Journal of Infection 88 (2024) 106134

Contents lists available at ScienceDirect

Journal of Infection

journal homepage: www.elsevier.com/locate/jinf

Review

Current state of COVID-19 in children: 4 years on

Annabel A. Powell [a,*], Alexander C. Dowell [b], Paul Moss [b], Shamez N. Ladhani [a,c], the sKIDs Investigation Team [1]

[a] Public Health Programmes, UK Health Security Agency, London, UK
[b] Institute of Immunology & Immunotherapy, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK
[c] Paediatric Infectious Diseases Research Group, St. George's University of London, London, UK

ARTICLE INFO

Article history:
Accepted 28 February 2024
Available online 2 March 2024

Keywords:
COVID-19
SARS-CoV-2
Children
Adolescents

SUMMARY

Children have been disproportionately affected by the COVID-19 pandemic. Despite evidence of a very low risk of severe disease, children were subjected to extensive lockdown, restriction and mitigation measures, including school closures, to control the rapid spread of SARS-CoV-2 in most parts of the world. In this review we summarise the UK experience of COVID-19 in children four years into the largest and longest pandemic of this century. We address the risks of SARS-CoV-2 infection, immunity, transmission, severity and outcomes in children. We also assess the implementation, uptake, effectiveness and impact of COVID-19 vaccination, as well as the emergence, evolution and near disappearance of PIMS-TS (paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2) and current understanding of long COVID in children. This review consolidates current knowledge on childhood COVID-19 and emphasises the importance of continued research and the need for research-driven public health actions and policy decisions, especially in the context of new variants and future vaccines.
© 2024 The Authors. Published by Elsevier Ltd on behalf of The British Infection Association. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

December 31, 2023, will mark the fourth anniversary of the start of the coronavirus disease 2019 (COVID-19) pandemic when the World Health Organisation (WHO) was first informed of a cluster of cases of pneumonia of unknown cause detected in Wuhan City, Hubei Province, China. The responsible agent was subsequently identified as a novel coronavirus on January 9, 2020 and formally named as SARS-CoV-2 in February 2020. Coronaviruses are a large family of related viruses that typically cause mild respiratory disease in animals and humans. Rare outbreaks of related coronaviruses, such as Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS), have been associated with more severe disease but these were rapidly brought under control by effective public health measures.[1] In contrast, the high transmission rate and rapid international spread of SARS-CoV-2 was unprecedented, leading the WHO to declare the COVID-19 outbreak a global pandemic on March 11, 2020.

In England, the first cases of SARS-CoV-2 were confirmed on January 31, 2020 and the first paediatric cases on February 29, 2020.[2] By early March 2020, it was evident that the early containment measures were unsuccessful in controlling the spread of SARS-CoV-2 in the UK, leading the Prime Minister to declare the first national lockdown on March 23, 2020, including school closures. Despite very limited evidence, however, children were disproportionally affected by the lockdowns, restrictions and mitigations imposed national institutions to control the pandemic. In many parts of the world, children endured extraordinary periods of isolation and exclusion from school, which not only disrupted their education, but also impacted their physical and mental well-being, as well as access to social services, school immunisations and school meals, with the most deprived being disproportionately affected, likely leading to wider inequity gaps in the long-term. These effects have been discussed in detail by others.[3–5] In this review, we summarise the current evidence on (i) the risk of infection, immunity, transmission and severity (ii) implementation, uptake and impact of COVID-19 vaccination, (iii) the emergence, evolution and near disappearance of PIMS-TS (Paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2, also known as MIS-C, multisystem inflammatory syndrome in children), and (iv) the risks of long COVID in children during the first four years of the pandemic. Unlike many other countries, children of all ages in the UK have remained largely in school after the first pandemic year, with only short periods of school closures during March–May 2020, January–March 2021. The

* Correspondence to: UKHSA, 61 Colindale Avenue, London NW9 5EQ, UK.
E-mail address: annabel.powell@ukhsa.gov.uk (A.A. Powell).
[1] See sKIDs Investigation team members in Appendix.

