

Partial COVID-19 vaccination, vaccination following SARS-CoV-2 infection and heterologous vaccination schedule: summary of evidence

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Key messages

This document provides a review of evidence on three topics of interest (effectiveness of partial vaccination, immunogenicity and effectiveness of vaccination for previously infected individuals and safety and immunogenicity of heterologous schedules) to inform ongoing decision-making in relation to national vaccination policies and strategies in the European Union and European Economic Area (EU/EEA) countries.

Partial vaccination

- Available data, across different population groups and SARS-CoV-2 variants of concern (VOCs), confirm that the protection against asymptomatic and symptomatic infection and severe disease conferred by two vaccine doses (Comirnaty, Spikevax and Vaxzevria) is significantly higher than with partial vaccination (i.e. one dose of a two-dose regimen). Evidence is limited on the long-term effectiveness of partial vaccination.
- Preliminary evidence from some studies indicates that individuals who are partially vaccinated are less protected against symptomatic infection with the B.1.617.2 (Delta) VOC than against the B.1.1.7 (Alpha) VOC, regardless of the vaccine type. However, full vaccination provides nearly equivalent protection against the Delta to that for the Alpha VOC.
- This supports ECDC's previous recommendation that, in the context of increasing circulation of the Delta VOC, full vaccination should be achieved as early as possible and the second vaccine dose be administered after the shortest possible interval, with priority given to population groups at highest risk of severe outcomes following SARS-CoV-2 infection.

Previously infected individuals

- Studies of single-dose regimens of Comirnaty, Spikevax and Vaxzevria in previously infected individuals indicate antibody and cellular immune responses are comparable to naïve individuals who complete the two-dose regimen. However, data on the long-term duration of protective immunity are sparse.
- Caution must be exercised in translating immunogenicity data into protection from COVID-19 clinical outcomes. No evidence is currently available on clinical endpoints, such as 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.
- Given the current evidence gaps, as a precaution, consideration should be given to the continued administration of a two-dose regimen, as per EMA authorisation, particularly for those individuals at greatest risk of severe outcomes following SARS-CoV-2 infection.

Heterologous vaccination

- Evidence from studies on heterologous ('mix and match') vaccination suggests that the combination of Vaxzevria and mRNA vaccines induces a robust humoral response against SARS-CoV-2 and elicits a higher T-cell response than homologous combinations. Although increased mild-to-moderate systemic reactogenicity was observed after administration of the second dose, heterologous regimens were generally well tolerated.
- Several EU/EEA countries are currently using 'mix and match' schedules, mainly with an mRNA vaccine (Comirnaty or Spikevax) following a first dose of Vaxzevria, especially to complete the vaccination course in the event of severe reactions after the first dose or for other precautionary reasons based on national protocols. Current evidence provides scientific grounds to expect these 'off-label' approaches to be safe and elicit a satisfactory immune response.
- While research is ongoing to provide more evidence on long-term safety, duration of immunity and effectiveness, the use of heterologous schedules may offer flexibility in terms of vaccination options, particularly to mitigate the impact on the vaccine rollout should a vaccine product not be available, or if it is discontinued or paused.

Scope of the document

This technical report provides an up-to-date summary of evidence in relation to:

- effectiveness of partial COVID-19 vaccination - i.e. effectiveness of the first dose of two-dose vaccine regimens;
- immunogenicity and effectiveness of single-dose vaccination in individuals previously infected with SARS-CoV-2;
- safety and immunogenicity of heterologous COVID-19 vaccination schedules, also known as the 'mix-and-match' approach.

This document focuses on available evidence for COVID-19 vaccines authorised for use in the European Union/European Economic Area (EU/EEA) and is meant to support ongoing decision-making on COVID-19 vaccination strategies and policies in EU/EEA countries.

The information presented in this report includes:

- data gathered from a rapid review of peer-reviewed and preprint articles;
- information on current COVID-19 vaccination policies gathered from answers to questions on vaccines sent 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, in particular, the ISAA report 71 (as of 28 June 2021) and 72 (as of 5 July 2021), and collected through the EU/EEA National Immunisation Technical Advisory Groups (NITAGs) Collaboration 23–29 June 2021.

Target audience

Target audiences for this document are the EC, the Health Security Committee (HSC), the EU/EEA NITAGs, national public health institutes and ministries of health in the EU/EEA, and public health experts and decision-makers at national and subnational levels.

Background

As of 19 July 2021, four vaccines have received conditional marketing authorisation in the EU/EEA following evaluation by the European Medicines Agency (EMA) [1]: Comirnaty (BNT162b2) developed by BioNTech/Pfizer, Spikevax (mRNA-1273) previously COVID-19 Vaccine Moderna, Vaxzevria (AZD1222) previously COVID-19 Vaccine AstraZeneca, and COVID-19 Vaccine Janssen (Ad26.COV 2.5). Comirnaty is now authorised for use in people aged 12 years and older [2,3], while the other three vaccines are currently registered for use in people aged 18 years and older [3-5].

In EU/EEA countries, the roll-out of COVID-19 vaccine campaigns started at the end of December 2020, when the first supplies of Comirnaty were delivered, and on 19 January 2021, the EC set out actions to step up the response against the pandemic and accelerate the rollout of vaccination campaigns with the targets of vaccinating at least 80% of people over the age of 80 years and 80% of health and social care professionals in every EU/EEA country by March 2021. In addition, a minimum of 70% of the adult population (i.e. above 18 years old) were due to be vaccinated by the summer of 2021 [6].

So far, countries have prioritised older adults (with various age thresholds), residents and personnel in long-term care facilities (LTCFs), and healthcare workers, and have gradually been progressing to social care personnel, people with certain comorbidities and younger age groups. Meanwhile, some countries have opened vaccination up to all. As of 19 July 2021, over 419 million doses have been administered to adults aged 18 years and above in the EU/EEA. The cumulative vaccine uptake has reached 66.4% for at least one vaccine dose and 49.2% for the full vaccination course in the EU/EEA (30 reporting countries). Thirteen countries (out of 27 reporting) have administered a full vaccination course to more than 80% of the population aged 80 years and above (80+), and eight countries (out of 17 reporting) have administered a full vaccination course to more than 80% of healthcare workers. More comprehensive data on the COVID-19 vaccine rollout in EU/EEA countries can be found on the ECDC Vaccine Tracker [7].

The appearance and dissemination of new variants of concern (VOCs) represents a significant challenge, in particular the SARS-CoV-2 Delta (B.1.617.2), the circulation of which is currently increasing in EU/EEA countries. This variant is 40–60% more transmissible than the Alpha (B.1.1.7) VOC and may be associated with a higher risk of hospitalisation. Based on the estimated transmission advantage of the Delta VOC and using modelling forecasts, it is projected that 70% of new SARS-CoV-2 infections will be due to this variant in the EU/EEA by early August and 90% of infections by the end of August [8]. As of 15 of July, based on data from 16 EU/EEA countries, the proportion of the Delta variant among all sequenced samples reached a median of 39.1% (range: 0.7–87.3%), although the Alpha variant is still more prevalent with a median of 42.5% (2.1–95.8%). At the same time, recent data show a 64.3% increase in weekly COVID-19 cases during week 27 against the previous week, with an increasing trend observed in 20 countries. The steepest increases and highest notification rates were reported among 15 to 24-year-olds, with limited increases in those aged over 65 years [9].

While EU/EEA countries are accelerating the rollout of their vaccine campaigns, they are also continuing to adjust their vaccination policies and strategies based on the current epidemiological situation, vaccine supply, and scientific evidence on the virus and vaccine performance. This document provides a review of evidence on COVID-19 vaccine safety, immunogenicity, efficacy and effectiveness¹ focusing on three topics of interest (partial vaccination, vaccination of previously infected individuals and heterologous schedules) to inform ongoing revision of vaccination policies and strategies.

¹ Definition: vaccine efficacy refers to the performance of the vaccine in research settings (randomised control trial) whereas effectiveness refers to the performance in real-world observational studies.

1. Partial vaccination

Apart from COVID-19 Vaccine Janssen, all other COVID-19 vaccines authorised for use in the EU/EEA require a two-dose schedule to complete the primary vaccination course according to EMA's summary of product characteristics (SPCs). Given current vaccine uptake estimates, in absolute terms over 236 million adults in the EU/EEA are partially vaccinated – i.e. they have only received one dose of a two-dose course under a COVID-19 vaccine regimen [7].

Below we summarise the evidence on the vaccine efficacy and effectiveness of partial COVID-19 vaccination from randomised and observational studies across population groups and relevant VOCs.

1.1 Data from randomised studies

In the Comirnaty trial, a 52.4% (95% confidence interval (CI): 29.584.5) reduction of symptomatic infection after a single dose was observed among all evaluable individuals in the trial. However, this included the first 13 days following the first dose, when protection is not yet established, and did not go beyond 21 days (i.e. time of the second dose in the vaccine trial). This compares with a 94.8% (95% CI: 89.8–97.6) efficacy against symptomatic infection from seven days after the second dose [10].

The Spikevax trial showed a 80.2% (95% CI: 55.2–92.5) efficacy at preventing symptomatic infection after the first dose with a median follow-up time of 28 days (range: 1-108 days). However, as in the Comirnaty trial, the analysis includes the first 13 days following the first dose, and the short median follow-up time limits the interpretation of these results [11]. This compares with a vaccine efficacy of 94.1% (95% CI: 89.3–96.8) against symptomatic infection from 14 days after the second dose [12].

From the pooled analysis of data from Vaxzevria trials there are different estimates of protection against symptomatic infection observed between 22 and 90 days following the first dose, ranging from 50% to 80%. A vaccine efficacy of 81.3% (95% CI: 60.3–91.2) was observed from 14 days after the second dose in participants who received two standard doses with ≥ 12 weeks interval [13]. In the Vaxzevria trial, the participants performed self-administered nose and throat swabs every week with an observed 63.9% (95% CI: 46–75.9) reduction in overall polymerase chain reaction (PCR)-positivity between 22 and 90 days after a single standard dose [13].

1.2 Data from observational studies

1.2.1 General population

Studies reporting population-based data on the effectiveness of partial vaccination have been published from Israel [14-18], United States [19,20], Spain [21], and Sweden [22] and results are summarised in Tables 1 to 3.

A large study conducted in Israel by Dagan et al. [14], including 596 618 vaccinated individuals matched 1-1 with unvaccinated controls, found that vaccination with one dose of Comirnaty was effective against any documented SARS-CoV-2 infection (46%; 95% CI: 40–51), symptomatic infection (57%; 95% CI: 50–63), hospitalisation (74%; CI 95%: 56–86), severe disease (62%; 95% CI: 39–80) and death (72%; 95% CI: 19–100) in the short follow up period of 14–0 days after the first dose and prior to receiving the second dose. Effectiveness improved from seven or more days after the second dose. Data were collected between 20 December 2020 and 1 February 2021 while there was an increase in the detection of Alpha VOC isolates (up to 80% towards the end of the study period).

