ≥42 days after the second dose, and 73.9% (95% CI: 33.0-89.9) ≥56 days after the second dose. Additionally, vaccine effectiveness against any severe or fatal COVID-19 disease was estimated at 72.3% (95% CI: 0.0-90.9) ≥14 days after the second dose, 85.0% (95% CI: 35.7-96.5) ≥42 days after the second dose, and 83.8% (95% CI: 31.3-96.2) ≥56 days after the second dose [65]. This analysis was conducted when the Alpha and Beta VOCs were dominant.

A US multicentre case-control analysis by Tenforde et al., including 1 210 adults hospitalised between 11 March to 5 May 2021, evaluated mRNA (Comirnaty or Spikevax) COVID-19 vaccine effectiveness to prevent COVID-19 hospitalisations. This analysis showed that vaccine effectiveness was significantly lower among patients with immunosuppression (59%; 95% CI: 11.9-81.1) than without immunosuppression (91%; 95% CI: 85.5-94.7). For immunocompromised patients with an active solid organ or hematologic malignancy or solid organ transplant, vaccine effectiveness was 51.2% (95% CI: -30.7-81.8). This analysis was conducted when the dominant VOC in circulation was Alpha (59.7% of sequenced viruses) [38].

Chodick et al. conducted a retrospective cohort study in Israel that evaluated the Comirnaty vaccine effectiveness at 71% (95% CI: 37-87) among immunosuppressed individuals (which included recipients of hematopoietic cell or solid organs transplant, patients under immunosuppressive therapy, with asplenia, and chronic renal failure: advanced kidney disease, dialysis, or nephrotic syndrome) compared to 90% vaccine effectiveness (95% CI: 79-95) overall in preventing SARS-CoV-2 infection confirmed with RT-PCR, between seven to 27 days after full vaccination. This analysis was conducted when the dominant VOC in circulation was Alpha [66].

Breakthrough infections in immunocompromised individuals

In Brosh-Nissimov et al.'s retrospective cohort study of 17 hospitals in Israel, 152 patients fully vaccinated with Comirnaty developed COVID-19 and required hospitalisation more than seven days after the second vaccine dose. A proportion of 40% (n=60) of the patients was immunocompromised (most common causes were chronic corticosteroid treatment, chemotherapy or anti-metabolite treatment, solid organ transplantation and anti-CD20 treatment). Overall, this cohort of patients had a high rate of predisposing co-morbidities to severe COVID-19 (hypertension (108; 71%), diabetes (73; 48%), congestive heart failure (41; 27%), chronic kidney and lung diseases (37; 24% each), dementia (29; 19%) cancer (36; 24%)), with only 4% (6) having no co-morbidities [67].

Antibody response immunocompromised individuals following a primary vaccine

A reduction in antibody response or reduced immunogenicity from mRNA vaccination (Comirnaty or Spikevax) has been detected in the following groups of individuals including those: taking immunosuppressive medications, like rituximab [71-74] or mycophenolate [74-77], with haematologic cancers [76,77], those on haemodialysis [78,79], and HIV-positive individuals with lowest CD4 counts (not similar to the general population) [77].

Evidence of effects of an additional COVID-19 vaccine dose in immunocompromised individuals

Initial studies have shown that an additional COVID-19 vaccine dose in immunocompromised individuals enhances antibody response. Several studies thus far have looked at seropositive responses with a third mRNA COVID-19 vaccine dose in immunosuppressed people. Among immunocompromised individuals who had no detectable antibody response following a full COVID-19 vaccination course, 33-50% developed an antibody response to an additional third dose [83-87].

Vaccine effectiveness against infection and onward transmission (test positivity, viral load, secondary attack rates)

Viral load

Studies of viral load in SARS-CoV-2 positive individuals conducted during late 2020 to early 2021 indicated that viral load was reduced in those who had received a COVID-19 vaccine. Very recent results now indicate that vaccination may have less effect in initially reducing viral load in infections caused by the Delta VOC.

A cohort study by Marks et al. identified 314 patients with COVID-19 using the electronic registry of the Epidemiological Surveillance Emergency Service of Catalonia (Spain). A secondary attack rate of 17% was found with a variation from 12% when the index case had a viral load lower than 1 × 106 copies per mL to 24% when the index case had a viral load of 1 × 1010 copies per mL or higher. This analysis showed that viral load of index cases was a leading driver of SARS-CoV-2 transmission [83].

A retrospective collection and analysis of positive SARS-CoV-2 test results performed at the Maccabi Healthcare Services central laboratory in Israel, between 21 December 2020 and 11 February 2021 found that the viral load was reduced for infections occurring 12 to 37 days after the first dose of the Comirnaty vaccine. By looking at the PCR cycle threshold (Ct) over time, Levine-Tiefenbrun et al found that the mean viral load decreased 12 days after vaccination with the first vaccine dose, and that Ct values of positive samples collected 12–37 days after vaccination with the first dose of Comirnaty (a second dose having been given on day 21 for all samples taken after day 21) were higher than Ct values of positive samples during the first 11 days after vaccination [84].

A small single-centre retrospective study of nursing home residents who had asymptomatic COVID-19 showed that receipt of a single dose of the Comirnaty vaccine was associated with lower nasopharyngeal viral load than in those who had not been vaccination. The mean $\log_{10}$ viral load was higher in unvaccinated (9.5; 95% CI: 9.3-9.8) compared to vaccinated residents (7.1; 95% CI: 5.4-8.8), respectively (p = 0.004). A limitation of this study is the small study size [85].

Petter et al. traced the Ct values of SARS-CoV-2 positive test conducted between 1 December 2020 to 30 January 2021 at the MyHeritage COVID-19 testing lab in Israel. Overall, it was estimates that vaccination reduced the viral load by 1.6x to 20x in individuals who were positive for SARS-CoV-2 [86].

A recent study by Pouwels et al., conducted with the Office for National Statistics COVID-19 Infection Survey in the UK, showed that individuals experiencing Delta VOC infections after two vaccine doses (with Comirnaty or Vaxzevria) had comparable peak levels of viral load to unvaccinated infected individuals. With the Alpha VOC, those infected after being vaccinated had much lower peak levels of viral load [40]. However, a study from Singapore showed that the viral load in individuals infected with Delta VOC after full vaccination decline more rapidly than viral loads in individuals naturally infected with the Delta VOC [87].

Vaccine effectiveness against SARS-CoV-2 transmission by healthcare workers to household members

Studies conducted when the Alpha was the predominant VOC circulating have shown that vaccination of healthcare workers reduced the risk of SARS-CoV-2 infection in household members.

A study by Salo et al. used national databases in Finland to assess indirect COVID-19 vaccine effectiveness among vaccinated healthcare workers and their unvaccinated adult household members. An indirect effectiveness (reduced transmission) of 8.7% (95% CI: -28.9-35.4) two weeks and 42.9% (95% CI: 22.3-58.1) 10 weeks after the first dose of mRNA (Comirnaty or Spikevax) vaccine, from healthcare workers vaccinated to a household spouse, was observed [88].

A national record linkage study in Scotland by Shal et al showed that household members of vaccinated healthcare workers had a lower risk of infection from SARS-CoV-2 compared to household members of unvaccinated healthcare worker (rate per 100 person-years 9.40 versus 5.93; HR 0.70, 95% CI: 0.63-0.78) [89].

Other studies of vaccine effectiveness against SARS-CoV-2 transmission

Several studies, from Spain, England, Israel, and the Netherlands, conducted when Alpha was the predominant VOC, have shown vaccine effectiveness against transmission ranging between 58-88%.

A prospective cohort of close contacts of SARS-CoV-2 positive individuals (20 961 participants) ≥ 18 years old from Navarra, Spain, showed a vaccine effectiveness of 65% (95% CI: 56-73) against infection in close contacts of SARS-CoV-2 positive index cases ≥ 14 days after full vaccination with Comirnaty. Whole genome sequencing was conducted on 17% of infected contacts and showed dominance of the Alpha VOC (n = 865; 68.9%) [57].

A cohort study in England, during the period 4 January 2021 to 28 February 2021, illustrated that contacts of vaccinated SARS-CoV-2 cases had lower odds of being secondary cases if the index case was vaccinated ≥ 14 days before testing positive. The unadjusted odds ratio for being a secondary case if the index case was vaccinated with Vaxzevria (vs. index case not vaccinated) was 0.55 (95% CI: 0.46-0.67), and 0.57 (95% CI 0.49-0.65) with Comirnaty [90].

Prunas et al. analysed the effectiveness of vaccination with Comirnaty against household transmission of SARS-CoV-2 in Israel, using two different analytic approaches applied to data from the Maccabi Healthcare Services (MHS) centralised database from 15 June 2020 to 24 March 2021. From their analysis, vaccine effectiveness against susceptibility to infection was 80-88%, and the overall vaccine effectiveness against transmission was assessed at 88.5% [91].

Based on routine contact monitoring data from the Municipal Health Services in the Netherlands, De Gier et al. estimated the vaccine effectiveness against transmission and the vaccine effectiveness against infection among household and other close contacts of confirmed cases of SARS-CoV-2 infection between 1 February and 27 May 2021. A vaccine effectiveness against transmission of 71% among household contacts of fully vaccinated index cases was observed. Specifically, for each vaccine, vaccine effectiveness against transmission values were estimated at 58% for Vaxzevria, 70% for Comirnaty, 88% for Spikevax and 77% for the Janssen vaccine [92].

Duration of protection: update of the evidence

Immunological memory is essential to protect from recurrent infection with the same virus. Immune cells specific for the virus, such as T and B cells are activated, modified during initial infection or vaccination, and help to fight the infection. B cells start to differentiate into so called plasma cells to produce antibodies against different compartments (antigens) of the virus. Neutralising antibodies play an important role in inhibiting entry of the virus into cells. Additionally, virus-specific T cells can destroy infected cells and monitor the inflammation. They are also crucial for the development of highly virus-specific B cells. After initial infection, memory T and B cells, as well as antibody-producing plasma cells persist in the body. Memory cells can quickly be reactivated after re-entry of the virus and persisting antibodies can inhibit invasion and mark the virus particles to be phagocytosed. The magnitude and decay rate of the different response types is very heterogenic, depending on the virus or vaccine, severity of disease and the individual itself. So far, the rate of re-infection is the best way to assess the duration of protective natural immunity. Moreover, immunological assays that measure specific immune responses, such as virus-specific antibody levels, especially for neutralising antibodies, have been used to estimate the duration of immunity. However, to date, the correlation between measured immunity and clinical protection from SARS-CoV-2 infection still needs to be established.

Duration of protective immunity following primary vaccination

Several studies have shown that COVID-19 vaccination is able to induce a robust immune response towards the spike protein of SARS-CoV-2 with the generation of T and B cell-antibody responses.

So far, three studies have correlated antibody (IgM and IgG) titres to vaccine efficacy (VE). Earle et al. assessed the relationship between antibody levels and VE of seven COVID-9 vaccines and detected a correlation between VE and virus-specific antibody levels [93]. Khoury et al. reported a correlation between neutralising antibody levels and the protection against symptomatic infection [94]. A recent preprint analysed participants (n=30 415) from the Coronavirus Efficacy (COVE) phase 3 trial and found a corelation between binding and neutralising antibodies with VE of Spikevax and risk of COVID-19 [95]. Neutralising antibodies reach their peak level approximately one week after the second dose and decline over time; however, they remain detectable at least 6 months post vaccination [96]. A recent study compared antibody levels between age groups and reported lower levels of spike-specific, and especially neutralising antibodies, in the older adults compared to younger individuals after vaccination with Comirnaty [97]. This suggests that older adults may have a weaker immune response to the vaccine. However, it is still not known what antibody levels are needed to protect from severe, symptomatic disease or infection with SARS-CoV-2. Additionally, these studies did not consider the impact of vaccine generated memory cells on the duration of protective immunity. The widely used serological tests, which are used to measure antibody levels, do not measure T cell responses.

Several studies have investigated if the vaccine is able to induce spike-specific T cell responses. A study from Singapore detected activated spike-specific T cells already 10 days after the first does of mRNA vaccination in 20 healthcare workers and T cell responses were associated with the onset of vaccine efficacy [98]. The generation of a strong T cell response after vaccination was further confirmed by a recent study from the US [99]. A preprint from the PITCH (Protective Immunity from T cells to COVID-19 in Health workers) consortium that analysed 503 individuals showed that T cell responses are further boosted in naive individuals after the second dose, with better response in individuals with longer dosing intervals [100]. Even though induction of memory T cells has been observed, the durability of these cells and role in protecting from infection remains unclear.

Interactions between T and B cells are critical for the development of most humoral immune responses and the generation of long-lived antibody secreting plasma cells and memory B cells. These can be protective in response to vaccination or infection [101,102]. Studies have shown that mRNA vaccination elicits a robust antigen-specific B-cell memory and antibody response comparable to natural infection [103], although Wang et al. also pointed out that the neutralising potential of the antibodies generated by the mRNA vaccine against variants was reduced. These studies have limitations due to their small sample size and underrepresentation of older age groups.

The vaccines generate a robust immune response with the generation of memory cells which have the potential to provide protective durable immunity. It is still unclear if the different vaccines induce a similar immune response, since most studies have investigated the immune response from mRNA vaccines.

As SARS-Cov-2 is a respiratory virus that infects the upper and lower airways, it is important to trigger a robust immune response at the sites of infection. In natural infection, memory cells persist in the respiratory tract and can rapidly recall an immune response [104]. Virus-specific antibodies, which can inhibit the entry of the virus, have been detected in the mucosa after vaccination and persist for at least three months [105] – the duration of these

antibodies is not known. Lack of or weak mucosal immune responses after vaccination could lead to infection with SARS-CoV-2, but the presence of memory cells that are directed to the site of inflammation could prevent severe disease in infected individuals.

