Key messages

- Surveillance data show that children aged 5-11 years have made up an increasing proportion of both notified cases and hospitalisations in EU/EEA countries in recent months. Although hospitalisations have increased in line with case rates in all age groups in the EU/EEA, disease severity of COVID-19 in children is generally mild with a favourable clinical outcome. Severe COVID-19 remains rare among children (of 65,800 notified symptomatic COVID-19 cases in children aged 5-11 years, reported from 10 EU/EEA countries during the period of B.1.617.2 (Delta) variant of concern (VOC) dominance, 0.61% were hospitalised and 0.06% needed intensive care unit (ICU)/respiratory support).
- The relative contribution of children to overall SARS-CoV-2 circulation may have increased due to factors including the emergence of the highly transmissible Delta VOC and increased vaccination coverage in older age groups.
- The presence of an underlying condition among children aged 5-11 years is associated with about 12 times higher odds of hospitalisation and 19 times higher odds of ICU admission. However, the majority (78%) of hospitalised children of this age had no reported underlying medical condition.
- Paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2/multi-inflammatory syndrome in children (PIMS-TS/MIS-C) and post COVID-19 condition have been reported in children aged 5-11 years, although it is difficult to quantify the prevalence and burden of these conditions. In a United States (US) Centers for Disease Control and Prevention (CDC) report, myocarditis was reported up to 37 times more often in unvaccinated children less than 16 years old with a COVID-19 diagnosis compared to other patients from the same age group.
- Beyond the direct health impacts of COVID-19 disease, the COVID-19 pandemic has affected the physical and mental health and well-being of children aged 5-11 years. Numerous factors, such as disruptions to important everyday social and educational activities, have caused anxiety and distress in this age group.
- Modelling data indicate that vaccinating children aged 5-11 years could reduce SARS-CoV-2 transmission in the whole population, although the extent and duration of this protection is currently unknown. It is estimated that the impact on the effective reproduction number ($R_t$) in the population as a whole would be a decrease of 11% (range: 6-15%, depending on vaccine uptake parameters of 30-70%) for an average country in the EU/EEA. This is comparable to the effect of some non-pharmaceutical interventions. The impact of vaccinating children is weaker for countries with a low adult vaccine uptake and stronger for countries with high uptake among adults.
- On 25 November 2021, the European Medicines Agency (EMA) granted a positive opinion for use of the Comirnaty COVID-19 vaccine in children aged 5-11 years based on a placebo-controlled randomised clinical trial in which more than 3,000 children in this age group received this vaccine.
• Children aged 5-11 years who are at risk of severe COVID-19 should be considered a priority group for vaccination against COVID-19, as in other age groups. However, since hospitalisation, PIMS-TS/MIS-C and post COVID-19 condition can also occur among children with no known risk factors, consideration could be given to the vaccination of all children aged 5-11 years.

• COVID-19 vaccine safety data in children aged 5-11 years are currently limited, and the level of natural immunity in the unvaccinated and its duration are currently unknown and likely heterogeneous across the population.

• The main priority of COVID-19 vaccination campaigns seeking to reduce COVID-19-related morbidity and mortality remains to increase vaccine uptake in the eligible adult population. Before taking policy decisions on COVID-19 vaccination in children, potential harms and benefits – including the direct and indirect effects on health and well-being – should be considered alongside the vaccine uptake and epidemiological situation in a particular country. Aspects around implementation and health equity should also be taken into consideration.

Scope of this document

This technical report provides information on the following aspects:

• Overview of current plans for COVID-19 vaccination of children aged 5-11 years in the EU/EEA
• Assessment of the burden of COVID-19 in children aged 5-11 years
• Role of children in SARS-CoV-2 transmission
• Available data on COVID-19 vaccines in children
• Estimated impact of vaccinating children on the R<sub>t</sub>
• Objectives of vaccination of children, considering individual benefits and population benefits

This technical report provides a set of interim public health considerations to support EU/EEA public health authorities taking decisions on the administration of COVID-19 vaccines to children aged 5-11 years. As new evidence is continuously being generated and safety is being monitored on an ongoing basis, it is essential to consider the latest available information and recommendations issued by regulatory and public health authorities at the national level.

Target audience

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

Background

As of 30 November 2021, four COVID-19 vaccines have received conditional marketing authorisation in the EU/EEA following evaluation by the European Medicines Agency (EMA). These vaccines are: COVID-19 vaccine Comirnaty, COVID-19 vaccine Spikevax, COVID-19 vaccine Vaxzevria, and COVID-19 vaccine Janssen. Comirnaty and Spikevax are authorised for use in people aged 12 years and older [1,2], while the other two vaccine products are currently only authorised for use in people aged 18 years and older [3,4].

In EU/EEA countries, the roll-out of COVID-19 vaccine campaigns started at the end of December 2020, when the first vaccine doses were delivered. On 19 January 2021, the European Commission set out actions to step up the response against the pandemic and accelerate the roll-out of vaccination campaigns, with the targets of vaccinating at least 80% of people over the age of 80 years and 80% of health and social care professionals in every Member State by March. In addition, a minimum of 70% of the adult (18 years and older) population were to be vaccinated by the summer [5]. EU/EEA countries initially prioritised vaccination of older adults, residents and personnel in long-term care facilities, healthcare and social care workers, and people with certain comorbidities, and have gradually progressed to vaccinating younger age groups in the general population [6].

As of 17 November (week 45), the cumulative vaccine uptake in the total population in the EU/EEA reached 69.8% (country range: 26.87-9.9%) for at least one vaccine dose and 65.4% (range: 23.9-81.4%) for the full vaccination course (pooled data from 30 reporting countries). Among adults in the EU/EEA as a whole, the cumulative vaccine uptake reached 81.3% for at least one vaccine dose (range: 31.1-99%) and 76.5% for the full vaccination course (range: 28.4-92.6%) (pooled data from 30 reporting countries) [7].

On 10 May 2021, the US Food and Drug Administration (FDA) issued an Emergency Use Authorization for the use of Comirnaty in 12-15-year-olds [8], and on 28 May it was approved by EMA after evaluation of data on efficacy and safety for the indicated age group [9]. On 23 July, Spikevax was also approved by EMA for this age group [10]. As of 30 November, all EU/EEA countries have initiated vaccination in children aged 12-15 years [6].
As of 19 November, the median cumulative uptake of at least one dose of COVID-19 vaccine and full COVID-19 vaccination in individuals under 18 years old was 18.3% (range: 1.3–32.8%) and 15.0% (range: 1.0–29.0%), respectively (based on 27 reporting countries) [11].

On 25 November 2021, EMA recommended granting an extension of indication for Comirnaty to include use in children aged 5-11 years [12]. The same application was evaluated by the US FDA and, on 29 October, Comirnaty was authorised by the FDA for emergency use in children aged 5-11 years [13]. While many EU/EEA countries continue to experience considerable case notification rates and varying rates of vaccination coverage in different age groups, the question of whether or not the vaccination strategy should be broadened to include children under the age of 12 years is gaining increased attention.

**Current status concerning vaccination of children in the EU/EEA**

**Planned vaccination of children under 12 years old**

According to information collected through the Integrated Situational Awareness and Analysis (ISAA) report in October 2021, 3 of 20 responding countries were planning to expand vaccination to children under the age of 12 years if the EMA authorised a COVID-19 vaccine for that age group. Several countries reported that this was under discussion [6].

**Table 1. Planned recommendation for COVID-19 vaccination of children under 12 years old (n = 20 countries)**

<table>
<thead>
<tr>
<th>Planned recommendation</th>
<th>Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccination of all children</td>
<td>Czechia, Lithuania, Hungary</td>
</tr>
<tr>
<td>Under discussion</td>
<td>Belgium, Croatia, Latvia, Luxembourg, Malta, Netherlands, Poland, Portugal, Spain</td>
</tr>
<tr>
<td>Other</td>
<td>Austria**, Germany**, Iceland**, Ireland***, Romania*, Norway***, Slovenia*, Sweden*</td>
</tr>
</tbody>
</table>

* Will be discussed after European Medicines Agency (EMA) recommendation.
** Likely to recommend vaccination, but currently undecided.
*** To be determined.

