SUNDHEDSSTYRELSEN

Date 06 December 2021 BES

Case no. 05-0600-1260

COVID-19 vaccination of children aged 5-11 years

In Denmark, the primary COVID-19 vaccination programme was initiated on 27 December 2020. When the primary vaccination programme entered into force, COVID-19 vaccination was offered to anyone aged 16 years and older. The 16-year age limit for COVID-19 vaccination was motivated by the fact that, at the time, documentation for the effect and safety of the vaccines among children below 16 years of age was lacking.

On 28 May 2021, the EU extended the authorisation for Comirnaty® to include children aged 12-15 years[1] and, in line herewith, on 23 April 2021 the EU approved an extension of the authorisation of Spikevax® for children and adolescents aged 12-17 years[2]. Subsequently, on 17 June 2021 the Danish Health Authority decided to recommend vaccination of children aged 12-15 years as part of the Danish COVID-19 vaccination programme. The basis for the decision is described in a memo published on 17 June 2021[3].

While Comirnaty® and Spikevax® have started being used among adolescents and adults, studies have been conducted to evaluate their effect and safety in children below 12 years of age. On 18 October 2021, Pfizer/BioNTech submitted an application for the EMA Comirnaty® to 5-11-year-old children[4]. On 25 November 2021, the European Medicines Agency (EMA) recommended that Comirnaty® be approved for use in 5-11-year-olds[5]. As per 26 November 2021, the EU Commission authorised the use of Comirnaty® in 5-11-year-olds based on the EMA assessment.

On 25 October 2021, Moderna issued a press release announcing the preliminary results of their study on Spikevax® in children aged 6-11 years[6]. In a press release issued on 31 October, Moderna informed that they are postponing their FDA application pending the conclusion of an FDA study

[1] https://www.ema.europa.eu/en/news/first-covid-19-vaccine-approved-children-aged-12-15-eu

[2] https://www.ema.europa.eu/en/news/covid-19-vaccine-spikevax-approved-children-aged-12-17-eu

[3] https://www.sst.dk/da/nyheder/2021/sundhedsstyrelsen-anbefaler-vaccination-af-12-15-aarige

[4] EMA press release, 18 Oct 2021: https://www.ema.europa.eu/en/news/ema-starts-evaluating-use-covid-19-vaccine-comirnaty-children-aged-5-11

[5] EMA press release. Comirnaty®, authorisation for use in 5-11-year-olds recommended. 25 November 2021. https://www.ema.europa.eu/en/news/comirnaty-covid-19-vaccine-ema-recommends-approval-children-aged-5-11

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

on the use of Spikevax® in 12-15-year-olds[7]. In parallel herewith, on 6 October the Danish Health Authority decided that children and adolescents below 18 years of age will receive the Comirnaty® vaccine until a PRAC assessment becomes available[8] regarding suspicion of increased risk of inflammation of the heart muscle (myocarditis) in children and adolescents below 18 years of age following vaccination with Spikevax®. On 10 November 2021, the EMA informed that they are initiating their evaluation of the use of Spikevax® in children aged 6-11 years.

In light of the current Danish epidemic and based on the EU Commission's authorisation of Comirnaty® for use in children aged 5-11 years, we present below the Danish Health Authority's assessment of the basis for a possible extension of the target group of Comirnaty® primary vaccination to include children down to the age of five years of age.

This memo should be interpreted in conjunction with the Danish Health Authority's recommendation to the Danish Ministry of Health of 21 December 2020 on COVID-19 vaccination and the Authority's assessment of 17 June 2021 concerning COVID-19 vaccination of children aged 12-15 years, etc.

Background

Legal basis

The recommendation to the Danish Ministry of Health published 21 December 2020 presents the Danish Health Authority's assessment of target groups and the medical framework of COVID-19 vaccination efforts when these efforts were initiated.

The Danish Minister of Health has established provisions on COVID-19 vaccination in Executive Order on Free COVID-19 Vaccination, cf. executive order no. 1719 of 24 August 2021[9]. Detailed procedures related to vaccination are described in the Danish Health Authority's guideline on COVID-19 vaccination[10].

The Danish Health Authority has issued guidelines that establish the framework for roll-out of the general vaccination programme using the vaccines[11] recommended by the Danish Health Authority,

[7] Moderna press release 31 Oct. 2021:https://investors.modernatx.com/news-relea-ses/news-release-details/moderna-provides-update-timing-us-emergency-use-authorization

[8] News item published by the Danish Health Authority, 6 October 2021: The Danish Health Authority continues to vaccinate children and adolescents below 18 years of age with the COVID-19 vaccine from Pfizer/BioNTech - Danish Health Authority

[9] Retsinformation. The Danish Ministry of Health. Act no. 1719 of 24/08/2021. https://www.retsinformation.dk/eli/lta/2021/1719

[10] Retsinformation. The Danish Ministry of Health. Guideline no. 9650 of 31/08/2021. https://www.retsinformation.dk/eli/retsinfo/2021/9650

[11] Danish Health Authority, 2021. Organisation of the COVID-19 vaccination efforts – Roll-out. [Organisering af vaccinationsindsatsen mod COVID-19 – udrulning]https://www.sst.dk/da/Udgivelser/2021/Organisering-af-vaccinationsindsatsen-mod-COVID-19-udrulning

including a description of the overall objectives of the vaccination efforts, principles for prioritisation of target groups and specific considerations regarding vaccination. The executive order, instructions and guidelines have been updated continuously.

For further information about the legal basis for vaccination in Denmark, including the Danish Health Authority's role, etc., please see memo on *Vaccination of children aged 12-15 years*[12].

Current framework for vaccination of children below 12 years of age

The Danish Health Authority recommends COVID-19 vaccination of everyone aged 12 years and older. Generally, vaccination is not recommended for children below 12 years of age as this age group does not form part of the approval population for the mRNA vaccines, i.e. Comirnaty® and Spikevax®.

In accordance with current guidelines, vaccination may be offered for children below 12 years of age in very special cases and following specific assessment by a medical specialist, as described in the Danish Health Authority's *Guideline on the Handling of COVID-19 Vaccination*[13]. In such cases, vaccination will be "off label", i.e. beyond the scope of the regulatory approval as described in the summary of product characteristics of the vaccine. Information is currently lacking on the recommended dose for children below 12 years of age and the remaining details describing how these children may be vaccinated against COVID-19.

However, the clinical use of the offer of off-label vaccination of children below 12 years of age has been very limited, as information about the recommended dose for children below 12 years of age has been lacking as have detailed provisions on how these children may receive COVID-19 vaccination.

Vaccination effort update

From its very onset, the roll-out of the general vaccination programme in Denmark has been characterised by a high effectiveness, sustained good progress and a high programme coverage.

The current status of the roll-out of the primary vaccination programme as per 21 November 2021 is that approx. 87% of the Danish population aged 12 years and older has received primary vaccination. Thus, the general vaccination programme enjoys a very high coverage, particularly among elderly people and vulnerable groups. Even so, some population groups are characterised by a somewhat lower coverage. The clear recommendation of the Danish Health Authority is that everyone aged 12 years and above receive COVID-19 vaccination and a wide range of initiatives is underway to increase the primary vaccination coverage.[14]

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[12] On vaccination of children aged 12-15 years [Vedrørende vaccination af børn på 12-15 år] - Danish Health Authority

[13] Guidelines on the Handling of COVID-19 Vaccination [Retningslinjer for håndtering af vaccination mod COVID-19] - Danish Health Authority

[14] Organisation of the COVID-19 vaccination efforts - Roll-out [Organisering af vaccinationsindsatsen mod COVID-19 - udrulning]

Specifics about the current status on paediatric vaccination

As per 21 November 2021, a total of 352,031 children and adolescents aged 12-18 years have completed their course of the primary vaccination programme, corresponding to approx. 74% of the entire age group. Thus, the overall coverage is high but lower than that of the remaining parts of the population. The lowest coverage was observed among the youngest children, as shown in the below table.

Table 1: Coverage of primary vaccination in 12-18-year-olds (as per 21 November)

Age	Booked	Invited	Has received the first vaccination shot	Has completed primary vaccination	Percentage of the age group that has completed primary vaccination
12 years*	1,944	19,213	7,395	30,130	45%
13 years	965	17,708	4,552	45,730	66%
14 years	891	14,438	3,937	48,807	72%
15 years	640	12,391	3,380	52,587	76%
16 years	385	8,761	1,932	57,311	84%
17 years	290	7,772	1,597	58,779	86%
18 years	290	7,941	1,699	58,687	85%
Total	**5,405**	**88,224**	**24,492**	**352,031**	**74%**

**Children are invited continuously as they turn 12 years old. Thus, the entire birth cohort has not been invited yet, and the coverage is therefore underestimated.*

On 21 November 2021, a total of 45 children below 12 years of age had received a minimum of one vaccine and a total of 14 children below 12 years had received primary vaccination, i.e. had received off-label vaccination as described above.

Update on booster vaccination efforts

On 28 September, the Danish Health Authority published an overall COVID-19 booster vaccination plan, in *Memo on COVID-19 booster vaccination [Notat vedr. revaccination mod COVID-19]*[15]. Already at that point in time, the Danish Health Authority had initiated booster vaccination of various population groups as part of the initial phase of the booster vaccination plan, including nursing home residents, severely immunosuppressed people and individuals aged 85 years or more. On 15 October, the Danish Health Authority initiated the second phase of the booster vaccination plan in which booster vaccination was offered to individuals aged 65-84 years, people at a particularly increased risk of running a serious COVID-19 course and healthcare and elderly service staff. Finally,

[15] Danish Health Authority, 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

on 25 November 2021, the Danish Health Authority recommended that everyone aged 18 years or more was offered booster vaccination six months after receiving their second dose.[16]

Booster vaccination coverage among the population groups who have access to vaccination varies considerably. Among nursing home residents, the coverage is high, as 96% of nursing home residents had received booster vaccination as per 21 November. Among immunosuppressed people, 84% have received booster vaccination, whereas the corresponding figure for people aged 85 years or more is 80%. Among everyone invited for vaccination as part of phase 2, 31% have received booster vaccination and an additional 23% have scheduled booster vaccination.

Framework and principles for paediatric vaccination programmes

General considerations about the introduction of new vaccines in national vaccination programmes

The Danish Health Authority continuously assesses if any new or already available vaccines should be introduced into the Danish childhood vaccination programme. Assessments frequently take as their starting point changed disease patterns or approval of new vaccines, and overall the Danish Health Authority does not recommend vaccinating against a disease simply because a vaccine is available in the market or solely for social or political reasons.

Thus, the decision basis for opting in or out of programme vaccines are reviews in which the Danish Health Authority assesses a range of aspects including the efficacy and any harmful effects of vaccines, the attitude in the target group towards introducing the vaccine, ethical considerations and healthcare financial consequences. The assessments are typically health technology assessments (HTA), which often take more than a year to prepare.

Based on an THA or another type of decision basis, the Danish Health Authority assesses if a vaccine should be introduced into the childhood vaccination programme. In recent years, when undertaking this type of assessments, the Authority has followed these six basic principles:

- **The severity and prevalence of the condition.** For a vaccination to be introduced, the condition needs to have a certain severity and prevalence in order to justify the risk of side effects in otherwise healthy children.
- **Broad experience with use of the vaccine in children.** The vaccine must have been tested in large groups of children to ensure its safety and efficacy for the individuals vaccinated.
- **Beneficial effect compared with possible side effects** Sufficient documentation must be in place to ensure that the benefits of the disease-preventive and health-promoting effect of the vaccine outweigh the risk of side effects.

[16]Danish Health Authority, COVID-19 booster vaccination for individuals aged 18 years and above

- **Interactions and adaptation to the vaccination programme.** The new vaccine being introduced into the programme may not affect other vaccines negatively (produce infections) or have undesired ecological effects (that the micro-organism targeted by the vaccine is replaced by others).
- **Parental accept.** Any new vaccine as well as the overall childhood vaccination programme must be acceptable to the parents.
- **Financial considerations.** The introduction of the vaccine must be financially feasible, meaning that its cost must seem reasonable in light of its potential benefits.

In the Danish childhood vaccination programme, the severity criterium is generally given considerable weight, i.e., vaccines are offered to prevent conditions that cause considerable morbidity and possibly mortality, and the three initial criteria - severity, broad experience with the use of the vaccine and beneficial impact on harmful effects - are pivotal in the assessment. The severity and prevalence of the disease targeted by vaccination are particularly relevant in relation to the target group that is to be offered vaccination. However, the effect of vaccination of the target group in question on the prevalence of the condition in the remaining population, including in any particularly vulnerable groups, will also be considered, provided a substantial potential to strengthen public health exists.

Many of the vaccines in the childhood vaccination programme protect against conditions that were initially rare, but which are associated with a high risk of serious disease and death if a child becomes infected (e.g., haemophilus influenzae serotype b). Other vaccines protect against infectious diseases that used to occur frequently in children and for which the relative risk of serious disease and death is lower, but where the prevalence of the infection entailed a relatively large number of serious annual cases (e.g. measles). Finally, it has been important when introducing new vaccines that vaccination of healthy children may lead to increased immunity in the population and therefore infer indirect protection (e.g. against rubella and mumps) for vulnerable children and adults who cannot be vaccinated or who do not enjoy the full effect of vaccination. Other examples of vaccines in the Danish childhood vaccination programme that are given to children to achieve indirect protection of other vulnerable individuals against serious disease are described in the Danish Health Authority's M*emo on vaccination of children aged 12-15 years.*

Special considerations regarding recommendations during a pandemic

In the current situation, in the midst of a pandemic where the speed by which a vaccination programme is rolled out is more decisive than is normally the case, it is not possible to complete a full health technology assessment.

In the assessment of COVID-19 vaccination for children aged 12-15 years and also children aged 5-11 years, the traditional principles are not applicable to the same extent due to the current extraordinary pandemic context where other considerations are also important. Therefore, in the assessment of COVID-19 vaccination offers and recommendations during the pandemic, the Danish Health Authority has established the following prioritised objectives for COVID-19 vaccination. These objectives were established before the implementation of the general vaccination programme:

1. Minimise death and serious disease due to COVID-19
2. Prevent transmission and control the epidemic
3. Ensure functions of vital importance to society

The Danish Health Authority's assessment of the expansion of the COVID-19 vaccination programme to also comprise children aged 5-11 years is based on these three prioritised objectives with a special focus on the objective of preventing transmission of the infection and controlling the epidemic, which, in turn, will minimise serious disease and death due to COVID-19 in the population. However, to the extent that this makes sense, the assessment will also build on the principles from the childhood vaccination programme described above. The trade-off between the efficacy of a vaccine and the risk of side effects for the individual vaccinee therefore remains decisive when determining if a vaccine should be authorised for use in a given target group. The Danish Health Authority finds that the threshold for documentation of the trade-off between potential benefits and harms should be particularly high when assessing prophylactic treatments for healthy children.

Even so, the assessment that precedes the introduction of a vaccination offer during a pandemic must also consider more broadly the possible benefits and risks for the entire population and for society as a whole; not just for the individual vaccinee. Whereas vaccination will always entail a risk for the individual being vaccinated in the form of side effects, vaccination efforts should thus provide an overall benefit for the population in general. Therefore, any extension of the vaccination programme should be considered in conjunction with other measures that may become necessary to control the epidemic.

Thus, the background for the Danish Health Authority's recommendation on COVID-19 vaccination of 12-15-year-old children was closely linked to the potential for increasing immunity in the population and limiting the general transmission of infection, which, in turn, will contribute to protecting unvaccinated individuals and individuals who do not enjoy the full benefits of vaccination against serious disease due to COVID-19.[17]

This memo presents data, documentation and experiences; in the final part of the memo, they form part of the basis for the assessment of the Danish Health Authority's medical recommendation on vaccination of children aged 5-11 years.

[17] Danish Health Authority, 2021. On vaccination of children aged 5-11 years [Vedr. vaccination af børn 5-11 år]. https://www.sst.dk/da/Udgivelser/2021/Vedroerende-vaccination-af-boern-paa-12-15-aar

Regulatory documentation

On 29 October 2021, the FDA authorised Comirnaty® for use in children aged 5-11 years[18]. The following description of the regulatory documentation is based on the EMA's summary of product characteristics[19], documentation from the FDA's approval procedure[20] and a peer-reviewed article from Pfizer/BioNTech comprising a description of the trial findings[21]. EMAs European Public Assessment Report has not yet become available. The assessment of efficacy and safety is based on results from an ongoing phase 1/2/3 study (C4591007) among children aged 5-11 years. The trial was designed in dialogue with the American and European pharmaceutical authorities, including how many children would be comprised by the trial and that the primary objective of the study was to assess the effect of vaccination on immune response (immunogenicity) and side effects. The trial forms part of the Paediatric Investigation Plan, which was approved by the Paediatric Committee of the EMA[22]. The children included in the trial had no risk factors for serious COVID-19 disease, no increased risk of SARS-CoV-2 exposure and no serological/virological signs of previous SARS-CoV-2 infection. The study was designed as a non-inferiority study in which immune response following vaccination was compared for 16-26-year-olds and 5-11-year-olds. The study assumed that a comparable immune response following vaccination will produce a comparable clinical effect. A total of 3,109 children receiving Comirnaty® and 1,528 children placebo were included.

On 25 November 2021, the EMA recommended that Comirnaty® be approved for vaccination of children aged 5-11 years.

Efficacy

Trial participants were randomised 2:1 for either Comirnaty® or placebo. The efficacy assessment comprised 1,518 children aged 5-11 years who received two doses of Comirnaty® 10 micrograms and a total of 750 children receiving placebo. The dose of the 5-11-year-olds (10 micrograms) was thus one third of the dose used in everyone aged 12 years and above (30 micrograms).

The efficacy of vaccination was assessed by so-called immuobridging, i.e. the efficacy of the vaccine is estimated via a surrogate marker, in this case antibodies. Trials comprising a large number of adults have compared the number of COVID-19 cases among vaccinated and unvaccinated participants. Concurrently, these trials have measured the antibody level among a subgroup of young and adult participants who have been vaccinated. A subgroup of the vaccinated children also had their

[18] FDA. Emergency use authorisation of Comirnaty® in 5-11-year-olds. 29 October 2021. https://www.fda.gov/news-events/press-announcements/fda-authorizes-pfizer-biontech-covid-19-vaccine-emergency-use-children-5-through-11-years-age

[19]EMA, Summary of Product Characteristics Comirnaty® 5-11-year-olds. Accessed 25 November 2021.https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf

[20] FDA Comirnaty® 5-11 years, briefing document. https://www.fda.gov/media/153447/download

[21] Walther EB et al. Evaluation of the BNT162b2 COVID-19 vaccine in children 5 to 11 years of age. NEJM 9. November 2021. https://www.nejm.org/doi/full/10.1056/NEJMoa2116298?query=TOC

[22] https://www.ema.europa.eu/en/documents/pip-decision/p/0179/2021-ema-decision-23-april-2021-acceptance-modification-agreed-paediatric-investigation-plan-highly_en.pdf

antibody level measured. If children have antibody levels corresponding to those recorded among young and adult participants, this underpins the supposition that the vaccine efficacy observed among young people and adults may be bridged to children. This method is known as immuno-bridging. In the study of the 5-11-year-old children, investigators also compared the number of COVID-19 cases among vaccinated and unvaccinated participants, but the number of children in the two groups who were infected by COVID-19 was limited.

The immune response (measured by antibodies) was compared with the immune response in a group of 16-25-year-old individuals who had been vaccinated with Comirnaty® as part of the original Phase 3 authorisation trial (C4591991).

Immunogenicity was tested among trail participants who presented no signs of SARS-CoV-2 for 1-2 months after receiving their second dose. Immunogenicity was assessed based on the average increase in neutralising antibodies, also known as the geometric mean titre (GMT). The result is presented in Table 2:

Table 2: Neutralising RGMT and GMT ratio one month after the second dose of Comirnaty®

GMT (95% confidence interval) 5-11-year-olds N = 264	**GMT (95% confidence interval) 16-25-year-olds N = 253**	**GMT ratio (95% confidence interval) (5-11-year-olds/16-25-year-olds)**
1197.6 (1106.1-1296.6)	1146.5 (1045.5-1257.2)	1.04 (0.93-1.18)

The ratio (geometric mean ratio, GMR) between the average increase in antibodies among the 5-11-year-olds and the 16-25-year-olds was 1.04 (95% confidence interval 0.93-1.18). It had been established in advance that if the lower limit of the confidence interval exceeded 0.67 and if the point estimate for the GMT ratio was ≥ 1, the results for the 2 groups were comparable. Both conditions were met and the results of the study therefore showed non-inferiority.

The effect of vaccination was also assessed based on sero-response, i.e. how many people recorded a ≥ 4 increase in antibodies at one month after their vaccination compared with their level before receiving vaccination. The sero-response rates are presented in Table 3:

Table 3: Sero-response rates one month after the second dose of Comirnaty®

Sero-response (95% confidence interval) 5-11-year-olds N = 264	**Sero-response (95% confidence interval) 16-25-year-olds N = 253**	**% difference in sero-response rate (95% confidence interval) (5-11-year-olds – 16-25-year-olds)**
99.2 (97.3-99.9)	99.2 (97.2-99.9)	0 (-2.0-2.2)

It had been established in advance that if the lower limit of the confidence interval was higher than -10% in case of a difference in sero-response, then the non-inferiority criterion was met. A 0% (95% CI -2.0-2.2%) difference was found for the sero-response of the 5-11-year-olds compared with the 16-25-year-olds. These results also complied with this non-inferiority criterion.

Overall, it is therefore assumed that the effect of vaccination with Comirnaty® is comparable for 5-11-year-olds and 16-25-year-olds.

Descriptive immunogenicity analyses among a total of 34 vaccinated children and four children receiving placebo showed that vaccination with 10 micrograms of Comirnaty® produced levels of neutralising antibodies against both the reference strain (Wuhan) and the Delta variant of SARS-CoV-2.

This clinical effect was characterised descriptively in the study. At data cut-off, a total of 19 confirmed COVID-19 cases were registered that had been diagnosed a minimum of seven days after receiving their second dose. Three cases of COVID-19 were observed among 1,305 children who had received Comirnaty®, and 16 COVID-19 cases were recorded among 663 children who had received placebo. This corresponds to an observed effect of vaccination with Comirnaty® against COVID-19 infection of 90.7% (95% CI 74%-98.3%). None of the 19 infected individuals had previously had SARS-CoV-2 infection and none of the 19 cases experienced a serious COVID-19 disease course. Most reports occurred during July-August 2021. It remains unknown which SARS-CoV-2 variant caused the infections as the samples were not sequenced.

Safety

All of the 3,109 children aged 5-11 years who received Comirnaty® and 1,528 children who received placebo were included in the safety assessment. The size of the trial ensures with great certainty the identification of side effects that are very common (occurs in ≥1/10 individuals), common (occurs in ≥1/100-<1/10 individuals), not common (occurs in ≥1/1,000-<1/100 individuals) and, in part, rare (occurs in ≥1/10,000-<1/1,000 individuals). Very rare side effects (occurring in <1/10,000 individuals) cannot be expected to have been identified in the authorisation study. Possible side effects were reported via an e-diary. Among the 1,511 children who submitted their e-diary data after vaccination with Comirnaty®, approx. 75% experienced local side effects at the injection site following either their first or second dose, whereas approx. 50% experienced systemic side effects following their second dose.

A total of three children receiving Comirnaty® experienced acutely arising side effects following injection (pain at the injection site) following their first dose. After the second dose, a total of four children experienced acutely arising side effects (1 nausea, 1 pain at the injection site, 1 redness at the injection site, 1 rash). At the time of data cut-off on 6 September 2021, a total of 1,444 children vaccinated with Comirnaty® and 714 children receiving a placebo had been followed for a minimum of two months after their second dose.

Reactogenicity

Reactogenicity denominates expected mild to moderate side effects occurring after an inflammatory reaction to vaccination. Among 5-11-year-olds, reactogenicity occurred more frequently after the second than after the first dose. Overall, reactogenicity among the 5-11-year-olds was comparable to reactogenicity among 16-25-year-olds. No difference was observed with respect to the occurrence of side effects when comparing 5-11-year-olds with and without signs of previous SARS-CoV-2 infection. The most frequently reported local side effects were pain at the injection site (> 80%), reddening (> 20%) and swelling (< 20%). The most frequently recorded systemic side effects were fatigue (> 50%), headache (> 30%), myalgia (> 10%) and shivers (> 10%). Generally, the occurrence of fever was low (2.5% after the first dose, 6.5% after the second dose). Most local and systemic side effects were mild to moderate. They occurred at a median two days after vaccination and typically receded 1-2 days after presenting. Among children receiving Comirnaty®, a total of four serious local side effects were seen (three cases of severe reddening and one case of severe swelling). Furthermore, one severe systemic side effect was seen (severe myalgia).

A total of 12 cases of chest pain were registered: Six cases among children receiving Comirnaty® and six cases among children receiving a placebo. All cases of chest pain receded spontaneously within 1-2 days after their onset. None of the cases required cardiological assessment or emergency room referral, and none of the 12 children required admission to hospital. In all 12 cases, it was assessed that the chest pain did not have a cardiac cause.

Possible serious side effects

The occurrence of possible serious side effects was 0.1% among children receiving Comirnaty® and also among children receiving placebo. Among children receiving Comirnaty®, side effects were reported for a total of four children (one arm fracture, one knee infection, one foreign body swallowed and one fracture of the epiphysis). None of the reported serious side effects were assessed to be associated with vaccination. No deaths occurred either among children receiving Comirnaty® or among children receiving placebo.

Comirnaty® is contraindicated if you have previously had serious allergies, including immediate anaphylactic reaction, against one of the ingredients used in the vaccine. After first use, rare immediate allergic reactions (anaphylaxis) have been reported among young people and adults aged 16 years and older. Furthermore, after first use, cases have been recorded of inflammation of the heart muscle (myocarditis) or inflammation of the sack-like tissue surrounding the heart (pericarditis) in younger adults. This is described in more detail in a subsequent section on safety on page 51.

Overall assessment

Based on the above, the EMA assessed that the benefits outweigh the drawbacks associated with giving Comirnaty® to 5-11-year-olds, and the indication was therefore extended to include this age group, too.

It is assessed that COVID-19 vaccination effectively prevents SARS-CoV-2 infection among children aged 5-11 years. Currently, longer-term safety follow-up has been conducted for only up to

two months following the second dose in a total of 1,444 children receiving Comirnaty® and 714 receiving placebo. Therefore, it remains uncertain if very rare and in part also rare side effects have been identified in the study. The evidence relating to rare or very rare side effects will not be generated until the data are available, i.e. after vaccination with Comirnaty® among 5-11-year-olds has been implemented at scale.

Paediatric formulation of Comirnaty®

As part of the approval of Comirnaty® for use in 5-11-year-olds, a paediatric formulation of the vaccine was approved that is slightly different from the formulation for adults. The paediatric formulation comprises a so-called TRIS buffer as opposed to the adult formulation which contains a PBS buffer. The paediatric formulation has a slightly longer shelf life in the refrigerator than the adult formulation (10 weeks versus 1 month)[23]. The Danish Health Authority has consulted with Danish allergy centres and with paediatric experts in allergology. The TRIS buffer is not a known allergen, and TRIS buffer is used in a wide range of medical products. On that basis, we do not expect that the TRIS buffer will cause allergy-related problems. We expect that recommendations and precautions relating to allergies, etc. will be the same for 5-11-year-olds as for individuals aged 12 years and older.

Differences in excipients have no impact on the safety or efficacy of the vaccines.
It has been assessed that vaccination of children aged 5-11 years may be done with precision and safely with 0.1 mL (10 microgram) of the adult formulation. If the paediatric formulation is not available for vaccination, the adult formulation may therefore be used. As the adult formulation of Comirnaty® was not approved for use in children below 12 years of age, using a third of the adult formulation for children will be off-label use.