Further research is needed to determine the duration and protective role of vaccine-induced immune responses to protect from disease and/or infection. There is only limited evidence available on the differences of immune responses between age groups after COVID-19 vaccines. Data from influenza vaccine effectiveness studies have shown that vaccine effectiveness may be reduced in older individuals [106]. Furthermore, higher transmissibility, exposure to higher viral loads, as well as partial escape of the virus variants from cellular and humoral responses, characteristics all linked to the currently dominant Delta VOC, can have a negative impact on protective immunity.

In a recent pre-print from a randomised controlled clinical trial, vaccine effectiveness of Comirnaty against laboratory-confirmed COVID-19 was confirmed to remain above 80% for up to six months after receiving the primary vaccination series [107]. A gradual decline from the peak vaccine effectiveness of 96.2% (95% CI: 93.3-98.1) observed between seven days and two months from the second dose was reported between two months and four months from the second dose (vaccine effectiveness = 90.1%; 95% CI: 86.6-92.9), and between four months and the data cut-off (vaccine effectiveness = 83.7%; 95% CI: 74.7-89.9).

A preliminary retrospective cohort study from Israel compared the incidence rates of breakthrough infections between early (January-February) and late (March-April) vaccinated individuals with Comirnaty and found that earlier vaccinated individuals had a statistically significant 53% (95% CI: 40-68%) 2.26-fold increased risk (95% CI: 1.80-3.01) for breakthrough infection compared to later vaccinated individuals [2]. No differences between age groups were observed.

A recent study from Israel investigated waning immunity of the Comirnaty vaccine using data from the Ministry of Health database on 4 785 245 residents of Israel who became fully vaccinated before 1 June 2021. Data included vaccination dates, PCR tests, hospitalisation admission date, severity, and demographic variables. The study compared the rate of infection among individuals vaccinated at different times and reported a reduction in protection in all age groups, pointing towards a potential waning of protective immunity. The rate of SARS-CoV-2 infections among those aged 60 years and above vaccinated in January was 3.2 cases for 1 000 people, compared to 2.1 and 1.6 for individuals from the same age group vaccinated in the second halves of February and March, respectively. For the analyses of severe disease among those aged 60 years and above, the rate of severe cases who were fully vaccinated in January is 0.29 for 1 000 persons, and is reduced to 0.23, 0.15 and 0.10 for those who were fully vaccinated in February, March, and April-May, respectively. The authors conclude that the results show immunity waning in all age groups after six months from vaccination. Further studies are needed to assess if the increase of breakthrough infections and reduced vaccine effectiveness is a result of the waning of protective immunity or due to other factors, and whether these results are generalisable to other contexts [44].

Duration of immunity following natural infection

There is limited evidence on the duration of protective immunity against the reinfection with SARS-CoV-2 virus. A study from Qatar suggests that natural infection protection against reinfection was 95% among individuals who tested positive and it lasted for at least seven months [108]. A study among health-care workers in the UK estimated a reduced risk of reinfection of 83% for at least five months after primary infection, while another study demonstrated 89% protection against reinfection lasting at least six months [109]. The reported reinfection events are rare and occur in less than 1% of all COVID-19 cases [108].

A recent study conducted in Denmark found that protection against repeated SARS-CoV-2 infection was robust in most individuals, protecting more than 80% of the naturally infected population younger than 65 years against reinfections. However, individuals aged 65 years and older had less than 50% protection against SARS-CoV-2 reinfection [110]. A study in Italy also concluded that reinfection events were rare, and that natural immunity elicited a protective effect for at least one year [111]. However, the observation period of the study ended before the beginning of spread of SARS-CoV-2 variants and it is unclear how well the natural immunity against wild-type virus would protect against the various variants. In addition, over 70% of baseline positive cases in this study were hospitalised, suggesting a severe disease. As the disease severity influences the strength of the immune response against SARS-CoV-2, the observed duration of protective immunity and reinfection rate might be significantly influenced by the study cohort [111].

Several studies have investigated the presence of SARS-CoV-2-specific antibodies and their neutralising effect to estimate the duration of immunity after a natural infection. Waning of SARS-CoV-2-specific antibodies have been described and the rate is dependent on the antibody specificity. Nucleoid capsid-specific antibodies have been shown to wane faster than spike-specific antibodies [112]. Waning of neutralising antibody levels have been reported around six months post-infection. However, antibody dynamics vary greatly between individuals, depending on disease severity, duration, and age [119,120], e.g. higher levels and persistence of neutralising antibodies has been associated with more severe disease.

Even though antibody levels are often used to assess duration of immunity, a direct correlation between protection against reinfection and neutralising antibody levels is still lacking, and waning neutralising antibody levels might be mitigated by the presence of cellular immunity. Different types of immune response and immune memory are generated by SARS-CoV-2 infection. Each of those have distinct kinetics, resulting in complex interrelationship between the abundance of T cell, B cell, and antibody immune memory over time. Substantial immune memory is generated after COVID-19, involving all four major types of immune memory, with about 95% of subjects retaining immune memory for at least six months after infection [115]. Circulating antibody levels are not predictive of T cell memory [116]. Thus, further research is needed to determine the duration of immunity against reinfection with SARS-CoV-2.

Little is known about the capability of new variants to escape the immune response generated by a natural SARS-CoV-2 infection. According to Public Health England National Surveillance of Reinfections, the risk of reinfection with the Delta VOC may be higher (aOR 1.46 (95% CI: 1.03-2.05)) compared to the Alpha VOC. The data showed that the risk of reinfection was not elevated for the Delta VOC if the primary infection was less than six months ago (aOR 0.79, (95% CI: 0.49-1.28)) but was higher for those with a prior infection more than six months ago (aOR 2.37, (95% CI: 1.43-3.93)) [117].

Current recommendations regarding additional COVID-19 vaccine doses in the EU/EEA and beyond

According to EMA's summary of product characteristics (SPCs) of COVID-19 vaccines authorised for use in the EU/EEA, no additional dose is currently recommended after the primary vaccination schedule [118]. Nevertheless, the adoption of polices and protocols on the off-label use of additional COVID-19 vaccine doses after the primary vaccination schedule is rapidly evolving in the EU/EEA and beyond.

Based on the most recent available information (see Table 1), eight EU/EEA countries (Austria, Belgium, France, Hungary, Liechtenstein, Lithuania, Luxembourg, and Slovenia) are currently recommending the use of an additional vaccine dose or booster dose (i.e. third dose for two-dose schedule and second dose for single-dose schedule vaccines), while Germany is planning its implementation in the autumn, and a decision is currently under discussion in 13 EU/EEA countries. All protocols, of those currently in place, recommend the use of an additional dose in immunocompromised or immunosuppressed individuals (see Table 1 for specific indications and definitions of eligibility due to immunodeficiency). In Austria, the indication is extended to other population groups, such as the elderly (65 years and above), LTCF residents, individuals with chronic diseases, individuals with a primary vaccination series with a vector-based vaccine, and front-line workers (details in Table 1). In Hungary, any individual aged 18 years or older becomes eligible for an additional dose six months after the completion of the primary vaccination series, but the additional dose is especially recommended for the elderly, those with chronic illness, and immunosuppressed individuals. The time interval of the administration of the additional dose varies from a minimum of four weeks to nine months after completion of the primary vaccination schedule for population groups considered at higher risk; and from four to 12 months for eligible individuals from the general population. When specified (four countries), it is recommended that mRNA-based vaccines be used for the additional dose, including in case of heterologous combination ('mix and match'); in Hungary, heterologous vaccination is strongly recommended, but homologous is available if there is a contraindication for the heterologous vaccines.

The scenario regarding the use of boosters or additional vaccine doses is evolving rapidly outside of the EU/EEA.

On 30 June 2021, the Joint Committee on Vaccination and Immunisation (JCVI) of the UK published a report with an overall outline of a booster programme to possibly begin in September 2021, with the primary objective being to maximise protection in individuals most vulnerable to serious COVID-19 ahead of the winter months [119]. Where possible, a synergistic approach to the delivery of COVID-19 and influenza vaccination could support delivery and maximise uptake of both vaccines. The first stage of the booster program in the UK would include: adults aged 16 years and over who are immunosuppressed; those living in residential care homes for older adults; all adults aged 70 years or over; adults aged 16 years and over who are considered clinically extremely vulnerable; and frontline health and social care workers. A second stage could follow as soon as practicable and would include: all adults aged 50 years and over; adults aged 16 to 49 years who are in an influenza or COVID-19 at-risk group [120]; and adult household contacts of immunosuppressed individuals. The benefits of booster vaccination in younger adults will be considered when more information will be available.

On 12 August 2021, the US Food and Drug Administration updated the emergency use authorisations for both Comirnaty and Spikevax to allow for the use of an additional dose in certain immunocompromised individuals, specifically solid organ transplant recipients or those who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise [121]. Following the meeting of the Centers for Disease Control (CDC) and Prevention's Advisory Committee on Immunization Practices (ACIP) on 13 August [122], an update of the clinical recommendations on the use of COVID-19 vaccines, including the use of an additional dose as part of a primary vaccination series in immunocompromised individuals, is pending. On 18 August, a joint statement from public health and medical experts was released by the US Department of Health and Human Services (HHS) with a proposed plan for COVID-19 booster shots with the objective of maximising vaccine-induced protection and prolonging its durability, provided regulatory FDA allowance and ACIP recommendation are granted. This was based on the evidence of reduced protection against mild and moderate disease and the consideration that protection against severe disease, hospitalisation, and death might diminish in the coming months, especially among those most at risk of severe COVID-19 or who were vaccinated early in the campaign. The administration of the booster doses could begin in autumn, starting with individuals who were fully vaccinated earliest in the vaccination rollout (eight months since the completion of the primary series), including healthcare workers, residents of long-term care facilities, and elderly people [123].

At the end of July, following the resurgence in COVID-19 cases and increasing circulation of the Delta VOC, Israel initiated a national plan to administer booster doses of Comirnaty, starting with the elderly. Currently, adults aged 50 years and above, HCWs, individuals with a high risk of severe COVID-19, LTCF residents, people in detention

settings and people working in detention settings, who have completed the primary vaccination series over five months ago, are all eligible to receive a third dose [124].

Table 1. Recommendation on the use of an additional vaccine dose in EU/EEA countries (as of 26 August 2021)

Country	Recommendation	Notes	Ref.
Austria[2,4]	Yes	**Indication**: (off-label use) for population groups at high risk (65+ years, LTCF residents, immunocompromised individuals and with chronic diseases, individuals with primary vaccination series with Vaxzevria or COVID-19 Vaccine Janssen); people over 18 years of age from the following population groups: personnel from nursing homes for the elderly and retirement homes; healthcare workers; personnel from mobile care, support, nursing and 24-hour care, as well as caregivers; staff in educational institutions. **Timing**: 6-9 months after completion of primary series for population groups at high risk; 9-12 for population groups from the general population (18 years or older). Adjustments will be made as new scientific evidence suggesting different duration of protection emerges. **Other considerations**: an mRNA vaccine (Comirnaty or Spikevax) should be used for the additional dose regardless of which product was administered as part of the primary vaccination series. The Austrian NITAG does not recommend the use of serologic assays to evaluate protection following vaccination in the general population because no clear correlate of protection has been defined yet. In particular cases (e.g., immunocompromised individuals), titres of neutralising antibodies can be measured and used to support evaluation of protection.	[125]
Belgium[6]	Yes	**Indication**: individuals with congenital immunodeficiency; on chronic kidney dialysis; HIV-positive patients whose CD4 cell count is <200/mm³; individuals with blood cancer or other malignant tumours, who are or were under active treatment; transplant recipients; individuals with inflammatory diseases treated with immunosuppressant.	[126]
Bulgaria[1]	No		
Croatia[2]	Under discussion	Under consideration for immunocompromised and elderly (65+ years).	
Cyprus[1]	No		
Czechia[1,4]	Under discussion	Under consideration for immunocompromised individuals, especially transplant recipients.	
Denmark[2]	No	Physicians may offer a third dose to immunocompromised individuals based on individual assessment.	
Estonia[2]	No		
Finland[2]	No		
France[2, 6]	Yes	**Indication**: For immunocompromised/immunosuppressed people (recipients of organ or hematopoietic stem cell transplant; under lymphopenic chemotherapy; treated with strong immunosuppressive drugs, such as antimetabolites and anti-CD20 agents; chronic dialysis patients after consulting their doctor who will decide on the need for appropriate examinations; on a case-by-case basis, people on immune-suppressants not falling within the above-mentioned categories or carriers of primary immunodeficiency).	[132-134]