**COVID-19 in children aged 5-11 years**

**What is the susceptibility of children aged 5-11 years to SARS-CoV-2 infection?**

It is important to note that throughout the pandemic there has been a high variability for reported SARS-CoV-2 prevalence among children across time and across geographical regions, as this depends on many factors, including testing policies, children's social mixing patterns (affected by whether schools have been open or closed), and mitigation measures implemented in specific settings such as schools and households. This has complicated the comparison of studies that assess the susceptibility of children to SARS-CoV-2 infection, as well as their contribution to onward transmission.

Children of all ages appear to be equally susceptible to SARS-CoV-2 infection compared to adults, even if severe disease is comparatively much less common in children [14]. However, the literature is quite heterogeneous on this topic. For example, a multicentre serologic study of SARS-CoV-2 transmission in households conducted in Germany in 2020, but published in 2021, concluded that children were less susceptible to SARS-CoV-2: the secondary attack rate in household members under 18 years of age was 8-13% lower than in adults [15]. While multiple additional studies have also suggested that unvaccinated children may be less susceptible to SARS-CoV-2 infection than unvaccinated adults [14,16], potential reporting biases due to lower case ascertainment in children may have contributed to this interpretation, particularly for studies conducted in 2020, when SARS-CoV-2 testing capacities were often limited and testing was prioritised for symptomatic patients [14].

More recent incidence and seroprevalence studies have tended to conclude that there are no significant differences in susceptibility to SARS-CoV-2 infection across age groups [17,18]. This is notably the case for study designs that have conducted repeated testing among study participants, irrespective of symptoms. A prospective cohort study from Austria repeatedly tested over 10 000 staff and students for SARS-CoV-2 infection using a gargling solution and RT-qPCR [19]. The authors concluded that SARS-CoV-2 prevalence did not differ across age groups, pupils or teachers, or primary or secondary schools, but did observe an association between prevalence and regional community incidence and social deprivation [19]. A prospective study of students, parents and teachers linked to a single school in Belgium, conducted between 21 September and 31 December 2020, involved weekly testing of all study participants [20] and found no significant difference in the infection rates between children and adults (odds ratio (OR): 0.58; 95% confidence interval (CI): 0.22-1.41). In the US, a large prospective cohort study of households in Utah and New York took place from September 2020 through April 2021 and involved weekly RT-PCR of all 1 236 included study participants, regardless of symptoms [21]. It was reported that the
interim public health considerations for COVID-19 vaccination of children aged 5-11 years

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incidence rate ratio (IRR) for children aged 5-11 years compared to adults was 0.9 (CI: 0.5-1.4; p=.55) [21]. The study also reported that 50% of positive cases among children aged 5-11 years were asymptomatic, as compared to 12% for adults [21]. Moving forward, the relative incidence of SARS-CoV-2 infection among children is likely to increase, depending upon the different levels of vaccine uptake across age groups.

It is important to note that most currently published scientific studies were conducted prior to the emergence (or the dominant circulation) of the Delta VOC, which is now predominant across the EU/EEA. As the Delta VOC has a significant transmission advantage over previously circulating SARS-CoV-2 strains, there is significantly increased susceptibility to SARS-CoV-2 infection among all age groups [22]. As far as children are concerned, for example, a COVID-19 outbreak caused by the Delta VOC at an elementary school demonstrated the high susceptibility of unvaccinated elementary school-aged children when exposed to an index patient (in this instance, an unvaccinated teacher), with an attack rate of 50% and the risk of infection among students correlated to the seating proximity to the teacher [23]. In England in September 2021, as the autumn semester started, the age groups with the highest weighted prevalence of SARS-CoV-2 (predominantly Delta VOC) were among school-aged children aged 5-12 years (2.32%) and 13-17 years (2.55%) [24]. In a follow-up round of the same study, school-aged children continued to have the highest weighted prevalence, which rose to 4.95% in children aged 5-12 years and 5.21% in children aged 13-17 years for the time period mid-October to mid-November 2021 [25].

What is the likelihood of secondary SARS-CoV-2 transmission by children aged 5-11 years?

Throughout much of the COVID-19 pandemic, research that has sought to ascertain the relative contribution of children to overall levels of SARS-CoV-2 transmission has been limited by factors such as school closures and lockdowns, which often altered children’s social mixing patterns differently than they did for adults; varying implementation of infection prevention and control measures in household and school settings; and case ascertainment in children, given that children are more likely than adults to have asymptomatic SARS-CoV-2 infection.

Despite such limitations, the scientific literature clearly demonstrates the possibility of onward transmission of SARS-CoV-2 by children of all ages [14]. Most of the scientific literature reports on SARS-CoV-2 transmission from strains that preceded the Delta VOC. Currently, the likelihood of secondary transmission from all age groups, including children aged 5-11 years, has likely increased due to the higher transmissibility and dominance of the Delta VOC over other SARS-CoV-2 strains [22].

Transmission by children likely depends on multiple factors, including symptom type and severity, viral load and shedding duration, host factors (such as baseline susceptibility and immune responses), as well as the viral variant [26]. The balance of evidence suggests that peak respiratory tract viral load in children infected with SARS-CoV-2 does not differ from adults, but that the duration of respiratory tract viral shedding is shorter in children when compared to the adult population [14,27]. In a recently published analysis of RT-PCR cycle threshold values, it was concluded that both symptomatic and asymptomatic children may have high SARS-CoV-2 viral loads, irrespective of a child’s age or of disease severity [28]. However, a separate study concluded that there was a higher viral load in the nasopharynx of symptomatic children, as compared to asymptomatic children [29].

There are mixed results in the literature (the vast majority of which does not report on the Delta VOC) about whether children are more or less likely to transmit SARS-CoV-2 than adolescents or adults, given equivalent vaccination status, as previously reported [14]. A recently published multicentre serologic SARS-CoV-2 household transmission study from Germany, conducted during 2020, concluded that the secondary attack rates increased with the age of the index patients: the lowest secondary attack rates were from children under 12 years old (12%), rising to around 31% for adolescents and adults less than 60 years old, and higher yet for adults over 60 years old [15]. Of note, is that less severe disease in children may lead to less seroconversion [30]. On the other hand, a study published in August 2021 examined 6,280 households with paediatric index cases in Ontario, Canada, between 1 June and 31 December 2020. The study concluded that, compared to 14-17-year-olds, 0-3-year-olds had higher odds of transmitting SARS-CoV-2 to household contacts. There were no significant differences in the odds of transmission by 4-8-year-olds or 9-13-year-olds in comparison with 14-17-year-olds [31]. A study published in September 2021 reported on a convenience sample of 202 COVID-19-positive patients in the US and found that contacts of index cases aged less than 18 years (and especially under 5 years old) were more likely to be symptomatic than contacts of index cases aged 18-44 years, although the results were not statistically significant [32]. A large, ongoing community survey of SARS-CoV-2 transmission in England reported that during the study period (mid-October to mid-November 2021) those living in larger households and those with children in the household had a higher prevalence of SARS-CoV-2 swab positivity than single-person households and those without children, although the odds ratios for specific age ranges of children in households was not reported [25]. Alongside households, educational settings offer a crucial source of evidence for understanding transmission of SARS-CoV-2 by children. Irrespective of the relative differences in secondary attack rates between children and adults, research from Sweden [33] and the US [34] has shown an elevated risk of SARS-CoV-2 infection for adults living in households with children attending schools in-person. While the Swedish study did not address children in the age group 5-11 years [33], the US study concluded that the risk to adults rose as school grade increased and was highest with children in grades 9 to 12 [34]. Notably, however,
the study also concluded that such risks can be mitigated through the introduction of appropriate control measures in educational settings. A separate study from Italy concluded that there was a lower probability of infection in children that had a school contact as compared to a household contact, speculating that in-school mitigation measures – for example, infrastructural adjustments, social distancing and symptomatic testing of pupils and staff – may have contributed to this finding [35]. A preprint systematic literature review concluded that transmission in educational settings during 2020 was minimal when appropriate measures were in place [36], although this review was completed prior to the dominance of the Delta VOC, which has increased the likelihood of transmission in school settings [14]. Conversely, a study of children, parents and teachers linked to a single school in Belgium concluded that among study participants testing positive for COVID-19, most transmission events occurred within the school setting and most household transmission events were from a child or teacher that had acquired the infection at school; however, this finding may have been affected by the study design [20]. While there are few official reports tallying SARS-CoV-2 outbreaks in school settings, data from Germany indicate that following the reopening of schools after the summer 2021 break, the number of reported outbreaks in school settings increased more rapidly, as compared to this period in 2020. This could be explained by such factors as the greater transmissibility of the Delta VOC or the expansion of testing in school settings [37].