Regulation

US Food and Drug Administration (FDA)

On 29 October 2021, the FDA issued a press release stating that the US Emergency Use Authorization (EUA) of Comirnaty® had been extended to also comprise children aged 5-11 years of age[24]. As is the case for the previously approved indication in the 12-15-year age group, the EUA will only remain in force while the conditions for an emergency use authorisation apply. EUAs are a tool that the FDA can deploy in case of public health emergencies, e.g. a pandemic. In such cases, the FDA can authorise use of non-approved pharmaceuticals, provided various conditions are met (e.g. no appropriate, approved available alternatives)[25]. EUAs may be revised of withdrawn if it is

[23]EMA summary of product characteristics Comirnaty®, accessed 25 November 2021.https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf

[24] FDA. Emergency use authorisation of Comirnaty® in 5-11-year-olds. 29 October 2021. https://www.fda.gov/news-events/press-announcements/fda-authorizes-pfizer-biontech-covid-19-vaccine-emergency-use-children-5-through-11-years-age

[25] FDA. Emergency Use Authorization. https://www.fda.gov/vaccines-blood-biologics/vaccines/emergency-useauthorization-vaccines-explained

assessed that the conditions described in the issue order (protection of public health or safety) are no longer present.

European Medicines Agency (EMA)

On 25 November, the EMA issued a press release stating that EMA recommends the approval of Comirnaty® for use in 5-11-year-old children[26].

In contrast to the US EUA, in the EU the authorisation is conditional; and a conditional authorisation differs from an emergency use authorisation. A conditional authorisation may be issued if an unmet medical need exists and for public health reasons in situations in which less exhaustive data than usual are available, provided the benefits associated with immediate availability outweigh the risk associated with a need for supplementary data[27]. All of the following points must be met for a conditional approval to be issued:

- The benefits of the medicinal product must outweigh its drawbacks
- It must be probable that the applicant can provide satisfactory data after the conditional approval has been issued
- The medicinal product must cover an unmet medicinal need
- The benefits associated with making the medicinal product available to patients immediately must outweigh the inherent risk associated with the unmet need at the time for supplementary data

A conditional marketing authorisation is always accompanied by specific obligations, e.g. conclusion of ongoing or new studies to generate additional data, which the applicant must comply with within established deadlines. In connection with the authorisation of medicinal products for children, pharmaceutical authorities like the EMA do not apply a special threshold for documentation of the trade-off between potential benefit and harm to preventive treatment of healthy children, as does Denmark, for instance, in lieu of the principles for paediatric vaccination. Pharmaceutical authorities focus exclusively on the trade-off between benefits and drawbacks at the individual level and must not take into account factors like the overall epidemic infectious pressure in parts of the population, the availability of other vaccines, alternative measures to limit transmission, etc.

EMA - regulatory requirements concerning COVID-19 vaccines for children

All the manufacturers who produce COVID-19 vaccines currently authorised by the EU Commission have a duty, imposed by the EMA, to conduct studies in children and adolescents: so-called Paediatric Investigation Plans (PIPs)[28]. The PIP requirements are generally linked to a need on the

[26]EMA press release. 25 November 2021. https://www.ema.europa.eu/en/news/comirnaty-covid-19-vaccine-ema-recommends-approval-children-aged-5-11

[27] EMA. Conditional marketing authorisation. https://www.ema.europa.eu/en/human-regulatory/marketingauthorisation/conditional-marketing-authorisation

[28] EMA. Paediatric Investigation Plans. https://www.ema.europa.eu/en/human-regulatory/researchdevelopment/paediatric-medicines/paediatric-investigation-plans

part of the pharmaceutical authorities to ensure that data are generated that may underpin the authorisation of medicinal products for use in children and adolescents. The Comirnaty® PIP describes that the EMA requires that a total of four paediatric studies are conducted[29]:

- Study 1: efficacy and safety in 12-17-year-olds
- Study 2: efficacy and safety in 5-17-year-olds
- Study 3: efficacy and safety in 0-4-year-olds
- Study 4: efficacy and safety in 0-17-year-olds

The Comirnaty® authorisation study for children aged 5-11 years was conducted in line with the EMA PIP for Comirnaty®. Thus, we may also expect that - as time passes - efficacy and safety data will be generated concerning Comirnaty® among children below five years of age; and a third dose has already been approved for children aged 12 years of more with reduced immune response. Similarly, paediatric data are also expected to become available about the other authorised COVID-19 vaccines[30]. On 10 November 2021, in a press release, EMA informed that the assessment of Spikevax® for 6-11-year-old children has been initiated[31].

Recommendations made by other countries and societies

This section describes recommendations for COVID-19 vaccination of 5-11-year-olds in selected countries, along with the recommendation published by the European Paediatric Society (EPA-UNEPSA). Further details about the national vaccination guidelines for 5-11-year-olds in selected countries are presented in Appendix 1.

In general, the majority of the countries studied, a total of 28 among 35, have not yet recommended or initiated vaccination of 5-11-year-olds or specific groups of 5-11-year-olds[32]. Specifically, only the US, Israel and Canada recommend vaccination of all 5-11-year-olds. As per 22 November, Israel initiated vaccination of 5-11-year-olds, and as per 25 November the US has vaccinated approx. 3.6 million children aged 5-11-years with a minimum of one dose, whereof 132,000 have completed their vaccination course. In Canada, vaccination of 5-11-year-olds has not yet been initiated, but when vaccination of the group starts, the children will receive two 10 microgram vaccination shots with the Pfizer-BioNTech at a three-week interval. Furthermore, before the recommendation from the EMA was published, Austria opened for vaccination of children in this age group specifically for the Vienna

[29] EMA. Paediatric Investigation Plans. EMA. Paediatric Investigation Plans. https://www.ema.europa.eu/en/human-regulatory/researchdevelopment/paediatric-medicines/paediatric-investigation-plans

[30] EMA. COVID-19 Vaccine Moderna® Paediatric Investigation Plan. https://www.ema.europa.eu/en/documents/pip-decision/p/0481/2020-ema-decision-30-november-2020- agreement-paediatric-investigation-plan-granting-deferral-mrna_en.pdf

[31] EMA. The assessment of Spikevax® for use in 6-11-year-olds has been initiated. 10 November 2021. https://www.ema.europa.eu/en/news/ema-starts-evaluating-use-covid-19-vaccine-spikevax-children-aged-6-11

[32]For more information about notifications made by Danish embassies to the Danish Ministry of the Exterior, please see Appendix 1.

area. Specifically, children may receive vaccination following a dialogue between the child, his or her parents and a healthcare professional, which at the time the recommendation was made was an off-label recommendation.

Additionally Slovakia, Sweden and Austria offer vaccination of 5-11-year-olds in special circumstances based on specific medical assessment. In all of the remaining countries, vaccination of 5-11-year-olds is not yet recommended, even though various countries expect to be able to initiate vaccination of the age group once a recommendation has been published by the European Medical Agency (EMA) (Appendix 1). Examples of such countries include the Czech Republic and Poland, both of which are awaiting the EMA recommendation before the health ministry of each country will present a final national recommendation and initiate vaccination of 5-11-year-olds. Even so, both countries have already pre-ordered COVID-19 vaccines for vaccination of the age group.

Concurrently, a large share of the countries studied, a total of 24 among 35, have not initiated a professional process about any national decision on vaccination of 5-11-year-olds, as the majority are awaiting EMA recommendations. Discussions, trials or approval processes are underway concerning vaccination of 5-11-year-olds in 11 of the countries studied (Australia, Canada, Estonia, Finland, Israel, Japan, Croatia, the Netherlands, Portugal and the UK).

Furthermore, the European Paediatric Society (EPA-UNEPSA) recommends vaccination of children below 12 years of age provided the vaccine used is safe and effective.[33] Among others, the recommendation is based on knowledge that internationally more cases and hospitalisations have been observed among children affected by the Delta variant, and that it is known from influenza vaccination that children play an important role in preventing transmission.

Update on the Danish epidemic

Since the beginning of July 2021, the Delta variant has been the overwhelmingly dominant virus variant in Denmark. The Delta variant is more infectious and also more virulent than previous variants. Infection with the Delta virus therefore entails a higher risk of running a serious COVID-19 disease course than infection with other variants.[34,35,36]
As expected, when autumn started and the Danish society was fully re-opened on 10 September, an increase in the number of individuals who test SARS-CoV-2 positive was seen as from mid-September 2021. As per 21 November, the national Danish incidence of individuals who test SARS-

[33] https://www.jpeds.com/article/S0022-3476(21)00886-6/fulltext

[34] Bager P, Wohlfahrt J, Rasmussen M, Albertsen M, Krause TG. Hospitalisation associated with SARS-CoV-2 Delta variant in Denmark. Lancet Infect Dis. 2021 Oct;21(10):1351.

[35] Sheikh A, McMenamin J, Taylor B et al. SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospitalisation, and vaccine effectiveness. Lancet. 2021 Jun 26;397(10293):2461-2462.

[36] Singanayagam A, Hakki S, Dunning J, et al. Community transmission and viral load kinetics of the SARS-CoV-2 delta (B.1.617.2) variant in vaccinated and unvaccinated individuals in the UK: a prospective, longitudinal, cohort study [published online ahead of print, 2021 Oct 29]. Lancet Infect Dis. 2021

CoV-2 positive is approx. 480 per 100,000 individuals. This corresponds to approx. 4,000 new cases every day in Denmark. Since early October, the infectious pressure has increased seven fold. This flare-up of the epidemic is due to various factors, including a seasonal effect associated with the shift from summer to autumn/winter, a changed contact pattern with more intergenerational contact in connection with the autumn holidays, a very infectious Delta variant, the fact that Danes spend more time indoors in autumn and a completely re-opened society. All of these factors have increased the transmission risk. Additionally, waning immunity seems to be in play among the individuals who completed their primary vaccination course early, as described in more detail in the Danish Health Authority's *Memo on COVID-19 booster vaccination.*[37]

Throughout most of the epidemic, the incidence among children has been lower than in the remaining age groups. Even so, as the epidemic has grown stronger, transmission among the 6-11-year-olds has increased since week 38; and particularly after the autumn holidays, a steep increase has been observed in the number of cases recorded among children in this age group. The 6-11-year age group corresponds to early primary and lower secondary school children in Denmark. This group is currently not comprised by the COVID-19 vaccination programme. The incidence among the 6-11-year-olds was 1,326 per 100,000 in week 45, which is the highest transmission level recorded in Denmark for any age group during the entire epidemic.

In comparison with the corresponding figures for the same time point last year, i.e. week 45 2020, the incidence was highest among 12-15-year-olds with 208 cases per 100,000, whereas the incidence among 6-11-year-olds was 131 cases per 100,000. After the introduction of a vaccination offer for the 12-15-year-olds, the infection pattern among children has changed, and the share of cases among children aged 6-11 years has increased and now comprises 21% of all cases recorded in week 45. In the 12-15-year age group, a considerable difference is seen in incidence depending on vaccination status. This also applies to the slightly older adolescents in the 16-19-year age group. Among 12-15-year-olds who have not accepted the vaccination offer, the incidence was 1,323 cases per 100,000 in week 45, whereas among vaccinated 12-15-year-olds the incidence was 184 cases per 100,000 in week 45. Overall, the incidence is highest among children aged 6-11 years and among the older children and adolescents who have not been vaccinated. Furthermore, it is assessed that the epidemic is currently driven by the younger unvaccinated part of the population.

Figure 1 presents the infectious pressure in the population below 50 years of age since 1 May 2021, by five-year age intervals. The figure shows that, until the conclusion of the majority of the primary vaccination programme in early August 2021, school-aged children (5-14-years) and children aged 0-4 years recorded the lowest incidences of diagnosed SARS-CoV-2. After the summer holiday ended in August 2021, a brief increase was observed, followed by a decline in the number of detected SARS-CoV-2 cases. Since week 36 and in particular as from week 42, the curve has increased steeply among children aged 5-14 years of age.

[37] On COVID-19 booster vaccination [Vedr. revaccination mod COVID-19]

In parallel with the increase in case numbers among children aged 6-11 years, an increase was registered in the number of possible COVID-19 outbreaks at primary and lower-secondary schools in [38]the ongoing monitoring scheme[39]. Outbreaks in schools were mainly detected in the initial intermediary levels of primary training in the autumn of 2021. A higher number was recorded in the Capital Region than in the remaining Danish regions. In the autumn of 2020, a large number of school-centred outbreaks were detected in the oldest grades of secondary training and at Danish high-schools. This pattern has changed as the transmission among children aged 6-11 years has increased, and the outbreaks are now typically recorded at the early and intermediary primary training levels.

Furthermore, the incidence among 35-45-year-olds increases following a short time interval, and the increase is also seen among those who have received vaccination in this age group. A large part of this transmission is assessed to reflect children transmitting the infection to their parents within households, even though the parents have previously been vaccinated. The increased infectious pressure is reflected in an increased risk of exposure among elderly citizens, whereby the number of breakthrough infections is increased, which is reflected in an increasing number of cases in the remaining age groups and, in consequence thereof, an increase in hospitalisations among vaccinated and unvaccinated people alike.

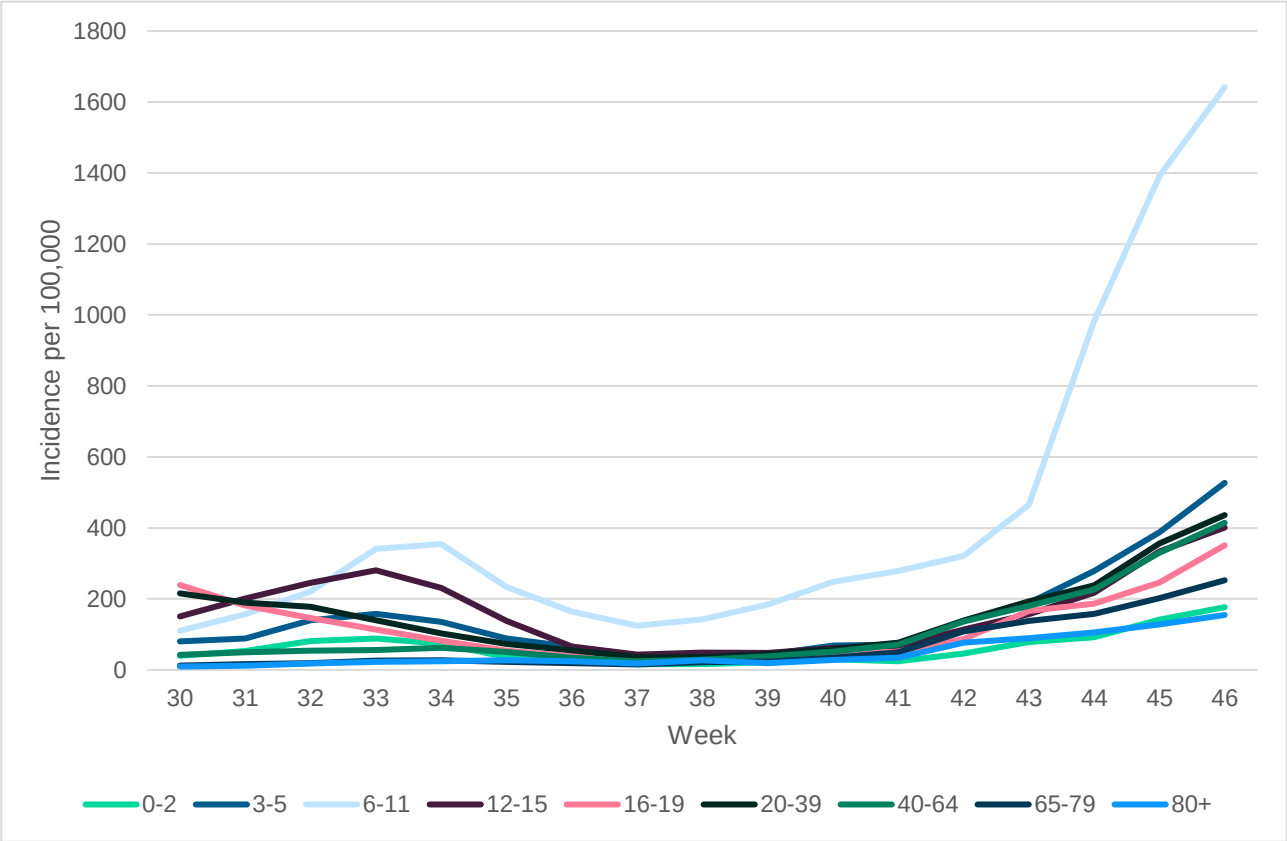
Overall, we are thus observing an epidemic that develops among children aged 6-11 years of age as the weekly incidence in the age group increases markedly, and a slightly delayed increase in the number of SARS-CoV-2 cases among vaccinated parents, which is underpinned by infection tracing data on transmission in households and outbreaks at schools. This pattern has changed since last year when a large number of infections and school outbreaks was seen among the group of unvaccinated children aged 12-15 years.

Even so, when interpreting the figures presented in Figure 1 and the steeply increasing SARS-CoV-2 incidence among children aged 5-11 years, it is important to take into account the heavily changed testing activity in the age group (see Table 5).

Figure 1: Incidence of diagnosed SARS-CoV-2 infections per 100,000 individuals in the population since Week 30.

[38]Definition of "possible COVID-19 outbreaks" (SSI): *"Three or more pupils with COVID-19 within 14 days who attend the same school and educational level. The outbreak concludes when no additional pupil has tested SARS-CoV-2 positive in the past 14 days".*https://covid19.ssi.dk/overvagningsdata/ugentlige-opgorelser-med-overvaagningsdata

[39]Weekly reporting of monitoring data: https://covid19.ssi.dk/overvagningsdata/ugentlige-opgorelser-med-overvaagningsdata



Immunity following infection with SARS-CoV-2 among children (dark figure, sero-prevalence and test activity)

Table 4 presents the total number of children diagnosed with SARS-CoV-2 in the past six months. The figure also shows how large a proportion of each birth cohort has tested SARS-CoV-2 positive in the course of the past six months and who may therefore be expected to maintain some immunity against SARS-CoV-2.

Table 4: Number of confirmed SARS-CoV-2 cases among children in the period from 11 May 2021 to 11 November 2021

Age at the time of sampling	Number of individuals in the birth cohort	Number of confirmed SARS-CoV-2 cases	Percentage confirmed cases of the full birth cohort (%)	Number of individuals tested in the birth cohort	Test rate (%)
0 years	48,015	549	1.1	9,463	19.7
1 year	61,354	797	1.3	20,203	32.9
2 years	61,748	880	1.4	27,674	44.8
3 years	62,029	1,187	1.9	34,822	56.1
4 years	62,214	1,326	2.1	37,874	60.9
5 years	62,814	1,750	2.8	40,910	65,1
6 years	59,791	2,367	4	42,825	71.6
7 years	59,126	2,921	4.9	45,231	76.5
8 years	58,598	3,157	5.4	48,386	82.6
9 years	60,960	3,332	5.5	51,255	84.1
10 years	62,187	4,280	6.9	55,983	90
11 years	66,762	4,357	6.5	60,487	90.6
12 years	66,492	2,852	4.3	60,517	91
13 years	68,888	2,514	3.6	60,801	88.3
14 years	68,018	2,420	3.6	61,499	90.4
15 years	68,937	2,377	3.4	61,512	89.2

“Dark figure” is the term used to denominate the number of people who have become infected by SARS-CoV-2 without testing positive. The dark figure is affected by the testing activity in the population. In the course of the epidemic, the testing activity has been affected by changing guidelines, a changing organisation of COVID-19 work-up and various initiatives as part of the re-opening of society following the lock-down. For a description of the changed guidelines concerning SARS-CoV-2 testing among children in the period leading up to June 2021, please see *Memo on vaccination of children aged 12-15 years*. Additionally, as from the beginning of October 2021, SARS-CoV-2 testing was initiated in Danish schools down to the age of nine years of age[40].

The increasing infectious pressure has triggered a considerably increased testing activity among children aged 5-11 years of age. Thus, more than 66,418 tests were made in week 44 and the number of tests made is expected to increase further in weeks to come as the climbing case number curve (Figure 1) will trigger an increase in the number of close contacts who will need testing several times a week. Although the testing activity has increased steeply, particularly among younger children, the positive percentage has also increased, and it is higher among children than in the remaining age groups. This supports the supposition that the increase in the number of children with SARS-CoV-2 is not due exclusively to increased testing in the age group. Fundamentally, a higher

[40] Update of the encouragement for COVID-19 testing in the child and school areas [Opdatering af opfordring til test af COVID-19 på børne- og undervisningsområdet] | Danish Ministry of Health (sum.dk)

positive percentage among children also reflects that the children are unvaccinated and more exposed to transmission from individuals close to them.

Table 5: Test activity and SARS-CoV-2 positive test results among 5-11-year-olds from July 2021 to November 2021.

	5-8 years			9-11 years			Other age groups		
Week	**Number of PCR tests**	**Number of individuals infected**	**Percentage of positive tests**	**Number of PCR tests**	**Number of individuals infected**	**Percentage of positive tests**	**Number of PCR tests**	**Number of individuals infected**	**Percentage of positive tests**
Week 30	9,832	227	2.3	11,972	236	2.0	424,725	6,376	1.5
Week 31	11,461	329	2.9	12,966	311	2.4	424,065	6,436	1.5
Week 32	12,638	454	3.6	12,792	451	3.5	425,547	6,879	1.6
Week 33	20,345	703	3.5	19,897	667	3.4	486,708	6,597	1.4
Week 34	23,848	688	2.9	24,552	698	2.9	550,254	6,086	1.1
Week 35	15,238	431	2.8	16,789	483	2.8	473,315	4,713	1.0
Week 36	10,829	282	2.6	11,163	364	3.3	415,056	3,417	0.8
Week 37	8,511	197	2.3	8,702	283	3.3	343,857	2,321	0.7
Week 38	8,511	194	2.3	8,965	354	3.9	315,017	2,703	0.9
Week 39	9,255	302	3.3	9,637	396	4.1	314,792	3,276	1.0
Week 40	11,509	392	3.4	12,003	556	4.6	339,284	4,475	1.3
Week 41	16,885	488	2.9	18,453	562	3.0	463,819	5,954	1.3
Week 42	15,924	573	3.6	15,472	673	4.3	627,408	11,282	1.8
Week 43	19,457	795	4.1	19,401	984	5.1	830,417	15,441	1.9
Week 44	35,667	1,580	4.4	30,998	2,119	6.8	1,017,307	19,036	1.9
Week 45	47,137	2,263	4.8	39,324	2,939	7.5	1,300,278	27,478	2.1
Week 46	53,360	2,736	5.1	43,393	3,409	7.9	1,387,169	34,360	2.5

The dark figure is expected to be higher in the beginning of the epidemic when children were tested only if symptomatic. The varying testing activity among children in the course of the epidemic is thus expected to affect the figure, which must therefore be interpreted with caution.

Table 4 shows that between 1.1% and 6.9% of children aged 0-15 years have received a positive SARS-CoV-2 PCR test in the past six months. These children may therefore be expected to have some measure of immunity. The highest number of positive tests among children was seen among school-aged children (i.e. children aged six years or more). This means that even though the number of infected children has increased considerably since August 2021, only a few percent of each birth cohort has become infected. The estimates are probably conservative. Firstly, the figure was obtained within the past six months. However, the duration of acquired SARS-CoV-2 immunity remains unknown and it may persist for more than six months. Similarly, any acquired immunity may be varying. Furthermore, a dark figure is expected to exist as some children may not have been tested because their infection was asymptomatic, mild or because personal reasons caused them to refrain from testing.

No national serology measurements have been made among children aged 5-11 years as an indicator of immunity acquired through SARS-CoV-2 infection. Statens Serum Institut has previously studied the occurrence of SARS-CoV-2 antibodies among unvaccinated individuals who were selected at random. Until July 2021, they found that approx. 7.1% of the 12-19-year-olds had SARS-CoV-2 antibodies, whereas an estimated 8.6% (CI 7.6-9.6%) of the total population had been infected.[41]

In the period from 20 September to 3 October, the Swedish health authorities studied the prevalence of antibodies in unused blood from blood samples collected by laboratories in eight regions. On average, antibodies were found in 76% of the blood samples: antibodies may be owed to infection as well as COVID-19 vaccination. Investigators found that 81.1% (95% CI 75.5-86.0%) of 16-19-year-olds had antibodies at a time when 64% of these birth cohorts had obtained the full effect of their primary vaccination (i.e. 14 days after receiving their second dose). Among 0-11-year-olds, 28.4% (95% CI 24.8-32.2%) had antibodies, whereas this was the case for 39.5% (34.4-44.8%) of the 12-15-year-olds. No one in the age groups 0-11 years and 12-15 years had received vaccination at the time the study was conducted[42]. In Sweden, schools have not been closed during the epidemic, and therefore we expect that more children there were exposed to infection than is the case in Denmark.

The US Centers for Disease Control and Prevention (SCDC) estimate that approx. 38% (95% CI 36-40%) of 5-11-year-olds have SARS-CoV-2 antibodies, which is higher than the corresponding rate among adults, but comparable to the rate recorded among 12-17-year-olds.[43]

It must be assumed that the estimates based on test results underestimate the number of children who have SARS-CoV-2 antibodies, whereas the real figure is likely lower than the figure reported from Sweden where fewer restrictions have been in place in organisations and at schools than was the case in Denmark; and particularly in the first half of 2021, Sweden experienced a considerably higher infectious pressure than Denmark. For use in the below calculations of immunity in the population, we therefore apply a 10-30% range to denominate the level of acquired immunity among children aged 5-11 years.

[41] The National COVID-19 Prevalence Study [Den Nationale Prævalensundersøgelse]. Results from the fifth round of the prevalence study with 75,000 selected citizens, week 19-23, 2021.

[42] Folkhälsomyndigheten: Covid-19: Påvisning av antikroppar mot SARS-CoV-2 i blodprov från öppenvården Uppdaterad 2021-10-28 med data för prover insamlade vecka 38 och 39, 2021.

[43] Slides from ACIP meeting 2-3 November 2021: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-11-2-3/03-COVID-Jefferson-508.pdf

Disease burden

Individuals hospitalised with a SARS-CoV-2 positive test result

The number of individuals hospitalised with SARS-CoV-2 is monitored by collecting data from the National Patient Registry, which is automatically combined with the Danish Microbiology Database (MiBa) which monitors infectious diseases and micro-organisms nationally, including positive and negative SARS-CoV-2 samples. The number of people hospitalised with SARS-CoV-2 is defined as the number of people admitted with a positive test obtained in the 14 days leading up to their hospitalisation. Individuals who undergo SARS-CoV-2 testing during hospitalisation are also registered as COVID-19-related hospitalisations.

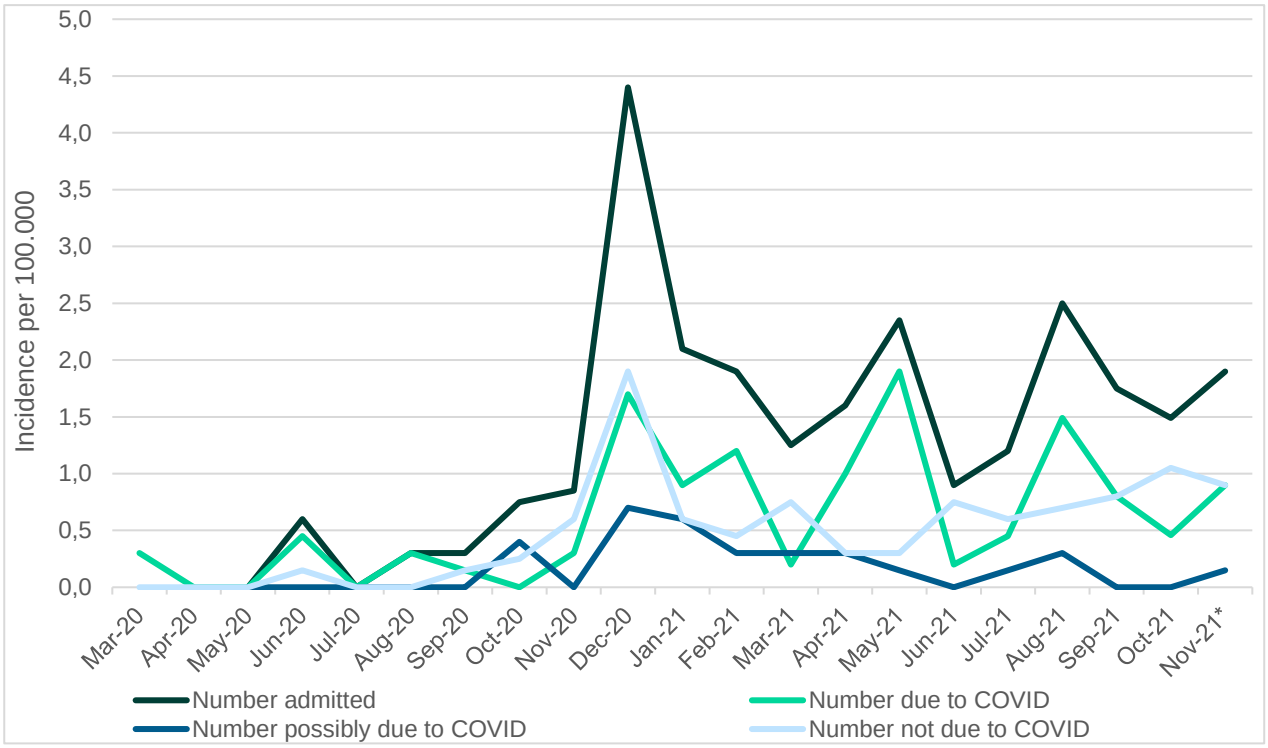
The number of people hospitalised with SARS-CoV-2 follows an increasing trend, and as per 21 November 2021, approx. 436 individuals are admitted among whom 50 are admitted to an intensive care unit. Despite the considerable increase in the number of individuals who have become infected with SARS-CoV-2, not quite the same increase is observed in the number of hospitalised individuals. This may mainly be owed to COVID-19 vaccination, but also to the fact that the younger age groups are driving transmission - age groups who do not generally fall seriously ill and therefore do not need hospitalisation due to COVID-19. Thus, it is seen that the number of children hospitalised due to COVID-19 is low and the burden on secondary healthcare for this age group is very limited compared with the burden caused by other known infectious conditions.