Based on the analysis conducted by Hass et al. [16] of the national surveillance data from the first four months of the nationwide vaccination campaign in Israel, among individuals aged 16 years and older, the estimated vaccine effectiveness between 14–21 days after the first dose of Comirnaty was 52% (95% CI: 48.9–55.0) for asymptomatic SARS-CoV-2 infection, 62.5% (95% CI: 59.3–65.4) for symptomatic infection, 75.7% (95% CI: 72.0-79.0) for hospitalisations, 75.6% (95% CI: 71.9-78.9) for severe and critical COVID-19 hospitalisations, and 77.0% (95% CI: 69.7–82.6) against deaths. Effectiveness against all outcomes increased significantly from two weeks after the second dose, respectively 93.8% (95% CI: 93.3–94.2), 97.7% (95% CI: 97.5–97.9), 98.0% (95% CI: 97.7–98.3), 98.4% (95% CI: 98.1–98.6) and 98.1% (95% CI: 97.6–98.5).

A second large scale study in Israel conducted by Goldberg et al. (preprint), also based on individual-level data registers, suggests low but statistically significant effectiveness up to two weeks after the first dose of Comirnaty: 20.6% (95% CI: 19.7–21.4) for documented SARS-CoV-2 infection, 45.7% (95% CI: 43.1–48.2) for hospitalisation, 49.3% (95% CI: 45.7–52.7) for severe illness, and 48.5% (95% CI: 42.8–53.7) for death. Effectiveness increased when assessed between two weeks after the administration of the first dose and up to six days after the administration of the second: 57.7% (95% CI: 57.1–58.4) for documented SARS-CoV-2 infection; 69.4% (95% CI: 67.5–71.2) for hospitalisation; 65.9% (95% CI: 63.1–68.5) for severe illness; and 62.7% (95% CI: 58.0–66.8) for death. Effectiveness against all outcomes was higher when assessed from one week after the second dose [18] and was similar to that reported by Haas et al. [16].

According to an observational study, conducted by Heymann et al. (preprint), in a sub-population of patients from a large health maintenance organisation in Israel who were repeatedly tested for SARS-CoV-2 infection

using a PCR test between 1 January 2021 and 11 February 2021, the estimated effectiveness against SARS-CoV-2 infection two weeks after the first vaccine dose of Comirnaty was 61% (95% CI: 49–71) and 89% (95% CI: 82–94) after the second dose [17].

A retrospective cohort study was conducted by Tande et al. in the United States (US) at Mayo Clinic campuses among asymptomatic patients who were screened for SARS-CoV-2 in the 48–72 hours prior to undergoing surgical or medical procedures [19]. A total of 48 333 molecular tests were performed in 39 156 asymptomatic adult patients. Out of the 3 006 vaccinated patients of the cohort, 2 299 had only had one dose prior to screening and the majority (94.0%) had received Comirnaty. The analysis showed that the risk of asymptomatic infection was reduced by 79% (risk reduction (RR)=0.21; 95% CI: 0.12–0.37) in vaccinated patients from 10 days after the first dose of Comirnaty or Spikevax.

A test-negative design case-control study (n= 325) conducted by Andrejko et al (preprint) [20] in California, US, estimated the effectiveness against PCR-positive SARS-CoV-2 infection to be 66% (95% CI: 69–93%) and 78% (95% CI: 23–94%), respectively one week after the administration of the first and second dose of any mRNA vaccine [20]. Protection conferred by partial vaccination with mRNA vaccines against severe outcomes was 77% (95% CI: 71–82) for hospitalisation and 64.2% (95% CI: 13.0–85.2) for death, while the effectiveness of full vaccination was 96% (95% CI: 95–99) and 98.7% (95% CI: 91.0–99.8), respectively.

A prospective cohort study was conducted in Spain by Martínez-Baz et al. to investigate vaccine effectiveness among 20 961 close contacts of confirmed SARS-CoV-2 cases diagnosed between January and April 2021 [21]. Non-brand-specific effectiveness after one and two doses was 35% (95% CI: 25–44) and 66% (95% CI: 57–74) against SARS-CoV-2 infection respectively, 42% (95% CI: 31–52) and 82% (95% CI: 74–88) against symptomatic infection, and 72% (95% CI: 47–85) and 95% (95% CI: 62–99) against hospitalisation. Study participants were vaccinated with either Comirnaty, Spikevax or Vaxzeria.

In a cohort study in Sweden by Björk et al. (preprint), the estimated vaccine effectiveness in preventing any SARS-CoV-2 infection at least seven days after the second dose of Comirnaty was 86% (95% CI 72–94), but only 42% (95% CI 14–63) at 14 days or more after the first dose [22].

Table 1. Adjusted vaccine effectiveness [% (95% CI); time after injection] of one and two doses against SARS-CoV-2 infection (any, symptomatic, asymptomatic) in the general population as reported in preprint/peer-reviewed studies (as of 14 July 2021)

	Comirnaty		Pooled analysis for several products		Ref
	Dose 1	Dose 2	Dose 1	Dose 2	
Any infection	46% (40-51) 14-20 days	92% (88-95) ≥7 days			[14]
	61% (49-71) ≥2 weeks	89% (82-94) Unknown			[17] [^]
			C/S 66% (69-93) ≥7 days	C/S 78% (23-94) ≥7 days	[20] [^]
			C/S/V 35% (25-44) ≥14 days	C/S/V 66% (57-74) ≥14 days	[21]
Symptomatic	42% (14-63) ≥14 days	86% (72-94) ≥7 days			[22] [^]
	57% (50-63) 14-20 days	94% (87-98) ≥7 days			[14]
	62.5% (59.3-65.4) 14-21 days	97.7% (97.5-97.9) ≥7 days			[16]
	20.6% (19.7-21.4) up to two weeks after the first dose	92.8% (92.6-93.0) ≥7 days			[18] [^]
	57.7% (57.1-58.4) from two weeks after the first dose to six days after the second dose		C/S/V 42% (31-52) ≥14 days	C/S/V 82% (74-88) ≥14 days	[21]
Asymptomatic	52% (48.9-55.0) 14–21 days	93.8% (93.3-94.2) ≥7 days			[16]
			C/S 79% (63-88) ≥10 days	-	[19] [^]

C (Comirnaty), S (Spikevax), V (Vaxzeria). [^]Preprint.

Table 2. Adjusted vaccine effectiveness [% (95% CI); time after injection] of one and two doses adjusted COVID-19 vaccine effectiveness against severe diseases and hospitalisation in the general population as reported in preprint/peer-reviewed studies (as of 14 July 2021)

	Comirnaty		Pooled analysis for several products		Reference
	Dose 1	Dose 2	Dose 1	Dose 2	
Severe disease	62% (39-80) 14-20 days	92% (75-100) ≥7 days			[14]
	49.3% (45.7-52.7) up to two weeks after the first dose	94.4% (93.6-95.0) ≥7 days			[18]^
	65.9% (63.1- 68.5) from two weeks after the first dose to six days after the second dose				
Hospitalisation	74% (56-86) 14-20 days	87% (55-100) ≥7 days			[14]
	Any hospitalisation 75.7% (72.0-79.0) 14-21 days	Any hospitalisation 98.0% (97.7-98.3) ≥7 days			[16]
	For severe illness 75.6% (71.9-78.9) 14-21 days	For severe illness 98.4% (98.1-98.6) ≥7 days			
	45.7% (43.1-48.2) up to two weeks after the first dose	94.2% (93.6-94.7) ≥7 days			[18]^
	69.4% (67.5-71.2) from two weeks after the first dose to six days after the second dose				
			C/S 77% (71-82) ≥7 days	C/S 96% (95-99) ≥7 days	[20]^
		C/S/V 72% (47-85) ≥14 days	C/S/V 95% (62-99) ≥14 days	[21]	

C (Comirnaty), S (Spikevax), V (Vaxzeria). ^Preprint.

Table 3. Adjusted vaccine effectiveness [% (95% CI); time after injection] COVID-19 vaccine effectiveness against death in the general population as reported in preprint/peer-reviewed studies (as of 14 July 2021)

	Comirnaty		Pooled analysis for several products		Ref
	Dose 1	Dose 2	Dose 1	Dose 2	
Death	72% (19-100) 14-20 days	-			[14]
	77.0% (69.7-82.6) 14-21 days	98.1% (97.6-98.5) ≥7 days			[16]
	48.5% (42.8-53.7) up to two weeks after the first dose	93.7% (92.5-94.7) ≥7 days			[18]^
	62.7% (58.0-66.8) from two weeks after the first dose to six days after the second dose				
			C/S 64.2% (13.0-85.2) ≥7 days	C/S 98.7% (91.0-99.8) ≥7 days	[20]^

C (Comirnaty), S (Spikevax), V (Vaxzeria). ^Preprint.

1.2.2 Individuals at risk of severe COVID-19 outcomes, elderly and residents in long-term care facilities

Studies among population groups at risk have been conducted in Denmark [23,24], Israel [18], USA [25,26], England [25,27,28] and Spain [21,29,30]. The results from observational studies among elderly, LTCF residents and other individuals at risk are presented below and summarised in Tables 4 to 6.

In Denmark, the data linkage of various health population registries provided early estimates of vaccine effectiveness in various priority groups at population level. A first study was conducted by Moustsen-Helms et al. (preprint) between 27 December 2020 and 18 February 2021 among LTCF residents (39 040) who received Comirnaty. No significant vaccine effectiveness against infection was observed in LTCF residents at any time point between the first and second dose. Effectiveness measured seven days after the administration of the second was 64% (95% CI: 14–84) [24]. A second study by Emborg et al. (preprint) [24], performed using the same data source up to 11 April 2021, concluded that among priority groups (LTCF residents, individuals aged 85 and above, individuals aged 65 and above at home but requiring support, individual with comorbidities and healthcare workers), the overall vaccine effectiveness against infection was significantly higher from seven days after the second dose (82%; 95% CI: 79–84) compared to the time period of 0–7 days after the second dose (42%; 95% CI: 33–50) [23]. The overall effectiveness against COVID-19 hospitalisation (93%; 95% CI: 89–96) and death (94%, 95% CI: 90–96) was higher from seven days after the second dose.

An observational study (preprint) conducted in Israel by Goldberg et al. [18] (see previous section) reported vaccine effectiveness by age group (see previous section). Among those aged 80+ years, the vaccine effectiveness against all studied outcomes was lower between 14 days after the first dose and seven days after the second dose, compared to seven days after the second dose: 36.6% (95% CI: 32.6–40.3) versus 85.6% (95% CI: 84.3–86.7) against infection; 54.1% (95% CI: 49.2–58.6) versus 91.9% (95% CI: 90.4–93.2) against hospitalisation; 55.8% (95% CI: 50.4–60.6) versus 91.2% (95% CI: 89.8–92.4) against hospitalisation for severe disease; and 56.6% (95% CI: 49.3–62.8) versus 92.6% (95% CI: 90.6–94.1) against death. Vaccine effectiveness observed among those aged 80+ years was lower than for any other younger age-group.