Country	Recommendation	Notes	Ref.
		The Haute Autorité de Santé announced a recommendation for a booster dose for people 65 years and above and for those at risk of severe forms of COVID-19 from the start of the influenza vaccination campaign scheduled for late October. **Timing**: four weeks after the second dose for immunocompromised individuals. **Other considerations**: for immunocompromised people who have received a Vaxzevria complete vaccination schedule (two doses), a third dose of Comirnaty or Spikevax will be used.	
Germany[2,4]	Yes (planned)	**Indication**: severely immunocompromised people, the very elderly and people in need of care. In addition, the offer of a booster vaccination will be made to all people who have completed a vaccination series with vector-based vaccines. Scientific discussion about target groups for the additional dose is ongoing; a decision should be made in September. **Timing**: at least six months; for those who have completed full vaccination with a vector-based vaccine, time schedule is under discussion. **Other considerations**: additional vaccine dose (mRNA-based vaccine) is planned to be offered to the very elderly and people in need of care, regardless of vaccine type previously received.	
Greece[2]	No	Review of evidence ongoing.	
Hungary[2,6]	Yes	**Indication**: to anyone who fulfils the following conditions: received a complete vaccination schedule (two doses or one dose of COVID-19 Vaccine Janssen); older than 18 years; four months or more have passed since the completion of primary vaccination. The third vaccine is especially recommended for the elderly, those with chronic illness, and individuals with a weakened immune system. **Timing**: four months or more. **Other considerations**: heterologous vaccination is strongly recommended, but homologous is available if there is contraindication for the heterologous vaccines.	[130]
Iceland[1]	Under discussion	Under consideration for immunocompromised individuals and the elderly; a second dose (probably with Comirnaty) to individuals vaccinated with COVID-19 Vaccine Janssen.	
Ireland[2,4]	Under discussion	Under consideration for immunocompromised and the elderly. Other groups to be considered, depending on evidence of breakthrough infection/hospitalisation risk, include HCWs, the elderly and vector-based vaccine recipients.	
Italy[2,4]	Under discussion	Under consideration for specific population groups at-risk, such as transplant recipients and immunocompromised.	
Latvia[1]	No		
Liechtenstein[5]	Yes	**Indication**: severe immunocompromised patients in case of low or missing antibodies a third dose of the mRNA vaccine is recommended. However, antibody-testing is not considered for the general population.	
Lithuania[6]	Yes	**Indication**: individuals with oncohaematological diseases, receiving treatment for oncohaematological diseases, on chronic dialysis; solid organ transplant recipients; individuals with autoimmune diseases receiving immunosuppressive therapy.	[131]

Country	Recommendation	Notes	Ref.
		Timing: six months after completion of primary vaccination series.	
Luxembourg[2,4]	Yes	**Indication**: severely immune suppressed patient (e.g., solid organ transplant recipients and haematopoietic stem cell recipients, patients on lymphopenic chemotherapy, or on immunosuppressive treatments like antimetabolites and anti-CD20 therapy, or on case-to-case basis), **Timing**: 0-4-12 week schedule for the first, second and third dose respectively (the third dose can also be administered after the 12th week, in case of catching up from a previous vaccination). **Other considerations**: boosters only with mRNA vaccines	[132]
Malta[2]	No		
Netherlands[2]	Under discussion		
Norway[1,4]	Under discussion		
Poland[2,4]	Under discussion	Under consideration for very immunocompromised individuals.	
Portugal[3]	Under discussion		
Romania[4]	Under discussion		
Slovakia[2]	Under discussion		
Slovenia[6]	Yes	**Indication**: may be offered to solid organ transplant recipients and severely immunocompromised **Timing**: at least four weeks after completion of primary series. **Other considerations**: an mRNA vaccine should be used.	[133]
Spain[1,4]	Under discussion	Under consideration for certain risk groups, such as immunocompromised subjects	
Sweden[6]	Under discussion	Under consideration for certain risk groups (elderly in long-term care facilities and 80+ years, immunocompromised)	[134]

Sources:
1. *Questions submitted by the European Commission (EC) to EU/EEA countries via the Integrated Situational Awareness and Analysis (ISAA) report prepared under the Integrated Political Crisis Response Mechanism (IPCR) of the Council of the European Union: 73 (as of 19 July), 74 (as of 26 July)*
2. *Questions submitted by the EC to Health Security Council members (6 August)*
3. *Request of information collected through the EU/EEA National Immunisation Technical Advisory Groups (NITAGs) Collaboration (23–29 June 2021)*
4. *Request of information collected through the EU/EEA NITAGs Collaboration (16-18 July 2021)*
5. *NITAGs exchange (July 2021)*
6. *Desk review of official sources.*

Public health considerations when assessing the need for additional doses of COVID-19 vaccines

Objectives of vaccination strategy

When assessing the need for possible booster doses of COVID-19 vaccine from the public health perspective, it is important to keep in mind the main objective of the vaccination strategy (i.e. preventing severe cases of COVID-19). Vaccine effectiveness against severe disease should preferably be chosen as the primary outcome of interest for assessing when there is a clear need for an additional vaccine dose in specific groups. Close monitoring of vaccine effectiveness data, particularly among vulnerable groups at risk of severe COVID-19 and among those living in closed settings, should be continued, and decisions adapted accordingly, should a substantial decrease in effectiveness be noted in one or more population groups.

Population immunity and viral circulation

Overall population immunity against SARS-CoV-2, and viral circulation, are factors to consider when evaluating urgent needs for a booster dose. Although no correlate of protection has been identified so far, recent and representative seroprevalence studies [135] could provide some indirect evidence of population immunity, although this may wane over time. By the end of 2020, before the COVID-19 vaccination campaigns had started, seropositivity from national surveys in Europe suggested low national SARS-CoV-2 seroprevalence (<10%) across the European region, with the exception of sub-national populations that had experienced intense community transmission. Population immunity could be broadly estimated by knowing the vaccination coverage and the proportion of the population with a previous natural infection. However, factors like waning immunity may affect the validity of this estimation. High vaccination coverage across age groups can be considered as a determinant of low viral circulation and reduced risk of SARS-CoV-2 infection. Nevertheless, waning immunity, and the presence and level of circulation of immune-escape variants, need to be added into the equation.

Populations to prioritise for additional vaccine dose

An important criterium for the choice of groups to prioritise for additional vaccine doses is the protection of groups at risk of severe disease due to reduced or waning immunity or due to vaccine escape of circulating variants of concern like the Delta VOC.

Individuals with reduced response to the primary vaccination series should probably be considered a priority group for an additional vaccine dose. Certain groups of immunocompromised individuals, such as solid organ transplant recipients and other individuals with a similar level of immunosuppression, may benefit from an extra COVID-19 vaccine dose as part of their primary series to mount a better immune response against SARS-CoV-2.

Vulnerable groups with possible earlier waning of immune response to the primary series, such as frail elderly, where immunosenescence may lead to faster waning of immune response, could also be considered a potential priority group for an additional dose, in particular if living in long-term care facilities where outbreaks caused by the Delta VOC among fully vaccinated individuals have been observed. In general, all individuals at increased risk of severe COVID-19 for medical reasons (e.g., underlying conditions) or with high exposure to SARS-CoV-2, could also be considered as potential target groups for a booster should a substantial decrease in vaccine effectiveness against severe disease be detected. Other groups for consideration of a booster dose could be healthcare workers and other staff who work in close contact with individuals at risk of severe COVID-19.

Timing (season and time since primary vaccination)

The timing of the potential administration of booster doses could be of great importance and should be based on epidemiological and practical considerations.

Generally speaking, vaccination and boosting of immunity obtain the maximum impact if administered before an epidemic wave and the minimum impact if administered at the end of an epidemic wave. Monitoring the epidemiological situation is therefore of key importance in deciding when an additional dose could be best administered in the presence of clear signs of reduced vaccine effectiveness against severe COVID-19 at least in some target groups.

Timing is also important for diseases that follow a seasonality pattern, like respiratory infections. Vaccinating before the beginning of the autumn, when people start spending more time indoors, could be an example of such an approach that would again aim at anticipating an epidemic wave and therefore maximise the impact of the vaccination. This is similar to what is routinely done with vaccination against seasonal influenza.

Moreover, the timing (and type) of completion of the primary series is also of importance for waning immunity, as the more recently completion is the more unlikely the need for a booster, unless a new VOC emerges and spreads with strong vaccine-escape potential.

Possible concomitance with influenza vaccination campaign

The co-circulation of influenza viruses during the ongoing COVID-19 pandemic in the autumn and winter months could have severe consequences for vulnerable populations and place an additional burden on health systems already strained by COVID-19. Unlike ahead of the influenza season 2020/21, a large part of the vulnerable population is now fully vaccinated against COVID-19 [6]. However, uptake differs amongst countries and, in light of continued community transmission of SARS-CoV-2, potentially waning immunity, and circulating variants of concern, additional preventative measures remain highly important.

Seasonal influenza vaccination campaigns are well established in EU/EEA countries, although uptake and acceptance is often suboptimal among target groups [136]. Influenza vaccination campaigns usually occur during the autumn in order to provide adequate protection in time for the start of the influenza season. Healthcare workers, older adults, pregnant women, individuals with chronic health conditions and children under five years old continue to be important target groups for influenza vaccination. Risk groups for influenza are overlapping with groups most at risk of severe COVID-19 disease including hospitalisation and death.

Ahead of the 2020/21 influenza season in the northern hemisphere, the WHO Regional Office for Europe published recommendations for influenza vaccination during the COVID-19 pandemic [136]. These recommendations highlight the need to ensure the best possible protection against influenza among risk groups, decrease the number of people requiring medical care as a result of influenza infection to limit pressures on health services while also reducing the potential for SARS-CoV-2 exposure while seeking treatment for influenza or being admitted to hospital for influenza. In addition, since pressure on health systems remains high due to the pandemic, it is important to reduce sickness among health workers and other healthcare providers who are essential to the COVID-19 response. In light of the ongoing pandemic, alternative approaches to the administration of influenza vaccination should be considered, including measures to minimise the risk of COVID-19 transmission.

There could be several benefits to the co-administration of possible COVID-19 vaccine booster doses with seasonal influenza vaccination campaigns, in presence of clear signs of reduced vaccine effectiveness against severe COVID-19 at least in some target groups. The infrastructure for seasonal influenza vaccination is already in place and can be modified according to the epidemiological context of COVID-19. If co-administration with influenza vaccination were chosen, adaptations would need to be made to the programmes. Risk groups for the two diseases overlap to a large part. In terms of COVID-19 vaccination, EU/EEA countries have primarily prioritised older adults, residents and personnel of long-term care facilities (LTCF), healthcare workers, social care personnel, and people with certain comorbidities [137]. As further vaccine doses become available, many EU/EEA countries are now in the stage where vaccination is offered to any adult individual irrespective of age, underlying condition, or priority group. Some countries are also offering vaccination to children aged 12 years and above [6].

The US American Committee on Immunisation Practices (ACIP) state in their recommendations that COVID-19 vaccines and other vaccines may be administered at the same time [138]. A pre-print paper on results from the phase 3 randomised trial of the safety and efficacy of NVX-CoV2373 (Novavax) shows that the safety, immunogenicity, and efficacy profile of the COVID-19 vaccine is maintained while co-administered with the seasonal influenza vaccine, with only a slight decrease in vaccine efficacy from 89.8% (95% CI: 79.7-95.5) to 87.5% (95% CI: -0.2, 98.4) [139]. Previous evidence from co-administration of other vaccines has not shown any particular safety or effectiveness concern, although mRNA vaccines have never been co-administered with other vaccines.

Measuring response to vaccination

Measuring the immune response following vaccination could be considered when selecting individuals that may need an additional vaccine dose. However, as previously discussed, there is currently no established correlate of protection against COVID-19 even at the population level. Neutralising antibodies have been suggested as possible surrogate indicators, but evidence is inconclusive.

In addition, measuring response to primary vaccine series would also pose relevant logistical challenges related to the need for testing for e.g., antibodies in all vaccinated individuals, or all individuals belonging to selected risk groups, some weeks after the completion of their primary vaccination series. Finally, there is a variety of serological tests currently available and a lack of standardisation that do not allow for comparisons.
Absence of seroconversion could instead be used in specific groups (e.g., the immunocompromised, elderly frail individuals) to inform the need for additional doses.

Previously infected individuals

Studies of single-dose regimens of Comirnaty, Spikevax, and Vaxzevria in previously infected individuals indicate that antibody and cellular immune responses are comparable to naïve individuals who complete the two-dose regimen, but data on the long-term duration of protective immunity are currently sparse [145,146].

There is also currently very limited evidence on clinical endpoints, such as the risk of laboratory-confirmed infection and symptomatic disease, for previously infected individuals receiving just one dose of a vaccine intended as a two-dose regimen [142].

Given the current evidence gaps, as a precaution, consideration should be given to the continued administration of a full-dose regimen to those individuals at greatest risk of severe outcomes following SARS-CoV-2 infection. However, no evidence currently suggests the need for a further additional dose [32].

Challenges in the documentation of a previous infection could complicate the implementation of different approaches for previously infected and naïve individuals, such as deprioritising boosters for previously infected and vaccinated individuals.

Additionally, the situation in the EU/EEA is rather complex regarding the administration of different vaccine products (including heterologous schedules), the timing of the primary series, intervals between doses, the completion of the primary series overall and by age group, and vaccination coverage overall and by age group, and it could become challenging to propose generally valid tailored approaches with the current evidence base.

Communication

When communicating with the public, a clear distinction needs to be made between (i) additional vaccinations that may be needed for some people who are either immunocompromised or older frail adults and who may therefore need an extra dose to facilitate their developing a good immune response against COVID-19, and (ii) booster shots that aim to address waning immunity or the emergence and spread of a vaccine escape variant in otherwise healthy, previously vaccinated people. While there is evidence to support the former, and, as shown in Table 1 above, this policy is now being considered by several EU/EEA countries, the synthesis presented in this report indicates that there is not yet a strong, evidence-based rationale for the latter. Clarity about the distinction between these two strategies is important as any confusion may undermine vaccination uptake, either among immunocompromised and old frail adults where the option of the extra dose should be considered, or among people in the wider population who have not yet been fully vaccinated. Previous studies, from both before and during the COVID-19 vaccine rollout, have shown that when vaccine benefits or effectiveness are perceived as limited, uptake can be sub-optimal [143,144]. Since communication relating to an additional vaccine dose may undermine people's positive perception of COVID-19 vaccine effectiveness, messages to the general public should therefore continue to highlight their effectiveness against severe disease, hospitalisation and death, including in relation to the VOCs currently circulating throughout the EU and the need to accept a primary vaccination offer if not done so yet. For immunocompromised people, community engagement strategies – such as two-way dialogue with relevant national and local support groups – can facilitate authorities' understanding of target populations' perceptions about the vaccine as well as any access challenges they may face, and this can enable them to design and implement tailored and effective health messaging [145].