We expect that some of those hospitalised will have been admitted for other causes than COVID-19 but have tested positive in connection with a screening in the 14 days leading up to their hospitalisation. Particularly in children and in younger age groups, the share hospitalised due to other causes than COVID-19 may be large.

Figure 2 below presents the incidence of hospitalisations with a positive SARS-CoV-2 test among children aged 1-11 years since the epidemic started. Overall, a total of 179 hospitalisations were recorded of children aged 1-11 years who had tested SARS-CoV-2 positive A total of three deaths have occurred. The figure presents the total number of hospitalisations and the estimated number of children (1-11 years) who are hospitalised due to COVID-19, possible due to COVID-19 and due to another condition but where SARS-CoV-2 is a secondary finding. The division was made based on a currently not fully validated study being conducted at Statens Serum Institut in which hospitalisations are categorised based on admission periods with specific diagnoses, procedures completed, etc. The results are therefore preliminary as paediatric validation is ongoing. Based on the used algorithm, it is shown that COVID-19 was the main cause of hospitalisation among 86 (48%) of the children. Hereof, 47 (56%) of the hospitalisations had a duration exceeding 12 hours (Figure 2). For 23 of the 179 children hospitalised with a positive SARS-CoV-2 test, it cannot be determined if the primary cause of hospitalisation was COVID-19 or another condition, whereas 70 of the 179 hospitalisations with a positive test result are estimated to be due to other causes than COVID-19, and

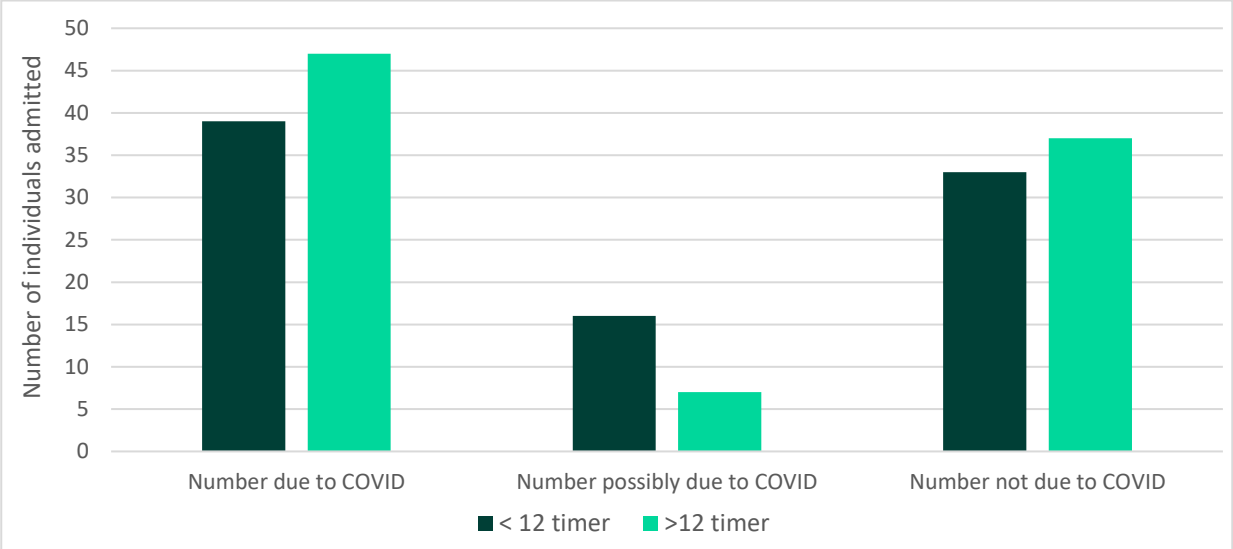
there the positive COVID-19 test was thus a secondary finding. The figure also shows that, generally, very few children are hospitalised due to COVID-19, and the incidence has remained largely unchanged over time.

Figure 2: Incidence of hospitalisations with a SARS-CoV-2 positive test among children aged 1-11 years



Note for Figure 2: The figures were stated as number (i) hospitalised due to COVID-19, (ii) possibly due to COVID-19 and (iii) not due to COVID-19. The statement is based on an algorithm developed by Statens Serum Institut, which has not yet been fully validated. Additionally, the data for November and, in part, October are incomplete and therefore not comparable to those for the other months.

Figure 3: Hospitalisation time above and below 12 hours among children (1-11 years) hospitalised with a positive SARS-CoV-2 test

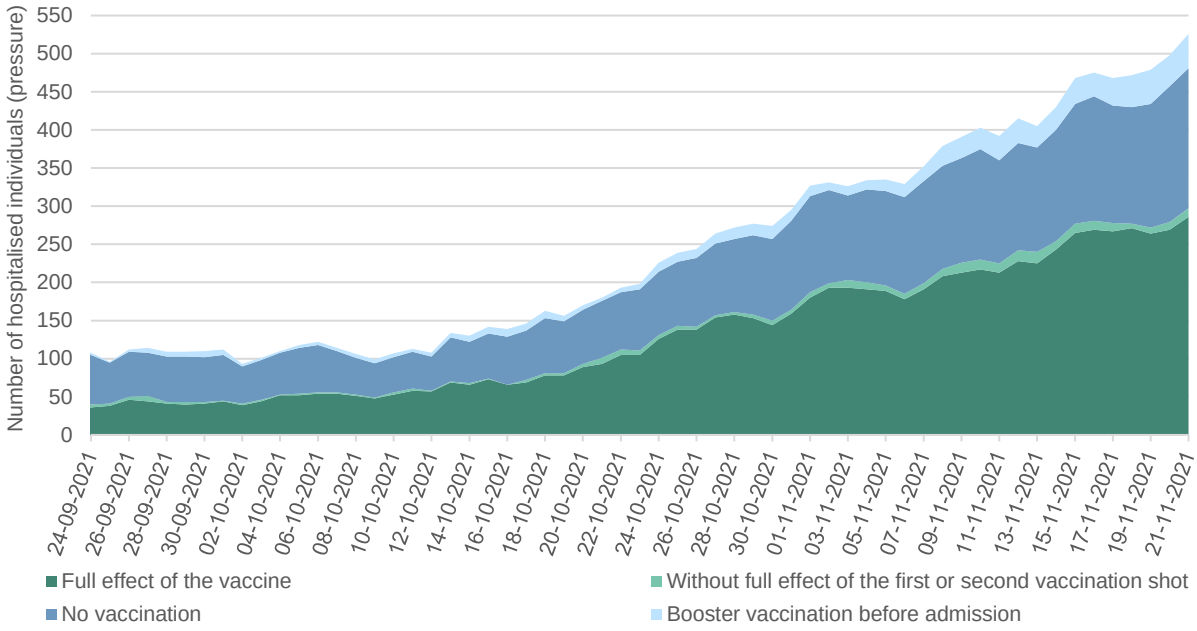


Note for Figure 3: The figures were stated as number hospitalised due to COVID-19, possibly due to COVID-19 and not due to COVID-19. The statement is based on an algorithm developed by Statens Serum Institut, which has not yet been fully validated.

In the remaining age groups, the distribution of vaccinated and unvaccinated individuals among hospitalised patients has changed, among others so that now approx. 2/3 of the hospitalised individuals had completed primary vaccination, whereas in mid-September 40% had completed primary vaccination. We expect that as a greater share of the population becomes vaccinated, more breakthrough infections will occur among those vaccinated. Additionally, a relatively higher number of hospital admissions are individuals who have not been vaccinated, compared with the share of unvaccinated people in the population, where the majority have been vaccinated.

No major increases have been observed in the burden caused by vaccinated +80-year-old patients since mid-October; thus, the number has remained stable. This indicates that the booster vaccination efforts made in the older part of the population are starting to take effect.

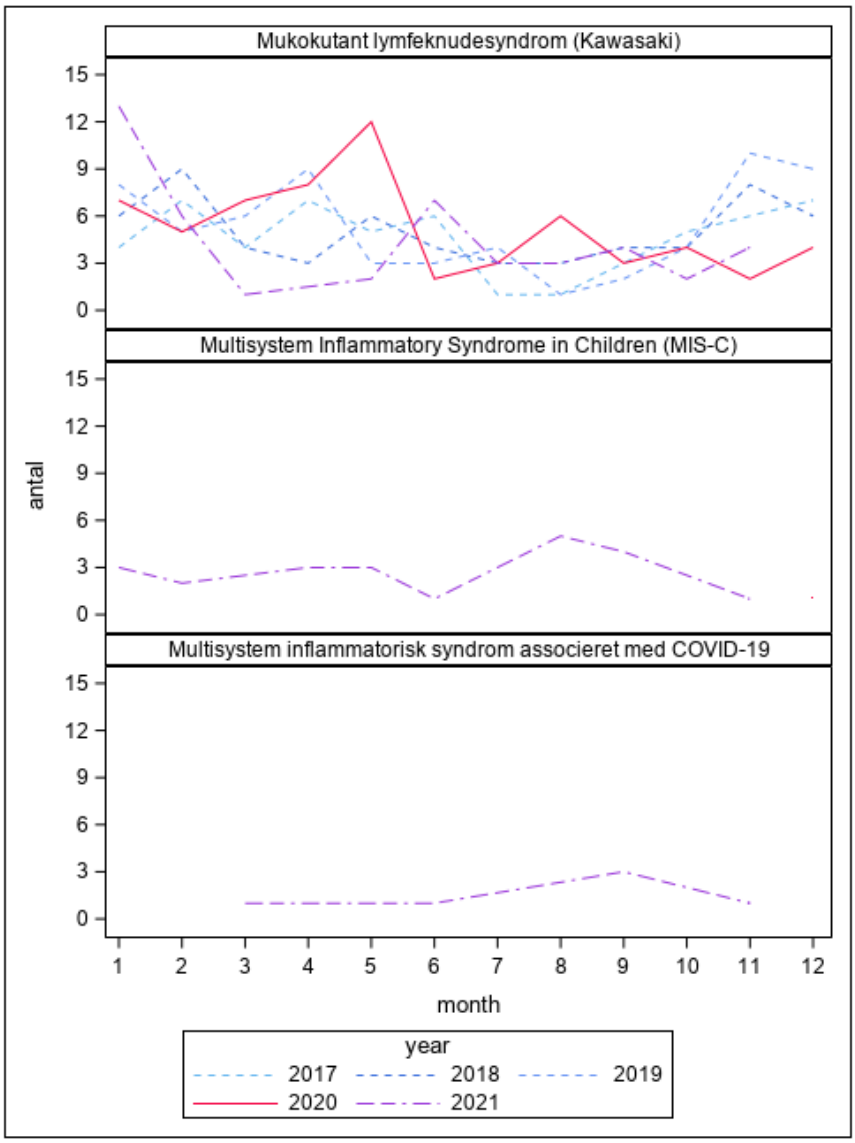
Figure 4: Number of hospitalised individuals with a SARS-CoV-2-positive test among vaccinated/booster vaccinated people, by vaccination status in the period from September to November 2021



MIS-C occurrence following SARS-CoV-2 infection

Statens Serum Institut has in place monthly monitoring of the occurrence of Multi Inflammatory Syndrome in Children (MIS-C) and compares the occurrence of similar symptom pictures from previous years (Kawasaki syndrome, etc.). The MIC-C condition is described in more detail on page 26. Below, Figure 5 presents the occurrence of MIS-C in 2021 and the occurrence of Kawasaki syndrome from 2017 to 2021. Monitoring data from Statens Serum Institut reveal that in 2021 a total of 29 cases of MIS-C were reported among children who had been infected by SARS-CoV-2. The median age was five years. The below statements show no increase in the number of MIS-C in the autumn months of 2021, when the number of children who have been infected has increased. Even so, the numbers are limited and reporting lag also cannot be excluded. MIS-C evolves approx. 2-6 weeks after infection with SARS-CoV-2 and it is not unlikely that increases will be observed in the number of MIS-C cases as paediatric case numbers increase.

Figure 5: Occurrence of MIS-C (multisystem inflammatory syndrome in children) and Kawasaki syndrome among children, 2017-2021 (data stated as per 23 November 2021)



The knowledge base concerning serious COVID-19 disease and rare serious complications to COVID-19 in children aged 5-11 years.

On a weekly basis and most recently in Week 47, the Danish Health Authority has conducted a systematic literature search to identify relevant studies among children aged 0-15 years of age diagnosed with COVID-19 infection.[44] The below section is based on the literature search, which was supplemented by relevant studies identified through reference lists and searches for newly published studies that have not yet been indexed, etc.

When reviewing international literature, we must make various reservations before extrapolating findings to a Danish context. For example, differences may apply with respect to socioeconomics,

[44] The Danish Health Authority, case number 05-0600-1224.

epidemic status, contact patterns, etc., which means that the findings are not directly applicable in a Danish context.

Serious COVID-19 disease

Children who become infected with SARS-CoV-2 typically experience mild symptoms, and many children infected with SARS-CoV-2 are asymptomatic.[45,46,47] Children carry a lower risk of developing a serious disease course than adults; and the risk of death due to COVID-19 is low, even among children with underlying disease, including weakened immune response and/or cancer disease.[48,49] Various systematic literature reviews have found that approx. 5% of children and young people below 18 years of age (in one study children/young people below 21 years of age) develop serious COVID-19, and that the mortality was low, estimated from 0 to less than 1%[50,51,52,53,54,55,56]. The estimates of the share of children admitted to intensive care vary considerably across the identified studies, which likely reflects varying clinical practice.

The literature search has identified various studies on complications in connection with COVID-19 among children, including neurological symptoms, sepsis and diabetic ketoacidosis, along with myocarditis, pericarditis and MIS-C, which are described below. Currently, only a limited number of studies have been published on the degree of severity following infection with the Delta variant.

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[45] Rubens JH, Akindele NP, Tschudy MM, Sick-Samuels AC. Acute covid-19 and multisystem inflammatory syndrome in children. BMJ. 2021 Mar 1;372:n385.

[46] Viner RM, Ward JL, Hudson LD, et al. Systematic review of reviews of symptoms and signs of COVID-19 in children and adolescents. Arch Dis Child. 2020;archdischild-2020-320972

[47] Irfan O, Muttalib F, Tang K, Jiang L, Lassi ZS, Bhutta Z. Clinical characteristics, treatment and outcomes of paediatric COVID-19: a systematic review and meta-analysis. Arch Dis Child. 2021;106(5):440-448

[48] WHO Scientific Brief 29 Sep 2021: https://www.who.int/publications/i/item/WHO-2019-nCoV-Sci_Brief-Children_and_adolescents-2021.1

[49] ECDC 1 June 2021: https://www.ecdc.europa.eu/sites/default/files/documents/Interim-public-health-considerations-for-COVID-19-vaccination-of-adolescents.pdf

[50] Shah K, Upadhyaya M, Kandre Y et al. Epidemiological, Clinical and Biomarker Profile of Pediatric Patients Infected with COVID-19 QJM: Monthly Journal of the Association of Physicians 2021

[51] Badal S, Thapa Bajgain K, Badal S et al. Prevalence, clinical characteristics, and outcomes of pediatric COVID-19: A systematic review and meta-analysis. Journal of Clinical Virology: the official publication of the Pan American Society for Clinical Virology 2021;135():104715 2021

[52] Cui, X, Zhao, Z, Zhang, T et al. A systematic review and meta-analysis of children with coronavirus disease 2019 (COVID-19). Journal of Medical Virology 2021;93(2):1057-1069 2021

[53] Amaral, L, Luis A, Gallardo E et al. COVID-19 in children: a systematic review and meta-analysis Current Topics in Virology 2020;17():1-49 2020

[54] Liu C, He Y, Liu L et al. Children with COVID-19 behaving milder may challenge the public policies: a systematic review and meta-analysis. BMC Pediatrics 2020;20(1):410 2020

[55] Levin, Andrew T.; Hanage, William P.; Owusu-Boaitey, Nana; Cochran, Kensington B.; Walsh, Seamus P.; Meyerowitz-Katz, Gideon. Assessing the age specificity of infection fatality rates for COVID-19: systematic review, meta-analysis, and public policy implications. European Journal of Epidemiology 2020;35 (12):1123-1138 2020

[56] Kitano et al. 2021. The differential impact of pediatric COVID-19 between high-income countries and low- and middle-income countries: A systematic review of fatality and ICU admission in children worldwide. PloS one 2021;16(1):e0246326 2021.

After Delta became the vastly predominant variant, more children have become infected with SARS-CoV-2.[57] The US CDC has reported increasing case numbers among 0-17-year-olds, more emergency department visits and more than a three-fold increase in the number of hospitalisations among children in the states that have recorded the lowest vaccination coverage among children aged 12 years or more.[58] Among adults, the Delta variant is associated with a higher risk of hospitalisation than the previous variants[59,60], but it remains unknown if the high hospitalisation rates are observed because the Delta variant causes more serious disease or if the increasing number of hospitalisations reflects that the Delta variant is more infectious and therefore increases case numbers along with the number of ill people. In the US, approx. one third of the 5-11-year-old children who are hospitalised with COVID-19 also need intensive unit care.[61]

Denmark has not recorded corresponding increases in the number of COVID-19 hospitalisations among children. This is so even though an increase has been recorded in the number of cases aged 5-11 years (as described in the above section).

Multisystem inflammatory syndrome in children (MIS-C) in connection with SARS-CoV-2 infection

In rare cases, SARS-CoV-2 infection triggers a syndrome of severe systemic inflammation among children, coined *multisystem inflammatory syndrome in children* (MIS-C).[62,63,64]. The corresponding condition in adults is termed MIS-A (A for adult). The condition is serious and often requires hospitalisation in an intensive care unit, but the prognosis for children in Denmark is good. MIS-C is described in the memo *Concerning vaccination of children aged 12-15 years* and in *Guideline on the handling of COVID-19 vaccination in the general vaccination programme*.

[57] Pettoello-Mantovani M, Carrasco-Sanz A, Huss G et al. Viewpoint of the European Pediatric Societies over Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Vaccination in Children Younger Than Age 12 Years Amid Return to School and the Surging Virus Variants. J Pediatr. 2021 Sep 15:S0022-3476(21)00886-6.

[58] Siegel DA, Reses HE, Cool AJ, et al. Trends in COVID-19 Cases, Emergency Department Visits, and Hospital Admissions Among Children and Adolescents Aged 0-17 Years - United States, August 2020-August 2021. MMWR Morb Mortal Wkly Rep. 2021 Sep 10;70(36):1249-1254.

[59] Wise J. Covid-19: Delta variant doubles risk of hospital admission compared with alpha variant, study shows. BMJ. 2021 Sep 1;374:n2152.

[60] Twohig KA, Nyberg T, Zaidi A et al. Hospitalisation and emergency care attendance risk for SARS-CoV-2 delta (B.1.617.2) compared with alpha (B.1.1.7) variants of concern: a cohort study. Lancet Infect Dis. 2021 Aug 27:S1473-3099(21)00475-8. doi: 10.1016/S1473-3099(21)00475-8. Epub ahead of print.

[61] ACIP 2 November 2021: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-11-2-3/08-COVID-Oliver-508.pdf

[62] Feldstein LR, Rose EB, Horwitz SM et al. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. N Engl J Med. 2020 Jul 23;383(4):334-346.

[63] Hartling UB, Andersen H, Nilsson AC et al. Ugeskr Laeger 2020;182:V06200431

[64] Rubens JH, Akindele NP, Tschudy MM, Sick-Samuels AC. Acute covid-19 and multisystem inflammatory syndrome in children. BMJ. 2021 Mar 1;372:n385.

A Danish study has reported data on MIS-C at Danish paediatric departments.[65] Based on the departments' own data, a total of 23 children were diagnosed with MIS-C in the period from 1 March 2020 to 28 February 2021. The median age of the hospitalised children was eight years (age range 2-17 years) and the average hospitalisation time was eight days (range 3-24 days). All these children received medicinal treatment and all survived. Based on data on 12-17-year-olds in the National Danish Prevalence Study, the authors assumed that approx. 8.1% of all children < 18 years of age had been infected with SARS-CoV-2. Thereby, they estimated that the MIS-C incidence was 1 per 4,100 children infected with SARS-CoV-2. The Danish MIS-C estimates are considerably lower than corresponding international estimates, which the authors explain by reference to more reliable Danish data on sero-prevalence than is the case internationally, where data may have been based on a selective test strategy. Furthermore, more pronounced socioeconomic differences may likely explain some of the observed differences, and access to specialised treatment and adequate medicinal treatment may possibly explain why the mortality in Denmark is lower than that observed abroad. Of note, data were stated before the Delta variant was observed in Denmark, and before the increasing paediatric case number was recorded.

A currently unpublished Danish register study comprising approx. 60,000 Danish children below 18 years who tested SARS-CoV-2 positive found a MIS-C incidence of approx. 1 per 2,100 children (95% CI 1,500-3,400) with documented SARS-CoV-2 infection. The estimate is based exclusively on children who tested SARS-CoV-2 positive and therefore cannot be extrapolated to the risk among all children who become infected with SARS-CoV-2[66].

Cardiac complications to COVID-19

The Danish Health Authority continuously searches the literature on the risk of cardiac complications among children aged 0-15 years who become infected with COVID-19[67]. Searches were made through week 46 2021. A total of four systematic reviews and 25 primary studies were identified. In Appendix 2, we present the systematic reviews. Owing to the methodology used, these reviews have produced the most reliable data. Furthermore, each primary study is described.

Overall, the studies show that COVID-19 typically runs a milder course among children than among adults. Even so, studies have been published presenting numerous examples of serious cardiac complications among children who have become infected with COVID-19, even though these cases are rare compared with the number of children who become infected. Among the reported complications are myocardial injury, heart failure, myocarditis and MIS-C with cardiac involvement. Among the cases of cardiac complications, a limited number of mortalities were reported. The risk of cardiac complications seems to be highest among children with preceding comorbidity,

[65] Holm M, Hartling UB, Schmidt LS et al. Multisystem inflammatory syndrome in children occurred in one of four thousand children with severe acute respiratory syndrome coronavirus 2. Acta Paediatrica. 2021;110:2581–2583.

[66] Kildegaard H et al. manuscript undergoing peer-review

[67] Danish Health Authority. Case number 05-0600-1224

but examples were also reported of previously healthy children who developed cardiac complications to COVID-19 infection.

Late sequelae following COVID-19

As part of the Danish Health Authority's preparation of recommendations concerning the organisation of efforts aiming to care for patients with persisting COVID-19 symptoms[68], efforts were made to describe the occurrence of late sequelae among children following COVID-19. A systematic literature search was performed covering the period from 14 December 2020 to 7 July 2021 to describe the status quo[69]. Considerable variation exists in the nomenclature and the time frame used by each study aiming to assess late sequelae to COVID-19 infection. The systematic search identified a total of 14 studies focusing on late sequelae to COVID-19 among children. Furthermore, we included studies identified subsequently, among others via recommendations on late sequelae to COVID-19 published by the British Institute for Health and Care Excellence (NICE)[70]. The NICE recommendations suggest using the post-COVID-19 syndrome to describe symptoms developing during or after COVID-19 infection that last for more than 12 weeks and that cannot be explained by any other diagnosis. Furthermore, symptoms persisting for more than four weeks are also assessed independently. The most important studies are described in Appendix 3.

In most children, COVID-19 infection is characterised by a mild disease course with limited symptoms. Generally, young children experience fewer symptoms than older children. However, among younger and older children alike, examples were observed of prolonged COVID-19 courses with symptoms persisting for many weeks. Late sequelae to COVID-19 may evolve even though the primary infection course did not require hospitalisation. Among the children who develop late sequelae to COVID-19, the symptoms are similar to those reported for late sequelae to COVID-19 among adults. Thus, the reported symptoms comprise fatigue, sleeplessness, reduced/changed sense of smell, headache, breathlessness, myalgia, arthralgia and difficulty concentration, among others.

The 5-11-year-olds' role in the epidemic

The contribution of children to infections in the general population depends on the children's risk of becoming infected with SARS-CoV-2 themselves, the severity of symptoms, the number of social contacts and behaviour to prevent infections. Furthermore, the number of children diagnosed with SARS-CoV-2 will depend on the testing strategy used, and it may therefore be difficult to compare infection risk among children across studies and between countries.

[68]Danish Health Authority. Late sequelae following COVID-19 [Senfølger efter COVID-19]. https://www.sst.dk/da/Udgivelser/2020/Senfoelger-efter-COVID-19

[69]Danish Health Authority. Case number 005-0600-1224

[70] NICE. COVID-19 rapid guideline: managing the long-term effects of COVID-19. 11 November 2021. https://www.nice.org.uk/guidance/ng188

Previously, a consensus was reached that children who have become infected with SARS-CoV-2 are less infectious than adults. This is described in more detail in the memo *Concerning vaccination of children aged 12-15 years*.[71] However, more recent studies have shown that the more limited infection among children observed in the beginning of the pandemic may have been driven primarily by behavioural changes.[72] Furthermore, the emergence of the more infectious Delta variant means that since the early autumn of 2021, an increasing number of infected children has been recorded in Denmark and in most European countries. The large number of cases observed among children alone will be an important factor causing the number of infections derived from children to their families and contacts to rise.

Preliminary and interim analyses of Danish data from the SSI seem to indicate that 31% of the infection that may be traced and which explain 17% of the total number of individuals infected in the period from 1 September 2021 to 1 November 2021 originated from non-vaccinated children aged 6-13 years of age. Further age differentiation shows that 23% of the infections originated from the group of 6-11-year-olds and 8% of the infections originated from the group of 12-13-year-olds who had not been vaccinated. In contrast, less than 0.2% of infections originated from the group of 12-13-year-olds who had been vaccinated and who comprised more than half of all 12-13-year-olds in the same period. As stated initially, these data are preliminary and are currently being analysed. The above data have therefore not been published and should therefore be interpreted with caution. Additionally, the data do not show to which extent infection from unvaccinated children contributes to hospitalisations with COVID-19 disease. Even so, we may expect infection from unvaccinated children to spread both within the household and beyond.

In a meta-analysis (i.e. an analysis comprising several studies), no differences were found with respect to spreading of the infection or susceptibility to the infection between age groups (0-9 years, 10-19 years, 20-39 years, 40-59 years and 60+ years).[73] A US study comprising 1,236 participants from 310 households demonstrated that children's risk of becoming infected with SARS-CoV-2 was comparable to that of adults' (incidence rate of 6.3 [95% CI 3.6-11.0], 4.4 [2.5-7.5], 6.0 [3.0-11.7] and 5.1 [3.3-7.8] per 1,000 person-weeks for 0-4-year-olds, 5-11-year-olds, 12-17-year-olds and ≥18-year-olds). Even so, children more often had an asymptomatic infection.[74]

Two Danish studies (preprints) showed that the risk of transmitting infection within the household declines with age for children and young individuals < 20 years of age, and increases with age

[71] https://www.sst.dk/da/Udgivelser/2021/Vedroerende-vaccination-af-boern-paa-12-15-aar

[72] Coffin SE, Rubin D. Yes, Children Can Transmit COVID, but We Need Not Fear. JAMA Pediatr. Published online August 16, 2021.

