The following information resources have been selected by the National Health Library and Knowledge Service Evidence Virtual Team in response to a question from the National Immunisation Advisory Committee (NIAC). The resources are listed in our estimated order of relevance to practicing healthcare professionals confronted with this scenario in an Irish context. In respect of the evolving global situation and rapidly changing evidence base, it is advised to use hyperlinked sources in this document to ensure that the information you are disseminating to the public or applying in clinical practice is the most current, valid and accurate. For further information on the methodology used in the compilation of this document—including a complete list of sources consulted—please see our National Health Library and Knowledge Service Summary of Evidence Protocol.

Question 214

How safe and effective are COVID-19 vaccines in adolescents, and what is the uptake of COVID-19 vaccines in adolescents?

Question 212 was prepared by the National Health Library and Knowledge Service in collaboration with the Research Subgroup of the National Immunisation Advisory Committee (NIAC).

Main Points

1. Authorization of the Pfizer-BioNTech COVID-19 vaccine for adolescents is based on an ongoing clinical trial that reports 100% vaccine efficacy against SARS-CoV-2 infection from 7 days after the second dose, and immunogenicity and adverse effect profiles comparable to those in the adult population. No vaccine-related severe adverse events have been observed.
2. Cases of myocarditis and pericarditis following mRNA vaccination in children and adolescents are rare and typically resolve rapidly.
3. Based on cross-sectional studies in Canada, Israel and Italy, intention to vaccinate children and adolescents against COVID-19 is high (~80%-90%). Obtaining reliable information about adolescent COVID-19 vaccine safety and efficacy, and having parents or guardians who have been vaccinated are among the factors that increase vaccination intent among both parents and adolescents. Parents inclined not to vaccinate indicate short development time and possible long-term effects as dissuading factors.

Please refer to the National Health Library Levels of Evidence Table used to grade the levels of evidence included below.

☑	Inclusion criteria:	All levels.
☒	Exclusion criteria:	None.

Please note that individual studies may not have been critically appraised and that designation at a certain level is not a final determination of the quality of a given study.

Summary of Evidence

COVID-19 VACCINES IN ADOLESCENTS

The Pfizer-BioNTech vaccine has been authorized for use in young people aged 12 to 15 years in many countries, including the European Union, Britain and the United States. Safe, effective vaccines are needed to protect the adolescent population, facilitate in-person learning and social interaction, and contribute to population immunity[12].

Authorization of the Pfizer-BioNTech COVID-19 vaccine is based on an ongoing randomised, placebo-controlled clinical trial in the United States that reports 100% (95% CI 75.3-100) vaccine efficacy against infection from SARS-CoV-2 from 7 days after the second dose[10, 12], and immunogenicity and adverse effect profiles comparable to those in the adult population[11, 12]. No vaccine-related severe adverse events have been observed[12, 18]. A stronger immune response is reported in younger adolescents: the geometric mean ratio of SARS-CoV-2 50% neutralizing titers after the second vaccine dose in 12- to 15-year-old participants relative to 16- to 25-

year-old participants was 1.76 (95% CI 1.47- 2.10)[12].

In respect of the reported incidence of myocarditis and pericarditis following mRNA vaccination in children and adolescents, Das et al.[13] report that among the 29 individuals included in their cross-sectional study, all cases were mild and resolved within a few days to a few weeks. The authors conclude that the risk of cardiac complications among children and adults due to SARS-CoV-2 infection far exceeds the minimal and rare risks of vaccination-related transient myocardial or pericardial inflammation[13]. In a case series of patients diagnosed with perimyocarditis following vaccination in Israel, Snapiri et al.[14] report that all cases were mild, and none required cardiovascular or respiratory support[14].

Marshall et al.[15] found that symptoms of acute myocarditis or myopericarditis among 7 adolescent males who developed chest pain within 4 days of receiving the Pfizer-BioNTech COVID-19 vaccine resolved rapidly, and that diagnostic evaluations for other myocarditis aetiologies were all negative. Based on a study of two adolescent male patients, Park et al.[16] conclude that the Pfizer-BioNTech COVID-19 vaccine may be associated with self-limited myocarditis, but that symptoms resolved, and patients were discharged within 4 days of hospitalization.

The Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) stated that early data for myocarditis and pericarditis in 12- to 39-year-old individuals after mRNA COVID-19 vaccines suggested that there were more cases after the second than after the first vaccine dose; that there was an incidence of 12.6 cases per 1,000,000 in the 21 days following vaccination; that incidence appeared to be higher in males *vs.* females; and that there was a clustering of myocarditis or pericarditis within the week following vaccination (most likely

within 0-5 days)[17].

VACCINE ACCEPTANCE AMONG ADOLESCENTS

In an early cross-sectional study prior to vaccine authorization for adolescents in the United States, Scherer et al.[20] reported that 55.5% of parents of unvaccinated adolescents aged 12-17 years would *"definitely"* or *"probably"* have their adolescent receive a COVID-19 vaccination; and that 51.7% of unvaccinated adolescents aged 13-17 years would *"definitely"* or *"probably"* receive a COVID-19 vaccination. Obtaining more information about adolescent COVID-19 vaccine safety and efficacy, as well as school COVID-19 vaccination requirements, were the most commonly cited factors that would increase vaccination intent among both parents and adolescents. Federal and local health officials and primary care professionals were the most trusted sources of COVID-19 vaccine information.

In a cross-sectional study in Shenzhen, China, conducted before COVID-19 vaccines had been developed and made available, Zhang et al.[24] reported a prevalence of parents' acceptability of COVID-19 vaccination for their children of 72.6%. Positive attitudes toward COVID-19 vaccination (aOR 1.70, 95% CI 1.50-1.91), perceived support from a family member (aOR 4.18, 95% CI 3.21-5.43) and higher exposure to positive information related to COVID-19 vaccination (AOR 1.35, 95% CI 1.17-1.56) were associated with higher parental acceptance of COVID-19 vaccination.

Using cross-sectional data from an ongoing COVID-19 cohort study in Montreal, Canada, McKinnon et al.[21] reported that intention to vaccinate children against COVID-19 was high, with only 12.4% of parents unlikely to accept vaccination. However, the authors identified marked social inequalities in COVID-19 vaccine

acceptance and uptake for children and adolescents. Parents with younger children were less likely to accept vaccination, as were those from lower-income households, racialized groups, and those born outside Canada. The percentage of parents whose child was vaccinated or very likely to be vaccinated was 18.4 percentage points lower among those with lower *vs.* higher annual household incomes (95% CI 10.1 to 26.7). Racialized parents reported greater unwillingness to vaccinate compared to White parents (aPD=10.3; 95% CI 1.5, 19.1). Vaccine-eligible adolescents from the most deprived neighbourhood studied were half as likely to be vaccinated compared to those from the least deprived neighbourhood (aPR = 0.48; 95% CI 0.18 to 0.77)[21].

In a cross-sectional study of vaccine hesitant parents in Israel, Atad et al.[22] found that parents who were vaccinated against COVID-19 were more likely to intend to vaccinate their children; that low accessibility of vaccination may be a dissuading factor for parents more inclined to vaccinate; that vaccine efficacy and gaining a *"Green Pass"* were positively associated with an intention to vaccinate; and that parents inclined not to vaccinate indicated short development time and possible long-term effects as dissuading factors.

In a cross-sectional study in Bologna, Italy, Montalti et al.[23] found that a majority (60.4%) of parents or guardians were inclined to vaccinate, with 29.6% still considering the opportunity, and 9.9% remaining hesitant. Highest vaccine hesitancy rates were detected among parents who were female, were guardians of children aged 6-10 years, were aged ≤29 years old, had a low educational level, relied on information found on the Internet or on social media, and opposed mandatory vaccination policies.

IMPACT OF LOCKDOWN ON ADOLESCENTS

UNESCO[27] reported that interrupted learning, disruption to formal exams, poor nutrition, increased drop-out rates, increased child exposure to violence and exploitation, social isolation, gaps in childcare, parental absenteeism from work and reduced productivity, and strain on health systems from health workers' absenteeism are among the harmful impacts of school closures on children and adolescents, and on society in general.

In a systematic review on the impact of school closures on the physical and mental health of children and adolescents, Viner et al.[26] found 27 studies that explored the impacts of school closures on emotional and behavioural well-being of children . 18%-60% of children and adolescents scored above risk thresholds for distress, particularly anxiety and depressive symptoms[26, 28]. Two studies reported non-significant rises in suicide rates. Self-harm and psychiatric attendances were markedly reduced, indicating a rise in unmet mental health needs. Child protection referrals fell 27%-39%, with a halving of the expected number of referrals originating in schools. 19 studies concerning health service use showed marked reductions in Emergency Department presentations and hospital admissions. Data suggested significant rises in screen-time and social media use, and reductions in physical activity.

Guessoum et al.[29] cautioned that the COVID-19 pandemic may result in increased psychiatric disorders such as post-traumatic stress, depressive and anxiety disorders, and grief-related symptoms. Adolescents with psychiatric disorders are at risk of an interruption or change in their care and management, and may experience increased symptoms.

TRAMSMISSION IN YOUTH SETTINGS

Larosa et al.[30] reported epidemiological investigations of the transmission of SARS-CoV-2 in 41 classes from 36 schools in Reggio Emilia province, northern Italy, from their reopening on 1 September to 15 October 2020. The overall secondary attack rate in schools was 3.2%, reaching 6.6% in middle and high schools.

Ismail[31] et al. found that SARS-CoV-2 infections and outbreaks were uncommon in educational settings during the 2021 summer half-term in England. A strong association with regional COVID-19 incidence emphasized the importance of controlling community transmission to protect educational settings. A median of 38,000 early childhood education settings (IQR 35,500-41,500), 15,600 primary schools (13,450-17,300) and 4,000 secondary schools (3,700-4,200) were open each day, with a median daily attendance of 928,000 students (630,000-1,230,000). There were 113 single cases of SARS-CoV-2 infection, 9 co-primary cases, and 55 outbreaks during the period of the cross-sectional study. The risk of an outbreak increased by 72% (95% CI 28-130) for every 5 cases per 100,000 population increase in community incidence (p<0·0001). Staff had higher incidence than students (27 cases [95% CI 23-32] per 100,000 per day among staff compared with 18 cases [14-24] in early childhood education students, 6.0 cases [4.3-8.2] in primary school students, and 6.8 cases [2.7-14] in secondary school students]); and most cases linked to outbreaks were in staff members (154 [73%] staff *vs.* 56 [27%] children out of 210 total cases). Probable direction of transmission was staff to staff in 26 outbreaks, staff to student in 8 outbreaks, student to staff in 16 outbreaks, and student to student in 5 outbreaks. The median number of secondary cases in outbreaks was one (IQR 1-2) for student index cases and one (1-5) for staff index cases.

In their cross-sectional and prospective cohort study in Italy during Italy's second wave of the COVID-19 pandemic, Gandini et al.[32] found that SARS-CoV-2 incidence among students was lower than in the general population. Secondary infections at school were <1%, and clusters of ≥2 secondary cases occurred in 5%-7% of the analyzed schools. Incidence among teachers was comparable to the population of similar age (p=0.23). Secondary infections among teachers were rare, occurring more frequently when the index case was a teacher than a student (37% *vs.* 10%, p=0.007). Before and around the date of school opening in Veneto, SARS-CoV-2 incidence grew maximally in 20-29- and 45-49-years old individuals, not among students. The lag between school opening dates in Italian regions and the increase in the regional COVID-19 (*Rt)* was not uniform. Finally, school closures in two regions where they were implemented before other measures did not affect the decrease in *Rt*. This analysis did not support a role for school opening as a driver of the second COVID-19 wave in Italy.