In a case-control study conducted by Tenforde et al. among hospitalised individuals aged 65 years and above in the US, the adjusted vaccine effectiveness against COVID-19-related hospitalisation was 94% (95% CI: 49–99) after full vaccination (i.e. both doses of a two-dose vaccine series, with the second dose received ≥ 14 days before illness onset) with either Comirnaty or Spikevax and 64% (95% CI: 28–82) after partial vaccination (one dose ≥ 14 days before illness onset or two doses with the second dose received < 14 days before illness onset) [26].

A test negative case-control study conducted by Bernal et al. in England using linked health databases (156 930 adults aged 70 years and over) assessed vaccine effectiveness against symptomatic infection at different time-points compared with the baseline risk of infection during the early period following vaccination (4–9 days) [27]. Among individuals aged 80+ from the study population, the effectiveness against symptomatic infection reached 70% (95% CI: 59–78) at 28–34 days after one dose of Comirnaty, followed by a plateau, but increased to 89% (95% CI: 85–93) from 14 days after the second dose. Among individuals aged 70+, the effectiveness against symptomatic infection reached 60% (95% CI: 41–73) at 28–34 days after one dose of Vaxzevria and 73% (95% CI: 27–90) from day 35 onwards. Compared to baseline risk; there was a 43% (95% CI: 33–52) reduced risk of emergency hospital admission and a 51% (95% CI: 37–62) reduced risk of death in those who received one dose of Comirnaty. In those who received one dose of Vaxzevria the reduced risk of emergency hospital admission was 37% (95% CI: 3%–59%), when estimated from 14 days after the injection. Follow-up was insufficient to assess the effectiveness of Vaxzevria on mortality.

Another study conducted by Shrotri et al. (preprint) in England among LTCF residents (median age 86 years) compared vaccine effectiveness of a first dose of either Vaxzevria or Comirnaty against SARS-CoV-2 infection using linked health databases. Both vaccines were associated with reduced risk of infection from four weeks to at least seven weeks after the injection. The effectiveness of the first dose was estimated to be 56% (95% CI: 19–76) at 28–34 days and 62% (95% CI: 23–81) at 35–48 days following a single dose of Comirnaty or Vaxzevria [28]. Estimates were similar to those observed by Britton et al. among LTCF residents in the US where partial vaccination with Comirnaty (from 14 days after the first dose until seven days after the second) was 63% (95% CI: 33–79) effective in preventing SARS-CoV-2 infection [25].

In a register-based cohort study conducted by Monge et al. (preprint) in Spain among LTCF residents aged 65 years and above who received Comirnaty between 27 December 2020 and 10 March 2021, the overall vaccine effectiveness against documented SARS-CoV-2 infection among individuals with and without previous history of COVID-19 was 51% (95% CI: 49.7–52) 15–21 days after the first dose, 61.9% (95% CI: 60.8–63) 22–28 days after the first dose and 81.2% (95% CI: 80.2–82.7) from 29 days after the first dose (considered as a *proxy* for ≥ 7 days after the median time of administration of the second dose at 21 days from the first dose) [30]. More recent estimates from the same study published by Mazagatos et al. showed that vaccine effectiveness of one dose (from 14 days after injection) in preventing SARS-CoV-2 infection, asymptomatic SARS-CoV-2 infection, hospitalisation and death was 50.5% (95% CI: 37.1–61.1), 58.0% (95% CI: 41.7–69.7), 53.0% (95% CI: 25.7–70.3) and 55.6% (95% CI: 26.6–73.2) respectively. The estimated vaccine effectiveness of full vaccination was 71.4% (95% CI: 55.7–81.5), 69.7% (95% CI: 47.7–82.5), 88.4% (95% CI: 74.9–94.7) and 97.0% (95% CI: 91.7–98.9) respectively [29].

A last study conducted by Martínez-Baz et al. in the general population in Navarre, Spain, reported that among people aged 60 years and above, the effectiveness of Comirnaty against symptomatic infection was 30% (95% CI: 10–35) and 77% (95% CI: 56–88) respectively from 14 days after the first dose and from 14 days after the second dose of any COVID-19 vaccine (Comirnaty, Spikevax or Vaxzeria) [21].

Table 4. Adjusted vaccine effectiveness [% (95% CI); time after injection] of one and two doses against SARS-CoV-2 infection (any, symptomatic, asymptomatic) in individuals at risk of severe COVID-19 outcome, elderly and LTCF residents as reported in preprint/peer-reviewed studies (as of 14 July 2021)

	Comirnaty		Vaxzeria		Pooled analysis for several products		Ref.
	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	
Any infection in LTCF residents	63% (33-79) 65% (29-83) at 35-48 days		68% (34-85)		V/C 56% (19-76) at 28–34 days 62% (23-81) at 35-48 days		[25] [28] [^]
	21% (-11-44) >14 days	64% (14-84) >14 days					[24] [^]
	-17% (-45-50) ≥14 days until dose 2	11% (-25-37) 0-7 days 53% (29-69) >7 days					[23] [^]
	51% (49.7-52.3) 15-21 days	81.2% (80-82) ≥29 days after dose 1					[30] [^]
	61.9% (60.8-63) 22-28 days						
					S/C 50.5% (37.1- 61.1) >14 days	S/C 71.4% (55.7- 81.5) ≥7 days	[29]
Asymptomatic infection in LTCF residents					S/C 58.0% (41.7- 69.7) >14 days	S/C 69.7% (47.7- 82.5) ≥7 days	[29]
Any infection in 65 + living at home requiring support	31% (6- 50) 14 days until dose 2	71% (46-85) 0-7 days 86% (78-91) >7days					[23] [^]
Symptomatic infection in 60+	30% (10-35) ≥14 days	77% (56-88) ≥14 days					[21]
Symptomatic infection in 70+			73% (27-90) >35 days [#]				[27]
Any infection in 80+	17.2% (12.4- 21.7) up to two weeks after the first dose	85.6% (84.3-86.7) seven days					[18] [^]
	36.6% (32.6- 40.3) from two weeks after the first dose to six days after the second dose						
Symptomatic infection 80+	70% (59-78) 2-34 days	89% (85-93) ≥14 days					[27]
Any infection in 85+	22% (-47-58) from 14 days until dose 2	55% (-9-82) 0-7 days 77% (50-89) >7days					[23] [^]
	19% (-4-38) from 14 days until dose 2	53% (32-68) 0-7 days 71% (58-80) >7 days					[23] [^]

S (Spikevax), C (Comirnaty), V (Vaxzeria). [^]Preprint

Table 5. Adjusted vaccine effectiveness [% (95% CI); time after injection] of one and two doses against COVID-19 related hospitalisation in individuals at risk of severe COVID-19 outcome, elderly and LTCF residents as reported in preprint/peer reviewed studies (as of 14 July 2021)

	Comirnaty		Vaxzevria		Pooled analysis for several products		Ref.
	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	
LCTF residents	44% (38-50)* 14 days until dose 2	50% (43-56)* 0-7 days					[23] [^]
	34% (4-55)** 14 days until dose 2	84% (56-94)** 0-7 days 50% (45-55)* >7 days 75% (46-89)** >7 days					
					C/V 53.0% (25.7-70.3) >14 days	C/V 88.4% (74.9-94.7) ≥7 days	[29]
Individuals 65+ living at home and requiring support	28% (23-33)* 14 days until dose 2	39% (33-44)* 0-7 days					[23] [^]
	36% (-13-63)** 14 days until dose 2	95% (61-99) ** 0-7 days 37% (34-41)* >7 days 87% (70-95)** >7 days					
Individuals at high risk of severe COVID-19	13% (7-18)* 14 days until dose 2	15 (8-20)* 0-7 days					[23] [^]
	18% (-48-54)** 14 days until dose 2	92% (42-99)** 0-7 days -1% (-3 - -17)* >7 days 81% (49-93)** >7 days					
Individuals 65+					C/S 64% (28-82) ≥14 days	C/S 94% (49-99) ≥14 days	[26]
Individuals 80+	43% (33-52) 2-34 days		37% (3-59) ≥14 days				[27]
	32.6% (26.3-38.5) 0-14 days	91.9% (90.4-93.2) >7 days					[18] [^]
Individuals 80+ (hospitalisation for severe disease)	54.1% (49.2-58.6) ≥14 days until seven days after dose 2						
	36.2% (29.2-42.4) 0-14 days	91.2% (89.8-92.4) >7 days					[18] [^]
Individuals 85+	55.8% (50.4-60.6) ≥14 days until seven days after dose 2						
	27% (18-35)* ≥14 days	48% (41-54)* 0-7 days					[23] [^]
	66% (-18-90)** 14 days until dose 2	45% (39-51)* >7 days No data on COVID-19 admission					

S (Spikevax), C (Comirnaty), V (Vaxzeria). *All cause admissions; **COVID-19-related admissions. [^]Preprint

Table 6. Adjusted vaccine effectiveness [% (95% CI); time after injection] of one and two doses against COVID-19 related death in individuals at risk of severe COVID-19 outcome, elderly and LTCF residents as reported in preprint/peer reviewed studies (as of 14 July 2021)

	Comirnaty		Vaxzevria		Pooled analysis for several products		Ref.
	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	
Death in LTCF residents	-23% (-9 - -39)* 14 days until dose 2	63% (54-70) 0-7 days*					[23]^
	-2% (-35-23)** 14 days until dose 2	No estimates for COVID-19 related death at 0-7 days 26% (17-34)* >7 days 89% (81-93)** >7 days					
					C/S 55.6% (26.6-73.2) > 14 days	C/S 97.0% (91.7-98.9) ≥7 days	[29]
Death in people older than 65 years living at home and requiring support	21% (11-30)* 14 days until dose 2	70% (61-77)* 0-7 days No estimates for COVID-19 related death at 0-7 days					[23]^
	2% (-54-37)** 14 days until dose 2	62% (57-66)* >7 days 97% (88-99)** >7 days					
Death in 80+	40.3% (31.3-48.1) 0-14 days	92.6% (90.6-94.1) >7 days					[18]^
	56.6% (49.3-62.8) ≥14 days until seven days after dose 2						
	51% (47-62) 2-34 days						[27]
Death in people older than 85 years	50% (38-60)* 14 days until dose 2	80% (70-87)* 0-7 days					[23]^
	-15% (-822-86)** 14 days until dose 2	73% (66-79)* >7 days No estimates for COVID related death					
Death in individuals at high risk of severe COVID-19	13% (1-25)* 14 days until dose 2	72% (60-80)* 0-7 days					[23]^
	41% (-437-93)** 14 days until dose 2	46% (37-54)* >7 days No estimates for COVID related death					
Death in all priority groups including frontline healthcare workers	7% (-15-25) 14 days until dose 2	94% (90-96) >7 days					[23]^

S (Spikevax), C (Comirnaty), V (Vaxzeria). *All death, **COVID-19-related death. ^Preprint

1.2.3 Healthcare workers

Vaccine effectiveness data among healthcare workers are available from several observational studies conducted in Denmark [23,24], the United Kingdom (UK) [31,32], the USA [33,34], Israel [35,36] and Italy [37]. Results are summarised in Table 7.