[73] Thompson H, Mousa A, Dighe A et al. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Setting-specific Transmission Rates: A Systematic Review and Meta-analysis, Clinical Infectious Diseases, Volume 73, Issue 3, 1 August 2021, Pages e754–e764

[74] Dawood FS, Porucznik CA, Veguilla V, et al. Incidence Rates, Household Infection Risk, and Clinical Characteristics of SARS-CoV-2 Infection Among Children and Adults in Utah and New York City, New York. JAMA Pediatr. 2021;10.1001/jamapediatrics.2021.4217. doi:10.1001/jamapediatrics.2021.4217

among adults > 20 years of age. Additionally, data seem to indicate that the highest risk of transmitting infection within the household is from children aged 0-14 years to the 20-39-year-olds, reflecting close contact between children and their parents. The studies also show that the youngest children aged 0-5 years and 5-10 years have higher odds of infecting their household contacts than do 15-20-year-olds.[75,76] This is in line with various international studies showing that transmission of infection to parents and siblings may stem, in particular, from the youngest children who cannot self-isolate and have difficulty complying with general recommendations aiming to limit infection.[77] Another study explored how the infection risk developed as a more infectious variant, the Alpha variant, was introduced. Data seem to indicate that the risk increases multiplicatively, which means that the infection risk from younger children, stated in absolute figures, increases more than the infection risk from older children.[78]

A Canadian study found that the odds that children aged 0-3 years who have become infected with SARS-CoV-2 transmit the infection to their household contacts is 1.43 times higher (95% CI 1.17-1.75) than for children and young people aged 14-17 years. The numbers were derived from a study comprising 6,280 households in which a child had become infected with SARS-CoV-2. The study was conducted in the period from June to December 2020, i.e. before COVID-19 vaccination was initiated and before the Delta variant emerged. In 27.3% of the households, a minimum of one and a median two of the child's household contacts were infected.

In connection with a camping trip in Georgia, US, a total of 224 children and young individuals aged 7-19 years were infected with SARS-CoV-2. Subsequently, 377 from a total of 526 (72%) household contacts to those who were infected were tested for SARS-CoV-2 among whom 12% tested positive. Transmission of SARS-CoV-2 infection to household contacts occurred in 35/194 households (18%). A total of 10% of those who became infected were hospitalised; none of whom were below 18 years of age. More older children and young people were capable of complying with the measures implemented to reduce transmission, such as maintaining a distance. Moreover, the risk that household contacts would become infected with SARS-CoV-2 was lower if the infected individual had maintained a distance (adjusted odds ratio of infection 0.4 [95% CI 0.1-0.9]) to household contacts than if the infected individual had maintained no distance. The study was conducted before the introduction of the Delta variant.[79]

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[75] Lyngse FP, Mølbak K, Franck KT et al. Association between SARS-CoV-2 Transmissibility, Viral Load, and Age in Households. Preprint in medRxiv 4. June 2021. doi: https://doi.org/10.1101/2021.02.28.21252608

[76] Lyngse FP, Kirkeby CT, Halasa T et al. COVID-19 Transmission Within Danish Households: A Nationwide Study from Lockdown to Reopening. Preprint in medRxiv 9. September 20201. doi: https://doi.org/10.1101/2020.09.09.20191239

[77] Coffin SE, Rubin D. Yes, Children Can Transmit COVID, but We Need Not Fear. JAMA Pediatr. Published online August 16, 2021.

[78] Lyngse, F. P., Mølbak, K., Skov, R. L., Christiansen, L. E., Mortensen, L. H., Albertsen, M. P., ... & Kirkeby, C. T. (2021b). Increased Transmissibility of SARS-CoV-2 Lineage B. 1.1. 7 by Age and Viral Load: Evidence from Danish-House-holds. MedRxiv. Accepted for publication in Nature Communications. https://www.medrxiv.org/content/10.1101/2021.04.16.21255459v1

[79] Chu VT, Yousaf AR, Chang K et al. Georgia Camp Investigation Team. Household Transmission of SARS-CoV-2 from Children and Adolescents. N Engl J Med. 2021 Sep 2;385(10):954-956.

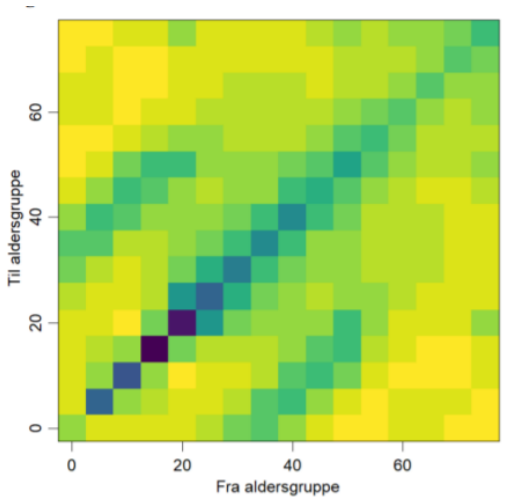
Contact patterns

The number of daily contacts among "infection-carrying contacts" has varied in the course of the epidemic, depending on restrictions and the perception of infection risk in the population. The lifting of all restrictions means that the level of infection-carrying contacts may be expected to remain at the present level, whereas improved hygiene and attention to the recommendations of the Danish Health Authority on prevention of infection may to some extent change the contact patterns that existed before the epidemic began. Thus, the contact pattern may possibly not cause as high a number of infection-carrying contacts as was the case before the epidemic started.

Contact patterns for children are described in the Danish Health Authority's *Memo on vaccination of 12-15-year-olds*. Overall, children and young people have a higher number of daily contacts than adults. In addition, the number of contacts with whom you come into contact is also important for the spreading of the infection. The Expert Group on Mathematical Modelling at the SSI has previously described how contact patterns described in international studies may apply to a Danish context.

The below illustration of a Danish contact pattern in a normal open society shows that most people are characterised by having a large number of peer or same-age contacts and that the number of contacts is generally higher in the younger proportion of the population (more dark-coloured rows). The figure shows that young children have only limited contact with individuals in the oldest age groups (yellow colours) but primarily come into contact with larger siblings and with their parents (green and blue colours, respectively).

Figure 6: Expected contact pattern in a non-restricted society, illustrated by mathematical modelling[80]



[80] Statens Serum Institut. 2021. https://files.ssi.dk/teknisk-gennemgang-af-modellerne-10062020

Expectations to the upcoming winter and seasons

Overall, the combination of an expected seasonal effect, a fully open society and the dominance of the very infectious Delta variant means that infection chains among unvaccinated school-aged children are no longer self-limiting. Even at the current infectious pressure, at which nearly 1% of the 5-11-year-olds become infected weekly, many weeks will pass before the immunity reaches a level at which the infection chains are limited, even in the absence of restrictions.

The very high level of infection currently being observed in younger age groups will contribute to increased infection among unvaccinated adults and vaccinated individuals in whom the vaccine has not reached full effect and who therefore carry an increased risk of breakthrough infection and illness in the near future.

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 transmission in the general population, focusing on the burden 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 burden 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 an additional burden on the hospital capacity thereby triggering a need to postpone planned surgery and out-patient treatments to varying degrees across Denmark.

Based on current experiences in Denmark, there are indications that the booster vaccination efforts may reduce the risk of breakthrough infection in the oldest part of the population. Furthermore, we expect that booster vaccination efforts will contribute to reducing the number of individuals hospitalised with COVID-19. In light of the current infection level and increased number of hospitalisations, it is essential to increase population immunity as much as possible to avoid spreading of the infection in society and the ensuing consequences for individuals at increased risk and for secondary healthcare.

Adopting a slightly longer perspective, we expect that a new equilibrium will be reached between spreading of the infection, population immunity and the occurrence of new virus variants. Various possible future scenarios with a longer-term outlook were described by the expert group aiming to prepare a long-term strategy for a re-opened Denmark in a background memo on future scenarios.[81]

[81]Background paper on future scenarios [Baggrundspapir om fremtidsscenarier] 2 Sep 2021: https://fm.dk/media/25239/1-baggrundspapir-fremtidsscenarier_a.pdf

The paper mentions the possibility that a risk of larger periodic outbreaks may exist or that the winter period may bring infection flare-up and a heightened risk of epidemics. Currently and at the global level, the Delta variant is the vastly dominant variant, but SARS-CoV-2 evolves with time, and in the future other variants may emerge. Currently, the vaccines are highly effective against the Delta variant, and signs of mixed immunity are being observed. This means that immunity developed after vaccination or infection with other variants also provides partial protection against the condition, particularly against serious COVID-19 morbidity and mortality, despite the fact that the virus has changed.[82] Hybrid immunity is also known from other viruses, e.g., influenza virus where a sufficiently high level of immunity is achieved at the population level owing to mixed immunity following previous infection/vaccination and where repeated vaccination campaigns may therefore be targeted at selected risk groups who carry an increased risk of running a serious disease course.

Immunity

Immunity may be achieved in several ways. You can acquire immunity after being affected by the infection or it may be induced by vaccination. For a more detailed description of the body's immune response, including how acquired and induced immunity develop, please see the memo *Concerning vaccination of children aged 12-15 years*[83].

The immunity achieved by acquired SARS-CoV-2 infection and induced by COVID-19 vaccination is not perfect. It is well known that the immune system weakens as part of natural ageing processes. Elderly individuals may therefore have a reduced immune response following SARS-CoV-2 infection or vaccination. In a similar manner, a less than optimal reaction to vaccination may be seen in some individuals with a weakened immune defence, e.g., due to some haematological conditions, immunosuppressant medicines given after transplantation or similar. Furthermore, we know that vaccines are not 100% effective.

Thus, immunity is not an absolute concept (immune/non-immune) but a continuum, meaning that individuals are more or less immune after infection or vaccination. The degree of immunity varies from one individual to the next and changes with time. Furthermore, the risk of becoming infected will depend on your degree of immunity and on your exposure to the virus; specifically the number of virus particles and the length of the period during which you come into contact with an individual who is infected.

Currently, it remains unknown how long time you remain immune following infection or after COVID-19 vaccination, because long-term follow-up data are, naturally, not yet available. Even so,

[82] Knowledge paper on infection and evolution of the virus [Videnspapir om smitte og virusevolution] 12 Sep 2021: https://fm.dk/media/25159/videnspapir-smitte-og-virusevolution.pdf

[83]Concerning vaccination of children aged 12-15 years [Notat vedr. vaccination af børn på 12-15 år] 17 June 2021 170621-Notat-vedr_-vaccination-af-boern-paa-12-15-aar.ashx (sst.dk)

from other types of corona virus it is known that after infection the antibody level declines with time and that the risk of becoming infected again will start to increase at some point in time.

Despite the presently incomplete knowledge base, data seem to indicate that the decline in induced immunity may be significant after six months. We also know that the decline is more pronounced among elderly individuals and individuals with underlying conditions. Additionally, we know that higher levels of antibodies are needed to protect against infection with the Delta variant. To enhance the induced immunity, booster vaccination is offered in Denmark depending on the time that has passed since you received the final vaccination shot under the primary vaccination regime[84]. It has been shown that booster vaccination yields higher antibody levels and also that higher levels of antibodies yield better protection against SARS-CoV-2, including against the Delta variant. Even so, it currently remains uncertain how much extra protection booster vaccination provides against infection, serious COVID-19 and transmission of infection.

Despite the broad vaccination measures, we expect that vaccine effectiveness will be reduced and/or waning with time in some individuals and groups. This will likely include elderly individuals and some patient groups who, regardless of their age, are particularly vulnerable due to, e.g., cancer therapy, transplants, congenital immunodeficiencies, etc. These individuals and groups will therefore carry an increased risk of serious COVID-19.

Specifically on immunity in children

A certain share of children aged 5-11 years have been infected previously and will have some degree of immunity. Knowledge is limited about how long time and to which degree immunity is maintained following infection in children. Some studies seem to indicate that an antibody response is maintained in the short term (4-6 months) that is comparable or superior to that of adults[85,86]. However, other studies seem to indicate that in the longer term, the antibody response in children wanes more rapidly in children than in adults[87,88].

Based on the available documentation from studies on adults, we cannot clearly conclude if vaccination generally produces a better and longer-lasting immunity than is observed after passing the

[84] Plan for COVID-19 booster vaccination (Phase II) [Plan for revaccination mod COVID-19 (FASE II)] - Danish Health Authority

[85] Garrido C, Hurst JH, Lorang CG, et al. Asymptomatic or mild symptomatic SARS-CoV-2 infection elicits durable neutralizing antibody responses in children and adolescents. JCI Insight. 2021;6(17):e150909. Published 2021 Sep 8. doi:10.1172/jci.insight.150909

[86] Dowell AC, Butler MS, Jinks E et al.Children develop robust and sustained cross-reactive spike-specific immune responses following SARS-CoV-2 infection. medRxiv [pre-print] 28. sept. 2021. doi: https://doi.org/10.1101/2021.04.12.21255275

[87] Bloise S, Marcellino A, Testa A, et al. Serum IgG levels in children 6 months after SARS-CoV-2 infection and comparison with adults. Eur J Pediatr. 2021;180(11):3335-3342. doi:10.1007/s00431-021-04124-w

[88] Lau EH, Hui DS, Tsang OT, et al. Long-term persistence of SARS-CoV-2 neutralizing antibody responses after infection and estimates of the duration of protection. EClinicalMedicine. 2021;41:101174. doi:10.1016/j.eclinm.2021.101174

infection[89,90]. Even so, documentation from studies on adults shows that a large proportion of those infected do not develop a measurable antibody response[91] and that vaccination increases the immunity among previously infected individuals[92,93,94,95]. Documentation also exists that the current extensive spreading of infection with the Delta variant challenges the immunity among vaccinated individuals who have not previously been infected and among unvaccinated individuals who have previously been infected with a non-Delta variant[96]. Children with previously documented COVID-19 infection are therefore also expected to benefit from vaccination.

Vaccine effectiveness

Below, we present knowledge about vaccine effectiveness based on the literature and Danish monitoring.

Vaccine effectiveness against SARS-CoV-2 infection and serious COVID-19

In memos published about booster vaccination, the Danish Health Authority has described the immunity following primary vaccination against COVID-19[97]. This presentation is based on a systematic literature search[98].

The latest memo from the Danish Health Authority, *Concerning booster vaccination of individuals who have completed primary vaccination after 1 July 2021*[99], summarises knowledge from a range of studies that have assessed the risk of COVID-19 breakthrough infection after completing primary vaccination, and the consequences hereof.

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[89] Shenai MB, Rahme R, Noorchashm N. Equivalency of Protection from Natural Immunity in COVID-19 Recovered Versus Fully Vaccinated Persons: A Systematic Review and Pooled Analysis. medRxiv [pre-print] 21. Sep. 2021. doi: https://doi.org/10.1101/2021.09.12.21263461

[90] Bozio CH, Grannis SJ, Naleway AL, et al. Laboratory-Confirmed COVID-19 Among Adults Hospitalized with COVID-19–Like Illness with Infection-Induced or mRNA Vaccine-Induced SARS-CoV-2 Immunity — Nine States, January–September 2021. MMWR Morb Mortal Wkly Rep 2021;70:1539–1544. DOI: http://dx.doi.org/10.15585/mmwr.mm7044e1

[91] Wei, J. Matthews P.C., Stoesser N. et al. Anti-spike antibody response to natural SARS-CoV-2 infection in the general population. Nat Commun 12, 6250 (2021). https://doi.org/10.1038/s41467-021-26479-2

[92] Shenai MB et al. (op. cit.)

[93] Havervall S, Marking U, Greilert-Norin N, et al., Impact of SARS-CoV-2 infection on longitudinal vaccine immune responses. medRxiv [pre-print] 21. Oct. 2021. doi: https://doi.org/10.1101/2021.10.16.21264948

[94] Wang Z., Muecksch F., Schaefer-Babajew D. et al. Naturally enhanced neutralizing breadth against SARS-CoV-2 one year after infection. Nature 595, 426–431 (2021). https://doi.org/10.1038/s41586-021-03696-9

[95] Planas D., Veyer D., Baidaliuk A. et al. Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization. Nature 596, 276–280 (2021). https://doi.org/10.1038/s41586-021-03777-9

[96] ECDC. Rapid Risk Assessment: Assessing SARS-CoV-2 circulation, variants of concern, non-pharmaceutical interventions and vaccine rollout in the EU/EEA, 16th update. 30. Sep. 2021. https://www.ecdc.europa.eu/sites/default/files/documents/covid-19-rapid-risk-assessment-16th-update-september-2021.pdf

[97] Vedr-revaccination-mod-COVID-19-280921.ashx (sst.dk) and COVID-19 booster vaccination plan (Phase II) [Plan for revaccination mod COVID-19 (FASE II)] - Danish Health Authority and https://www.sst.dk/da/Udgivelser/2021/Revaccination-af-personer-over-18-aar

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

[99] https://www.sst.dk/da/Udgivelser/2021/Revaccination-af-personer-over-18-aar

The study findings confirm that both Comirnaty® and Spikevax® provide a high level of protection against COVID-19 infection and, in particular, against hospitalisation and mortality due to COVID-19. The VE peaks approx. two months after completed primary vaccination and then recedes. After approx. six months, VE against infection has declined, whereas VE against hospitalisation remains largely intact. Study results also underpin that COVID-19 disease courses are generally milder if you experience breakthrough infection after an infection than if you are a non-vaccinated individual.

For further information about the studies, please see the Danish Health Authority's memo *Concerning booster vaccination of individuals who have completed primary vaccination after 1 July 2021*.

Data collected from Danish monitoring efforts

Statens Serum Institut monitors the VE of the COVID-19 vaccines. The reports from 12 November 2021[100] show that VE to SARS-CoV-2 infection wanes with time. The decline is more pronounced among the ≥ 65-year-olds, which is likely due to a combination of the fact that elderly individuals generally have a weaker immune response than younger individuals, and that this age group was vaccinated before the others. Thus, the waning VE is also a reflection of waning vaccine effectiveness with time.

The VE for hospitalisation due to breakthrough infection remains high, also among ≥ 65-year-olds, where VE among those who have completed vaccination with Comirnaty® and Spikevax® reaches 76.1% (95% CI: 63.4-84.4) and 88.3% (95% CI: 74.0-94.7%), respectively. The latest report from 12 November 2021 [101] comprising data from the period from 9 October to 6 November shows continued good protection against hospitalisation among ≥ 65-year-olds with a VE to hospitalisation for Comirnaty® and Spikevax® of 77.2% (95% CI: 69.6-82.9%) and 88.3% (95% CI: 79.8-93.2%), respectively.

Among individuals ≥ 65 years who have received booster vaccination, VE against infection and hospitalisation is high for Comirnaty® (73.2% (95% CI: 65.7-79.1%) and 89.8% (95% CI: 82.6-94.0%)). As ≥ 65-year-olds who have received booster vaccination with Spikevax® constitute a relatively small population, the VE estimates against infection and hospitalisation are not presented for this group.

The same presentation based on data from the same period show that VE against infection among the < 65-year-olds who have completed vaccination with Comirnaty® or Spikevax® has now declined to 65.4% (95% CI: 64.4-66.4%) and 80.6% (95% CI: 79.4-81.7%) compared with the previous period (from 11 September to 9 October), when VE was 78.7% (95% CI: 77.5-79.8%) and

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

[101] Statens Serum Institut, 12 November 2021, *COVID-19 – Infections after vaccination and vaccine effectiveness:* Infections following vaccination and vaccine effectiveness (ssi.dk)

89.4% (95% CI: 87.9-90.7), respectively.[102] Please note that vaccinated individuals are now to a higher degree being compared with unvaccinated individuals, which may help explain the VE decline. Furthermore, when interpreting VE, it is important to take into account that the small group of unvaccinated individuals may have an infection risk that differs from that of vaccinated individuals. This may potentially affect the estimates.

Protection against hospitalisation remains high for Comirnaty® (93.0% (95% CI: 90.7-94.7%)) and for Spikevax® (94.2% (95% CI: 88.7-97.1%)).

Among individuals < 65 years who have received booster vaccination, VE against infection is high for Comirnaty® (83.9% (95% CI: 80.2-87.0%)) and Spikevax® (90.4% (95% CI: 85.2-93.7%)). As only a limited number of individuals below 65 years have been hospitalised after booster vaccination, VE is not estimated here.

ENFORCE data

ENFORCE (National Cohort Study of Effectiveness and Safety of SARS-CoV-2 vaccines) is a clinical study designed to assess the effectiveness and safety of the available vaccines against corona virus in adult Danish citizens[103]. 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, respectively, after the initial visit).

Based on data from the third visit (i.e. three months after initiating the vaccination course), ENFORCE found that a minor proportion of the vaccinated individuals were so-called low responders, i.e. individuals who fail to produce a solid immune response after vaccination, corresponding to approx. 5%. This percentage is higher in some subgroups than in others, e.g., among immuno-deficient patients, cancer patients and patients with renal disorders and multi-disease.

Vaccine effectiveness with respect preventing transmission

Several studies have shown that vaccination reduces the risk of transmitting infection to others. Among others, this was demonstrated in the finding that vaccinated individuals have a considerably lower risk of becoming infected and presenting with symptoms than unvaccinated individuals.[104,105] This is so even though vaccination does not provide complete protection against infection or against

[102] 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)

[103] Home (enforce.dk)

[104] Prunas O, Warren JL, Crawford FW et al. Vaccination with BNT162b2 reduces transmission of SARS-CoV-2 to household contacts in Israel. medRxiv. 16 July 2021; https://www.medrxiv.org/content/10.1101/2021.07.13.21260393v1

[105] Shah ASV, Gribben C, Bishop J, et al. Effect of vaccination on transmission of SARS-CoV-2. N Engl J Med. Published online 28 October, 2021

transmitting the infection to others. This indicates that the protection against transmitting the infection is lower for infections with the more infectious Delta variant.[106]

Furthermore, a Swedish register study conducted when the Alpha variant was dominant has shown that the risk of transmitting infection was lower when more family members had been vaccinated. Thus, non-immune family members had an approx. 45-61% (hazard ratio 0.39-0.55, 95% CI 0.37-0.61) lower risk of COVID-19 infection if one family member was immune than families in which no family member had SARS-CoV-2 immunity.[107]

It is assumed that the risk of transmitting infection increases with an increasing viral load. It seems that vaccinated individuals who experience breakthrough infection with the Delta variant have as high a viral load as unvaccinated individuals, even though vaccinated individuals clear the infection more rapidly than unvaccinated individuals. Thus, it seems that the viral load declines more rapidly among vaccinated individuals than among unvaccinated individuals, and that the period during which you can transmit the infection is therefore shorter for vaccinated individuals.[108]

A retrospective cohort study from Singapore[109] has studied the attack rate (i.e. how many become infected) among household contacts to individuals who tested SARS-CoV-2 positive in the period from 1 September 2020 to 31 May 2021.

The household attack rate was calculated based on the prevalence of SARS-CoV-2 cases among household contacts. A total of 1,024 household contacts to 301 index individuals were included, i.e. individuals with a SARS-CoV-2-positive test result. Hereof, 753 household contacts were exposed to the Delta variant and 248 to other variants. Among household contacts who were exposed to the Delta variant, 70.4% were unvaccinated. All vaccinated individuals had received an mRNA vaccine.

A total of 15 cases of SARS-CoV-2 infection were recorded among primary vaccinated household contacts exposed to the Delta variant compared with 137 cases among unvaccinated household contacts. These findings correspond to a 25.8% (95% CI 20.6-31.5%) attack rate among unvaccinated household contacts - i.e. an unvaccinated household contact exposed to infection with the Delta variant has an approx. 25% probability of becoming infected compared with 11.3% (95% CI 6.1-17.3%) among vaccinated individuals. Furthermore, the attack rate for unvaccinated household contacts who had been exposed to the remaining virus variants was lower (12.9% (95% CI 7.0-20.0%)). If the household contacts who were exposed to the Delta variant had received primary vaccination,

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[106] Eyre et al. The impact of SARS-CoV-2 vaccination on Alpha & Delta variant transmission. medRxiv 2021. doi: https://doi.org/10.1101/2021.09.28.21264260

[107] Nordström P, Ballin M, Nordström A. Association Between Risk of COVID-19 Infection in Nonimmune Individuals and COVID-19 Immunity in Their Family Members. JAMA Intern Med. Published online 11 October 2021.

[108] Klompas M. Understanding Breakthrough Infections Following mRNA SARS-CoV-2 Vaccination. JAMA. Published online 4 November 2021.

[109] https://www.thelancet.com/journals/lanwpc/article/PIIS2666-6065(21)00208-X/fulltext

the odds of infection would have been 67% lower than those of unvaccinated household contacts (aOR 0.33, 95% CI 0.17-0.63). The risk of becoming infected in the household was thus markedly more limited if the household contact had been vaccinated.

Furthermore, the study found that the vaccination status of the index individual was insignificant in determining if the household contact was infected (aOR 0.73 (95%CI 0.38-1.40)), i.e. once the index individual becomes infected, his or her risk of transmitting the infection to another individual in the household is independent of this individual's vaccination status.

A retrospective cohort study from England[110] has also studied the attack rate among household contacts to individuals who tested SARS-CoV-2 positive in the period from 13 September 2020 to 15 September 2021. The study included a total of 231 household contacts to 162 index individuals who had tested positive to the Delta variant. The attack rate among household contacts exposed to infection with the Delta variant was 25% (95% CI: 18-33) for fully vaccinated individuals compared with 38 % (95% CI: 24-53) for unvaccinated individuals.

The attack rate among household contacts exposed to infection from a vaccinated index individual was comparable to that of household contacts exposed to infection from unvaccinated index individuals (25% (95% CI: 15-35) for vaccinated compared with 23% (95% CI: 15-31) for unvaccinated individuals).

Vaccinated individuals who experienced a breakthrough infection with the Delta variant had a maximal viral load comparable to that of unvaccinated individuals but recorded a faster decline in virus load than unvaccinated individuals.

The study thus found that vaccination reduces the risk of infection with the Delta variant and advances a decline in viral load, i.e. vaccinated individuals with breakthrough infection will presumably remain infectious for a shorter period of time. Even so, the study showed that vaccinated individuals with breakthrough infection have a maximal viral load comparable to that of unvaccinated individuals, and that vaccinated individuals with breakthrough infection may transmit infection to other individuals in the household, including to fully vaccinated individuals.

Theoretical herd immunity for the Delta variant

The theoretical concept of herd immunity is a form of indirect protection against infectious diseases that is achieved when a sufficiently large proportion of the population has gained immunity against an infection with an infectious disease so that the infection cannot be passed to the limited proportion of the population remaining non-immune. The immune proportion of the population may have achieved immunity through previous infection of by vaccination. The more infectious a disease is, the more individuals need to be immune to achieve herd immunity.

[110] Singanayagam A, Hakki S, Dunning J et al. Community transmission and viral load kinetics of the SARS-CoV-2 delta (B.1.617.2) variant in vaccinated and unvaccinated individuals in the UK: a prospective, longitudinal, cohort study. Lancet Inf Dis. Published 29 October 2021 DOI:https://doi.org/10.1016/S1473-3099(21)00648-4

Additionally, other factors such as the properties of the virus, including its ability to be transmitted between animals and humans, and its stability may have an impact on the possibility of ultimately reaching the theoretical herd immunity threshold and thereby achieving prolonged or even lifelong immunity as is the case for viruses like polio and smallpox. These viruses have been almost completely eradicated worldwide. This has been possible among others because polio virus and smallpox virus are very stable viruses characterised by a low degree of antigen drift. Furthermore, these viruses can survive only in humans. In contrast, SARS-CoV-2 and influenza are unstable viruses; both are capable of being transmitted between animals and humans and a need is observed to boost the induced immunity as is the case for seasonal influenza and the current COVID-19 booster vaccination programme.

Below we use the concept of herd immunity exclusively to illustrate a theoretical level at which we may - in the current Danish context in which the Delta variant is the vastly dominant variant - expect to reach a level of population immunity that is sufficiently high to approach the theoretical threshold level for herd immunity.