Macartney et al.[33] reported that SARS-CoV-2 transmission rates were low in New South Wales educational settings during the first COVID-19 epidemic wave, consistent with mild infrequent disease in the 1.8 million child population. With effective case-contact testing and epidemic management strategies and associated small numbers of attendances while infected, children and teachers did not contribute significantly to COVID-19 transmission via attendance in educational settings.

Buja et al.[34] reported a significant increase in the number of new daily cases in many European countries following the re-opening of schools. However, the authors acknowledge that confounding factors — such as the re-opening of workplaces, retail outlets and the hospitality sector at the same time as schools — were not

adjusted for.

POST-COVID SEQULAE

In a cross-sectional study of 129 children diagnosed with COVID-19 between March and November 2020, Buonsenso et al.[24] found that after the initial diagnosis of COVID-19, 41.8% completely recovered; 35.7% had one or two persisting symptoms; and 22.5% had three or more persisting symptoms. Insomnia (18.6%), respiratory symptoms including pain and chest tightness (14.7%), nasal congestion (12.4%), fatigue (10.8%), muscle (10.1%) and joint (6.9%) pain, and concentration difficulties (10.1%) were the most frequently reported symptoms. These symptoms — described both in children with symptomatic and asymptomatic acute COVID-19 — were particularly frequent in those assessed more than 60 days after the initial diagnosis.

Magnusson et al.[37] reported a substantial elevation in short-term primary care use for children testing positive for SARS-CoV-2 during the first month following a positive test result when compared to children testing negative (relative elevation 1-5 years: 325%, 95% CI 296-354; 6-15 years: 434%, 95% CI 415-453; 16-19 years: 360%, 95% CI 342-379). There was still elevated primary care use at 2 months (1-5 years: 21%, 95% CI 4-38; 6-15 years: 13%, 95% CI 2-25) and at 3 months (1-5 years: 26%, 95% CI 7-45, 6-15 years: 15%, 95% CI 3-26) for young children, but not at 2 or 3 months for older children (16-19 years: 10%, 95% CI -1-22 and 6%, 95% CI -5-18, respectively). The 1-5-year-old children also had a long-term (up to 6 months) increase of primary care (14%, 95% CI 1-26) that was not observed for older age groups, when compared to same-aged children testing negative.

Osmanov et al.[39] reported that one quarter of children experienced persistent symptoms months after hospitalization with acute COVID-19 infection, with 8.4% experiencing multi-system involvement. 24.3% of study participants reported persistent symptoms, among which fatigue (10.7%), sleep disturbance (6.9%), and sensory problems (5.6%) were the most common. Multiple symptoms were experienced by 8.4% of participants. Risk factors for persistent symptoms were: older age "6-11 years" (OR 2.74 (95% CI 1.37-5.75)) and "12-18 years" (OR 2.68, 1.41-5.4); and a history of allergic diseases (OR 1.67, 1.04-2.67).

Brackel et al.[40] reported that among 89 children aged 2–18 years with suspected long COVID in Holland, 36% experienced severe limitations in daily function. The most common complaints were fatigue, dyspnoea and concentration difficulties (87%, 55% and 45%, respectively). In a separate case series of 6 paediatric patients, the authors emphasized the non-specific and broad clinical manifestations seen in post-COVID complaints.

In respect of pulmonary sequelae, Knoke et al.[36] reported that pulmonary function was rarely impaired in children and adolescents after COVID-19 except in those with severe infection. Bottino et al.[38] concluded that children with an asymptomatic or mildly symptomatic SARS-CoV-2 infection might be less prone to developing pulmonary complications than adults.

Irish and/or International Guidance

Level 1

[European Centre for Disease Prevention and Control (2021) Interim public health considerations for COVID-19 vaccination of adolescents in the EU/EEA. 1 June 2021[1]]

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 adolescents (12 to 18 years). As new evidence is continuously being generated and safety monitored on an ongoing basis, it is essential to consider the latest available information and recommendations issued by regulatory and public health authorities at national level.

This technical report focuses on the overall potential public health impact as opposed to the individual benefits and risks of COVID-19 vaccination in adolescents.

See Section: KEY MESSAGES

- ☐ The vaccination of adolescents against COVID-19 should be considered in the broader context of the COVID-19 vaccination strategy for the whole population, including its overarching goals, the status of implementation, and its priorities.

[1] European Centre for Disease Prevention and Control. Interim public health considerations for COVID-19 vaccination of adolescents in the EU/EEA. 1 June 2021. Stockholm: ECDC; 2021. https://www.ecdc.europa.eu/en/publications-data/interim-public-health-considerations-COVID-19-vaccination-adolescents-eueea.

- ☐ The vaccination of adolescents at high risk of severe COVID-19 should be considered a priority, as with other age groups.
- ☐ The overall direct benefits of vaccinating adolescents will mainly depend on the incidence of SARS-CoV-2 infection and on the prevalence of underlying conditions increasing the risk of severe COVID-19 in this age group.
- ☐ The individual direct benefits from COVID-19 vaccination in adolescents are expected to be limited in comparison to older age groups.
- ☐ The overall benefit for the general population of vaccinating adolescents will be proportional to the SARS-CoV-2 transmission within and from this age group.
- ☐ Given the anticipated reduced individual benefit-risk ratio from COVID-19 vaccination of adolescents compared to older age groups, careful consideration of the epidemiological situation and of vaccine uptake in older age groups should be given before targeting this age group.
- ☐ It is important to continue to monitor the spread of variants of concern among younger individuals and to continue to assess the actual burden of COVID-19 in younger age groups also in relation to COVID-19 sequelae (eg 'long COVID').
- ☐ Equity issues concerning vaccine availability and access need to be carefully considered when deciding on expansion of COVID-19 vaccination to groups with lower individual risk of severe disease.

Level 1

Centers for Disease Control and Prevention (United States) COVID-19 Vaccines in Children and Teens (May 27, 2021)[2]

Although fewer children have been infected with COVID-19 compared to adults, children can:

- ☐ be infected with the virus that causes COVID-19
- ☐ get sick from COVID-19
- ☐ spread COVID-19 to others

CDC recommends everyone 12 years and older should get a COVID-19 vaccination to help protect against COVID-19. Widespread vaccination is a critical tool to help stop the pandemic [...] Children 12 years and older are able to get the Pfizer-BioNTech COVID-19 Vaccine.

INFORMATION ABOUT COVID-19 VACCINES FOR CHILDREN AND TEENS

- ☐ COVID-19 vaccines are safe and effective.
- ☐ COVID-19 vaccines have been used under the most intensive safety monitoring in US history, which includes studies in adolescents.
- ☐ Your child will need a second shot of the Pfizer-BioNTech COVID-19 Vaccine 3 weeks after their first shot.

[2] Centre for Disease Control and Prevention (2021) COVID-19 Vaccines for Children and Teens. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/adolescents.html.

- ☐ Your child can't get COVID-19 from any COVID-19 vaccine, including the Pfizer-BioNTech vaccine.
- ☐ Your child may get a COVID-19 vaccine and other vaccines at the same visit or without waiting 14 days between vaccines.

Level 1

Centers for Disease Control and Prevention (United States). on Immunization Practices (June 2021) Use of mRNA COVID-19 Vaccine After Reports of Myocarditis Among Vaccine Recipients: Update from the Advisory Committee on Immunization Practices Advisory Committee — United States, June 2021[3]

What is already known about this topic?

An elevated risk for myocarditis among mRNA COVID-19 vaccinees has been observed, particularly in males aged 12–29 years.

What is added by this report?

On June 23, 2021, the Advisory Committee on Immunization Practices concluded that the benefits of COVID-19 vaccination to individual persons and at the population level clearly outweighed the risks of myocarditis after vaccination.

What are the implications for public health practice?

Continued use of mRNA COVID-19 vaccines in all recommended age groups will prevent morbidity and mortality from COVID-19 that far exceed the number of cases of myocarditis expected. Information regarding the risk for myocarditis with mRNA COVID-19

[3] Gargano JW, Wallace M, Hadler SC, et al Use of mRNA COVID-19 Vaccine After Reports of Myocarditis Among Vaccine Recipients: Update from the Advisory Committee on Immunization Practices — United States, June 2021. MMWR Morb Mortal Wkly Rep 2021;70:977–982.
DOI: http://dx.doi.org/10.15585/mmwr.mm7027e2external icon.

vaccines should be disseminated to providers to share with vaccine recipients.

Level 1

World Health Organization European Technical Advisory Group of Experts on Immunization (June 2021) Interim recommendations: Inclusion of adolescents aged 12–15 years in national COVID-19 vaccination programmes[4]

SAGE RECOMMENDATIONS ON THE USE OF PFIZER-BIONTECH COVID-19 VACCINE

The [WHO] Strategic Advisory Group of Experts on Immunization (SAGE) reviewed data from Pfizer-BioNTech Phase 2/3 randomized controlled trial in adolescents 12–15 years of age and concluded that the known and potential benefits of BNT162b2 outweigh the known and potential risks in this age group. SAGE indicated the intended use of BNT162b2 for persons 12 years of age and older. SAGE recommended that countries should consider using BNT162b2 in adolescents age 12–15 only when high coverage with a complete vaccination series has been achieved in the high priority groups as identified in the WHO Prioritization Roadmap. Adolescents 12–15 years of age with comorbidities that put them at significantly higher risk of serious COVID-19 disease, alongside other high-risk groups, may be offered vaccination.

SAGE stated that as a matter of global equity, as long as many parts of the world are facing extreme vaccine shortages, WHO recommends that countries that have achieved high vaccine

[4] World Health Organization European Technical Advisory Group of Experts on Immunization (ETAGE) (2021) Interim recommendations, June 2021: Inclusion of adolescents aged 12–15 years in national COVID-19 vaccination programmes. https://apps.who.int/iris/bitstream/handle/10665/342163/WHO-EURO-2021-2782-42540-59113-eng.pdf.

coverage in the high-risk populations prioritize global sharing of COVID-19 vaccines through the COVAX facility before proceeding to vaccination of children and adolescents who are at low risk for severe disease.

BURDEN OF COVID-19 IN ADOLESCENTS

In the WHO European Region, children and adolescents age 5-14 years accounted for around 6%– 9% of total COVID-19 cases reported weekly in the period from October 2020 – April 2021. Since the week of 22 March 2021, the age-specific case notification rates showed a decreasing trend in all age groups. However, starting from the week of 26 April 2021, children and adolescents age 5-14 years represent a growing proportion of recent COVID-19 cases. This trend may reflect decreasing morbidity in older population due to increasing cumulative vaccination rates, as well as changes in testing strategies in schools. Most adolescents infected with SARS-CoV-2 experience a mild, moderate or asymptomatic COVID-19, and cases of severe illness in adolescents are rare: cumulative rates of COVID-19 associated hospitalization in children and adolescents age 10-19 years was 0.8% in European Union (EU)/European Economic Area (EEA) countries in the period from 1 August 2021 through 6 June 20215. During the period October 2020 to April 2021, 87 deaths due to COVID-19 were reported in children and adolescents 5-14 years of age in the WHO European Region among 18 reporting countries. Current evidence suggests that adolescents with chronic medical conditions may be at increased risk of severe illness from SARS-CoV-2 infection that may require hospitalization. A study conducted in the United States found that asthma, gastrointestinal conditions, diabetes, immunosuppression and obesity were associated with higher risk

of hospitalization in adolescents. Risk factors may vary across countries and may be influenced by health systems and the management of chronic diseases. Adolescents infected with SARS-CoV-2, including those with a mild or asymptomatic course, are at risk of developing Multisystem Inflammatory Syndrome in Children (MIS-C), a severe, potentially fatal, rare, multi-organ inflammatory condition with persistent fever. Half of MIS-C occurred in children and adolescents between the ages of 4 and 13 years; the median age was 8-9 years. The evidence on MIS-C is limited and risk-factors are not yet known. In addition, SARS-CoV-2 infection can result in prolonged illness, known as *"post COVID condition"* or *"long COVID,"* despite an asymptomatic or mild course of COVID-19 disease. This condition, not yet clearly defined, has also been described in adolescents, though less often than in adults.