Looking ahead, it is clear that both the evidence base and the epidemiological circumstances are evolving, and that some national authorities may decide to provide booster vaccinations to the wider population in the coming weeks and months. Through trusted spokespeople and using the well-established risk communication principles of consistency, transparency about uncertainty, and clarity [146], the public should in the meantime be kept informed about scientific and epidemiological developments. This will facilitate people's understanding of the rationale to amend the vaccination programme to include booster shots, should such a decision be made, which is essential if high levels of uptake are to be achieved.

Global equity and supply

With many countries still struggling to receive and administer enough doses of vaccine to their populations, consideration should be given to the current global shortage of COVID-19 vaccines that could be further worsened by the administration of additional COVID-19 vaccine doses in EU/EEA countries. The WHO recently called for a moratorium on booster shots until at least the end of September 2021 in order to improve the availability of vaccines for low- and middle-income countries [147].

Potential concerns around further viral mutations and the emergence of new VOCs in other continents are also to be considered by EU/EEA countries when choosing whether to provide additional doses to large proportions of already fully vaccinated populations, as this could further delay the primary vaccination series of eligible individuals in several non-European countries, cause additional burden globally from COVID-19, and facilitate the emergence of new VOCs.

Equity considerations within countries and within EU/EEA should also be taken into account.

Final considerations

Closing the immunity gap with the primary vaccination series (i.e. vaccinating those who have not yet completed the primary series) for all eligible individuals should remain the current priority of COVID-19 vaccination programmes in the EU/EEA.

It is important to distinguish between booster doses for people who responded adequately to vaccination and additional doses for those with weakened immune systems who did not respond adequately. Booster doses are given to vaccinated people (i.e. people who have completed a primary vaccination) to restore protection after protection would have waned. On the other hand, additional doses as part of a primary vaccination series may be given to people with severely weakened immune systems, as they may not achieve an adequate level of protection from the standard primary vaccination.

Moreover, reduced vaccine effectiveness due to waning immunity should also be differentiated from reduced vaccine effectiveness caused by vaccine-escape. Although both phenomena may be occurring simultaneously, and are therefore sometimes difficult to disentangle, they may lead to different considerations and decisions (e.g., changes in the formulation of the booster vaccine).

When assessing the need for possible booster doses of COVID-19 vaccine from the public health perspective, it is important to keep in mind the main objective of the vaccination strategy (i.e. preventing severe cases of COVID-19). Vaccine effectiveness against severe disease should preferably be chosen as primary outcome of interest for assessing when there is a clear need for an additional vaccine dose in specific groups.

The available evidence on 'real world' vaccine effectiveness and the duration of protection shows that all vaccines authorised in the EU/EEA are currently highly protective against COVID-19-related hospitalisation, severe disease, and death, suggesting no urgent need for the administration of additional doses of vaccines to fully vaccinated individuals in the general population.

The option of administering an additional vaccine dose to subjects who may experience a limited response to the primary series of COVID-19 vaccination, such as some categories of immunocompromised individuals (e.g., solid organ transplant recipients), should already be considered now. This is to be seen as an extension of the primary vaccination series for these specific groups, and not as a booster. Consideration could be given to providing as a precaution an additional dose to older frail individuals, in particular those living in closed settings (e.g., residents of long-term care facilities).

Close monitoring of vaccine effectiveness data, particularly among vulnerable groups at risk of severe COVID-19 and among those living in closed settings, should be continued, and decisions adapted accordingly, should a substantial decrease in effectiveness be noted in one or more population groups.

Full vaccination against COVID-19 of all family contacts and close contacts, including professionals providing care, of immunocompromised and vulnerable individuals should also be considered.

When in contact with individuals at risk of severe disease, physical distancing (when applicable), the wearing of face masks (especially when physical distancing cannot be kept), and hand and respiratory hygiene remain pivotal measures for reducing the risk of SARS-CoV-2 transmission. These non-pharmaceutical interventions should always complement vaccination, particularly in high-risk settings such as long-term care facilities or hospital wards with patients at risk of severe COVID-19.

More solid data are needed to inform future policies on booster doses. Knowledge gaps are particularly related to the appropriate correlate of protection to consider for the different population groups and time from primary vaccination series, and duration of immunity according to e.g. different age and risk groups, vaccine product, dosing interval, VOC, and homologous/heterologous schedule. Prospective vaccine effectiveness studies, as well as surveillance of breakthrough infections in the general population and in specific groups, are needed to answer these questions.

The benefits and risks of booster doses need to be clearly outlined and compared. Benefits may include increased protection against severe disease, moderate disease, post COVID-19 condition (often called 'long COVID'), SARS-CoV-2 infection, and virus transmission. Risks include possible safety concerns and public health implications (e.g., the impact on vaccine confidence and uptake, global availability of vaccines).

Data on the co-administration of COVID-19 vaccines and vaccines against other diseases (e.g., influenza) are currently limited, although no safety or reduced effectiveness concern has emerged from co-administration of other vaccines to date.

Safety data on COVID-19 vaccine booster doses are currently limited. Possible dose-related adverse events associated with vaccination could be elicited by additional vaccine doses. In case of the administration of booster doses, close post-authorisation monitoring of potential adverse events should be performed as rare adverse events

are unlikely to be captured by pre-authorisation studies. An appropriate dosage for boosters should be determined ahead of authorisation for each vaccine product.

A strategy for monitoring the safety and effectiveness of heterologous boosting will need to be prepared as it may not be possible to gather these data from pre-licensing studies.

For decision-making, it will be critical to identify the moment when offering a booster dose to specific target groups will become preferable over the goal of reaching all eligible people with primary vaccination series. This decision could be based on several factors, e.g. challenges in reaching unvaccinated pockets of the population with diminishing returns in terms of vaccine coverage, demonstrated decreased vaccine effectiveness against severe disease in specific groups or overall.

Communication about possible additional vaccine doses should be carefully pondered and delivered in a transparent, proactive and clear way to avoid any consequence on vaccine confidence. The distinction between strengthening the response to primary vaccination series, in e.g. immunocompromised individuals, and boosters for waning immune response or vaccine escape, should be clearly made.

In the context of many countries outside of the EU/EEA still struggling to receive and administer enough doses of vaccine to their populations, special consideration should be given to the current global shortage of COVID-19 vaccines that could be further worsened by the administration of additional COVID-19 vaccine doses in the EU/EEA countries.

Knowledge gaps

- Absence of an established correlate of protection for assessing if and when a vaccine booster against COVID-19 is needed.
- Limited data on vaccine effectiveness against different outcomes caused by the circulating SARS-CoV-2 variants (e.g., Delta VOC) for each risk group.
- Scarce information on COVID-19 vaccine efficacy, immunogenicity, and safety of heterologous boosting overall and by risk group.
- Limited evidence of vaccine effectiveness against transmission of the Delta VOC.
- No currently available data on COVID-19 vaccine efficacy, immunogenicity and safety data on booster doses including fractional doses.
- No available information on COVID-19 vaccine efficacy, immunogenicity, safety and benefit-risk data in children.
- Limited evidence of post COVID-19 condition (also called 'long COVID-19') after an infection following vaccination.
- Limited information from surveillance systems on characterisation of breakthrough infection and reinfection cases.
- Limited knowledge about seroprevalence and population immunity after the COVID-19 vaccine roll-out in the EU/EEA.

Contributing and consulted experts

ECDC experts (in alphabetical order): Kim Brolin, Christiana Carstairs, Orlando Cenciarelli, Edoardo Colzani, Theresa Enkirch, Luca Freschi, John Kinsman, Csaba Ködmön, Angeliki Melidou, Kate Olsson, Lucia Pastore Celentano, Pasi Penttinen, Giovanni Ravasi, Gabrielle Schittecatte, Natalie Sippl

External experts: Marco Cavaleri (EMA)

Disclaimer

All data published in this document are correct to the best of our knowledge at the time of publication.

All external experts have submitted declarations of interest, and a review of these declarations did not reveal any conflicts of interest.

References

1. European Centre for Disease Prevention and Control (ECDC). COVID-19 country overviews. Stockholm: ECDC; 2021. Available at: https://covid19-country-overviews.ecdc.europa.eu/#Weekly_surveillance_summary
2. Mizrahi B, Lotan R, Kalkstein N, Peretz A, Perez G, Ben-Tov A, et al. Correlation of SARS-CoV-2 Breakthrough Infections to Time-from-vaccine; Preliminary Study. medRxiv [Preprint]. 2021. DOI: 10.1101/2021.07.29.21261317. Available at: https://www.medrxiv.org/content/10.1101/2021.07.29.21261317v1
3. Rosenberg ES, Holtgrave DR, Dorabawila V, Conroy M, Greene D, Lutterloh E, et al. New COVID-19 Cases and Hospitalizations Among Adults, by Vaccination Status — New York, May 3–July 25, 2021. MMWR Morb Mortal Wkly Rep [Preprint]. 2021. DOI: 10.15585/mmwr.mm7034e1. Available at: https://www.cdc.gov/mmwr/volumes/70/wr/mm7034e1.htm?s_cid=mm7034e1_w
4. Public Health England (PHE). COVID-19 vaccine surveillance report - Week 33. London: PHE; 2021. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1012420/Vaccine_surveillance_report_-_week_33.pdf
5. Istituto Superiore di Sanità and Ministry of Health, Italy. Impact of COVID-19 vaccination on the risk of SARS-CoV-2 infection and hospitalization and death in Italy (27.12.2020 - 14.07.2021). English version of the ISS report. Rome: ISS and MoH; 2021. Available at: https://www.iss.it/documents/5430402/0/ISS+report+Impact+of+COVID-19+vaccination+EN.pdf
6. European Centre for Disease Prevention and Control (ECDC). The COVID-19 Vaccine Tracker. Stockholm: ECDC; 2021. Available at: https://vaccinetracker.ecdc.europa.eu/public/extensions/COVID-19/vaccinetracker.html#uptake-tab
7. European Centre for Disease Prevention and Control (ECDC). COVID-19 Vaccine rollout overview. Stockholm: ECDC; 2021. Available at: https://covid19-vaccine-report.ecdc.europa.eu
8. European Centre for Disease Prevention and Control (ECDC). SARS-CoV-2 variants of concern as of 16 August 2021. Stockholm: ECDC; 2021. Available at: https://www.ecdc.europa.eu/en/covid-19/variants-concern
9. European Centre for Disease Prevention and Control (ECDC). Threat Assessment Brief: Emergence of SARS-CoV-2 B.1.617 variants in India and situation in the EU/EEA. Stockholm: ECDC; 2021. Available at: https://www.ecdc.europa.eu/en/publications-data/threat-assessment-emergence-sars-cov-2-b1617-variants
10. Sheikh A, McMenamin J, Taylor B, Robertson C. SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness. Lancet. 2021;397(10293):2461-2. Available at: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)01358-1/fulltext
11. Fisman DN, Tuite AR. Progressive Increase in Virulence of Novel SARS-CoV-2 Variants in Ontario, Canada. medRxiv [Preprint]. 2021. DOI: 10.1101/2021.07.05.21260050. Available at: https://www.medrxiv.org/content/10.1101/2021.07.05.21260050v3
12. Public Health England (PHE). SARS-CoV-2 variants of concern and variants under investigation in England - Technical briefing 13. London: PHE; 2021. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/990339/Variants_of_Concern_VOC_Technical_Briefing_13_England.pdf
13. Li B, Deng A, Li K, Hu Y, Li Z, Xiong Q, et al. Viral infection and transmission in a large, well-traced outbreak caused by the SARS-CoV-2 Delta variant. medRxiv [Preprint]. 2021. DOI: 10.1101/2021.07.07.21260122. Available at: https://www.medrxiv.org/content/10.1101/2021.07.07.21260122v2
14. Tang P, Hasan MR, Chemaitelly H, Yassine HM, Benslimane FM, Khatib HAA, et al. BNT162b2 and mRNA-1273 COVID-19 vaccine effectiveness against the Delta (B.1.617.2) variant in Qatar. medRxiv [Preprint]. 2021. DOI: 10.1101/2021.08.11.21261885. Available at: https://www.medrxiv.org/content/10.1101/2021.08.11.21261885v1
15. Riemersma KK, Grogan BE, Kita-Yarbro A, Halfmann P, Kocharian A, Florek KR, et al. Shedding of Infectious SARS-CoV-2 Despite Vaccination when the Delta Variant is Prevalent - Wisconsin, July 2021. medRxiv [Preprint]. 2021. DOI: 10.1101/2021.07.31.21261387. Available at: https://www.medrxiv.org/content/10.1101/2021.07.31.21261387v3
16. Acevedo ML, Alonso-Palomares L, Bustamante A, Gaggero A, Paredes F, Cortés CP, et al. Infectivity and immune escape of the new SARS-CoV-2 variant of interest Lambda. medRxiv [Preprint]. 2021. DOI: 10.1101/2021.06.28.21259673. Available at: https://www.medrxiv.org/content/10.1101/2021.06.28.21259673v1
17. Tada T, Zhou H, Dcosta BM, Samanovic MI, Mulligan MJ, Landau NR. SARS-CoV-2 Lambda Variant Remains Susceptible to Neutralization by mRNA Vaccine-elicited Antibodies and Convalescent Serum. bioRxiv [Preprint]. 2021. DOI: 10.1101/2021.07.02.450959. Available at: https://www.biorxiv.org/content/10.1101/2021.07.02.450959v1
18. Kimura I, Kosugi Y, Wu J, Yamasoba D, Butlertanaka EP, Tanaka YL, et al. SARS-CoV-2 Lambda variant exhibits higher infectivity and immune resistance. bioRxiv [Preprint]. 2021. DOI:

