SUNDHEDSSTYRELSEN

Date 25-11-2021 BES

Case no. 05-0601-1671

COVID-19 booster vaccination for individuals older than 18 years of age

Below we summarise the medical updates and recommendations concerning COVID-19 booster vaccination for individuals older than 18 years of age. Thus, with this memo, the Danish Health Authority updates medical recommendations for booster vaccination of anyone aged 18 years or above who has received the second vaccination shot with either Comirnaty® or Spikevax®.

On 28 September 2021, the Danish Health Authority published an overall plan for booster vaccination in *Memo on COVID-19 booster vaccination* [*Notat vedr. revaccination af COVID-19];* and on 15 October, we published a *medical update* to *the Danish Health Authority's memo on booster vaccination (Phase II)* [*Sundhedsstyrelsens notat om revaccination (FASE II)*].

The Danish Health Authority follows the evolution of the epidemic continually and monitors the vaccine effectiveness (VE) and safety of primary as well as booster vaccination. Furthermore, we keep up to date on the recommendations published by other countries with respect to the need for booster vaccination. As part of this process, the Danish Health Authority continually consults with the COVID-19 Booster Vaccination Expert Group.

Background

The Danish Health Authority has gradually initiated booster vaccination of the population based on a medical assessment of the need for booster vaccination. As per 8 September 2021, booster vaccination was initiated at nursing homes, and shortly after followed booster vaccination of individuals with a specially weakened immune system.

As per 28 September 2021, the Danish Health Authority recommended booster vaccination of individuals aged more than 85 years.

As from 15 October, booster vaccination was gradually initiated of individuals who had concluded their primary vaccination course six months earlier. Because of the roll-out sequence of the primary vaccination programme and in line with the Danish Health Authority's medical recommendation, those invited for booster vaccination were mainly individuals aged 65-84 years, individuals at specially increased risk of running a serious COVID-19 disease course

and staff in the healthcare, social and elderly care sectors with contact to individuals at risk of serious COVID-19 disease. As per 12 November 2021, the interval was reduced to six months from the second vaccine shot.

For the groups already offered booster vaccination, a direct prophylactic potential exists for each individual who receives booster vaccination, i.e. prevention of infection and disease. Specifically, this is so because of the advanced age, underlying conditions and diseases, own risk of serious COVID-19 disease and the risk of transmitting the condition to others who are at special risk of serious COVID-19 disease.

Additionally, as from 5 October 2021, people receiving cross vaccination (the first vaccination shot with Vaxzevria® from AstraZeneca and the second shot with an mRNA vaccine) have had the opportunity to receive a third shot to resolve challenges related to travelling activity[1]. People who have received cross vaccination and who have yet to receive their third shot will be invited for booster vaccination six months after receiving their second vaccination shot. Individuals who have received COVID-19 vaccination with the COVID-19 Vaccine Janssen® from Johnson & Johnson have received an invitation for booster vaccination with an mRNA vaccine a minimum of 12 weeks after their vaccination. Overall, the groups currently comprised by booster vaccination offers count approx. 1.34 million individuals.

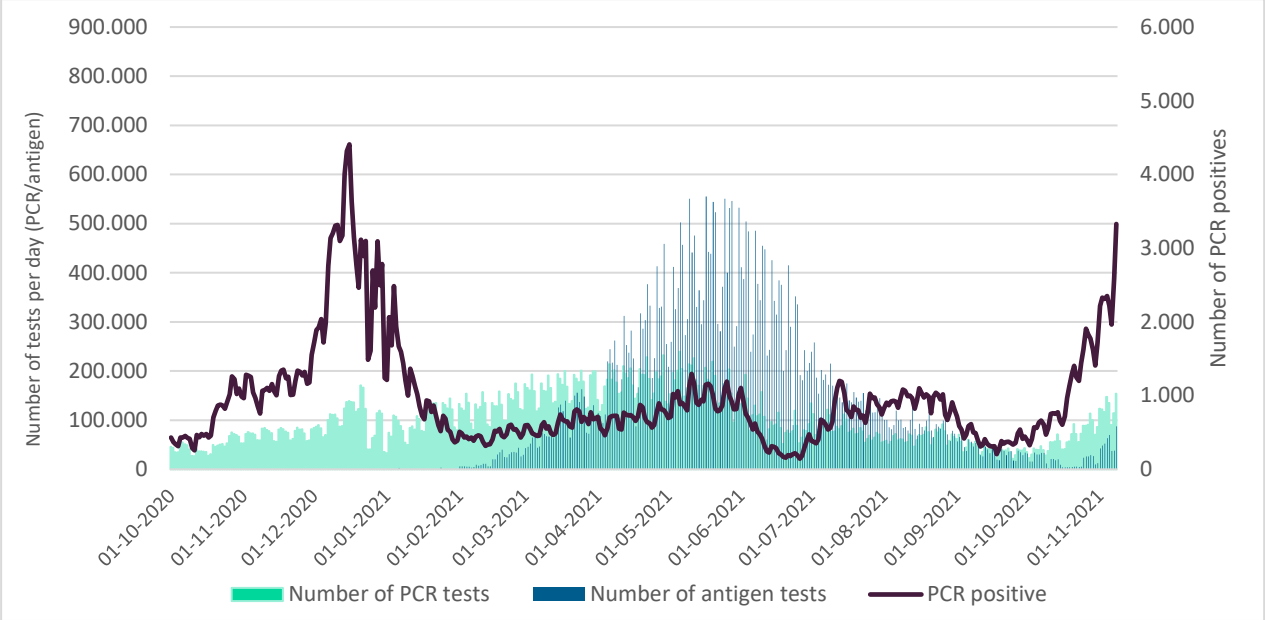
Update on the epidemic

Denmark has experienced a flare-up of the epidemic primarily driven by the transition from summer to autumn and winter, an open society with few restrictions and increased generational mixing during the autumn holidays. Additionally, the testing activity has been increased considerably, why more people will have tested SARS-CoV-2 positive.

The figure below presents the increasing trend in PCR-positive tests and in the total number of tests performed by PCR and antigen tests since 1 October. As shown in the figure, an increasing number of daily PCR-positive samples has been observed since 1 November 2021. Thus, the daily number of infected people has exceeded 4,000 in recent weeks.

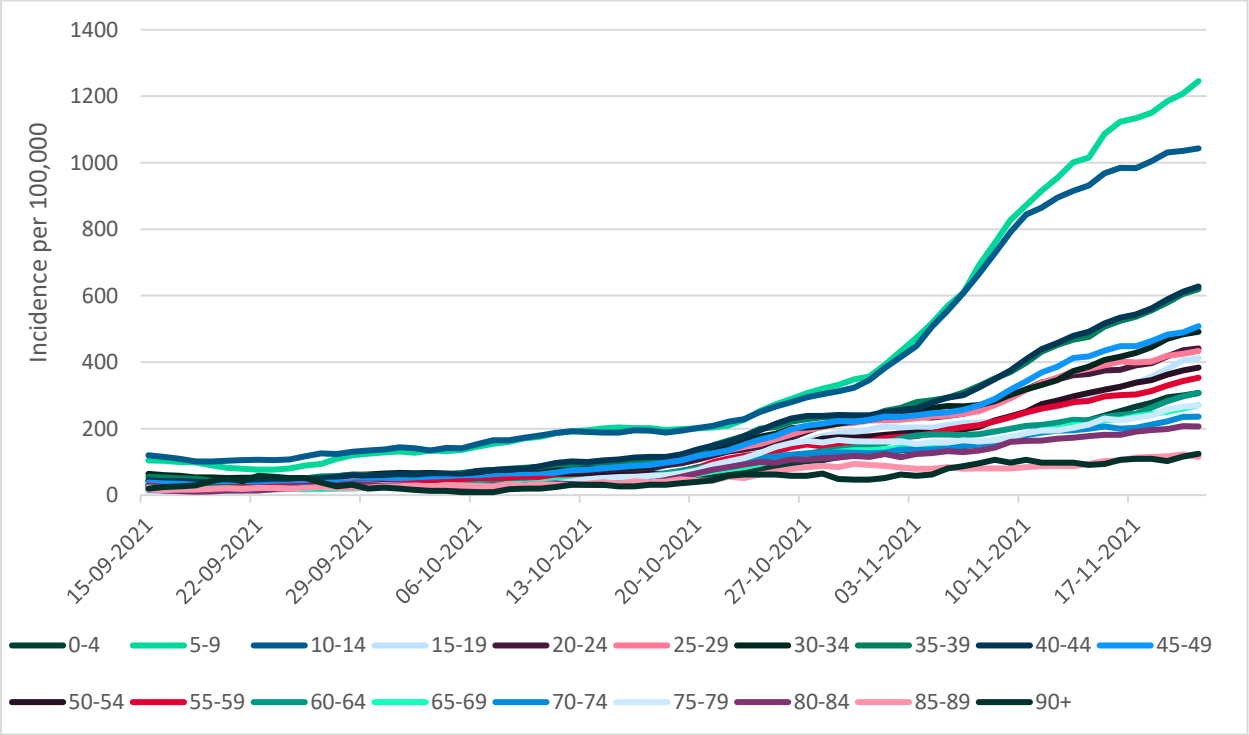
[1]The Danish Health Authority, 5 October 2021, *Memo concerning COVID-19 vaccination for cross-vaccinated individuals [Notat ang. tilbud om vaccination mod COVID-19 til krydsvaccinerede]*. https://www.sst.dk/da/Udgivelser/2021/Notat-ang-tilbud-om-vaccination-mod-COVID-19-til-krydsvaccinerede

Figure 1: Development in PCR positive and total number of tests, by PCR and antigen tests



Following the transition from summer to autumn, an increasing infection level has been observed in all age groups, as shown in Figure 2. The incidence of infection is particularly high among children in the 5-14-year age group, where the increasing infection numbers are driven by children aged 5-11 years. This is seen in conjunction with an increasing incidence of infection among the age groups who presumably include the parents of the 5-14-year-old children. The lowest incidence is observed among individuals aged more than 80 years, as shown in the three lowermost curves in Figure 2.

Figure 2: Development in rolling seven-day incidence per 100,000, by age groups



Number of hospitalised people and cause of hospitalisation

Figure 3 shows that the proportion of patients admitted to hospital - both vaccinated and unvaccinated people - has changed over time. Thus, 2/3 of those hospitalised are currently individuals who have concluded their vaccination course. For comparison, in September 40% of those hospitalised had completed their vaccination course.

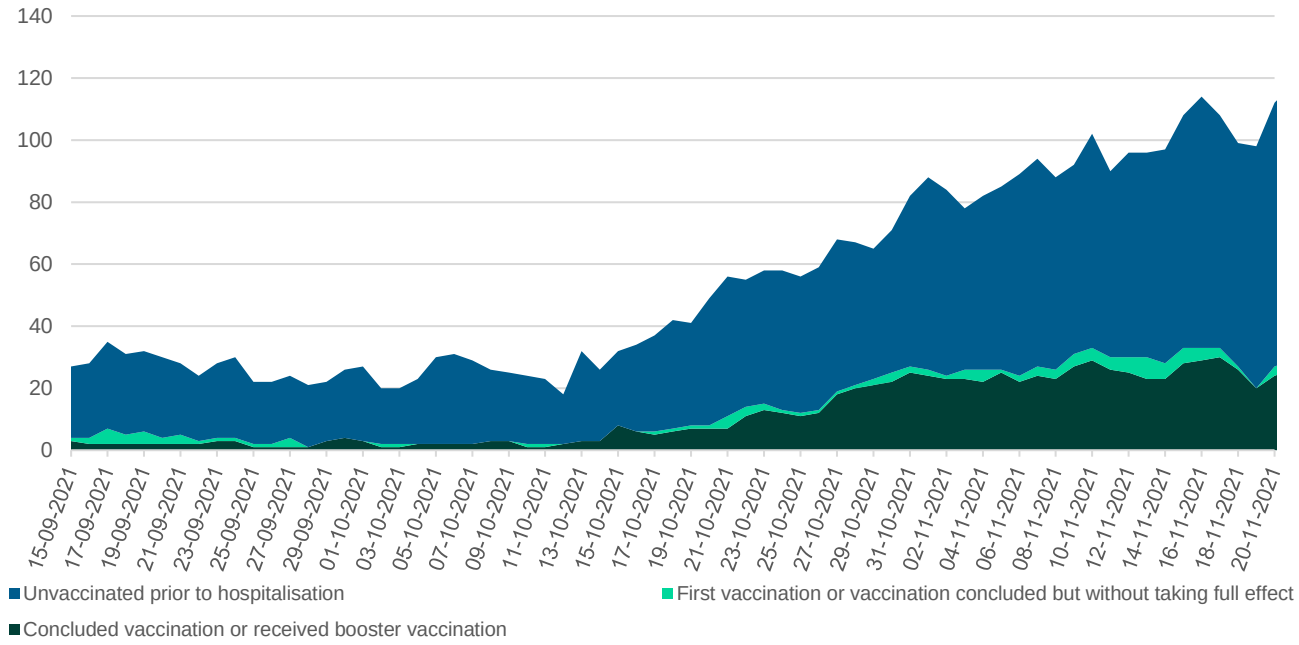
A study has been initiated by Statens Serum Institut (SSI) to determine if SARS-CoV-2 positive patients are hospitalised *with* or *due to* COVID-19. We expect this study to conclude by 1 December 2021. Even so, the working group has released a number of preliminary findings[2].

Based on 15,425 COVID-19-related hospitalisations in the period from 1 June 2020 to 31 October 2021, the SSI concludes that 82.6% of all patients who tested SARS-CoV-2 positive were hospitalised due to COVID-19; 3.5% of the hospitalised individuals were possibly hospitalised due to COVID-19 and 13.9% of the patients were hospitalised with a positive PCR test for SARS-CoV-2. Among younger adults and children, the proportion was lower. More recently, the proportion of COVID-19-related hospitalisations that were likely not caused by COVID-19 disease has been slightly higher in the summer and autumn of 2021, comprising 20% of COVID-19 hospitalisations in the period from June to October 2021. Even so, it is important to note that for hospitalisations where SARS-CoV-2-positive patients were hospitalised for another primary cause than COVID-19, the patients also increase the pressure on the Danish healthcare system due to the infection hygiene measures needed, including the need for isolation of patients and increased use of protection gear among staff, and because some tests and treatments need to follow enhanced infectious hygiene requirements.

The Danish Health Authority assesses that, in relation to the assessment of the need for booster vaccination in the future, it is critical to ensure detailed (near) real-time reporting of the hospitalisation causes of SARS-CoV-2-positive patients. In particular, knowledge is needed about the proportion of SARS-CoV-2-positive patients who are hospitalised with serious disease, e.g., pneumonia, due to COVID-19. For further information, please see the section on additional follow-up.

[2]Memo on the categorisation of COVID-19-related hospitalisations. [Notat om kategorisering af covid-19-relaterede indlæggelser] Statens Serum Institut, 17 November 2021. https://www.ssi.dk/-/media/arkiv/dk/aktuelt/nyheder/2021/notat-om-rsag-til-covid-19-relaterede-indlggelser_17112021_ver2.pdf?la=da

Figure 3: Number of hospitalised patients



Among the group aged more than 80 years, nearly 90% of those hospitalised have concluded their vaccination course, see Figure 4. Many have also received booster vaccination. Since October, the proportion of hospitalised people who have completed their vaccination course has remained stable at approx. 60%. Figure 5 presents the same trend among the 65-79-year-olds. This indicates that the booster vaccination efforts made in the older part of the population are starting to take effect.