Level 1

World Health Organization (June 2021) COVID-19 advice for the public: Getting vaccinated[5]

Who should get vaccinated?

The COVID-19 vaccines are safe for most people 18 years and older, including those with pre-existing conditions including auto-immune disorders, hypertension, diabetes, asthma, pulmonary, liver and kidney disease; as well as chronic infections that are stable and controlled.

If supplies are limited in your area, discuss your situation with your care provider if you:

[5] World Health Organization (June 2021) COVID-19 advice for the public: Getting vaccinated. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/COVID-19-vaccines/advice.

- ☐ have a compromised immune system
- ☐ are pregnant (if you are already breastfeeding, you should continue after vaccination)
- ☐ have a history of severe allergies, particularly to a vaccine (or any of the ingredients in the vaccine)
- ☐ are severely frail

Children and adolescents tend to have milder disease compared to adults, so unless they are part of a group at higher risk of severe COVID-19, it is less urgent to vaccinate them than older people, those with chronic health conditions and health workers.

More evidence is needed on the use of the different COVID-19 vaccines in children to be able to make general recommendations on vaccinating children against COVID-19.

Level 1

Centre for Disease Control and Prevention (United States) (June 2021) COVID Data Tracker Weekly Review: Trending: Teens[6]

A recent CDC study found COVID-19-associated hospitalization rates among adolescents ages 12-17 years increased during March and April, following declines in January and February 2021. This trend differed from hospitalization rates among people aged 65 years and older—the age group with the highest COVID-19 vaccination coverage—who saw hospitalization rates stabilize during the same timeframe.

While rates of COVID-19-associated hospitalization in adolescents are lower than those in adults, cases of severe disease (including

[6] Centre for Disease Control and prevention (June 2021) COVID Data Tracker Weekly Review: Trending: Teens. https://www.cdc.gov/coronavirus/2019-ncov/COVID-data/COVIDview/past-reports/06042021.html.

those requiring ICU admission or mechanical ventilation) have been documented in this age group. Recent increases in COVID-19-associated hospitalization rates and the potential for severe disease in adolescents reinforce the importance of continued prevention strategies, including vaccination and the correct and consistent use of masks in those who are not yet fully vaccinated.

Vaccinating adolescents is an important step toward stopping the spread of COVID-19. As of June 3, 2021, more than 5.9 million adolescents ages 12-17 years have received at least one dose of a COVID-19 vaccine. Fully vaccinated adolescents are at low risk of symptomatic or severe infection and are less likely to transmit COVID-19 to others. If you or someone you know is considering adolescent vaccination, talk with your pediatrician or healthcare provider about the benefits of vaccination.

Level 1

Centers for Disease Control and Prevention (United States) (2021) Hospitalization of Adolescents Aged 12–17 Years with Laboratory-Confirmed COVID-19 — COVID-NET, 14 States, March 1, 2020–April 24, 2021[7]

What is already known about this topic?

Most COVID-19–associated hospitalizations occur in adults, but severe disease occurs in all age groups, including adolescents aged 12–17 years.

What is added by this report?

[7] Havers FP, Whitaker M, Self JL, et al Hospitalization of Adolescents Aged 12–17 Years with Laboratory-Confirmed COVID-19 — COVID-NET, 14 States, March 1, 2020–April 24, 2021. https://www.cdc.gov/mmwr/volumes/70/wr/mm7023e1.htm?s_cid=mm7023e1_w.

COVID-19 adolescent hospitalization rates from COVID-NET peaked at 2.1 per 100,000 in early January 2021, declined to 0.6 in mid-March, and rose to 1.3 in April. Among hospitalized adolescents, nearly one third required Intensive Care Unit admission, and 5% required invasive mechanical ventilation; no associated deaths occurred.

What are the implications for public health practice?

Recent increased hospitalization rates in spring 2021 and potential for severe disease reinforce the importance of continued COVID-19 prevention measures, including vaccination and correct and consistent mask wearing among persons not fully vaccinated or when required.

Level 1

British National Formulary (BNF) for Children (2021). COVID-19 vaccine[8]

CHILDREN AGED 16 YEARS AND OVER IN CLINICAL ATRISK GROUPS

Children aged 16 years and over in clinical at-risk groups include those considered to be at moderate risk [clinically vulnerable] and high risk [clinically extremely vulnerable: those on the Shielded Patient List] of severe illness or fatality from COVID-19, and should be prioritised for immunisation in accordance with the JCVI recommendations. Clinical at-risk groups include the following:

- ☐ individuals with:
  - — chronic respiratory disease;

[8] British National Formulary (BNF) for Children (2021). COVID-19 vaccine. https://doi.org/10.18578/BNFC.274507200.

- — chronic heart and vascular disease;
- — chronic kidney disease;
- — chronic liver disease;
- — chronic neurological disease;
- — diabetes mellitus (any type);
- — immunosuppression;
- — asplenia or splenic dysfunction;
- — morbid obesity;
- — severe mental illness;

☐ individuals in long-stay nursing and residential care

Within the clinical at-risk groups, individuals are further defined as being clinically extremely vulnerable if they fall into the following categories:

☐ solid organ transplant recipients;

☐ those with specific cancers;

☐ those with severe respiratory conditions;

☐ those with rare diseases that significantly increase the risk of infections;

☐ those on immunosuppression therapies sufficient to increase infection risk;

☐ those with splenic dysfunction or who have had a splenectomy;

☐ pregnant females with significant heart disease (congenital or acquired).

For further information on clinically extremely vulnerable groups, see https://tinyurl.com/y6lxvvzd.

These lists are not exhaustive. Based on clinical judgement, a clinician may add to the Shielded Patient List any child aged 16 years and over identified as being at very high risk of serious illness from COVID-19 infection.

The JCVI also advises local teams to consider offering vaccination to individuals experiencing homelessness and rough sleeping alongside delivery of vaccination to at-risk groups.

CHILDREN AGED UNDER 16 YEARS

Immunisation against COVID-19 is not routinely recommended in children aged under 16 years, as the risk of severe disease or death from COVID-19 infection is very low. Immunisation may be considered for children with serious neurological disabilities (including cerebral palsy, severe autism and Down's syndrome) who regularly spend time in specialised residential care settings. There is currently no basis to recommend immunisation of children with other underlying health conditions; this will be reviewed when additional data on the use of vaccines in adults are available.

Level 1

American Academy of Pediatrics Committee on Infectious Diseases (2021) COVID-19 vaccines in children and adolescents[9]

Vaccines are safe and effective in protecting individuals and popu-lations against infectious diseases. New vaccines are evaluated by a

[9] Committee on Infectious Diseases. COVID-19 vaccines in children and adolescents. Pediatrics. 2021; doi: 10.1542/peds.2021-052336.

long-standing, rigorous and transparent process through the US Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC) by which safety and efficacy data are reviewed prior to authorization and recommendation.

RECOMMENDATIONS: The American Academy of Pediatrics (AAP) recommends the following related to COVID-19 vaccine in children and adolescents:

- COVID-19 vaccination for all children and adolescents 12 years of age and older who do not have contraindications using a COVID-19 vaccine authorized for use for their age. Any COVID-19 vaccine authorized through Emergency Use Authorization by the FDA, recommended by the CDC, and appropriate by age and health status can be used for COVID-19 vaccination in children and adolescents.

Point-of-Care Tools

Level 2

BMJ Best Practice (2021) Coronavirus disease 2019 (COVID-19)[10]

ADOLESCENTS

Adolescents appear to have similar susceptibility to infection as adults.

In the United States, hospitalizations in adolescents peaked at 2.1 per 100,000 in early January 2021, declined to 0.6 per 100,000 in March, and rose to 1.3 per 100,000 in April. Among hospitalized adolescents, approximately one third required admission to the Intensive Care Unit, and 5% required mechanical ventilation. Data were based on 204 adolescents who were likely hospitalized primarily for COVID-19 from January 1 to March 31, 2021. The cumulative number of hospitalizations in the 5- to 17-year-old age group from March 2020 to June 2021 was 1909 cases.

CHILDREN

Evidence suggests that children have a lower susceptibility to infection compared with adults, with an odds ratio of 0.56 for being an infected contact compared with adults. Most cases in children are from familial clusters, or from children who have a history of close contact with an infected patient. It is rare for children to be the index case in household transmission clusters. Infection rates vary according to geographic location. The mean age of children with infection was 6.5 years in the first wave. In contrast to adults,

[10] BMJ Best Practice (2021) Coronavirus disease 2019 (COVID-19). https://bestpractice.bmj.com/topics/en-gb/3000201/prevention.

children do not seem to be at higher risk for severe illness based on age or sex.

In Britain, a prospective observational cohort study found that children and young adults represented 0.9% of all hospitalized patients at the time. The median age of children admitted to hospital was 4.6 years, 56% were male, 35% were under 12 months of age, and 42% had at least one comorbidity. In terms of ethnicity, 57% were White, 12% were South Asian, and 10% were Black. Age under 1 month, age 10 to 14 years and Black race were risk factors for admission to critical care.

In the United States, a retrospective cohort study of over 135,000 children found that the mean age of infected children was 8.8 years, and 53% were male. In terms of ethnicity, 59% were White, 15% were Black, 11% were Hispanic, and 3% were Asian. Only 4% of children tested positive for SARS-CoV-2 in this population, and clinical manifestations were typically mild. Cases in children, adolescents and young adults increased from October to December, 2020; however, hospitalizations, Intensive Care Unit admissions and deaths remained low for these age groups (2.5%, 0.8%, and <0.1% respectively, based on available data).

Globally, the case fatality rate in children appears to be higher in low- and middle-income countries compared with high-income countries.

See also Section: PRIMARY PREVENTION: VACCINES: SPECIAL POPULATIONS: CHILDREN AND ADOLESCENTS

- The Pfizer/BioNTech vaccine has been authorised for use in young people aged 12 to 15 years in many countries, including Britain, the European Union and the United

States. Authorisation was based on an ongoing randomised, placebo-controlled clinical trial in the United States with more than 2,000 participants that reports 100% efficacy from 7 days after the second dose. Due to the limited number of children included in the study, the trial could not have detected rare adverse effects.

- The World Health Organization recommends considering use of the Pfizer/BioNTech vaccine in children aged 12 to 15 years only when high vaccine coverage with 2 doses has been achieved in high-priority groups. Children aged 12 to 15 years with comorbidities that put them at significantly higher risk of serious disease, alongside other high-risk groups, may be offered vaccination.
- The European Medicines Agency and the US Food and Drug Administration are evaluating an application to extend the use of the Moderna vaccine to include young people aged 12 to 17 years.

Level 2

UpToDate (2021) COVID-19: Vaccines to prevent SARS-CoV-2 infection[11]

See Section: SPECIAL POPULATIONS: CHILDREN

The authors recommend that eligible children undergo COVID-19 vaccination. Specifically, in the United States, the Pfizer-BioNTech COVID-19 vaccine is authorized for adolescents aged 12-15 years based on evidence that efficacy, immunogenicity and the adverse effect profile in that population are comparable to those in older

[11] UpToDate (2021) COVID-19: Vaccines to prevent SARS-CoV-2 infection. https://www.uptodate.com/contents/COVID-19-vaccines-to-prevent-sars-cov-2-infection.

individuals. Studies with other vaccines and in younger children are underway.