https://doi.org/10.1016/j.jinf.2024.106134
0163-4453/© 2024 The Authors. Published by Elsevier Ltd on behalf of The British Infection Association. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

decision to close schools early in the pandemic was based largely on experiences with previous influenza pandemics and modelling studies identifying children as major drivers of infection and transmission of respiratory viruses,[6] alongside the uncertain role of children in SARS-CoV-2 transmission.[7]

Children and SARS-CoV-2 infection

Early in the pandemic, children were considered to be at lower risk of SARS-CoV-2 infection than adults, based mainly on data from PCR-testing of symptomatic individuals in healthcare and household contact settings.[2,7] In England, too, children accounted for only a small proportion of PCR-confirmed cases during the first pandemic wave, when testing for the virus was limited to healthcare settings.[2] With increasing availability and widespread use of SARS-CoV-2 PCR- and antigen-testing, high rates of asymptomatic and mild, transient infections were identified in children.[8,9] The true burden of childhood SARS-CoV-2 infection at a population level, however, could only be determined using serological tests to measure past exposure.[10] During the first pandemic wave, our first study measured serum SARS-CoV-2 nucleocapsid antibodies in children of healthcare workers in five UK cities during April–May 2020,[11] followed by primary school students and staff in 45 English schools in June 2020.[12] We found that SARS-CoV-2 nucleocapsid antibody seroprevalence (a marker of SARS-CoV-2 infection) was similar in children and adults, indicating that children were as likely to be infected as adults, but were more likely to remain asymptomatic.

Higher infection rates reported in school-aged children compared to adults when the alpha variant emerged in November 2020 could be explained by adults being in various stages of local and national lockdown, whilst children continued to attend school.[13] With the emergence of the delta variant and the first cases identified in the UK in March 2021, infection rates in children increased rapidly alongside adult infection rates, mainly after national lockdown restrictions were eased for adults in May 2021.[13] The subsequent emergence of the Omicron variant in November 2021, which evaded both natural and vaccine-induced immunity, was associated with very high infection rates across all age groups, including young children who were the least infected age-group at the time.[14] Our outbreak, longitudinal and cross-sectional studies in educational settings during the first two years of the pandemic consistently demonstrated that SARS-CoV-2 infection rates in educational settings generally reflected local community infection rates, indicating that educational settings were not hubs of community infection.

Cross-sectional community seroprevalence work in 0–18-year-olds undertaken in seven English regions between October 2019 and June 2021 showed adjusted seroprevalence rising from 0% to 5% after the first wave (June–August 2020), to 18% after the second wave (January–March 2021) and 20% by April–June 2021.[15] Seroprevalence ranged from 14% in 0–4-year-olds to 33% in 15–18-year-olds. In educational settings, our initial seroprevalence work led to the development and validation of an oral fluid assay for SARS-CoV-2 nucleocapsid and spike protein antibodies,[16] which was subsequently used to estimate regional and national seroprevalence in school-aged children in England. We found that, by December 2021, prior to the emergence of Omicron, 40% of primary school-aged students (5–11 year-olds) had SARS-CoV-2 antibodies through prior exposure and 82% of secondary school-aged children (12–18 year-olds) had antibodies through a combination of prior exposure and, around half the adolescents sampled, COVID-19 vaccination.[17] By February 2020, the large surge in Omicron infections, which peaked in January 2022, resulted in seroprevalence increasing to 62% for primary school-aged children and 97% for secondary school-aged children, and then to 82% and 99%, respectively, by March 2022.[18]

These findings are consistent with national seroprevalence estimates using residual clinical blood samples from hospitalised children. During November–December 2021, seropositivity rates were 37% in 1–4-year-olds, 54% in 5–11-year-olds, 78% in 12–15-year-olds and 87% in 16–17-year-olds. By September 2022, seroprevalence had increased to 93%, 98%, 99% and 99%, respectively.[19] Notably, despite large differences in mitigation measures and variable vaccination rates in the United States, nucleocapsid antibody seroprevalence (indicating prior SARS-CoV-2 exposure irrespective of vaccination status) by February 2022 was 75% in 0–11-year-olds and 74% in 12–17-year-olds, with one-third of the children becoming newly seropositive since December 2021.[20]

In summary these data indicate that the emergence of Omicron marked a watershed moment in the pandemic, resulting in most children becoming infected with SARS-CoV-2, irrespective of vaccinations or mitigations. By mid-2022, nearly all children had experienced one or more natural SARS-CoV-2 infections.