Figure 4: Number of patients hospitalised with COVID-19 aged more than 80 years, by vaccination status

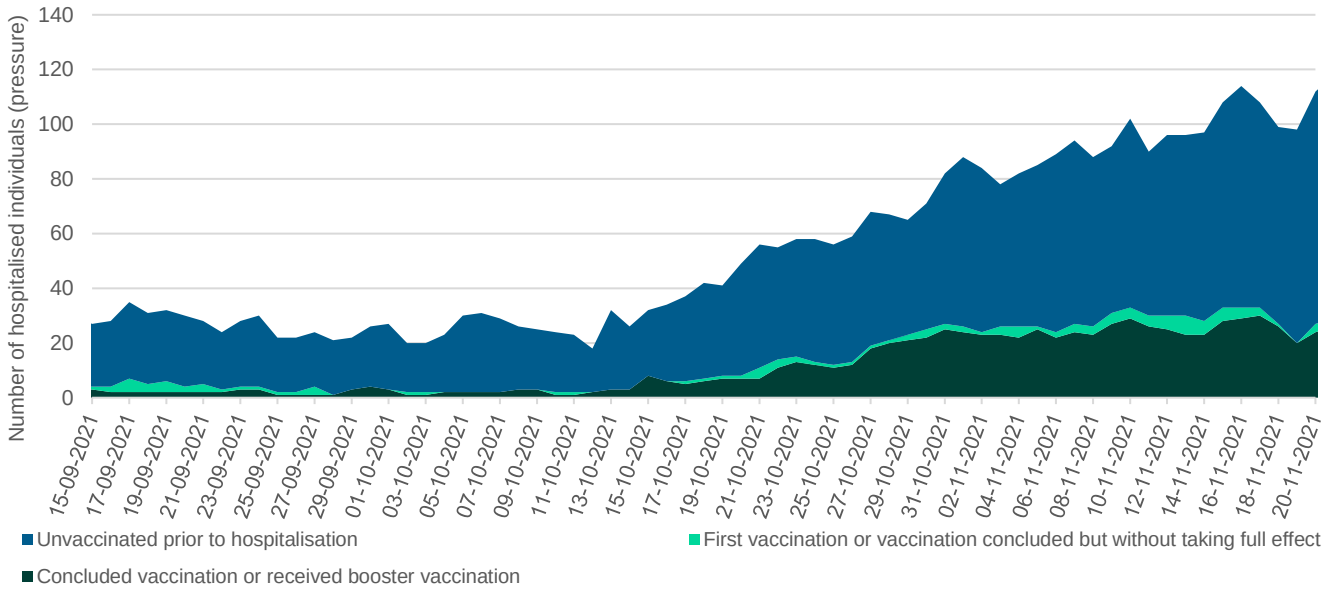


Figure 5: Number of patients hospitalised with COVID-19 in the 65-79-year age group, by vaccination status

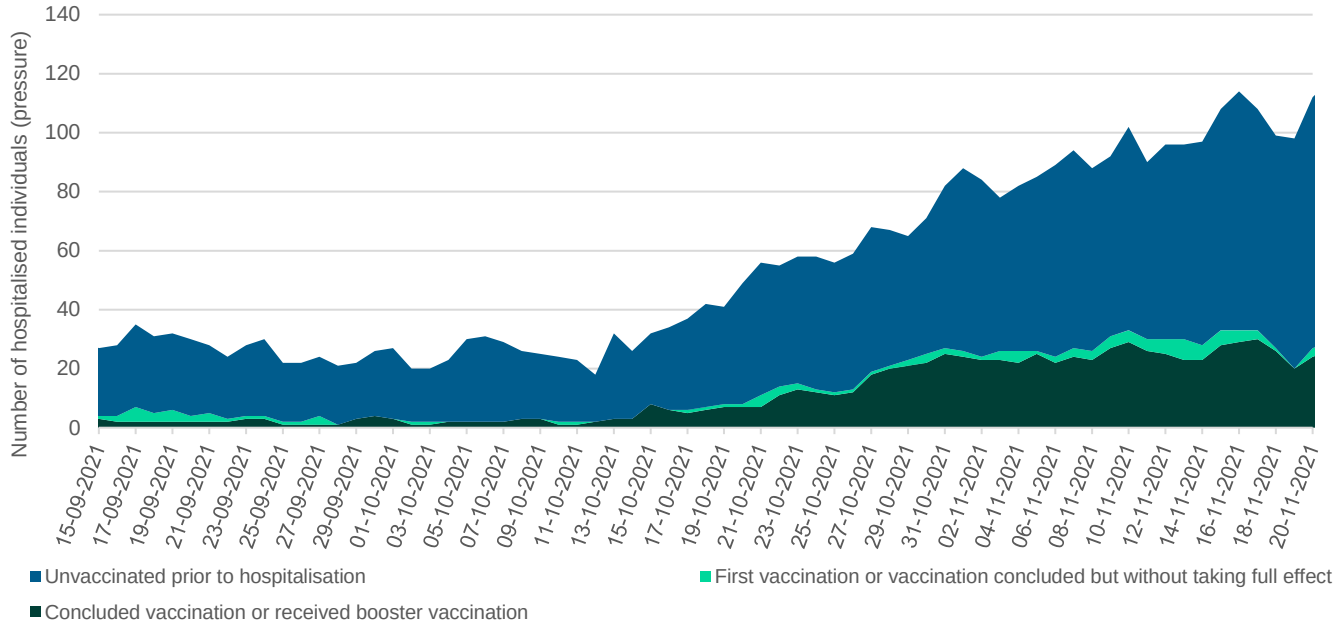
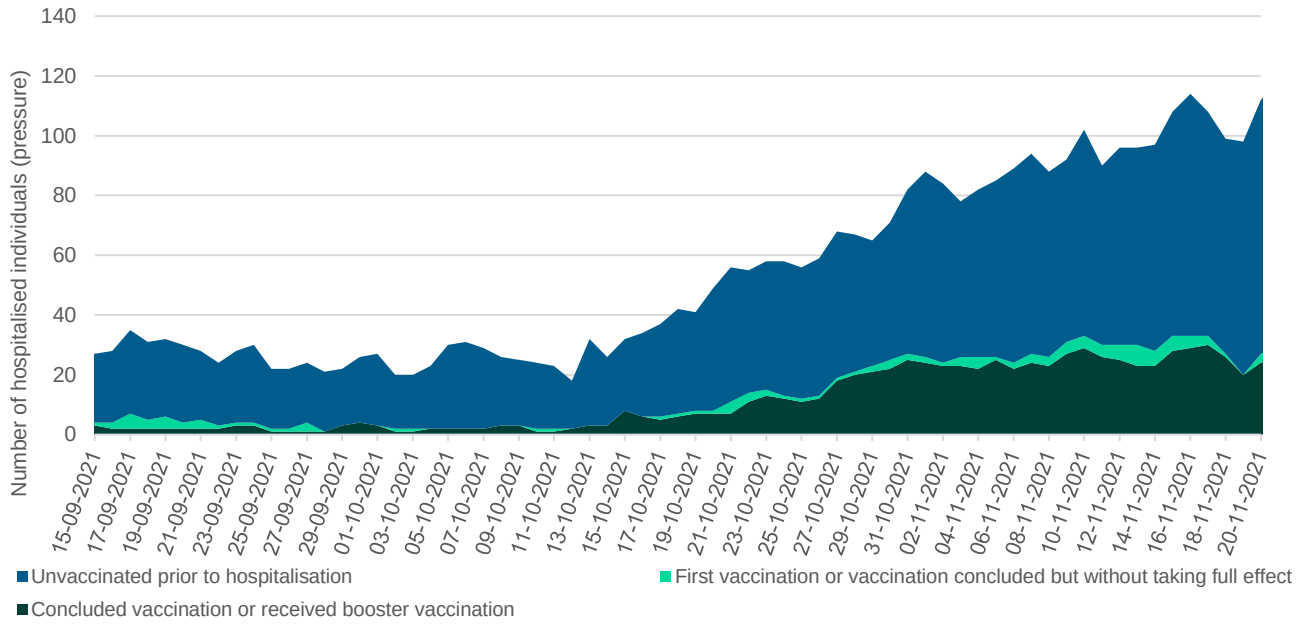


Figure 6 shows that the highest proportion of unvaccinated patients is found in the 50-64-year age group. Even so, since mid-October, it seems that the number of individuals who have completed their vaccination course with breakthrough disease, comprise an increasing proportion of the total number of hospitalised individuals, from approx. 20% in mid-October to 50% in November.

Figure 6: Number of patients hospitalised with COVID-19 in the 50-64-year age group, by vaccination status



Among individuals below 50 years of age, more hospitalisations are observed in individuals who have concluded their vaccination course (Figure 7), even though the level is somewhat lower than in the remaining age groups as their share of the total number of hospitalised patients has increased from approx. 10% to 25%.

Figure 7: Number of patients hospitalised with COVID-19 in the below 50 years age group, by vaccination status

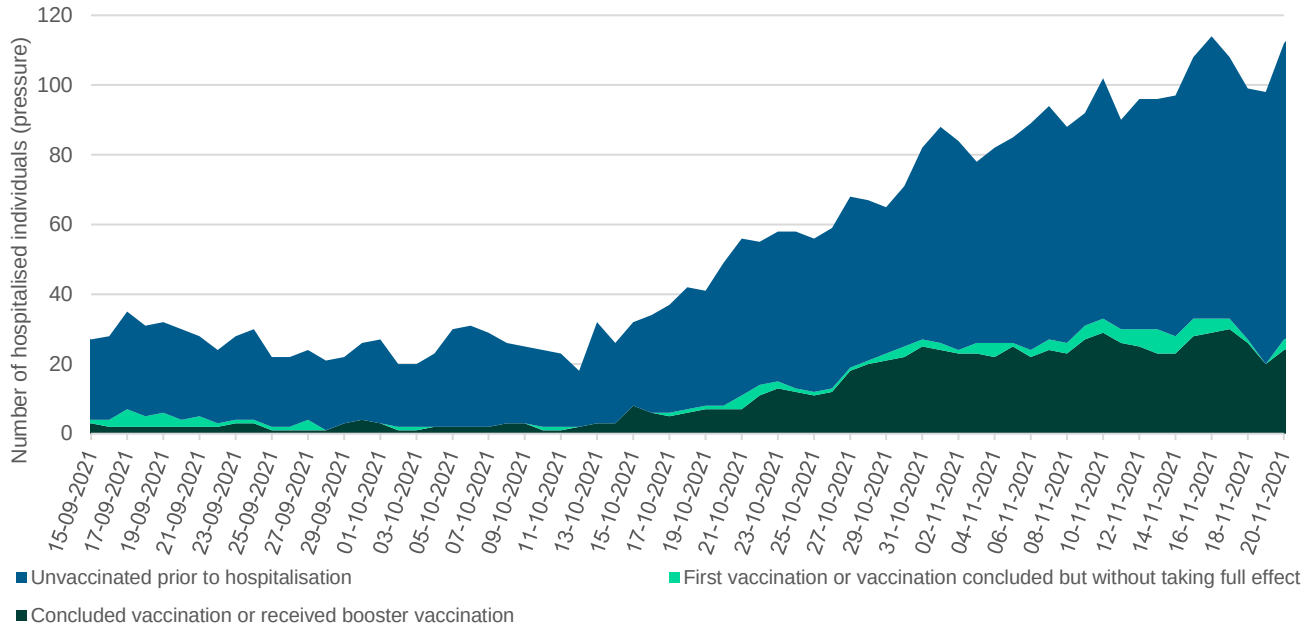
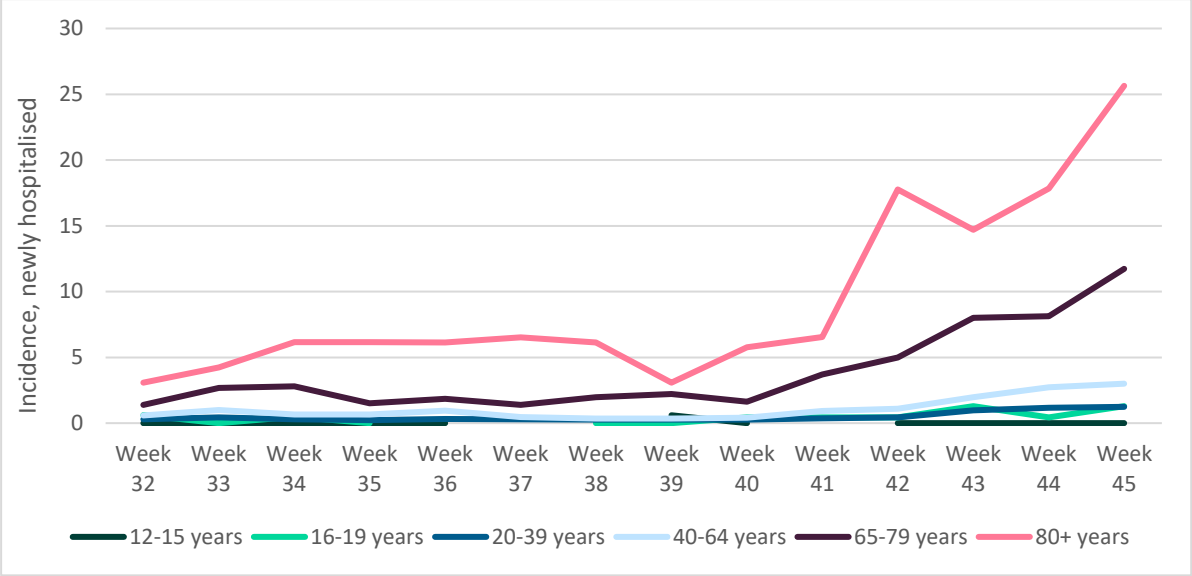


Figure 8 presents the incidence per 100,000 new hospitalisations who have concluded their vaccination course, by age groups. The figure shows that new hospitalisations among individuals aged more than 70 years account for the majority of hospitalisations even though there are indications of an increasing number of newly hospitalised patients down to 50 years of age.

Figure 8: Number of new hospitalisations per 100,000 among people who have concluded their vaccination course



The pressure on hospitals still follows in increasing trend. More and more cases of breakthrough disease are seen in all age groups, but the increased number of hospitalisations is more pronounced in the age groups down to 50 years of age.

Expectations related to the epidemic

The very high infection incidence currently observed in the younger age groups will contribute to increasing the transmission from children in the younger age groups to their parents, which, in turn, carries a risk of increasing the transmission to the grandparent generation. This produces an increased risk of breakthrough disease among the older, vaccinated part of the population in weeks to come.

Particularly in the period around the Christmas holydays, increased contact may be expected across age groups, and thereby exposure of the age groups who are at a specially high risk of experiencing serious COVID-19 disease.

In the memo: *Hospital capacity challenged in the autumn and winter of 2021/2022*, the Danish Health Authority prepared a risk assessment to gauge the importance of increased community transmission, focusing on the pressure caused on secondary healthcare. The Danish Health Authority assesses that the acute departments at hospitals are currently under considerable pressure and that the bed occupancy rate is high, particularly at medical wards. Patients are primarily hospitalised with other health issues than COVID-19 and influenza. The total pressure on secondary healthcare is currently due to a large number of hospitalisations but also to reduced bed capacity because of staff vacations, reduced flexibility and vacant positions. The Danish Health Authority assesses that in weeks to come, the expected increase in the number of individuals hospitalised with COVID-19, along with influenza and other infectious diseases, will place additional pressure on the hospital capacity and thereby trigger a

need to postpone planned surgery and out-patient treatments to varying degrees across Denmark.

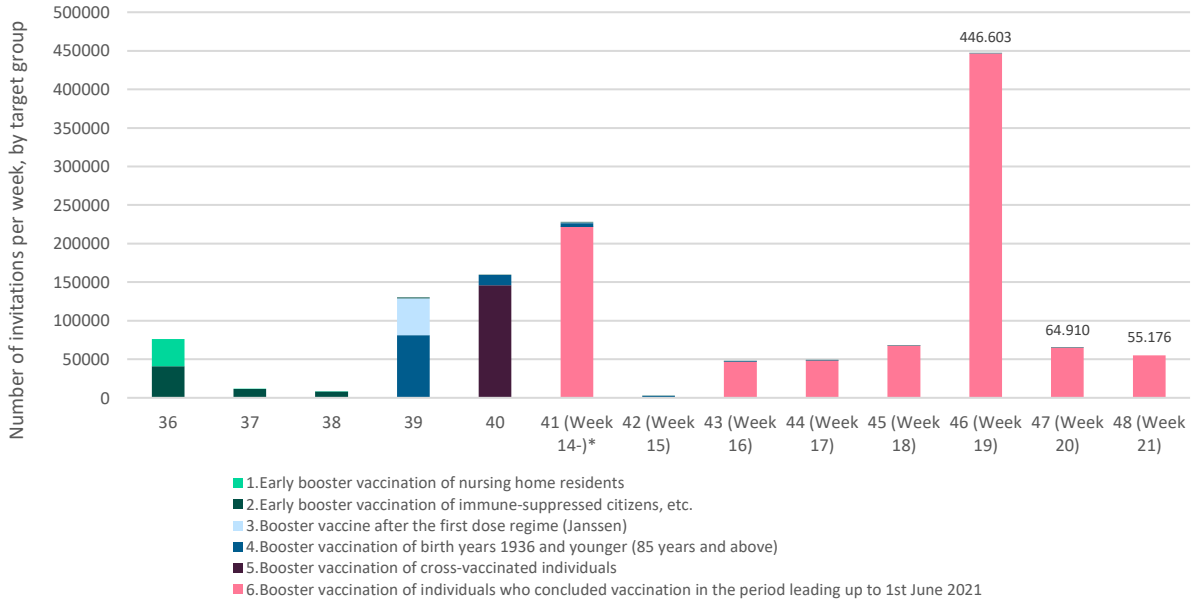
However, based on current experiences in Denmark, there are indications that the booster vaccination efforts may reduce the risk of breakthrough disease in the oldest part of the population. This will be described further in the next section. Thus, this will contribute to reducing the number of people hospitalised with COVID-19.

Booster vaccination status

In the period leading up to 1 December 2021, we expect that booster vaccination will be offered to individuals at increased risk, immuno-suppressed and cross-vaccinated people (first shot with Vaxzevria® from AstraZeneca and then the second shot with an mRNA vaccine), individuals vaccinated with COVID-19 Vaccine Janssen® and a considerable proportion of individuals above 65 years of age. Overall, the groups currently comprised by booster vaccination offers correspond to approx. 1.34 million individuals.

The roll-out of the booster vaccination efforts initiated on 15 October 2021 is based on the date of the final vaccination shot of the primary vaccination course. The booster vaccination efforts primarily cover individuals aged 65-84 years, individuals at increased risk of running a severe disease course and staff in the healthcare and elderly care sectors. This means that regardless of age and initial priority group, anyone who has received the final shot of their primary vaccination course more than six months ago will receive a booster vaccination invitation. The Danish Health Authority considers this approach to be adequate as it ensures an effective roll-out based on a transparent principle that does not hinge on specific assessments of a large group of individuals.

Figure 9: Number of individuals invited, by target groups and expected number of invited individuals until 1 December 2021 (as per 25 November 2021)



The blue-shaded area in Table 1 below shows that more than 90% of all individuals aged more than 70 years will have received the second vaccination shot more than six months ago and will therefore be invited for booster vaccination before 1 December.

Table 1: Overview of time since vaccination was concluded, by age groups, as per 16 November

Age group	0-2 months	3-5 months	6-8 months	9-11 months
12-15 years	18%	82%	0%	0%
16-19 years	3%	95%	1%	0%
20-24 years	4%	88%	7%	1%
25-29 years	6%	81%	11%	3%
30-34 years	7%	79%	11%	4%
35-39 years	5%	80%	11%	4%
40-44 years	2%	83%	10%	4%
45-49 years	1%	84%	10%	4%
50-54 years	1%	84%	10%	4%
55-59 years	1%	82%	12%	5%
60-64 years	0%	62 %	32%	6%
65-69 years	0%	21%	74%	5%
70-74 years	0%	4%	92%	4%
75-79 years	0%	2%	91%	6%
80-84 years	0%	2%	87%	11%
85-89 years	0%	1%	30%	68%
90-94 years	0%	1%	24%	75%
95+ years	0%	1%	15%	83%

The coverage seen in the various target groups of the booster vaccination programme is currently high and expected to conclude above 85% for the majority of the target groups (Figure 10%).