COVID-19 is generally less severe in children than adults; nevertheless, the risk of the multisystem inflammatory syndrome in children (MIS-C) following acute infection, the risk of severe disease in children with underlying medical conditions, and the general desire to prevent COVID-19 in children remain compelling reasons for vaccination of children. Given the hypothesis that MIS-C is associated with immune dysregulation precipitated by SARS-CoV-2 infection, immune-related side effects following vaccination in children must be closely monitored.

See Section: BNT162B2 (PFIZER-BIONTECH COVID-19 VACCINE)

This mRNA vaccine is delivered in a lipid nanoparticle to express a full-length spike protein. It is given intramuscularly in two doses three weeks apart. BNT162b2 has been authorized for use in several locations, including the United States, Britain, the European Union, and Canada. Clinical use of the vaccine is discussed elsewhere.

- **Immunogenicity**: In a phase I/II randomized, placebo-controlled, observer-blind dose escalation study in healthy adults 18 to 85 years of age, binding and neutralizing antibody responses were demonstrated that were comparable to those in convalescent plasma from patients who had asymptomatic or moderate SARS-CoV-2 infection. Responses in participants ≥65 years old were generally lower than in younger subjects, but still comparable to titers in convalescent plasma. Neutralizing antibody titers in recipients aged 12 through 15 years were significantly higher than those induced in individuals aged 16 to 25 years.

- **Efficacy**: In a large placebo-controlled phase III trial, this vaccine had 95 % efficacy (95% CI 90.3-97.6) in preventing symptomatic COVID-19 at or after day 7 following the second dose [90,91]. This effect was assessed after an analysis of 170 confirmed COVID-19 cases (8 in the vaccine group and 162 in the placebo group) among over 36,000 participants aged 16 years and older with a median of two months' follow-up after vaccination. Nine of the 10 severe cases that occurred during the study were in the placebo group. Among adults ≥65 years who had other medical comorbidities or obesity, vaccine efficacy was 91.7 % (95% CI 44.2-99.8). Among the entire trial population, the rate of COVID-19 in the vaccine group started to decrease relative to the rate in the placebo group approximately two weeks after the first dose. Vaccine efficacy after two doses was also high among 1983 adolescent trial participants aged 12 through 15 years without evidence of prior infection, with 0 and 16 symptomatic cases among vaccine and placebo recipients, respectively (efficacy 100 %, 95% CI 75.3-100).
- **Safety and Side Effects**: Local and systemic adverse effects are relatively common, particularly after the second dose; most are of mild or moderate severity and are limited to the first two days after vaccination. Among 1.6 million vaccine recipients 16 years or older in the United States who responded to post-vaccination surveys, an injection site reaction (mainly pain, but also redness, swelling, and pruritus) was reported in approximately 65 % after each dose; fatigue, headache, and myalgias were reported in 29%, 25% and 17% after the first dose and in 48%, 40% and 37 % after the second, respective-

ly. After the second dose, fevers, chills, and joint pain each occurred in approximately 20%. Reactions were most frequently reported on the day following vaccination. These reactions were also commonly reported among adolescents aged 12 through 15 years following the second dose (fatigue, headache, chills, and myalgia in 66%, 65%, 42% and 32 %, respectively). Local and systemic reactions occur less frequently among recipients 65 years or older but are still relatively common.

Irish and/or International Literature

COVID-19 VACCINES IN ADOLESCENTS

Level 2

[Frenck et al (2021) [Randomized Controlled Trial] Safety, Immunogenicity, and Efficacy of the BNT162b2 COVID-19 Vaccine in Adolescents][12]

Until very recently, vaccines against SARS-CoV-2 had not been authorized for emergency use in persons younger than 16 years of age. Safe, effective vaccines are needed to protect this population, facilitate in-person learning and social interaction, and contribute to herd immunity.

METHODS: In an ongoing multinational, placebo-controlled, observer-blinded trial, the authors randomly assigned participants in a 1:1 ratio to receive two injections, 21 days apart, of 30 ug of the Pfizer-BioNTech BNT162b2 vaccine or placebo. Non-inferiority of immune response to BNT162b2 in 12- to 15-year-old participants was an immunogenicity objective. Safety and efficacy against confirmed COVID-19 (onset, >7 days after dose 2) in the 12- to 15-year-old cohort were assessed.

CONCLUSION: No vaccine-related severe adverse events were observed. The geometric mean ratio of SARS-CoV-2 50%

[12] Frenck RW Jr, Klein NP, Kitchin N, Gurtman A, Absalon J, Lockhart S, Perez JL, Walter EB, Senders S, Bailey R, Swanson KA, Ma H, Xu X, Koury K, Kalina WV, Cooper D, Jennings T, Brandon DM, Thomas SJ, Türeci Ö, Tresnan DB, Mather S, Dormitzer PR, Şahin U, Jansen KU, Gruber WC; C4591001 Clinical Trial Group. Safety, Immunogenicity, and Efficacy of the BNT162b2 COVID-19 Vaccine in Adolescents. N Engl J Med. 2021 Jul 15;385(3):239-250. doi: 10.1056/NEJMoa2107456. Epub 2021 May 27. PMID: 34043894; PMCID: PMC8174030.

neutralizing titers after dose 2 in 12- to 15-year-old participants relative to 16- to 25-year-old participants was 1.76 (95% CI, 1.47 to 2.10).

Level 2

Das et al (2021) [Cross-Sectional Study] Myocarditis and Pericarditis Following mRNA COVID-19 Vaccination: What Do We Know So Far?[13]

In this cross-sectional study of 29 published cases of acute myopericarditis following COVID-19 mRNA vaccination, the most common presentation was chest pain within 1-5 days after the second vaccine dose. All patients had an elevated troponin. Cardiac MRI revealed late gadolinium enhancement consistent with myocarditis in 69% of cases. Most patients were treated with non-steroidal anti-inflammatory drugs for symptomatic relief, and 4 received intravenous immune globulin and corticosteroids.

The authors speculate a possible causal relationship between vaccine administration and myocarditis. Data from their analysis confirms that all myocarditis and pericarditis cases were mild and resolved within a few days to a few weeks. The authors conclude that the risk of cardiac complications among children and adults due to SARS-CoV-2 infection far exceeds the minimal and rare risks of vaccination-related transient myocardial or pericardial inflammation.

[13] Das BB, Moskowitz WB, Taylor MB, Palmer A. Myocarditis and Pericarditis Following mRNA COVID-19 Vaccination: What Do We Know So Far? Children (Basel). 2021 Jul 18;8(7):607. doi: 10.3390/children8070607. PMID: 34356586; PMCID: PMC8305058.

Level 5

Snapiri et al (2021) [Case Series] Transient Cardiac Injury in Adolescents Receiving the BNT162b2 mRNA COVID-19 Vaccine[14]

OBJECTIVE: [Pfizer-BioNTech] BNT162b2 is approved for the vaccination of adolescents over 16 years of age in Israel. In clinical trials, systemic adverse events were scarce — although the pre-tested cohort of the adolescent age group was relatively small. The objective of the current study is to raise awareness for potential adverse reactions.

METHODS: A case series of patients diagnosed with perimyocarditis following vaccination. Patients were compiled from 3 paediatric medical centers in Israel and data regarding cases were collected. Incidence of perimyocarditis during the vaccination period was also compared with previous years.

RESULTS: All patients were males 16-18 years old, of Jewish descent, who presented with chest pain that began 1-3 days following vaccination. In 6 of the 7 patients, symptoms began following the second vaccine dose and in 1 patient following the first vaccine dose.

CONCLUSION: All cases were mild and none required cardiovascular or respiratory support. The incidence of perimyocarditis during the vaccination period was elevated in comparison to previous years.

[14] Snapiri O, Rosenberg Danziger C, Shirman N, Weissbach A, Lowenthal A, Ayalon I, Adam D, Yarden-Bilavsky H, Bilavsky E. Transient Cardiac Injury in Adolescents Receiving the BNT162b2 mRNA COVID-19 Vaccine. Pediatr Infect Dis J. 2021 Jun 2. doi: 10.1097/INF.0000000000003235. Epub ahead of print. PMID: 34077949.

Level 6

Marshall et al (2021) [Preprint] [Case Series] Symptomatic Acute Myocarditis in Seven Adolescents Following Pfizer-BioNTech COVID-19 Vaccination[15]

The authors' report from 7 cases of acute myocarditis or myopericarditis among adolescent males who developed chest pain within 4 days of receiving the Pfizer-BioNTech vaccine and were hospitalized found that 6 of 7 patients had negative SARS-CoV-2 nucleocapsid antibody assays, and all patients' symptoms resolved rapidly. 3 patients were treated with non-steroid anti-inflammatory drugs and 4 received intravenous immune globulin and corticosteroids. Diagnostic evaluations for other myocarditis etiologies, including respiratory pathogens from nasopharyngeal swabs, and diagnostics for other infectious agents, were all negative.

Level 6

Park et al (2021) [Preprint] Self-limited myocarditis presenting with chest pain and ST segment elevation in adolescents after vaccination with the BNT162b2 mRNA vaccine[16]

The authors report on two adolescent males presenting within 3 days after the first and second dose of the Pfizer-BioNTech BNT162b2 vaccine with chest pain. Elevated troponin levels, ST

[15] Marshall M, Ferguson ID, Lewis P, Jaggi P, Gagliardo C, Collins JS, Shaughnessya R, Carona R, Fuss C, Corbin KJE, Emuren L, Faherty E, Hall EK, Di Pentima C, Oster ME, Paintsil E, Siddiqui S, Timchak DM, Guzman-Cottrill JA. Symptomatic Acute Myocarditis in Seven Adolescents Following Pfizer-BioNTech COVID-19 Vaccination. Pediatrics. 2021 Jun 4:e2021052478. doi: 10.1542/peds.2021-052478. Epub ahead of print. PMID: 34088762.

[16] Park J, Brekke DR, Bratincsak A. Self-limited myocarditis presenting with chest pain and ST segment elevation in adolescents after vaccination with the BNT162b2 mRNA vaccine. Cardiol Young. 2021 Jun 28:1-4. doi: 10.1017/S1047951121002547. Epub ahead of print. PMID: 34180390.

segment elevation and enhancement of the myocardium in cardiac MRI suggested myocarditis. Left ventricular function remained normal, symptoms resolved, and patients were discharged in 4 days.
The authors conclude that the Pfizer-BioNTech COVID-19 vaccine may be associated with self-limited myocarditis in youth.

Level 7

Centers for Disease Control and Prevention (United States). Advisory Committee on Immunization Practices (ACIP) (June 2021) ACIP Presentation Slides: June 23-25, 2021 Meeting. Update on COVID-19 vaccine safety, including myocarditis after mRNA vaccines[17]
Early data for myocarditis/pericarditis in 12–39-year-olds suggest:

- ☐ More cases after dose 2 *vs.* dose 1 of mRNA COVID-19 vaccine
- ☐ Incidence of 12.6 cases per 1,000,000 second doses of any mRNA vaccine in the 21 days following vaccination
- ☐ Incidence appears to be higher in males *vs.* females
- ☐ Clustering of myocarditis/pericarditis within the week following vaccination (most likely 0-5 days)

Available outcome data indicate that patients generally recover from symptoms and do well.

[17] Centers for Disease Control and Prevention (United States). Advisory Committee on Immunization Practices (ACIP) (June 2021) ACIP Presentation Slides: June 23-25, 2021 Meeting. Update on COVID-19 vaccine safety, including myocarditis after mRNA vaccines. https://pubmed.ncbi.nlm.nih.gov/34159636/.

Level 7

Glickman et al (2021) [Editorial] Vaccinating children and adolescents against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-The Israeli experience[18]

As of 1 April 2021, 1,028 doses of BNT162b2 were administered to 618 children aged 12–15 years who had risk factors for severe COVID-19. Active assessment of adverse events in this population did not find serious or severe adverse events.