COVID-19 transmission

Early on in the pandemic, although it appeared children were at a lower risk of infection, their role in transmission was unclear. Due to lockdowns and children living at home, the majority of the early studies assessing transmission were in household investigations which reported that children were less susceptible to SARS-CoV-2 infection or transmission than adults.[21] In England, prospective follow up of 126 cases in children aged < 19 years reported to PHE during March–November 2020 and their 248 contacts found a secondary attack rate of 33% when utilising both PCR-testing and SARS-CoV-2 antibody testing to diagnose current or past infection, respectively, with the lowest secondary attack rates among contacts aged 0–10 years (16%).[22] Children had fewer symptoms overall, and the risk of the primary case transmitting to other household contacts was lower in those without respiratory or systemic symptoms. A subsequent meta-analysis of studies that only utilised PCR-testing for confirmation of SARS-CoV-2 infection estimated a secondary attack rate of 17%.[23]. In educational settings, PHE also initiated enhanced surveillance after the partial re-opening of schools in June 2020. Most cases linked to outbreaks occurred among staff members only (73%), with staff-to-staff transmission being the most common mode of infection spread.[23] The risk of infection for students and staff during the summer term was low overall but regional community incidence was found to be strongly associated with the number of outbreaks in educational settings, thus acknowledging that higher community infection rates increased the chances of seeding events into educational settings. A systematic review and meta-analysis published in 2021 found that children had lower odds of infection in educational settings compared to household and community clusters (OR = 0.53, 95% CI; 0.38–0.75).[24] This is consistent with a later meta-analyses which found a pooled secondary attack rate when the index case was a child was lower in educational settings compared to household studies ($p = 0.002$).[25] These observations could be due to a variety of reasons including effective infection control measures in place in educational settings compared to schools thereby reducing the risk of transmission, or the type of contact within settings, with prolonged and closer contact expected in households, thus increasing the risk of transmission in these settings.[25] Additionally, during 2020 and 2021, children with confirmed SARS-CoV-2 infection were excluded from school and, therefore, would spend more time at home, thus potentially increasing the risk of infection for household contacts. With the emergence of the highly transmissible Delta and Omicron variants, there have been fewer studies assessing risk of transmission in children. One study conducted in Japan found that, compared with earlier strains, transmission in children was 3–4 times higher with the delta variant, and 8–10 times higher with the Omicron variant.[26]

Most studies on vaccine effects on SARS-CoV-2 transmission have been conducted in adults. In England, COVID-19 vaccine

effectiveness was assessed against onward transmission from an adult index case infected with the Alpha variant, and Delta variant to their household contacts.[27] After two doses on BNT162b2 this was found to be 57% (CrI: 2–85) and 36% (CrI: −1 to 66) respectively. Another study found no difference in the secondary attack rate for household contacts exposed to vaccinated vs unvaccinated index cases (25% [95% CI: 15–35] vs 23% [15–31]).[28] They also found peak viral load increase to be associated with increasing age. A contact tracing study in Belgian from 2021 to 2022 showed comparatively higher estimates of vaccine effectiveness against transmission following two doses of BNT162b2, likely due to not restricting to household contacts only, although showed a significant decrease in protection against Omicron (31% [95% CI: 25–37]) than Alpha (96% [95% CI 95–97]) and Delta (87% (95% CI 84–88)).[29]

In children a cohort study in schools and childcare settings during September-December 2021 in Australia found that secondary cases were 4 times more likely to occur after Delta and Omicron infections compared with previous strains.[30] Vaccination, either in the index case or the contact, reduced secondary transmission more compared to no vaccination for the Delta variant, but had less of an impact on transmissions with the Omicron variant.[30] Where the index case was unvaccinated and the contact was vaccinated, the secondary attack rate was 0.7 (0.3–1.4) during the Delta period, but 5.1 (2.7–8.5) during the Omicron period.