In a cohort study by Emberg et al. among 440 748 healthcare workers in Denmark based on linked health databases, vaccine effectiveness after the first dose of Comirnaty and up to the administration of the second was 16% (95% CI: 4–26) against SARS-CoV-2 infection and 18% (95% CI:-48–54) against COVID-19-related

hospitalisation, increasing to 80% (95% CI: 77–83) and 81% (95% CI: 77–83) respectively after the second dose [23]. In a second Danish study by Moustsen-Helms et al. (331 039 healthcare workers), effectiveness against infection was 17% (95% CI: 4–28) measured 14 days after the first dose and before the second. Effectiveness measured seven days after the administration of the second dose increased to 90% (95% CI: 82–95) [24].

An observational study conducted by Fabiani et al. among 6 423 healthcare workers in Treviso Province in Italy showed vaccine effectiveness against any SARS-CoV-2 infection to be 84% (95% CI: 40–96) 14–21 days after the first dose and 95% (95% CI: 62–99) at least seven days from the second dose [37].

In a cohort study conducted by Hall et al. among healthcare workers participating in the SARS-CoV-2 Immunity & Reinfection EvaluationN (SIREN) project in the UK (23 000 healthcare workers with weekly swabbing), a single dose of Comirnaty showed a vaccine effectiveness of 72% (95% CI: 58–86) 21 days after the first dose and 86% (95% CI: 76–97) seven days after the second dose against any SARS-CoV-2 infection. However, it should be noted that this cohort was vaccinated and followed-up when the dominant VOC in circulation was Alpha [32].

A second observational healthcare worker cohort study conducted by Lumley et al. in the UK aimed to assess the protection of either one or two doses of Vaxzevria or Comirnaty against symptomatic and asymptomatic infection. Compared to unvaccinated seronegative healthcare workers and up to 42 days after the first injection, a single dose of either Vaxzevria or Comirnaty reduced the incidence of symptomatic infection by 67% (95% CI: 48–79) and any asymptomatic infection by 64% (95% CI: 50–74). Two vaccine doses or seropositivity (previous infection) reduced the incidence of any PCR-positive result with or without symptoms by 90% (95% CI: 62–98) and 85% (95% CI: 74–92), respectively [31].

Effectiveness of Spikevax and Comirnaty was assessed in an observational cohort study conducted by Thompson et al. among healthcare workers, first responders and other essential and frontline workers in the US [33]. Effectiveness of partial immunisation against PCR-confirmed SARS-CoV-2 infection was 80% (95% CI: 59–90), measured from 14 days after the first dose up until the second one, while for full immunisation with two doses of an mRNA vaccine, effectiveness was 90% (95% CI: 68–97). Levels of protection were similar to those reported by Pilishvili et al (see Table 7 below) [38].

In a large cohort study by Swift et al. among healthcare workers in the US (preprint), the effectiveness of partial vaccination (from 14 days after the first dose to 14 days after the second) with either of the two mRNA vaccines available (Comirnaty, Spikevax) against PCR-confirmed SARS-CoV-2 infection was 78% vs. 96% after full vaccination (from 14 days after the second dose) [34].

In a retrospective cohort study conducted by Angel et al. in Tel Aviv, Israel, including 6 710 healthcare workers who underwent periodic testing for SARS-CoV-2 infection, vaccination with two doses of Comirnaty was effective against both symptomatic (adjusted VE=98%; 95% CI: 93–100) and asymptomatic infection (adjusted VE=91%; 95% CI: 75–97). Vaccine effectiveness of one dose was not significant for asymptomatic disease but significant, though to a lesser extent, when compared to the effectiveness seen after two doses against symptomatic disease [35]. In another study in Israel by Tang et al. at Jude Children's Research Hospital, routine screening of asymptomatic workers and targeted testing for symptomatic individuals and those with known exposure was initiated. The study showed that vaccine effectiveness against asymptomatic infection was 42% (95% CI: -13–70) after the first dose and before the second (median interval between doses, 21 days [range, 11–49 days]), 75% (95% CI: -9–89) within seven days of the second dose, and 90% (95% CI: 78–96) seven days or more after the second dose [36].

Table 7. Adjusted vaccine effectiveness [% (95% CI); time after injection] of one and two doses against COVID-19 infection (any, asymptomatic or symptomatic) in healthcare workers as reported in preprint/peer-reviewed studies (as of 14 July 2021)

Outcome	Comirnaty		Spikevax		Pooled analysis for several products		Ref.
	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	
Any infection	16% (4-26) until second dose	80% (77-83) more than seven days after the second dose					[23]^
	17% (4-28) 14 days	90% (82-95) seven days after					[24]^
	78% (71-82) More than 14 days after first dose and ≤14 days after second dose	96% (95-97) More than 14 days after second dose	91% (80-96) More than 14 days after first dose and ≤14 days after second dose	98% (90-99) More than 14 days after second dose			[34]^
	84% (40-96) 14-21 days	95% (62-99) at least seven days					[37]
Symptomatic infection					C/S 80 (59-90) 14 days after first dose but before second dose	C/S 90 (68-97) ≥14 days	[33]
					C/S 81.7% (74.3-86.9) ≥14 days	C/S 93.5% (86.5-96.9) ≥7 days	[38]
	83.3% (14.8-96.7) 14-21 days	93.7% (50.8- 99.2) ≥7 days					[37]
					C/S 67% (48-79) up to 42 days after vaccination	C/S 90% (62-98) 14 days following a second vaccination	[31]
Asymptomatic infection	97% (91-99) 7-21 days after first dose	98% (93-100) >7 days					[35]
					C/S 64% (50-74) up to 42 days after vaccination	C/S 85 (74-98) 14 days following a second vaccination	[31]
	42% (-13-70) within 21 days after dose 1	90% (78-96) ≥7 days					[36]
52% (-26 - 81) 7-21 days after first dose	91% (75-97) >7 days					[35]	
Hospital admission	18% (-48-54) until second dose	81% (43-93) more than seven days after the second dose					[23]^

1.2.4 Vaccine effectiveness against variants of concern

Several studies have indicated that, although the sera of convalescents and those having been vaccinated demonstrate reduced neutralisation capacity against VOCs, including the Delta, when compared to ancestral strains, they still effectively neutralise VOCs in-vitro [39-41]. One study that evaluated the neutralising capability of sera collected from vaccinated individuals 28 days after receiving two doses of BBV152 (Covaxin, an inactivated virus-based COVID-19 vaccine developed by Bharat Biotech) (n=17), observed a reduction in neutralising titres of 2.7-fold and 3.0-fold against Delta and Beta VOCs, respectively, when compared to the B.1 (D614G) variant [40]. In another study that assessed the neutralisation capacity after a single dose of Vaxzevria the levels of antibodies neutralising Delta and Beta VOCs were significantly lower, when compared to D.614G and the Alpha VOC [39]. Five weeks after the second dose of Comirnaty, there was a three-fold and 16-fold reduction in neutralising titres against Delta and Beta VOCs, respectively, when compared to the Alpha VOC.

Evidence on vaccine effectiveness against VOCs comes from several observational studies, most of them based on a test-negative design, and linked databases as data sources. Tables 8 and 9 summarise the results of vaccine effectiveness by outcome, type of vaccine and VOC.

A recent population-based study conducted by Nasreen et al. (preprint) in Ontario, Canada, used linked vaccination, laboratory testing, and extensive health administration reported data on effectiveness of Spikevax, Comirnaty and Vaxzevria against symptomatic infection and severe outcomes due to VOCs [42]. Vaccine effectiveness data were higher against any outcomes due to the Alpha variant. After partial vaccination, vaccine effectiveness against severe outcomes caused by any VOCs was generally higher than effectiveness reported against symptomatic infection, irrespective of the vaccine administered. Full vaccination was assessed seven days after the second dose and effectiveness increased against all outcomes, when data were available.

A study conducted in England by Bernal et al. (preprint) using a test negative design reports that the vaccine effectiveness against symptomatic infection with Delta VOC after a single vaccine dose (21 days or more after the first dose up to the day before the second) of either Comirnaty or Vaxzevria was 33%, reaching 88% and 61% after two doses (14 days or more after the second dose) of Comirnaty and Vaxzevria, respectively. After one vaccine dose of either Comirnaty or Vaxzevria, the effectiveness against symptomatic infection with the Delta VOC was reduced by approximately 20% compared to Alpha. However, after two vaccine doses the reduction was smaller for both Comirnaty and Vaxzevria [43].

A cohort study conducted by Sheik et al. in Scotland between 1 April and 6 June 2021, observed that the full course of both Comirnaty and Vaxzevria (at least 28 days after second dose) was effective in reducing the risk of SARS-CoV-2 infection, while the effectiveness of a single dose (at least 28 days after the first dose) was notably lower for both vaccines. The effect of the full vaccination course for both vaccines on infection with Delta VOC appeared to be diminished when compared to the Alpha VOC [44].

A test-negative case-control study conducted by Abu-Raddad in Qatar estimated that the vaccine effectiveness of one dose of Comirnaty against any documented infection with the Beta VOC was low (16.9%; 95% CI: 10.4–23.0), reaching 75.0% (95% CI: 70.5–78.9) 14 days or more after the second dose [45]. The estimated effectiveness against any documented infection with the Alpha VOC was 29.5% (95% CI: 22.9–35.5) after the first dose and 89.5% (95% CI: 85.9–92.3) 14 days or more after the second dose. Pooled vaccine effectiveness against severe, critical, or fatal disease due to any SARS-CoV-2 variant (Alpha or Beta) was very high after the second dose (97.4%; 95% CI: 92.2–99.5) compared to 39.4% (95% CI: 24.0–51.8) after one dose.

For two doses, the estimates above follow the same trend as those reported by Stowe et al. during routine effectiveness monitoring in the UK (preprint): vaccine effectiveness against hospitalisation with Delta was similar to that seen with Alpha: 94% (46–99) and 96% (86–99) after one dose and after two doses of Comirnaty respectively; 71% (51–83) and 92% (75–97) after one dose and after two doses of Vaxzevria respectively [46].