Level 8: UNCLASSIFIED

Mahase (2021) [Press Release] COVID-19: Pfizer reports 100% vaccine efficacy in children aged 12 to 15[19]

The Pfizer-BioNTech COVID-19 vaccine has shown 100% efficacy against SARS-CoV-2 in the preliminary results of a phase III trial among children aged 12 to 15. Pfizer announced the results in a press release, although full details have yet to be published.

The phase III trial included 2260 children in the United States. A total of 18 cases of COVID-19 were observed in the placebo group (n=1129), with none reported in the vaccinated group (n=1131). The vaccine also elicited robust antibody responses and was well tolerated, with side effects consistent with those observed in participants aged 16 to 25.

Pfizer will now submit the data for peer review and publication, and trial participants will be monitored for two years to determine long-term protection and safety.

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[18] Glikman D, Stein M, Shinwell ES. Vaccinating children and adolescents against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-The Israeli experience. Acta Paediatr. 2021 Sep;110(9):2496-2498. doi: 10.1111/apa.15982. Epub 2021 Jun 22. PMID: 34159636.
[19] Mahase E. COVID-19: Pfizer reports 100% vaccine efficacy in children aged 12 to 15. BMJ. 2021 Apr 1;373:n881. doi: 10.1136/bmj.n881. PMID: 33795232.

Stephen Griffin, Associate Professor at the University of Leeds School of Medicine, said: "Demonstrating efficacy and safety in younger patients is an important step forward in terms of enabling eventual population immunity against SARS-CoV-2 and will enable a long-term programme of school-based vaccination to be implemented following the initial rollout, ensuring that our population is well protected from the virus in the future."

VACCINE ACCEPTANCE AMONG ADOLESCENTS

Level 2

Scherer et al (2021) [Cross-Sectional Study] Acceptability of Adolescent COVID-19 Vaccination Among Adolescents and Parents of Adolescents — United States, April 15–23, 2021[20]

Using data from nonprobability-based Internet panel surveys administered by the Healthcare and Public Perceptions of Immunizations Survey Collaborative, the acceptability of adolescent COVID-19 vaccination and self-reported factors increasing vaccination intent were assessed among independently recruited samples of 985 adolescents aged 13-17 years and 1,022 parents and guardians of adolescents aged 12-17 years during April 15-April 23, 2021, prior to vaccine authorization for this age group in the United States. Approximately one quarter (27.6%) of parents whose adolescents were already vaccine-eligible — ie aged 16-17 years — reported their adolescent had received at least one COVID-

[20] Scherer AM, Gedlinske AM, Parker AM, Gidengil CA, Askelson NM, Petersen CA, Woodworth KR, Lindley MC. Acceptability of Adolescent COVID-19 Vaccination Among Adolescents and Parents of Adolescents - United States, April 15-23, 2021. MMWR Morb Mortal Wkly Rep. 2021 Jul 16;70(28):997-1003. doi: 10.15585/mmwr.mm7028e1. PMID: 34264908; PMCID: PMC8314712.

19 vaccine dose, similar to the proportion reported by vaccine-eligible adolescents aged 16-17 years (26.1%). However, vaccine receipt reported by parents of adolescents differed across demographic groups: parents identifying as female or Hispanic or with an education lower than primary degree level reported the lowest adolescent COVID-19 vaccination receipt. Among parents of unvaccinated adolescents aged 12-17 years, 55.5% reported that they would *"definitely"* or *"probably"* have their adolescent receive a COVID-19 vaccination. Among unvaccinated adolescents aged 13-17 years, 51.7% reported they would *"definitely"* or *"probably"* receive a COVID-19 vaccination. Obtaining more information about adolescent COVID-19 vaccine safety and efficacy, as well as school COVID-19 vaccination requirements, were the most commonly cited factors that would increase vaccination intent among both parents and adolescents. Federal and local health officials and primary care professionals were the most trusted sources of COVID-19 vaccine information.

Level 2

McKinnon et al (2021) [Preprint] [Cross-Sectional Study] Social inequalities in COVID-19 vaccine acceptance and uptake for children and adolescents in Montreal, Canada: a cross-sectional study[21]

The authors examined social determinants of parental COVID-19 vaccine acceptance and uptake for children and adolescents. METHODS: Cross-sectional data from an ongoing COVID-19 cohort study in Montreal, Canada, including all parents of 2 to 18-year-old children who completed an online questionnaire from May 18 to June 26, 2021 (n=809). Age-adjusted prevalence

[21] McKinnon, B., Quach, C., Dubé, E., Tuong Nguyen, C., Zinszer, K.
Social inequalities in COVID-19 vaccine acceptance and uptake for children and adolescents in Montreal, Canada: a cross-sectional study.
medRxiv 2021.05.08.21256831; doi: https://doi.org/10.1101/2021.05.08.21256831

estimates of vaccine acceptance by parental education, race/ethnicity, birthplace, household income and neighbourhood were calculated. Multinomial logistic regression was used to estimate adjusted prevalence differences (aPD) and ratios (aPR). Social determinants of vaccine uptake were estimated for the vaccine-eligible sample of 12 to 18 year-olds (n=306).
RESULTS: Intention to vaccinate children against COVID-19 was high, with only 12.4% of parents unlikely to have their child vaccinated. Parents with younger children were less likely to accept vaccination, as were those from lower-income households, racialized groups, and those born outside Canada. The percentage of parents whose child was vaccinated or very likely to be vaccinated was 18.4 percentage points lower among those with annual household incomes <$100,000 *vs.* ≥$150,000 (95% CI: 10.1 to 26.7). Racialized parents reported greater unwillingness to vaccinate compared to White parents (aPD=10.3; 95% CI: 1.5, 19.1). Vaccine-eligible adolescents from the most deprived neighbourhood were half as likely to be vaccinated compared to those from the least deprived neighbourhood (aPR = 0.48; 95% CI: 0.18 to 0.77).
INTERPRETATION: This study identified marked social inequalities in COVID-19 vaccine acceptance and uptake for children and adolescents. Efforts are needed to reach disadvantaged and marginalized populations with tailored strategies that promote informed decision making and facilitate access to vaccination.

Level 2

Atad et al (2021) [Preprint] [Cross-Sectional Study] Vaccine-Hesitant Parents' Considerations Regarding COVID-19 Vaccination of Adolescents[22]

Israel led a rapid vaccine rollout against COVID-19, leading to a local remission of the epidemic and easing of most public health measures. Further vaccination among those aged 12 to 15 years may be hindered by public perceptions of the necessity and safety of vaccination.

METHODS: The authors examined the considerations of vaccine hesitant parents (VHPs) regarding vaccination of children against COVID-19.

RESULTS: Among 456 survey respondents, parents who were vaccinated against COVID-19 were more likely to intend to vaccinate their children ($r=-0.466$, $p<0.01$). Low accessibility of vaccination may be a dissuading factor for VHPs more inclined to vaccinate. Vaccine efficacy and gaining a *"Green Pass"* were positively associated with an intention to vaccinate and statistically significant. VHPs inclined not to vaccinate indicated short development time and possible long-term effects as dissuading factors.

[22] Atad, E., Netzer, I., Peleg, O., Landsman, K., Dalyot, K., Edan Reuven, S., Baram-Tsabari, A. Vaccine-Hesitant Parents' Considerations Regarding COVID-19 Vaccination of Adolescents medRxiv 2021.05.25.21257780; doi: https://doi.org/10.1101/2021.05.25.21257780.

Level 2

Montalti et al (2021) [Cross-Sectional Study] Would Parents Get Their Children Vaccinated Against SARS-CoV-2? Rate and Predictors of Vaccine Hesitancy According to a Survey over 5000 Families from Bologna, Italy[23]

Vaccine hesitancy (VH) could limit the ability to reach the coverage threshold required to ensure herd immunity. The objective of this study was to investigate the prevalence and determinants of VH among parents or guardians toward a potentially available COVID-19 vaccination for children and adolescents. An online survey was performed in parents or guardians of children aged <18 years, living in Bologna, Italy. 5054 questionnaires were collected. A majority (60.4%) of parents or guardians were inclined to vaccinate, with 29.6% still considering the opportunity, and 9.9% remaining hesitant. Highest vaccine hesitancy rates were detected in female parents or guardians of children aged 6-10 years, ≤29 years old, with low educational level, relying on information found on the Internet or on social media, and opposing mandatory vaccination policies. Although preliminary, these data could help in designing target strategies to implement adherence to a vaccination campaign, with special regard to Internet-based information.

[23] Montalti M, Rallo F, Guaraldi F, Bartoli L, Po G, Stillo M, Perrone P, Squillace L, Dallolio L, Pandolfi P, Resi D, Fantini MP, Reno C, Gori D. Would Parents Get Their Children Vaccinated Against SARS-CoV-2? Rate and Predictors of Vaccine Hesitancy According to a Survey over 5000 Families from Bologna, Italy. Vaccines (Basel). 2021 Apr 10;9(4):366. doi: 10.3390/vaccines9040366. PMID: 33920109; PMCID: PMC8069076.

Level 2

Zhang et al (2020) [Cross-Sectional Study] Parental Acceptability of COVID-19 Vaccination for Children Under the Age of 18 Years: Cross-Sectional Online Survey[24]

Vaccinating children against COVID-19 would contribute to the control of the pandemic and the recovery of the global economy. For children under the age of 18 years, parents are usually the decision makers regarding their children's vaccination.

OBJECTIVE: The objective of this study was to investigate parental acceptability of COVID-19 vaccination for children under the age of 18 years in China.

METHODS: Secondary analysis of a cross-sectional closed online survey among 2053 factory workers in Shenzhen, China, implemented from September 1 to 7, 2020. Participants of the online survey were full-time employees aged ≥18 years who had resumed work in factories in Shenzhen. Factory workers in Shenzhen are required to receive physical examinations once a year. Eligible workers attending six designated physical examination sites were invited to complete an online survey. This study was based on a subsample of those who had at least one child under the age of 18 years (N=1052). After being briefed that COVID-19 vaccines developed by China are likely to be available by the end of 2020, participants were asked about the likelihood of having their children under the age of 18 years take up COVID-19 vaccination provided by the government. Multivariate logistic regression models were fitted to examine the associations of

[24] Zhang KC, Fang Y, Cao H, Chen H, Hu T, Chen YQ, Zhou X, Wang Z. Parental Acceptability of COVID-19 Vaccination for Children Under the Age of 18 Years: Cross-Sectional Online Survey. JMIR Pediatr Parent. 2020 Dec 30;3(2):e24827. doi: 10.2196/24827. PMID: 33326406; PMCID: PMC7775376.

perceptions related to COVID-19 vaccination based on the theory of planned behavior (TPB) and exposure to information related to COVID-19 through social media with parental acceptability, after controlling for significant background characteristics.

RESULTS: The prevalence of parents' acceptability of COVID-19 vaccination for their children was 72.6% (764/1052). After adjusting for significant background characteristics, positive attitudes toward COVID-19 vaccination (adjusted odds ratio (AOR) 1.70, 95% CI 1.50-1.91), the perception that a family member would support them in having their children take up COVID-19 vaccination (AOR 4.18, 95% CI 3.21-5.43) and perceived behavioral control to have the children take up COVID-19 vaccination (AOR 1.84, 95% CI 1.49-2.26) were associated with higher parental acceptability of COVID-19 vaccination. Regarding social media influence, higher exposure to positive information related to COVID-19 vaccination was associated with higher parental acceptability of COVID-19 vaccination (AOR 1.35, 95% CI 1.17-1.56). Higher exposure to negative information related to COVID-19 vaccination was negatively associated with the dependent variable (AOR 0.85, 95% CI 0.74-0.99).