Figure 10: Coverage among individuals invited for booster vaccination per 21 November 2021

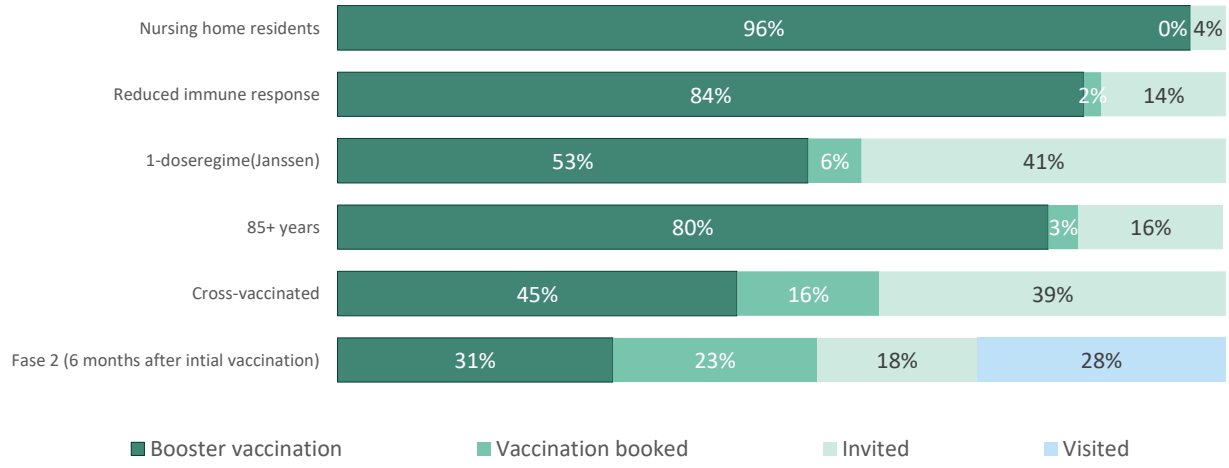


Figure 11 shows the coverage among invited individuals in various weeks. It appears from the figure that individuals invited in Weeks 41 and 42 have a coverage of approx. 75%.

Figure 11: Booster vaccination coverage among those invited per week

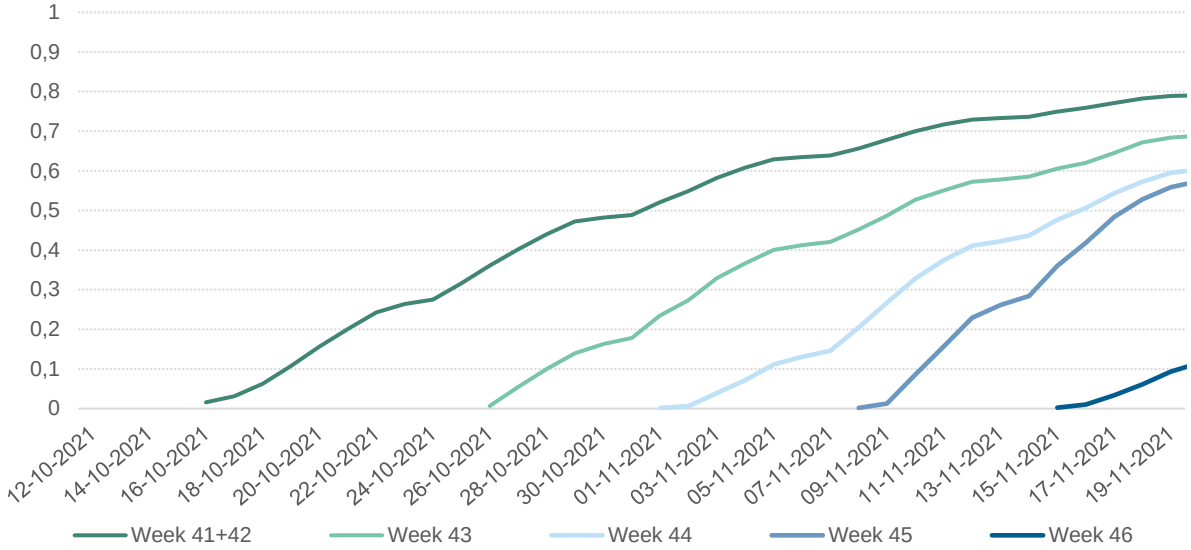


Figure 12 below presents a decline in the incidence among employees at hospitals coinciding with the initiation of booster vaccination in Week 41.

Figure 12: COVID-19 incidence among hospital employees

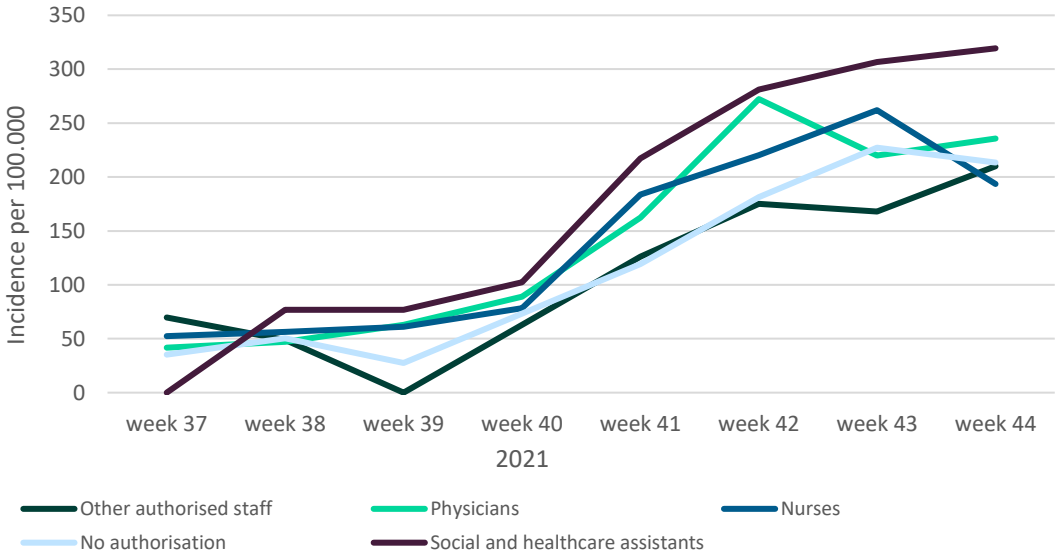
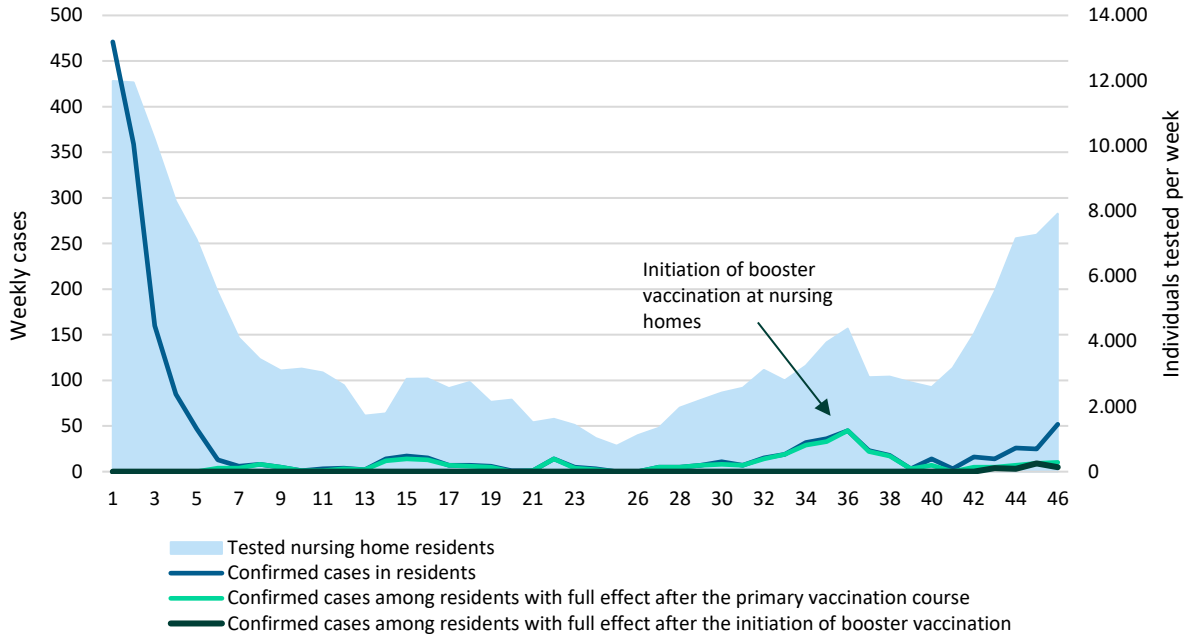


Figure 13 shows the number of confirmed COVID-19 cases recorded in Danish nursing homes since 1 January 2021. In addition to the significant effect of the vaccination efforts made early in the year, the effect of the initiation of the booster vaccination programme at nursing homes is also reflected in the graph. However, the figure also shows that, in step with the increasing number of community infections, an increase was observed in the number of breakthrough infections despite booster vaccination efforts. This is probably because some nursing home residents have a very weakened immune system and therefore fail to generate an effective immune response to primary vaccination and booster vaccination. However, the

total number of infected individuals at nursing homes remains low at approx. 50 weekly cases in a population group counting more than 40,000 individuals.

Figure 13: Number of confirmed SARS-CoV-2 cases in nursing homes since Week 21



Monitoring of vaccine effectiveness in Denmark

Statens Serum Institut monitors the VE of the COVID-19 vaccines. The reports from 1 November 2021[3] now clearly show that VE to SARS-CoV-2 infection wanes with time. The decline is observed more clearly among the ≥ 65-year-olds, which may likely be explained by the fact that this group was also the first to receive vaccination. Thus, the waning VE is a reflection of receding vaccine immunity over time.

The report also reveals that the effectiveness of the vaccines against hospitalisation due to COVID-19 breakthrough disease remains high among the ≥ 65-year-olds. Specifically, VE against hospitalisation among those who have concluded their vaccination course with BioNTech-Pfizer and Moderna is 76.1% (95% confidence interval (CI): 63.4-84.4; 88,3), 95% (95% CI: 74.0-94.7%), respectively.

The latest report from 12 November 2021 [4] comprising data from the period from 9 October to 6 November thus also shows continued good protection against hospitalisation among ≥ 65-year-olds with a VE to hospitalisation for BioNTech-Pfizer and Moderna of 77.2% (95% CI: 69.6-82.9%) and 88.3% (95% CI: 79.8-93.2%), respectively.

[3] Statens Serum Institut, 1 November 2021, *COVID-19 – Infections after vaccination and vaccine effectiveness [COVID-19 – infektioner efter vaccination og vaccineeffektivitet]:* gennembrudsinfektion-covid19-uge44-2021-su21.pdf (ssi.dk)

[4] Statens Serum Institut, 12 November 2021, *COVID-19* –Infections following vaccination and vaccine effectiveness [Infektioner efter vaccination og vaccineeffektivitet] (ssi.dk)

Among booster-vaccinated individuals ≥ 65 years, VE against infection increases markedly after the third vaccination shot for people vaccinated with BioNTech-Pfizer (73.2% [65.7-79.1%]) and a corresponding, although more limited, increase is seen in the VE against hospitalisation (89.8% [82.6-94.0%]). As ≥ 65-year-olds who have received booster vaccination with Moderna currently constitute a relatively small population, the VE estimates against infection and hospitalisation are not yet presented for this group. However, they are expected to increase after the third vaccination shot in line with the estimates observed for the BioNTech-Pfizer vaccine.

Data from the period from 9 October to 6 November show that VE to infection among the < 65-year-olds who have concluded their primary vaccination course with BioNTech-Pfizer or Moderna has declined to 65.4% (64.4-66.4%) and 80.6% (79.4-81.7%), respectively, compared with the previous period (from 11 September to 9 October), when VE was 78.7% (77.5-79.8%) and 89.4% (87.9-90.7%), respectively[5].

The VE against hospitalisation remains high; (93.0% (90.7-94.7%) for BioNTech-Pfizer and 94.2% (88.7-97.1%) for Moderna). Among individuals aged < 65 years who have received booster vaccination, VE against infection is rising for BioNTech-Pfizer (83.9% [80.2-87.0%]) and Moderna (90.4% [85.2-93.7%]) alike. As only few hospitalisations are observed following booster vaccination among individuals below 65 years of age, VE has not been stated for this group.

Overall, VE calculations demonstrate that booster vaccination with a third vaccination shot markedly increases protection against infection among individuals below and above 65 years of age.

Documentation

Authorisation for booster vaccination of individuals above 18 years of age

The EU Commission has approved the administration of a third dose of Comirnaty® and a third dose of Spikevax® as booster vaccination for individuals aged 18 years or above at a minimum 6-month interval after the second dose administered in the primary vaccination course. Comirnaty® may be used for booster vaccination giving the full dose (30 microgram)[6]. Spikevax® may be used for booster vaccination giving half the normal dose (50 microgram)[7]. Both treatment regimens have been authorised and can be given on-label.

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[5] Statens Serum Institut, 15 October 2021, *COVID-19 – Infections following vaccination and vaccine effectiveness [COVID-19 – infektioner efter vaccination og vaccineeffektivitet]:* gennembrudsinfektion-covid19-uge41-2021-jk14 (ssi.dk)

[6]EMA Summary of Product Characteristics Comirnaty®. Accessed 9 November 2021. https://www.ema.europa.eu/en/documents/productinformation/comirnaty-epar-product-information_en.pdf

[7]EMA Summary of Product Characteristics Spikevax®. Accessed 9 November 2021. https://www.ema.europa.eu/en/documents/product-information/spikevax-previously-covid-19-vaccine-moderna-epar-product-information_en.pdf

In a press statement, BioNTech-Pfizer has informed that supplementary data from the Comirnaty® booster vaccination authorisation trial were submitted to the US Food & Drug Administration (DFA) and to the European Medicines Agency (EMA)[8]. Furthermore, BioNTech-Pfizer presented data at the latest meeting of the US Advisory Committee on Immunization Practices (ACIP) held under the auspices of the US Centers for Disease Control and Prevention on 19 November 2021[9]. Data have currently not been submitted to the EMA.

The supplementary material comprises data from approx. 10,000 phase 3 study subjects conducted as a sequel to the primary authorisation study, which focused exclusively on subjects aged 16 years or above. All trial participants had completed a primary vaccination regime consisting of two doses of Comirnaty®. The subjects were randomised for booster vaccination with Comirnaty® or placebo a minimum of six months after receiving their second dose. A total of 14.8% received their booster vaccination from ≥ 6 months to < 8 months after completing their primary vaccination course; 16.1% from ≥ 8 months to < 10 months, 63.5% from ≥ 10 months to < 12, and only a few received their booster vaccination earlier than six months or later than 12 months after completing their primary vaccination course. The median period between the second dose and booster vaccination was approx. 11 months. Approx. 50% of the subjects were women and 50% were men. The median age of the study subjects was 53 years. A total of 55.5% of the study subjects were aged 16-55 years (hereof 0.9% 16-17 years, and 54.6% 18-55 years), whereas 44.5% were > 55 years old (hereof 21.2% 56-64 years old, 23.3% ≥ 65 old). At baseline, 94.5% had a negative SARS-CoV-2 status, whereas 5.4% had a positive SARS-CoV-2 status. For 0.2% of the subjects, the SARS-CoV-2 status was unknown.

Effect was stated seven days after booster vaccination, and the median follow-up period was 2.5 months. Overall, the results showed an effect of COVID-19 booster vaccination in a period during which the epidemic was dominated by the Delta variant. The observed effect was slightly higher among 16-55-year-olds (96.5%, 95% CI 89.3%-99.3%) and slightly lower among > 55-year-olds (93.1%, 95% CI 78.4%-98.6%).

The most frequently recorded side effects were local symptoms from the injection site (up to 21%), whereas systemic side effects comprised reports of, e.g., fever, fatigue and shivers (up to 21%), myalgia and arthralgia (up to 6.7%), headache (up to 5.6%), swelling of the lymph nodes (2.7% following booster vaccination compared with 0.4% following the second shot of the primary vaccination course) and nausea and diarrhoea (up to 1.7%) A total of three side effects were reported that were categorised as serious and likely associated with Comirnaty®. Specifically, reports concerned one case of palpitations presenting eight days after booster vaccination and receding ten days after booster vaccination, and two cases of increased hepatic enzymes, one of which presented five days after booster vaccination (receding 37 days

[8] Pfizer-BioNTech Press release 9 November 2021. https://cdn.pfizer.com/pfizercom/2021-11/Booster_10K_Efficacy_EUA_Submission_Statement_Final_11921.pdf?linkId=139453336

[9] Pfizer Presentation 19 November 2021. Efficacy & Safety of BNT162b2 booster – C4591031 2 months interim analysis. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-11-19/02-COVID-Perez-508.pdf

after booster vaccination) and the other presented 49 days after booster vaccination (remained present at data cut-off, but was subsequently assessed as a possible side effect to atorvastatin therapy). No cases of myocarditis (inflammation of the heart muscle) or pericarditis (inflammation of the thin saclike tissue surrounding the heart) were observed.

Knowledge basis for booster vaccination

The Danish Health Authority continuously conducts literature searches focusing on breakthrough infection following COVID-19 primary vaccination [10]and booster vaccination[11].

Previous memos on booster vaccination described the results from the literature searches conducted through Week 40, 2021[12]. Subsequently, literature searches conducted through Week 47 have identified a total of nine new studies on booster vaccination and 18 new studies on breakthrough infection. Furthermore, studies identified elsewhere were added, e.g. studies identified in reference lists. Below, we describe the more important new studies with respect to effectiveness and safety.

All studies identified were observational, and the value of the evidence presented is therefore generally lower than if randomised controlled trials had been conducted (random allocation to one of several study groups). Observational studies carry a higher risk of confounding (systematic errors that cannot be adjusted for by statistical correction) and selective reporting, and they should therefore be interpreted with caution. For example, several of the studies calculating VE fail to take into account that the testing patterns of vaccinated and unvaccinated people are different. This type of bias may lead to an incorrect estimation of VE, particularly of protection against infection.