Severe COVID-19 and hospitalisations

In adults, hospitalisation with a positive SARS-CoV-2 test provided a useful proxy to assess the risk of severe COVID-19 and the impact of vaccination early in the pandemic.[31] In children, however, the vast majority of SARS-CoV-2 infections were asymptomatic or mild. Since all children were until recently routinely PCR-tested for SARS-CoV-2 when attending healthcare settings, irrespective of their presenting complaint, hospitalisation with a positive SARS-CoV-2 PCR-test was not a useful indicator for severe COVID-19 in children.[32,33] In south London, for example, between December 1, 2020 and January 31, 2022, of the 147 children hospitalised with a positive SARS-CoV-2 PCR test, only 10% (n = 15) had severe COVID-19 presenting as pneumonitis, with most hospitalisations for severe COVID-19 occurring during the alpha variant wave (10/15, 67%), affecting older children aged 12–18 years (9/15, 60%) and those with comorbidities (11/15, including 8 with immunosuppression).[32] In a further 33% (49/147), of children hospitalised with a positive SARS-CoV-2 test, SARS-CoV-2 likely contributed to hospitalisation, however clinical presentations were typical of other childhood viral illnesses (including fever without a focus in infants, acute asthma exacerbation and febrile convulsion) while, in the remaining 57% (83/147), SARS-CoV-2 infection was incidental in children hospitalised for other non-infectious medical conditions.[32]

The emergence of the Omicron variant was associated with very high infection rates across all age groups, especially young children who were the last uninfected and unvaccinated age-group at the time. During this period, hospitalisations in children with a positive SARS-CoV-2 test also increased, although a substantial proportion of cases had incidental infection.[32] In South Africa, for example, when the Omicron variant first emerged during October-December 2021, 462/6287 (7%) of those aged 19 years or younger were hospitalised with a positive SARS-CoV-2 test. However, of those with available medical records, less than half (61/138, 44%) had a primary diagnosis of COVID-19 and their median hospital stay was only 2 days (IQR, 1–3 days).[34] In the UK, there were reports of infants under 1 year of age being disproportionally affected with Omicron compared to previous variants but further review found that most infants hospitalised with Omicron were less sick, required less support and were discharged earlier than infants hospitalised with previous variants.[35] The pattern of illness observed with Omicron in infants and young children is consistent with other common respiratory viruses, that typically cause upper respiratory infections in young children. Other recent studies also report a lower risk of severe disease with Omicron, which disproportionately affected younger children but with a shorter hospitalisation stay, fewer intensive care admissions and more favourable outcomes.[36]

A recent comprehensive analysis using multiple national databases of childhood hospitalisations in England during July 2020 to February 2022 identified 3.2 million children with recorded first SARS-CoV-2 infection including 29,230 (0.9%) SARS-CoV-2 associated hospital admissions, of which SARS-CoV-2 was the cause or a contributory factor for hospitalisation in 21,000 (71.8%).[37] The authors used broader definitions of SARS-CoV-2 suspected involvement, which likely explains the higher contribution of SARS-CoV-2 to hospitalised cases compared to other studies, and were only able to link to confirmed cases of COVID-19 despite nearly all children having been exposed to the virus during the study period (~12 million estimated vs 3 million confirmed). Those who were hospitalised primarily due to SARS-CoV-2 infection had the lowest disease severity compared to other groups and, reassuringly, 25% of children were hospitalised for one day, and 50% for two days or less, indicating that, for the majority of children, their disease was inconsistent with the course of severe disease in adults and children, along with the very low requirement for intensive care admission (n = 1710; 5.9% of 29,230 SARS-CoV-2 associated admissions, 0.05% of 3.2 million children with confirmed infections and 0.01% of ~12 million children in England). These findings provide further reassurance of a very low risk of severe COVID-19 in children, irrespective of underlying conditions or COVID-19 vaccination status. It is also important to note that these data are limited to the first two pandemic years. This is important because, even in this study, although the number of infections were highest during Omicron, SARS-CoV-2 associated hospitalisation rates declined during the Delta and Omicron periods compared to the original wild type and alpha variant waves, as did the proportion requiring ICU care.