**What is the incidence of SARS-CoV-2 infection and COVID-19 symptomatic disease in children aged 5-11 years in the EU/EEA?**

Analysis of pooled data reported by 10 EU/EEA countries (Austria, Cyprus, Finland, Germany, Ireland, Italy, Luxembourg, Malta, Slovakia, Sweden) to The European Surveillance System (TESSy) showed that weekly notification rates of symptomatic COVID-19 cases increased sharply in all age groups from July 2021 (Figure 1a). Among children aged 5-11 years, case rates increased between 5 July and 3 October 2021, from 5.9 to 65.0 per 100 000 population, an 11-fold increase and the second highest rate after the 12-17 years age group (71.9 per 100 000). In the same period, the 5-11 years age group, which makes up 6.6% of the combined population of these countries, went from accounting for 3.8% to 11.2% of weekly cases, a 3-fold increase (Figure 1b).

**Figure 1. Pooled age-specific weekly rate of notified and hospitalised symptomatic cases per 100 000 population and age distribution of notified and hospitalised cases reported to TESSy, 3 August 2020 to 3 October 2021.**
What are the frequency and proportion of hospitalisations and deaths from COVID-19 in children aged 5-11 years in the EU/EEA?

Hospitalisation of children diagnosed with COVID-19 has also increased, broadly in line with the rise in cases in this age group, but remains at much lower levels in children than in adults. For symptomatic cases reported in the same period (5 July to 3 October 2021), the weekly rate of hospitalised cases in children aged 5-11 years rose from 0.025 to 0.24 per 100 000 population, a nine-fold increase (Figure 1c). At the same time, this group went from contributing 0.3% to 0.8% of weekly hospitalised cases, a 2.7-fold increase (Figure 1d).

Crude risks for severe outcomes were estimated using pooled data from the 10 EU/EEA countries with complete data on hospitalisation, severe hospitalisation (ICU admission and/or requiring ventilation or extracorporeal membrane oxygenation) and death, for the period in which the Delta VOC became and remained dominant (weeks 28 to 39 2021). Among the 65 800 symptomatic cases aged 5-11 years that were notified during this period, 399 were hospitalised (risk: 0.61%; 95% CI: 0.55-0.67%) and 42 were severely hospitalised (risk among all cases: 0.06% (95% CI: 0.05-0.09%); risk among hospitalised cases: 10.5% (95% CI: 7.7-14.0%)). Deaths were extremely rare, with only two reported. There were no differences in the distribution by sex of these outcomes (chi-squared p>0.22).

What are the factors associated with COVID-19 hospitalisation and severe disease in children aged 5-11 years?

From the analysis of pooled data reported by 10 EU/EEA countries (Austria, Cyprus, Finland, Germany, Ireland, Italy, Luxembourg, Malta, Slovakia, Sweden) to TESSy for the period 3 August 2020 to 3 October 2021, the presence of an underlying condition among hospitalised cases aged 5-11 years was associated with 12.0 (range: 9.0-16.0) times higher odds of hospital admission and 19.0 (range: 10.1-34.1) times higher odds of severe hospitalisation. Despite the higher odds in children with one or more underlying condition, the majority (78%) of hospitalised children of this age had not reported an underlying medical condition. Diabetes, cancer and cardiac disease were most commonly reported among hospitalised cases with a comorbidity. However, this may depend on context, as different access to care, hospitalisation criteria and prevalence of underlying conditions could affect the associations observed in surveillance data and the literature.

According to the literature, underlying conditions increase the risk of hospitalisation or severe outcomes [38,39]. The most common comorbidities reported in hospitalised children are diabetes and gastrointestinal, neurological, cardiac and pulmonary diseases, specifically asthma [40,41]. A significant proportion of hospitalised children with SARS-CoV-2 infection are also obese [42,43]. Data based on 2 293 hospitalised children with confirmed COVID-19 in the US demonstrated that obesity (adjusted risk ratio (aRR): 1.4; 95% CI: 1.2–1.6) was associated with increased risk of severe COVID-19 in children aged 5-11 years [44]. A recently published systematic review and meta-analysis identified underlying conditions, such as neurological diseases and obesity, to be associated with increased odds of death [39]. They also found seven studies showing that age less than 10 years increased the odds of death by 1.76 times, and only two studies with low-quality evidence concluding that age less than 6 months was associated with severe disease. Authors addressed that findings from these studies should be interpreted with caution, as the various sample sizes or differences in definitions could lead to contradictory conclusions on risk factors associated with severe disease or death. It is also important to note that pre-existing underlying diseases in children would likely lower the threshold for hospital admission and potentially inflate the observed associations.

Another systematic review and data analysis mainly covering wildtype and Alpha VOC circulation showed that sex was not associated with critical care or death [45]. Compared with children aged 1-4 years, infants (less than 1 year old) had increased odds of admission to critical care (OR: 1.63; 95% CI: 1.40-1.90) and death (OR: 2.08; 95% CI: 1.57-2.86). Odds of death were increased among children older than 10 years (10-14 years age group OR: 2.15 (95% CI: 1.54-2.98); >14 years age group OR: 2.15 (95% CI: 1.61-2.88)). A higher number of comorbid conditions was associated with higher odds of admission to critical care and death for COVID-19. For critical care admission, odds ratios were: one comorbidity OR: 1.49 (95% CI: 1.45-1.53); two comorbidities OR: 2.58 (95% CI: 2.41-2.75); three or more comorbidities OR: 2.97 (95% CI: 2.04-4.32). The odds ratios for death were: one comorbidity OR: 2.15 (95% CI: 1.98-2.34); two comorbidities OR: 4.63 (95% CI: 4.54-4.74); three or more co-morbidities OR: 4.98 (95% CI: 3.78-6.65). The odds of admission to critical care were increased for all comorbidities except for asthma (OR: 0.92; 95% CI: 0.91-0.94) and malignancy (OR: 0.85; 95% CI: 0.75-0.97), with increased odds of death in all co-morbidities considered, except for asthma. Neurological and cardiac comorbidities were associated with the greatest increase in odds of severe disease or death. Obesity increased the odds of severe disease and death independently of other comorbidities. Among hospitalised children and adolescents, severe disease or death from SARS-CoV-2 infection was more often observed among infants, teenagers, those with cardiac or neurological conditions, those with two or more comorbid conditions, and those who were obese. While odds ratios were high, the absolute increase in risk for most comorbidities was small compared to children without underlying conditions.
According to the scientific literature, what is the burden of COVID-19 in children aged 5-11 years?

Notified cases in children are dependent on the testing frequency in this age group, which has varied over time and between countries. In-school testing approaches are likely to have been expanded over time with the broader implementation of rapid antigen detection tests (RADTs) and in an effort to keep schools open. Furthermore, children are more likely to have mild disease and evidence suggests that overall asymptomatic rates of COVID-19 in children range from 13-50% [14,21,46,47].

The level of immunity from natural infection in children can be estimated from seroprevalence studies but may vary considerably between geographic areas and populations. Several studies show that seroprevalence has increased over time since the beginning of the pandemic and is increasing among children [18,48]. Some studies on European populations (with data collected between May and July 2021) have reported seroprevalence rates ranging from 15-31% in children under 12 years old [48-51]. According to a national seroprevalence study in the US, the seroprevalence in the 5-11 years age group increased from 13% in Nov to Dec 2020 to 42% in May to June 2021 [52]. Reporting delays limit the ability to provide an up-to-date estimate of the current seroprevalence in the EU/EEA. It should be noted that not all children seroconvert after an infection with SARS-CoV-2 [30] and the proportion that seroconvert may be lower than the proportion in adults [53].

Based on data from the United Kingdom (UK) that was prospectively collected from a cohort of children aged 5-17 years, presentation to the emergency department or admission to hospital was reported for 14 of 276 (2.2%) children aged 5-11 years with Alpha VOC infection and 8 of 227 (3.5%) children in this age group with Delta VOC infection [54]. According to surveillance data from Israel, 291 628 children have been registered in the national COVID-19 registry. Of these, 568 (0.35%) were admitted to the hospital, 8% had moderate/severe disease, and none died [55].