Breakthrough infection following primary vaccination

A range of studies have assessed the risk of COVID-19 breakthrough infection in patients who have concluded their primary vaccination, and the consequences hereof.

A register-based cohort study explored waning immunity following vaccination with Comirnaty® in Israel Data were collected on confirmed COVID-19 infection and a serious COVID-19 disease course in the period from 11 July 2021 to 31 July 2021 for all Israelis who had completed vaccination before June 2021. A total of 4,791,398 contributed data. Among these, 13,426 had tested positive by PCR, whereas 403 had experienced a serious COVID-19 disease course. Generally, those receiving vaccination early were older than those who had

[10]The Danish Health Authority, Case number 05-0600-1201.

[11]The Danish Health Authority, Case number 05-0600-1090.

[12]Danish Health Authority, 28 September 2021. Concerning COVID-19 booster vaccination [Vedr. revaccination mod COVID-19]. https://www.sst.dk/da/Udgivelser/2021/Revaccination-mod-COVID-19

Danish Health Authority, 15 October 2021. Booster vaccination plan (PHASE II) [Plan for revaccination (FASE II]: https://www.sst.dk/-/media/Udgivelser/2021/Corona/Vaccination/Revaccination/Revaccination-fase-II/Plan-for-revaccination-mod-COVID-19-i-fase-2.ashx?la=da&hash=3717E965648B3285D728E42AD86901CC9FD8800E

been vaccinated more recently because of the risk-based vaccination strategy adopted by Israel. The rate of confirmed SARS-CoV-2 infection showed a clear increase over time as from vaccination. Among individuals ≥ 60 years who had concluded their vaccination course in the second half of January, the rate of confirmed infections per 1,000 individuals in the course of the study period was 3.3, whereas it was 2.2 per 1,000 individuals among individuals who had concluded vaccination in the second half of February, and 1.7 per 1,000 individuals among individuals who had concluded vaccination in the second half of March. For other age groups, defined by decades, a similar pattern was observed. With respect to the risk of running a serious COVID-19 disease course, fully vaccinated individuals ≥ 60 years recorded 0.34 cases per 1,000 individuals among those who had concluded vaccination in March and 0.12 cases per 1,000 individuals among those who had concluded vaccination in April/May. Too few serious cases were recorded among younger individuals to allow researchers to draw any conclusions concerning VE against serious COVID-19 in these groups [13].

A retrospective cohort study included approx. 3.4 million individuals covered by Kaiser Permanente healthcare from 14 December 2020 to 8 August 2021. Among fully vaccinated people (Comirnaty®), the effectiveness against SARS-CoV-2 infection was 73% (95% CI 72-74), whereas effectiveness against hospitalisation was 90% (95% CI 89-92). The total effectiveness against infection declined from 88% (86-89) during the first month after full vaccination to 47% (43-51) after five months. Sequenced samples showed that the VE against the Delta variant was high in the course of the first month after completing the vaccination course (93% (95% KI 85-97)) but declined to 53% (95% CI 39-65) after four months. VE against infection requiring hospitalisation due to the Delta variant was 95% (95% CI 84-96) up to six months after vaccination[14].

A register-based study explored VE on symptomatic COVID-19 disease, hospitalisations and death in a nine-month period after primary vaccination from 13 December 2020 to 8 September 2021. A total of approx. 10.6 million individuals were comprised by the study. For a concluded two-dose Comirnaty® regime, VE against risk of infection peaked at 94.9% (95% CI 94.5-95.2) at two months (after the first dose) and then declined to 70.1% (95% CI 68.9-71.2) at seven months. VE against hospitalisation due to COVID-19 peaked at 96,4% (95% KI 94,7-97,5) and then declined to 87.7% (95% CI 84.3-90.4) at seven months. VE against death peaked at 95.9% (95% CI 92.9-97.6) at two months and then declined to 88.4% (95% CI 83.0-92.1) at seven months. For a concluded two-dose Spikevax® regime, VE against risk of infection peaked at 96.0% (95% CI 95.6-96.4) at two months and then declined to 81.9% (95% CI 81.0-82.7) at seven months. VE against hospitalisation due to COVID-19 peaked at 97.5% (95% KI 96.3-98.3) and then declined to 92.3% (95% CI 89.7-94.3) at seven months. VE against death peaked at 96.0% (95% CI 91.9-98.0) at three months and then declined to

[13] Goldberg Yair et al. Waning immunity after the BNT162b2 vaccine in Israel. NEJM 2021, 27 October. https://www.nejm.org/doi/full/10.1056/NEJMoa2114228

[14] Tartof SY et al. Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study. Lancet 2021, 16 October, vol 398 (10309), 1407-1416. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)02183-8/fulltext

93.7% (95% CI 90.2-95.9) at seven months. For both Comirnaty® and Spikevax®, the pattern characterising the increase and the decline in VE was homogeneous across age groups and sexes, and for both vaccines VE was lowest in the group aged ≥ 65 years[15].
A cohort study comprising 427,905 Finnish healthcare workers conducted from December 2020 to October 2021 showed that the effectiveness of a two-dose primary vaccination regime with mRNA vaccine against SARS-CoV-2 infection was 82% (95% CI 79-85%) within the first 14-90 days after the second dose. Even so, over time the effectiveness receded, reaching 62% (55%-68%) 91-180 days after the second dose. Of note, the same period recorded no receding effectiveness against hospitalisation due to COVID-19 disease[16].

A retrospective study focused on individuals who had previously had a positive SARS-CoV-2 test. The study included a total of 10,024 individuals who had been vaccinated against COVID-19 with either Comirnaty®, Spikevax® or COVID-19 Vaccine Janssen® a minimum of two weeks before their SARS-CoV-2 infection. These individuals were matched against 9,479 individuals who had tested SARS-CoV-2 positive and who had not been vaccinated. The study showed that COVID-19 vaccination was associated with a lower risk of death, compromised breathing, hospitalisation to an intensive care unit, intubation/assisted breathing, hypoxia, need for oxygen treatment, myocarditis, hypercoagulopathy/venous thromboembolism, spasms, psychotic disease and alopecia. In contrast, no difference was detected between vaccinated and unvaccinated people with respect to the occurrence of various other COVID-19 sequelae, kidney disease, type 2 diabetes, mood and anxiety conditions and sleep disorders[17].

An Israeli cohort study including adults above 16 years of age who had been vaccinated with Comirnaty® studied breakthrough infections in two groups; a group that had been vaccinated early, in January-February 2021 (935,781 individuals), and another group vaccinated in March-April of 2021 (416,663 individuals). The study reported age-related breakthrough infections by vaccination time. The incidence rates for breakthrough infections per 10,000 for individuals who concluded their vaccination course in January, February, March and April were 36.5 (95% CI 34.8–38.2), 33.65 (95% CI 31.9–35.3), 23.06 (95% CI 21.5–24.6), and 16.98 (95% CI 13.1–20.8), respectively. In the follow-up period, when individuals who had been vaccinated early were matched individually to individuals who had been vaccinated late, a total of 1,151 breakthrough infections were recorded among individuals vaccinated early and 760 among individuals vaccinated late. After adjustment for underlying comorbidities, a 51% ($P < 0.001$) increased risk of breakthrough infection was found among individuals who

[15] Lin DY et al. Effectiveness of COVID-19 vaccines in the United States over 9 months: surveillance data from the state of North Carolina. Preprint. MedRxiv 26 October 2021. https://www.medrxiv.org/content/10.1101/2021.10.25.21265304v1

[16] Poukka E et al. Cohort study of COVID-19 VE among healthcare workers in Finland, December 2020-October 2021. Preprint. MedRxiv 4 November 2021. https://www.medrxiv.org/content/10.1101/2021.11.03.21265791v1

[17] Taquet M et al. Six-months sequelae of post-vaccination SARS-CoV-2 infections: a retrospective cohort study of 10,024 breakthrough infections. Preprint. MedRxiv 26 October 2021. https://www.medrxiv.org/content/10.1101/2021.10.26.21265508v1

had been vaccinated early. Following stratification by age, the same trend was observed across age groups. The study carries several potential sources of bias related to different behaviours and underlying conditions in the groups, but the study adjusted for these factors[18].

An Israeli study was previously mentioned while in preprint. The study has now been published. The study documents a waning effect of primary vaccination over time. The study compares the amount of virus (viral load) during breakthrough infection among vaccinated individuals with the amount of virus in individuals who have not been vaccinated and have not been infected. The study showed that six months after concluding their primary vaccination, the viral load among vaccinated individuals with breakthrough infection is the same as that of individuals who have not been vaccinated and have not been infected. The study showed that - at six months after primary vaccination - it is no longer possible to detect a different viral load among infected people. The study also showed that booster vaccination reestablished the effect achieved by primary vaccination and that booster vaccination reduces the infection risk in connection with breakthrough infections - including Delta variant breakthrough infections[19].

Summary of findings relating to breakthrough infection

Study results confirm that both Comirnaty® and Spikevax® yield a high level of protection against COVID-19 infection and particularly against hospitalisation and death. The effectiveness peaks approx. two months after concluded primary vaccination and then recedes. After approx. six months, VE to infection has declined, whereas VE to hospitalisation remains largely intact. Study results also underpin that COVID-19 disease courses are generally milder if you experience breakthrough infection despite vaccination than the COVID-19 course you experience if you have not been vaccinated.

Effect of booster vaccination

In the studies conducted, the effects of booster vaccination reported are based on different endpoints. They are partly based on measuring antibody titre after booster vaccination and partly on measuring the effect of booster vaccination on infection and serious disease, including hospitalisation.

The studies providing the basis for the authorisation of booster vaccination with Comirnaty® and Spikevax® are non-inferiority studies which observed a comparable increase in antibody titre after the second and third shot and thus concluded that the effect was comparable. This

[18] Mizrahi et al. 2021. Correlation of SARS-CoV-2-breakthrough infections to time-from-vaccine https://www.nature.com/articles/s41467-021-26672-3

[19] Levine-Tiefenbrun M et al. Viral loads of Delta-variant SARS-CoV-2 breakthrough infections after vaccination and booster with BNT162b2. Nature Medicine 2021, 2 November. https://www.nature.com/articles/s41591-021-01575-4

conclusion was made based on a total of 210 study subjects in the Comirnaty®[20] booster vaccination study and 149 study subjects in the Spikevax®[21] booster vaccination study.

A prospective cohort study was based on data from approx. 4.6 million Israelis who had either only concluded primary vaccination with Comirnaty® or who had received a booster shot ≥ 12 days ago. Among those who had concluded their primary vaccination, only approx. 91 million person days and 80,900 confirmed COVID-19 infections were reported along with 1,140 cases of serious disease and 178 deaths. Among those who had received a booster shot, approx. 86 million person days and 5,708 confirmed infections were reported along with 158 cases of serious disease and 23 deaths. The group receiving the booster shot comprised relatively more men (49.1% versus 47.8%), more individuals aged ≥ 70 years (30.2% versus 11.6%), fewer individuals < 40 years (16.6% versus 46.0%) and more individuals receiving their second dose in January of 2021 (43.9% versus 13.1%). The statistical analysis adjusted for these inter-group differences.

Comparing the group of individuals who had received primary vaccination only with the one that had received booster vaccination revealed that the infection incidence was higher in the former group. The relative rate ratio for people who had received primary vaccination only versus those who had received booster vaccination was: ≥ 60 years 12.4 (95% CI 11.9-12.9), 50-59 years 12.2 (95% CI 11.4-13.1), 40-49 years 9.7 (95% CI 9.2-10.4), 30-39 years 8.8 (95% CI 8.2-9.5) and 16-29 years 17.6 (95% CI 15.6-19.9). Comparing the group of individuals who had received primary vaccination only with the one that had received booster vaccination revealed a higher incidence of serious COVID-19 disease in the former group. The relative rate ratio for people who had received primary vaccination only versus those who had received the booster vaccine for serious COVID-19 disease was: ≥ 60 years 18.7 (95% CI 15.7-22.4), 40-59 years 22.0 (95% CI 10.3-47.0). For the endpoint death, the low number of observations limited analysis to the group aged ≥ 60 years. Comparing the group of individuals who had received primary vaccination only with the one that had received booster vaccination revealed a higher incidence of death due to COVID-19 in the former group. The relative rate ratio of the primary vaccinated only group versus the booster vaccinated group for death due to COVID-19 disease was: ≥ 60 years 14.7 (95% CI 9.4-23.1)[22].

An Israeli register-based case-control study focused on the effect of booster vaccination on serious COVID-19 disease. The study was based on data from 30 July 2021 to 23 September 2021, coinciding with the fourth pandemic wave in Israel during which the Delta variant was dominant. A total of 728,321 individuals aged 12 years of above participated. All had received the third dose of the BNT162b2 vaccine. These individuals were matched 1:1 with a

[20] FDA Briefing document. Application for licensure of a booster dose for Comirnaty® (COVID-19 Vaccine, mRNA). 17 September 2021. https://www.fda.gov/media/152176/download

[21] FDA Briefing document. EUA amendment request for a booster of the Moderna COVID-19 vaccine. 14 October 2021. https://www.fda.gov/media/152991/download

[22] Bar-On YM et al. Protection across age groups of BNT162b2 vaccine booster against COVID-19. Preprint. MedRxiv 7 October 2021. https://www.medrxiv.org/content/10.1101/2021.10.07.21264626v1

total of 728,321 individuals based on potential confounders: age, sex, place of residence, underlying chronic conditions, calendar months receiving the second dose and number of PCR tests in the nine months leading up to the index date (as a proxy for COVID-19 behaviour). In all, the study comprised more than 12,000,000 person days of follow-up. The participants were continuously placed in the various analysis groups based on their changing vaccination status. Thus, 198,476 individuals shifted from the unvaccinated cohort to the vaccinated cohort in the course of the study.

The participants' median age was 52 years (interquartile range (IQR) 37-68), and 51% were women. The average follow-up time was 13 days (IQR 6-21) in both groups. The effect, assessed a minimum of seven days after receiving the third dose compared with receiving two doses only at least five months earlier, was estimated to be a 93% (95% CI 88-97) lower risk of COVID-19-related hospitalisation, 92% (95% CI 82-97 for serious disease, and 81% (95% CI 59-97) for COVID-19-related death. The effect remained unchanged for both sexes, all age groups (40-69 and 70+ years) and number of comorbidities. The study also included a population level analysis, which revealed that the infection rate started declining for each age group 7-10 days after the age group in question was invited for booster vaccination.

Preliminary data from a prospective cohort study in which 346 healthcare workers received booster vaccination with Comirnaty® after a median 32 weeks showed increasing antibody titre in all but two study participants. In 95.7% of the study participants, the antibody titre after booster vaccination exceeded the upper quantification threshold for the analysis method employed. Thus, the antibody response is robust in the vast majority of those who have received booster vaccination. Data cannot be linked to clinical effect on protection against infection, hospitalisation-requiring disease or death. No serious adverse reactions were reported[23].

An Israeli cohort study has explored the effect of booster vaccination on infection and serious disease in individuals below 60 years of age. The study compared the daily mean incidence of three groups, including primary-vaccinated individuals (received 1-2 doses more than six months ago), booster-vaccinated individuals (received the third dose a minimum of seven days earlier) and unvaccinated individuals. The daily average incidence (per 100,000) for infections in the group below 60 years of age was 66.9 (95% CI: 57.6-76.2) in the group that had received primary vaccination compared with 14.8 (95% CI: 11.7-17.9) in the group that had received the third dose, corresponding to an incidence ratio of 0.22 (95% CI: 0.22-0.23). Generally, the incidence was lower in individuals aged more than 60 years (1-2 doses: 39, 95% CI: 33.9-44.1; 3 doses: 6.2, 95% CI: 5.2-7.2) corresponding to an incidence ratio of 0.16 (95% CI: 0.15 (0.17). For serious disease, the incidence among individuals below 60 years of age who had received primary vaccination was 0.18 (95% CI: 0.15-0.21). Among elderly people aged more than 60 years who had received their third dose, very few (no serious infections

[23] Saiag E et al. Immunogenicity of a BNT162b2 vaccine booster in health-care workers. Correspondence Lancet 11. October 2021. https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(21)00272-X/fulltext

in the group that received the third dose in 50% of the follow-up period) severe disease cases were observed (0.06, 95% CI: 0.04-0.09) corresponding to an incidence ratio of 0.33 (95% CI: 0.21 (0.52). In the group of elderly people aged more than 60 years who had received the third dose, the incidence of serious disease was 0.51 (95% CI: 0.41-0.61) compared with the group that had received primary vaccination, 4.29 (95% CI: 3.86-4.73), corresponding to an incidence ratio of 0.12 (95% CI: 0.10 (0.14). A trend was observed towards fewer new cases among non-vaccinated people below 60 years of age, possibly because of the incipient effect of booster vaccination on overall prevalence or because of the newly implemented restrictions in Israel as the authors were unable to separate or control for these data[24].

A case-control study compared the vaccination status among symptomatic individuals aged more than 50 years with PCR-confirmed COVID-19 to the vaccination status among symptomatic individuals ≥ 50 with a negative test. Tests were included from Week 37 2021 onwards (booster vaccination was offered as from 15 September 2021 (Week 37)). A total of 271,747 tests were comprised by the study. A total of 13,569 belonged to non-vaccinated individuals, 149,434 to individuals who had received booster vaccination with Vaxzevria® and 84,506 to individuals who had received booster vaccination with Comirnaty® (booster vaccination defined as a third dose a minimum of 140 days after the second dose). VE increased in the days following booster vaccination and then stabilised around Day 11. VE was 84.4% (95% CI 82.2-85.8) among individuals above 50 years of age who had received primary vaccination as well as booster vaccination with Comirnaty® compared with those who had only received primary vaccination with Comirnaty®. Thus, booster vaccination with Comirnaty® produced a significant increase in the protection against symptomatic COVID-19 among individuals aged ≥ 50 years compared with the patients who had received primary vaccination only[25].