In a preprint by Chung et al. (preprint) in Ontario, Canada, two doses of mRNA vaccines (Comirnaty or Spikevax) showed high effectiveness against both symptomatic infection (91%, 95% CI: 89–93) and severe outcomes (98%, 95% CI: 88–100) due to the Alpha variant. Effectiveness of one dose was lower compared to two doses and increased from 48% (95% CI, 41–54%) at 14–20 days to reach a plateau of 71% (95% CI: 63–78%) at 35–41 days [47].

In a sub-analysis of individuals aged 70+ (excluding LTCF residents) by Chung et al., vaccine effectiveness against symptomatic infection due to the Alpha variant increased from 24% (95% CI: 7–38) between 21–27 days after injection to 85 (95% CI: 38–97) at 42–48 days. Effectiveness of one dose protection against severe outcomes due to the Alpha variant also increased from 58% (95% CI: 35–72) at 14–20 days to 93% (95% CI: 71–98) at ≥ 35 days [47]. The level of protection with the second dose (≥ 7 days) was 94 (95% CI: 87–97) and 97 (95% CI: 86–99) respectively against symptomatic infection and severe outcomes.

Estimates from Skowronski et al. (preprint) from a case control study in individuals aged 70+ showed that single dose vaccine effectiveness against any infection due to non-VOC, Beta, and Gamma was respectively 72% (95% CI: 58–81), 67% (95% CI: 57–75) and 61% (95% CI: 45–72), 21 days or more after administration [48].

Table 8. Adjusted vaccine effectiveness [% (95% CI); time after injection] of one and two doses of against COVID-19 infection (any or symptomatic) caused by any of the Alpha, Beta, Gamma and Delta VOCs as reported in preprint/peer reviewed studies (as of 14 July 2021)

VOC	Spikevax		Comirnaty		Vaxzeria		Pooled analysis for several products		Ref
	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	
Non-VOCs	SI 54% (28-70) ≥14 days	SI 89% (65-96) ≥7 days	SI 61% (54-68) ≥14 days	SI 93% (86-96) ≥7 days	SI 67% (38-82) ≥14 days				[42] [#]
							S/C AI 72% (58-81) ≥21 days		[48]
Alpha	SI 83% (80-86) ≥14 days	SI 92% (86-96) ≥7 days	SI 66% (64-68) ≥14 days	SI 89% (86-91) ≥7 days	SI 64% (60-68) ≥14 days				[42] [^]
			SI 49.2% (42.6-55.0) ≥21 up to dose 2	SI 93.4% (90.4-95.5) ≥14 days	SI 51.4% (47.3-55.3) ≥21 up to dose 2	SI 66.1% (54.0-75.0) ≥14 days	C/V SI 51.1% (47.3-57.7) ≥21 up to dose 2	SI 86.8% (83.1-89.6) ≥14 days	[43] [^]
			SI 27% (13-39)	SI 92% (88-94)	SI 39% (32-45)	SI 81% (72-87)		SI 92% (90-93)	[44]
			AI 38% (29-45) at least 28 days after dose 1	AI 92% (90-93) at least 28 days after dose 2	AI 37 (32-42) at least 28 days after dose 1	AI 73% (66-78) at least 28 days after dose 2		at least 28 days after dose 2	[45]
			AI* 29.5% (22.9-35.5)	AI* 89.5% (85.9-92.3) ≥14 days					[47]
							S/C SI 60% (57-64) ≥14 days	S/C SI 91% (89-93) ≥7 days	[48] [^]
Beta			AI 16.9% (10.4-23.0)	AI 75.0% (70.5-78.9) ≥14 days				[45]	
Beta/Gamma	SI 77% (63-86) ≥14 days		SI 60% (52-67) ≥14 days	SI 84% (69-92) ≥7 days	SI 48% (28-63) ≥14 days			[42] [^]	
Gamma							S/C AI 61% (45-72) ≥21 days	[48] [^]	
Delta	SI 72% (57-82) ≥14 days		SI 56% (45-64) ≥14 days	SI 87% (64-95) ≥7 days	SI 67% (44-80) ≥14 days				[42] [^]
			SI 33.2% (8.3-51.4) ≥21 up to dose 2	SI 87.9% (78.2-93.2) ≥14 days	SI 32.9% (19.3-44.3) ≥21 up to dose 2	SI 59.8% (28.9-77.3) ≥14 days	C/V SI 33.5% (20.6-44.3) ≥21 up to dose 2	C/V SI 80.9% (70.7-87.6) ≥14 days	[43]
			SI 33% (15-47)	SI 83% (78-87)	SI 33% (23-41)	SI 61% (51-70)		C/V SI 79% (75-82) at least 28 days after dose 2	[44]

S (Spikevax), C (Comirnaty), V (Vaxzeria), NE (no estimate), SI (Symptomatic infection), AI (any infection). [^]Preprint
[#] Non-VOC specimens with no lineage information and N501Y-/E484K- specimens collected prior to 1 April 2021.

& Non-VOC: Whole Genom Sequencing=non-VOC or Screening RT-PCR=Negative for N501Y (presumptive) *In ≥70 years old.

Table 9. Adjusted vaccine effectiveness [% (95% CI); time after injection] of one and two doses of against severe COVID-19 infection caused by any of the Alpha, Beta, Gamma and Delta VOCs as reported in preprint/peer-reviewed studies (as of 14 July 2021)

Variant	Spikevax		Comirnaty		Vaxzeria		Pooled analysis for several products		Ref
	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	
Non- VOC	H/D 57% (28-75) ≥14 days	H/D 96% (70-99) ≥7 days	H/D 68% (54-78) ≥14 days	H/D 96% (82-99) ≥7 days					[42]#^
Alpha	H/D 79% (74-83) ≥14 days	H or D 94% (89-97) ≥7 days	H/D 80% (78-82) ≥14 days	H/D 95% (92-97) ≥7 days	H/D 85% (81-88) ≥14 days				[42]^
			H/D 54.1% (26.1-71.9)*	H/D (81.7- 100) ≥14 days*					[45]
			H 83% (62-93)	H 95% (78-99)	H 76% (61-85)	H 86% (53-96)	C/V H 78% (65-86)	C/V H 92% (78-97)	[46]^
							S/C H/D 70% (60-77) ≥14 days	S/C H/D 98% (88-100) ≥7 days	[47]^
Beta			H/D 0.0% (0.0-19.0)* Unknown	H/D 100% (73.7- 100) ≥14 days*					[45]
Alpha/ Beta			H/D 39.4% (24.0-51.8)*	H/D 97.4% (92.2- 99.5) ≥14 days*					[45]
Gamma	H/D 89% (73-95) ≥14 days		H/D 77% (69-83) ≥14 days	H/D 95% (81-99) ≥7 days	H/D 83% (66-92) ≥14 days				[42]^
Delta	H/D 96% (72-99) ≥14 days		H/D 78% (65-86) ≥14 days		H/D 88% (60-96) ≥14 days				[42]
			H 94% (46-99)	H 96% (86-99)	H 71% (51-83)	H 92% (75-97)			[46]^

S (Spikevax), C (Comirnaty), V (Vaxzeria). H (Hospitalisation) D (Death). ^Preprint.

* Severe, critical, or fatal disease

Non-VOC specimens with no lineage information and N501Y-/E484K- specimens collected prior to 1 April 2021.

1.3 Summary of the evidence and knowledge gaps

Available data, across different population groups and SARS-CoV-2 variants of concern (VOCs), confirm that the protection against asymptomatic and symptomatic infection and severe disease outcomes conferred by two vaccine doses (Comirnaty, Spikevax and Vaxzevria) is higher than with partial vaccination (i.e. one dose of a two-dose regimen). The effectiveness of a single dose tends to increase over time following its administration, but the evidence on its long-term effectiveness is limited.

Observational studies conducted in the general population were based on large cohorts and diverse settings. These studies showed similar results in terms of a greater vaccine effectiveness of a two-dose course of vaccination against asymptomatic and symptomatic infection and severe outcomes, including hospitalisation and death, compared to partial vaccination [14,21]. Some effectiveness against asymptomatic infection has also been reported, which is an important aspect for controlling the circulation of the virus [19]. These results from real-life settings confirm previous findings on vaccine effectiveness from randomised controlled trials for Comirnaty, Spikevax and Vaxzevria. Given that most observational studies were performed in the initial phase of the COVID-19 campaigns, as well as in countries where only or predominantly mRNA vaccines were used, most of the data refer to this type of vaccine (mostly Comirnaty).

Several observational studies were performed in those priority groups initially targeted by national campaigns because of their higher risk of severe SARS-Cov 2 infection outcomes (e.g. elderly, LTCF residents) or exposure (healthcare workers). These studies confirm the superiority of a two-dose course of vaccination over a single

dose to protect against SARS-CoV-2 infection, hospitalisation and death. However, interestingly the effectiveness seems to vary, depending on the outcome, the vaccine product and the specific risk group, and in some cases it is lower than in the general population. Overall, data gathered from observational studies conducted among healthcare and other frontline workers provide similar results to those from randomised trials and studies in the general population. Healthcare workers were also prioritised during the early phase of the rollout in most countries and real-life data show that a complete two-dose vaccination course ensured higher protection against asymptomatic and symptomatic infection than a partial one.

Available vaccine effectiveness data on partial and full vaccination against different outcomes and VOCs show that the level of protection conferred by one dose varies depending on the vaccine product, the outcomes studied (asymptomatic infection, symptomatic infection and severe disease, including hospitalisation and death) and the variant against which the effectiveness is tested (Alpha, Beta/Gamma and Delta). The available evidence indicates that individuals who are partially vaccinated are less protected against symptomatic infection with the Delta VOC than against the Alpha VOC, regardless of the vaccine type. However, the effectiveness of a two-dose regimen is higher than partial vaccination across outcomes and VOCs, and confers nearly equivalent protection against the Delta to that for the Alpha VOC.

In general, the estimated effectiveness of partial vaccination seems to be largely affected by the time after injection or time interval used for the analysis, and generally increases with time. However, the evidence of long-term effectiveness of partial vaccination is limited by the fact that the second dose is generally given a few weeks after the first dose. Further analysis of the effectiveness of partial vaccination for different outcomes, vaccine products, population groups and VOCs with longer follow-up between first and second dose may provide additional evidence on the potential advantages of a delayed second dose in special situations.

There are several limitations related to observational studies. Since the vaccine rollout is a dynamic process, with different vaccines administered and different populations registered over time based on phased implementation and prioritisation strategies, studies may differ in terms of population characteristics, products used and circulation of VOCs. This may affect the estimate of the effectiveness against specific outcomes. In addition, different definitions were used to define and estimate the vaccine effectiveness of partial and full vaccination in terms of days from the injection and time intervals for the assessment of outcomes. Sample collection approaches (self-sampling, systematic sampling, sampling following symptoms) also varied across studies which may affect comparability. For some studies, performed during the initial phase of the vaccination campaign, data on the effectiveness of the second dose are lacking because the follow-up period of the study was too short. Finally, observational studies are subject to confounding factors and misclassification issues that can occur in relation to the outcome, the exposure (vaccine), and the virus characterisation for those studies assessing effectiveness against VOCs.