Data from the German paediatric COVID-19 registry (for the period March 2020 to August 2021) showed that among 1680 children hospitalised due to COVID-19, 85 children (5%) were admitted to ICU and 13 died (0.8%), but COVID-19 was confirmed as the main cause of death for only 6 of the 13 children who died [56].

According to an analysis from the US CDC, the rate of new COVID-19 cases and COVID-19-related emergency department visits increased for the age groups 0–4 years, 5–11 years, and 12–17 years after the Delta VOC became the predominant circulating variant (August 2020 to June 2021, compared to July to August 2021) [57]. Hospital admissions of patients with confirmed COVID-19 also increased in the 0–17 years age group during this period. It could not be concluded from the analysis whether the increase in emergency department visits and hospitalisations were related to an increased severity of disease caused by the Delta VOC compared to earlier circulating variants, or to other factors such as increased transmission during that time.

A national study from England provides further estimates of mortality among children [58]. A total of 3105 children and young people died from all causes during the first year of the COVID-19 pandemic in England. Of these deaths, 61 occurred in individuals who tested positive for SARS-CoV-2. Of these, 25 individuals died of SARS-CoV-2 infection, 22 from acute infection and 3 from PIMS-TS/MIS-C. A proportion of 99.995% of children and young people with a positive SARS-CoV-2 test survived. The 25 individuals who died of SARS-CoV-2 equates to a mortality rate of two per million for the 12 023 568 children and young people living in England. In the age group 5-9 years, the corresponding mortality rate was 1 per million.

Mortality estimates from national statistical data reported by Germany, Italy, Spain and France up to February 2021 ranged from one to two per million in the age group 0-9 years [59].

What are the possible clinical manifestations of COVID-19 in children aged 5-11 years?

The clinical manifestations of COVID-19 in children aged 5-11 years are well documented. Most children with COVID-19 have mild symptoms or asymptomatic disease and a very low risk of death [14,59]. In a prospective cohort study from the UK, children in this age group reported three symptoms as a median and experienced shorter hospital stays (five days; interquartile range (IQR): 2-9 days) than adolescents [60]. The most common symptoms for the age group 5-11 years were fever, headache, fatigue, and sore throat.

Most published literature on disease severity in children report data from the time before the Delta VOC became predominant. Some studies that covered both adults and children have suggested that individuals infected with the Delta VOC are at higher risk of hospitalisation compared to previous dominant variants [61,62]. According to a UK prospective cohort study including 109 626 children aged 5-17 years, COVID-19 caused by the Delta VOC in children aged 5-11 years resembles COVID-19 caused by the Alpha VOC [54]. The median illness duration in this age group was approximately five days (IQR: 2–9.75) for both variants (Delta VOC: 5 days (IQR: 2–9): Alpha VOC: 5 days (IQR: 2–9.75)), while the number of symptoms appeared slightly greater with Delta VOC compared to Alpha VOC infection. In this age group, the most common symptoms were the same for both variants: rhinorrhea (i.e. runny nose) \( n = 130 \) (47.1%) of 276), headache \( n = 110 \) (39.9%) of 276), and fatigue \( n = 107 \) (38.8%) of 276) with Alpha
what is the occurrence of multisystem inflammatory syndrome (PIMS-TS/MIS-C) and of post COVID-19 condition in children aged 5-11 years who are infected with SARS-CoV-2?

Following the initial wave of COVID-19 hospitalisations, a novel syndrome with hyperinflammatory response in children emerged, initially identified by physicians in the UK in April 2020. The Royal College of Paediatrics and Child Health defined it as paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS), while the World Health Organization (WHO) and the US CDC refer to it as multisystem inflammatory syndrome in children (MIS-C) [66,67]. Unfortunately, there is currently no specific test available to diagnose this syndrome. [66]. Hence, the diagnosis of PIMS-TS/MIS-C is based on clinical signs and symptoms, as well as evidence of a previous SARS-CoV-2 infection or exposure. Children who develop the syndrome are generally previously healthy, and the primary infection with SARS-CoV-2 is usually mild or asymptomatic [68].

PIMS-TS/MIS-C is rare and shares common clinical features with other paediatric inflammatory syndromes such as Kawasaki disease, toxic shock syndrome, and macrophage activation syndrome. Children with PIMS-TS/MIS-C often present four to six weeks after infection, with a wide clinical spectrum including Kawasaki disease-like symptoms, life-threatening shock, and milder forms of illness such as persistent fever, inflammation, and gastrointestinal manifestations [68]. The median age of children diagnosed with the syndrome is eight years [69].

Most children with critical illness due to PIMS-TS/MIS-C have a favourable outcome and recover with intensive care support and appropriate treatment. According to studies, 60% of children with PIMS-TS/MIS-C need to be admitted to an intensive care unit (ICU), with an average length of ICU stay of around 5 days and an average total hospital stay of around 10 days [42,68]. In a cohort of 286 children and adolescents from 55 centres across 17 European countries, a high incidence (93%) of myocardial involvement was evident [70]. A multi-institutional study on PIMS-TS/MIS-C in 76 children found that myocarditis, heart failure and coronary artery involvement were the most common cardiovascular manifestations [71]. Critical illness is associated with increasing age of children in some studies [72,73]. A population-based study of PIMS-TS/MIS-C found that 36% of children had persistent symptoms eight weeks after diagnosis [74]. The mortality associated with PIMS-TS/MIS-C was approximately 1% in an observational cohort study of young people admitted to the hospital with COVID-19 in the UK [41].

A systematic review covering 68 studies of various study designs reported data from a total of 953 PIMS-TS/MIS-C cases [75]. The clinical pattern was heterogeneous among the studies and the most commonly reported symptoms were fever (99.4%), gastrointestinal symptoms (85.6%) and cardiocirculatory manifestations (79.3%). The median time of hospitalisation was 8 days (IQR: 7–12) in single cases and 4-12 days in cohorts, and 18 of the reported cases were fatal. The most common risk factor for the condition was being overweight, which was present in 25% of the cases. Data analysis from the Norwegian national COVID-19 registry showed an increased risk of PIMS-TS/MIS-C in children with chronic comorbidities [76].

Early recognition and prompt treatment of PIMS-TS/MIS-C cases is essential. Limited evidence for treatment options supports the use of intravenous immunoglobulin (IVIG), corticosteroids, inotropes and other biological immunomodulation agents [77,78].

As children often present with mild symptoms of COVID-19 and are less frequently tested than adults, the true proportion of cases that develop PIMS-TS/MIS-C remains unknown. The incidence of PIMS-TS/MIS-C across seven US regions was estimated to be approximately 3 per 10 000 individuals younger than 21 years of age infected with SARS-CoV-2 [79]. There is no comprehensive overview of PIMS-TS/MIS-C cases in the EU/EEA. Germany and Switzerland published data from a case series study of children with severe COVID-19 infection leading to PIMS-TS/MIS-C and even death [80,81]. The German Society for Paediatric Infectious Diseases has
identified 389 children who developed PIMS-TS/MIS-C as of August 2021, with an estimated incidence of 2-5 cases per 10 000 SARS-CoV-2-infected children and no deaths [56]. The French national surveillance system registered 648 children with PIMS-TS/MIS-C between March 2020 and September 2021, with a median age of seven years (25% of cases were 4 years old or younger and 75% were 11 years old or younger). Among them, 40% were girls, 41% had a history of admission to a paediatric ICU and one nine-year-old died. In France, the cumulative incidence of the syndrome is estimated at 44.6 cases per million children [82,83]. In Spain, a paediatric COVID-19 registry indicated that among children hospitalised due to PIMS-TS/MIS-C, 61% developed cardiac complications [84]. Sweden has reported 260 children diagnosed with PIMS-TS/MIS-C, most of them without any underlying disease and, while around 25% of them were admitted to ICU, no deaths have been recorded as of September 2021 [85]. During the same period, Norway identified 22 children with PIMS-TS/MIS-C, resulting in an incidence of 1.0 per 1 000 SARS-CoV-2-infected children [76]. A nationwide cohort study in Denmark estimated the occurrence of PIMS-TS/MIS-C cases among SARS-CoV-2-infected children as 1 in 4 100 in children younger than 12 years and 1 in 3 700 in children older than 12 years [86]. Monitoring for potential long-term health consequences of PIMS-TS/MIS-C should be performed as information is currently limited.