Summary of expected booster vaccination effect

The documentation provided by the latest studies underpins that booster vaccination has good effect. The effect of booster vaccination was documented by an increasing antibody level and by a decline in infection and serious disease, including hospitalisation. The effect of booster vaccination is observed across age groups and booster vaccination reduces the risk of COVID-19 infection, of running a serious COVID-19 disease course and of dying due to COVID-19.

[24] Bomze et al, 2021. Effect of a nationwide booster vaccine rollout in Israel on SARS-CoV-2 infection and severe illness in young adults https://www.sciencedirect.com/science/article/pii/S1477893921002362?via%3Dihub

[25] Andrews N et al. Effectiveness of BNT162b2 (Comirnaty, Pfizer-BioNTech) Covid-19 booster vaccine against COVID-19 related symptoms in England: test negative case-control study. Preprint. MedRxiv 15. November 2021. https://www.medrxiv.org/content/10.1101/2021.11.15.21266341v1

Booster vaccination safety

A total of 306 individuals participate in the authorisation study on Comirnaty® booster vaccination and 344 individuals participate in the authorisation study on Spikevax® booster vaccination[26].[27] Generally, reactogenicity is comparable after the second and third vaccination shot. Reactogenicity was typically mild to moderate and receded spontaneously within few days. For both vaccines, an increased occurrence was observed of swollen lymph nodes after the third vaccine shot compared with the second shot (Comirnaty® (full study population): 5.2% versus 0.4%; Spikevax® (18-< 65 years): 24.8% versus 11.6%, Spikevax® (≥ 65 years): < 5.3% versus 4.7%). No serious side effects were observed within the first 30 days after booster vaccination for either Comirnaty® or Spikevax®. But in relation to assessing the safety profile for booster vaccination with the vaccines, the systematic clinical experience from the authorisation studies is limited.

Continuous monitoring is in place of the vaccination efforts, including booster vaccination, in Denmark as well as internationally. The pharmacovigilance of the Danish Medicines Agency has currently not produced safety signals that raise suspicion of serious side effects in connection with booster vaccination[28].

On 5 November 2021, the *COVID-data tracker weekly review, published by* the US Center for Disease Control and Preventions, informed that approx. 21.5 million booster vaccination doses have been administered in the US to individuals who had concluded their primary vaccination course[29]. Furthermore, it was reported that the side effects following booster vaccination, including in large population groups, are similar to those observed after the second vaccination shot. The most frequently reported side effects following booster vaccination are fever, headache, fatigue and pain at the site of infection, and most side effects were mild to moderate[30].

In Great Britain, the health authorities recommend booster vaccination for individuals aged 50 years or above, social and healthcare staff and younger individuals with an increased risk of

[26]EMA Summary of Product Characteristics Comirnaty®, accessed 8 November 2021. https://www.ema.europa.eu/en/documents/productinformation/comirnaty-epar-product-information_en.pdf

[27] EMA Summary of Product Characteristics Spikevax®, accessed 8 November 2021. https://www.ema.europa.eu/en/documents/product-information/spikevax-previously-covid-19-vaccine-moderna-epar-product-information_da.pdf

[28] Danish Medicines Agency, accessed 15 November 2021, *Side effects notified for COVID-19 vaccines [Indberettede bivirkninger ved COVID-19 vacciner]:* https://laegemiddelstyrelsen.dk/da/nyheder/temaer/indberettede-bivirkninger-ved-covid-19-vacciner/

[29] CDC, 5 November 2021, *COVID-data tracker weekly review*: https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html

[30] ACIP, Early safety monitoring for additional COVID-19 vaccine doses: Reports to VAERS and v-safe. 21 October 2021. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-10-20-21/05-COVID-Hause-508.pdf

running a serious COVID-19 disease course. The authorities there inform that you may expect the same side effects after the third shot as after the second shot[31].

This phase 1/2 study aimed to explore safety, side effects (including reactogenicity) and optimal dosage. The study was unblinded and included a total of 458 healthy adults who had concluded primary COVID-19 vaccination a minimum of 12 weeks before their booster vaccination with either Comirnaty®, Spikevax® or COVID-19 Vaccine Janssen®. Heterologous booster vaccination was permitted. The study included a total of 50 individuals who had received Comirnaty® primary vaccination and booster vaccination and 51 individuals who had received Spikevax® both as primary and booster vaccination. The study used 100 microgram Spikevax® at booster vaccination, which is double the dose used in the approved booster vaccination regime. For participants receiving homologous booster vaccination, slightly more cases of reactogenicity were generally observed in the first seven days among those receiving Comirnaty® than among those receiving Spikevax®. Conversely, slightly more cases of systemic reactogenicity were generally seen among those receiving Spikevax® than among those receiving Comirnaty®. Most cases of reactogenicity were mild to moderate, but a few of those receiving Spikevax® experienced serious reactogenicity, impeding normal daily activities (severe cases of shivers, fever, headache, myalgia or nausea). This initial, preliminary study indicated that homologous and heterologous booster vaccination were comparable with respect to effect and safety. By now, it is relatively well-established that heterologous booster vaccination may be expected to give as good an effect as homologous vaccination. However, our knowledge about the safety of heterologous booster vaccination is currently limited[32].

After the COVID-19 vaccines started being used, cases of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the sack-like tissue surrounding the heart) have been reported in the period after vaccination. On this basis, the EMA's side effects committee (PRAC) has concluded that myocarditis and pericarditis may occur in very rare cases following vaccination with Comirnaty® or Spikevax®[33]. In Denmark, more than 8.8 million doses of COVID-19 vaccine have currently been administered; and as per 9 November 2021, the Danish Medicines Agency has assessed 163 notifications of myocarditis and pericarditis following vaccination with Comirnaty® or Spikevax®. In 64 cases of myocarditis and 35 cases of pericarditis, it cannot be excluded that the vaccine was a contributory cause. In ten cases, it is not possible to assess if the condition was caused by the vaccine or by morbidity in the citizen concerned. The notified cases were mainly seen among younger men below 30

[31] Gov.uk. COVID-19 vaccination: a guide to booster vaccination. 19 October 2021. https://www.gov.uk/government/publications/covid-19-vaccination-booster-dose-resources/covid-19-vaccination-a-guide-to-booster-vaccination

[32] Atmar RL et al. Heterologous SARS-CoV-2 booster vaccinations – preliminary report. MedRxiv. 13 October 2021. Preprint: https://www.medrxiv.org/content/10.1101/2021.10.10.21264827v1

33 EMA, 9 July 2021, accessed 15 November 2021,
Comirnaty and Spikevax: possible link to very rare cases of myocarditis and pericarditis: Comirnaty and Spikevax: possible link to very rare cases of myocarditis and pericarditis | European Medicines Agency (europa.eu)

years of age, more often after the second than after the first dose, and most cases were mild and receded within few days.

On 6 October, the Danish Health Authority stated that children and adolescents below 18 years of age will continue to receive vaccination with Comirnaty® and that the Danish Health Authority will follow the EMA assessment regarding the risk of myocarditis following vaccination with Spikevax®[34] when published. On 25 October 2021, Moderna issued a press release announcing the preliminary results of their study on Spikevax® in children aged 6-11 years[35]. The company has submitted data for approval to the FDA and the EMA. In a press release from 10 November 2021, the EMA informed that they have initiated an assessment of Spikevax® for children aged 6-11 years[36].

For the Moderna and BioNTech-Pfizer alike, the booster dose authorisation studies were small; data were stratified for 18-55-year and 65-85-year age groups, and the group > 65 years counts only few participants. Based on the authorisation studies, it is therefore not possible to determine if the side effects profile changes with declining age in the age interval from 65 years to 18 years. However, data from the authorisation studies do not seem to indicate that the side effects profile of 18-55-year-olds is poorer than that of the 65-85-year-olds[37].

For both mRNA vaccines, the side effects profile following booster vaccination was comparable to the side effects profile following the second vaccination shot of the primary vaccination course, apart from the fact that the frequency of lymphadenopathy was higher following booster vaccination. At primary vaccination, the frequency of myocarditis increases with decreasing age in the interval from 65 years to 18 years for both mRNA vaccines, and as the side effects profiles following booster vaccination and after the second vaccination shot of the primary vaccination course are comparable (see above), we also expect that the frequency of myocarditis will increase with decreasing age interval from 65 to 18 years for both mRNA vaccines following booster vaccination[38].

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[34] News Danish Health Authority, 6 October 2021: https://www.sst.dk/da/Nyheder/2021/SST-fortsaetter-med-at-vaccinere-boern-og-unge-under-18-aar-med-COVID-19-vaccinen-fra-Pfizer-Bion

[35]Moderna press release, 25 October 2021:https://investors.modernatx.com/news-rele-ases/news-release-details/moderna-announces-positive-top-line-data-phase-23-study-covid-19

[36]EMA press release, 10 November 2021: EMA starts evaluating use of COVID-19 vaccine Spikevax in children aged 6 to 11 | European Medicines Agency (europa.eu)

[37]EUA application, boosters, BioNTech/Pfizer COVID-19 vaccine https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-september-17-2021-meeting-announcement and https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-october-14-15-2021-meeting-announcement#event-materials

[38] Presentations made by the CDC and FDA on myocarditis side effects of COVID-19 vaccines; presented at a WHO webinar on the relevance of COVID-19 vaccine boosting; 25 October 2021 https://www.who.int/news-room/events/detail/2021/10/25/default-calendar/who-consultation-on-covid-19-vaccines-research-emerging-evidence-on-safety-and-the-need-for-additional-doses-of-covid-19-vaccines

Safety data from a large authorisation study on homologous booster vaccination with Comirnaty® in individuals aged > 12 years are expected shortly[39].

Summary on the safety of booster vaccination

Overall, the previous monitoring of the booster vaccination efforts and the continuous literature search confirm that reactogenicity is comparable after the second and third vaccination shot. The data material is currently limited, but it is furthermore expected that only few serious side effects will be associated with booster vaccination. Currently, no knowledge is available to establish if booster vaccination will provide long-term protection against COVID-19.

ENFORCE

The ENFORCE study included approx. 7,000 individuals. The study analyses samples from six different visits (1st visit before vaccination, 2nd visit before the second dose, and the 3rd-6th visit at 3, 6, 12 and 24 months after the initial visit). Two additional visits will be added to study booster vaccination at one month before and at one month after the third vaccination shot, if any. The analysis phase is currently progressing at full speed, and new findings will be published continuously in the course of November and December (and as more data are collected from 4th visits (six months after the 1st visit) for the less vulnerable groups.

All follow-up work related to the 3rd visit (i.e. three months after initiated vaccination) has now been concluded. The preliminary data are confirmed by the final analysis. In all risk groups, the majority of those vaccinated respond well to vaccination. Even so, a minor proportion is so-called low/non responders, i.e. individuals who do not produce a solid immune response following vaccination. Overall, this group constitutes approx. 5%. In some subgroups, however, the proportion of low/non responders is higher (in the 10-25% range), e.g., in immuno-deficient patients, cancer patients and patients with renal disorders and multi-disease.

By now, data have also been collected for more than 3,000 individuals at the 4th visit (i.e. six months after initiated vaccination). Because of the vaccination roll-out strategy, data collected at the 4th visit mainly cover elderly and very vulnerable individuals. Even though a decline may be expected in antibodies from the 3rd to the 4th visit, the antibody levels of most patients remain high. Even so, the group of low/non responders comprises approx. 10% at the 4th visit compared with the previously mentioned 5% at the 3rd visit. Additionally, approx. 50-100 individuals have experienced breakthrough infection; this was documented either by sero-converted antibodies targeting nucleocapsid (who have therefore had an infection as the vaccine does not contain this antigen) and/or detection of COVID-19 in tests performed as part of the Danish testing infrastructure. Analyses that compare breakthrough infections with the vaccines' effect assessed on the basis of antibodies are currently being conducted.

[39] PFIZER AND BIONTECH SUBMIT REQUEST TO AMEND U.S. FDA EMERGEN-CY USE AUTHORIZATION OF THEIR COVID-19 VACCINE BOOSTER TO INCLUDE ALL INDIVIDUALS 18 AND OLDER https://cdn.pfizer.com/pfizercom/2021-11/Booster_10K_Efficacy_EUA_Submission_Statement_Final_11921.pdf?76VzPPb3rskJCCSWMFTwnKsU609LBGbx

Population immunity

In a memo from 17 June 2021 *On vaccination of children aged 12-15 years*[40] and in a memo of 28 September 2021 *On COVID-19 booster vaccination*[41], the Danish Health Authority described various theoretical population immunity estimates depending on the size of the vaccination target group, vaccination coverage, circulating variants, etc., which were used to estimate overall population immunity. The estimate will be used to illustrate the decline in immunity over time since primary vaccination comprising two vaccination shots and to quantify the scope of the beneficial effect of immunity achieved by booster vaccination In the current Danish context, increased population immunity may be achieved in the following ways: 1) Through targeted efforts aiming to increase primary vaccination coverage in the population, and 2) through booster vaccination to maintain the vaccination effect achieved by primary vaccination.

The estimate of the overall population immunity as per 1 October 2021 (from memo published on 28 September 2021) was on a par with the estimate published on 17 June (66.6%). The estimate indicated that no general decline had been observed in the broad population immunity at the time and that it was not necessary to launch a broad booster vaccination scheme targeting the full population.

Around 88% of the overall Danish population is currently being offered vaccination (everyone aged more than 12 years), and the Danish Health Authority expects to achieve a vaccination coverage of 90% of those invited, which is very high compared with other countries. Coverage may possibly end up being slightly higher, but part of the target group will opt out of the vaccination offer. As per 16 November 2021, 90% of the Danes asked answered that they had either initiated or already concluded vaccination, 1.5% of those asked stated that they are still considering if they should accept the vaccination offer and the remaining 8.5% have decided against vaccination[42].

Below, we present an estimate of the expected population immunity as per 1 December 2021, at which time the Delta variant is dominant. At this time, approx. 90% of the Danish population aged more than 12 years have concluded vaccination and 1.34 million will likely have been invited for booster vaccination, among whom 85% are expected to accept the offer.

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[40] Danish Health Authority, 17 June 2021, *On vaccination of children aged 12-15 years [Vedr. vaccination af børn på 12-15 år]:* https://www.sst.dk/-/media/Udgivelser/2021/Corona/Vaccination/Notater/170621-Notat-vedr_-vaccination-af-boern-paa-12-15-aar.ashx?la=da&hash=9DFE78439CBD001876E4E497A160D98DD7ABFAD6

[41] Danish Health Authority, 28 September 2021, *On COVID-19 booster vaccination [Vedr. revaccination mod COVID-19]:* https://www.sst.dk/-/media/Udgivelser/2021/Corona/Vaccination/Revaccination/Vedr-revaccination-mod-COVID-19-280921.ashx?la=da&hash=8F220749B81743A9CC35C3715CB1409CCF26FB5C

[42] The HOPE Project, 16 November 2021, Transmission-preventing behaviours and perceptions among Danes [*Danskernes Smitteforebyggende Adfærd og Opfattelser]*: Danskernes_Smitteforebyggende_Adfærd_Og_Opfattelser_1116 (1).pdf

The below calculations were performed to illustrate what may be achieved by focusing on population immunity through booster vaccination. Importantly, the population immunity estimates presented are rough estimates based on limited knowledge and various assumptions that make no use of modelling. Thus, the estimates should be interpreted with caution.

Assumptions employed in the calculations

The calculations assume a population size of 5.8 million people, among whom everyone aged 12 years or above has been offered COVID-19 primary vaccination, corresponding to approx. 5.1 million individuals (88%). The calculations employ an overall estimate for concluded primary vaccination coverage of approx. 90% among individuals aged more than 12 years.

Among those who have received primary vaccination, 1.34 million are expected to have been invited for booster vaccination by 1 December 2021. Among those invited, 85% booster vaccination coverage is assumed. Part of this group will not yet have received booster vaccination as per 1 December 2021, but the calculations assume 85% coverage.

The calculations employ an estimate of acquired immunity owing to previous SARS-CoV-2 infection in the population of unvaccinated people, including children aged 0-11 years. The estimate was adjusted upwards after the publication of the memo of 28 September, when it was assumed that immunity was 8.6%. Subsequently, transmission in the population has followed an increasing trend, including among unvaccinated children aged 0-11 years. Consequently, the estimate of acquired immunity in the population was adjusted upwards in the current calculations. Thus, the present calculation assumes that 15% of the unvaccinated population will have acquired immunity by 1 December 2021.

The estimate of VE with respect to preventing transmission of the Delta variant is assumed to be on a par with the calculations published in the memo of 28 September 2021. The estimate at that point in time was 85.5%. On the basis of the ENFORCE study, we assume that 5% of the primary vaccinated proportion of the population will have a very low or lacking effect of their vaccination due to a lacking/reduced immune response. Additionally, estimates are provided on waning immunity in the period passed since vaccination was concluded. In this context, we have used knowledge from a follow up on the authorisation study of Comirnaty® conducted after six months. The follow-up study described that the VE peaks seven days to two months after the second dose, after which the effectiveness declines, at an average rate 6% every second month[43]. For the estimation of declining immunity, we have therefore applied a linear 3% decline a month, starting two months after vaccination was concluded. Additionally, we have taken into account knowledge about the percentage distribution in the population of time passed since vaccination was concluded (see Table 2).

By 1 December 2021, everyone who received their second vaccination shot more than six months ago will have been invited for booster vaccination (n = approx. 1,340,000). Among

[43] https://www.medrxiv.org/content/10.1101/2021.07.28.21261159v1.full.pdf

this group, we expect to achieve an 85% booster vaccination programme coverage (n = approx, 1,130,000).

As we expect the individuals who receive booster vaccination to achieve full immunological effect following their third shot, 85% of those invited for booster vaccination as per 1 December 2021 will achieve an effect corresponding to the one achieved when they concluded their primary vaccination and they will once again belong to the group in the calculations that has completed vaccination/booster vaccination within the past two months.