As described in the Danish Health Authority's memo *On vaccination of children aged 12-15 years*, despite the current COVID-19 vaccination offer for everyone aged 12 years or more and a continuous offer of COVID-19 booster vaccination, some individuals in the Danish population will not achieve the expected immunity, either due to a weakening of their immune system with increasing age or due to medical reasons, i.e. various levels of immune deficiency. Additionally, we know that the induced immunity following primary vaccination declines gradually with time and that the decline may be considerable after a period of six months. Therefore, some individuals may have an increased risk of SARS-CoV-2 infection and, in the worst-case scenario, of falling seriously ill due to COVID-19 because they have opted out of booster vaccination or due to waning immunity in the interval separating primary vaccination from booster vaccination. Finally, in some situations it may not be possible to administer the vaccine correctly, or a vaccinated individual who achieves immunity may fall ill anyway because the vaccine is not 100% effective. At a high level of population immunity, individuals whose immunity is reduced or lacking for the above-mentioned reasons will achieve protection because they will not encounter as many infection carriers, whereby infectious chains may be broken.

A high level of immunity in the population is achieved through broad vaccination efforts in the population. Ultimately, the objective of the COVID-19 vaccination programme is to achieve a population immunity that is sufficiently high to curb the epidemic. Just how high the vaccination coverage needs to be to curb the epidemic depends, among others, on how infectious the disease in question is, the vaccines' effect in relation to prevention of spreading of the infection, the duration of immunity, etc. The share of the population that has already achieved immunity following infection also contributes to the total immunity.

A frequently used approach to describing how infectious is a condition like COVID-19 is to use the "basic reproductive number", coined R_0[111,112] (R naught). R_0 describes the average number of individuals to whom an infected individual will transmit the disease in a population where no one has come into contact with the infection and everyone is therefore fully susceptible to infection. Thus, R_0 is a theoretical number that describes the potential for spreading of the infection. R_0 is typically estimated based on mathematical models.
R_0 for the Delta variant is estimated to be approx. 6 (6.4 (95% CI: 3.7- 9.3)), compared with an estimated R_0 of nearly three for the original Wuhan variant.[113,114] An individual who has become infected with the original Wuhan variant will therefore, on average, infect three individuals each of whom will, in turn, infect another three individuals. Thus, after two rounds, a total of nine individuals will have been infected (3 x 3 = 9) and after three rounds, the number of infected individuals will be 27 (3 x 3 x 3 = 27). For comparison, after two rounds of infection with the Delta variant, a total of 36 individuals will have been infected (6 x 6 = 36), and 216 individuals will have become after three rounds (6 x 6 x 6 = 216). As described above, this applies in a population where no one has been vaccinated and no other measures have been implemented to prevent infection.

Based on knowledge about R_0, it is possible to calculate an estimate for just how high the vaccination coverage in a population needs to be to reach the theoretical level of herd immunity. This threshold value may be estimated by using the formula $1 - 1/R_0$[115].

Because of the many reservations and assumptions associated with calculating R_0 and herd immunity, these estimates are typically calculated using complex mathematical models. We therefore need to stress that the below calculations come with a number of uncertainties.

For more information about the reservations associated with the calculation of theoretical R_0 estimates and additional information about the effective reproductive number R_e, please see the Danish Health Authority's *Memo concerning vaccination of children aged 12-15 years*.

Estimates for R_0 and herd immunity for the Delta variant.
Herd immunity may, as described above, be calculated as $1- 1/R_0$. Below, in Table 6, we present a theoretical estimate of the threshold level for expected herd immunity in the current Danish epidemic along with estimates from susceptibility analyses (presented in parentheses) where the Delta

[111] Randolph HE, Barreiro LB. Herd Immunity: Understanding COVID-19. Immunity. 2020 May 19;52(5):737- 741.

[112] Anderson, R., May, R. Vaccination and herd immunity to infectious diseases. Nature 318, 323–329 (1985).

[113] Kang M, Hualei X, Yuan J et al. Transmission dynamics and epidemiological characteristics of Delta variant infections in China. [pre-print] medRxiv 13 August 2021. doi: https://doi.org/10.1101/2021.08.12.21261991

[114] Liu Y, Rocklöv J. The reproductive number of the Delta variant of SARS-CoV-2 is far higher compared to the ancestral SARS-CoV-2 virus. J Travel Med. 2021;28(7):taab124.

[115] Fine P, Eames K, Heymann DL. "Herd Immunity": A Rough Guide. Clin Infect Dis. 2011 Apr 1;52(7):911-6.

variant is assumed to be more or less infectious. Based on various studies, R_0 for the Delta variant is assumed to be approx. 6 (6.4 (95% CI: 3.7- 9.3).[116,117]

Table 6: Theoretical herd immunity threshold (Delta variant)

Virus variant	R_0	Estimated theoretical herd immunity threshold, %
Delta variant	6.4 (3.7- 9.3)	84% (73-89)

As shown in Table 6, it is estimated that the theoretical threshold level for herd immunity in the current Danish epidemic where the Delta variant is vastly dominant is approx. 84%, ranging from 73-89% depending on how the infectiousness of the Delta variant is estimated.
For comparison, an Australian modelling study estimated that 60-70% immunity was needed in the population to control the original Wuhan variant, but because the Delta variant is more infectious (the reproductive number was estimated to be 5), an 85% vaccination coverage in the entire Australian population is needed to achieve herd immunity and thereby achieve a receding epidemic.[118]

Population immunity

In the current Danish context, increased population immunity may be achieved in the following four ways: 1) by targeted attempts to increase primary vaccination coverage in the population, 2) by extending primary vaccination to larger proportions of the population, e.g., by including 5-11-year-olds, 3) by booster vaccination to maintain the effect of primary vaccination efforts or 4) by combining measures 1, 2 and 3.

Thus, the below calculations illustrate an approximate level for the current herd immunity as per 1 December 2021 and show to which extent children aged 5-11 years contribute to the total immunity via acquired SARS-CoV-2 and owing to the COVID-19 vaccination offer.

Calculations for estimated immunity in the population

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 completed vaccination and 1,34 million will likely have been invited for booster vaccination, among whom 85% are expected to accept the offer.

[116] Kang M, Hualei X, Yuan J et al. Transmission dynamics and epidemiological characteristics of Delta variant infections in China. [pre-print] medRxiv 13 August 2021. doi: https://doi.org/10.1101/2021.08.12.21261991

[117] Liu Y, Rocklöv J. The reproductive number of the Delta variant of SARS-CoV-2 is far higher compared to the ancestral SARS-CoV-2 virus. J Travel Med. 2021;28(7):taab124.

[118] McBryde ES, Meehan MT, Caldwell JM et al. Modelling direct and herd protection effects of vaccination against the SARS-CoV-2 Delta variant in Australia. Med J Aust. 2021 Nov. 1;215(9):427-432.

The below calculations were performed to illustrate what may be achieved by focusing on population immunity achieved through primary vaccination and 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 for population immunity calculations

The estimates for the expected population immunity as per 1 December 2021 are presented below in Table 7 and based on a range of assumptions described in the Danish Health Authority's memo *Concerning booster vaccination of individuals aged 18 years and older*[119]. For more information about the assumptions upon which the calculations on immunity in the population are based, please see this memo.

In the below table, one additional assumption is made about acquired immunity, which is different from the memo *Concerning booster vaccination of individuals aged more than 18 years*, as children aged 5-11 years were not included in the total amount of acquired immunity because this age group's contribution to immunity is calculated separately in Table 8. Thus, this memo employs an overall estimate of how many children in the age interval 0-4 years and how many unvaccinated children and adults aged 12 years and older have acquired immunity following a previous SARS-CoV-2 infection. The estimate for acquired immunity among the unvaccinated proportion of the population was adjusted upwards after the calculations of immunity in the population published in the Danish Health Authority's memo of 28 September *Concerning COVID-19 booster vaccination.* In this memo, Statens Serum Institut's reports on seroprevalence formed the basis of an 8.6% estimate. Subsequently, transmission in the population has followed an increasing trend, including among unvaccinated children. Consequently, the estimate of acquired immunity in the population was adjusted upwards to 15% in the current calculations.

Estimates concerning population immunity

Based on the above assumptions and assumptions from the Danish Health Authority's memo *Concerning booster vaccination of individuals aged 18 years and older*, the expected immunity around 1 December 2021 may be calculated.

Table 7 shows that approx. 5.1 million individuals (approx. 88% of the total population) have been offered COVID-19 vaccination, among whom 5% of the part of the population that has received primary vaccination will have achieved only an insufficient effect of their vaccination. The overall population immunity as per 1 December 2021 may be expected to reach approx. 63.5% (Table 7). This estimate assumes an overall vaccine effectiveness with respect to prevention of infection spreading immediately after the primary and booster vaccination of 85.5%, an estimated total decline in population immunity due to time passed since vaccination of approx. 4% as per 1 December 2021 (as described in memo *Concerning Booster vaccination of individuals aged 18 years and older*) and, finally, an acquired immunity among the unvaccinated population of approx. 15%.

[119] https://www.sst.dk/da/Udgivelser/2021/Revaccination-af-personer-over-18-aar

Table 7: Estimated population immunity as per 1 December 2021, not counting the contribution from the 5-11-year-olds

Population offered vaccination, % (n)	**Total population share with induced immunity following primary vaccination at an expected maximum 90% coverage, % (n)** (n)	**Total population share 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, cf. assumptions (weighted average)**	**Effectiveness with respect to prevention of transmission following decline over time, %**	**Overall induced population immunity following primary vaccination and booster vaccination in the population, % (n)**	**Acquired immunity among unvaccinated adults and 0-4-year-olds** (n)	**Overall population immunity (not counting the contribution from the 5-11-year-olds), %**
88% (5,104,000)	79% (4,593,600)	75% (4,363,920)	85.5% (84.9 – 86.1) (Delta variant)	Total decline including booster vaccination (weighted average) = ~ 3.9% in the population*	~ 81.6%	~ 61.4% (3,560,959)	123,116**	~ 63.5

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

**Calculated based on data from Statistics Denmark (https://www.dst.dk/da/Statistik/emner/borgere/befolkning/befolkningstal): 15% of the 0-4-year-olds (46,616) + 15% of unvaccinated individuals aged 12 years or older (76,500) = 123,116.

Assumptions concerning the contribution from children aged 5-11 years

The calculations concerning the contribution of 5-11-year-olds to the total immunity in the population are based on a population of 5-11-year-olds of approx. 431,000 according to data from Statistics Denmark[120].

To illustrate how much acquired versus induced immunity in the 5-11-year age group may be expected to contribute to the total immunity in the population, we have taken as our starting point a range of scenarios for acquired immunity following SARS-CoV-2 infection and COVID-19 vaccination coverage in the age group. This is supplemented by susceptibility analyses comprising best- and worst-case scenarios to illustrate scenarios in which the children's contribution to the total immunity fall in the high and low extreme of the expected range.

As described in the above section on the current state of the Danish epidemic, we expect a proportion of undiagnosed cases to exist among children in particular, i.e. children who have become infected with SARS-CoV-2 without testing positive. In the period leading up to July 2021, the SSI studied the occurrence of SARS-CoV-2 antibodies among randomly selected unvaccinated individuals down to 12 years of age and found that approx. 7% of the 12-19-year-olds had SARS-CoV-2 antibodies. Even so, since July 2021, a considerable increase has occurred in the SARS-CoV-2 case number recorded in the age group. For comparison, antibodies were found in approx. 28% of 0-11-year-olds in Sweden, where fewer restrictions have been in place throughout the epidemic and where a higher infectious pressure has been observed. To take into account the proportion of undiagnosed children in the population, the calculations employ a range for acquired immunity to SARS-CoV-2 among children aged 5-11 years of 10-30%, as described in previous sections on pages 19-20, and where 30% of acquired immunity among children was considered a high estimate.

Based on knowledge about the COVID-19 vaccination coverage in the 12-15-year age group and expectations to parental acceptance of a vaccination offer for 5-11-year-olds, the calculations employ a vaccination coverage range for primary vaccination in the age group 5-11-years of 50-90%. In this range, 50% may be considered a worst-case scenario based on HOPE's upcoming report[121] in which 57% of the parents asked stated that they would have their 6-9-year-old children receive COVID-19 vaccination. Similarly, 90% may be considered a best-case scenario in which the expected overall vaccination coverage corresponds to that of the primary vaccination programme.

For good reason, the vaccines' effectiveness in preventing spreading of the infection among children has yet to be established. As a proxy for vaccine effectiveness with respect to preventing spreading of the infection among children aged 5-11 years, we use the vaccine effectiveness estimate for prevention of SARS-CoV-2 infection recorded in the authorisation study, where supplementary descriptive data were used to calculate an effect of COVID-19 vaccination among 5-11-

[120] Population figures - Statistics Denmark (dst.dk)

[121] Danish parents are willing to have their children vaccinated against Corona virus [Danske forældre er villige til at lade børn vaccinere mod corona] - politiken.dk

year-olds of 90.7%. This effect estimate is, however, not the primary outcome in the study, and the primary objective of the study was not to establish effect among 5-11-year-olds. In contrast, the study has demonstrated that vaccination produced antibody increases on a par with those of vaccinated adults; moreover, owing to the design used in the study, it is possible to extrapolate expectations to the effect from adults to children. Among adults, an effect of approx. 95% was recorded. The observed effect of 90.7% among 5-11-year-olds may therefore be considered a conservative estimate, and it should be considered that these analyses were supplementary analyses that the authorisation study was not designed to underpin.

Table 8: 5-11-year-old children's estimated contribution to population immunity based on assumptions about acquired immunity and COVID-19 vaccination coverage.

	Population	**Scenarios for 5-11-year-old children's contribution to the population immunity, via acquired and induced immunity** *Including susceptibility analyses for coverage and estimates for acquired immunity*	**Expected vaccine effectiveness immediately after primary vaccination among children aged 5-11 years, %**	**Immunity among children aged 5-11 years**	**Overall immunity in the population (not including the contribution of the 5-11-year-olds) cf. Table 7**	**Total population immunity, %**
The 5-11-year-old children's contribution to population immunity *With respect to acquired and induced immunity*	431,256	**Acquired immunity**	-	**Acquired immunity**	63.5	**Acquired immunity**
		15%, corresponding to a population = 64,688		15%, corresponding to a population = 64,688		64.6
		10%, corresponding to a population = 43,126		10%, corresponding to a population = 43,126		64.2
		30%, corresponding to a population = 129,377		30%, corresponding to a population = 129,377		65.7
		Induced immunity	90.7%	**Induced immunity**		**Induced immunity**
		90%, corresponding to a population = 388,130		82%, corresponding to a population = 353,630		69.6
		70%, corresponding to a population = 301,879				68.2

				63%, corresponding to a population = 273,804		
		50%, corresponding to a population = 215,628		45%, corresponding to a population = 195,575		66.9

Estimates based on assumptions concerning the contribution of 5-11-year-old children to the population immunity

The above estimates illustrate different scenarios for the 5-11-year-old children's contribution to the total population immunity.

In a situation in which we chose to extend the COVID-19 vaccination target group to include the 5-11-year-olds, the induced immunity in the population will increase. The 5-11-year-olds constitute approx. 431,000 individuals, corresponding to approx. 7.4% of the total population.

Assuming a 70% vaccination coverage among children aged 5-11 years, corresponding to a population of approx. 300,000 and a vaccine effectiveness of approx. 90.7%, this corresponds to 273,804 children in the age group (approx. 63%) achieving immunity to SARS-CoV-2. At population level, this will increase the total population immunity by approx. 5 percentage points (from 63.5 to 68.2). If we furthermore assume that 15% of children aged 5-11 years have achieved acquired immunity before the vaccination campaign, corresponding to 64,688 children, vaccination of the age group will contribute with an additional 3.5-4 percentage points (from 64.6 to 68.2) to the total population immunity, assuming that all children with acquired immunity are among the 70% who are vaccinated.

Overall, expanding the vaccination target group to also include 5-11-year-olds will contribute 1.2-5.4 percentage points to total population immunity, depending on the vaccination coverage in the age group and how large a share is assumed to have acquired vaccination ahead of vaccination (see Table 8).

Overall assessment

As described above, an increased population immunity may be achieved by increasing the coverage for primary vaccination in the population, by booster vaccination to maintain the vaccine effectiveness owing to primary vaccination or by a combination of these measures.

In principle, increased immunity may also be achieved through a higher level of acquired immunity, but this is not assessed to be a possible or responsible strategy during the COVID-19 pandemic. This will not only cause increased morbidity in the groups that have not received vaccination but will also produce a risk of infection of individuals who have been vaccinated and are at an increased risk of serious COVID-19; according to ENFORCE, which found that approx.. 5% of the vaccinated individuals are so-called low responders, i.e. individuals who fail to produce a solid immune response following vaccination.

Under the current primary vaccination programme, it is unlikely that vaccine-induced herd immunity may be achieved in the population (as shown in Table 6). Approx. 88% of the population is currently being offered vaccination. We are very close to achieving 90% coverage of the primary vaccination programme, which is an extremely high level 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. We therefore do not expect the coverage to rise much

above 90%, even if structural measures are also employed in the future, e.g., informer corps, proactive vaccination offers in areas or groups recording a low coverage, etc.

Furthermore, a high proportion of booster vaccination is required among the population groups who are assessed to experience a significant decline in induced immunity to ensure that the immunity achieved through primary vaccination may be maintained. The Danish Health Authority expects that the coverage of the booster vaccination programme will be high and close to the level observed for the primary vaccination programme among 65+-year-olds, whereas the coverage among younger age groups is expected to be lower.

By expanding the target group offered COVID-19 vaccination to include 5-11-year-old children, we estimate that the immunity in the population may be increased by an additional 1.2-5-4 percentage points, depending on how large the acquired immunity in the age group is assumed to be. Thus, calculations indicate that by vaccinating the 5-11-year-olds, we may increase the level of immunity in the population additionally. The calculations specifying how much vaccination of children aged 5-11 years contributes to the total immunity come with the implicit assumption that all parents to children with a previous SARS-CoV-2-acquired infection opts into vaccination (as the contribution from children with acquired immunity is subtracted from the contribution from children who are vaccinated). It may be expected that some parents to children who have acquired immunity do not feel a similar need to have their child vaccinated. The group of children with acquired immunity should therefore be assumed to comprise a proportion of those who opt out of vaccination. To achieve a more correct image of how much 5-11-year-olds contribute to the total level of immunity, one should therefore deduct a smaller proportion of children with acquired immunity than was done in the calculations above. On this basis, we assess that the contribution to the total immunity level achieved by vaccinating children aged 5-11-years may be expected to fall in the high end of the range 1.2-5.4.

The percentage point contribution is on a par with that calculated for the group of 12-15-year-olds in the memo of 17 June 2021, *Concerning COVID-19 vaccination of children aged 12-15 years* [Vedr. vaccination af børn på 12-15 år mod COVID-19]. Furthermore, the calculations indicate that the 5-11-year-olds' contribution alone will not allow us to reach the theoretical threshold level for herd immunity.

However, the estimates should be interpreted with caution. Primarily, it is important to stress that the figures presented in Tables 6, 7 and 8 are rough estimates based on a series of assumptions and prepared without the use of mathematical modelling, why they must be interpreted with caution.

The calculations in this memo are thus simple estimates that may be used to obtain an indication of how large a population immunity we may achieve by extending the population offered vaccination to include the 5-11-year-olds. The calculations do not include assumptions about

differences in the contact patterns of the different age groups, about behaviour to prevent infection or about so-called pockets in society, e.g. groups of unvaccinated individuals among whom the virus may continue to circulate and where vaccination - all else being equal - may be expected to contribute more to the overall immunity by breaking infectious chains.

Despite booster vaccination of a proportion of the population, the above estimate of total population immunity (without the contribution from the 5-11-year-olds) of approx. 63.5% is lower than the population immunity estimated in memo of 28 September 2021 entitled *Concerning COVID-19 booster vaccination [Vedr. revaccination mod COVID-19]*, in which population immunity was estimated to 66%. This was to be expected as for a large proportion of the population, more time has passed since primary vaccination. Thus, until a larger share of the population has received booster vaccination and the effect of booster vaccination gains foothold, we may expect that estimations of the level of immunity in the population will be slightly lower. Furthermore, it deserves mention that the contribution of the 5-11-year-olds to the total immunity owing to acquired immunity is calculated separately in Table 8, why the total population immunity estimate is likely somewhat underestimated. According to Table 8 below, owing to acquired immunity the contribution of this age group is estimated to fall in the range from 0.7 to 2.2 percentage points, assuming that 10-30% of the age group has acquired immunity to SARS-CoV-2.

In the calculations, the vaccine effectiveness for infection with the Delta variant was used as a proxy for effectiveness in relation to prevention of infection spreading. This is considered reasonable because several studies have shown that vaccination reduces the risk of transmitting infection to others, among others because vaccinated individuals have a considerably lower risk of infection and experiencing symptoms than unvaccinated individuals. Even though there are indications that the protection against transmitting infection is lower for the Delta variant, and that the viral load of vaccinated individuals who have breakthrough infection is as high as that of unvaccinated individuals, vaccination should very much be expected to contribute to protecting against transmitting the infection by breaking infectious chains. Additionally (according to the above literature review), studies show that even if a vaccinated individual does experience breakthrough infection, the viral load declines more rapidly than among unvaccinated individuals, and therefore the period during which he or she may transmit the infection is shorter than is the case for vaccinated individuals.

Finally, it deserves mention that the vaccine effectiveness estimate for infection with the Delta variant is based on data from the continuous vaccine effectiveness monitoring of Statens Serum Institut. Therefore, the estimate constantly changes and has done so in the past. Reservations associated with the Statens Serum Institut vaccine effectiveness calculations are presented in the above section.

Knowledge from modelling studies about immunity

Several modelling studies have attempted to calculate the optimal vaccination strategy for COVID-19. One study found that provided all age groups were equally susceptible to infection (i.e. that children and young individuals had as large a risk of becoming infected as adults), vaccination of individuals below 20 years of age yielded a larger reduction of infection than vaccination of individuals aged 20-49 years.[122] The authors found that the greatest possible reduction in deaths would be achieved if individuals aged 60 years or older were prioritised for vaccination early in the course of the pandemic, but that prioritising the vaccination of younger individuals later in the course of the pandemic would yield the greatest effect with respect to reducing infection. The authors assumed (based on early epidemic data) that SARS-CoV-2 was less infectious among children, why models showed that vaccinating 20-49-year-olds was more effective. But if they assumed that the risk of infection for children was as large as that of adults, they found that vaccination of children and young individuals < 20 years would have the greatest effect in relation to reducing infection and preventing deaths.

A modelling group counting researchers from a range of American universities estimated that COVID-19 vaccination of 5-11-year-olds would reduce the cumulative incidence of SARS-CoV-2 infections by approx. 8% in the period from November 2021 to March 2022.[123]

In connection with the health technology assessment of influenza vaccination while modelling various vaccination scenarios, researchers found that the total number of influenza cases in the population will decline by 48.6% following vaccination of children aged 2-6 years. The models are based, among others, on knowledge about contact patterns for the population in the time before the COVID-19 pandemic, a vaccination coverage in the population that is considerably lower for COVID-19 and a vaccine effectiveness that was considerably lower than the mRNA vaccines' coverage against the Delta variant.

Mathematical modelling

Statens Serum Institut has calculated how much new hospitalisations may be prevented if the 5-11-year-olds are vaccinated. The model calculations include simulations in which the epidemic is carried forward to late January and late February 2022, based on various assumptions of coverage to the vaccination programme among the 5-11-year-olds. The objective of the scenarios was to estimate the relative reduction in new hospitalisations in all age groups that may be achieved by vaccinating the 5-11-year age group. The objective is not to estimate the number of new hospital admissions or infected individuals in the period.

Calculations were made for three coverage scenarios: 0% (i.e. that vaccination of 5-11-year-olds is not initiated), 40% of the 5-11-year-olds are vaccinated and 80% of the 5-11-year-olds are vaccinated. It was assumed that vaccination roll-out will be initiated in week 48 when the 10-11-year-olds are offered vaccination. Subsequently, the assumption is that the 8-9-year-

[122] Bubar KM, Reinholt K, Kissler SM, Lipsitch M, Cobey S, Grad YH, Larremore DB. Model-informed COVID-19 vaccine prioritisation strategies by age and serostatus. Science. 2021 Feb 26;371(6532):916-921.

[123] COVID-19 Scenario Modeling Hub: https://covid19scenariomodelinghub.org/viz.html

olds are vaccinated in week 49 and the remaining in week 50, meaning that all children in the age group are offered their first vaccination shot before Christmas. With respect to the roll-out, we assumed that the second dose is given 21 days after the first dose, and that everyone who opts in within the relevant age group is vaccinated in the week they are offered vaccination. Finally, it was assumed that the vaccine effectiveness against infection starts at 95% among the 5-19-year-olds, whereas individuals aged 19 years or older have a vaccine effectiveness against infection in the models starting at 80-95%. The model calculations use two different estimates for waning immunity against infection of 30% and 50% in the course of the six-month period and in all age groups. In the model, vaccine effectiveness against serious illness and hospitalisation is assumed to decline by 9% in the course of six months for all age groups. Various additional assumptions are described in Statens Serum Institut's memo *Modelling of reduction in new hospitalisations following vaccination of children aged 5-11 years of age* [Modellering af reduktion i nyindlæggelser ved vaccination af børn i alderen 5-11 år].

The model calculations show that vaccination roll-out for children aged 5-11 years from 1 December may reduce the total number of new hospitalisations due to COVID-19 as from early January. The scope of the reduction of new hospitalisations is estimated to fall in the range 11-31% by the end of January and 24-64% at the end of February, depending on the coverage achieved in the age groups (40% versus 80%). Calculations carry some uncertainty, particularly in relation to waning vaccine effect and social activity, and because the simulations extend several months into the future.

Table 9: Range of relative new hospitalisations as per 31 January and 27 February in the different vaccination scenarios.

Relative reduction in new hospitalisations		
Scenario	**31 January 2022**	**27 February 2022**
Scenario with 40% coverage	11-19%	24-47%
Scenario with 80% coverage	19-31%	37-64%

To illustrate, this means that in a situation with 80 daily COVID-19-related hospitalisations (corresponding to the current daily number of new hospitalisations) from 1 January 2022 to 28 February 2022, it would be possible to prevent an average 8-24 daily hospitalisations as from 31 January 2022, depending on the vaccination coverage. The daily relative reduction in the number of new hospitalisations is higher, but also more uncertain when we reach 27 February 2022.

The full effect of vaccination of the 5-11-year-olds will not be achieved until February as the transmission of infection from children to elderly individuals who have the highest risk of hospitalisation must first be reduced.

Safety

The authorisation study for Comirnaty® for 5-11-year-olds has a safety profile that is very similar to the known safety profile of Comirnaty® for use in individuals aged 12 years or more. The reactogenicity following vaccination of the 5-11-year-olds is comparable to the reactogenicity following vaccination of 16-25-year-olds.

Very common (occurs in ≥1/10 individuals), common (occurs in ≥1/100-<1/10 individuals), not common (occurs in ≥1/1,000-<1/100 individuals) and, in part, rare (occurs in ≥1/10,000-<1/1,000 individuals) side effects may be expected to have been characterised in the authorisation study, which included 3,109 children aged 5-11 years. But very rare side effects (occurring in <1/10,000 individuals) cannot be expected to have been identified in the authorisation study. At a 10 microgram dose, a frequency of local and systemic side-effects was seen among 5-11-year-old children comparable to that of young and adults receiving 30 micrograms.

The Comirnaty® summary of product characteristics describes rare side effects in the form of anaphylaxis, acute peripheral facial paralysis (Bell's palsy), erythema multiforme, swelling of the vaccinated arm, facial swelling and myocarditis/pericarditis[124]. This is based primarily on experience from the vaccines in individuals aged 12 years or more. These rare side effects have not been observed in the study comprising children aged 5-11-years. It cannot be determined with certainty to which degree the expectations for rare side effects may be extrapolated from individuals aged 12 years or more to children aged 5-11 years. Even so, we expect that a risk will exist for the same rare side effects.