In addition to PIMS-TS/MIS-C, the presence of post COVID-19 condition has been reported in cohorts of children from a number of countries [87]. Post COVID-19 condition is characterised by persistent symptoms such as headache, fatigue, dyspnoea, chest pain, cognitive impairment, and sleeping disturbances that last up to several months after SARS-CoV-2 infection. A review covering 14 studies from 12 countries reporting on persistent symptoms following COVID-19 in children and adolescents found a considerable variation in estimated prevalence between the studies, from 4-66% of cases [87]. There were also considerable variations regarding the age group of the study population, the definition of the condition and symptoms, and the follow-up time. Six studies reported a positive correlation between the prevalence of persisting symptoms and increasing age. Some studies also reported correlations between prevalence and female sex, allergic diseases and worse pre-infection physical and mental health. In the majority of studies, symptoms did not persist longer than 12 weeks in most children. Of five studies that included a control group consisting of children and adolescents without SARS-CoV-2 infection, two did not find persistent symptoms to be more prevalent in children and adolescents with evidence of SARS-CoV-2 infection [87].

Data from the UK’s National Statistics Office has also shown a significant number of children reporting symptoms several weeks after their initial SARS-CoV-2 infection, estimating the prevalence for the 2-11 years age group to be 0.2% [88]. A large cohort study (the ClOck study) surveyed 3 065 children and young people aged 11-17 years who tested PCR positive for SARS-CoV-2 and 3 739 who tested PCR negative [89]. Three months after the test result, 30.3% and 16.2%, respectively, experienced more than three symptoms. In a similar but smaller study in Latvia, among 236 children who tested positive for SARS-CoV-2, 53% had two or more persistent symptoms [90]. A national survey in the Netherlands showed that among the 89 children suspected of post COVID-19 condition, 18% were admitted to hospital due to long-term symptoms [91]. A large German study based on data from 11 950 children and adolescents with confirmed COVID-19 recently published findings on morbidity outcomes three months after the date of COVID-19 diagnosis [92]. The paediatric cohort had significantly higher incidence rates of symptoms across both physical (IRR overall: 1.31 (95% CI:1.24-1.38); IRR confirmed COVID-19: 254.58; IRR control group: 194.45) and mental (IRR overall: 1.39 (95% CI:1.28-1.52); IRR confirmed COVID-19: 102.17; IRR control group: 73.24) health outcome domains. The outcomes with the highest IRR were malaise/fatigue/exhaustion, cough, and throat/chest pain. Similar IRRs were found in the age groups 0-11 years and 12-17 years. In conclusion, there is evidence that children can suffer from long-term sequelae after SARS-CoV-2 infection, but the exact burden is still to be determined and is a priority for further research.

What is the indirect impact of the COVID-19 pandemic on the health and well-being of children aged 5-11 years?

The COVID-19 pandemic has indirectly impacted the health and well-being of children aged 5-11 years in multiple ways. Restrictions such as physical distancing, school closures, and cancelled sport and recreation activities drastically decreased peer interaction, as well as contact with older family and community members. It will take years before we can truly assess the overall impact of COVID-19 on children's health and development. In terms of loss of family members, it has been estimated that by 30 April 2021, over 1.1 million children globally experienced the death of a primary caregiver during the COVID-19 pandemic [93]. Such children are expected to be at an elevated risk of experiencing mental health problems, violence, and family poverty [93].

School disruptions have affected millions of children globally and in the EU/EEA since the onset of the pandemic and this, in turn, has affected not only their education [94,95] but also their health [14]. There has also been a disproportionate impact on the most vulnerable children and their families [14,96,97]. While the pandemic has not uniformly led to the deterioration of children's physical or mental health [98], as some children may have experienced benefits (e.g. increased family time) [99], the overall evidence points to increased risks to children's health during the pandemic. A systematic review based on 72 studies from 20 countries demonstrated that school closures had considerable impact on children and adolescents’ mental health, as between 18-60% of young people were found to be at risk of psychological distress, particularly anxiety and depressive symptoms. Screen time and social media use increased, physical activity was reduced, and sedentary behaviour and unhealthy dietary habits increased [100]. A rapid systematic review on the impact of school closures on child and
adolescent health reported negative impacts on child sleep quality and behaviour (including a worsening capacity for inhibitory self-control), as well as predictions for increased levels of childhood obesity and greater learning challenges for children from disadvantaged families (due to lack of parental abilities to support, lack of internet access, and digital disparities) [101]. In the UK, one preprint study reporting on a time that included a period of lockdown reported worsening mental health and an increase in behavioural problems among 4-11-year-olds [102]. A study documenting the impact of the COVID-19 pandemic on health inequalities in England reported an increased risk of child poverty and developing mental health issues for children from disadvantaged backgrounds [103]. The report also highlighted increases in domestic abuse [103], and it has elsewhere been highlighted that children are at increased risk of domestic violence when schools are closed [104]. A study from Germany reported that, during the pandemic, increases in children witnessing domestic violence and verbal/emotional abuse were associated with families with higher parental stress, job losses, and younger parent and child ages [99]. In the first year of the pandemic in the US, a rise was observed in young patients with eating disorders, depression and suicidal thoughts [105,106]; these concerns, and the other factors described herein, led the American Academy of Paediatrics, the American Academy of Child and Adolescent Psychiatry, and the Children’s Hospital Association to declare a national state of emergency in children’s mental health in 2021 [107].

Isolation and quarantine measures are often linked to reports of COVID-19 in educational settings and continue to cause substantial disruptions to children’s lives, particularly to their learning. Remote learning quality and effectiveness is significantly lower than in-school learning and varies greatly by context, learners’ background, family digital literacy, as well as access to internet and technology [108]. School closures may have disproportionately affected students that were low-achieving prior to the pandemic [109]. In addition to direct loss of learning, negative impacts on children’s education include reduced educational performance, increased risk of disengagement and school dropout, and a reduction in motivation and feelings of connection with the school community [14,94,100,110-112].

Education and development of skills is a strong health determinant, as well as predictor for future labour opportunities and earnings. This relationship is expected to disadvantage children affected by the COVID-19 pandemic in multiple ways. In terms of economic consequences, the loss of learning and skills are estimated to cause a reduction in future earnings and income possibilities [113]. For each month of skill loss, about a 1% drop in lifetime earnings for affected children has been projected, which constitutes an estimated decrease in national income by 0.5% per year [114]. These impacts are greater on vulnerable populations, and disruptions in schooling and recreational activities have interacted with other COVID-19-related hardships to disproportionately affect students with lower socio-economic backgrounds [115,116].

**Efficacy, safety and anticipated impact of COVID-19 vaccination of children aged 5-11 years**

What are the preliminary data on efficacy and safety of COVID-19 vaccines in children aged 5-11 years?

As of 30 November 2021, clinical trials in children are ongoing for the vaccines Comirnaty and Spikevax (Table 2). A published study from the clinical trial of Comirnaty in children aged 5-11 years has reported neutralising antibody responses generally consistent with those in adolescents and adults, and vaccine efficacy against COVID-19 infection of 90.7% (95% CI: 67.7 to 98.3) [117]. Previous clinical trials on adolescents (12-17 years old) have shown high efficacy for both vaccines in this age group [118,119] and a cohort study on adolescents from Israel during the period when the Delta VOC was dominant demonstrated high vaccine effectiveness for Comirnaty against SARS-CoV-2 infection in adolescents [120].
Table 2. Ongoing clinical trials for COVID-19 vaccination of children under 12 years old

<table>
<thead>
<tr>
<th>Title</th>
<th>Population studied</th>
<th>Endpoints</th>
<th>Main findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer/BioNTech (Comirnaty): A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, and Immunogenicity of an RNA Vaccine Candidate Against COVID-19 in Healthy Children and Young Adults, NCT04816643 [121]</td>
<td>11 422 participants, 6 months to 30 years old.</td>
<td>Safety/efficacy/ immunogenicity</td>
<td>According to a study published on 20 September 2021, reporting data from 2 268 children aged 5-11 years, participants who received two 10 µg doses had antibody titres and a side effect pattern comparable to those in the age group 16-25 years who received two 30 µg doses [117].</td>
<td>Results from the age group six months to five years are expected in the fourth quarter of 2021.</td>
</tr>
<tr>
<td>ModernaTX, Inc (Spikevax): A Study to Evaluate Safety and Effectiveness of mRNA-1273 COVID-19 Vaccine in Healthy Children Between 6 Months of Age and Less Than 12 Years of Age, NCT04796896 [122]</td>
<td>13 275 participants, 6 months to 11 years old.</td>
<td>Safety/efficacy/ immunogenicity</td>
<td>According to a press release from the company on 25 October 2021, reporting data from 4 753 children aged 6-11 years, participants who received two doses of 50 µg had a robust neutralising antibody response and a safety and tolerability profile generally consistent with those in adolescents and adults [123].</td>
<td>Estimated primary completion date: 12 June 2023.</td>
</tr>
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Only vaccines currently authorised in the EU/EEA are listed in the table.