Table 2. Time passed since concluded vaccination of booster vaccination by population as per 1 December 2021 and estimated waning immunity over time

Time passed since vaccination was concluded	**0-2 months + booster vaccination as per 1 December**	**3-5 months**	**6-11 months**	**Total**
Population (N)	1,221,898*	2,705,630	436,392	4,363,920
Population (%)	28%	62 %	10%	100%
Estimated waning immunity	0%	3-9%	12-27%	

*Approx. 1,130,000 individuals are expected to have received booster vaccination as per 1 December 2021 (85% coverage). Additionally, approx. 92,000 people are expected to have received primary vaccination within 0-2 months as per 1 December 2021.

Population immunity estimates

Based on the above assumptions, the expected population immunity as per 1 December 2021 may be calculated.

Table 3 shows that approx. 5.1 million individuals (88% of the total population) were offered COVID-19 vaccination. Based on the assumption of 90% coverage, 79% of the total population will have received primary vaccination. Additionally, on the basis of the ENFORCE study, we assume that 5% of the primary vaccinated proportion of the population will have a very low or no effect of their vaccination due to a lacking/reduced immune response.

By assuming that the overall effect of the vaccines to prevent transmission is 85.5% and by estimating a total decline in population immunity due to time passed since vaccination of approx. 3.9% as per 1 December 2021 (stated based on the percentage distribution of the population and time passed after concluding the primary vaccination course, Table 2), and finally assuming a natural immunity among the remaining unvaccinated population of approx. 15%, the overall population immunity as per 1 December 2021 may be expected to reach approx.

64.6%. Compared with the 66.6% population immunity estimated in the memo published on 28 September 2021, the new estimate as per 1 December 2021 is now 64.6% despite the fact that most of the population above 65 years of age have received booster vaccination.

Table 3. Population immunity estimate as per 1 December 2021

Population offered vaccination, % (n)	Total population proportion with induced immunity following primary vaccination at an expected maximum 90% coverage, % (n)	Total population proportion with induced immunity following primary vaccination assuming 5% low responders, % (n)	Vaccine effectiveness with respect to prevention of transmission	Immunity decline, including contribution from booster vaccination, according to assumptions (weighted average) %	Effectiveness with respect to prevention of transmission following decline over time, %	Overall population immunity following primary vaccination and booster vaccination in the population, %	Acquired immunity among unvaccinated people, % (n)	Total population immunity, %
88% (5,104,000)	79% (4,593,600)	75% (4,363,920)	85.5% (84.9 – 86.1) (Delta variant)	~ 3.9% of the population*	81.6%	~ 61.4%	15% (265,176)**	~ 64.6

*28% of the population is assumed to have concluded primary vaccination or to have received booster vaccination within 0-2 months, corresponding to a VE decline of 0%; 62% of the population is assumed to have concluded primary vaccination within 3-5 months, corresponding to a 6% decline in VE; and 10% of the population is assumed to have concluded primary vaccination within 6-11 months, corresponding to an approx. 18% decline in VE.

**Calculated based on the assumption that 79% (n = 4,032,160) of the total population (n = 5,800,000) has received primary vaccination.

Population immunity will continue to decline gradually after 1 December 2021, provided the rest of the population below 65 years of age does not receive booster vaccination. In the following, we estimate the population immunity as per 1 February 2022 in various scenarios, where the share of the population offered vaccination is changed.

The various scenarios assume that - as per 1 February 2022 - the majority of the individuals who have received primary vaccination did so more than six months ago. Furthermore, the scenarios are based on the assumptions described above in connection with the calculation of population immunity as per 1 December 2021.

Provided booster vaccination is offered to everyone above 40 years of age, we assume that, compared with 1 December 2021, approx. 1,300,000 individuals will have been offered booster vaccination (assuming an 85% coverage among those invited).

Provided booster vaccination is offered to anyone aged 30 years or above, it is assumed that the booster vaccination offer will include an additional approx. 1,775,000 individuals compared with 1 December 2021 (again assuming an 85% coverage).

Provided booster vaccination is offered to anyone aged 18 years or above, it is assumed that compared with 1 December 2021, the booster vaccination offer will comprise an additional approx. 2,330,000 (assuming an 85% coverage).

Additionally, it is assumed that 60,000 individuals will receive primary vaccination in the period from 1 December 2021 to 1 February 2022. This figure includes children who turn 12 old in the period. Furthermore, it is assumed that individuals who received booster vaccination before 1 December 2021 will maintain a high immunological effect after their third vaccination shot as per 1 February 2022, thereby avoiding a decline in VE. The estimated population immunity as per 1 February 2022 in four different scenarios is presented below in Table 4.

Table 4. Estimation of total population immunity as per 1 February 2022 assuming a booster vaccination offer is given to different age groups

Booster vaccination offer	Estimated population immunity as per 1 February 2022
No further booster vaccination after 1 December	59.7%
40-64 years	63.2%
30-64 years	64.6%
18-64 years	66.9%

If booster vaccination is not offered to any additional individuals after 1 December 2021, the estimated population immunity will decline from 64.6% as per 1 December 2021 to 59.7% as

per 1 February 2022. If the lower age threshold for booster vaccination is set to 40 years, the estimated population immunity as per 1 February 2022 will be 63.2%. If booster vaccination is offered to any citizen aged 30 years or above, the estimated population immunity as per 1 February 2022 will be 64.6%. An increased population immunity reaching 66.9% is expected as per 1 February 2022 compared with the estimated population immunity as per 1 December 2021 (64.6%), provided booster vaccination is offered to anyone in the population aged 18 years or above.

Recommendations from other countries, etc.

On 24 November 2021, the European Centre for Disease Prevention and Control (ECDC) recommended that all adults aged 18 years or above in the EU/EEA are offered COVID-19 booster vaccination a minimum of six months after receiving the second vaccination shot of the primary vaccination regime[44]. The recommendation was made based on the assessment that the effect of booster vaccination will contribute to reducing transmission of infection; and booster vaccination as from 18 years of age was described as a necessary adjunct to non-pharmacological measures aiming to limit community transmission. The ECDC recommended prioritising booster vaccination of elderly and vulnerable people and healthcare staff. Additionally, the ECDC sees a need for booster vaccination of individuals aged 40 years or above, but generally booster vaccination of all adults aged 18 years or above is recommended as a waning effect of primary vaccination is observed across age groups.

To provide an overview of the recommendations made by other countries concerning COVID-19 booster vaccination, the Danish Health Authority on 18 November 2021 received notifications from selected countries via the Danish Ministry of Foreign Affairs. This overview is enclosed as Appendix 1 and needs to be read with the reservation that the information provided was collected by the embassies and thus not directly from the respective various national vaccine-responsible authorities.

From a total of 35 countries, 34 have already initiated booster vaccination, either of select target groups or of the entire primary vaccinated population. Owing to a strengthened knowledge base, mainly based on data from Israel, a shift has occurred in the international perception of booster vaccination. Now, a stronger medical consensus exists that booster vaccination may be recommended for a larger proportion of the population. Thus, several countries, including Norway, the US, Holland and Germany, are now offering booster vaccination for everyone aged 18 years or above.

The following sections describe the booster vaccination programmes in the selected countries. Descriptions are provided in descending order, by proportion of the population currently offered booster vaccination.

[44] ECDC Assessment of the current SARS-CoV-2 epidemiological situation in the EU/EEA, projections for the end-of-year festive season and strategies for response, 17th update. 24 November 2021. https://www.ecdc.europa.eu/sites/default/files/documents/RRA-SARS-CoV-2-17th-update-Nov-2021.pdf

In the majority of the countries described, a total of 21 of 35 countries, booster vaccination is recommended to the general population that has already concluded primary vaccination. Specifically, these countries include Australia, the US, Belgium, Cyprus, Estonia, Greece, Island, Israel, Croatia, Lithuania, Malta, the Netherlands, Norway, Rumania, Poland, Slovakia, Slovenia, the Czech Republic, Germany, Hungary and Austria. However, most countries have only just initiated booster vaccination of selected groups, primarily elderly people, healthcare and nursing staff and immunodeficient people, whereas large shares of the remaining population will expectedly receive booster vaccination in 2022. Furthermore, several countries have established a lower age threshold for booster vaccination. Thus, in Australia, Cyprus, the US, Estonia, Greece, Poland Slovenia and Hungary, booster vaccination is recommended to anyone aged 18 years or above, whereas it is recommended for anyone aged 12 years or above in Malta. In the remaining countries, anyone who has concluded primary vaccination is recommended booster vaccination; however, without any further details on any age threshold.

In the second-largest group, counting a total of eight of 35 countries, booster vaccination is recommended for elderly people above an established age, nursing home residents, individuals with a weakened immune response or underlying conditions and staff at nursing homes, and frontline healthcare staff. Specifically, this applies in Bulgaria, Canada, France, Italy, Latvia, Luxembourg, Great Britain and Sweden. The age limit determining when each country currently offers booster vaccination to elderly people is set to everyone above 70 years in Canada; 65 years in Bulgaria, France, Luxembourg and Sweden; 60 years in Italy; 50 years in Latvia; and 40 years in Great Britain. However, in France, the age limit for booster vaccination will soon be reduced to everyone above 50 years of age and in Italy to everyone above 40 years. In addition to the mentioned groups, Canada offers booster vaccination for individuals vaccinated with AstraZeneca or Johnson & Johnson and to the indigenous peoples of Canada. France also offers booster vaccination for people who have been vaccinated with Johnson & Johnson. In Latvia, individuals below 65 years of age who have been vaccinated with Moderna will not be offered booster vaccination as evidence shows that the vaccine remains affective for eight months after concluding the primary vaccination course.

A third group, counting a total of five countries (Finland, Ireland, Portugal, Switzerland and Spain) offer booster vaccination for elderly people, nursing home residents and individuals with a weakened immune response or underlying conditions. The age limit determining when elderly people in each country are currently offered booster vaccination to everyone is: everyone above 75 years of age in Switzerland, 70 years in Spain, 65 years in Portugal, 60 years in Finland and 50 years in Ireland. In addition to these broad groups, each country offers booster vaccination to a range of specific groups. Individuals with underlying conditions below 50 years in Ireland and above 65 years in Switzerland are offered booster vaccination. In addition to the above mentioned groups, Finland also offers booster vaccination to individuals who have received primary vaccination at a less than six-week dose interval. The need for booster vaccination of the rest of the population will be assessed at a later point in time. In Spain, the

government has proposed booster vaccination for healthcare staff and elderly people aged more than 60 years. A final decision on this topic is expected soon.

As the only one of the countries studied, Japan has not yet initiated booster vaccination. Even so, Japan is expected to initiate booster vaccination as from 1 December 2021. Healthcare staff will be the first group to receive booster vaccination. A final plan for roll-out has not yet been established.

Vaccine technologies

Currently, only mRNA vaccines are used in the general vaccination programme, but the EMA has recently announced that an additional COVID-19 vaccine is being assessed[45]. The vaccine in question is based on classic protein technology, i.e. adjuvanted spike protein, from the manufacturer Novavax. Denmark has entered into an agreement on advance purchase of this vaccine[46]. None of the previously authorised COVID-19 vaccines use this technology, but the technology is well-known from other vaccines (e.g., hepatitis B vaccine).

Generally, this type of vaccine provides longer-lasting, robust immunity[47]. If this will also be the case for a COVID-19 vaccine based on this vaccine technology remains unknown, but it may be the case. Therefore, we cannot exclude that it may be considered advantageous in the future to combine the COVID-19 immunity, which people have achieved thanks to COVID-19 mRNA vaccines, with a booster based on COVID-19 spike protein (a classic protein-based vaccine). However, a more detailed assessment of this option cannot be made until the regulatory approval for future COVID-19 vaccines have been published.

Overall medical assessment

The EU Commission has approved the administration of a third dose of Comirnaty® or Spikevax® as booster vaccination for individuals aged 18 years or above at a minimum six-month interval after the second dose administered in the primary vaccination course. Comirnaty® may be used for booster vaccination giving the full dose (30 microgram)[48]. Spikevax® may be used for booster vaccination giving half the normal dose (50 microgram)[49]. It currently remains uncertain how long-lasting the effect of COVID-19 booster vaccination will be. From other vaccination regimes, it is known that additional vaccinations may be needed. This, e.g., applies to hepatitis B (inflammation of the liver), which is given in a vaccination regime counting a total of three vaccination shots, the third of which provides

[45] EMA press release 17 November 2021. https://www.ema.europa.eu/en/news/ema-receives-application-conditional-marketing-authorisation-novavaxs-covid-19-vaccine-nuvaxovid

[46]The Danish Ministry of Health 11 August 2021. https://sum.dk/nyheder/2021/august/danmark-indkoeber-en-ny-type-covid-19-vacciner-fra-novavax

[47] Clark TG et al. Recombinant subunit vaccines: potentials and constraints. Developments in Biologicals 2005;121:153-163. https://europepmc.org/article/med/15962478

[48]EMA, Summary of Product Characteristics Comirnaty®. Accessed 9 November 2021. https://www.ema.europa.eu/en/documents/productinformation/comirnaty-epar-product-information_en.pdf

[49]EMA Summary of Product Characteristics Spikevax®. Accessed 9 November 2021: https://www.ema.europa.eu/en/documents/product-information/spikevax-previously-covid-19-vaccine-moderna-epar-product-information_en.pdf

long-lasting immunity. For other vaccines, e.g., against influenza, annual vaccination is required.

The Danish Health Authority has initiated booster vaccination of everyone who received their second vaccination shot before 1 June, which primarily means individuals aged more than 65 years, staff serving in the healthcare and elderly sector and individuals with an increased risk of running a serious disease course.

In this memo, the Danish Health Authority has provided an update on the COVID-19 epidemic and reviewed the updated knowledge basis for booster vaccination to assess booster vaccination for the rest of the population.

Updated knowledge base

The knowledge base available for assessment of the effect of booster vaccination against infection and serious disease due to COVID-19 remains incomplete. However, new data are published continually, and the knowledge base is now more robust than at the drafting of the Danish Health Authority's previous booster vaccination memos[50,51].

Thus, several studies from various countries have documented that the immunity after vaccination is waning over time, and that the decline in immunity may be considerable after six months. Previously, we mainly had documentation supporting a decline in the immunity among elderly individuals and individuals with underlying conditions, but now documentation exists that waning immunity also occurs in younger age groups.

The updated knowledge base shows that it is not possible to measure the effect of booster vaccination by an increase in antibodies. However, it also shows that booster vaccination is effective in providing protection by enhancing protection against infection and against serious disease, hospitalisation and death. This effect seems to be homogenous across sexes, age groups and regardless of the number of other conditions (comorbidity).

Data from Denmark and other countries continue to show that primary vaccination with the mRNA vaccines generally provides good protection against COVID-19 disease, hospitalisation and death six months after primary vaccination; and that the effect is generally preserved beyond six months.
However, the protective effect against SARS-CoV-2 infection and mild-to-moderate COVID-19 is lower and wanes more rapidly. This has now been documented through laboratory tests and epidemiological studies alike. This probably also means that the risk of passing on the infection increases with time.

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[50]Danish Health Authority, 28 September 2021, On COVID-28 booster vaccination [Vedr. revaccination mod COVID-19]: https://www.sst.dk/da/Udgivelser/2021/Revaccination-mod-COVID-19

[51] Danish Health Authority, 15 October 2021, *Plan for COVID-19 booster vaccination (PHFASE II) [Plan for revaccination mod COVID-19 (FASE II)]*: https://www.sst.dk/da/Udgivelser/2021/Plan-for-revaccination-mod-COVID-19--FASE-II

Update on the epidemic and the pressure it causes on secondary healthcare
Denmark is currently experiencing a flare-up of the epidemic primarily driven by the transition from summer to autumn and winter, but also by increased generational mixing during the autumn holidays facilitated by an open society and absence of restrictions. High and increasing case numbers are being recorded, but the period after the autumn holidays has also brought a considerable rise in the number of hospitalised patients from approx. 100 to more than 400 hospitalised patients. Whereas we previously observed a preponderance of unvaccinated people among those hospitalised with COVID-19, vaccinated people now account for the majority of those hospitalised.

We expect that the transmission of SARS-CoV-2 will increase additionally in the course of the autumn and winter, with an ensuing increased risk of rising morbidity and more hospitalisations. In contrast to the autumn and winter season last year, societal activities have now normalised. Other things equal, we therefore expect a sustained increase in the number of hospitalised people, and not only people hospitalised due to COVID-19 but also due to influenza and other serious airway diseases and other acute conditions. This will increase the pressure, in particular on emergency rooms, medical wards, operation theatres and intensive care units. The Danish Health Authority harbours considerable concern for the pressures that may affect Danish hospitals in the winter of 2021/22[52], which was described in the memo *Hospital capacity challenged in the autumn and winter 2021/2022*, published on 5 November 2021.

Currently, the situation is different as an increasing level of community transmission is observed that may be expected to rise additionally in months to come. Furthermore, a higher rate of breakthrough disease across age groups is observed, and documentation is building in support of waning immunity after vaccination over time and across age groups.

Effect versus harm
The updated knowledge base shows that booster vaccination contributes effectively to preventing SARS-CoV-2 transmission in all age groups. The updated knowledge basis also shows that booster vaccination is effective in avoiding serious disease and hospitalisation. The knowledge base is limited by the fact that follow-up periods are currently relatively short. Additionally, Denmark has observed a decline in infection at nursing homes, in the oldest age groups and among healthcare workers coinciding with booster vaccination, which was presumably therefore an effect of booster vaccination.