Notably, a study comparing SARS-CoV-2 infection in children during more recent periods when other respiratory viruses were also circulating in Colorado, United States, found that the majority of hospitalisations were due to RSV in children aged < 4 years, with RSV cases more likely to require oxygen support, longer hospital stay and higher risk of pneumonia and bronchitis than SARS-CoV-2 or influenza. Comparatively COVID-19 cases were more likely to require invasive mechanical ventilation and influenza carried the greatest risk of ICU admission.[38]

In England, UKHSA has been regularly reporting on hospitalisations in different age-groups using the Severe Acute Respiratory Infection (SARI) surveillance system, which was established in 2020 to report the number of laboratory-confirmed influenza and COVID-19 cases admitted to hospital and critical care units in National Health Service (NHS) hospitals across England (Fig. 1). Childhood hospitalisation rates reported through SARI typically follow community infection rates, with increased hospitalisations during peak periods of community infection with the different SARS-CoV-2 variants, but with hospitalisations rates substantially below adult rates. Notably, since the first Omicron peak in January 2022, there were six other infection peaks due to Omicron variants until June 2023, children aged 5–14 years had the lowest hospitalisation rates compared to all other age-groups whereas hospitalisation rates for 0–4-year-olds were higher than for younger adults for the first time in the pandemic. This is consistent with other upper-respiratory tract infections and a higher rate of infection for this age group than previous waves, additionally younger adults who were already at a lower risk of severe disease were protected through vaccination and infection.[39] Although the completeness of reporting through SARI is

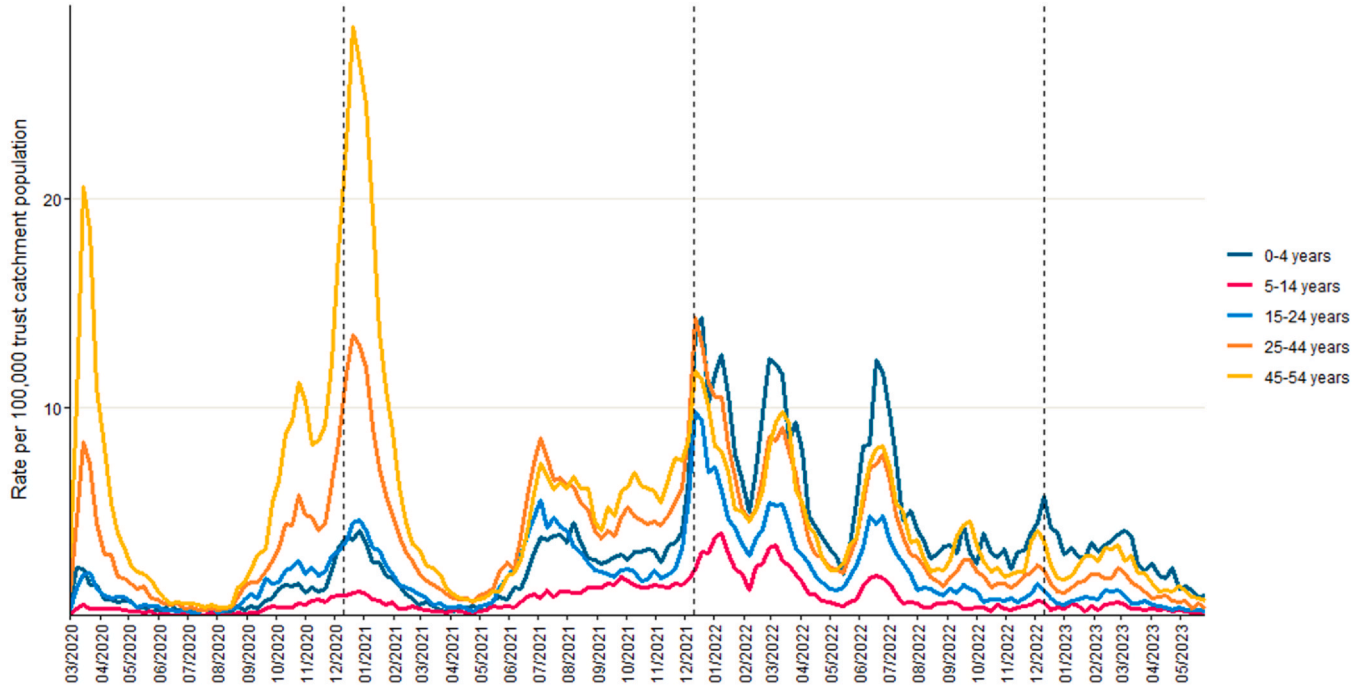

Fig. 1. COVID-19 hospitalisation rates by age-group and week using UKHSA SARI-watch surveillance data in children and adults (excluding older adults), England 2020-2023.

difficult to ascertain, which may limit comparison with other hospitalisation data, the observed trends over time would be expected to remain comparable across variant waves.