Regarding safety aspects, assessment of COVID-19 vaccines in the adult and adolescent populations have shown a number of side effects, of which most are mild to moderate, while some safety signals have been reported and are being continuously investigated [124]. In the clinical trial of Comirnaty in children aged 5-11 years, the safety data showed some mild to moderate side effects that improved within a few days and no severe event was detected [117]. The safety profile was reported to be similar to that of adolescents [119], with the most common side effects being fever, injection-site pain, severe fatigue, headache, chills, and muscle pain. However, it should be noted that this trial did not have the power to detect rare events because of the sample size (n = 1 517 children received the vaccine). Data from additional participants was added to the safety assessment in the application to EMA and the FDA (n = 3 100 children received the vaccine) [13]. Besides the available data from the clinical trial, there is uncertainty regarding potential rare adverse events in this specific age group that could only be detected with increasing vaccination numbers and longer follow-up time.

From the post-authorisation safety monitoring in adults and adolescents, there have been reports of an association between vaccination against COVID-19 and myocarditis and pericarditis, particularly for mRNA vaccines [125-128]. The cases have primarily been detected among male adolescents aged 16 years or older after the second dose of the vaccine, and most cases have recovered relatively quickly. Myocarditis and pericarditis have been added to the list of side effects in the product information of Comirnaty and Spikevax [129,130], but further monitoring and evaluation are ongoing in order to assess the magnitude and importance of this complication in adolescents and adults.

In this context, it should be noted that SARS-CoV-2 infection is also associated with an increased risk of myocarditis that is exacerbated in young males [64,131,132].
What is the estimated impact of vaccinating children aged 5-11 years on the effective reproduction number ($R_I$)?

Although the direct physical health burden of COVID-19 in children is generally considered to be low, there could be a significant indirect contribution of children to the overall COVID-19 burden in the whole population, due to SARS-CoV-2 infections that are transmitted from children to adults. In order to estimate the impact of vaccinating children aged 5-11 years on the $R_I$ in the whole population, ECDC’s internal mathematical modelling approach has been used. Other related work has also estimated the impact of vaccinating children on the spread in the whole population [133-135].

The impact of vaccinating children on viral transmission in the community depends on various parameters, including the contact rates (the number of daily contacts that people have) between different age groups; the vaccination coverage, dosage and schedules, as well as type of vaccines administered, in the adult (18 years and older) and adolescent (12-17 years) populations; the vaccine effectiveness against transmission and its duration; the age distribution of the population; and the age-specific susceptibility and infectivity of individuals. Many of these parameters are known with substantial uncertainty and some parameters are country specific. In order to take these uncertainties into account, the model considers that every parameter lies within a given range; for instance, the fraction of individuals that have had a SARS-CoV-2 infection is likely between 10-50% [22,136]. By repeating the calculation for all parameter ranges and their combinations, the model can predict a range of estimates for the possible decrease of the $R_I$ in the whole population attributable to the vaccination of children.

In the model, the population is divided into four age groups: 0-5 years, 5-11 years, 12-17 years, and 18 years or older [137]. The motivation for considering separate age groups was two-fold. First, it allows for specification of the vaccination coverage, vaccine efficacy and prevalence of natural immunity independently for each age group. Second, it allows for the capture of heterogeneous contact rates within and between age groups; for instance, the number of contacts between children and adults (e.g. at kindergarten or school) or the number of contacts among adults, due to leisure (e.g. at the gym) or work. The contact rates were directly linked to viral transmission from one age group to another. Contact rates between age groups were obtained from the contact mixing study CoMix [138]. The CoMix study provides longitudinal contact data from more than 20 European countries during different phases of the COVID-19 pandemic. For this model, contact rates between age groups were averaged over countries [138].

The reduction of the $R_I$ depends strongly on country-specific parameters, particularly on the vaccination coverage in the adult population. Thus, the impact of vaccinating children aged 5-11 years is estimated for four different settings. First, parameters that reflect the EU average of 75% adult vaccination coverage were considered. For the EU average parameters, the impact of a child vaccination coverage of 30-70% was evaluated. Second, four different hypothetical scenarios were considered as country settings with: a high vaccine uptake in both adults (85%) and children (50-70%), a high vaccine uptake in adults (85%) but a low vaccine uptake in children (30-50%), a low vaccine uptake in adults (55%) but a high vaccine uptake in children (50-70%), and a low vaccine uptake in both adults (55%) and children (30-50%).

The results show that the decrease of the $R_I$ occurs once the child vaccine uptake has reached the low or high plateau of 30-50% or 50-70%, respectively. The reduction of the $R_I$ and a decrease of hospitalisations and deaths due to child vaccinations will only be seen progressively, in the medium to long term, depending on the speed of the child vaccination roll-out.
Figure 2. The estimated impact of vaccinating children on the spread of SARS-CoV-2

A: The blue bars show the estimated range of the relative decrease of the effective reproduction number ($R_t$) due to vaccinating children aged 5-11 years for five parameter settings: the EU average and four hypothetical countries with different vaccination coverages for adults and children (aged 5-11 years). The width of these bars represents the 95% confidence interval (CI), which is due to uncertainties in parameters such as vaccine effectiveness and waning of immunity.

B: To contextualise the relative changes in SARS-CoV-2 transmission, $R_t$ was computed for all EU/EEA countries over time, from 1 August 2021 (the start of the dominance of the Delta variant of concern) to 31 October 2021. The relative changes of $R_t$ from one month to the next were then computed and rounded, and are shown as dot plots in grey (one dot represents a change in transmission in one country, either from August to September or from September to October). The majority of these changes (80%) lie between -30% and +15% and are likely caused by a variety of factors, including continued vaccine roll-out, changes in human contact rates, and seasonal transmission patterns.

Figure 2 shows the estimated relative reduction of the $R_t$ in the population as a whole for the EU average and four hypothetical country settings with different vaccine uptakes in adults and children. For the EU average, it is estimated that vaccinating children aged 5-11 years decreases the $R_t$ in the population as a whole by 10.9% (95% CI: 2.8-22.4%). For a country with high vaccine uptake in adults and high vaccine uptake in children, a reduction of the $R_t$ by 14.7% (95% CI: 3.4-26.3%) is estimated. For a country with high adult vaccination coverage but low child vaccination coverage, an effect of 9.9% (95% CI: 2.4-18.9%) is estimated. For a country with low adult vaccination coverage but high child vaccination coverage, an effect of 11.7% (95% CI: 3.0-19.0%) is estimated. Finally, for a country with low adult vaccination coverage and low child vaccination coverage, a reduction of 7.88% (95% CI: 2.1-13.9%) is estimated. Although results indicate similar impact on the $R_t$ for high adult and low child vaccination coverage as for low adult and high child vaccination coverage, this does not imply that vaccinating children can be a substitute for high vaccination coverage of adults, not least because of the different frequencies of severe disease between age groups. These comparisons are designed only to illustrate how vaccination of children, at a fixed adult coverage level, may impact transmission.

These modelling estimates indicate that vaccinating children reduces the $R_t$ at most by about 15% (within a likely range of 3-26%), with the greatest proportional impact if a high adult vaccination coverage has already been accomplished. For countries with low adult vaccination coverage, the incremental effect of vaccinating children is weaker. When seen in the context of recent changes in viral transmission intensity, these estimates fall well within the observed range of fluctuations in the $R_t$ (Figure 2B). This indicates that the estimated effect of vaccinating children on SARS-CoV-2 transmission is comparable to the magnitude of the effect of factors that are driving recent changes in transmission, such as changes in response measures and human behaviour, seasonal changes in transmission, and vaccination roll-out.
Potential objectives for vaccinating children aged 5-11 years

Protecting children from the direct health risks of COVID-19

The primary objective of vaccinating children is the protection of their individual health against COVID-19. It is clear from the data presented that not all children in this age group have the same risk of developing severe COVID-19 or experiencing its sequelae (e.g. post COVID-19 condition) [139]. Children at high medical risk of severe COVID-19 (i.e. those with underlying conditions that increase the risk of severe COVID-19) would particularly benefit from vaccination and should be prioritised once the vaccine is authorised in their age group. Other children, such as those belonging to socially vulnerable groups, could also be more frequently exposed to SARS-CoV-2 and to the risk of more severe health outcomes [140-142].