10.1101/2021.07.28.454085. Available at: https://www.biorxiv.org/content/10.1101/2021.07.28.454085v1.full
19. Carreño JM, Alshammary H, Singh G, Raskin A, Amanat F, Amoako A, et al. Reduced neutralizing activity of post-SARS-CoV-2 vaccination serum against variants B.1.617.2, B.1.351, B.1.1.7+E484K and a sub-variant of C.37. medRxiv [Preprint]. 2021. DOI: 10.1101/2021.07.21.21260961. Available at: https://www.medrxiv.org/content/10.1101/2021.07.21.21260961v1
20. World Health Organization (WHO). Tracking SARS-CoV-2 variants. Geneva: WHO; 2021. Available at: https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/
21. Laiton-Donato K, Franco-Munoz C, Alvarez-Diaz DA, Ruiz-Moreno HA, Usme-Ciro JA, Prada DA, et al. Characterization of the emerging B.1.621 variant of interest of SARS-CoV-2. Infect Genet Evol [Preprint]. 2021. DOI: 10.1016/j.meegid.2021.105038. Available at: https://www.sciencedirect.com/science/article/pii/S1567134821003361
22. Public Health England (PHE). SARS-CoV-2 variants of concern and variants under investigation in England - Technical Briefing 20. London: PHE; 2021. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1009243/Technical_Briefing_20.pdf
23. Jangra S, Ye C, Rathnasinghe R, Stadlbauer D, Personalized Virology Initiative study g, Krammer F, et al. SARS-CoV-2 spike E484K mutation reduces antibody neutralisation. Lancet Microbe. 2021;2(7):e283-e4. Available at: https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(21)00068-9/fulltext
24. Greaney AJ, Starr TN, Barnes CO, Weisblum Y, Schmidt F, Caskey M, et al. Mapping mutations to the SARS-CoV-2 RBD that escape binding by different classes of antibodies. Nat Commun. 2021;12(1):4196. Available at: https://www.nature.com/articles/s41467-021-24435-8
25. Hu J, Peng P, Wang K, Fang L, Luo FY, Jin AS, et al. Emerging SARS-CoV-2 variants reduce neutralization sensitivity to convalescent sera and monoclonal antibodies. Cell Mol Immunol. 2021;18(4):1061-3. Available at: https://www.nature.com/articles/s41423-021-00648-1
26. Messali S, Bertelli A, Campisi G, Zani A, Ciccozzi M, Caruso A, et al. A cluster of the new SARS-CoV-2 B.1.621 lineage in Italy and sensitivity of the viral isolate to the BNT162b2 vaccine. J Med Virol. 2021 Available at: https://onlinelibrary.wiley.com/doi/10.1002/jmv.27247
27. The International Vaccine Access Center (IVAC), Johns Hopkins Bloomberg School of Public Health. VIEW-hub. 2021. Available at: https://view-hub.org/resources
28. International Vaccine Access Center, Johns Hopkins Bloomberg School of Public Health and World Health Organization (WHO). Results of COVID-19 Vaccine Effectiveness & Impact Studies: An Ongoing Systematic Review - Methods. 2021. Available at: https://view-hub.org/sites/default/files/2021-07/COVID19%20VE%20%26%20Impact%20Lit%20Review%20Methods.pdf
29. International Vaccine Access Center, Johns Hopkins Bloomberg School of Public Health and World Health Organization (WHO). Results of COVID-19 Vaccine Effectiveness Studies: An Ongoing Systematic Review - Weekly Summary Tables2021. Available at: https://view-hub.org/sites/default/files/2021-08/COVID19%20Vaccine%20Effectiveness%20Transmission%20%20Impact%20Studies%20-%20Summary%20Tables_20210812.pdf
30. International Vaccine Access Center, Johns Hopkins Bloomberg School of Public Health and World Health Organization (WHO). Results of COVID-19 Vaccine Effectiveness Studies: An Ongoing Systematic Review - Forest Plots2021. Available at: https://view-hub.org/sites/default/files/2021-08/COVID19%20VE%20Studies_Forest%20Plots_0.pdf
31. Coronavirus Variants Rapid Response Network. COVID-19 Living Evidence - Synthesis #6. Ontario: McMaster University; 2021. Available at: https://www.mcmasterforum.org/docs/default-source/product-documents/living-evidence-syntheses/covid-19-living-evidence-synthesis-6.15---what-is-the-efficacy-and-effectiveness-of-available-covid-19-vaccines-in-general-and-specifically-for-variants-of-concern.pdf?sfvrsn=9584d3d8_5
32. European Centre for Disease Prevention and Control (ECDC). Partial COVID-19 vaccination, vaccination following SARS-CoV-2 infection and heterologous vaccination schedule: summary of evidence. Stockholm: ECDC; 2021. Available at: https://www.ecdc.europa.eu/en/publications-data/partial-covid-19-vaccination-summary
33. Harder T, Koch J, Vygen-Bonnet S, Külper-Schiek W, Pilic A, Reda S, et al. Efficacy and effectiveness of COVID-19 vaccines against SARS-CoV-2 infection: interim results of a living systematic review, 1 January to 14 May 2021. Euro Surveill. 2021;26(28):2100563. Available at: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2021.26.28.2100563
34. Abu-Raddad LJ, Chemaitelly H, Butt AA. Effectiveness of the BNT162b2 Covid-19 Vaccine against the B.1.1.7 and B.1.351 Variants. N Engl J Med. 2021;385(2):187-9. Available at: https://www.nejm.org/doi/full/10.1056/NEJMc2104974
35. Nasreen S, Chung H, He S, Brown KA, Gubbay JB, Buchan SA, et al. Effectiveness of COVID-19 vaccines against variants of concern in Ontario, Canada. medRxiv [Preprint]. 2021. DOI: 10.1101/2021.06.28.21259420. Available at: https://www.medrxiv.org/content/10.1101/2021.06.28.21259420v2

36. Lopez Bernal J, Andrews N, Gower C, Gallagher E, Simmons R, Thelwall S, et al. Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. N Engl J Med. 2021;385(7):585-94. Available at: https://www.nejm.org/doi/10.1056/NEJMoa2108891
37. Stowe J, Andrews N, Gower C, Gallagher E, Utsi L, Simmons R, et al. Effectiveness of COVID-19 vaccines against hospital admission with the Delta (B.1.617.2) variant. kHub [Preprint]. 2021. Available at: https://khub.net/documents/135939561/479607266/Effectiveness+of+COVID-19+vaccines+against+hospital+admission+with+the+Delta+%28B.1.617.2%29+variant.pdf/1c213463-3997-ed16-2a6f-14e5deb0b997?t=1623689315431
38. Tenforde MW, Patel MM, Ginde AA, Douin DJ, Talbot HK, Casey JD, et al. Effectiveness of SARS-CoV-2 mRNA Vaccines for Preventing Covid-19 Hospitalizations in the United States. Clinical Infectious Diseases [Preprint]. 2021. DOI: 10.1093/cid/ciab687. Available at: https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab687/6343399
39. Elliott P, Haw D, Wang H, Eales O, Walters C, Ainslie K, et al. REACT-1 round 13 final report: exponential growth, high prevalence of SARS-CoV-2 and vaccine effectiveness associated with Delta variant in England during May to July 20212021. Available at: https://spiral.imperial.ac.uk/bitstream/10044/1/90800/2/react1_r13_final_preprint_final.pdf
40. Nuffield Department of Medicine - University of Oxford. Impact of Delta on viral burden and vaccine effectiveness against new SARS-CoV-2 infections in the UK. Oxford: NDM; 2021. Available at: https://www.ndm.ox.ac.uk/covid-19/covid-19-infection-survey/results/new-studies
41. Puranik A, Lenehan PJ, Silvert E, Niesen MJM, Corchado-Garcia J, O'Horo JC, et al. Comparison of two highly-effective mRNA vaccines for COVID-19 during periods of Alpha and Delta variant prevalence. medRxiv [Preprint]. 2021. DOI: 10.1101/2021.08.06.21261707. Available at: https://www.medrxiv.org/content/10.1101/2021.08.06.21261707v2
42. Tenforde MW, Self WH, Naioti EA, Ginde AA, Douin DJ, Olson SM, et al. Sustained Effectiveness of Pfizer-BioNTech and Moderna Vaccines Against COVID-19 Associated Hospitalizations Among Adults - United States, March–July 2021. MMWR Morb Mortal Wkly Rep [Preprint]. 2021. DOI: 10.15585/mmwr.mm7034e2. Available at: https://www.cdc.gov/mmwr/volumes/70/wr/mm7034e2.htm?s_cid=mm7034e2_w
43. Statens Serum Institute (SSI). Der er fortsat høj vaccineeffektivitet for covid-19-vaccinerne. Copenaghen: SSI; 2021. Available at: https://www.ssi.dk/aktuelt/nyheder/2021/der-er-fortsat-hoj-vaccineeffektivitet-for-covid-19-vaccinerne
44. Goldberg Y, Mandel M, Bar-On YM, Bodenheimer O, Freedman L, Haas EJ, et al. Waning immunity of the BNT162b2 vaccine: A nationwide study from Israel. [Preprint]. 2021. Available at: https://www.gov.il/BlobFolder/reports/vaccine-efficacy-safety-follow-up-committee/he/files_publications_corona_immunity-waning-082021.pdf
45. European Centre for Disease Prevention and Control (ECDC). COVID-19 outbreaks in long-term care facilities in the EU/EEA in the context of current vaccination coverage. Stockholm: ECDC; 2021. Available at: https://www.ecdc.europa.eu/en/publications-data/rapid-risk-assessment-covid-19-outbreaks-long-term-care-facilities-eueea
46. Emborg H-D, Valentiner-Branth P, Schelde AB, Nielsen KF, Gram MA, Moustsen-Helms IR, et al. Vaccine effectiveness of the BNT162b2 mRNA COVID-19 vaccine against RT-PCR confirmed SARS-CoV-2 infections, hospitalisations and mortality in prioritised risk groups. medRxiv [Preprint]. 2021. DOI: 10.1101/2021.05.27.21257583. Available at: https://www.medrxiv.org/content/10.1101/2021.05.27.21257583v1
47. Cabezas C, Coma E, Mora-Fernandez N, Li X, Martinez-Marcos M, Fina-Aviles F, et al. Effects of BNT162b2 mRNA Vaccination on COVID-19 Disease, Hospitalisation and Mortality in Nursing Homes and Healthcare Workers: A Prospective Cohort Study Including 28,594 Nursing Home Residents, 26,238 Nursing Home Staff, and 61,951 Healthcare Workers in Catalonia. Preprints with The Lancet [Preprint]. 2021. DOI: 10.2139/ssrn.3815682. Available at: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3815682
48. Mazagatos C, Monge S, Olmedo C, Vega L, Gallego P, Martin-Merino E, et al. Effectiveness of mRNA COVID-19 vaccines in preventing SARS-CoV-2 infections and COVID-19 hospitalisations and deaths in elderly long-term care facility residents, Spain, weeks 53 2020 to 13 2021. Euro Surveill. 2021;26(24):pii=2100452. Available at: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2021.26.24.2100452
49. Moustsen-Helms IR, Emborg H-D, Nielsen J, Nielsen KF, Krause TG, Mølbak K, et al. Vaccine effectiveness after 1st and 2nd dose of the BNT162b2 mRNA Covid-19 Vaccine in long-term care facility residents and healthcare workers – a Danish cohort study. medRxiv [Preprint]. 2021. DOI: 10.1101/2021.03.08.21252200. Available at: https://www.medrxiv.org/content/10.1101/2021.03.08.21252200v1
50. Monge S, Olmedo C, Alejos B, Lapeña MF, Sierra MJ, Limia A, et al. Direct and indirect effectiveness of mRNA vaccination against SARS-CoV-2 infection in long-term care facilities in Spain. medRxiv [Preprint]. 2021. DOI: 10.1101/2021.04.08.21255055. Available at: https://www.medrxiv.org/content/10.1101/2021.04.08.21255055v2
51. Britton A, Jacobs Slifka KM, Edens C, Nanduri SA, Bart SM, Shang N, et al. Effectiveness of the Pfizer-BioNTech COVID-19 Vaccine Among Residents of Two Skilled Nursing Facilities Experiencing COVID-19

Outbreaks - Connecticut, December 2020-February 2021. MMWR Morb Mortal Wkly Rep. 2021;70(11):396-401. Available at: https://www.cdc.gov/mmwr/volumes/70/wr/mm7011e3.htm