2. Vaccination of previously infected individuals

Of the four COVID-19 vaccines currently authorised for use in the EU/EEA, three of them have a two-dose regimen: Comirnaty, Spikevax and Vaxzevria. For individuals that have recovered from a prior SARS-CoV-2 infection, a number of studies indicate that a single dose of Comirnaty, Spikevax or Vaxzevria generates antibody and cellular immune responses that are comparable - in the short term - to naïve individuals who complete a two-dose regimen. However, no evidence is yet available about clinical endpoints, such as 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.

2.1 Data from randomised controlled trials

In results published from clinical trials for Comirnaty, no data are available on effectiveness in previously infected individuals [49,50]. For the COVID-19 vaccines Spikevax and Vaxzevria, data from clinical trials were insufficient to assess vaccine effectiveness in participants with evidence of prior SARS-CoV-2 infection [1].

2.2 Data from observational studies

Pre-print and peer-reviewed data on immune responses in previously infected individuals receiving a single dose of vaccine are largely drawn from longitudinal healthcare worker cohort studies, with most publications focusing on the mRNA vaccines Comirnaty and Spikevax.

For Comirnaty, several studies have demonstrated that previously infected individuals develop significantly higher titres of anti-spike serum antibodies following a single dose immunisation, when compared to naïve individuals receiving a single dose [51-57]. Furthermore, the capacity of serum antibodies, developed after a single dose in previously infected individuals, to neutralise Alpha, Beta and Gamma VOCs in vitro is comparable to the neutralising capacity of serum antibodies derived from naïve individuals completing a two dose regimen [51,52,58].

In a pre-print study, Angyal et al. use a multi-centre, prospective, observational cohort of healthcare workers enrolled in the UK PITCH (Protective Immunity from T cells to Covid-19 in Health workers) study to compare individuals receiving one (n=216) or two (n=21) Comirnaty doses, evaluated 28 days post vaccination. SARS-CoV-2-specific T-cell responses were six-fold higher in previously infected individuals receiving one dose of Comirnaty than in naïve individuals receiving a single dose, with vaccination also improving the breadth of T-cell responses generated in previously infected individuals. T-cell responses in previously infected individuals receiving one dose of Comirnaty were equivalent to naïve individuals receiving two Comirnaty doses. Serum anti-spike IgG titres following a single dose in those previously infected were 6.8-fold higher than in naïve individuals following a single dose, and 2.9-fold higher than in naïve individuals given two doses three weeks apart. Finally, the study compared post-vaccine antibody responses to spike proteins representing D614G and SARS-CoV-2 Alpha, Beta and Gamma VOCs in a subset of naïve and SARS-CoV-2-infected individuals using a surrogate neutralisation assay, based on competition for ACE2 binding to spike. A single dose of Comirnaty resulted in significantly higher surrogate neutralisation titres in those with prior infection than in naïve healthcare workers.

Several studies investigating single dose regimens for previously infected individuals have assessed immune responses in cohorts where either Comirnaty or Spikevax mRNA vaccines are administered, without disaggregating analyses by individual vaccine brand. In all studies, previously infected individuals develop significantly higher titres of anti-spike serum antibodies following a single dose of mRNA vaccine, when compared to naïve individuals receiving a single dose of mRNA vaccine [59-62].

Krammer et al. [63] use a convenience sample from the US PARIS (Protection Associated with Rapid Immunity to SARS-CoV-2) cohort study. Among 110 individuals who received a first dose of Comirnaty or Spikevax, 67 were seronegative and 43 seropositive prior to vaccination. Seropositive individuals developed earlier antibody responses (within four days) and sustained higher antibody titres up to day 27 when compared to seronegative individuals. Antibody titres of those vaccinated with pre-existing immunity were 10 to 45 times as high as those of persons vaccinated without pre-existing immunity at all time points after the first vaccine dose. Moreover, their titres also exceeded the median antibody titres measured in participants without pre-existing immunity after the second vaccine dose by more than a factor of 6. Although the antibody titres of those vaccinated without pre-existing immunity increased by a factor of 3 after the second vaccine dose, no increase in antibody titres was observed in the COVID-19-recovered individuals who received the second vaccine dose. The authors undertake separate analyses by vaccine brand, observing no substantial difference in the dynamics of antibody responses elicited by Comirnaty and Spikevax after the first dose of vaccine.

Saadat et al. [61] evaluated antibody responses at days 0, 7 and 14 post vaccination with a single dose of Comirnaty or Spikevax in a US healthcare worker cohort. Among 59 individuals, 17 had experienced no prior SARS-CoV-2 infection, while 16 had experienced prior asymptomatic infection, and 26 had experienced prior

symptomatic infection. Antibody responses at day 7 were observed exclusively in those that had experienced prior infection, with equivalent responses, irrespective of symptoms. At day 14, previously infected healthcare workers showed significantly higher antibody levels than those who had not been infected, with equivalent responses seen when comparing between symptomatic and asymptomatic individuals.

Although several studies demonstrate robust serological responses to a single dose of mRNA vaccines in individuals previously infected with SARS-CoV-2, studies evaluating serological responses following a single dose of the Vaxzevira adenovector vaccine are limited. In a pre-print study of Swedish healthcare workers, Havervall et al. [64] compared spike-specific IgG and pseudo-neutralising spike-ACE2 blocking antibodies against SARS-CoV-2 wild type and Alpha, Beta and Gamma VOCs following two doses of Comirnaty and a single dose of Vaxzevira in 232 healthcare workers with and without previous COVID-19. The post-vaccine levels of spike-specific IgG and neutralizing antibodies against the SARS-CoV-2 wild type and all three VOCs were similar or higher in participants receiving a single dose of Vaxzevira post SARS-CoV-2 infection (both <11 months post infection (n=37) and ≥11 months post infection (n=46)) compared to participants who received two doses of Comirnaty (n=149).

Additional work by Tut et al. [58], currently in pre-print, highlights the impact of prior infection on humoral and cellular responses following a single administration of Comirnaty or Vaxzevira. Among 89 staff and 35 residents at an LTCF, 20% of staff and 34% of residents had evidence of prior infection. In naïve LTCF residents, spike-specific IgG antibody responses developed more slowly than among younger staff after a single dose, with notably poor responses in the first 21 days. No differences were observed between age groups at 22–42 days or 42+ days after the single dose vaccination. However, in previously infected vaccine recipients, antibody generation was rapid, occurring within 21 days in all individuals, irrespective of age. Single vaccination in infection-naïve individuals generated antibodies that provided only moderate Spike-ACE2 binding inhibition for Alpha, Beta and Gamma VOCs, whereas inhibition was significantly higher for previously infected individuals receiving a single dose of vaccine. Spike-specific cellular responses post vaccination, as determined by peripheral blood mononuclear cells (PBMC) IFN- γ T cell ELISpot assay, were modest in those without prior infection and detected in 45% of those below the age of 65 years and 44% of those above this age. In contrast, cellular responses were detectable in 100% of individuals with a prior history of infection vaccinated with a single dose, and were of larger magnitude, with no differences observed across age groups. Although individuals received one dose of either Comirnaty or Vaxzevira in the study, the authors observed no statistical difference in immune responses between the two vaccines.

Real-world data on antibody response post-vaccination in the general population are limited. However, in a pre-print seroconversion study of 45 965 adults enrolled in the UK's national COVID-19 Infection Survey, 3 767 (8.2%) and 2 067 (4.5%) previously infected participants received one dose of Vaxzevira or Comirnaty, respectively. In total, 23 368 (50.8%), 14 894 (32.4%), and 1 869 (4.1%) participants without evidence of prior infection received one dose of Vaxzevira, one dose of Comirnaty, and two doses of Comirnaty, respectively. In those without evidence of prior infection, older participants had lower anti-spike IgG responses than younger participants after receiving a single dose of vaccine, with especially marked effects in those over 60 years. Two vaccine doses in a conventional prime-boost regimen achieved high responses across all age groups. In participants with prior evidence of infection, a high percentage (≥94%) of individuals achieved positive antibody responses 28 days after vaccination, irrespective of age and vaccine given, similar to the positivity rate in participants without prior infection who received two doses of Comirnaty. However, the authors highlight the need for vaccine effectiveness data against clinical outcomes, given the incomplete relationship between protection from infection and seroconversion [65].

2.3 Summary of the evidence and knowledge gaps

Pre-print and peer-reviewed data on immune responses in previously infected individuals receiving a single dose of vaccine are largely drawn from longitudinal healthcare worker cohort studies. Studies of single-dose regimens of Comirnaty, Spikevax and Vaxzevira for previously infected individuals indicate antibody and cellular immune responses are comparable to naïve individuals who complete the two-dose regimen. However, immunological assessment in these studies typically occurs between one and four weeks post single dose vaccination, and data are sparse for comparing the long-term duration of protective immunity for such individuals with naïve persons completing a two-dose regimen [66]. Although serum antibodies developed after a single dose in previously infected individuals have been shown to neutralise the Alpha, Beta and Gamma VOCs in vitro, neutralisation data for the newly emerged Delta VOC is lacking. In the absence of a formal comparison taking into account a diverse set of previous infections, and COVID infections of different severity, caution must be exercised in translating immunogenicity data to protection from COVID-19 clinical outcomes. No evidence is currently available on clinical endpoints, such as risk of laboratory-confirmed infection and symptomatic disease for previously infected individuals receiving just one dose of vaccine intended as a two-dose regimen. In the context of the current lack of evidence for clinical endpoints and durability of immune responses generated via single-dose regimens in previously infected individuals, as a precaution countries should continue to administer two doses, as per EMA authorisation, particularly for older individuals and those at greatest risk of severe outcomes following SARS-CoV-2 infection, and with more rapid decline of antibodies and memory cells.

3. Heterologous vaccination schedules

Heterologous prime-boost vaccination schedules, also known as 'mix-and-match', involve using different vaccines for priming (first dose) and for boosting (second dose) the immune response to a specific microbe or antigen. Heterologous prime-boost regimens have been studied previously, although mostly in animal and pre-clinical research, for HIV, viral hepatitis, tuberculosis and malaria [68]. More recently, heterologous regimens against the human papillomavirus (HPV) [69] and Ebola virus [70] have been demonstrated to be immunogenic and safe in clinical trials.

In the case of COVID-19, a good immune response could be expected from combining different COVID-19 vaccines, as all licensed vaccines induce an immune response against the SARS-CoV-2 spike protein, and mixing vaccines could potentially boost the immune response [71]. Preliminary studies on heterologous prime-boost strategies (e.g. combining mRNA and adenoviral-vector vaccines) were conducted in animal models and indicated good immunogenicity for both humoral and cellular immune response [72,73].