For the majority of children, the risk of developing severe COVID-19 appears to be low (lower than 0.01%); however, some may experience the rare but severe PIMS-TS/MIS-C or disease sequelae like post COVID-19 condition, which may affect their quality of life for an unclear amount of time.

Protecting children from the indirect impacts of the COVID-19 pandemic

The formative years of early childhood are crucial to future health and well-being, during which children experience rapid cognitive, social, emotional, and physical development. The COVID-19 pandemic restrictions have had a strong negative impact on children and their families. Significant negative effects on the physical and mental health, as well as the overall well-being, of children have been documented [14,93,99-101,143,144].

Vaccinating children could offer them increased opportunities to more safely spend time with friends and extended family, resume social and extracurricular activities, and socialise safely.

The negative impact of school disruption has been substantial during the COVID-19 pandemic, including direct loss of learning, reduced educational performance, and increased risk of disengagement and school dropout [14,110-112]. For vulnerable or at-risk children, including those with medical vulnerabilities or special education needs, vaccination could help to ensure their safe access to education. With continued community transmission, vaccination of children more generally could significantly prevent repetitive learning disruptions due to isolation and quarantine practices after exposure to a confirmed case.

Furthermore, vaccination could allow for the relaxation of in-school protection measures and non-pharmaceutical interventions, such as the use of masks and physical distancing, which may in some contexts be disruptive to normal school life.

Reducing the overall burden of COVID-19 among children

As the Delta VOC is highly transmissible, a large number of infections could rapidly occur among unvaccinated populations with frequent social interactions. Despite the low individual risk of developing severe COVID-19 faced by healthy children aged 5-11 years, a very high number of infections in this age group could nonetheless lead to a large absolute number of severe cases over a limited time period.

Non-pharmaceutical measures, such as physical distancing or the wearing of face masks, are helpful in reducing SARS-CoV-2 transmission. However, it may be challenging to implement these measures in this age group, perhaps particularly outside of controlled settings (e.g. school) and over a long period of time.

Vaccination against COVID-19 could therefore be helpful in reducing the overall burden of COVID-19 among children aged 5-11 years, given a favourable individual benefit-risk profile and sufficient and lasting protection against SARS-CoV-2 transmission, which could reduce the need for strict non-pharmaceutical measures.

Reducing SARS-CoV-2 circulation in the overall population

The overall circulation of SARS-CoV-2 may remain moderate-to-high if some age groups with a lot of contacts (e.g. children) are largely unvaccinated. In countries where transmission rates remain high, this could also have important public health consequences with regard to the frequency of severe disease and the pressure on healthcare.

According to the modelling analysis in this report, which is in line with results from other studies [134], vaccinating children – particularly in contexts where vaccine uptake in adults has already reached a high coverage level – could significantly contribute to reducing the overall viral circulation in the population and potential increases in the number of severe cases and hospitalisations. This will strongly depend on how much the vaccination of children reduces SARS-CoV-2 transmission and on the duration of such protection [139].
Considerations around implementation

Programmatic considerations
To date, there are not yet programmes in place for wide-scale vaccination of children aged 5-11 years in the EU/EEA, but should such programmes be developed they could either be offered:

- as a stand-alone vaccination apart from routine vaccination in this age group or
- concomitantly to other vaccines, as per national vaccination policies.

There are several examples of locations and settings that can be used to deliver COVID-19 vaccination to children. According to information collected from EU/EEA countries in October 2021, COVID-19 vaccination in adolescents has primarily been offered at vaccination centres, general practitioner (GP) clinics or family doctors, and schools [6]. Several countries also offered COVID-19 vaccination at hospitals, paediatrician clinics, mobile vaccination sites or pharmacies.

Regardless of the chosen approach, the following questions can be considered:

- What setting will allow for the highest uptake in this age group?
- Will there be a positive or negative impact on existing vaccination programmes?
- How will data on concomitant vaccination be collected?
- Can access to the vaccine be facilitated for all family members (i.e. children and unvaccinated family members may become vaccinated in the same setting) to increase uptake based on convenience?

Facilitating vaccination acceptance and uptake
An extension of the use of COVID-19 vaccines for children under 12 years of age will pose a series of communications challenges. The 5Cs model (confidence, constraints, complacency, calculation, and collective responsibility) provides a framework for understanding and is a tool that Member States can use to understand factors influencing vaccine acceptance among parents and caregivers, as well as for designing strategies to promote uptake [145].

A review of studies investigating COVID-19 vaccination acceptance in parents found that while levels of parental vaccine acceptance vary between countries, there has been an overall trend towards more acceptance of the COVID-19 vaccine over time [146-149]. This may be because initial concerns about safety and the speed of the vaccine’s development (confidence, as in the 5Cs model) have been allayed in many parents’ minds. In several studies conducted in the EU/EEA, and based on data collected in June 2021 or later, more than 70% of parents reported that they would like to have their children vaccinated against COVID-19 [147,149-151]. Nonetheless, parents of younger children have been found to be more hesitant than parents of older children [151,152], while a small but consistent minority of parents in all of the studies where this particular issue was investigated report that they will refuse COVID-19 vaccination for their children [147,153,154].

As it has been stressed in communications on COVID-19, most children who get the disease have mild symptoms and are at very low risk of severe disease or death. This has informed parental risk perception and may have led to the 5C of complacency, thereby decreasing vaccine acceptance. Surveys done in Germany, for example, show that only around one third of parents perceive the risk of infection and severity of infection to be high in children under 12 years of age if they would remain unvaccinated [155]. This leads to questions about why children should be vaccinated at all [156,157]. To address this issue, communication initiatives will need to clearly state the rationale behind recommendations to vaccinate children (including specific risk groups). The benefits in relation to direct protection versus societal benefits – such as limiting community spread, controlling spread in schools, normalising the lives of children and families, and restoring children’s well-being – should be addressed.

Parental concerns around the safety of COVID-19 vaccines for children would also need to be addressed. In some national and regional contexts, concerns could have emerged from previous safety anxieties related to other vaccination programmes for children and adolescents, and these may affect trust in the safety of the vaccine [158]. Fear of unknown long-term consequences, side effects, and insufficient information about COVID-19 vaccines have been cited by parents in a study in the Netherlands as the primary reasons for not wanting their children to be vaccinated [151]. Such concerns may be exacerbated by reports (either false, misconstrued, or amplified) of children who have been enrolled in vaccine trials and who subsequently experienced vaccine injury [159] or by unsubstantiated concerns that COVID-19 vaccines can cause infertility [156]. Consequently, to increase confidence in the safety of vaccines there should be clearly communicated, up-to-date and transparent information from trusted sources on vaccine efficacy and safety, including information about the rigorous clinical trials conducted and the processes in place to continuously monitor safety of the vaccines for children [160,161].

Risk communication strategies for COVID-19 vaccination in children should leverage trusted sources such as teachers, family paediatricians and GPs [162]. A previous study conducted across 18 EU/EEA countries has shown that parents who consult GPs regarding vaccination of children are more likely to be confident in vaccination than those who do not. In addition, those who discuss vaccination with their paediatricians as a trusted source are more likely than those speaking to GPs to be confident in vaccinating their children [163]. Efforts should therefore be made to prepare GPs and paediatricians to discuss COVID-19 vaccination with parents and children, and to ensure that parents do not feel judged for raising their concerns [164].
Similarly, schools may also play a key role in increasing health literacy of children and their parents, promoting critical thinking and decision-making skills around vaccination [165,166], while also providing a familiar environment for such learning and decision-making to take place [14,167]. Resources could be created to guide teachers in promoting health literacy and awareness of vaccination, in addition to information (e.g. posters, leaflets, presentations) created by schools for both parents and children, as is being done for families and children aged 12-18 years in France and Poland [165,166]. Schools may also be used as vaccination venues, thereby increasing access to vaccination for children and adolescents, as is already being done for young people aged 12-18 years in many EU/EEA countries [6]. Children should also be included in risk communication and engagement strategies. Where appropriate, children should be encouraged to learn about vaccination and decision-making on vaccination [168]. By providing children with the opportunity to ask questions and have their concerns addressed, young people can contribute actively and in an age-appropriate way to their own vaccination decision-making process [151].