52. Lefèvre B, Tondeur L, Madec Y, Grant R, Lina B, van der Werf S, et al. Impact of B.1.351 (beta) SARS-CoV-2 variant on BNT162b2 mRNA vaccine effectiveness in long-term care facilities of eastern France: a retrospective cohort study. medRxiv [Preprint]. 2021. DOI: 10.1101/2021.07.28.21261285. Available at: https://www.medrxiv.org/content/10.1101/2021.07.28.21261285v1
53. Williams C, Al-Bargash D, Macalintal C, Stuart R, Seth A, Latham J, et al. COVID-19 Outbreak Associated with a SARS-CoV-2 P.1 Lineage in a Long-Term Care Home after Implementation of a Vaccination Program - Ontario, April-May 2021. Clin Infect Dis [Preprint]. 2021. DOI: 10.1093/cid/ciab617. Available at: https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab617/6317716
54. Nanduri S, Pilishvili T, Derado G, Soe MM, Dollard P, Wu H, et al. Effectiveness of Pfizer-BioNTech and Moderna Vaccines in Preventing SARS-CoV-2 Infection Among Nursing Home Residents Before and During Widespread Circulation of the SARS-CoV-2 B.1.617.2 (Delta) Variant — National Healthcare Safety Network, March 1–August 1, 2021. MMWR Morb Mortal Wkly Rep [Preprint]. 2021. DOI: 10.15585/mmwr.mm7034e3. Available at: https://www.cdc.gov/mmwr/volumes/70/wr/mm7034e3.htm?s_cid=mm7034e3_w
55. Public Health England (PHE). COVID-19 vaccine surveillance report - Week 20. London: PHE; 2021. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/990089/Vaccine_surveillance_report_-_week_20.pdf
56. Kissling E, Hooiveld M, Sandonis Martin V, Martinez-Baz I, William N, Vilcu AM, et al. Vaccine effectiveness against symptomatic SARS-CoV-2 infection in adults aged 65 years and older in primary care: I-MOVE-COVID-19 project, Europe, December 2020 to May 2021. Euro Surveill. 2021;26(29):pii=2100670. Available at: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2021.26.29.2100670
57. Martinez-Baz I, Miqueleiz A, Casado I, Navascues A, Trobajo-Sanmartin C, Burgui C, et al. Effectiveness of COVID-19 vaccines in preventing SARS-CoV-2 infection and hospitalisation, Navarre, Spain, January to April 2021. Euro Surveill. 2021;26(21):pii=2100438. Available at: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2021.26.21.2100438
58. Baum U, Poukka E, Palmu AA, Salo H, Lehtonen TO, Leino T. Effectiveness of vaccination against SARS-CoV-2 infection and Covid-19 hospitalization among Finnish elderly and chronically ill – An interim analysis of a nationwide cohort study. medRxiv [Preprint]. 2021. DOI: 10.1101/2021.06.21.21258686. Available at: https://www.medrxiv.org/content/10.1101/2021.06.21.21258686v1
59. Tenforde MW, Olson SM, Self WH, Talbot HK, Lindsell CJ, Steingrub JS, et al. Effectiveness of Pfizer-BioNTech and Moderna Vaccines Against COVID-19 Among Hospitalized Adults Aged >/=65 Years - United States, January-March 2021. MMWR Morb Mortal Wkly Rep. 2021;70(18):674-9. Available at: https://www.cdc.gov/mmwr/volumes/70/wr/mm7018e1.htm?s_cid=mm7018e1_x
60. Public Health England. PHE monitoring of the early impact and effectiveness of COVID-19 vaccination in England London: PHE; 2021. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/968977/COVID-19_vaccine_effectiveness_surveillance_report_February_2021.pdf
61. Mason T, Whitston M, Hodgson J, Watkinson RE, Lau Y-S, Abdulrazeg O, et al. Effects of BNT162b2 mRNA vaccine on Covid-19 infection and hospitalisation among older people: matched case control study for England. medRxiv [Preprint]. 2021. DOI: 10.1101/2021.04.19.21255461. Available at: https://www.medrxiv.org/content/10.1101/2021.04.19.21255461v1
62. Goldberg Y, Mandel M, Woodbridge Y, Fluss R, Novikov I, Yaari R, et al. Protection of previous SARS-CoV-2 infection is similar to that of BNT162b2 vaccine protection: A three-month nationwide experience from Israel. medRxiv [Preprint]. 2021. DOI: 10.1101/2021.04.20.21255670. Available at: https://www.medrxiv.org/content/10.1101/2021.04.20.21255670v1
63. Ranzani OT, Hitchings MDT, Dorion M, D'Agostini TL, Cardoso de Paula R, Pereira de Paula OF, et al. Effectiveness of the CoronaVac vaccine in the elderly population during a Gamma variant-associated epidemic of COVID-19 in Brazil: A test-negative case-control study. medRxiv [Preprint]. 2021. DOI: 10.1101/2021.05.19.21257472. Available at: https://www.medrxiv.org/content/10.1101/2021.05.19.21257472v3
64. Khan N, Mahmud N. Effectiveness of SARS-CoV-2 Vaccination in a Veterans Affairs Cohort of Patients With Inflammatory Bowel Disease With Diverse Exposure to Immunosuppressive Medications. Gastroenterology. 2021;161(3):827-36. Available at: https://linkinghub.elsevier.com/retrieve/pii/S0016-5085(21)03066-3
65. Chemaitelly H, AlMukdad S, Joy JP, Ayoub HH, Yassine HM, Benslimane FM, et al. SARS-CoV-2 vaccine effectiveness in immunosuppressed kidney transplant recipients. medRxiv [Preprint]. 2021. DOI: 10.1101/2021.08.07.21261578. Available at: https://www.medrxiv.org/content/10.1101/2021.08.07.21261578v1
66. Chodick G, Tene L, Rotem RS, Patalon T, Gazit S, Ben-Tov A, et al. The effectiveness of the TWO-DOSE BNT162b2 vaccine: analysis of real-world data. Clin Infect Dis [Preprint]. 2021. DOI: 10.1093/cid/ciab438. Available at: https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab438/6276888
67. Brosh-Nissimov T, Orenbuch-Harroch E, Chowers M, Elbaz M, Nesher L, Stein M, et al. BNT162b2 vaccine breakthrough: clinical characteristics of 152 fully vaccinated hospitalized COVID-19 patients in Israel. Clin

Microbiol Infect [Preprint]. 2021. DOI: 10.1016/j.cmi.2021.06.036. Available at: https://www.sciencedirect.com/science/article/pii/S1198743X21003670
68. Boyarsky BJ, Ruddy JA, Connolly CM, Ou MT, Werbel WA, Garonzik-Wang JM, et al. Antibody response to a single dose of SARS-CoV-2 mRNA vaccine in patients with rheumatic and musculoskeletal diseases. Ann Rheum Dis [Preprint]. 2021. DOI: 10.1136/annrheumdis-2021-220289. Available at: https://ard.bmj.com/content/80/8/1098.long
69. Boyarsky BJ, Werbel WA, Avery RK, Tobian AAR, Massie AB, Segev DL, et al. Antibody Response to 2-Dose SARS-CoV-2 mRNA Vaccine Series in Solid Organ Transplant Recipients. JAMA. 2021;325(21):2204-6. Available at: https://jamanetwork.com/journals/jama/fullarticle/2779852
70. Chavarot N, Ouedrani A, Marion O, Leruez-Ville M, Villain E, Baaziz M, et al. Poor Anti-SARS-CoV-2 Humoral and T-cell Responses After 2 Injections of mRNA Vaccine in Kidney Transplant Recipients Treated with Belatacept. Transplantation [Preprint]. 2021. DOI: 10.1097/TP.0000000000003784. Available at: https://journals.lww.com/transplantjournal/_layouts/15/oaks.journals/PageNotFound.aspx
71. Rozen-Zvi B, Yahav D, Agur T, Zingerman B, Ben-Zvi H, Atamna A, et al. Antibody response to SARS-CoV-2 mRNA vaccine among kidney transplant recipients: a prospective cohort study. Clin Microbiol Infect. 2021;27(8):1173 e1-e4. Available at: https://www.sciencedirect.com/science/article/pii/S1198743X21002160?via%3Dihub
72. Grupper A, Katchman H. Reduced humoral response to mRNA SARS-CoV-2 BNT162b2 vaccine in kidney transplant recipients without prior exposure to the virus: Not alarming, but should be taken gravely. Am J Transplant. 2021 Aug;21(8):2909. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34080285
73. Itzhaki Ben Zadok O, Shaul AA, Ben-Avraham B, Yaari V, Ben Zvi H, Shostak Y, et al. Immunogenicity of the BNT162b2 mRNA vaccine in heart transplant recipients - a prospective cohort study. Eur J Heart Fail [Preprint]. 2021. DOI: 10.1002/ejhf.2199. Available at: https://onlinelibrary.wiley.com/doi/abs/10.1002/ejhf.2199
74. Rabinowich L, Grupper A, Baruch R, Ben-Yehoyada M, Halperin T, Turner D, et al. Low immunogenicity to SARS-CoV-2 vaccination among liver transplant recipients. J Hepatol. 2021;75(2):435-8. Available at: https://www.sciencedirect.com/science/article/pii/S0168827821002555
75. Monin L, Laing AG, Munoz-Ruiz M, McKenzie DR, Del Molino Del Barrio I, Alaguthurai T, et al. Safety and immunogenicity of one versus two doses of the COVID-19 vaccine BNT162b2 for patients with cancer: interim analysis of a prospective observational study. Lancet Oncol. 2021;22(6):765-78. Available at: https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(21)00213-8/fulltext
76. Herishanu Y, Avivi I, Aharon A, Shefer G, Levi S, Bronstein Y, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia. Blood. 2021;137(23):3165-73. Available at: https://ashpublications.org/blood/article/137/23/3165/475742/Efficacy-of-the-BNT162b2-mRNA-COVID-19-vaccine-in
77. Nault L, Marchitto L, Goyette G, Tremblay-Sher D, Fortin C, Martel-Laferrière V, et al. Covid-19 vaccine immunogenicity in people living with HIV-1. bioRxiv [Preprint]. 2021. DOI: 10.1101/2021.08.13.456258. Available at: https://www.biorxiv.org/content/10.1101/2021.08.13.456258v1
78. Ducloux D, Colladant M, Chabannes M, Yannaraki M, Courivaud C. Humoral response after 3 doses of the BNT162b2 mRNA COVID-19 vaccine in patients on hemodialysis. Kidney Int [Preprint]. 2021. DOI: 10.1016/j.kint.2021.06.025. Available at: https://www.sciencedirect.com/science/article/pii/S0085253821006554
79. Espi M, Charmetant X, Barba T, Pelletier C, Koppe L, Chalencon E, et al. Justification, safety, and efficacy of a third dose of mRNA vaccine in maintenance hemodialysis patients: a prospective observational study. medRxiv [Preprint]. 2021. DOI: 10.1101/2021.07.02.21259913. Available at: https://www.medrxiv.org/content/10.1101/2021.07.02.21259913v1
80. Kamar N, Abravanel F, Marion O, Couat C, Izopet J, Del Bello A. Three Doses of an mRNA Covid-19 Vaccine in Solid-Organ Transplant Recipients. N Engl J Med. 2021;385(7):661-2. Available at: https://www.nejm.org/doi/10.1056/NEJMc2108861
81. Longlune N, Nogier MB, Miedouge M, Gabilan C, Cartou C, Seigneuric B, et al. High immunogenicity of a messenger RNA based vaccine against SARS-CoV-2 in chronic dialysis patients. Nephrol Dial Transplant [Preprint]. 2021. DOI: 10.1093/ndt/gfab193. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34057463
82. Werbel WA, Boyarsky BJ, Ou MT, Massie AB, Tobian AAR, Garonzik-Wang JM, et al. Safety and Immunogenicity of a Third Dose of SARS-CoV-2 Vaccine in Solid Organ Transplant Recipients: A Case Series. Ann Intern Med. 2021 Available at: https://www.acpjournals.org/doi/full/10.7326/L21-0282
83. Marks M, Millat-Martinez P, Ouchi D, Roberts CH, Alemany A, Corbacho-Monne M, et al. Transmission of COVID-19 in 282 clusters in Catalonia, Spain: a cohort study. Lancet Infect Dis. 2021;21(5):629-36. Available at: https://www.sciencedirect.com/science/article/pii/S1473309920309853
84. Levine-Tiefenbrun M, Yelin I, Katz R, Herzel E, Golan Z, Schreiber L, et al. Initial report of decreased SARS-CoV-2 viral load after inoculation with the BNT162b2 vaccine. Nat Med. 2021;27(5):790-2. Available at: https://www.nature.com/articles/s41591-021-01316-7
85. McEllistrem MC, Clancy CJ, Buehrle DJ, Lucas A, Decker BK. Single dose of a mRNA SARS-CoV-2 vaccine is associated with lower nasopharyngeal viral load among nursing home residents with asymptomatic COVID-