Myocarditis, pericarditis and myopericarditis following vaccination

According to the summary of product characteristics of both Comirnaty® and Spikevax®, myocarditis and pericarditis are known side effects associated with the use of these vaccines. This observation is based on spontaneous notifications and it has not been possible to estimate an exact frequency, but these side effects are very rare. Additionally, myocarditis and pericarditis typically run a mild disease course and recede spontaneously. If treatment is needed, the treatment options are good.[125] The side effects committee of the EMA, the PRAC, is currently assessing additional data on myocarditis and pericarditis in connection with both Comirnaty® and Spikevax® to qualify the safety assessment[126]. Among others, the EMA has instructed the manufacturers to analyse all published data on the association between myocarditis and pericarditis. A Nordic register study, which has not yet been published, forms part of the EMA's assessment. Data from the Nordic countries contribute no information about 5-11-year-olds as

[124]EMA, Summary of Product Characteristics Comirnaty® 5-11-year-olds. Accessed 25 November 2021.https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf

[125]The Danish Health Authority, Guideline on the handling of COVID-19 vaccination in the general vaccination programme [Retningslinje for håndtering af vaccination mod COVID-19 i det generelle vaccinationsprogram]

[126] EMA PRAC meeting highlights 25-28 October 2021. https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-25-28-october-2021

children in this age group have not yet received COVID-19 vaccination in the Nordic countries.

As per 19 November 2021, the Danish Medicines Agency had received seven notifications about myocarditis as a presumed side effect following COVID-19 vaccination of 12-15-year-olds. When the data were analysed, (19 November 2021), a total of approx. 175,000 children aged 12-15 years had completed primary vaccination with two doses of COVID-19 vaccine. For approx. 163,000 of these children, a minimum of four weeks had passed since they received their second vaccination shot. Generally, the disease courses have been mild and the affected children have recovered.

In a study of spontaneously reported cases of myocarditis and pericarditis forming part of the pharmacovigilance of the mRNA vaccines in Great Britain, the EMA and the FDA compare notifications across pharmaceutical authorities. Data include all age groups. From use of the COVID-19 vaccines was initiated to 21 October 2021, three pharmaceutical authorities have recorded a total of 5,295 reported cases of myocarditis and 3,453 reported cases of pericarditis. A total of 73.3% and 75.9% of the reported cases concerning myocarditis and pericarditis, respectively, occurred following vaccination with Comirnaty®. A higher occurrence of myocarditis and pericarditis was seen among younger adults than among older adults, and most cases were recorded in individuals < 40 years of age. The occurrence was higher among men than among women, particularly the occurrence of myocarditis. A total of 74.9% of all reports of myocarditis concerned vaccination of men, whereas a total of 56.9% of all reports of pericarditis concerned vaccination of men. Most reports were observed following the second dose of mRNA vaccine. A limited number of reported cases were fatal, but the vast majority were mild clinical courses from which the patients recovered completely.

Considering data divided by pharmaceutical authority, it is possible to estimate frequencies, but an unknown number of unknown cases may exist as the observations are based on spontaneous notifications. In Great Britain at the time data were analysed, a total of approx. 23.2 million first doses of Comirnaty® and 20.1 million second doses of Comirnaty® had been administered. Following vaccination with Comirnaty®, a total of 350 cases of myocarditis and 274 cases of pericarditis were recorded. This corresponds to a rate of approx. 15.09 cases of myocarditis per 1,000,000 after a minimum of one vaccination and 11.81 cases of pericarditis per 1,000,000 after a minimum of one vaccination with Comirnaty®. Furthermore, 85 reports of myocarditis and 53 reports of pericarditis were made based on a total of 1.5 million first doses of Spikevax® and 1.3 million second doses of Spikevax®. This corresponds to a rate of approx. 56.67 cases of myocarditis and 40.77 cases of pericarditis per 1,000,000 vaccinated individuals. Corresponding rates were calculated for the US. Here, the estimated rate among fully vaccinated individuals was 12.52 cases of myocarditis per 1,000,000 and 7.78 cases of pericarditis per 1,000,000 after Comirnaty®, and 8.92 cases of myocarditis per 1,000,000 and 6.51 cases of pericarditis per 1,000,000 following Spikevax®. Finally, the rate was also estimated among EMA reports. Here, the estimated rate among fully vaccinated individuals who had received a minimum of one vaccination was 8.30 cases of myocarditis per 1,000,000 and

5.72 cases of pericarditis per 1,000,000 after Comirnaty®, and 17.62 cases of myocarditis per 1,000,000 and 8.15 cases of pericarditis per 1,000,000 following Spikevax®[127].

Myocarditis and the related condition pericarditis are both conditions that occur at a certain incidence in the background population. The background risk of developing myo- or pericarditis is lower among children than among young individuals and adults. Statens Serum Institut has announced that in the 2015-2019 period in Denmark, the median age was 43 years (interquartile range 25-63 years) for cases developing myocarditis and 48 years (interquartile range 32-64 years) for cases developing pericarditis for individuals aged ≥ 12 years.

On 6 October 2021, the Danish Health Authority announced that children and young people under 18 years of age will continue to receive vaccination with Comirnaty®. On 4 November 2021, the CDC made the same decision to recommend Comirnaty® for individuals below 18 years of age[128]. The Danish Health Authority will follow the EMA assessment concerning the risk of myocarditis among children and young people under 18 years of age following vaccination with Spikevax® when it becomes available[129].

MIS-C after vaccination

The disease process behind MIS-C remains unknown, and we therefore also do not know if MIS-C may occur following COVID-19 vaccination. MIS-C has not previously been described in connection with other vaccines.[130]

On 29 October 2021, the EMA's side effects committee, the PRAC, announced that no documentation has been established for an association between COVID-19 vaccination and MIS[131]. The Committee studied a possible association between COVID-19 vaccination and the MIC condition after the Danish Medicines Agency in August informed the EMA of a MIS-C case in a 17-year-old boy. Following treatment, the 17-year-old boy has recovered. On this basis, the PRAC decided to raise a flag calling for a study of the possible association between MIS and COVID-19 vaccination. On 29 October 2021, the PRAC announced that the documentation in support of an association was insufficient.[132]

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[127] Lane S. Reports of myocarditis and pericarditis following mRNA COVID-19 vaccines: A systematic review of spontaneously reported data from the UK, Europa, and the US and of the literature. Preprint. MedRxiv 12 November 2021. https://www.medrxiv.org/content/10.1101/2021.09.09.21263342v2

[128] CDC. COVID-19 vaccines for children and teens. 4 November 2021. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/children-teens.html

[129] News item, 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

[130] 7 Vogel TP, Top KA, Karatzios C, et al. Multisystem inflammatory syndrome in children and adults (MISC/A): Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2021;39(22):3037-3049.

[131] Press release, Danish Medicines Agency 29 Oct 2021: https://laegemiddelstyrelsen.dk/da/nyheder/2021/ema-ikke-tilstraekkelig-dokumentation-for-en-sammenhaeng-mellem-covid-19-vacciner-og-betaendelsestilstanden-mis-/

[132] EMA press release, 29 Oct 2021: https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-25-28-october-2021

Anaphylaxis

Anaphylaxis is an acute allergic reaction to, e.g., medicinal products (including vaccines), insect venom or foods to which you are allergic. The symptoms may vary from mild local reactions (e.g., severe swelling at the injection site, itching of the skin, etc.) to severe reactions that may involve all organ systems and produce a life-threatening condition of shock (anaphylactic shock). Anaphylaxis is a rare condition seen in a total of approx. three in 100,000 inhabitants per year, corresponding to approx. 150 annual Danish cases[133]. If anaphylaxis is treated timely, the symptoms typically recede leaving no late sequelae.

Since the initiation of COVID-19 vaccination, the Danish Medicines Agency has closely monitored notifications of side effects following vaccination. The Danish Medicines Agency data basis gives no reason to suspect that strong allergic reactions, including anaphylactic reactions, occur more frequently than expected due to vaccination with Comirnaty®[134].
An American register study found no differences in the occurrence of anaphylaxis across age groups following vaccination with various common vaccines[135]. No separate data are available on anaphylaxis in children who have been vaccinated with COVID-19 vaccines. Therefore, we do not know if their risk is higher, comparable or lower than that of adults. Even so, it seems reasonable to assume that 12-15-year-olds will be the group that is most similar to the 5-11-year-olds. In the European Public Assessment Report (EPAR) on Comirnaty® for use in 12-15-year-olds, two cases of anaphylaxis are described among the vaccinated individuals[136]. Both cases arose after unblinding of the study among study participants who originally received placebo, but who were subsequently offered vaccination. Both cases of anaphylaxis occurred three days after vaccination. One of the study participants had turned 16 years old at the time of vaccination with Comirnaty®.

In Denmark, COVID-19 vaccination of 12-15-year-olds was initiated on 14 April 2021[137]. At present (24 November 2021), approx. 196,000 children aged 12-15 years have received a minimum of one COVID-19 vaccination short and 177,000 have also received their second shot[138]. The overwhelming majority of the group was vaccinated with Comirnaty® as this was

[133] Lægehåndbogen. Updated 19 April 2021. https://www.sundhed.dk/sundhedsfaglig/laegehaandbogen/akut-og-foerstehjaelp/tilstande-og-sygdomme/hjerte-kar/anafylaksi/

[134] Danish Medicines Agency Overview of side effects notified to COVID-19 vaccines. Accessed 24 November 2021. https://laegemiddelstyrelsen.dk/da/nyheder/temaer/Indberettede%20bivirkninger%20ved%20COVID-19%20vacciner/

[135] McNeil MM et al. Risk of anaphylaxis after vaccination in children and adults. J Allergy Clin Immunol. 2016;137(3):868-878. https://pubmed.ncbi.nlm.nih.gov/26452420/

[136] EPAR Comirnaty®, authorisation for use in 12-15-year-olds. 22 July 2021. https://www.ema.europa.eu/en/documents/variation-report/comirnaty-h-c-5735-ii-0030-epar-assessment-report-variation_en.pdf

[137]Danish Health Authority. News item 14 July 2021. https://www.sst.dk/da/Nyheder/2021/I-dag-bliver-alle-boern-i-alderen-12-15-aar-inviteret-til-vaccination-mod-COVID-19

[138] Statens Serum Institut. COVID-19 vaccination dashboard Accessed 24 November 2021. https://experience.arcgis.com/experience/9824b03b114244348ef0b10f69f490b4/page/page_3/

the only COVID-19 vaccine approved at the time when the group of 12-15-year-olds was invited. The Danish Medicines Agency informs that it has received < 3 notifications of anaphylaxis following vaccination against COVID-19 among 12-15-year-olds.

Experience with COVID-19 vaccination of children

Literature review

The Danish Health Authority continuously conducts a systematic literature search on the evidence for COVID-19 vaccination for children aged 5-11 years to supplement the evidence from the assessment studies[139]. The literature was searched through week 47, 2021. Overall, one systematic review and two mathematical modelling studies were identified. Additionally, 12 ongoing studies were identified among which data are available only from one primary study (the peer-reviewed presentation of data concerning Comirnaty® for 5-11-year-olds that we refer to in the section on regulatory documentation). The systematic review is described in the following.

A systematic review with a narrative description, including a total of eight published studies comprising a total of 2,852 children below 18 years of age. Seven of the studies only included children aged 12 years or more, but all of these studies focused on Comirnaty®. The final study included children aged 3-17 years, but the vaccine studies are not approved in the EU (CoronaVac, an inactivated COVID-19 vaccine). Among the 12-15-year-olds who were vaccinated with Comirnaty®, an immune response was seen that met the non-inferiority requirement compared with 16-25-year-olds, and the point estimate indicated that the 12-15-year-olds in fact had higher antibody titre increases than the 16-25-year-olds (GMR 1.75, 95% confidence interval 1.47-2.10). Effect data from this study cannot with certainty be extrapolated to 5-11-year-olds. The most frequently observed side effects in connection with vaccination were fever, headache and fatigue. The majority of side effects were mild to moderate in severity. No deaths were reported. Overall, 27 cases of myocarditis and/or pericarditis were identified leading to hospitalisation for a minimum of one day and a maximum of six days (median three days). All cases occurred after the second Comirnaty® vaccine dose, the median age of the children was 16 years (range 12-17) and most of the patients were boys (26/27 (96.3%). Safety data from this study cannot with certainty be extrapolated to 5-11-year-olds.[140]

Currently, the evidence of effect and safety concerning COVID-19 vaccination of 5-11-year-olds is limited, apart from the data generated in the assessment studies. The identified systematic review covers the population aged 5-11 years less than would be desirable, but other studies have not been identified. The study confirms the known effect and safety profile of Comirnaty® in 12-17-year-olds. Data cannot with certainty be extrapolated to 5-11-year-olds,

[139]Danish Health Authority. Case number 05-0600-1222

[140] Meng LV et al. Safety, immunogenicity and efficacy of COVID-19 vaccines in children and adolescents: a systematic review. Vaccines 2021;9(10):1102. https://www.mdpi.com/2076-393X/9/10/1102

even though 12-17-year-olds is the group that may be expected to have the most comparable effect and safety from Comirnaty® compared with 5-11-year-olds.

Experience with vaccination of children aged 12-15 years

In Denmark, experience exists from nearly 177,000 children aged 12-15 years who have completed COVID-19 vaccination, and in Europe nearly 2.5 million in the age group have completed primary vaccination.[141] Overall, it is assessed that the vaccines are effective and safe for use in children in the age group.

The Danish Medicines Agency maintains a special focus on monitoring of the group of 12-15-year-olds following vaccination. Based on the available data, the general adverse event profile in the group is comparable to what has been observed in the rest of the population, i.e. mainly known and transitory side effects[142,143]. Monitoring of myocarditis, pericarditis and MIS-C in connection with vaccination is described in detail in the section on safety. As mentioned, as per 19 November 2021, the Danish Medicines Agency had received seven notifications about myocarditis as a presumed side effect following COVID-19 vaccination of 12-15-year-olds.

In the US, more than 15 million 12-17-year-olds have received at least one dose of COVID-19, whereas nearly 13 million have completed a vaccination course (as per 24 November 2021)[144]. On 2 November 2021, the Advisory Committee on Immunization Practices (ACIP) under the CDC presented updated data on the occurrence of myocarditis among 12-15-year-olds. The risk is greater after the second vaccination shot than after the first shot, and is greater among boys than among girls. Among 12-15-year-old children, the frequency after the second vaccination shot with mRNA vaccine was 39.9 per 1,000,000 vaccinated individuals in the seven-day period following vaccination. The corresponding frequency among 12-15-year-old girls after the second vaccination shot with mRNA vaccine was 3.9 per 1,000,000 vaccinated individuals in the seven-day period following vaccination[145]. This needs to be compared with a myocarditis background incidence in the US which is estimated to 0.2-1.9 per 1,000,000 in the course of a seven-day period.

However, it is important to keep in mind that the American estimates are based on an overall assessment of the myocarditis risk following vaccination with an mRNA vaccine. Thus, the risk is not considered separately for Comirnaty® and Spikevax®. It is well-known that a small risk

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[141] ECDC Vaccine Tracker (accessed 24 Nov. 2021) https://vaccinetracker.ecdc.europa.eu/public/extensions/COVID-19/vaccine-tracker.html#age-group-tab

[142] Danish Medicines Agency, Overview of s*ide effects notified for COVID-19 vaccines* [oversigt over indberettede bivirkninger ved COVID-19 vacciner]*:* https://laegemiddelstyrelsen.dk/da/nyheder/temaer/indberettede-bivirkninger-ved-covid-19-vacciner/

[143] Hause AM, Gee J, Baggs J, et al. COVID-19 Vaccine Safety in Adolescents Aged 12–17 Years — United States, December 14, 2020–July 16, 2021. MMWR Morb Mortal Wkly Rep 2021;70:1053-1058. https://www.cdc.gov/mmwr/volumes/70/wr/mm7031e1.htm

[144] CDC Vaccine tracker: https://covid.cdc.gov/covid-data-tracker/#vaccination-demographic

[145] ACIP. mRNA COVID-19 Vaccine-Associated Myocarditis. 2 November 2021. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-11-2-3/04-COVID-Oster-508.pdf

of myocarditis is associated with the use of the COVID-19 vaccines [146,147]. The PRAC is currently assessing if the risk of myocarditis following vaccination with Spikevax® is higher than the same risk following vaccination with Comirnaty® among younger individuals. A suspicion hereof was raised, among others on the basis of currently unpublished Nordic register data. The PRAC is currently preparing an additional assessment of the association between vaccination with mRNA vaccines and myocarditis[148].

Experiences with vaccination of children aged 5-11 years [Erfaringer fra vaccination af de 12-15-årige kan ikke nødvendigvis direkte overføres til de 5-11-årige]. It is, however, likely that the safety profile will be comparable to that of 12-15-year-olds. This means that myocarditis and pericarditis will probably also be observed in 5-11-year-olds who are vaccinated. The assessment study recorded no cases.

Experiences with vaccination of children aged 5-11 years

Since 3 November 2021, the US CDC has recommended COVID-19 vaccination of 5-11-year-old children[149]. As per 24 November 2021, a total of approx. 3.3 million children aged 5-11 years have received their first dose of COVID-19 vaccine, whereas approx. 134,000 have completed vaccination[150].

Data on side effects to vaccination among 5-11-year-old children have not yet been published from the US monitoring efforts. These will likely be published shortly.

Indirect consequences of the COVID-19 pandemic for children

As case numbers rise in the course of autumn and winter, there is a risk that more restrictions will be introduced which affect the everyday lives of children. Vaccination may reduce the need for isolation due to illness or unknown infectious status, and possibly confinement in the home in case of larger outbreaks - all of which may increase the risk of loneliness, loss of interaction with friends and others, lost learning opportunities, reduced physical activity, etc. In particular for previously exposed and vulnerable children, it may be important to maintain a normal everyday routine to ensure wellbeing[151]. To illustrate, a study has identified that approx. one fifth of pupils who had a particularly hard time due to lock-downs experienced poor teacher contact during home learning sessions, low self-confidence and difficulty obtaining

[146]EMA Summary of Product Characteristics Comirnaty®. Accessed 19 November 2021. https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_da.pdf

[147]EMA Summary of product characteristics Spikevax®. Accessed 19 November 2021. https://www.ema.europa.eu/en/documents/product-information/spikevax-previously-covid-19-vaccine-moderna-epar-product-information_da.pdf

[148] EMA PRAC highlights 29 October 2021. https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-25-28-october-2021

[149]CDC recommendation on COVID-19 vaccination of 5-11-year-old children 3 November 2021. https://www.cdc.gov/vaccines/covid-19/planning/children.html

[150] CDC Vaccine Tracker: https://covid.cdc.gov/covid-data-tracker/#vaccination-demographic

[151] https://tidsskrift.dk/learningtech/article/view/120865/169768

help from parents for school assignments. The same pupils generally achieved lower mental health scores than their peers.[152]

During school lock downs in the spring of 2020, nearly half of the 3rd-9th grade (approx. 9-14-year-olds) pupils stated in a questionnaire that they did not feel happy; 92% stated that they missed their friends, and nearly as many missed their leisure activities.[153] Generally, older pupils coped better with home-based teaching than younger pupils did.[154] Nearly a fifth of the pupils who participated felt lonely, whereas many seemed to enjoy spending more time with their family. Thus, it deserves mention that the life satisfaction level during the lock-down increased for some youths and that many enjoyed the absence of social expectations.[155]

Vaccinated children in the older age groups are already encountering more lenient requirements with respect to tests as part of the continual screening in place at schools[156]. Similar measures may be expected in the younger age groups if they are vaccinated.

Overall, we assess that by preventing infection and disease among children, vaccination may contribute to maintaining normal everyday lives to the extent possible and avoiding interruption due to a constant attention to testing, infection risk and other worries. This will generally be a benefit for children because they will not miss out on time with friends and leisure-time activities and because they will be able to attend school. These benefits will be particularly important in relation children who are fragile or exposed as they will not be affected negatively by lacking contact to their networks.

Parental accept

In Denmark, the coverage of the childhood vaccination programme is generally good (88% or above for all vaccines, except HPV) and the vast majority of patents have their children vaccinated in accordance with the recommendations of the Danish Health Authority.[157] Even so, the coverage of influenza vaccination among children aged 2-6 years and COVID-19 vaccination among children aged 12-15 years have currently not achieved as high a coverage as the traditional childhood vaccinations. The two mentioned vaccines are new and were introduced rapidly. Thus, 64.8% of children aged 12-15 years have currently completed primary vaccination against COVID-19. The coverage of influenza vaccination among children aged 2-6 years

[152] https://www.egmontfonden.dk/sites/default/files/2020-08/Forskning%20i%20unge%20og%20corona.pdf

[153] https://unipress.dk/media/17311/9788772192871_ncs_e-journal_nr07_4k.pdf

[154] https://www.egmontfonden.dk/sites/default/files/2020-08/Forskning%20i%20unge%20og%20corona.pdf

[155] https://www.egmontfonden.dk/sites/default/files/2020-08/Egmont%20Rapporten%202020_0.pdf

[156] https://www.uvm.dk/aktuelt/i-fokus/information-til-uddannelsesinstitutioner-om-coronavirus-covid-19/lovgivning-og-retningslinjer/vejledninger-og-retningslinjer
https://www.sst.dk/da/udgivelser/2021/vejledning-for-haandtering-af-smitte-hos-boern-i-grundskoler-og-i-dagtilbud-mv

[157] https://www.ssi.dk/-/media/arkiv/dk/aktuelt/nyhedsbreve/epi-nyt/2019/boernevaccination_aarsrapport_2018.pdf?la=da

is 25%. The experiences from the influenza vaccination offer have not yet been analysed, but the Danish Health Authority assesses that a lacking sense of necessity may be in play, a concern for side effects associated with a vaccine that has not previously been used and an insufficient offer, or, more likely, a combination of all of the above causes. With respect to COVID-19 vaccination, many parents have likely needed to be convinced of the benefits of having their children vaccinated with a vaccine that many parents may not have felt was safe in the long term.

Questionnaire study on COVID-19 vaccination among parents

In early September 2021, the Danish Health Authority ordered a questionnaire study on COVID-19 vaccination among parents to children aged 6-11 years. Data were collected from a representative share of parents who were invited to participate via e-Boks (free online digital mail for all Danes).

Among of parents with children aged 6-11 years, 60% were in favour of COVID-19 vaccination of children, whereas a third had doubts. The share of doubters increased with decreasing age of the child. For parents to children aged 12-15 years who were already then comprised by the vaccination programme, the corresponding figures were 87% and 8%, respectively. According to the latest figures from the HOPE project, 57% of parents have decided if they want to have their child aged 6-9 years vaccinated against COVID-19[158].

Nearly half of the parents to 6-11-year-olds who participated stated that their decision on vaccination for their children depends on the level of COVID-19 infection and related restrictions in the autumn. Among parents, 79% agreed that it is important that all of the family helps protect other individuals in society against COVID-19.

Around half of the participating parents were either unsure about or agreed that COVID-19 vaccines may have unknown long-term sequelae or cause developmental disorders in children of their child's age.

Drivers and barriers

Analyses showed that the strongest driver behind parental willingness to have their children vaccinated is if they experience that vaccination will allow their child to lead a more normal everyday life. Parents who do not think or are in doubt whether vaccination will help to normalise their child's everyday life are less likely to accept the vaccination offer. Furthermore, vaccination willingness increases if the parent believes that the vaccines provide good protection against COVID-19 in children.

[158] Danish parents are willing to have their children vaccinated against Corona virus [Danske forældre er villige til at lade børn vaccinere mod corona] - politiken.dk

In contrast, vaccination willingness is affected negatively if the parents have heard of children who have experienced negative side effects following vaccination or if they believe that children rarely become seriously ill from COVID-19, and that immunity achieved following infection is therefore preferable.

The perception of the seriousness of the condition being vaccinated against has also been shown to be important in determining if parents support new vaccines for children in previous studies[159]. Thus, it is important to ensure that any future recommendation of COVID-19 vaccination for 5-11-year-old children does not undermine the remaining recommendations of accepting the vaccines offered under the Danish childhood vaccination programme. In a previous qualitative study[160], parents have expressed that to some extent they considered a truism their obligation to have their children vaccinated in accordance with the childhood vaccination programme. For many parents, this is based on trust in the health authorities' recommendations and a feeling that the childhood vaccination programme primarily comprises vaccination against serious diseases.

With the recommendation to vaccinate against a condition that parents rarely experience as serious in children, a risk may exist that parents may question the need that their children follow the childhood vaccination programme in the future, or that parents consider the programme an offer that you can opt into or out of depending on the vaccination in question. In the longer term, this may affect the coverage of the total childhood vaccination programme negatively.

Practical barriers

In the questionnaire study, only 6% of the parents asked agreed that it is difficult to find time for vaccination of their children in a stressed everyday life, but as two vaccinations are needed within a relatively short time span, we nevertheless expect this to constitute some impediment for parents in a situation in which some parents are not convinced of the need for vaccination. Among parents, 44% stated that their child is afraid of syringes. Even so, the analysis was unable to confirm that this fear affected vaccination willingness.

The above indicates that a vaccination offer for children aged 5-11 years will likely be well-received among a certain share of parents, particularly if vaccination was shown to be effective in the age group in question and to have a decisive impact on spreading of the infection in

[159] https://www.sst.dk/-/media/Udgivelser/2012/Publ2012/Vaccination-mod-rotavirus---en-medicinsk-teknologivurdering/Vaccination-mod-rotavirus-%E2%80%93-en-medicinsk-teknologivurdering.ashx?la=da&hash=7E4D8A42FBC14D9C5FC444E9B2160B20B5B0FB62

https://www.sst.dk/-/media/Udgivelser/2021/Influenza-2021-MTV/Medicinsk-teknologivurdering-_MTV_-af-influenzavaccination_310821.ashx?la=da&hash=78C51C501E3DC81103F53D2514F95F91B5CBCB4A

[160] https://www.sst.dk/-/media/Udgivelser/2012/Publ2012/Vaccination-mod-rotavirus---en-medicinsk-teknologivurdering/Vaccination-mod-rotavirus-%E2%80%93-en-medicinsk-teknologivurdering.ashx?la=da&hash=7E4D8A42FBC14D9C5FC444E9B2160B20B5B0FB62

society. However, the findings also show that many parents will have a massive need for information about the background for the recommendation, including the special circumstances under which the recommendation is made. Furthermore, parents need reassurance that children in the age group in question may be vaccinated safely. Additionally, the offer should be made as safe and readily available as possible to ensure that practical barriers or insecurity concerning the practical vaccination setup will not keep patents from having their children vaccinated.

Adaptation to the childhood vaccination programme

When introducing a COVID-19 vaccination offer for children aged 5-11 years, other vaccination recommendations for the age group in question should be taken into account.

Thus, children aged 5 years are recommended vaccination with a booster vaccine against diphtheria, tetanus, whooping cough and polio (DiTeKiPolHib); and children aged five and six years are offered influenza vaccination and children aged four years are offered their second dose of MMR vaccine. Even though most children whose parents want to accept the MMR vaccination offer may be expected to have received vaccination before they turn five years old, a limited number of children may not have received vaccination at five years of age.

All of the mentioned vaccines can be administered concurrently or at any interval between doses.

Even so, none of the three above-mentioned vaccines are currently offered in the regional vaccination centres, and therefore these vaccines cannot presently be administered concurrently with a COVID-19 vaccine.

Assessment of principles concerning COVID-19 vaccination of children aged 5-11 years

In this section, we draw on the documentation and knowledge presented in the rest of this memo to describe the objectives for vaccination during an epidemic or pandemic with a special focus on the objective to prevent spreading of infection and control the epidemic. These objectives are presented in conjunction with selected fundamental principles for the introduction of vaccines into the Danish childhood vaccination programme, etc., giving special attention to the individual child or other vulnerable individuals, the beneficial effect in relation possible side effects and previous experience with the use of the vaccine. The principles for adaptation to existing programmes and parental accept were discussed above and will form part of the overall assessment, whereas economics as a principle is not comprised by this memo.

After this section follows an overall assessment of all principles and based on this follows the Danish Health Authority's recommendation concerning COVID-19 vaccination of children aged 5-11 years.

As initially described, the Danish Health Authority always applies a very high threshold level to the effect and safety of vaccines provided as preventive treatment to healthy children. Additionally, a number of special considerations come into play when we assess the introduction of a vaccination offer during a pandemic as it is important to assess more broadly the possible benefits and risks for the entire population and for society as a whole; not just for the individual who receives vaccination.

Severity and prevalence

The assessment made to determine if COVID-19 vaccination should be offered to the 5-11-year-olds comprises an assessment of direct health effects for the child, i.e. how serious COVID-19 is for the individual child, and how the epidemic affects child wellbeing, etc., and an assessment of the indirect population level health effects, particularly in relation to individuals at increased risk of serious COVID-19.