CONCLUSIONS: Parents' acceptability of COVID-19 vaccination for their children under 18 years of age was high in China. The TPB is a useful framework to guide the development of future campaigns promoting COVID-19 vaccination targeting parents. Transparency in communicating about the vaccine development process and vaccine safety testing is important. Public health authorities should also address misinformation in a timely manner.

Level 2

Office for National Statistics (Great Britain) (2021) Coronavirus and vaccine hesitancy, Great Britain: 26 May to 20 June 2021[25]

86% of adolescents aged 16-17 years reported positive sentiment towards a COVID-19 vaccine, with 14% reporting vaccine hesitancy. This was the highest reported level of vaccine hesitancy compared with those aged 18-21 years (9%), those aged 22-25 years (10%), and in all adults (4%).

IMPACT OF LOCKDOWN ON ADOLESCENTS

Level 1

Viner et al (2021) [Systematic Review and Narrative Synthesis] Impacts of school closures on physical and mental health of children and young people: a systematic review[26]

METHODS: The authors conducted a systematic review of published or preprint observational quantitative studies of the impacts of school closures for any reason on the health, wellbeing and educational outcomes of children and young people, excluding impacts of closure on transmission of infection. A machine learning approach for screening articles was used, with decisions

[25] Office for National Statistics (Great Britain) (2021) Coronavirus and vaccine hesitancy, Great Britain: 26 May to 20 June 2021. https://www.ons.gov.uk/releases/coronavirusandvaccinehesitancygreatbritain26mayto20june2021.

[26] Impacts of school closures on physical and mental health of children and young people: a systematic review.
Russell Viner, Simon Russell, Rosella Saulle, Helen Croker, Claire Stansfeld, Jessica Packer, Dasha Nicholls, Anne-Lise Goddings, Chris Bonell, Lee Hudson, Steven Hope, Nina Schwalbe, Anthony Morgan, Silvia Minozzi..
medRxiv 2021.02.10.21251526; doi: https://doi.org/10.1101/2021.02.10.21251526

on inclusion and data extraction performed independently by two researchers. Quality was assessed for study type. A narrative synthesis of results was undertaken as data did not allow meta-analysis.

RESULTS: 16,817 records were screened, of which 151 were reviewed in full-text; 72 studies were included from 20 countries. 33% were cohort studies using historical control periods; 19% pre-post studies; and 46% cross-sectional studies which assessed change by comparison with population reference data. 63% were high-quality, 25% medium-quality and 13% low-quality. Cause of closure in all studies was the first COVID-19 pandemic wave with the exception of 5 influenza studies and one teachers' strike.

27 studies concerning mental health identified considerable impacts across emotional, behavioural and restlessness or inattention problems. 18%-60% of children and adolescents scored above risk thresholds for distress, particularly anxiety and depressive symptoms. Two studies reported non-significant rises in suicide rates. Self-harm and psychiatric attendances were markedly reduced, indicating a rise in unmet mental health needs. Child protection referrals fell 27%-39%, with a halving of the expected number of referrals originating in schools.

19 studies concerning health service use showed marked reductions in Emergency Department presentations and hospital admissions, with evidence of delayed presentations and potential widening of inequalities in vaccination coverage. Data suggested significant rises in screen-time and social media use, and reductions in physical activity; however, data on sleep and diet were inconclusive. Available data suggested likely higher harms in children and adolescents from more deprived populations.

CONCLUSIONS: School closures as part of broader social distancing

measures are associated with considerable harms to the health and wellbeing of children and young people. Available data are short-term, and longer-term harms are likely to be magnified by further school closures. Data are urgently needed on longer-term impacts using strong research designs, particularly among vulnerable groups. These findings are important for policy-makers seeking to balance the risks of transmission through school-aged children with the harms of closing schools.

Level 1

UNESCO (2021) Adverse consequences of school closures[27]

School closures carry high social and economic costs and exacerbate already existing disparities within the education system. The effects of school closures include interrupted learning, disruption to formal exams, poor nutrition, increased drop-out rates, increased child exposure to violence and exploitation, social isolation, gaps in childcare, parental absenteeism from work and reduced productivity, and strain on health systems from health workers' absenteeism.

[27] UNESCO (2021) Adverse consequences of school closures. https://en.unesco.org/COVID19/educationresponse/consequences.

Level 1

Jones et al (2021) [Systematic Review and Narrative Synthesis] Impact of COVID-19 on Mental Health in Adolescents: A Systematic Review[28]

Due to a dearth of sufficient data on the psychological toll of the COVID-19 pandemic on adolescent mental health, this systematic analysis aims to evaluate the impact of the pandemic on adolescent mental health. 16 quantitative studies conducted in 2019-2021 with 40,076 participants are included in the systematic review and narrative synthesis. Globally, adolescents of varying backgrounds experience higher rates of anxiety, depression and stress due to the pandemic. Adolescents also have a higher frequency of using alcohol and cannabis during the COVID-19 pandemic. However, social support, positive coping skills, home quarantining and parent-child discussions seem to positively impact adolescent mental health. Whether in the United States or abroad, the COVID-19 pandemic has impacted adolescent mental health. Therefore, it is important to seek and to use all of the available resources and therapies to help adolescents mediate the adjustments caused by the pandemic.

Level 6

Guessoum et al (2020) [Narrative Review] Adolescent psychiatric disorders during the COVID-19 pandemic and lockdown[29]

The authors reviewed the literature on adolescent psychiatric

[28] Jones EAK, Mitra AK, Bhuiyan AR. Impact of COVID-19 on Mental Health in Adolescents: A Systematic Review. Int J Environ Res Public Health. 2021 Mar 3;18(5):2470. doi: 10.3390/ijerph18052470. PMID: 33802278; PMCID: PMC7967607.
[29] Guessoum SB, Lachal J, Radjack R, Carretier E, Minassian S, Benoit L, Moro MR. Adolescent psychiatric disorders during the COVID-19 pandemic and lockdown. Psychiatry Res. 2020 Sep;291:113264. doi: 10.1016/j.psychres.2020.113264. Epub 2020 Jun 29. PMID: 32622172; PMCID: PMC7323662.

disorders related to the COVID-19 pandemic and lockdown. Stressful life events, extended home confinement, brutal grief, intra-familial violence and overuse of the Internet and social media are factors that were found to potentially influence the mental health of adolescents during lockdown. The authors caution that the COVID-19 pandemic may result in increased psychiatric disorders such as post-traumatic stress, depressive and anxiety disorders, and grief-related symptoms. Adolescents with psychiatric disorders are at risk of an interruption or change in their care and management, and may experience increased symptoms. There is still no data on the long-term impact of the pandemic. Adolescents' individual, familial and social vulnerability, as well as individual and familial coping abilities, are factors related to adolescent mental health in crisis scenarios.

TRAMSMISSION IN YOUTH SETTINGS

Level 2

Larosa et al (2020) [Population-Based Study] Secondary transmission of COVID-19 in preschool and school settings in northern Italy after their reopening in September 2020: a population-based study[30]

The authors report epidemiological investigations of the transmission of SARS-CoV-2 in 41 classes from 36 schools in

[30] Larosa E, Djuric O, Cassinadri M, Cilloni S, Bisaccia E, Vicentini M, Venturelli F, Giorgi Rossi P, Pezzotti P, Bedeschi E; Reggio Emilia COVID-19 Working Group. Secondary transmission of COVID-19 in preschool and school settings in northern Italy after their reopening in September 2020: a population-based study. Euro Surveill. 2020 Dec;25(49):2001911. doi: 10.2807/1560-7917.ES.2020.25.49.2001911. PMID: 33303065; PMCID: PMC7730487.

Reggio Emilia province, northern Italy, from their reopening on 1 September to 15 October 2020. The overall secondary case attack rate was 3.2%, reaching 6.6% in middle and high schools. More timely isolation and testing of classmates could be effective in reducing virus transmission in this setting.

Level 2

Ismail et al (2021) [Cross-Sectional Study] SARS-CoV-2 infection and transmission in educational settings: a prospective, cross-sectional analysis of infection clusters and outbreaks in England[31]

Understanding SARS-CoV-2 infection and transmission in educational settings is crucial for ensuring the safety of staff and children during the COVID-19 pandemic. The authors estimated the rate of SARS-CoV-2 infection and outbreaks among staff and students in educational settings during the summer half-term (June-July, 2020) in England.

METHODS: A prospective, cross-sectional analysis. Public Health England initiated enhanced national surveillance in educational settings in England that had reopened after the first national lockdown, from June 1 to July 17, 2020. Educational settings were categorised as early childhood education settings (<5-year-olds), primary schools (5-11-year-olds; only years 1 and 6 allowed to return), secondary schools (11-18-year-olds; only years 10 and 12), or mixed-age settings spanning a combination of the above. Further education colleges were excluded. Data were recorded in HPZone, an online national database for events that require public health management. RT-PCR-confirmed SARS-CoV-2 event rates and case rates were calculated for staff and students, and direction

[31] Ismail SA, Saliba V, Lopez Bernal J, Ramsay ME, Ladhani SN. SARS-CoV-2 infection and transmission in educational settings: a prospective, cross-sectional analysis of infection clusters and outbreaks in England. Lancet Infect Dis. 2021 Mar;21(3):344-353. doi: 10.1016/S1473-3099(20)30882-3. Epub 2020 Dec 8. PMID: 33306981; PMCID: PMC7833602.

of transmission was inferred on the basis of symptom onset and testing dates. Events were classified as single cases, co-primary cases (at least two confirmed cases within 48 hours, typically within the same household), and outbreaks (at least two epidemiologically linked cases, with sequential cases diagnosed within 14 days in the same educational setting). All events were followed up for 28 days after educational settings closed for the summer holidays. Negative binomial regression was used to correlate educational setting events with regional population, population density, and community incidence.
FINDINGS: A median of 38,000 early childhood education settings (IQR 35,500-41,500), 15,600 primary schools (13,450-17,300), and 4,000 secondary schools (3,700-4,200) were open each day, with a median daily attendance of 928,000 students (630,000-1,230,000) overall. There were 113 single cases of SARS-CoV-2 infection, 9 co-primary cases, and 55 outbreaks. The risk of an outbreak increased by 72% (95% CI 28-130) for every 5 cases per 100,000 population increase in community incidence (p<0·0001). Staff had higher incidence than students (27 cases [95% CI 23-32] per 100,000 per day among staff compared with 18 cases [14-24] in early childhood education students, 6·0 cases [4·3-8·2] in primary school students, and 6·8 cases [2·7-14] in secondary school students]), and most cases linked to outbreaks were in staff members (154 [73%] staff *vs.* 56 [27%] children out of 210 total cases). Probable direction of transmission was staff to staff in 26 outbreaks, staff to student in 8 outbreaks, student to staff in 16 outbreaks, and student to student in 5 outbreaks. The median number of secondary cases in outbreaks was one (IQR 1-2) for student index cases and one (1-5) for staff index cases.
INTERPRETATION: SARS-CoV-2 infections and outbreaks were uncommon in educational settings during the summer half-term

in England. The strong association with regional COVID-19 incidence emphasises the importance of controlling community transmission to protect educational settings. Interventions should focus on reducing transmission in and among staff.

Level 2

Gandini et al (2021) [Cross-Sectional and Cohort Study] A cross-sectional and prospective cohort study of the role of schools in the SARS-CoV-2 second wave in Italy[32]

During the COVID-19 pandemic, school closure have been mandated, but it is unclear whether schools are early COVID-19 amplifiers.

METHODS: A cross-sectional and prospective cohort study in Italy during the second wave of the COVID-19 pandemic from September 30, 2020 until at least February 28, 2021. Databases from the Italian Ministry of Education and the Veneto regional systems of SARS-CoV-2 case notification and of schools' secondary case tracing to compare SARS-CoV-2 incidence in students and school staff against incidence across age groups in the general population. Number of tests, secondary infections by type of index case and ratio of cases or tests per school were estimated using an adjusted multivariable generalized linear regression model. Regional reproduction numbers (*Rt*) were estimated from Italian Civil Protection daily incidence data with posterior distribution using a Markov Chain Monte Carlo algorithm.