19. Clin Infect Dis [Preprint]. 2021. DOI: doi.org/10.1093/cid/ciab263. Available at: https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab263/6188727
86. Petter E, Mor O, Zuckerman N, Oz-Levi D, Younger A, Aran D, et al. Initial real world evidence for lower viral load of individuals who have been vaccinated by BNT162b2. medRxiv [Preprint]. 2021. DOI: 10.1101/2021.02.08.21251329. Available at: https://www.medrxiv.org/content/10.1101/2021.02.08.21251329v1
87. Chia PY, Ong SWX, Chiew CJ, Ang LW, Chavatte J-M, Mak T-M, et al. Virological and serological kinetics of SARS-CoV-2 Delta variant vaccine-breakthrough infections: a multi-center cohort study. medRxiv [Preprint]. 2021. DOI: 10.1101/2021.07.28.21261295. Available at: https://www.medrxiv.org/content/10.1101/2021.07.28.21261295v1
88. Salo J, Hägg M, Kortelainen M, Leino T, Saxell T, Siikanen M, et al. The indirect effect of mRNA-based Covid-19 vaccination on unvaccinated household members. medRxiv [Preprint]. 2021. DOI: 10.1101/2021.05.27.21257896. Available at: https://www.medrxiv.org/content/10.1101/2021.05.27.21257896v2
89. V Shah AS, Gribben C, Bishop J, Hanlon P, Caldwell D, Wood R, et al. Effect of vaccination on transmission of COVID-19: an observational study in healthcare workers and their households. medRxiv [Preprint]. 2021. DOI: 10.1101/2021.03.11.21253275. Available at: https://www.medrxiv.org/content/10.1101/2021.03.11.21253275v1
90. Harris RJ, Hall JA, Zaidi A, Andrews NJ, Dunbar JK, Dabrera G. Effect of Vaccination on Household Transmission of SARS-CoV-2 in England. New England Journal of Medicine. 2021;385:759-60. Available at: https://www.nejm.org/doi/full/10.1056/NEJMc2107717
91. Prunas O, Warren JL, Crawford FW, Gazit S, Patalon T, Weinberger DM, et al. Vaccination with BNT162b2 reduces transmission of SARS-CoV-2 to household contacts in Israel. medRxiv [Preprint]. 2021. DOI: 10.1101/2021.07.13.21260393. Available at: https://www.medrxiv.org/content/10.1101/2021.07.13.21260393v1
92. de Gier B, Andeweg S, Joosten R, ter Schegget R, Smorenburg N, van de Kassteele J, et al. Vaccine effectiveness against SARS-CoV-2 transmission and infections among household and other close contacts of confirmed cases, the Netherlands, February to May 2021. Euro Surveill. 2021;26(31):2100640. Available at: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2021.26.31.2100640
93. Earle KA, Ambrosino DM, Fiore-Gartland A, Goldblatt D, Gilbert PB, Siber GR, et al. Evidence for antibody as a protective correlate for COVID-19 vaccines. Vaccine. 2021;39(32):4423-8. Available at: https://www.sciencedirect.com/science/article/pii/S0264410X21006587
94. Khoury DS, Cromer D, Reynaldi A, Schlub TE, Wheatley AK, Juno JA, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. Nat Med. 2021;27(7):1205-11. Available at: https://www.nature.com/articles/s41591-021-01377-8
95. Gilbert PB, Montefiori DC, McDermott A, Fong Y, Benkeser DC, Deng W, et al. Immune Correlates Analysis of the mRNA-1273 COVID-19 Vaccine Efficacy Trial. medRxiv [Preprint]. 2021. DOI: 10.1101/2021.08.09.21261290. Available at: https://www.medrxiv.org/content/10.1101/2021.08.09.21261290v4
96. Widge AT, Rouphael NG, Jackson LA, Anderson EJ, Roberts PC, Makhene M, et al. Durability of Responses after SARS-CoV-2 mRNA-1273 Vaccination. N Engl J Med. 2021;384(1):80-2. Available at: https://www.nejm.org/doi/full/10.1056/NEJMc2032195
97. Muller L, Andree M, Moskorz W, Drexler I, Walotka L, Grothmann R, et al. Age-dependent immune response to the Biontech/Pfizer BNT162b2 COVID-19 vaccination. Clin Infect Dis [Preprint]. 2021. DOI: 10.1093/cid/ciab381. Available at: https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab381/6255965
98. Kalimuddin S, Tham CYL, Qui M, de Alwis R, Sim JXY, Lim JME, et al. Early T cell and binding antibody responses are associated with COVID-19 RNA vaccine efficacy onset. Med (N Y). 2021;2(6):682-8 e4. Available at: https://pubmed.ncbi.nlm.nih.gov/33851143/
99. Painter MM, Mathew D, Goel RR, Apostolidis SA, Pattekar A, Kuthuru O, et al. Rapid induction of antigen-specific CD4+ T cells is associated with coordinated humoral and cellular immune responses to SARS-CoV-2 mRNA vaccination. Immunity [Preprint]. 2021. DOI: 10.1016/j.immuni.2021.08.001. Available at: https://www.sciencedirect.com/science/article/pii/S1074761321003083
100. Payne RP, Longet S, J.A. A, Skelly DT, Dejnirattisai W, Adele S, et al. Sustained T cell immunity, protection and boosting using extended dosing intervals of BNT162b2 mRNA vaccine2021. Available at: https://www.pitch-study.org/PITCH_Dosing_Interval_23072021.pdf
101. Stebegg M, Kumar SD, Silva-Cayetano A, Fonseca VR, Linterman MA, Graca L. Regulation of the Germinal Center Response. Frontiers in Immunology. 2018;9(2469) Available at: https://www.frontiersin.org/article/10.3389/fimmu.2018.02469
102. Gatto D, Brink R. The germinal center reaction. J Allergy Clin Immunol. 2010;126(5):898-907. Available at: https://linkinghub.elsevier.com/retrieve/pii/S0091-6749(10)01416-8
103. Wang Z, Schmidt F, Weisblum Y, Muecksch F, Barnes CO, Finkin S, et al. mRNA vaccine-elicited antibodies to SARS-CoV-2 and circulating variants. Nature. 2021;592(7855):616-22. Available at: https://www.nature.com/articles/s41586-021-03324-6

104. Jeyanathan M, Afkhami S, Smaill F, Miller MS, Lichty BD, Xing Z. Immunological considerations for COVID-19 vaccine strategies. Nat Rev Immunol. 2020;20(10):615-32. Available at: https://www.nature.com/articles/s41577-020-00434-6
105. Isho B, Abe KT, Zuo M, Jamal AJ, Rathod B, Wang JH, et al. Mucosal versus systemic antibody responses to SARS-CoV-2 antigens in COVID-19 patients. medRxiv [Preprint]. 2020. DOI: 10.1101/2020.08.01.20166553. Available at: https://www.medrxiv.org/content/10.1101/2020.08.01.20166553v2
106. McLean HQ, Thompson MG, Sundaram ME, Kieke BA, Gaglani M, Murthy K, et al. Influenza Vaccine Effectiveness in the United States During 2012–2013: Variable Protection by Age and Virus Type. The Journal of Infectious Diseases. 2014;211(10):1529-40. Available at: https://academic.oup.com/jid/article/211/10/1529/1825780?login=true
107. Thomas SJ, Moreira ED, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Six Month Safety and Efficacy of the BNT162b2 mRNA COVID-19 Vaccine. medRxiv [Preprint]. 2021. DOI: 10.1101/2021.07.28.21261159. Available at: https://www.medrxiv.org/content/10.1101/2021.07.28.21261159v1
108. Abu-Raddad LJ, Chemaitelly H, Coyle P, Malek JA, Ahmed AA, Mohamoud YA, et al. SARS-CoV-2 antibody-positivity protects against reinfection for at least seven months with 95% efficacy. EClinicalMedicine. 2021;35:100861. Available at: https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00141-3/fulltext
109. Hall VJ, Foulkes S, Charlett A, Atti A, Monk EJM, Simmons R, et al. SARS-CoV-2 infection rates of antibody-positive compared with antibody-negative health-care workers in England: a large, multicentre, prospective cohort study (SIREN). Lancet. 2021;397(10283):1459-69. Available at: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00675-9/fulltext
110. Hansen CH, Michlmayr D, Gubbels SM, Molbak K, Ethelberg S. Assessment of protection against reinfection with SARS-CoV-2 among 4 million PCR-tested individuals in Denmark in 2020: a population-level observational study. Lancet. 2021;397(10280):1204-12. Available at: https://linkinghub.elsevier.com/retrieve/pii/S0140-6736(21)00575-4
111. Vitale J, Mumoli N, Clerici P, De Paschale M, Evangelista I, Cei M, et al. Assessment of SARS-CoV-2 Reinfection 1 Year After Primary Infection in a Population in Lombardy, Italy. JAMA Intern Med. 2021 Available at: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2780557
112. Ripperger TJ, Uhrlaub JL, Watanabe M, Wong R, Castaneda Y, Pizzato HA, et al. Orthogonal SARS-CoV-2 Serological Assays Enable Surveillance of Low-Prevalence Communities and Reveal Durable Humoral Immunity. Immunity. 2020;53(5):925-33 e4. Available at: https://www.sciencedirect.com/science/article/abs/pii/S1074761320304453#!
113. Chia WN, Zhu F, Ong SWX, Young BE, Fong SW, Le Bert N, et al. Dynamics of SARS-CoV-2 neutralising antibody responses and duration of immunity: a longitudinal study. Lancet Microbe. 2021;2(6):e240-e9. Available at: https://www.sciencedirect.com/science/article/pii/S2666524721000252
114. Post N, Eddy D, Huntley C, van Schalkwyk MCI, Shrotri M, Leeman D, et al. Antibody response to SARS-CoV-2 infection in humans: A systematic review. PLoS One. 2020;15(12):e0244126. Available at: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0244126
115. Shrotri M, van Schalkwyk MCI, Post N, Eddy D, Huntley C, Leeman D, et al. T cell response to SARS-CoV-2 infection in humans: A systematic review. PLoS One. 2021;16(1):e0245532. Available at: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0245532
116. Dan JM, Mateus J, Kato Y, Hastie KM, Yu ED, Faliti CE, et al. Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. Science. 2021;371(6529):eabf4063. Available at: https://science.sciencemag.org/content/371/6529/eabf4063
117. Public Health England (PHE). SARS-CoV-2 variants of concern and variants under investigation in England - Technical briefing 19. London: PHE; 2021. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1005517/Technical_Briefing_19.pdf
118. European Medicines Agency (EMA). COVID-19 vaccines: authorised. Amsterdam: EMA; 2021. Available at: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/vaccines-covid-19/covid-19-vaccines-authorised
119. Joint Committee on Vaccination and Immunisation. JCVI interim advice: potential COVID-19 booster vaccine programme winter 2021 to 2022. London: JCVI; 2021. Available at: https://www.gov.uk/government/publications/jcvi-interim-advice-on-a-potential-coronavirus-covid-19-booster-vaccine-programme-for-winter-2021-to-2022/jcvi-interim-advice-potential-covid-19-booster-vaccine-programme-winter-2021-to-2022
120. Public Health England (PHE). Immunisation against infectious disease. London: PHE; 2020. Available at: https://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book
121. Administration USFaD. Coronavirus (COVID-19) Update: FDA Authorizes Additional Vaccine Dose for Certain Immunocompromised Individuals. Silver Spring: FDA; 2021. Available at: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-additional-vaccine-dose-certain-immunocompromised
122. Advisory Committee on Immunization Practices (ACIP). ACIP Presentation Slides: August 13, 2021 Meeting. Atlanta: CDC; 2021. Available at: https://www.cdc.gov/vaccines/acip/meetings/slides-2021-08-13.html

123. U.S. Department of Health and Human Services (HHS). Joint Statement from HHS Public Health and Medical Experts on COVID-19 Booster Shots. Washington: HHS; 2021. Available at: https://www.hhs.gov/about/news/2021/08/18/joint-statement-hhs-public-health-and-medical-experts-covid-19-booster-shots.html
124. Ministry of Health, Israel. Third Dose of the COVID-19 Vaccine. 2021. Available at: https://govextra.gov.il/ministry-of-health/covid19-vaccine/en-covid-19-vaccine-3rd-dose/
125. Bundesministerium - Soziales, Gesundheit, Pflege und Konsumentenschutz. COVID-19-Impfungen: Anwendungsempfehlungen des Nationalen Impfgremiums - Version 5. 2021. Available at: https://www.sozialministerium.at/dam/jcr:5a09d8d2-f9e8-4547-81a6-a36087f69edb/COVID-19-Impfungen_Anwendungsempfehlung_des_Nationalen_Impfgremiums_Version_5_(Stand%2017.08.21).pdf
126. Service Public Federal - Sante Publique, Securite de la Chaine Alimentaire et Environnement, Belgium. La CIM décide de proposer un vaccin supplémentaire aux personnes présentant une immunité réduite. 2021. Available at: https://www.health.belgium.be/fr/news/conference-interministerielle-sante-publique-0
127. Haute Autorité de santé (HAS). Vaccination en très haute priorité des personnes à très haut risque 2021. Available at: https://solidarites-sante.gouv.fr/IMG/pdf/liste_maladies_rares_cosv_fmr-2.pdf
128. Haute Autorité de santé (HAS). Avis n° 2021.0051/AC/SEESP du 15 juillet 2021 du collège de la Haute Autorité de santé sur l'identification des données nécessaires pour permettre d'évaluer la pertinence éventuelle d'un rappel chez les personnes ayant eu une primovaccination complète contre la Covid-19. 2021. Available at: https://www.has-sante.fr/jcms/p_3278153/fr/avis-n-2021-0051/ac/seesp-du-15-juillet-2021-du-college-de-la-haute-autorite-de-sante-sur-l-identification-des-donnees-necessaires-pour-permettre-d-evaluer-la-pertinence-eventuelle-d-un-rappel-chez-les-personnes-ayant-eu-une-primovaccination-complete-contre-la-covid-19
129. Haute Autorité de Santé (HAS). Covid-19: la HAS précise les populations éligibles à une dose de rappel de vaccin. Saint-Denis La Plaine: HAS; 2021. Available at: https://www.has-sante.fr/jcms/p_3283153/fr/covid-19-la-has-precise-les-populations-eligibles-a-une-dose-de-rappel-de-vaccin
130. Hungarian Government - koronavirus.gov.hu. Magyarország az első, ahol már a harmadik oltásra is lehet időpontot foglalni2021. Available at: https://koronavirus.gov.hu/cikkek/magyarorszag-az-elso-ahol-mar-harmadik-oltasra-lehet-idopontot-foglalni
131. Lietuvos Respublikos sveikatos apsaugos ministerija. Nustatyta tvarka, kaip trečia doze bus revakcinuojami imunosupresiniai pacientai. 2021. Available at: https://sam.lrv.lt/lt/naujienos/nustatyta-tvarka-kaip-trecia-doze-bus-revakcinuojami-imunosupresiniai-pacientai
132. Conseil Superieur des Maladies Infectieuses. Recommandation du CSMI concernant la 3ème dose de vaccin contre la COVID-19 chez des personnes immunodéprimées. Luxembourg: CSMI; 2021. Available at: https://sante.public.lu/fr/espace-professionnel/recommandations/conseil-maladies-infectieuses/covid-19/covid-19-annexes/CSMI-recommandation-3eme-dose-vaccin-COVID-19-personnes-immunodeprimees.pdf
133. Nacionalni inštitut za javno zdravje (NIJZ). Priporočila za cepljenje proti COVID-19. 2021. Available at: https://www.nijz.si/sites/www.nijz.si/files/uploaded/priporocila_za_cepljenje_proti_covid_uskl_psc_apr_2021.pdf
134. Public Health Agency of Sweden. Tredje dos mot covid-19 troligen nästa år. Stockholm: PHAS; 2021. Available at: https://www.folkhalsomyndigheten.se/nyheter-och-press/nyhetsarkiv/2021/augusti/tredje-dos-mot-covid-19-troligen-nasta-ar/
135. SeroTracker. SeroTracker. 2021. Available at: https://serotracker.com/en/Explore
136. European Centre for Disease Prevention and Control (ECDC). Seasonal influenza vaccination and antiviral use in EU/EEA Member States. Stockholm: ECDC; 2018. Available at: https://www.ecdc.europa.eu/en/publications-data/seasonal-influenza-vaccination-antiviral-use-eu-eea-member-states
137. European Centre for Disease Prevention and Control (ECDC). Overview of the implementation of COVID-19 vaccination strategies and deployment plans in the EU/EEA. Stockholm: ECDC; 2021. Available at: https://www.ecdc.europa.eu/en/publications-data/overview-implementation-covid-19-vaccination-strategies-and-deployment-plans
138. Advisory Committee on Immunization Practices (ACIP). Coadministration of COVID-19 vaccines with other vaccines. Atlanta: CDC; 2021. Available at: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html#Coadministration
139. Toback S, Galiza E, Cosgrove C, Galloway J, Goodman AL, Swift PA, et al. Safety, Immunogenicity, and Efficacy of a COVID-19 Vaccine (NVX-CoV2373) Co-administered With Seasonal Influenza Vaccines. medRxiv [Preprint]. 2021. DOI: 10.1101/2021.06.09.21258556. Available at: https://www.medrxiv.org/content/10.1101/2021.06.09.21258556v1
140. Deng X, Garcia-Knight MA, Khalid MM, Servellita V, Wang C, Morris MK, et al. Transmission, infectivity, and antibody neutralization of an emerging SARS-CoV-2 variant in California carrying a L452R spike protein mutation. medRxiv [Preprint]. 2021. DOI: 10.1101/2021.03.07.21252647. Available at: https://www.medrxiv.org/content/10.1101/2021.03.07.21252647v1
141. Stamatatos L, Czartoski J, Wan Y-H, Homad LJ, Rubin V, Glantz H, et al. mRNA vaccination boosts cross-variant neutralizing antibodies elicited by SARS-CoV-2 infection. Science. 2021;372(6549):1413-8. Available at: https://science.sciencemag.org/content/372/6549/1413