It has been documented that the risk of running a serious disease course with hospitalisation due to COVID-19 increases with age. In October 2021, the average at hospitalisation was 62 years[53]. Even so, it is not possible to establish a lower age limit for the hospitalisation risk. In

[52] Danish Health Authority, 5 November 2021, *Hospital capacity challenged in the autumn and winter 2021/2022 [Udfordring af sygehuskapaciteten i efterår og vinter 2021/2022]* https://www.sst.dk/-/media/Udgivelser/2021/Sygehuskapacitet/Styring-af-sygehuskapacitet-i-efteraar-og-vinter-2021-2022.ashx?la=da&hash=C540178DF815821BDB17E304686E289C63E7BDC0

[53]Data from the Danish Health Data Authority.

the group of people aged 50-65 years, some individuals will thus achieve a direct and individual effect of booster vaccination against COVID-19, whereas vaccinated individuals below 50 years generally have a low risk of serious disease and death due to COVID-19. Booster vaccination of the younger part of the population will therefore be necessary only to a limited degree to protect individuals against serious disease. Indirect benefits may, however, be associated with booster vaccination in the group aged less than 50 years. Firstly, booster vaccination may serve to reduce the risk of transmitting the infection to relatives, which may reduce the risk of infection and therefore, in turn, the need for testing, infection tracing, self-isolation, etc. Thereby, booster vaccination of people aged less than 50 years may serve to establish and extend overall population immunity.

The Danish Health Authority assesses that the safety of booster vaccination is high. Based on the documentation and knowledge base, we do not assess that a risk exists of new rare, serious side effects from a third vaccination shot. The current knowledge basis also underpins that the reactogenicity of the second and third vaccination shot is comparable. In the group of younger individuals below 50 years of age, a potential risk exists of an increased immune response from booster vaccination and therefore a higher prevalence of the side effects known from primary vaccination. According to the Danish Medicines Agency, no special side effects signal has been raised following the booster vaccination of healthcare workers, a group in which most are healthy and below 65 years of age.

It is known that inflammation of the heart muscle (myocarditis) and inflammation of the sac-like tissue surrounding the heart (pericarditis) may occur in very rare cases following vaccination with Comirnaty® or Spikevax®. Myocarditis and pericarditis are well-known diseases that are also seen in connection with, e.g., virus infections also without any relation to vaccination. Myocarditis and pericarditis may give rise to similar symptoms and often co-occur. Both diseases are inflammatory conditions, that may, e.g., be triggered by a virus infection, toxins or an immunological reaction. The prevalence of these diseases in Europe is estimated to be approx. 1-10 per 100,000 individuals annually and they are primarily observed in younger men[54]. The notified cases were thus mainly seen among younger men below 30 years of age, more often after the second than after the first dose, and most cases were mild and receded within few days. Data indicate that the disease course for myocarditis and pericarditis following vaccination is in line with the typical courses for these conditions.
Myocarditis and pericarditis are normally benign and may lead to unspecific influenza-like symptoms days to weeks after acute febrile disease or airway infection. Other typical symptoms include chest pain, shortness of breath and palpitations. Most cases recover completely with no sequelae. Myocarditis and pericarditis are typically self-limiting, i.e. the conditions recede spontaneously, and the treatment options are good if treatment is needed. However, in rare cases, the disease can pass to a chronic phase leading to various degrees of heart failure.

[54] Danish Medicines Authority, 11 June 2021. https://laegemiddelstyrelsen.dk/da/nyheder/2021/mulig-risiko-for-udvikling-af-myokarditis-og-perikarditis-efter-vaccination-med-covid-19-vacciner-undersoeges/

According to the Danish Medicines Agency, no cases of myocarditis have been observed after booster vaccination in Denmark. This may, however, be expected as we have primarily vaccinated the older proportion of the population where the risk of myocarditis is low, as most cases are reported in men below 30 years of age. At primary vaccination, the frequency of myocarditis increases with decreasing age in the interval from 65 years to 18 years for both mRNA vaccines; moreover, as the side effects profiles following booster vaccination and after the second vaccination shot of the primary vaccination course are comparable (see above), we also expect that the frequency of myocarditis will increase with decreasing age in the interval from 65 to 18 years for both mRNA vaccines following booster vaccination. The risk of myocarditis and pericarditis is currently expected to be on a par with the risk observed for the second dose.

The Danish Health Authority continuously follows the safety updates concerning myocarditis and pericarditis published by, among other things, the Danish Medicines Agency, the PRAC and Danish monitoring data.

Overall assessment

Based on the current knowledge, the Danish Health Authority recommends booster vaccination for all individuals aged more than 18 years six months after the second vaccination shot of the primary vaccination regime.

The EU Commission has approved the administration of a third dose of Comirnaty® and a third dose of Spikevax® as booster vaccination for individuals aged 18 years or above at a minimum six-month interval after the second dose administered in the primary vaccination course. Due to the concerning spreading of infection in the EU area, the European Centre for Disease Prevention and Control (ECDC) recommends that all adults in the EU be offered booster vaccination.

The Danish Health Authority assesses that booster vaccination is effective in preventing waning immunity after six months across age groups. The updated knowledge basis shows that it is possible to measure the effect of booster vaccination by an increase in antibodies. It also shows that booster vaccination is effective in providing protection in enhancing protection against infection and against serious disease, hospitalisation and death. The effect of booster vaccination seems to be homogenous across sexes, age groups and regardless the number of other conditions.

Currently no evidence-based knowledge exists about the optimal booster vaccination time, i.e., if booster vaccination should be given at six months or at a longer interval. Even so, from other vaccination regimes we know that you can achieve long-lasting immunity by boosting a primary vaccination course. This, e.g., applies to hepatitis B vaccination.

The Danish Board of Health assesses that booster vaccination provides individual-level protection for individuals who are at risk of running a serious COVID-19 disease course. Additionally, booster vaccination may contribute to protecting individuals against infection and the consequences hereof, and to lowering the risk of transmitting infection to other individuals. The younger an individual is, the lower is his or her risk of running a serious COVID-19 disease course. The average age at hospitalisation was 62 years in October 2021[55], but some individuals below this age may experience a serious disease course.

It is known that myocarditis and pericarditis may occur in very rare cases following vaccination with Comirnaty® or Spikevax®. These disease courses are mild and typically pass spontaneously. This will be described in the Danish Health Authority's information material.

The Danish Health Authority assesses that booster vaccination of the population in combination with an increased primary vaccination coverage contributes to enhancing population immunity. In this memo, the Danish Health Authority has estimated Danish population immunity. If the population below 65 years of age does not receive booster vaccination, immunity will decline. A decline in immunity may have a considerable impact on the evolution of the COVID-19 epidemic in a winter season, including a risk of increased morbidity and increased pressure on hospitals.

Internationally, the medical consensus on the need for booster vaccination is building. Many of the countries with whom we typically compare Denmark, including Germany, Holland and Norway, are planning booster vaccination initiatives comprising anyone in their populations aged more than 18 years.

Additional steps

The Danish Health Authority recommends that anyone above 18 years of age be offered booster vaccination in line with the authorisation basis six months after receiving the final vaccination shot of the primary vaccination regime. Individuals above 18 years of age are thus invited for booster vaccination based on the date at which they received the final vaccination shot in the primary vaccination regime. Booster vaccination invitations comprise the same vaccine type (Cominarty® or Spikevax® (half a dose of Spikevax® is given) as the one received in the primary vaccination regime.

To underpin the booster vaccination recommendation six months after primary vaccination for all individuals aged more than 18 years, an update is needed of the Danish Health Authority's dissemination material, including a folder, the invitation, the website, etc.

Looking forward, a need exists to ensure detailed near-real-time data on individuals hospitalised with COVID-19, to monitor the effect of booster vaccination.

[55]Data from the Danish Health Data Authority.

The following information will be relevant:

1. Number of individuals hospitalised due to COVID-19 pneumonia/pulmonary failure (acute respiratory distress syndrome (ARDS)).
2. Number of individuals hospitalised for treatment with monoclonal antibodies or other recent medicinal products used for prevention of serious disease.
3. Number of individuals hospitalised due to COVID for other causes than those stated above - typically for observation and/or other concurrent disease.
4. Other primary cause of hospitalisation than COVID-19 but with a positive COVID-19 test.

Work is currently ongoing to establish if this may be done using national Danish registers.

Additionally, it will be relevant to complete virus sequencing of people who have completed their primary vaccination course/received booster vaccination and who are hospitalised with COVID-19 pneumonia/pulmonary failure.

Appendix 1. COVID-19 booster vaccination in the EU/Schengen and selected third countries

Through the Danish Ministry of Foreign Affairs, the Danish Health Authority has collected information on COVID-19 booster vaccination from all embassies in the EU, the Schengen countries and also Great Britain, the US, Canada, Australia, Israel and Japan (update reported as per 18 November 2021). The status reported by the embassies needs to be read with the reservation that it has not been possible in all countries to confirm if the information provided actually reflects the respective national vaccine-responsible authorities' current recommendations.

COVID-19 booster vaccination in the EU/Schengen and selected third countries

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On the Danish Health Authority's request, the Danish Ministry of Foreign Affairs on 12 November 2021 instructed all embassies in the EU and Schengen countries and also in Australia, Canada, Israel, Japan, Great Britain and the US to obtain information on COVID-19 booster vaccination. The instruction asked the embassies to inform of the booster vaccination status in each of the countries including the recommended time interval between the primary vaccination course and booster vaccination.

In the below memo, the concept of booster vaccination is used as an umbrella term covering measures by which people who have completed their primary vaccination course receive an additional vaccination shot.

Overall, it should be stressed that all of the 35 studied countries, apart from Japan, have already initiated booster vaccination of selected population groups or of all citizens who have completed their primary vaccination course. Furthermore, in line with EMA recommendations, a large share of the countries studied also recommend that booster vaccination is made a minimum of six months after concluding the primary vaccination course or 28 days for individuals with a weakened immune response. The following sections describe the booster vaccination programmes in the selected countries. Descriptions are provided in descending order, by proportion of the population currently offered booster vaccination. Subsequently, the next sections describe the comprised countries' recommendations for the time interval separating a concluded primary vaccination from booster vaccination.

Update on the countries' booster vaccination programmes

In the majority of the countries described, a total of 20 of 35 countries, booster vaccination is recommended to the general population that has already concluded primary vaccination. Specifically, these countries include **Australia, the US, Belgium, Cyprus, Estonia, Greece, Island, Israel, Croatia, Lithuania, Malta, the Netherlands, Norway, Rumania, Poland, Slovakia, Slovenia, the Czech Republic, Germany, Hungary** and **Austria**. However, most countries have only just initiated booster vaccination of selected groups, primarily elderly people, healthcare and nursing staff and immunodeficient people, whereas large shares of the remaining population will expectedly receive booster vaccination in 2022. Furthermore, several countries have established a lower age threshold for booster vaccination. Thus, in Australia, Cyprus, Estonia, Greece, Poland Slovenia and Hungary, booster vaccination is recommended to anyone aged 18 years or above, whereas it is recommended for anyone aged 12 years or above in Malta. In the remaining countries, anyone who has concluded primary vaccination is recommended booster vaccination; however, without any further details on any age threshold.

In the second-largest group, counting a total of eight of 35 countries, booster vaccination is recommended for elderly people exceeding an established age, nursing home residents, individuals with a weakened immune response or underlying conditions and staff at nursing homes, and frontline healthcare staff. Specifically, this applies in **Bulgaria, Canada, France, Italy, Latvia, Luxembourg, Great Britain** and **Sweden.** The age limit determining when each country currently offers booster vaccination to elderly people is set to everyone above 70 years in Canada; 65 years in Bulgaria, France, Luxembourg and Sweden; 60 years in Italy; 50 years in Latvia; and 40 years in Great Britain. However, in France, the age limit for booster vaccination will soon be reduced to everyone above 50 years of age and in Italy to everyone above 40 years. In addition to the mentioned groups, Canada offers booster vaccination for individuals vaccinated with AstraZeneca or Johnson & Johnson and to the indigenous peoples of Canada. France also offers booster vaccination for people who have been vaccinated with Johnson & Johnson. In Latvia, individuals below 65 years of age who have been vaccinated with Moderna will not be offered booster vaccination as evidence shows that the vaccine remains affective for eight months after concluding the primary vaccination course.

A third group, counting a total of six countries; **Finland, Ireland, Portugal, Switzerland and Spain** and the **US**, offers booster vaccination for elderly people, nursing home residents and individuals with a weakened immune response or underlying conditions. The age limit determining when elderly people in each country is currently offered booster vaccination to everyone is: everyone above 75 years of age in Switzerland, 70 years in Spain, 65 years in Portugal and the US, 60 years in Finland and 50 years in Ireland. In addition to these broad groups, each country offers booster vaccination to a range of specific groups. Booster vaccination is offered to individuals with underlying conditions below 50 years in Ireland and above 50 years in Switzerland and 65 years in the US. Additionally, the US also offers booster vaccination to people who have been vaccinated with Johnson & Johnson. In addition to the above mentioned groups, Finland also offers booster vaccination to individuals who have received primary vaccination at a less than six-week dose interval. The need for booster vaccination of the rest of the population will be assessed at a later point in time. In Spain, the government has proposed booster vaccination for healthcare staff and elderly people aged more than 60 years. A final decision on this topic is expected soon.

As the only of the countries studied, **Japan** has not yet initiated booster vaccination. Even so, Japan is expected to initiate booster vaccination as from 1 December 2021. Healthcare staff will be the first group to receive booster vaccination. A final plan for roll-out has not yet been established.

Table 1: Target groups in the countries studied that are currently offered booster vaccination

Groups offered booster vaccination	Countries
• The full population that has concluded primary vaccination.	AU, BE, CY, EE, GR, IS, IL, HR, LT, MT, NL, NO, RU, PL, SK, SI, CZ, DE, HU, AT
• Elderly people from an established age limit; • Nursing home residents; • Individuals with a weakened immune system or morbidity; • Nursing home and frontline healthcare staff	BU, CA, FR, IT, LV, LU, UK, SE

• Elderly people from an established age limit; • Nursing home residents; • Individuals with a weakened immune system or disease;	FI, IE, PT, CH, ES, US
• None (booster vaccination not initiated)	JP

Time interval between the primary vaccination course and booster vaccination

Furthermore, in line with EMA recommendations, the overwhelming majority of the countries studied, 29 of 35 countries also recommend that booster vaccination is made a minimum of six months after concluding the primary vaccination course. Specifically, this recommendation applies for: **Australia, Bulgaria, Canada, Cyprus, Estonia, Finland, Greece, Ireland, Italy, Croatia, Latvia, Luxembourg, Malta, the Netherlands, Norway, Rumania, Poland, Portugal, Switzerland, Slovakia, Slovenia, Spain, Sweden, Great Britain, the Czech Republic, Germany, the US** and **Austria.**

Additionally, various special measures apply in several of the countries mentioned above in which the time interval separating the primary vaccination course from booster vaccination may be reduced for some groups. Thus, in line with EMA recommendations, a total of 13 of the 29 countries - **Belgium, Canada, Cyprus, Italy, Latvia, Norway, Rumania, Poland, Slovakia, Slovenia, Spain,** the **Czech Republic,** the **US** and **Austria** recommend that individuals with a weakened immune response receive booster vaccination already 28 days after concluding their primary vaccination course.

Additionally, various of the 29 countries listed above have established special national recommendations relating to the time interval between the primary vaccination course and booster vaccination for some person groups. These national recommendations supplement the EMA recommendation that booster vaccination is generally given at a minimum six-month interval after concluding the primary vaccination course. In **Bulgaria**, booster vaccination is thus recommended six months after completing the primary vaccination course and following an antibody test and medical assessment. In **Estonia**, individuals vaccinated with AstraZeneca or Johnson & Johnson are recommended booster vaccination no less than five months after concluding their primary vaccination course. In **Greece**, people who have received the Johnson & Johnson vaccine are eligible for booster vaccination already two months after concluding their primary vaccination course. In **Ireland**, booster vaccination may in some cases be recommended two months after concluding the primary vaccination course. In **Latvia**, individuals aged more than 18 years who have received the Johnson & Johnson vaccine may receive booster vaccination 12 weeks after concluding their primary vaccination course. In **Malta**, elderly people aged more than 65 years are recommended booster vaccination already 28 days after concluding their primary vaccination course. In **the Netherlands,** the recommendation is not to give booster vaccination until at least two weeks after an influenza vaccine was given. In **Slovenia**, individuals vaccinated with vector vaccines, e.g., the vaccines from AstraZeneca and Johnson & Johnson, are recommended booster vaccination no sooner than two months after concluding their primary vaccination course In **Great Britain**, individuals in exposed groups may receive booster vaccination before six months have passed. In **Sweden**, individuals aged more than 65 year and nursing home residents and people receiving home care may be offered booster vaccination five months after concluding

their primary vaccination course. In individuals with a weakened immune response, booster vaccination may be given already two months after concluding the primary vaccination course. In the **US**, individuals who have received the Johnson & Johnson vaccine may receive booster vaccination two months after concluding their primary vaccination course. And finally, in **Austria**, all citizens in the capital of Vienna may receive booster vaccination already four months after concluding their primary vaccination course.

The remaining five countries of the 35 countries studied, **Island**, **Israel**, **Japan, Lithuania** and **Hungary**, do not follow the EMA recommendations. In Island, booster vaccination is recommended depending on population group, vaccine type and side effects registered at primary vaccination between one and six months after concluding the primary vaccination course. **Israel** recommends booster vaccination as from five months after concluding the primary vaccination course. **Japan**, as mentioned, has yet to initiate booster vaccination. Once booster vaccination is initiated, it will be recommended eight months after concluding the initial vaccination course. Local authorities may shorten the interval to six months, e.g., in the context of increasing case numbers. In Lithuania and Hungary, booster vaccination is recommended no earlier than four months after concluding the primary vaccination course. Previously, Lithuania recommended a minimum interval of six months.

Table 2: Time interval between the primary vaccination course and booster vaccination

Time period:	Countries
• Six months after concluding the primary vaccination course	AU, LU, PT, RU, CH, DE
• Six months after concluding the primary vaccination course; • 28 days after concluding the primary vaccination course for individuals with a weakened immune system	BE, CA, CY, IT, LT, NO, RU, PL, SK, SI, ES, CZ, US, AT
• Six months after concluding the primary vaccination course; • National recommendations as to the time interval between the primary vaccination course and booster vaccination for select groups	BU, EE, GR, IE, LV, MT, NL, SI, UK
• National recommendations as to the time interval between the primary vaccination course and booster vaccination	IS, IL, JP, LT, HU

Additional details about the various national booster vaccination guidelines are presented in Table 3 on the following pages.