FINDINGS: SARS-CoV-2 incidence among students was lower than in the general population. Secondary infections at school were <1%, and clusters of ≥2 secondary cases occurred in 5-7% of the

[32] Gandini S, Rainisio M, Iannuzzo ML, Bellerba F, Cecconi F, Scorrano L. A cross-sectional and prospective cohort study of the role of schools in the SARS-CoV-2 second wave in Italy. Lancet Reg Health Eur. 2021 Jun;5:100092. doi: 10.1016/j.lanepe.2021.100092. Epub 2021 Mar 26. PMID: 34104904; PMCID: PMC7995620.

analyzed schools. Incidence among teachers was comparable to the population of similar age (p=0.23). Secondary infections among teachers were rare, occurring more frequently when the index case was a teacher than a student (37% *vs.* 10%, p=0.007). Before and around the date of school opening in Veneto, SARS-CoV-2 incidence grew maximally in 20-29- and 45-49-years old individuals, not among students. The lag between school opening dates in Italian regions and the increase in the regional COVID-19 *Rt* was not uniform. Finally, school closures in two regions where they were implemented before other measures did not affect *Rt* decrease.
INTERPRETATION: This analysis does not support a role for school opening as a driver of the second COVID-19 wave in Italy, a large European country with high SARS-CoV-2 incidence.

Level 4

Macartney et al (2020) [Cohort Study] Transmission of SARS-CoV-2 in Australian educational settings: a prospective cohort study[33]

School closures have occurred globally during the COVID-19 pandemic. However, empiric data on transmission of SARS-CoV-2 among children and in educational settings are scarce. In Australia, most schools have remained open during the first epidemic wave, albeit with reduced student physical attendance at the epidemic peak. The authors examined SARS-CoV-2 transmission among children and staff in schools and early childhood education (ECE) settings in the Australian state of New South Wales.
METHODS: Laboratory-confirmed paediatric and adult COVID-19 cases who attended a school or ECE setting while considered

[33] Macartney K, Quinn HE, Pillsbury AJ, Koirala A, Deng L, Winkler N, Katelaris AL, O'Sullivan MVN, Dalton C, Wood N; NSW COVID-19 Schools Study Team. Transmission of SARS-CoV-2 in Australian educational settings: a prospective cohort study. Lancet Child Adolesc Health. 2020 Nov;4(11):807-816. doi: 10.1016/S2352-4642(20)30251-0. Epub 2020 Aug 3. PMID: 32758454; PMCID: PMC7398658.

infectious — defined as 24 hours before symptom onset based on national guidelines during the study period — in New South Wales from Jan 25 to April 10, 2020, were investigated for onward transmission. All identified school and ECE settings close contacts were required to home quarantine for 14 days, and were monitored and offered SARS-CoV-2 nucleic acid testing if symptomatic. Enhanced investigations in selected educational settings included nucleic acid testing and SARS-CoV-2 antibody testing in symptomatic and asymptomatic contacts. Secondary attack rates were calculated and compared with state-wide COVID-19 rates.
FINDINGS: 15 schools and 10 ECE settings had children (n=12) or adults (n=15) attend while infectious, with 1,448 contacts monitored. Of these, 633 (43·7%) had nucleic acid testing, or antibody testing, or both, with 18 secondary cases identified (attack rate 1·2%). 5 secondary cases (three children; two adults) were identified (attack rate 0·5%; 5/914) in 3 schools. No secondary transmission occurred in 9 of 10 ECE settings among 497 contacts. However, one outbreak in an ECE setting involved transmission to 6 adults and 7 children (attack rate 35·1%; 13/37). Across all settings, 5 (28·0%) of 18 secondary infections were asymptomatic (three infants [all aged 1 year], one adolescent [age 15 years], and one adult).
INTERPRETATION: SARS-CoV-2 transmission rates were low in New South Wales educational settings during the first COVID-19 epidemic wave, consistent with mild infrequent disease in the 1·8 million child population. With effective case-contact testing and epidemic management strategies and associated small numbers of attendances while infected, children and teachers did not contribute significantly to COVID-19 transmission via attendance in educational settings. These findings could be used to inform modelling and public health policy regarding school closures

during the COVID-19 pandemic.

Level 6

Buja et al (2021) [Preprint] [Ecological Study] Opening schools and trends in SARS-CoV-2 transmission in European countries[34]

It is important to understand the role of schools in the community transmission of SARS-CoV-2, bearing in mind that children and adolescents can spread the infection within families, even when their own symptoms are mild. The aim of this study was to examine the trends of contagion before and after schools reopened across 27 countries in the European Union.

METHODS: All data on the number of people testing positive for COVID-19 in each European country were collected from 20 days before schools re-opened to 45 days afterwards. The Joinpoint regression method was used to detect single change points on the trend of contagion. The Bayesian Information Criterion (BIC) was used for model selection purposes.

RESULTS: 27 linear regression models for the daily case numbers of SARS-CoV-2 infection in the 27 countries from 20 days before schools reopened to 45 days afterward were calculated. A significant increase in the number of daily infections was seen for 21 countries after a change point in the linear regression lines. The change points in different countries varied, ranging from 10 to 42 days after schools reopened, with the majority occurring beyond the 21st day.

CONCLUSION: The authors observed a significant increase in the number of new daily cases in most countries. However, there may

34
Alessandra Buja, Matteo Paganini, Vittorio Cristofori, Tatjana Baldovin, Riccardo Fusinato, Giovanna Boccuzzo, Silvia Cocchio, Silvia Coretti, Vincenzo Rebba, Maria Parpinel. Opening schools and trends in SARS-CoV-2 transmission in European countries.
medRxiv 2021.02.26.21252504; doi: https://doi.org/10.1101/2021.02.26.21252504.

be confounding factors — such as the re-opening of workplaces, retail outlets and the hospitality sector at the same time as schools, season — that are not adjusted for.

POST COVID SEQULAE

Level 2

[Buonsenso et al (2021) [Cross-Sectional Study] Preliminary evidence on long COVID in children[35]]

This cross-sectional study included all children ≤18 years diagnosed with microbiologically confirmed COVID-19 in Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy. Only children with a SARS-CoV-2 infection diagnosed 30 days before the assessment were included.

129 children diagnosed with COVID-19 between March and November 2020 were enrolled (mean age of 11 ± 4.4 years; 62 (48.1%) female). 6 children with severe neurocognitive impairment were excluded. 109 children (84.5%) were interviewed by phone-call, and the remainder during outpatient assessment. During the acute phase of COVID-19 illness, 33 children (25.6%) were asymptomatic, and 96 (74.4%) had symptoms. Overall, 6 (4.7%) children were hospitalized, and 3 (2.3%) needed Paediatric Intensive Care Unit admission. After the initial diagnosis of COVID-19, 3 developed multisystem inflammatory syndrome (2.3%) and 2 myocarditis (1.6%). Patients were assessed on average 162.5 ± 113.7 days after COVID-19 microbiological diagnosis. 41.8%

[35] Buonsenso D, Munblit D, De Rose C, Sinatti D, Ricchiuto A, Carfi A, Valentini P. Preliminary evidence on long COVID in children. Acta Paediatr. 2021 Apr 9. doi: 10.1111/apa.15870. Epub ahead of print. PMID: 33835507.

completely recovered; 35.7% had one or two symptoms; and 22.5% had three or more symptoms.

Insomnia (18.6%); respiratory symptoms including pain and chest tightness (14.7%); nasal congestion (12.4%); fatigue (10.8%); muscle (10.1%) and joint (6.9%) pain; and concentration difficulties (10.1%) were the most frequently reported symptoms. These symptoms — described both in children with symptomatic and asymptomatic acute COVID-19 — were particularly frequent in those assessed more than 60 days after the initial diagnosis.

20 out of 30 children (66.6%) assessed between 60 and 120 days after initial COVID-19 had at least one persisting symptom; 13 had one or two symptoms; 7 had three or more symptoms. 35 of 68 children (27.1%) had at least one symptom 120 days or more after diagnosis; 21 had one or two symptoms; 14 had three or more symptoms. 29 out of the 68 children assessed ≥120 days from diagnosis (42.6%) were still distressed by these symptoms.

CONCLUSION: There is increasing evidence that restrictive measures aimed at limiting the pandemic are having a significant impact on children's mental health. Childhood is a delicate and fundamental period of life, critical for acquisition of social, behavioral and educational development. Evidence that COVID-19 may also have a long-term impact on children, including those with asymptomatic/paucisymptomatic COVID-19, highlights the need for paediatricians, mental health experts and policymakers to implement measures to reduce the impact of the pandemic on children's health. Further prospective studies, not only based on surveys but with objective clinical assessment and including healthy controls that never had COVID-19 are needed to better understand the burden of long COVID in children.

Level 2

Knoke et al (2021) [Preprint] [Cross-Sectional Study] More complaints than findings - Long-term pulmonary function in children and adolescents after COVID-19[36]

The frequency of persistent symptoms after COVID-19 in adults varies from 4.5% to 87%. Pulmonary function can also show long-term impairment in adults: 10% of hospitalised adults had reduced spirometry values, and 24% had decreased diffusion capacity. To date, only preliminary evidence is available on persistent respiratory sequelae in children and adolescents. The objective of this study was to examine the long-term effects of COVID-19 on pulmonary function in the paediatric population.

METHODS: Multiple-breath washout, body plethysmography and diffusion capacity testing were performed after an average of 2.6 months (range 0.4–6.0) following COVID-19 in 73 children and adolescents (age 5–18 years) with different disease severity. Cases were compared to 45 controls with and without infection within 6 months prior to assessment after exclusion of SARS-CoV-2.

RESULTS: Of the 19 patients (27.1%) who complained about persistent or newly emerged symptoms since COVID-19, 8 (11.4%) reported respiratory symptoms. Comparing patients with COVID-19 to controls, no significant differences were detected in frequency of abnormal pulmonary function (COVID-19: 12, 16.4%; controls: 12, 27.7%; OR 0.54, 95% CI 0.22–1.34). Only two patients with persistent respiratory symptoms showed abnormal pulmonary function. Multivariate analysis revealed reduced forced vital capacity (p=0.045) in patients with severe infection regardless of

[36] Leona Knoke, Anne Schlegtendal, Christoph Maier, Lynn Eitner, Thomas Lücke, Folke Brinkmann. More complaints than findings - Long-term pulmonary function in children and adolescents after COVID-19. medRxiv 2021.06.22.21259273; doi: https://doi.org/10.1101/2021.06.22.21259273.

SARS-CoV-2 infection.

DISCUSSION: Pulmonary function is rarely impaired in children and adolescents after COVID-19 except in those with severe infection. The discrepancy between persistent respiratory symptoms and normal pulmonary function suggests a different underlying pathology such as dysfunctional breathing.

Level 3

Magnusson et al (2021) [Preprint] [Pre-Post Study] Health care use up to 6 months after COVID-19 in 700,000 children and adolescents: a pre-post study[37]

OBJECTIVES: To explore whether and for how long COVID-19 among children gives an increase in the use of health services, when compared to children with no COVID-19.

METHODS: Studying all Norwegian residents aged 1-5, 6-15 and 16-19 years from August 1, 2020 to February 1, 2021 (N= 768,560), the authors contrasted rates of monthly all-cause primary and specialist health service use before and after testing for SARS-CoV-2 (% relative change), for children testing positive (non-hospitalized in the acute phase) (N=10,306) *vs.* children with no COVID-19 (N=758,254).