Throughout most of the Danish epidemic, the incidence of SARS-CoV-2 among children has been lower than in the remaining age groups. Since week 38 2021, case numbers among 6-11-year-olds have increased; particularly after the autumn holidays, a considerable increase has been observed in the number of children in the age group who test SARS-CoV-2 positive. In Week 45, the incidence among the 6-11-year-olds was 1,362 per 100,000 children per week, which is the highest transmission level recorded in Denmark for any age group during the entire epidemic. Naturally, this should be seen in light of the fact that the Delta variant, which is more infectious than the previous variants, is currently the overwhelmingly dominant variant. Furthermore, most restrictions have been eliminated, and seasonal variation likely also contributes to the high case numbers recorded.

Internationally, an increasing case number among children has been recorded accompanied by an increasing number of paediatric hospitalisations. This has not been observed in Denmark. Generally, children who become infected with SARS-CoV-2 present mild or no symptoms. Even among children with underlying conditions, only very few fall seriously ill, and only few children have been hospitalised with serious COVID-19. So far, the number of hospitalisations in Denmark among children aged 5-11 years has been very limited (estimated at less than 100 due to COVID-19) and the admission time is short.

However, as paediatric case numbers increase, we expect that a limited number of children are at risk of being hospitalised. Additionally, a risk exists that a limited number of children develop the rare but serious complication MIS-C, which is an inflammatory condition that may evolve 2-6 weeks after SARS-CoV-2 infection, typically after a mild infection. MIS-C occurs slightly more frequently among young than among older children, and the incidence in Denmark is estimated at approx. 1/4,100 infected children. Finally, late sequelae have been reported among children. The exact occurrence remains unknown, but is likely limited. Thus, vaccination also carries the potential to prevent rare but very serious disease in the individual children.

Even so, the primary effect of vaccinating the 5-11-year-olds will be prevention of infection of the rest of the population, in particular transmission from children to parents and potentially also transmission to grandparents. In Denmark, we currently record a high infectious pressure among school-aged children who have a large number of social contacts. Furthermore, monitoring data show that after a few weeks of lag, higher case numbers are seen among adults (parents). Thus, there is a subsequent risk of increasing hospitalisation numbers among elderly people.

The rising infection numbers should be seen in the context of the currently declining effect of primary vaccination. A majority of the individuals who belong to the older age groups or individuals at increased risk of serious COVID-19 will have been offered booster vaccination at the time when vaccination of children aged 5-11 years is introduced (if this occurs). Despite the continuous offer of COVID-19 booster vaccination, some individuals in the Danish population will not achieve the expected immunity, either due to weakening of the immune system with increasing age or due to medical reasons, i.e. various levels of immune deficiency. Additionally, some individuals may have an increased risk of SARS-CoV-2 infection and, in the worst-case scenario, of falling seriously ill due to COVID-19 because they have opted out of booster vaccination or due to waning immunity in the interval separating primary vaccination from booster vaccination.

Finally, we know that the vaccines do not provide 100% protection, and the objective of achieving a high vaccine coverage is to provide general protection, i.e. to ensure that individuals who are not protected despite vaccination (as described in the ENFORCE study) and individuals who cannot be vaccinated gain indirect protection owing to extensive vaccination of

the population. Various risk factors have been identified for not developing a sufficient immune response following vaccination, but individuals with risk factors may be difficult to identify, among others because it currently remains unknown which level of antibodies provides effective protection against COVID-19. Therefore, testing cannot be used to identify with certainty individuals with lacking immunity and individuals who are at risk of serious COVID-19 despite an effective COVID-19 vaccination roll-out.

From a population perspective, it may therefore be preferable to vaccinate the 5-11-year-olds provided the benefits in the form or prevention of serious disease and mortality among the oldest and other vulnerable individuals in the population outweigh the risk of side effects in the individuals who are vaccinated. Therefore, it also reasonable to consider indirect protection of other target groups with an increased risk of serious COVID-19 disease as part of the assessment.

No published study has established with certainty how large the effect of vaccinating the 5-11-year-olds may be with respect to reducing the number of serious disease cases and the number of hospitalisations. The Danish Health Authority has estimated that vaccination of children may contribute an additional approx. 1.2-5.4% percentage points to the total population immunity. Furthermore, modelling from Statens Serum Institut shows that it is possible to reduce the number of new hospitalisations by 11-31% by the end of January and by 24-64% by the end of February depending on the vaccination coverage achieved in the age group (40% versus 80%).

Thus, in a population perspective, a possible indirect potential for prevention is linked to vaccination of the 5-11-year-olds because prevention of infection and spreading of infection may contribute to protecting individuals who for various reasons have not achieved sufficient immunity to SARS-CoV-2. Vaccination of 5-11-year-olds may also provide direct protection of the limited number of children in the age group who develop sequelae to SARS-CoV-2 infection, e.g., MIS-C or late sequelae.

Furthermore, benefits may be associated with achieving controlled immunity through vaccination rather than uncontrolled acquired immunity following SARS-CoV-2 infection. We know that the immune response developed during SARS-CoV-2 infection may vary from individual to individual, whereas the immune response following vaccination is more predictable and provides good and prolonged protection against COVID-19.

Finally, advantages related to the individual child’s wellbeing may be associated with offering vaccination. Vaccination may thus contribute to normalising and establishing continuity in the everyday lives of children by reducing the need for isolation due to illness or unknown infectious status, and possibly confinement in the home in case of larger outbreaks - all of which may increase the risk of loneliness, loss of interaction with friends and others, lost learning opportunities, reduced physical activity, etc. In particular for previously exposed and vulnerable children, or children from socially exposed families, etc., a normalisation of everyday life

may be important to increase wellbeing. Additionally, lacking vaccination may give children who are relatives to individuals at increased risk of running a serious disease course worries about being infected and transmitting the infection within their family. Furthermore, vaccination will likely reduce the need for the array of tests currently performed by children in some age groups, either because they are close contacts or as part of ongoing screening efforts.

Beneficial effect compared with possible side effects

The clinical trial that forms the basis for the authorisation of Comirnaty® for use in 5-11-year-olds documented a robust increase in antibodies in line with the increase among 16-25-year-olds. It also documented high effect in relation to preventing infection with SARS-CoV-2 and COVID-19 in this age group; also against the Delta variant. Additionally, a large body of knowledge is now available about the effect of the mRNA vaccines and their safety among individuals aged 12 years or more from the roll-out of mass-vaccination in Denmark and internationally. In Denmark, experiences exist from nearly 177,000 children aged 12-15 years who have completed COVID-19 vaccination. Additionally, experiences have been reported from vaccination of several million children in Europe and the rest of the world (nearly 15 million in the US, nearly 2.5 million in Europe). Overall, the vaccines used in Denmark are effective in prevention of infection and serious COVID-19 disease. Furthermore, the vaccines are safe and have a good safety profile. Experiences from individuals aged 12 years or more cannot necessarily be transferred to younger children, but there is no theoretical reason why either the effect or the safety profile should differ substantially between the two groups. The regulatory approval of Comirnaty® for use in 5-11-year-olds and preliminary data from the roll-out of COVID-19 vaccination among 5-11-year-olds in the US also support that Comirnaty® has a good safety profile among 5-11-year-olds.

The protection of other individuals that would be achieved by vaccinating 5-11-year-olds should be weighed against the safety for the individual child. The benefits of vaccinating children aged 5-11-years will fall not to the child but to other individuals to a considerable extent, whereas the risk of serious side effects is limited exclusively to the vaccinated child. The drawbacks associated with being a child in a society with COVID-19 do not form part of the assessment of the advantages and drawbacks in connection with authorisation of the vaccine. It should be noted that when authorising medicinal products for use in children, unlike Denmark, the EMA will not apply a special threshold for documentation of the trade-off between potential benefits and drawbacks with respect to preventive treatment for healthy children.

In the authorisation study, side effects were mild, self-limiting and comparable to those observed in older children and adults and those observed when administering other vaccines to children. The most frequent side effects were local reactions at the injection site and transient general symptoms such as, e.g., fatigue, headache and myalgia.

After COVID-19 vaccines have started being used, a possible association has been established between very rare cases of myocarditis and pericarditis and vaccination with mRNA vaccines. The background risk of developing myo- or pericarditis is lower among children than among

young individuals and adults. We expect that fewer children than adults will develop these conditions. On the other hand, the development of myo- or pericarditis will constitute a health risk that needs to be balanced against important population-level benefits and this health risk is acceptable only if good treatment opportunities are available. Observation of myocarditis and pericarditis after COVID-19 vaccination is based on spontaneous notifications, and it has not been possible to estimate an exact frequency, but these side effects are rare. Data indicate that the course of myocarditis and pericarditis after vaccination is in line with the typical course of these conditions, which are typically self-limiting (i.e. the conditions recede spontaneously), and treatment options are good if treatment is needed. Myocarditis and pericarditis very rarely cause chronic sequelae. It is likely that myocarditis will also be observed in 5-11-year-olds who are vaccinated. The assessment study recorded no cases. It should also be noted that the approved Comirnaty® dose for children aged 5-11 years is reduced compared with the approved dose for individuals aged 12 years or more.
Previously, a suspicion was raised of a possible association between vaccination and development of MIS-C, but the PRAC has not found documentation in support of such an association. The authorisation study for 5-11-year-old children found no signs of serious side effects among children. After Comirnaty® has started being used in 12-15-year-olds, no serious side effects to the vaccine have been observed.

It is not straightforward to assess if the risk that the individual vaccinated healthy child may have side effects after having received preventive treatment is equal to the risk that the individual infected child may develop complications to an infectious disease. The assessment depends, among others, on the likelihood of becoming infected in the current context. In the current Danish epidemic with the very infectious Delta variant, there is reason to assume that you will be infected with SARS-CoV-2 at some point in time unless you are vaccinated. Currently, we assess that the risk that the individual child falls seriously ill with COVID-19 or experiences complications to the infection is low even among children with underlying conditions, but the next month will show if the increase in the number of infected children is followed by an increase of MIS-C or SARS-CoV-2 infection. Thus, the risk of serious disease in children with COVID-19 remains unknown, whereas the risk of serious side effects following COVID-19 is very limited.

On the current data basis, the Danish Health Authority assesses that vaccination of 12-15-year-olds is safe and effective. The Danish Health Authority continuously monitors safety data from the enhanced monitoring in place in connection with the roll-out of the COVID-19 vaccination programme, among others via the Danish Medicines Agency's weekly update on notifications of presumed side effects and the European Medicine Authority's monthly safety updates related to the COVID-19 vaccines.

Preventing the infection from spreading and epidemic control

Currently, in an open Danish society, we are experiencing a growing COVID-19 epidemic with increasing case numbers, particularly among children aged 6-11 years, and an increasing

number of adults hospitalised with COVID-19. A relatively higher share of hospital admissions is accounted for by individuals who have not been vaccinated compared with the proportion of unvaccinated people in the population, where the vast majority have been vaccinated. We expect that the number of COVID-19 hospitalisations will increase in the course of the winter and that an increase will be observed in the number of individuals admitted to intensive care units.

Vaccination is the most effective tool available to control an epidemic. Even so, it is not the only tool available to reduce spreading of infection and ensuing morbidity due to COVID-19. Vaccination, including an extension of the target group for COVID-19 vaccination, should therefore be weighed against the alternatives to achieve epidemic control, where regulation of behaviour, including implementation of restrictions. is currently the primary alternative tool.

The Danish Health Authority has a strong focus on increasing primary vaccination and booster vaccination coverage in order to achieve the highest possible level of immunity in the population. We expect that booster vaccination will contribute considerably to enhancing and maintaining waning population immunity while increasing immunity among individuals who have an increased risk of serious COVID-19. Even so, and despite booster vaccination efforts, a proportion of the population does not react sufficiently to vaccination and therefore does not achieve protection against COVID-19. Furthermore, some individuals will opt out of booster vaccination. As previously mentioned, it is difficult to identify the individuals who do not achieve sufficient immunity through vaccination.

According to the estimates of the Danish Health Authority, population immunity may be increased by 2-6% by also offering COVID-19 vaccination to 5-11-year-old children. Thus, vaccination of 5-11-year-olds alone will likely not boost the population immunity sufficiently to reach the theoretical threshold level for herd immunity. On the other hand, the effect in relation to breaking infection chains is considered considerable. Preliminary analyses by the SSI seem to indicate that 31% of the infection that may be traced and which explains 17% of the total number of individuals infected in the period from 1 September 2021 to 1 November 2021 originated from non-vaccinated children aged 6-13 years of age. When the individual child achieves immunity to SARS-CoV-2, the child will not become infected and will therefore also not transmit the infection to others, whereby an infectious chain is broken. However, a risk always exists that a vaccinated individual may transmit infection to a non-vaccinated individual without having any symptoms him- or herself. However, according to the literature review provided previously in this memo, the risk of transmitting infection will be lower because vaccination reduces the time period during which an individual with breakthrough infection may transmit the infection.

The children are not an isolated group that is independent from the remaining part of the epidemic. If you do not vaccinate the 5-11-year-olds, pockets will remain in the population, i.e. an unvaccinated age group with many social contacts will exist where SARS-CoV-2 may circulate and continue to entail a risk of transmission to individuals who are at an increased risk

of serious COVID-19. Furthermore, a risk exists that virus mutations will develop that may potentially have a reduced sensitivity to the current vaccines. Despite the current high infectious pressure, we expect that many months will pass before the majority of children in the 5-11-year age group achieve acquired immunity following SARS-CoV-2 infection. In the same period, we expect that more restrictions will be introduced to limit infection. This may ultimately affect the children's wellbeing and have derived effects for the parents who may need to remain at home for a period of time, etc.

In light of the current Danish epidemic, the stress it generates on hospitals and the expectations to the upcoming winter season, there is a high risk that restrictions may be introduced to limit spreading of the infection. We already observe measures aiming to prevent infection at schools, and - given the characteristics of the current epidemic - it is difficult to imagine that the restrictions will be removed in the short term as long as the majority of children have not gained immunity to SARS-CoV-2.

Additionally, the Danish regions have limited possibilities for prioritising additional bed capacity in a context of additional stress caused by infectious diseases in the upcoming winter season. Additional capacity is primarily achieved by regulating the planned activity, including both outpatient visits and planned surgery. Furthermore, in the autumn of 2021, the Danish healthcare system is less robust than was the case previously. This is due to various factors, including an extraordinarily high workload since the epidemic started among all clinical staff groups and challenges related to critical staff resources like, e.g., the nursing area. Furthermore, as social activity returns roughly to normal levels during this autumn and winter season, we expect a seasonal increase in the number of hospitalised individuals due, among others, to influenza, COVID-19, other serious airway conditions and other acute diseases. We expect the disease burden to be particularly heavy from December to mid-February because infections with influenza typically peak in January and February, and because celebrations, gatherings, etc, around Christmas and New Year typically increase infections. This will increase the pressure, in particular, on emergency rooms, medical wards, operation theatres and intensive care units. In particular, patients with COVID-19, influenza and certain other infectious diseases require extra resources due to the need for isolation, use of personal protective gear, etc., which reduces the time that staff can dedicate to providing treatment and care for the remaining patients.

Thus, vaccination of children aged 5-11 years is assessed to directly prevent infection thereby affording the rest of the population and Danish healthcare with various advantages. In a national perspective, the timing of a possible vaccination offer is pivotal if vaccination of the 5-11-year-olds is to limit the spreading of infection and prevent serious COVID-19. In the context of the current epidemic, characterised by increasing infection and hospitalisation numbers, we assess that the largest benefit of a vaccination offer may be achieved if vaccination is rolled out as quickly as possible. Furthermore, vaccination may contribute to easing the restrictions in place to prevent infection, which may in turn have a number of advantages for the

individual children. Most importantly, vaccination of children will contribute to breaking infection chains and - as children rarely fall seriously ill due to COVID-19 - a large proportion of the beneficial effect from vaccination falls to other individuals than the vaccinated children.

Overall assessment

For nearly two years, the COVID-19 pandemic has had considerable public health consequences globally. In Denmark in the autumn of 2021, we are witnessing an epidemic that generates high case numbers among unvaccinated children. Currently, children aged 6-11 years record the highest incidence of SARS-CoV-2 infection seen to date for any age group since the beginning of the epidemic. Additionally, we see an increased morbidity due to COVID-19 in the population, increasing hospitalisation numbers and an increased strain on an already strained healthcare system. We assess that a combination of a seasonal effect, a fully open society and the dominance of the very infectious Delta variant contribute to the high infectious pressure we are currently witnessing in Denmark.

In the assessment aiming to determine if the COVID-19 vaccination programme should be extended to comprise children aged 5-11 years, the Danish Health Authority considers various prioritised objectives related to the pandemic: to minimise serious COVID-19 morbidity and mortality, to prevent spreading of infection and achieve control of the epidemic, and to ensure critical key functions in society. The assessment also considers a number of basic principles known from the introduction of vaccines, among others into the Danish childhood vaccination programme. Here, considerable importance is attributed to a special assessment of the seriousness and prevalence of the condition in the individual child or other vulnerable individuals, the beneficial effect in relation to possible side effects and previous experience with the use of the vaccine. The child's own risk of serious COVID-19 is low. In contrast, spreading of the infection may potentially have considerable consequences during a pandemic and the indirect effect of vaccination, i.e. prevention of serious COVID-19 at the social level, is attributed considerable importance in the assessment. Finally, the Danish Health Authority always applies a very high threshold level to the effect and safety of vaccines provided as preventive treatment to children.

The children are not an isolated group that is independent from the remaining part of the epidemic. If an unvaccinated population of children below 12 years of age remains, the virus may circulate within an age group with many social contacts characterised by a low degree of immunity and therefore a high level of infection. From such a population, there is a high risk of transmitting the infection to parents, grandparents and individuals who are at increased risk of serious COVID-19 and who have not achieved sufficient effect from vaccination.

The Danish Health Authority assesses that extending the vaccination target group to also include children aged 5-11 years will contribute considerably to reducing infection in other groups and thereby indirectly afford protection against serious COVID-19 for unvaccinated

individuals and individuals who have not achieved full effect of vaccination. Despite the very high coverage of the primary vaccination scheme and broad booster vaccination efforts made, we assess that vaccination of children aged 5-11 years may contribute to breaking infectious chains and thereby hampering the transmission of infection to elderly and vulnerable individuals who are at risk of serious COVID-19.

This is particularly important as we enter a winter season during which we expect a seasonal increase in the number of hospitalised individuals due, among others, to influenza, COVID-19, other serious airway conditions and other acute diseases. In the context of an increased disease burden and a less robust healthcare system than previously, the Danish Health Authority assesses that the risk is imminent that Danish hospitals may face critical challenges from December onwards.

No published study has established with certainty how large the effect of vaccinating the 5-11-year-olds may be with respect to reducing the number of serious disease cases and the number of hospitalisations. The Danish Health Authority has estimated that vaccination of children may contribute an additional approx. 1.2-5.4% percentage points to the total population immunity. Furthermore, modelling from Statens Serum Institut shows that it is possible to reduce the number of new hospitalisations by 11-31% by the end of January and by 24-64% by the end of February depending on the vaccination coverage achieved in the age group (40% versus 80%). The Danish Health Authority expects that we will see the full effect of vaccinating the 5-11-year-olds on the number of hospitalisations only by late February when the spreading of the infection declines because the children have been vaccinated.

Additionally, indirect benefits related to the wellbeing of children may be associated with vaccination of children aged 5-11 years. Vaccination may allow the individual child to feel more secure because of the reduced risk that he or she may transmit the infection to any vulnerable family members. Furthermore, vaccination may contribute to normalising the children's everyday lives, thereby avoiding the risk of confinement to the homes, limiting the need for testing and infection tracing and reducing any derived negative consequences. Additionally, vaccination of children aged 5-11 years may contribute to a normalisation of the families' everyday lives, where a lack of security and predictability may generate considerable stress.

Finally, it is assessed that COVID-19 vaccination effectively prevents SARS-CoV-2 infection among children aged 5-11 years. Owing to its high effect, vaccination will protect the limited number of children who might otherwise have become seriously ill due to COVID-19 or have developed complications to COVID-19, e.g., in the form of MIS-C, late sequelae or similar. However, serious COVID-19 is a rarely occurring condition in children. The prophylactic potential related to serious disease in children without special risk factors is therefore considered to be limited despite the high effect of vaccination.

It is a fundamental principle that the individual being vaccinated should have more benefit than risk of harm from the vaccine. We thus need to weigh the prophylactic potential at the

population level and the possible indirect benefits for the individual child in the form of increased wellbeing against the risk of serious side effects carried by the individual child receiving the vaccine, a child who is generally not at risk of serious COVID-19 him- or herself. Possible side effects to vaccination thus need to be weighed against considerable population-level benefits and are acceptable only if good opportunities for treatment and cure are available. After COVID-19 vaccines have started being used, a possible association has been established between very rare cases of myocarditis and pericarditis and vaccination with mRNA vaccines among individuals aged 12 years and older. The Comirnaty® authorisation study for 5-11-year-olds recorded no such cases. The background risk of developing myo- or pericarditis is lower among children than among young people and adolescents, and we expect that fewer children than adults will develop these conditions. The course of myocarditis and pericarditis after vaccination is in line with the typical course of these conditions which are typically self-limiting, and treatment options are good if treatment is needed.

The authorisation study included 3,109 children aged 5-11 years receiving Comirnaty®. Thus, the data basis is sufficiently large to identify with great certainty very common, common, uncommon and, to some extent rare side effects, whereas the size of the authorisation study means that we cannot expect to identify possible very rare side effects occurring among fewer than 1 per 10,000 individuals. Prolonged safety follow-up lasting a minimum of two months among 1,444 children aged 5-11 years was completed. Therefore, it is uncertain if very rare and to some extent rare side effects have been identified in the study. However, the autumn of 2021 has provided massive experience with and safety data concerning vaccination of several million children aged 12-15 years worldwide and we also have massive experience with vaccination of adults. We expect that the type and frequency of side-effects will be comparable to those recorded for 12-15-year-olds. We also assess that it is very unlikely that any new, unknown age-dependent side-effects should exist, which will only become known following the rollout of vaccination for 5-11-year-olds.

Conclusion

Overall, on the current knowledge base, the Danish Health Authority assesses that vaccination of children aged 5-11 years is safe and effective, and that the sum of total benefits achieved by vaccination of the age group outweighs the possible risks. It is assessed that vaccination of this age group may contribute to increasing immunity in the population, break infection chains and thereby contribute to reducing the transmission of infection in the population; and that vaccination is an important contribution to upholding epidemic control in Denmark.

In the course of the current epidemic, the speed and effect of vaccination efforts have considerable consequences for the individual, the population and for society alike. In a social perspective, the timing of COVID-19 vaccination offers for 5-11-year-olds is thus decisive in ensuring that vaccination of the age group has a significant effect. The number of new SARS-CoV-2 cases among children aged 6-11 years currently increases exponentially, and a need therefore exists to initiate vaccination of 5-11-year-olds as quickly as possible to ensure that their vaccination may serve to limit transmission of the infection in winter. On this basis, the

Danish Health Authority finds that an offer of COVID-19 vaccination of the 5-11-year-olds in Denmark should be initiated.

The Danish Health Authority continuously monitors safety data from the enhanced monitoring in place in connection with the roll-out of the COVID-19 vaccination programme, among others via the Danish Medicines Agency's weekly update on notifications of presumed side effects and the European Medicine Authority's monthly safety updates related to the COVID-19 vaccines etc.

Appendix 1 - Recommendations from other countries

Table 10: National guidelines on COVID-19 vaccination of 5-11-year-olds in selected countries

Via the Ministry of Foreign Affairs of Denmark, the Danish Health Authority has collected information about the current status on COVID-19 vaccination of 5-11-year-old children in selected countries. The below is the situation as per 25 November 2021.

Country	Is vaccination of 5-11-year-olds recommended?	Is vaccination being discussed
Australia	**No**, vaccination in the below-12-year age group has not yet been initiated in Australia. In the age group of slightly older children (12-15 years), the current vaccination rate is 57.7%, whereas 83% of the total population (above 16 years of age) has been vaccinated.	**Yes**, the Australian medicinal authorities (the Therapeutic Goods Administration – TGA) are currently analysing data concerning children aged 5-11 years. The analysis efforts are expected to conclude by early January, and shortly after vaccination of the age group will likely be initiated. In the local press, it has been mentioned that rollout for this group may initially be targeted at vulnerable children with underlying conditions who are particularly vulnerable if they become infected with coronavirus.
Belgium	**No**, COVID-19 vaccination for children aged 5-11- years is not recommended.	**No**, but in days to come, we expect that the Belgian politicians will decide if COVID-19 will be recommended for children aged 5-11 years. Currently, Belgium awaits the European Medicines Agency's assessment of this topic.
Bulgaria	**No**, in Bulgaria no children below 12 years of age are being vaccinated.	**No**, no discussions are voiced about vaccination of children below 12 years of age.
Canada	**Yes**, on 19 November 2021, Health Canada authorized the use of the Pfizer-BioNTech Comirnaty COVID-19 vaccine in children aged 5-11 years of age. The National Advisory Committee in Immunization (NACI) recommends that a complete series with the Pfizer-BioNTech COVID-19 vaccine (10 mcg) may be offered to children 5-11 years of age	**Yes**, on 16 November, Health Canada received a submission from Moderna to authorize the use of the Spikevax COVID-19 vaccine in children aged 6-11 years of age. According to polls, more than half of all parents plan to have their children vaccinated while the rest is hesitant.

	who do not have contraindications to the vaccine, with a dosing interval of at least eight weeks between first and second dose.	
Cyprus	**No**, in Cyprus only children aged 12 years or older can currently be vaccinated. As far as the Embassy is aware, no exceptions are in place regarding selected groups of children aged 5-11 years with a weakened immune response. Booster vaccination is only offered to individuals aged 18 years and above.	**No,** there are currently no plans to vaccinate children aged 5-11 years of age.
Estonia	**No**, currently does not have in place a vaccination program covering children aged 5-11 years or specific groups of children aged 5-11 years.	**Yes**, the Estonian National Commission on Immunoprophylaxis is currently assessing whether it will recommend vaccination against COVID-19 of children aged 5-11 years.
Finland	**No**	**Yes**, the vaccination of children aged 5-11 is currently being discussed in Finland. The Finnish National Expert Group on Vaccinations (KRAR) will consider the issue in early December. If the decision is to go ahead with vaccinations, their timing will depend on the timing of the EMA approval and the availability in Finland of a sufficient number of vaccines.
France	**No**, France currently does not yet recommend COVID-19 vaccination in children below 12 years of age.	**No**, on 10 November, the French Minister of Health Olivier Véran stated that he was awaiting the European Medicines Agency's statement on vaccination of 5-11-year-old children in December. The French health authority "Haute Autorité de Santé" (HAS) will thereafter publish its recommendations for France, but Minister of Health Véran stated that no decision will be made until the end of 2021 or even early 2022.
Greece	**No**, Greece has no current plans to extend the vaccination to comprise children aged 5-11 years. In contrast, children aged 12 years and above are recom-	**No**, no plan is in place for the rollout of vaccination for children aged 5-11 years and, apparently, no recommendations are being prepared for this age group.

	mended vaccination. As far as the Embassy is aware, no exceptions are in place regarding selected groups of children aged 5-11 years with a weakened immune response. Booster vaccination is only offered to individuals aged 18 years and above.	
Ireland	**No**, vaccination of 5-11-year-old children has not yet been initiated in Ireland.	**No**, the government states that it is not opposed to vaccination of the age group in principle, but that it is awaiting an authorisation and recommendation from the EMA, NIAC (National Immunisation Advisory Committee) and from the government's medical advisory group (NPHET), before a final decision will be made. There are rumours that no professional assessment of the process is currently ongoing with respect to the decision to vaccinate the age group.
Iceland	**No**, children aged 5-11 years are not offered vaccination. Children aged 12-15 years are offered the Pfizer vaccine exclusively. 66% of the children in this age group have completed vaccination and an additional 7% have received their initial vaccination shot.	**No**, no decision has been made as to the vaccination of children below 12 years of age as vaccines for children in that age group have not been authorised in Island. Island is awaiting the conclusions of European Medicines Agency's studies of the Pfizer vaccine in children below 12 years of age before this question will be decided upon again. This information was provided by the Chief Epidemiologist of Island on 29 October.
Israel	**Yes**, the Israeli Ministry of Health has approved COVID-19 vaccination of all children aged 5-11 years with the paediatric vaccine from Pfizer (10-microgram dose) after the government's COVID-19 expert panel voted in favour of the vaccine (73-2). Children will be vaccinated at a three-week interval between the first and second dose. Vaccination was initiated on 22 November.	