142. Cavanaugh AM, Spicer KB, Thoroughman D, Glick C, Winter K. Reduced Risk of Reinfection with SARS-CoV-2 After COVID-19 Vaccination - Kentucky, May-June 2021. MMWR Morb Mortal Wkly Rep. 2021;70(32):1081-3. Available at: https://www.cdc.gov/mmwr/volumes/70/wr/mm7032e1.htm
143. Janssen C, Maillard A, Bodelet C, Claudel A-L, Gaillat J, Delory T, et al. Hesitancy towards COVID-19 Vaccination among Healthcare Workers: A Multi-Centric Survey in France. Vaccines. 2021;9(6):547. Available at: https://www.mdpi.com/2076-393X/9/6/547
144. European Commission (EC). State of Vaccine Confidence in the EU 2018. Luxembourg: : Publications Office of the European Union; 2018. Available at: https://ec.europa.eu/health/sites/default/files/vaccination/docs/2018_vaccine_confidence_en.pdf
145. Burgess RA, Osborne RH, Yongabi KA, Greenhalgh T, Gurdasani D, Kang G, et al. The COVID-19 vaccines rush: participatory community engagement matters more than ever. Lancet. 2021;397(10268):8-10. Available at: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32642-8/fulltext
146. World Health Organization (WHO). Communicating risk in public health emergencies: a WHO guideline for emergency risk communication (ERC) policy and practice. Geneva: WHO; 2018. Available at: https://www.who.int/publications/i/item/9789241550208
147. World Health Organization (WHO). WHO Director-General's opening remarks at the media briefing on COVID-19 - 4 August 2021. Geneva: WHO; 2021. Available at: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-4-august-2021
148. Davies NG, Abbott S, Barnard RC, Jarvis CI, Kucharski AJ, Munday JD, et al. Estimated transmissibility and impact of SARS-CoV-2 lineage B.1.1.7 in England. Science. 2021 Apr 9;372(6538):eabg3055. Available at: https://science.sciencemag.org/content/372/6538/eabg3055.long
149. Volz E, Mishra S, Chand M, Barrett JC, Johnson R, Geidelberg L, et al. Assessing transmissibility of SARS-CoV-2 lineage B.1.1.7 in England. Nature. 2021;593(7858):266-9. Available at: https://www.nature.com/articles/s41586-021-03470-x
150. Statens Serum Institut (SSI). Kontakttal for virusvariant B.1.1.7. Copenaghen: SSI; 2021. Available at: https://covid19.ssi.dk/-/media/cdn/files/kontakttal-for-b117-d-3-februar-2021_04022021.pdf?la=da
151. Public Health England (PHE). Investigation of novel SARS-CoV-2 variant - Variant of Concern 202012/01 - Technical briefing 5. London: PHE; 2021. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/959426/Variant_of_Concern_VOC_202012_01_Technical_Briefing_5.pdf
152. Davies NG, Jarvis CI, Group CC-W, Edmunds WJ, Jewell NP, Diaz-Ordaz K, et al. Increased mortality in community-tested cases of SARS-CoV-2 lineage B.1.1.7. Nature. 2021;593(7858):270-4. Available at: https://www.nature.com/articles/s41586-021-03426-1
153. Bager P, Wohlfahrt J, Fonager J, Rasmussen M, Albertsen M, Michaelsen TY, et al. Risk of hospitalisation associated with infection with SARS-CoV-2 lineage B.1.1.7 in Denmark: an observational cohort study. Lancet Infect Dis [Preprint]. 2021. DOI: 10.1016/S1473-3099(21)00290-5. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34171231
154. Graham MS, Sudre CH, May A, Antonelli M, Murray B, Varsavsky T, et al. Changes in symptomatology, reinfection, and transmissibility associated with the SARS-CoV-2 variant B.1.1.7: an ecological study. Lancet Public Health. 2021;6(5):e335-e45. Available at: https://www.sciencedirect.com/science/article/pii/S2468266721000554
155. Chen Y, Shen H, Huang R, Tong X, Wu C. Serum neutralising activity against SARS-CoV-2 variants elicited by CoronaVac. Lancet Infect Dis. 2021;21(8):1071-2. Available at: https://linkinghub.elsevier.com/retrieve/pii/S1473-3099(21)00287-5
156. Tegally H, Wilkinson E, Giovanetti M, Iranzadeh A, Fonseca V, Giandhari J, et al. Detection of a SARS-CoV-2 variant of concern in South Africa. Nature. 2021;592(7854):438-43. Available at: https://www.nature.com/articles/s41586-021-03402-9
157. Madhi SA, Baillie V, Cutland CL, Voysey M, Koen AL, Fairlie L, et al. Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant. N Engl J Med. 2021;384(20):1885-98. Available at: https://www.nejm.org/doi/10.1056/NEJMoa2102214
158. National Institute of Infectious Diseases (NIID), Japan. Brief report: New Variant Strain of SARS-CoV-2 Identified in Travelers from Brazil. NIID; 2021. Available at: https://www.niid.go.jp/niid/en/2019-ncov-e/10108-covid19-33-en.html
159. Fujino T, Nomoto H, Kutsuna S, Ujiie M, Suzuki T, Sato R, et al. Novel SARS-CoV-2 Variant in Travelers from Brazil to Japan. Emerg Infect Dis. 2021;27(4):1243–5. Available at: https://wwwnc.cdc.gov/eid/article/27/4/21-0138_article
160. Faria NR, Mellan TA, Whittaker C, Claro IM, Candido DDS, Mishra S, et al. Genomics and epidemiology of the P.1 SARS-CoV-2 lineage in Manaus, Brazil. Science. 2021;372(6544):815-21. Available at: https://science.sciencemag.org/content/372/6544/815
161. Souza WM, Amorim MR, Sesti-Costa R, Coimbra LD, Brunetti NS, Toledo-Teixeira DA, et al. Neutralisation of SARS-CoV-2 lineage P. 1 by antibodies elicited through natural SARS-CoV-2 infection or vaccination with an inactivated SARS-CoV-2 vaccine: an immunological study. The Lancet Microbe [Preprint]. 2021. DOI: 10.1016/S2666-5247(21)00129-4. Available at: https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(21)00129-4/fulltext

Annex. Characteristics of the other four variants designated as VOCs by ECDC

ECDC regularly assesses new evidence on variants detected through epidemic intelligence, rules-based genomic variant screening, and other scientific sources.

Alpha

Several studies provide evidence of increased transmissibility of the Alpha VOC [8,153-155], based on contact tracing data from the UK. Attack rates are around 10-55% higher across most age groups when the case is infected with the Alpha VOC compared to earlier circulating variants in the UK [151]. In addition, studies in the UK and Denmark demonstrate that the Alpha VOC is associated with increased severity and mortality. The hazard of death associated with the Alpha VOC is 61% (95% CI: 42-82%) higher than with pre-existing variants [152] and infection with lineage the Alpha VOC is associated with an increased risk of hospitalisation compared to other lineages (adjusted odd ratio (OR) 1.64 (95% CI: 1.32-2.04)) [153]. Researchers in the UK demonstrated that rates of COVID-19 reinfection are not higher for the Alpha VOC compared to other pre-existing variants [154]. Several studies on vaccine effectiveness from EU authorised vaccines including Comirnaty, Spikevax, Vaxzevria show strong protection against symptomatic disease, severe disease, hospitalisation and death following a full vaccination course in the general population, in LTCF population and in older adults [34-38].

B.1.1.7+E484K

Data about transmissibility, severity and immunity of this variant are still very limited. However, the E484K mutation of the spike protein has been associated with a reduction in neutralisation activity by convalescent and vaccinee sera in multiple studies. For instance, this mutation was shown to reduce the antibody neutralisation compared to a wild type variant when introduced in the USA-WA1/2020 background [23]. Another study evaluated the neutralising activity against SARS-CoV-2 variants of the serum of healthcare workers vaccinated with CoronaVac. They found that the neutralisation efficiency was significantly decreased for viruses with the Beta, Gamma VOCs or B.1.526 (Iota) VOI genetic backgrounds (which all carry the E484K spike protein change) compared to the Alpha VOC and B.1.429 (which do not carry the change) [155].

Beta

The Beta variant was first identified in South Africa and data show that this lineage was likely to have emerged after the first wave of the epidemic in September 2020. The Beta variant rapidly replaced other variants in the country, suggesting that this lineage may be associated with increased transmissibility or immune escape [156]. A study from Qatar showed that the effectiveness of Comirnaty against any documented infection with the Beta VOC was 75.0% (95% CI: 70.5-78.9) at 14 or more days after the second dose [34]. Another study investigated the efficacy of Vaxzevria in South Africa with a multi-centre, double-blind, randomised controlled trial [157]. A two-dose regimen of this vaccine did not show protection against mild-to-moderate COVID-19 caused by the Beta VOC. In a secondary-outcome analysis, efficacy against the Beta VOC was not evident (vaccine efficacy (VE), 10.4%; 95% CI: −76.8-54.8). No cases of hospitalisation for severe COVID-19 were observed in the study, making the trial findings inconclusive with respect to whether Vaxzevria protects against severe COVID-19 caused by infection with the Beta VOC.

Gamma

In January 2021, Japan reported the detection of a new SARS-CoV-2 variant in travellers who arrived at Tokyo airport from Amazonas state, north Brazil [158,159]. The Gamma VOC is thought to have emerged in Brazil in November 2020. It was detected in samples collected in December 2020 in Manaus through genomic surveillance, after a rapid increase in hospitalisations [160]. In a recent modelling study, P.1 was estimated to be 1.7 to 2.4 times more transmissible compared to other variants circulating in Brazil. In the same study, protection against reinfection by Gamma or non-Gamma VOC was estimated; the Gamma VOC evades 21 to 46% of protective immunity elicited by a previous infection (with a non-Gamma VOC) compared to other variants [160]. Another study evaluated the levels of Gamma VOC neutralisation following natural infection and vaccination with CoronaVac, an inactivated COVID-19 vaccine developed by Sinovac Biotech. The vaccine has been approved in several countries, among them Brazil, China, Mexico, Thailand, and Turkey; it has not been authorised for use in the EU, but is under review. Plasma from COVID-19-convalescent donors had six times less neutralising activity against the Gamma VOC compared to the B-lineage. Moreover, five months after booster immunisation with CoronaVac, plasma from vaccinated individuals failed to efficiently neutralise the P.1 variant. This suggests that Gamma VOC may escape from neutralising antibodies derived from previously circulating variants of SARS-CoV-2 [161].