RESULTS: A substantial elevation in short-term primary care use for children testing positive for SARS-CoV-2 during the first month following positive test when compared to children testing negative was observed (relative elevation 1-5 years: 325%, 95% CI=296-354; 6-15 years: 434%, 95% CI=415-453; 16-19 years:

[37] Health care use up to 6 months after COVID-19 in 700.000 children and adolescents: a pre-post study. Karin Magnusson, Katrine Damgaard Skyrud, Pål Suren, Margrethe Greve-Isdahl, Ketil Størdal, Doris Tove Kristoffersen, Kjetil Telle.
medRxiv 2021.06.02.21258211; doi: https://doi.org/10.1101/2021.06.02.21258211.

360%, 95% CI=342-379). There was still elevated primary care use at 2 months (1-5 years: 21%, 95% CI= 4-38; 6-15 years: 13%, 95% CI=2-25) and at 3 months (1-5 years: 26%, 95% CI=7-45, 6-15 years: 15%, 95% CI=3-26) for young children, but not at 2 or 3 months for older children (16-19 years: 10%, 95% CI=-1-22 and 6%, 95% CI=-5-18, respectively). The 1-5-year-olds also had a long-term (up to 6 months) increase of primary care (14%, 95% CI=1-26) that was not observed for older age groups, when compared to same-aged children testing negative. No elevated use of specialist care was observed.

CONCLUSION: Children in pre-school age used health services for a longer time (3-6 months) after COVID-19 than children in primary and secondary school age (1-3 months).

Level 4

Bottino et al (2021) Can Asymptomatic or Non-Severe SARS-CoV-2 Infection Cause Medium-Term Pulmonary Sequelae in Children?[38]

Pulmonary complications in adults who recovered from SARS-CoV-2 have been reported even in minimally symptomatic patients. In this study, lung ultrasound (LUS) findings and pulmonary function of children who recovered from an asymptomatic or mildly symptomatic SARS-CoV-2 infection were evaluated. Patients younger than 18 years who recovered from SARS-CoV-2 infection at the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, were prospectively followed up for at least 30 days. All enrolled patients underwent LUS. Airway resistance measured by the interrupter technique test

[38] Bottino I, Patria MF, Milani GP, Agostoni C, Marchisio P, Lelii M, Alberzoni M, Dell'Era L, Castellazzi ML, Senatore L, Madini B, Pensabene MC, Rocchi A. Can Asymptomatic or Non-Severe SARS-CoV-2 Infection Cause Medium-Term Pulmonary Sequelae in Children? Front Paediatr. 2021 May 13;9:621019. doi: 10.3389/fped.2021.621019. PMID: 34084763; PMCID: PMC8168403.

was assessed in subjects aged 4-6 years, whereas forced spirometry and measurement of diffusing capacity of the lungs for carbon monoxide were performed in subjects older than 6 years. To evaluate a possible correlation between pulmonary alterations and immune response to SARS-CoV-2, two semi-quantitative enzyme immune assays were used. 16 out of 23 eligible children were enrolled in the study. The median age of enrolled subjects was 7.5 (0.5-10.5) years, with a male to female ratio of 1.7:1. No subject presented any abnormality on LUS, airway resistance test, forced spirometry, and diffusing capacity of the lungs for carbon monoxide. On the other hand, all subjects presented IgG against SARS-CoV-2. In contrast to adults, the authors did not detect any pulmonary complications in the cohort. These preliminary observations suggest that children with an asymptomatic or mildly symptomatic SARS-CoV-2 infection might be less prone to developing pulmonary complications than adults.

Level 4

Osmanov et al (2021) [Cohort Study] Risk factors for long COVID in previously hospitalised children using the ISARIC global follow-up protocol: A prospective cohort study[39]

The long-term sequelae of COVID-19 in children remain poorly characterised. This study aimed to assess long-term outcomes in children previously hospitalised with COVID-19 and associated risk factors.

METHODS: A prospective cohort study of children (≤18 years old)

[39] Osmanov IM, Spiridonova E, Bobkova P, Gamirova A, Shikhaleva A, Andreeva M, Blyuss O, El-Taravi Y, DunnGalvin A, Comberiati P, Peroni DG, Apfelbacher C, Genuneit J, Mazankova L, Miroshina A, Chistyakova E, Samitova E, Borzakova S, Bondarenko E, Korsunskiy AA, Konova I, Hanson SW, Carson G, Sigfrid L, Scott JT, Greenhawt M, Whittaker EA, Garralda E, Swann O, Buonsenso D, Nicholls DE, Simpson F, Jones C, Semple MG, Warner JO, Vos T, Olliaro P, Munblit D; Sechenov StopCOVID Research Team. Risk factors for long COVID in previously hospitalised children using the ISARIC Global follow-up protocol: A prospective cohort study. Eur Respir J. 2021 Jul 1:2101341. doi: 10.1183/13993003.01341-2021. Epub ahead of print. PMID: 34210789.

admitted with confirmed COVID-19 to Z.A. Bashlyaeva Children's Municipal Clinical Hospital in Moscow, Russia, between April 2, 2020 and August 26, 2020. Telephone interviews using the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) COVID-19 Health and Wellbeing paediatric At the time of the follow-up interview 126 (24.3%) participants reported persistent symptoms among which fatigue (53, 10.7%), sleep disturbance (36, 6.9%), and sensory problems (29, 5.6%) were the most common. Multiple symptoms were experienced by 44 (8.4%) participants. Risk factors for persistent symptoms were: older age "6-11 years" (odds ratio 2.74 (95% CI 1.37 to 5.75) and "12-18 years" (2.68, 1.41 to 5.4); and a history of allergic diseases (1.67, 1.04 to 2.67).follow-up survey were conducted. Persistent symptoms (>5 months) were further categorised by system(s) involved.
FINDINGS: 518 of 853 (61%) of eligible children were available for the follow-up assessment and included in the study. Median age was 10.4 years (IQR, 3-15.2) and 270 (52.1%) were girls; median follow-up since hospital discharge was 256 (223-271) days.
INTERPRETATION: A quarter of children experienced persistent symptoms months after hospitalization with acute COVID-19 infection, with 8.4% experiencing multi-system involvement. Older age and allergic diseases were associated with higher risk of persistent symptoms at follow-up.

Level 5

Brackel et al (2021) [Case Series] Pediatric long COVID: An overlooked phenomenon?[40]

Long COVID is a well-documented multisystem disease in adults. Far less is known about the long-term sequelae of COVID-19 in children. The authors report on the occurrence of long COVID in Dutch children.

PATIENTS AND METHODS: The authors conducted a national survey asking Dutch paediatricians to share their experiences of long COVID in children; and describe a case series of 6 children with long COVID to explore clinical features in greater detail.

RESULTS: With a response rate of 78% of Dutch paediatric departments, the authors identified 89 children aged 2–18 years with various complaints and suspected of long COVID. Of these children, 36% experienced severe limitations in daily function. The most common complaints were fatigue, dyspnea and concentration difficulties (87%, 55% and 45%, respectively). The case series emphasized the non-specific and broad clinical manifestations seen in post-COVID complaints.

CONCLUSION: Long COVID is also present in the paediatric population. Symptoms resemble those previously described in adults. This novel condition demands a multidisciplinary approach with international awareness and consensus to aid early detection and effective management.

[40] Brackel CLH, Lap CR, Buddingh EP, van Houten MA, van der Sande LJTM, Langereis EJ, Bannier MAGE, Pijnenburg MWH, Hashimoto S, Terheggen-Lagro SWJ. Pediatric long COVID: An overlooked phenomenon? Pediatr Pulmonol. 2021 Aug;56(8):2495-2502. doi: 10.1002/ppul.25521. Epub 2021 Jun 8. PMID: 34102037; PMCID: PMC8242715.

Produced by the members of the National Health Library and Knowledge Service Evidence Team†. Current as at 30 August 2021. This evidence summary collates the best available evidence at the time of writing and does not replace clinical judgement or guidance. Emerging literature or subsequent developments in respect of COVID-19 may require amendment to the information or sources listed in the document. Although all reasonable care has been taken in the compilation of content, the National Health Library and Knowledge Service Evidence Team makes no representations or warranties expressed or implied as to the accuracy or suitability of the information or sources listed in the document. This evidence summary is the property of the National Health Library and Knowledge Service and subsequent re-use or distribution in whole or in part should include acknowledgement of the service.

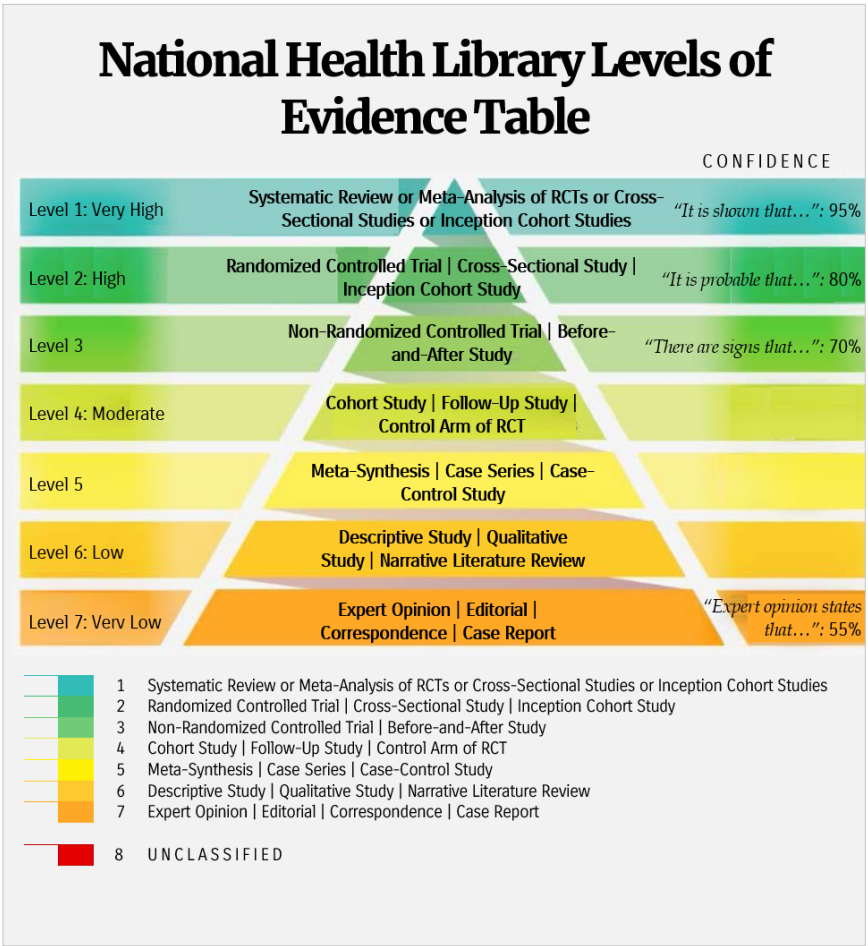
The following PICO(T) was used as a basis for the evidence summary:

Population	ADOLESCENTS ~12-18 YEARS
Intervention	SARS-CoV-2 VACCINATION
Comparison	
Outcome	EFFICACY; ADVERSE EFFECTS; TOLERANCE; ACCEPTANCE

The following search strategy was used:

1 exp Coronavirinae/ (50999)
2 COVID-19.ab,ti. (115210)
3 coronavirus.ab,ti. (57105)
4 "corona virus".ab,ti. (2013)
5 (Wuhan adj3 virus).ab,ti. (113)
6 ("2019-nCoV" or "2019 ncov").ab,ti. (1263)
7 "severe acute respiratory syndrome coronavirus 2".ab,ti. (12277)
8 ("2019" and (new or novel) and coronavirus).ab,ti. (9717)
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (147731)

The following schema was used to grade the levels of evidence included:



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