Italy	**No**, currently no vaccines have been authorised by the Italian medicines authority (AIFA) for use in children below 12 years of age. Regardless of their state of health, children aged 5-11 years are not being offered COVID-19 vaccination in Italy.	**No**, in accordance with the previous procedure, the AIFA will not make a decision as to a possible recommendation of COVID-19 vaccination for children aged 5-11 years until the EMA has published its assessment of the topic. Currently, debates are ongoing among medical experts in Italy about the question of vaccination of children below 12 years of age. The society of Italian paediatricians is positive towards the idea of extending the vaccination programme to also comprise children aged 5-11 years of age. The Italian Minister of Health, Roberto Speranza, has also confirmed that the Italian health authorities may possibly extend their vaccination campaign to comprise children aged 5-11 years once the EMA has published its assessment of this topic.
Japan	**No,** no children aged 5-11 years of age are currently being offered vaccination.	**Yes**, last week BioNTech-Pfizer applied to have their vaccine authorised for use in children aged 5-11 years, and their application is being processed by the Japanese authorities. The authorities have not made any statements as to when they expect to conclude their processing of the application. On 16 November, the Japanese Ministry of Health encouraged local authorities to prepare to administer vaccines to children aged 5-11 years. If this is decided, it will not be implemented until February 2022 at the earliest. Various health experts have voiced concern and warned against the use of vaccines for children in this group based on the associated uncertainties. In a recent study among parents to children aged 5-11 years of age, 33.6% stated that they were

		cautious about having their children vaccinated.
Croatia	**No**, only children older than 12 years are offered vaccination; children with chronic diseases that increase the risk of severe COVID-19 are given priority. The evaluation of clinical documentation for the use of vaccines in children under 12 years of age is ongoing.	**Yes**, the evaluation of clinical documentation for the use of vaccines in children under 12 years of age is ongoing.
Latvia	**No**, in Latvia vaccination is not offered to children below 12 years of age, not even in special cases, e.g. children with a weak immune system.	**No**, Latvia is expecting recommendations on the vaccination of children below 12 years of age from the EMA.
Lithuania	**No**, Lithuania does not yet offer vaccination for children below 12 years of age.	**No**, the authorities are currently awaiting a final assessment from the European Medicines Agency, but if the Agency authorises vaccination of children in this age group, the vaccination process will be initiated immediately among 5-11-year-olds.
Luxembourg	**No**, At present, no decision has been made in Luxembourg about COVID-19 vaccination of children aged 5-11 years (children as from 12 years of age are currently being vaccinated).	**No**, but awaiting the assessment of the European Medicines Agency, the Luxemburgish Health director (under the auspices of the Ministry of Health), Jean-Claude Schmit, has stated in a press release that the intention is to initiate the vaccination programme as soon as possible in the stated group of children, particularly with a view to limiting the transmission of virus among elderly people. They thus expect to engage in detailed planning of these vaccines in late November to be ready for vaccine rollout in the course of December. In the past few weeks, Luxembourg has witnessed quite a few protests against the described paediatric vaccinations, among others with collection of protests from (currently) 4,500 citizens.
Malta	**No,** currently, children aged 5-11 years are not offered COVID-19 vaccination in Malta.	**No**, the Maltese health authorities are awaiting the EMA's authorisation of vaccination of children below 12 years of

		age before deciding if the Maltese vaccination programme will be extended to include children aged 5-11 years.
The Netherlands	**No**, the Netherlands (NL) have not yet decided on COVID-19 vaccination of children aged 5-11 years.	**Yes**, the acting Minister of Health, De Jonge, has asked the Dutch Healthcare Council to provide recommendations regarding COVID-19 vaccination of children aged 5-11 years who are particularly vulnerable, among others, children with a weakened immune response. We expect that the recommendations will be published before the end of 2021. During the parliamentary debates on 16 November on the overall evolution of COVID-19 in the NL, the Social-liberals (D66) presented a motion for a resolution in which the government was requested to ensure that in dialogue with their general practitioner parents may have their children aged 5-11 years vaccinated. The acting Minister of Health recommended against the motion as he prefers to await the recommendations of the Health Council. The motion was not decided upon by voting, but remains in place until the recommendation of the Health Council is published. Please note that if the EMA authorises the Pfizer vaccine for use in young children, the first delivery will arrive in the NL on 20 December. Case numbers are currently rising particularly fast among school-children. Figures provided by the National Institute for Public Health and the Environment (RIVM) show that case numbers are rising in all age groups, but that the majority of new infections are recorded among 4-12-year-olds.

Norway	**No**, in Norway, no children below 12 years are currently being vaccinated, according to an overview document from the Folkehelseintsituttet (FHI).	**No**, but the FHI follows the latest knowledge on COVID-19 vaccination and so far the government has followed the FHI's recommendations in the COVID-19 vaccination programme. If the EMA authorises COVID-19 vaccination of individuals < 12 years, it seems natural that the FHI should recommend this to the government.
Poland	**No**, not currently.	**No**, Poland awaits the EMA's assessment of whether children aged 5-11 years should be eligible for vaccination with BioNTech/Pfizer vaccines. Once the EMA has made its decision, the Polish Ministry of Health is expected to publish a statement confirming that Poland now allows vaccination of children aged 5-11 years with this vaccine. According to Minister of Health Adam Niedzielski, this may occur already before the end of November. According to the Polish Ministry of Health, the first shipment of COVID-19 vaccines for children aged 5-11 years is expected to reach Poland in December.
Portugal	**No**, Portugal does not yet offer vaccination for children below 12 years of age.	**Yes**, the Portuguese health authorities are currently assessing if children aged 5-11 should receive COVID-19 vaccination. Furthermore, the authorities are awaiting the statement from the EMA before a final decision will be made.
Romania	**No**, Rumania has not yet initiated vaccination of 5-11-year-olds. The expectation from Rumania is to initiate vaccination of the age group by mid-December, provided that the EMA publishes the expected authorisation.	
Switzerland	**No.**	**No**, currently there are not sufficient data.
Slovak Republic	**Yes, in special cases.** Children between 5 and 11 years are offered COVID-19 vaccination only in special circumstances. Initially, the child's parents and	**No**

	a general practitioner must recommend vaccination. Subsequently, a specialist makes the final decision. Once the final decision has been made and provided the child is referred for COVID-19 vaccination, 1/3 of the normal dose is used of Pfizer-BioNTech.	
Slovenia	**No**, Slovenia has adopted the same position as Denmark, as vaccination for children aged 5-11 years is not yet being offered.	**Yes**, the Slovenian *National immunization technical advisory group* (NITAG) will discuss the question on 23 November 2021.
Spain	**No**, children below 12 years are currently not offered COVID-19 vaccination in Spain. This is also not the case for children below 12 years of age with a weakened immune system or for other special risk groups below 12 years of age. Vaccination is not offered because, currently, no vaccine has been authorised for use in the age group.	**No**, but the Spanish health authorities closely follow the recommendations published by the EMA, particularly with respect to the question of administration of a COVID-vaccine for children below the age of 12 years. Provided that the EMA recommends expanding vaccination to children below 12 years of age, this will require approval by the Spanish authorities. Specifically, the Spanish Vaccine Committee will need to recommend vaccination to the Interterritorial Council for Spanish Healthcare before administration of the vaccine for children below 12 years of age may be initiated. It has yet to be decided if Spain will follow a future recommendation (if any) from the EMA concerning an expansion of the vaccination programme for children below 12 years of age. In Spain, it is currently being debated if the benefits of expanding the vaccination programme to comprise children below 12 years of age outweigh any risks and drawbacks. On 26 October, the Chairman of the Spanish Vaccine Committee stated that, keeping the current transmission pattern in mind, it does not make sense to initiate mass-vaccination of children be-

		low 12 years of age. Even so, the Chairman pointed out that vaccinating children below 12 years of age may become necessary if the level of transmission worsens. Along the same lines, Health Ministry Representative Fernando Simón (Center for Health Warnings and Emergencies of the Spanish Ministry of Health) has also expressed doubts as to the benefits of a possible extension of the vaccination programme to include children below 12 years of age. The above should be considered in the context of an overall 14-day incidence as per 17 November of 96.12/100,000 in the Spanish population. For children below 12 years, the 14-day incidence as per 17 November was 141.08/100,000.
Great Britain	**No**, currently the COVID vaccine is not offered to children aged 5-11 years. The first vaccine dose is offered to children aged 12-15 years, whereas the second dose is offered only to risk-group children. As per 15 November, the government decided that adolescents aged 16-17 years will be offered both vaccine doses.	**Yes**. Clinical trials with vaccines for children aged 5-11 years have been initiated in Great Britain. According to the expert committee that provides advice to the health authorities of Great Britain, vaccines for this group may be authorised by late 2021/early 2022.
Sweden	**Yes, in special cases.** Sweden does not offer children aged 5-11 years COVID-19 vaccination. Even so, following an individual assessment by the child's general practitioner, children below 12 years with risk factors may receive COVID-19 vaccination.	**No**, the Public Health Agency of Sweden has not indicated that any current plans exist for COVID-19 vaccination of children aged 5-11 years. Generally, the Public Health Agency of Sweden has indicated that decisions concerning vaccination should not be made in haste. Thus, children aged 12-15 years were not offered vaccination until 16 September 2021, as for a considerable amount of time, the Public Health Agency of Sweden awaited a more solid scientific basis to assess the need for a general recommendation for this age group.

The Czech Republic	**<u>Yes, in special cases.</u>** The Czech Republic has not currently introduced across-the-board vaccination of children aged 5-11 years, but preparations to do so have been made. Currently, the Ministry of Health informs that based on an individual case-by-case medical assessment, COVID-19 may exceptionally be administered off-label to children below 12 years of age. This is mainly for children following an operation or due to chronic diseases. At present, around 150 children under 12 years have received at least one dose of the COVID-19 vaccine in the Czech Republic.	**<u>No</u>**, but this summer the Czech Republic pre-ordered a total of 700,000 vaccine doses from Pfizer/BioNTech for children aged 5-11 years, i.e. for 86% of all of the approx. 809,000 children in this age group. According to Minister of Health Adam Vojtěch, the authorities are now awaiting the authorisation of the European Medicines Agency (EMA). There are also signs that the Czech Society for Vaccinology will support vaccination of children. A week ago, Vice-chair Hana Cabrnochová informed that the society has started preparing guidelines for vaccination of children aged 5-11 years, if needed. The Society will present recommendations and arguments concerning the safety and effectiveness of the vaccine and its benefits in this age group. The Czech Paediatric Society is currently still analysing the available data and has not made a final statement on the topic. If all statements are positive, including the final statement made by the Ministry of Health, it will likely be possible to vaccinate young children before end of year. The children will be vaccinated at their general practitioner. According to the Ministry of Health, the first vaccine supplies are expected in the second half of December.
Germany	**<u>No.</u>**	**<u>No</u>**, it will depend on the conclusions drawn by the EMA and ultimately on the recommendation (if any) made by the Vaccine Committee.
Hungary	**<u>No</u>**, vaccination of children aged 5-11 years has not yet been initiated in Hungary. When the process is initiated, children with chronic diseases who may be at risk of developing serious symptoms if	**<u>No</u>**, the Hungarian Government awaits EMA authorisation but, according to the Prime Minister's Office, plans exist to initiate vaccination of 5-11-year-olds as soon as the EMA authorises this. The

	infected (e.g., cystic fibrosis) will likely be prioritised as was the case during the roll-out of the vaccination plan for 16-18-year-olds.	president of the Hungarian Chamber of Paediatricians has recommended that all children aged more than 18 months are vaccinated. Other experts have also publicly signalled their support for the plan to vaccinate children below 12 years of age.
The US	**Yes**, the FDA has issued an emergency use approval of the COVID-19 from BioNTech-Pfizer for children aged 5-11 years, and the CDC has issued a guideline for administration of the vaccine for this age group. According to the CDC, the safety of COVID-19 vaccines is monitored under the most comprehensive and intense safety monitoring programme ever seen in US history. The CDC monitors the safety of all COVID-19 vaccines that have been authorised or have obtained an emergency use approval. Monitoring also includes the risk of myocarditis in children aged 5-11 years.	-
Austria	**Yes, in special cases.** Children between 5 and 11 years are offered COVID-19 vaccination only in special circumstances. Even so, children in this age group may already now receive COVID-19 vaccination, among others if their general practitioner or attached medical specialists assess that the significant reasons exist in favour of vaccination - e.g., in children with chronic conditions or similar. As from 15 November this year, children aged 5-11 years residing in Vienna have had access to COVID-19 vaccination, but with Comirnaty from P/B exclusively. Ahead of any vaccination of children in this age group, the child and his or her parents will receive comprehensive information about the vaccine, possible side	**No**, at the federal level Austria's national vaccine council (NIG) will first and foremost await the assessment and final recommendation of the EMA. Even so, the vaccine council, among others, is engaged in continuous analyses of relevant data from other countries.

	effects, etc. during a conversation with a healthcare professional.	

Table 11: The studied countries' recommendations on vaccination of 5-11-year-olds

Is vaccination of 5-11-year-olds recommended?	Countries
Yes, all 5-11-year-olds	US, IL, CA
Yes, special groups of 5-11-year-olds	SK, SE, CZ, AT
No, no 5-11-year-olds are recommended vaccination	AU, BU, BE, CY, EE, FI, FR, GR, IE, IS, IT, JP, HR, LV, LT, LU, MT, NL, NO, PL, PT, RU, CH, SI, ES, UK, DE, HU

Table 12: Update on the dialogue on vaccination of 5-11-year-olds in the studied countries

Is vaccination of 5-11-year-olds being discussed?	Countries
Yes	AU, CA, EE, FI, IL, JP, HR, NL, PT, SI, UK
No	BU, BE, CY, FR, GR, IE, IS, IT, LV, LT, LU, MT, NO, PL, RU, CH, SK, ES, SE, CZ, DE, HU, AT

Appendix 2 - Systematic literature search concerning cardiac complications to COVID-19

Appendix 2 describes a literature search on the risk of cardiac complications among children aged 0-15 years who become infected with COVID-19[161]. Searches were made through Week 46 in 2021. A total of four systematic reviews and 25 primary studies were identified. Below, we present the systematic reviews. Owing to the methodology used, these reviews have produced the most reliable data. Furthermore, each primary study is described.

One systematic review included seven Chinese studies comprising a total of 2,300 patients aged from two months to 18 years who had become infected with COVID-19. A total of 21 had cardiovascular affection, and 13 hereof had either myocardial injury or cardiac failure. The authors conclude that even though children generally pass COVID-19 infection with fewer and less serious symptoms than adults, cardiovascular affection does occur in children as a complication to COVID-19 infection[162].

A systematic review included a total of 23 studies with 517 COVID-19-infected children below 18 years of age, all of whom had a chest computed tomography (CT) performed. A total of 70% of the children had abnormal findings on their chest CT, primarily various pulmonary manifestations, whereas pericardial effusion was rare. Generally, the changes observed on CTs of the chest among children with COVID-19 were milder than the CT changes observed on the chest CTs of adults with COVID-19. Thus, data support a generally milder COVID-19 course among children than among adults, but the changes observed on chest CTs also occur in children[163].

A systematic review included a total of eight cohort studies with a control group, 20 case series and one cohort study with no control group. The cohort studies with a control group counted a total of 2,204 COVID-19 patients, among whom 443 developed cardiac damage during their infection. The included case series comprised at total of 45 COVID-19 patients with cardiac damage. Among these 45 patients, 78% were children or adolescents. Among the patients included in the systematic review, a total of 29 patients below 16 years had myocarditis. Five of these patients developed Kawasaki-like symptoms. All children who developed myocarditis eventually recovered except one who developed multiple organ dysfunction syndrome (MODS). Myocarditis was the most frequently occurring condition associated with cardiac damage among children below 16 years of age with COVID-19. Myocarditis was also observed among adult COVID-19 patients, but in general the variation in the type of cardiac

[161]Danish Health Authority. Case number 05-0600-1224

[162] Sanna G et al. Children's heart and COVID-19: Up-to-date evidence in the form of a systematic review. Eur J Paediatr. 2020 Jul;179(7):1079-1087. https://pubmed.ncbi.nlm.nih.gov/32474800/

[163] Zang ST et al. Imaging characteristics of coronavirus disease 2019 (COVID-19) in pediatric cases: a systematic review and meta-analysis. Transl Pediatr. 2021 Jan;10(1): 1-16. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7882282/

damage was far more extensive among adults with COVID-19 than among children. Whereas the children had benign myocarditis courses, the cases observed in adults comprised a limited number with serious cardiac damage and a limited number of deaths. These cases were characterised by sighs of blood clot to the heart, cardiac rhythm disturbances, etc., which was not observed in the children[164].

A systematic review in preprint explored the possibility of developing a scoring system to assist in the clinical diagnosis of MIS-C among children with COVID-19. In all, 333 children were included from 119 studies with patient data on children below 18 years of age with COVID-19 and no MIS-C. A total of 44/333 children (13.3%) with COVID-19 were asymptomatic, whereas 289/333 children with COVID-19 (86.7%) were symptomatic. A total of 52/289 children (17.9%) met the criteria for MIS-C as specified in the scoring system, and blinded validation of the cases confirmed the diagnosis. A total of 42/52 (80.8%) children with MIS-C had cardiac involvement, whereas this was the case for only 3/237 (1.3%) of the children with no MIS-C. Mortality was 5/52 (9.6%) among children with MIS-C, whereas it was 1/237 (0.4%) among children who did not have MIS-C. The study concluded that children with COVID-19 who develop MIS-C as a complication have a more serious disease course than children who have COVID-19 without MIS-C as a complication[165].

A case series among hospitalised paediatric patients included a total of 19 COVID-19-infected hospitalised children aged from two months to 18 years of age (median age: 8 years). The group comprised ten boys and nine girls. A total of five of the children developed acute myocardial injury. Their median age was 7 years. Among the 19 children, a total of 12 (63%) had comorbidities in the form of severe neurological impairment (n = 5) or severe obesity (n = 3), whereas one case of each of the following diagnoses was recorded; congenital cardiac disease, cardiomyopathy, metastasising cancer, asthma, hypertension, sickle cell anaemia, previous thromboembolic event, and Fragile X syndrome. A total of two children died, both had comorbidity. The authors conclude that even though COVID-19 has a mild and uncomplicated course in children compared to that experienced by adults, examples exist of serious disease courses, particularly among children with comorbidity[166].

A retrospective observational study included a total of 20 critically ill children hospitalised in a paediatric intensive care unit with COVID-19 complicated by shock. The median age was 10 years (IQR 2.9-15 years). Half of the children were boys and half were girls. None of the children had known comorbidity. All children had acute myocarditis with affected left ventri-

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[164] Aldien AS et al. Systemic inflammation may induce cardiac injury in COVID-19 patients including children and adolescents without underlying cardiovascular diseases: A systematic review. Cardiovasc Revasc Med. 2021 Apr 15;S1553-8389(21)00195-0. https://pubmed.ncbi.nlm.nih.gov/33952432/

[165] Surve SV et al. A systematic review on multisystem inflammatory syndrome in children (MIS-C) with COVID-19: Development of a scoring system for clinical diagnosis. Preprint. MedRxiv. 2021 27 July https://www.medrxiv.org/content/10.1101/2021.04.23.21255879v1.full.pdf

[166] Blumfield E et al. COVID-19 in pediatric patients: a case series from the Bronx, NY. Pediatric Radiology 2020, 50: 1369-1374. https://link.springer.com/article/10.1007/s00247-020-04782-2

cle ejection fraction. All but one of the children needed circulatory support. None of the children met the criteria for Kawasaki-like disease. None of the children died and all were discharged from intensive care with normal left ventricle function. The authors noted that the 20 critically ill children with COVID-19 obtained a better outcome than equally critically ill children in other COVID-19 case series[167].

A case series included nine children who were hospitalised for intensive paediatric care with COVID-19. Five of the children developed cardiac damage with mild to moderate heart dysfunction. Their average age was 84.4 months (approx. 12 years) (range 2-168 months corresponding to from 2 months to 14 years of age). All of the children were previously healthy. Four of the children needed circulatory support. All five children were discharged after an average of 7.2 days hospitalisation (range 5-10 days) with normal cardiac function. The authors encourage attention towards cardiac symptoms among children who have become infected with COVID-19[168].

[167] Grimaud M et al. Acute myocarditis and multisystem inflammatory emerging disease following SARS-CoV-2 infection in critically ill children. Annals of Intensive Care 2020, 10:69. https://annalsofintensivecare.springeropen.com/articles/10.1186/s13613-020-00690-8

[168] Wolfler A et al. Acute myocardial injury: a novel clinical pattern in children with COVID-19. Lancet Child & Adolescent Health 2020, vol 4(8), E26-E27. https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(20)30168-1/fulltext

Appendix 3 - Systematic literature review on late sequelae following COVID-19

Appendix 3 describes a literature search focusing on late sequelae following COVID-19.

A prospective cohort study included self-reported data from 5-17-year-old symptomatic children (either self-reported or parent-reported). Data from a total of 258,790 children were included. A total of 75,529 had a valid SARS-CoV-2 test. Among these children, 1,734 tested SARS-CoV-2 positive (588 younger children aged 5-11 years and 1,146 older children aged 12-17 years). The most frequently observed symptoms were headache (1,079/1,724 (62.2%)) and fatigue (954/1,734 (55.0%)). The median illness duration was six days (interquartile range (IQR) 3-11 days) among those who tested positive compared with three days (IQR 2-7) among those who tested negative. The median illness duration was longer for older children (7 days (IQR 3-12)) than for younger children (five days (IQR 2-9 days)). A total of 77/1,734 (4.4%) of the children had an illness duration of 28 days or more. This was observed more frequently among older children (59/1,146 (5.1%)) than among younger children (18/588 (3.1%)). The most frequently reported symptoms in the initial four weeks among these children were fatigue (65/77 (84.4%)), headache (60/77 (77.9%)) and lacking sense of smell (60/77 (77.9%)). Generally, the symptom burden receded and it was highest in the first week and lowest in the fourth week. A total of 25/1,379 (1.8%) experienced symptoms lasting a minimum of 56 days. Overall, data show that - even though most children who become infected with COVID-19 experience short disease courses with limited symptoms - some children experience prolonged disease, which nevertheless recedes within 56 days in most cases[169].

An observational study included 34 children hospitalised with COVID-19. The study comprised follow-up with respect to assessment of persisting pulmonary sequelae 30 days after infection. All participants had a CT performed during their hospitalisation. Pulmonary CT performed at follow-up after 30 days was available for 14 children (four boys and ten girls). In 7/14 (50%) of the children, sequelae related to the lungs were observed on the CT performed after 30 days. The changes included blurry spots or areas (3/14 (21%)) and fibrosis (4/14 (29%)). In the remaining seven cases, radiological normalisation of the lungs was observed. No difference was observed in the degree of shortness of breath between children with and without pulmonary changes on CT after 30 days. The authors concluded that pulmonary changes may be observed on CTs made 30 days after discharge from hospital in some children who have been hospitalised with COVID-19 even though they do not present with any clinical symptoms of shortness of breath[170].

[169] Molteni E et al. Illness duration and symptom profile in symptomatic UK school-aged children tested for SARS-CoV-2. Lancet 2021 3. august. https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(21)00198-X/fulltext

[170] Zhang C et al. Pulmonary sequelae of pediatric patients after discharge for COVID-19: an observational study. Pediatr Pulmonol 2021;56(5):1266-1269. https://pubmed.ncbi.nlm.nih.gov/33559979/

A cohort study included 129 children < 18 years diagnosed with COVID-19 between March 2020 and October 2020. The mean age was 11 years ± 4.4 years. A total of 62/129 (48.1%) were girls. Six children were excluded due to neuro-cognitive functional impairment (and ensuing lacking ability to report symptoms). A total of 109 children (84.5%) were interviewed by phone and the remaining as part of their out-patient assessment. A total of 33 children (25.6%) were asymptomatic, and 96 children (74.4%) were symptomatic. Six children (4.7%) required admission to hospital and three children (2.3%) needed intensive care. A total of three children developed MIS-C and two children developed myocarditis. On average, patients were assessed 162.5 days ± 113.7 days after being diagnosed. At that time, 41.8% had recovered completely, 35.7% still had 1-2 symptoms, whereas 22.5% still had three or more symptoms. The most frequently reported symptoms were sleeplessness (18.6%), respiratory symptoms including chest pain and chest fatigue (14.7%), nasal congestion (12.4%), fatigue (10.8%), myalgia (10.1%), arthralgia (6.9%) and difficulty concentrating (10.1%). The study documented that children with a primary COVID-19 course that did not require admission to hospital may have persisting symptoms many weeks after having recovered from their infection[171].

A prospective cohort study included children ≤ 18 years hospitalised with confirmed COVID-19 from 2 April 2020 to 26 August 2020. The patient's parents were contacted by phone in the period from 31 January 2021 to 27 February 2021 to complete a questionnaire on late COVID-19 sequelae. From a total of 853 children hospitalised with COVID-19, 518 (62%) participated in the questionnaire study. The median age was 10.4 years (IQR: 3-15.2 years) and 272 (52.2%) were girls. The median follow-up period as from hospitalisation was 268 days (IQR 233-284 days). Some children had comorbidity. The most frequently occurring comorbidities were food allergy (13%), allergic rhinitis and asthma (9.7%), gastrointestinal problems (9.3%), eczema (8.8%) and neurological problems (8.4%). A total of 55.3% had no reported comorbidities. At the completion of the questionnaire, a total of 128/518 (24.7%) reported a minimum of one persisting symptom. The most frequently reported symptoms were fatigue (10.6%), sleeplessness (5.19%), reduced/changed sense of smell (4.7%) and headache (3.5%). A total of 44/518 (8.5%) reported more than one symptom. The most frequently reported combination of symptoms was fatigue and sleep problems among 1.9% of the children, and fatigue and tiredness and sensory problems among 1.5% of the children. More advanced age was associated with an increased probability of persisting symptoms. Using children aged two years as a reference, children aged 6-11 had an odds ratio of 2.74 (95% CI 1.37-5.75) for persisting symptoms and children aged 12-18 years of age had an odds ratio of 2.68 (95% CI 1.41-5.4). Over time, a gradual decline was observed in the number of children who reported persisting symptoms[172].

[171] Buonsenso D et al. Preliminary evidence on long COVID-19 in children. Acta Paediatr. 2021;110(7):2208-2211. https://pubmed.ncbi.nlm.nih.gov/33835507/

[172] Osmanov IM et al. Risk factors for long COVID in previously hospitalised children using the ISARIC Global follow-up protocol: A prospective cohort study. Eur Resp J 2021. https://erj.ersjournals.com/content/early/2021/06/10/13993003.01341-2021

An observational cross-sectional study conducted from 18 December 2020 to 6 February 2021 included questionnaires from a total of 57 Dutch hospitals, which comprised 78% of all Dutch hospitals with a paediatric department. A total of 89 children with suspected COVID-19-related late sequelae were described. The median age was 13 years (IQR 9-15 years). A total of 47/89 (52.8%) had a positive PCR test, 31/89 (34.8%) had a positive serology, whereas 34/89 (38.2%) had a clinical diagnosis. The groups overlap. In a total of 8/89 (9.0%) children, it was uncertain how the COVID-19 diagnosis had been made. The most frequently reported complaints were fatigue (87%), shortness of breath (49%), concentration difficulties (40%), headache (34%), chest pain (31%), stomach pain (29%), myalgia (25%) and diarrhoea (21%). At the time when late sequelae were diagnosed, 8% reported no changes in their habitual activities, 48% reported a mild limitation of activities (e.g. attends school but with more fatigue than normal), whereas 36% reported extensive limitation of activities in the form of no or only limited school attendance. A total of 29% of the children needed help from a multidisciplinary team, 25% needed physiotherapy and 16% were seen by a psychologist. Three patients were referred for a paediatric cardiologist (causes not described) and one patient had kidney failure and was referred to a nephrologist, but it remained unclear if the symptoms were late sequelae from COVID-19[173].

[173] Brackel CLH et al. Pediatric long-COVID: An overlooked phenomenon? Pediatr Pulmonol 2021;56(8):2495-2502. https://pubmed.ncbi.nlm.nih.gov/34102037/