Table 3: Booster vaccination in selected countries

Country	Has booster vaccination been initiated?	Time interval between the primary vaccination course and booster vaccination
Australia	**Yes,** booster vaccination for individuals with a weakened immune response was initiated on 11 October. Since 8 October, booster vaccination has been recommended and available to anyone more than 18 years of age.	Booster vaccination is recommended no earlier than six months after concluding the primary vaccination course.
Belgium	**Yes**, elderly people aged more than 65 years, nursing home residents, individuals with a weakened immune response and individuals who have received vaccination with AstraZeneca or Johnson & Johnson are recommended vaccination. A political decision in principle was made that everyone will be offered booster vaccination in 2022. Details of the time schedule and prioritised groups will likely be published by late November 2021.	Booster vaccination is recommended no earlier than six months after concluding the primary vaccination course. Even so, for some groups, booster vaccination is recommended 2-3 months after receiving the second vaccination shot with mRNA vaccines.
Bulgaria	**Yes**, booster vaccination was initiated in late September. Elderly people aged more than 65 years, nursing home staff, frontline healthcare staff and individuals with a weakened immune response are recommended vaccination.	Booster vaccination is recommended six months after completing the primary vaccination course and following an antibody test and medical assessment.
Canada	**Yes,** booster vaccination has been initiated. Elderly people aged more than 70 years, nursing home residents, frontline healthcare workers, individuals with a weakened immune response, individuals who have received vaccination with AstraZeneca or Johnson & Johnson and indigenous people receive booster vaccination.	Booster vaccination is recommended no earlier than six months after concluding the primary vaccination course. Even so, individuals with a weakened immune response receive booster vaccination already 28 days after concluding the primary vaccination course.
Cyprus	**Yes**, booster vaccination was initiated in early September. Individuals aged more than 18 years, individuals with a weakened immune response, residents and staff at nursing homes and healthcare workers may receive booster vaccination. Individuals who have received vaccination with Johnson & Johnson will be offered booster vaccination with the same vaccine or an mRNA vaccine. The remaining people are only offered mRNA vaccines.	Booster vaccination is recommended no earlier than six months after concluding the primary vaccination course. Individuals with a weakened immune response are recommended booster vaccination 28 days after concluding their primary vaccination course.
Estonia	**Yes**, booster vaccination was initiated in early October for individuals aged more than 18 years. Elderly people aged more than 65 years, nursing home residents, individuals with a weakened immune response and social, healthcare and educational workers are	Booster vaccination is recommended no earlier than six months after concluding the primary vaccination course. Individuals vaccinated with AstraZeneca or Johnson & Johnson is recommended

	recommended booster vaccination. Only mRNA vaccines are used.	booster vaccination no less than five months after concluding their primary vaccination course.
Finland	**Yes,** booster vaccination has been initiated. Individuals aged more than 60 years, individuals with a weakened immune response or who form part of certain risk groups, individuals living at nursing institutions and individuals who have received vaccination at a dose interval of less than six weeks receive booster vaccination. Currently, however, booster vaccination is not recommended for men below 30 years, unless they belong to a risk group or have a reduced immune response. The situation for the rest of the population will be considered at a later point in time. As per 16 November, 2.5% of the population has received booster vaccination.	Booster vaccination should not be given less than two months after the second vaccination shot and with an mRNA vaccine.
France	**Yes,** booster vaccination was initiated on 1 September. Nursing home residents, elderly people aged more than 65 years, social, healthcare and fire service workers, people vaccinated with Johnson & Johnson and younger individuals with a weakened immune response need to receive vaccination before 15 December for their corona passport to remain valid. From the beginning of December, the booster vaccination offer is extended to comprise the age group 50-64 years.	Booster vaccination is recommended no earlier than six months after concluding the primary vaccination course. Individuals with a weakened immune response are recommended booster vaccination two months after concluding their primary vaccination course.
Greece	**Yes**, booster vaccination was initiated by mid-September 2021. Anyone who has completed the primary vaccination course and who is more than 18 years of age may receive booster vaccination. Only mRNA vaccines are used for booster vaccination, unless you have been vaccinated with Johnson & Johnson. If you were vaccinated with Johnson & Johnson, you will be offered booster vaccination with either Johnson & Johnson or an mRNA vaccine.	Booster vaccination is recommended no earlier than six months after concluding the primary vaccination course. Individuals with a weakened immune response may be offered booster vaccination sooner. People who have received the Johnson & Johnson vaccine are eligible for booster vaccination already two months after concluding their primary vaccination course.
Ireland	**Yes**, booster vaccination was initiated in late September for individuals aged more than 75 years and individuals with a weakened immune response. This scheme has now been extended to include everyone aged more than 50 years and individuals below 50 years of age with underlying conditions.	Booster vaccination is recommended no earlier than six months after concluding the primary vaccination course. However, booster vaccination may in some cases be recommended two months after concluding the primary vaccination course.

Iceland	**Yes**, everyone is recommended vaccination, but some population groups are given priority. These groups include elderly individuals aged more than 60 years, individuals with a weakened immune response, healthcare workers and individuals vaccinated with Johnson & Johnson. Currently, approx. 18% of the population has received booster vaccination.	Booster vaccination is recommended depending on population group, vaccine type and side effects registered at primary vaccination, between one and six months after concluding the primary vaccination course.
Israel	**Yes**, booster vaccination has been underway since 29 August for everyone who has completed their primary vaccination course. Booster vaccination of exposed target groups was initiated even earlier. Booster vaccination is by the BioNTech-Pfizer vaccine. Approx. 65% has received booster vaccination as per mid-November.	Booster vaccination is recommended no earlier than five months after concluding the primary vaccination course.
Italy	**Yes**, booster vaccination was initiated in September. Elderly people aged more than 60 years, nursing home workers, frontline healthcare staff and individuals with a weakened immune response are recommended vaccination. Only mRNA vaccines are used. As from 1 December 2021, the booster vaccination recommendation is extended to also include 40-59-year-olds.	Booster vaccination is recommended no earlier than six months after concluding the primary vaccination course. Even so, individuals with a weakened immune response receive booster vaccination already 28 days after concluding the primary vaccination course.
Japan	**No**, booster vaccination of healthcare workers is expected to start as per 1 December. A final plan for roll-out has not yet been established. Initially, only BioNTech-Pfizer will be used for booster vaccination. Individuals who have been vaccinated with Moderna or AstraZeneca will therefore receive booster vaccination with a vaccine different to the one they originally received.	Booster vaccination is recommended after eight months, but local authorities may shorten the interval to six months if they find that this measure is necessary - e.g., in the context of rising case numbers.
Croatia	**Yes**, booster vaccination was initiated on 12 October. Booster vaccination is recommended to people with a weakened immune response, elderly people aged more than 65 years and everyone who concluded their primary vaccination course more than six months ago. Only mRNA vaccines are used.	Booster vaccination is recommended no earlier than six months after concluding the primary vaccination course. Even so, individuals with a weakened immune response receive booster vaccination already 28 days after concluding the primary vaccination course.
Latvia	**Yes**, booster vaccination has been initiated of people aged more than 50 years, everyone aged more than 18 years with chronic conditions, nursing home residents, individuals with a weakened immune response and frontline workers who come into contact with COVID-19 patients and unvaccinated	Booster vaccination is recommended no earlier than six months after concluding the primary vaccination course. Individuals aged more than 18 years who have received the Johnson & Johnson vac-

	people. However, individuals vaccinated with the Moderna vaccine will not be offered booster vaccination as evidence suggests that the vaccine provides immunity for at least eight months, though not in individuals aged more than 65 year who are offered booster vaccination as from 4 November. Individuals who were vaccinated with AstraZeneca will receive booster vaccination with BioNTech-Pfizer or, in very rare cases, with the same vaccine used in the primary vaccination course.	cine may receive booster vaccination 12 weeks after concluding their primary vaccination course.
Lithuania	**Yes**, all citizens who have completed their primary vaccination course are offered booster vaccination four months after concluding the primary vaccination course.	Booster vaccination is recommended no earlier than four months after concluding the primary vaccination course.
Luxembourg	**Yes**, booster vaccination has been initiated of individuals with a weakened immune response, elderly people aged more than 65 years and healthcare workers. Only mRNA vaccines are used.	Booster vaccination is recommended no earlier than six months after concluding the primary vaccination course.
Malta	**Yes,** booster vaccination has been initiated. Individuals with a weakened immune response, nursing home residents, healthcare and nursing workers, educational staff and individuals above 65 years are recommended booster vaccination. Only mRNA vaccines are used. The Maltese health authorities have decided to offer booster vaccination to everyone aged more than 12 years. The 45-64-year age group is expected to be offered booster vaccination in a step-wise fashion as from December 2021.	Booster vaccination is recommended no earlier than six months after concluding the primary vaccination course. Even so, individuals with a weakened immune response and older individuals aged more than 65 years are recommended booster vaccination only 28 days after concluding their primary vaccination course
The Netherlands	**Yes,** booster vaccination for individuals with a severely weakened immune response was initiated in October. Individuals aged more than 80 years, nursing institution residents above 18 years and healthcare workers with patient contact are recommended booster vaccination. This group will initiate booster vaccination as per 19 November 2021. Once this group has been vaccinated, booster vaccination of individuals aged more than 60 years will begin. Subsequently, the rest of the population will follow. Only mRNA vaccines are used.	Booster vaccination is recommended no earlier than six months after concluding the primary vaccination course. The recommendation is not to give booster vaccination until at least two weeks after an influenza vaccine was given.

	The acting minister of health has instructed the Health Council to provide a recommendation concerning booster vaccination of individuals who were vaccinated with the Johnson & Johnson vaccine. The reasons for the instruction are signals that the protection provided by the vaccine may be waning.	
Norway	**Yes**, booster vaccination was initiated on 10 September of individuals who are receiving immunosuppressant medicine and individuals with a severely weakened immune response. The booster vaccination offer for older people aged more than 65 years was initiated at the October-November turn of month. Elderly people aged more than 65 years and individuals with a weakened immune response are recommended vaccination. Individuals who have been vaccinated with Johnson & Johnson are also offered booster vaccination. Only mRNA vaccines are used. The government plans to invite everyone aged 18-64 years for booster vaccination in 2022, once a minimum of six months has passed after receiving the second vaccine dose.	Booster vaccination is recommended no earlier than six months after concluding the primary vaccination course in the general population. For individuals with a weakened immune response, the booster vaccination time is adapted to their other treatments and the decision is made in consultation with the treating physician. Even so, the interval between the second and the third dose will be a minimum of four weeks.
Poland	**Yes**, booster vaccination of all individuals aged more than 18 years has been offered since 2 November. Only mRNA vaccines are used.	Booster vaccination is recommended no earlier than six months after concluding the primary vaccination course. Even so, individuals with a weakened immune response receive booster vaccination already 28 days after concluding the primary vaccination course.
Portugal	**Yes**, elderly people aged more than 65 years and individuals with a weakened immune response receive booster vaccination concurrently with the influenza vaccine in a sequence prioritised by age. 5.4% of the population has received booster vaccination.	Booster vaccination is recommended no earlier than six months after concluding the primary vaccination course.
Romania	**Yes**, booster vaccination was initiated on 28 September. Anyone who has completed the primary vaccination course may also receive booster vaccination. However, booster vaccination is recommended in particular to individuals above 60 years of age, individuals with a reduced immune response, nursing home residents and frontline workers in the	Booster vaccination is recommended no earlier than six months after concluding the primary vaccination course.

	social and healthcare sectors. Booster vaccination should only be done using mRNA vaccines. Individuals who have received vaccination with Moderna only receive half a Moderna dose at their booster vaccination.	
Switzerland	**Yes**, booster vaccination has been initiated of individuals with a weakened immune response, nursing home residents, elderly people aged more than 75 years and elderly people above 65 years with underlying conditions. Citizens above 65 years with underlying conditions receive booster vaccination only in special cases.	Booster vaccination is recommended no earlier than six months after concluding the primary vaccination course.
Slovak Republic	**Yes**, booster vaccination was initiated of anyone who has concluded their primary vaccination course. The initial focus is on individuals with a weakened immune response, individuals over 55 years of age and nursing home residents, individuals over 18 years with a high risk of serious COVID-19 affection and frontline workers. Following primary vaccination with AstraZeneca, Johnson & Johnson, Sputnik and Pfizer/BioNTech, booster vaccination is by a full dose of Pfizer/BioNTech. In contrast, booster vaccination after primary vaccination with Moderna is half the normal dose of Moderna.	Booster vaccination is recommended no earlier than six months after concluding the primary vaccination course. Even so, individuals with a weakened immune response receive booster vaccination already 28 days after concluding the primary vaccination course.
Slovenia	**Yes**, booster vaccination is available to anyone aged more than 18 years. Booster vaccination is recommended for patients with insufficient immunity after primary vaccination, individuals with waning immunity, individuals above 50 years, chronically ill or vulnerable patients regardless of age and their household members. Booster vaccination is also available to nursing home residents, individuals vaccinated with vector vaccines and individuals who are specially exposed to infection because of their occupational function. Booster vaccination should be done using mRNA vaccines.	Booster vaccination is recommended no earlier than six months after concluding the primary vaccination course. Individuals who were vaccinated with vector vaccines are recommended booster vaccination a minimum of two months after their primary vaccination. In case of immune deficiency, booster vaccination may be given already four weeks after primary vaccination.
Spain	**Yes**, booster vaccination was initiated of individuals aged more than 70 years, nursing home residents and individuals with a weakened immune response. Additionally, a proposal was presented by the Spanish government to vaccinate healthcare workers and individuals above 60 years of age. The final decision will be made in the Inter-territorial	Booster vaccination is recommended no earlier than six months after concluding the primary vaccination course. Individuals with a weakened immune response may, in special cases, receive booster vaccination already 28 days or six

	Council consisting of the national government and the autonomies.	months after concluding the primary vaccination course.
Great Britain	**Yes**, vaccination has been initiated of people aged more than 40 years, nursing home workers, frontline healthcare staff and individuals with a weakened immune response. Individuals are invited for booster vaccination six months after their primary vaccination course. Even so, individuals in very vulnerable groups may receive booster vaccination less than six months after their primary vaccination course if this is estimated to be expedient.	Booster vaccination is recommended six months after concluding the primary vaccination course at the earliest. However, the possibility exists to provide booster vaccination after a shorter interval to individuals in exposed population groups.
Sweden	**Yes**, booster vaccination was initiated on 1 September. Booster vaccination is recommended of individuals aged more than 65 years, nursing home residents, individuals relying on municipal home services or home-based nursing care and individuals with a weakened immune response and nursing sector workers. Booster vaccination is by the same vaccine as used during the primary vaccination course (barring people receiving primary vaccination with AstraZeneca; in these cases booster vaccination is by an mRNA vaccine). Only half the normal dose of Moderna's vaccine is used for booster vaccination, unless the vaccinee has a weakened immune response in which case the full dose is administered. Sweden has temporarily paused the use of Moderna for individuals born in 1991 or later.	Booster vaccination is recommended no earlier than six months after concluding the primary vaccination course. Individuals aged more than 65 year, nursing home residents and people receiving home care may be offered booster vaccination already five months after concluding their primary vaccination course. In individuals with a weakened immune response booster, vaccination may be given already two months after the primary vaccination course.
The Czech Republic	**Yes**, the booster vaccination offer was initiated on 20 September. Citizens may receive booster vaccination at hospital-based vaccination centres or with their general practitioner. Anyone who has completed the primary vaccination course may also receive booster vaccination. However, booster vaccination is recommended in particular to individuals above 60 years of age, individuals with a reduced immune response, nursing home residents and frontline workers in the social and healthcare sectors. Only mRNA vaccines are used.	Booster vaccination is provided a minimum of six months after concluding the primary vaccination course. Even so, individuals with a severely weakened immune response may receive booster vaccination already 28 days after concluding the primary vaccination course.
Germany	**Yes**, booster vaccination was initiated on 1 September. Booster vaccination is recommended of individuals aged more than 70 years, nursing home residents, individuals	Booster vaccination is recommended no earlier than six months after concluding the primary vaccination course.

	with a disability and individuals with a weakened immune response. Additionally, individuals who received AstraZeneca or Johnson & Johnson in their primary vaccination course may be booster vaccinated with mRNA vaccine. In principle, booster vaccination is available to anyone who has completed their primary vaccination course.	
Hungary	**Yes,** booster vaccination has been initiated. Anyone above 18 years of age is recommended booster vaccination. BioNTech-Pfizer, Moderna, Sinopharm, AstraZeneca, Sputnik V and Johnson & Johnson are used for booster vaccination. As per mid-November, 1,629,000 individuals, corresponding to approx. 17% of the population, have received booster vaccination.	Booster vaccination is recommended no earlier than four months after concluding the primary vaccination course.
The US	**Yes,** booster vaccination has been initiated. Booster vaccination is recommended for individuals with a weakened immune response, elderly people aged more than 65 years, individuals aged more than 50 years with underlying conditions, individuals who received the Johnson & Johnson vaccine and nursing home residents and similar. Vaccination is done after the primary vaccination course has been completed using BioNTech-Pfizer or Moderna.	Booster vaccination is recommended no earlier than six months after concluding the primary vaccination course with BioNTech-Pfizer or Moderna. For individuals vaccinated with Johnson & Johnson, booster vaccination is recommended a minimum of two months after the first vaccination and for individuals with a weakened immune response, booster vaccination is recommended a minimum of 28 days after concluding the primary vaccination course.
Austria	**Yes,** booster vaccination has been initiated. Anyone above 18 years of age is recommended booster vaccination. Individuals below 30 years are recommended booster vaccination with a full dose of BioNTech-Pfizer exclusively, whereas persons aged more than 30 years may also receive booster vaccination with half the normal dose of Moderna.	Booster vaccination is recommended no earlier than six months after concluding the primary vaccination course. All citizens in the capital of Vienna may receive booster vaccination already four months after concluding their primary vaccination course. Even so, individuals with a weakened immune response receive booster vaccination already 28 days after concluding the primary vaccination course.

Source: Notifications from Danish embassies