By May 2021, following investigations by EMA's Pharmacovigilance Risk Assessment Committee (PRAC) and Committee for Medicinal Products for Human Use (CHMP) into very rare events of thrombosis with thrombocytopenia syndrome (TTS) after vaccination with Vaxzevria [74], five EU/EEA countries had started recommending the use of a second dose of an mRNA vaccine (Comirnaty or Spikevax) to individuals who received a first dose of Vaxzevria. At present, up to fifteen countries (Austria, Bulgaria, Czechia, Denmark, Finland, France, Germany, Iceland, Italy, Luxembourg, the Netherlands, Norway, Portugal, Slovenia and Spain) are using 'mix and match' schedules for people below a certain age threshold who received a first dose of Vaxzevria, or for individuals with risk factors or a history of thromboembolic conditions who already received a first dose of Vaxzevria. In Germany, where Delta variant cases have been increasing, on 1 July 2021 the Standing Committee on Vaccination (STIKO) published a draft recommendation on the use of an mRNA vaccine as the second dose for all individuals who received a first dose of Vaxzevria, irrespective of age and with a minimum interval of four weeks between doses [75].

Several ongoing studies are assessing the immunogenicity and reactogenicity of heterologous prime-boost combinations, most of them investigating 'mix and match' schedules of Vaxzevria with mRNA vaccines. Evidence currently available from randomised and observational clinical studies is summarised in the sections below.

3.1 Data from randomised studies

The ComCov is an ongoing UK-based multicentre, participant-blind, randomised trial to assess the immune response, efficacy and safety of four homologous and heterologous prime-boost COVID-19 vaccination schedules of Vaxzevria and Comirnaty (Vaxzevria/Vaxzevria, Vaxzevria/Comirnaty, Comirnaty/Comirnaty or Comirnaty/Vaxzevria) with four-week or 12-week dosing intervals [76]. The study started in February 2021, recruiting participants aged 50 years and above with no or mild-to-moderate comorbidity. In April, the trial was expanded to include Spikevax and NVX-CoV2373 by Novavax.

The interim safety analysis, based on self-reported solicited local and systemic symptoms collected in the seven days after both the first and second dose, indicated that both heterologous schedules induced greater systemic reactogenicity following the second dose compared to the corresponding homologous ones. Increased frequency of side effects such as fever, chills, fatigue, headache, joint pain, malaise, and muscle ache was observed, but no hospitalisations occurred due to these symptoms, which were mostly observed in the 48 hours after immunisation [77]. Furthermore, in the study arm where the first and second dose of the vaccine were given with a 4-week interval, no significant difference was observed among the vaccine schedules studied in terms of unsolicited adverse events within 28 days of the second dose. Up to 6 June 2021 (date of data-lock), among all participants there had been four serious adverse events across all groups, none of which were considered to be related to immunisation [78].

In terms of immunogenicity, according to the analysis of non-inferiority between each heterologous schedule and its homologous counterpart, the geometric mean concentration (GMC) of day 28 post second dose SARS-CoV-2 anti-spike IgG in Vaxzevria/Comirnaty recipients (12,906 ELU/ml) was superior to that in Vaxzevria/Vaxzevria recipients (1,392 ELU/ml), with a geometric mean ratio (GMR) of 9.2 (one-sided 97.5% CI: 7.5, ∞). In participants primed with Comirnaty, the study failed to show non-inferiority of the heterologous schedule Comirnaty/Vaxzevria (GMC 7,133 ELU/ml) against the homologous one (GMC 14,080 ELU/ml) with a GMR of 0.51 (one-sided 97.5% CI: 0.43, ∞). The geometric mean of T cell response at 28 days post second dose in the Vaxzevria/Comirnaty group was 185 SFC/106 PBMCs (spot-forming cells/106 peripheral blood mononuclear cells) compared to 50, 80 and 99 SFC/106 PBMCs for Vaxzevria/Vaxzevria, Comirnaty/Comirnaty and Comirnaty/Vaxzevria, respectively [78]. In summary, the highest antibody response was observed in individuals receiving the standard two doses of Comirnaty, but the response in the Vaxzevria/Comirnaty group was almost as high. In addition, despite the Comirnaty/Vaxzevria regimen not meeting non-inferiority criteria against its homologous counterpart, the GMCs of both heterologous schedules were higher than the homologous Vaxzevria schedule. The heterologous combination Vaxzevria/Comirnaty showed the highest T-cell response 28 days after the second dose, followed by Comirnaty/Vaxzevria.

Additional evidence is available from the CombivacS study [79], a multicentre, open-label, randomised, controlled, phase 2 trial conducted in April 2021 at five university hospitals in Spain in individuals aged 18–60 years. Study participants (mean age 44 years; 382 [57%] women and 294 [43%] men) had been previously vaccinated with a single dose of Vaxzevria eight to 12 weeks before enrolment and had not been previously infected with SARS-CoV-2. Participants were randomly assigned either to receive Comirnaty (intervention group: 450) or continue observation (control group: 226). Reactions within the first week after receiving Comirnaty as a second dose were mild or moderate. Most commonly reported adverse events were injection site pain, induration, headache, and myalgia; and no serious adverse events were reported. The study showed that individuals in the intervention group presented a significant increase in the geometric mean titres of receptor binding domain antibodies [from 71,5 BAU/mL (95% CI: 59,8-85,3) to 7756,7 BAU/mL (95% CI: 7371,5–8162) and IgG against trimeric spike protein [from 98,4 BAU/mL (95% CI: 85,7-113) to 3684,9 BAU/mL (3429,9–3958,8)] 14 days after administration of Comirnaty as a second dose following a first dose of Vaxzevria. The interpretation of these results is that a second dose of Comirnaty in individuals previously vaccinated with Vaxzevria induced a robust immune response, with an acceptable and manageable safety profile; although the lack of a homologous vaccination comparator is a limitation of the study.

3.2 Data from observational studies

An observational study (pre-print) from Germany conducted by Schmidt et al. [80] reported reactogenicity and immunogenicity data from a prospective cohort of 216 individuals, primarily healthcare workers, with no history of SARS-CoV-2 infection. Participants were given either a heterologous vector/mRNA prime-boost regimen (Vaxzevria/Comirnaty or Vaxzevria/Spikevax), or the standard homologous regimens. The time between prime and booster dose was shorter for mRNA-primed (4.3 ± 1.1 weeks) than for vector-primed individuals, with no difference between vector-based heterologous (11.2 ± 1.3 weeks) and homologous regimens (10.8 ± 1.4 weeks). As regards reactogenicity, both local and systemic events after the second dose were less frequent among recipients of the homologous vector/vector schedule. The second dose of an mRNA vaccine was less well tolerated, and a similar spectrum of local and systemic adverse events was observed for both vector- and mRNA-primed individuals. Spike-specific IgG levels after heterologous vaccination were similar to the homologous mRNA/mRNA vaccine group (3602 (IQR 3671) and 4932 (IQR 4189) BAU/ml respectively), whereas IgG-levels after homologous vector/vector vaccination were significantly lower (404 (IQR 510) BAU/ml, $p < 0.0001$). This difference was also observed for neutralising antibody activity quantified by surrogate neutralisation test. The majority of individuals in the vector/mRNA and mRNA/mRNA group had 100% inhibitory activity, while this was significantly lower in the vector/vector group. In addition, the heterologous vector/mRNA schedule induced the highest percentages of spike-specific CD8 T cells (0.28% (IQR 0.55%)), compared with homologous vector/vector (0.04% (IQR 0.08%)) and mRNA/mRNA (0.06% (IQR 0.19)) regimens.

Further evidence is available from a prospective, observational cohort study (pre-print) conducted by Hillus et al. [81] among 340 healthcare workers immunised between 27 December 2020 and 21 May 2021 at a tertiary care centre in Berlin, Germany, either with two doses of Comirnaty three weeks apart, or an initial dose of Vaxzevria followed by a heterologous boost with Comirnaty 10–12 weeks later. Results indicate that the reactogenicity of a heterologous Vaxzevria/Comirnaty schedule is largely comparable to the homologous Comirnaty-based one and well tolerated. There was a notable difference between the regimens in terms of systemic reactions, which were most frequent after prime immunisation with Vaxzevria (86%; 95% CI: 79–91%), and less frequent after the second dose of Comirnaty in both homologous (65%; 95% CI: 56–72%) and heterologous schedules (48%, 95% CI: 36–59%), or Comirnaty prime immunisation (38.76%; 95% CI: 31.9–46.1%). No potentially life-threatening reactions were reported after any of the vaccine regimens in this study. Serum antibody responses and T cell reactivity were strongly increased after the second dose in both homologous and heterologous regimens, and immunogenicity overall was robust and comparable between regimens in this cohort, with slightly increased S1-IgG avidity and T cell responses post second dose in heterologous immunisation.

A smaller observational study (pre-print), also conducted in Germany by Gross et al. [82], in a cohort of 26 individuals aged 25–46 years (median: 30.5 years) who received a Vaxzevria prime followed by Comirnaty with an eight-week interval, suggests that this heterologous schedule was not associated with serious adverse events and cumulative self-reported solicited reactions were higher after the Vaxzevria prime than the second dose of Comirnaty. The heterologous regimen resulted in a significant increase in antibody titres two weeks after the second dose and elicited T cell reactivity. One point of particular interest is that the study assessed the neutralising activity of sera obtained two weeks after full vaccination against VOCs. The neutralising activity against the Beta VOC was reduced two-fold compared to the prevalent Alpha, while it was similar for Delta. In addition, for the prevalent Alpha VOC the neutralising activity was 3.9-fold higher compared to the serum from individuals receiving the homologous Comirnaty vaccination.

One more observational study from Germany on the immunogenicity of the heterologous schedule Vaxzevria/Comirnaty was conducted by Barros-Martins et al. [83] among healthcare workers participating in the COVID-19 Contact (CoCo) Study at the Hannover Medical School. The study included people who had been vaccinated with Vaxzevria as a first dose without previous SARS-CoV-2 infection, 32 receiving a homologous schedule and 55 receiving a heterologous one with Comirnaty as second dose. Immune response was measured

before and three weeks after the administration of the second dose. After the second dose, the heterologous Vaxzevria/Comirnaty regimen led to a significant 11.5-fold increase in anti-S IgG ($P < 0.0001$), compared to a 2.9-fold increase after the homologous Vaxzevria schedule ($P < 0.0001$). Similar changes were observed for anti-S IgA, and both anti-S IgG and IgA concentrations after the heterologous regimen were within the range of the heterologous one with Comirnaty (comparison group from the study). An enzyme-linked immunosorbent assay (ELISA)-based surrogate virus neutralisation test (sVNT) was used to test for neutralising activity of antibodies. While the homologous Vaxzevria regimen increased neutralisation of the Alpha VOC in some individuals, but showed no effect against the Beta and Gamma VOC, the heterologous regimen induced neutralising antibodies at high frequencies against all VOC analysed. In addition, the frequencies for spike-specific CD4+ T cells increased in both groups after the second dose, but were significantly higher in the heterologous regimen group, as observed in other studies.