**Ethical considerations**

Before any decision on vaccination strategies, a careful analysis of potential harms and benefits must be undertaken, in which ethical aspects from a broad perspective should be included. This is particularly important when the target group consists of young children, who are in need of special safeguards and care because of their physical and mental immaturity [169]. Moreover, children aged 5-11 years are dependent on their guardians to decide whether or not they will take the vaccine (or national authorities in the case of mandatory vaccinations), meaning that they are unable to take autonomous consensual decisions. In the balancing of harms and benefits, the issues discussed earlier in this report regarding indirect health risks and societal aspects must be added to the direct medical concerns, as well as aspects regarding acceptability of the vaccine and health equity. This assessment is complicated by the limited evidence about the effect of vaccinating children on the overall burden of disease in this age group and in the general population.

Decisions on vaccination raise questions regarding individual versus societal benefits. One general principle is that vaccines should be beneficial for the individual or at least for the specific age group that is concerned. However, the fact that vaccination of children has the potential to reduce transmission of the disease and thereby protect the general population cannot be neglected and may have an impact on national or regional decisions regarding vaccination of children. A discussion that can follow, is whether it is justified to vaccinate children if it is interpreted as a substitute for non-pharmaceutical interventions or to make up for a failure to reach adequate vaccination coverage in other age groups, as well as how impactful such an intervention would be over time with the currently available vaccines. In this context, it should be acknowledged that any harm caused either by the vaccine itself or related to the implementation of the vaccination strategy can have a negative impact on the general trust in vaccines [170]. For any decision on the vaccination of children, it is therefore important to provide transparent and adequate information regarding the facts and principles that guided the decision [171,172].

Another aspect that should be considered is how COVID-19 vaccination may impact health equity among children. It is known that the pandemic has affected socio-economically vulnerable children and adolescents disproportionately [115,116,173]. It has therefore been argued that vaccination of children could reduce health inequalities, and that vaccination campaigns should be designed to reach vulnerable groups of children [173]. Although it is known from other vaccination programmes that vaccination coverage rates in general are lower in socio-economically vulnerable groups [174], it could also be argued that unvaccinated children could benefit from the expected reduced viral circulation following vaccination in this age group.

With regards to global health equity, ethical consideration should also be given to the current shortage of COVID-19 vaccines in many countries – a disparity that could be worsened by the administration of additional COVID-19 vaccine doses in EU/EEA countries. Earlier this year, WHO called for a moratorium on additional doses in order to improve the availability of vaccines for low- and middle-income countries [175], and a similar argument has been made regarding expanding vaccination to new age groups [176].

**Conclusions**

- Surveillance data show that children aged 5-11 years have made up an increasing proportion of both notified cases and hospitalisations in EU/EEA countries in recent months. Although hospitalisations have increased in line with case rates in all age groups in the EU/EEA, disease severity of COVID-19 in children is generally mild with a favourable clinical outcome. Severe COVID-19 remains rare among children (of 65 800 notified symptomatic COVID-19 cases in children aged 5-11 years, reported from 10 EU/EEA countries during the period of B.1.617.2 (Delta) variant of concern (VOC) dominance, 0.61% were hospitalised and 0.06% needed intensive care unit (ICU)/respiratory support).
- The relative contribution of children to overall SARS-CoV-2 circulation may have increased due to factors including the emergence of the highly transmissible Delta VOC and increased vaccination coverage in older age groups.
The presence of an underlying condition among children aged 5-11 years is associated with about 12 times higher adjusted odds of hospitalisation and 19 times higher odds of ICU admission. However, the majority (78%) of hospitalised children of this age had no reported underlying medical condition.

Paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2/multi-inflammatory syndrome in children (PIMS-TS/MIS-C) and post COVID-19 condition have been reported in children aged 5-11 years, although it is difficult to quantify the prevalence and burden of these conditions. In a United States (US) Centers for Disease Control and Prevention (CDC) report, myocarditis was reported up to 37 times more often in unvaccinated children less than 16 years old with a COVID-19 diagnosis compared to other patients from the same age group.

Beyond the direct health impacts of COVID-19 disease, the COVID-19 pandemic has affected the physical and mental health and well-being of children aged 5-11 years. Numerous factors, such as disruptions to important everyday social and educational activities, have caused anxiety and distress in this age group.

Modelling data indicate that vaccinating children aged 5-11 years could reduce SARS-CoV-2 transmission in the whole population, although the extent and duration of this protection is currently unknown. It is estimated that the impact on the effective reproduction number ($R_t$) in the population as a whole would be a decrease of 11% (range: 8-15%, depending on vaccine uptake parameters of 30-70%) for an average country in the EU/EEA. This is comparable to the effect of some non-pharmaceutical interventions. The impact of vaccinating children is weaker for countries with a low adult vaccine uptake and stronger for countries with high uptake among adults.

On 25 November 2021, the European Medicines Agency (EMA) granted a positive opinion for use of the Comirnaty COVID-19 vaccine in children aged 5-11 years based on a placebo-controlled randomised clinical trial in which more than 3,000 children in this age group received this vaccine.

Children aged 5-11 years who are at risk of severe COVID-19 should be considered a priority group for vaccination against COVID-19, as in other age groups. However, since hospitalisation, PIMS-TS/MIS-C and post COVID-19 condition can also occur among children with no known risk factors, consideration could be given to the vaccination of all children aged 5-11 years.

COVID-19 vaccine safety data in children aged 5-11 years are currently limited, and the level of natural immunity in the unvaccinated and its duration are currently unknown and likely heterogeneous across the population.

The main priority of COVID-19 vaccination campaigns seeking to reduce COVID-19-related morbidity and mortality remains to increase vaccine uptake in the eligible adult population. Before taking policy decisions on COVID-19 vaccination in children, potential harms and benefits – including the direct and indirect effects on health and well-being – should be considered alongside the vaccine uptake and epidemiological situation in a particular country. Aspects around implementation and health equity should also be taken into consideration.

Limitations and knowledge gaps

- COVID-19 vaccine efficacy and safety data in children aged 5-11 years are currently scarce and are being monitored.
- Incidence and overall burden of post COVID-19 condition in children aged 5-11 years cannot be accurately quantified.
- In the modelling analysis of the impact of vaccination of children on viral transmission, variations in social behaviour according to spatial/geographical heterogeneities, fluctuations of contacts over time, heterogeneities within age groups, age-specific transmissibility and risk of infection could not be quantified and accounted for.
- Potential changes in social behaviour and mixing patterns in the coming months are difficult to predict and assess.
- The impact of vaccinating children aged 5-11 years on the total burden of COVID-19 (including hospitalisation and deaths) in various age groups is uncertain.
- Data on vaccine effectiveness against transmission of the Delta VOC are currently limited and missing for children aged 5-11 years.
- Data on waning vaccine effectiveness are difficult to disentangle from reduced vaccine effectiveness due to the Delta VOC and could vary by disease outcome and age group.
- Accurate data on natural immunity in the unvaccinated population (and by age) is missing and its duration is currently unknown and likely heterogeneous across the population.
- The likelihood of getting infected with the Delta VOC for different age groups is difficult to quantify.
- The emergence of new variants of concern will introduce new uncertainties, thereby necessitating reassessment of the potential impact of vaccinating children.
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All data published in this report is correct to the best of our knowledge at the time of publication.
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Appendix 1

Figure A1. Pooled weekly COVID-19 age-specific case notification rates, week 32 2020–week 39 2021

Pooled data from Austria, Cyprus, Finland, Germany, Ireland, Italy, Luxembourg, Malta, Slovakia and Sweden.
Appendix 2

Figure A2. The estimated impact of vaccinating children on the spread of SARS-CoV-2 for different values of adult vaccine uptake

Estimated effect from vaccinating 5-11-year-olds

A. High adult vaccination coverage

B. Intermediate adult vaccination coverage

C. Low adult vaccination coverage

D. Recent monthly changes in SARS-CoV-2 transmission for context