3.3 Summary of evidence and knowledge gaps

Evidence from a single randomised controlled trial on the safety of heterologous schedules among people over 50 years who were followed up for four weeks suggests that 'mix and match' regimens of Vaxzevria and Comirnaty may have a slightly higher systemic reactogenicity in the first week following the second dose compared to the corresponding homologous ones, with symptoms mainly occurring during the first 48 hours. No significant difference was identified in terms of unsolicited adverse events within 28 days post second dose and no serious immunisation-related adverse events were observed. Overall, symptoms were mild to moderate and manageable. Results from observational studies, only available for vector/mRNA heterologous regimens, confirm these findings or indicate largely comparable safety profiles with the homologous ones and overall good tolerability. On the other hand, evidence on long-term safety is lacking and studies were not sized to detect possible rare severe events or assess differences across age groups or other population groups.

With regard to immunogenicity, one randomised controlled trial showed preliminary evidence that heterologous schedules of Vaxzevria and Comirnaty with doses given four weeks apart induce a high humoral response. Both heterologous schedules (Vaxzevria/Comirnaty; Comirnaty/Vaxzevria) induced higher humoral response compared to the homologous Vaxzevria regimen, but not higher than the homologous Comirnaty one. Both heterologous regimens also elicited higher T-cell response than homologous combinations. Results from observational studies corroborate these findings. Nevertheless, the evidence is still limited on the duration of the immune response following heterologous regimens and, no data is currently available on the effectiveness of these regimens in terms of preventing infection, severe disease and death, including across age groups or other specific population groups.

Current reactogenicity and immunogenicity data on the use of heterologous schedules are encouraging and provide a preliminary evidence base for the 'off-label' use of these regimens. More extensive, long-term and follow-up studies are needed, including different vaccine products and intervals of administration, and disaggregate analysis for different population groups and variants of concern.

4. Programmatic considerations

4.1 Partial vaccination

The evidence that emerges from observational studies, performed both in the general population and specific population groups (e.g. the elderly, healthcare workers, LTCF-residents) confirms and further expands the findings from randomised trials that the administration of a full vaccination course offers significantly higher protection than only one dose of a two-dose vaccine. In the early phase of the rollout, in the context of widespread SARS-CoV-2 community transmission, many countries adopted a vaccination strategy with a prolonged interval between first and second dose in order to optimise the available vaccine supplies and maximise the number of people receiving at least one vaccine dose to ensure that they were at least partially protected against COVID-19 [84].

Given the evidence that individuals who have only received the first dose of a two-dose vaccination course are less protected against symptomatic infection with the Delta VOC than against the currently dominant Alpha, and with the Delta variant increasing in circulation across the EU/EEA, ECDC advises that full vaccination of all groups at increased risk of severe COVID-19 should be achieved as early as possible. Moreover, individuals at highest risk of severe outcomes for SARS-CoV-2 should receive a second vaccine dose in the shortest possible interval following the administration of the first dose [8]. At present, at least eight countries (Czechia, Denmark, Spain, Croatia, Ireland, Liechtenstein, Norway and Poland) have already reduced the timing between the first and second dose, within the authorised interval, in order to accelerate the uptake of full vaccination in the population, especially in individuals at higher risk of severe COVID-19.

Finally, given current inconsistencies in vaccine uptake, including a significant number of people that are only partially vaccinated and therefore not fully protected against the Delta variant, non-pharmaceutical interventions (NPIs) should be maintained at a level sufficient to contain community transmission of this variant until larger numbers of people are fully vaccinated, in order to avoid a resurgence of cases with a possible increase in hospitalisations and mortality.

4.2 Vaccination with one dose of previously infected individuals

Based on a recent assessment of vaccine deployment in the EU/EEA, countries have adopted different approaches in terms of policies and the timing for providing a single vaccine dose following SARS-CoV-2 infection, with some recommending one dose 30 days after infection and others up to eight months. Additionally, verification of previous infection of individuals varies between countries, with some countries requiring a PCR positive test while others do not require proof of previous infection. In addition, the recording of vaccination status of previously infected individuals provided with one dose in vaccination registries also differs among countries [84].

Documentation of a previous infection may be challenging in terms of implementation, acceptance and heterogeneity across regions and countries. Although rapid serological tests, undertaken just prior to receiving a single dose of vaccine, may help to ensure a consistent approach to the verification of previous infection, the accuracy of the different tests available will require careful assessment - particularly where the interval between prior infection and serological testing is prolonged.

The emergence of immune escape variants, such as Delta, and possible future vaccine escape variants, may require the need for a second vaccine dose in people with previously documented infection. From a programmatic perspective, given that evidence is still lacking for clinical endpoints and durability of immune responses generated via single-dose regimens in previously infected individuals, consideration should be given to the continued administration of two vaccine doses, as per EMA authorisation, as a precaution. This is particularly relevant for those individuals at greatest risk of severe outcomes following SARS-CoV-2 infection and more prone to waning immunity.

4.3 Heterologous vaccination schedules

According to EMA's summary of product characteristics for all 2-dose vaccines authorised for use in the EU/EEA, only homologous vaccination schedules are currently recommended. Nevertheless, 'off-label' heterologous vaccination schedules are being used in several EU/EEA countries based on national recommendations, more frequently based on a second dose of an mRNA-based vaccine (Comirnaty or Spikevax) following a first dose of Vaxzevria. Current evidence provides scientific grounds to expect these approaches to be safe and elicit a satisfactory immune response against COVID-19.

The interchangeability of vaccine products through the use of heterologous schedules may offer flexibility of vaccination options to mitigate impact on the vaccine rollout should a vaccine product not be available, have been discontinued or paused. In particular, this applies to individuals who experience severe side effects, and those who have already received a first dose, if certain restrictions are subsequently adopted at national level (e.g. age threshold administration criteria for Vaxzevria). From an operational perspective, the possibility of administering heterologous regimens may offer flexibility to mitigate vaccine supply chain disruptions or shortages of certain vaccine products. This may be more relevant for countries with limited access to vaccines, or where different vaccine products are expected to become available at different times. On the other hand, the implementation of heterologous schedules also involves operational challenges related to the different logistic requirements of vaccine products (e.g. shipment, storage, shelf-life, etc.) Appropriate logistics need to be in place if heterologous schedules are to be administered.

Emerging data on immunogenicity of heterologous schedules may inform future considerations concerning their use in specific population groups (e.g. the elderly, immunocompromised people) due to the preliminary findings of higher induced cellular response. However, evidence on the immunogenicity and effectiveness of heterologous regimens in specific groups and against VOCs is still limited or missing. More data are also needed on the immunogenicity and safety of the administration of homologous or heterologous 'boosters' following a complete homologous or heterologous primary vaccination course. Research is ongoing to provide more evidence on the safety, immunogenicity and effectiveness of heterologous vaccination schedules to inform decision-making in relation to their use at the level of both regulatory agencies and national immunisation programs.

4.4 Risk communication

Given the increased circulation of the Delta VOC, communication efforts need to focus on raising awareness of the importance of receiving a full vaccination course to ensure adequate protection and, for two-dose vaccines, of completing the vaccination course within the shortest possible recommended interval. Strategies should also facilitate access to and uptake of full vaccination. The population needs to be aware that full vaccination is crucial, with variants of concern becoming dominant in many countries. Communication efforts and strategies to promote uptake should also be enhanced in those countries where population groups at highest risk of severe disease are not yet fully vaccinated, as these groups will have significantly less protection against infection, severe disease and death.

Strategies to ensure a high uptake of a full course of vaccination can include:

- monitoring vaccine acceptance and potential barriers through behavioural insights research [85] (e.g. on factors affecting uptake of second dose) to inform communication strategies;
- using behavioural insights related to medical adherence to encourage people to take the second dose (e.g. planning for the second dose, sending reminders, framing the second dose as the default option) [86];
- making vaccines available in safe, familiar and convenient settings in order to facilitate uptake [87];
- encouraging people to support family and friends who are uncertain about vaccination, or who face difficulties in accessing services [88];
- addressing misinformation that can impact vaccine uptake [89].

A communication challenge during the pandemic is the need to change or adapt recommendations, including in relation to vaccination (e.g. schedules, intervals between doses, requirements for being considered fully vaccinated, use of a different vaccine to complete the vaccination course, etc.) in the context of new and evolving evidence. Therefore it is important to acknowledge uncertainty, as some people may misinterpret changes as signs of incompetence or mistakes on the part of government or scientists [90]. Continuous, clear and transparent communication to the public, and also to the media, is needed in relation to any adjustments that are made, including explanations as to the rationale behind decisions and the nature of the evolving evidence.

Despite the need to adapt vaccine deployment to a dynamic landscape and changes in COVID-19 epidemiology, it is crucial to minimise changes to the recommendations on COVID-19 vaccination in order to maintain vaccine confidence in the population and avoid the perception that there is a lack of clarity in the competent institutions.

Conclusions

This rapid review of evidence provides an overview of the current knowledge on emerging issues relevant for immunisation programmes in the EU/EEA countries. The review is designed to facilitate discussions on the adjustment of national vaccination policies and strategies, based on the current epidemiological situation, vaccine supply, and scientific evidence relating to the virus and vaccine performance.

With emerging immune escape variants becoming dominant in many countries, vaccination with a single dose for vaccine products that would require two doses may offer significantly reduced protection against moderate disease, infection and probable onward transmission. Partially vaccinated vulnerable individuals may have significantly less protection, resulting in hospitalisation, severe disease and death. Among previously infected individuals, vaccination with one dose may provide comparable immunogenicity compared to fully vaccinated individuals. In the absence of a correlate of protection, it is still unclear whether this will translate into comparable protection and duration of protection, in particular in the light of immune escape variants. In this context, accelerating vaccine rollout is critical in order to ensure full vaccination coverage of all population groups at increased risk of severe COVID-19.

The preliminary evidence from 'mix and match' vaccination studies indicates that heterologous schedules induce a robust immune response with a probable increased early reactogenicity, although no major safety signal has been identified as yet. In addition to the topics of interest addressed in this review, the option of a 'booster' dose after the primary vaccination course, (including if, when and who would benefit most) is becoming an increasingly prominent subject for discussion and is currently also under investigation. However, the evidence is currently still limited. ECDC will continue to monitor, collect and disseminate up-to-date information on these critical issues, and other new topics of interest, to support decision making in EU/EEA countries and facilitate the revision and adjustment of COVID-19 vaccination policies and strategies.

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Disclaimer

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