Overall, childhood risk of hospitalisation for severe COVID-19 has always remained very low, and the length of hospital stays are for most children was two days or less, highlighting low disease severity. Additionally, and reassuringly, the risk of hospitalisation was lower with the Omicron variant compared to earlier SARS-CoV-2 variants. Importantly, the risk of hospitalisation was found to be higher amongst certain groups, including infants, children with underlying health conditions, and children living in areas with higher levels of deprivation highlighting the need to appropriately focus interventions.

COVID-19 deaths and infection-fatality rates

As part of enhanced national surveillance during 2020–21, we followed up all fatal cases within 100 days of confirmed SARS-CoV-2 infection in England and found that 81/185 (44%) deaths were due to COVID-19; of these, 61 (75.3%) had an underlying condition, most commonly severe neurodisability (n = 27) and other immunocompromising conditions (n = 12) (Fig. 2).[40] In our analysis until the end of 2021, SARS-CoV-2 was responsible for 1.2% (81/6790) of all childhood deaths. The estimated infection fatality rate using modelled national SARS-Cov-2 infection rates was 0.70/100,000 SARS-CoV-2 infections in < 20-year-olds and a mortality rate of 0.61/100,000. In Germany, the estimated case fatality rate until May 2021 was 0.9/100,000 children based on a total of 14 paediatric COVID-19 fatalities.[41] Our on-going analysis found that, despite a large number of Omicron infections in children, the infection fatality rate during the Omicron wave was substantially lower than previous variant waves at 0.2/100,000 cases compared to 0.7/100,000 during March 2020 to December 2021.[42] As in previous waves, the majority of COVID-19 fatalities were in children with severe underlying comorbidities.

In the German study, the case fatality rate in children without comorbidities was 0.3 per 100,000, with no deaths due to COVID-19 reported in children older than five years.[43] Additionally, a recent systematic review found that the risk of death due to COVID-19 increased with increasing number of comorbidities compared to children with no comorbidities.[44] While all comorbidities assessed in the systematic review were associated with an increased risk of death except asthma, those with neurological and cardiac comorbidities had the greatest increase in odds of severe disease and death. Together, these studies demonstrate a much higher risk of severe disease and death in children with underlying conditions compared to healthy children, highlighting a need for targeted public health action for clinically vulnerable children.

COVID-19 vaccines for Children

In the UK, vaccination against COVID-19 began in December 2020, prioritising those at the highest risk of severe disease and death, namely older adults and those with underlying at-risk conditions. Uniquely, the UK implemented an extended 12-week interval rather than the authorised 3-week interval for the two-dose vaccine schedule to expedite the number of people receiving the first dose.[45] The UK was also unique in offering the vaccine to children aged 12–15 years with severe neurodisabilities in January 2021, despite not being tested or authorised in this age-group, because of their high risk of severe and fatal COVID-19.[46] In this cohort of children, we showed that both mRNA and adenovirus-based vaccines were immunogenic, although vaccine uptake has remained very low in this high-risk age-group.[47,48]

Countries such as the United States and Israel rapidly implemented COVID-19 vaccination for children as soon as the vaccines became authorised for the respective childhood age groups.[49] In contrast, the UK opted for a more cautious approach.[50] Early concerns about mRNA vaccine-associated myocarditis, mainly after the second vaccine dose in adolescent and young adult males, led the UK scientific committee (the Joint Committee on Vaccination and Immunisation, JCVI) to recommend a single dose in the first instance for 16–17-year-olds in August 2021 and, in September 2021, recommended against vaccination for 12–15-year-olds because of their very low risk of severe COVID-19.[51] This decision was, however, based primarily on a health perspective and, in order to evaluate the

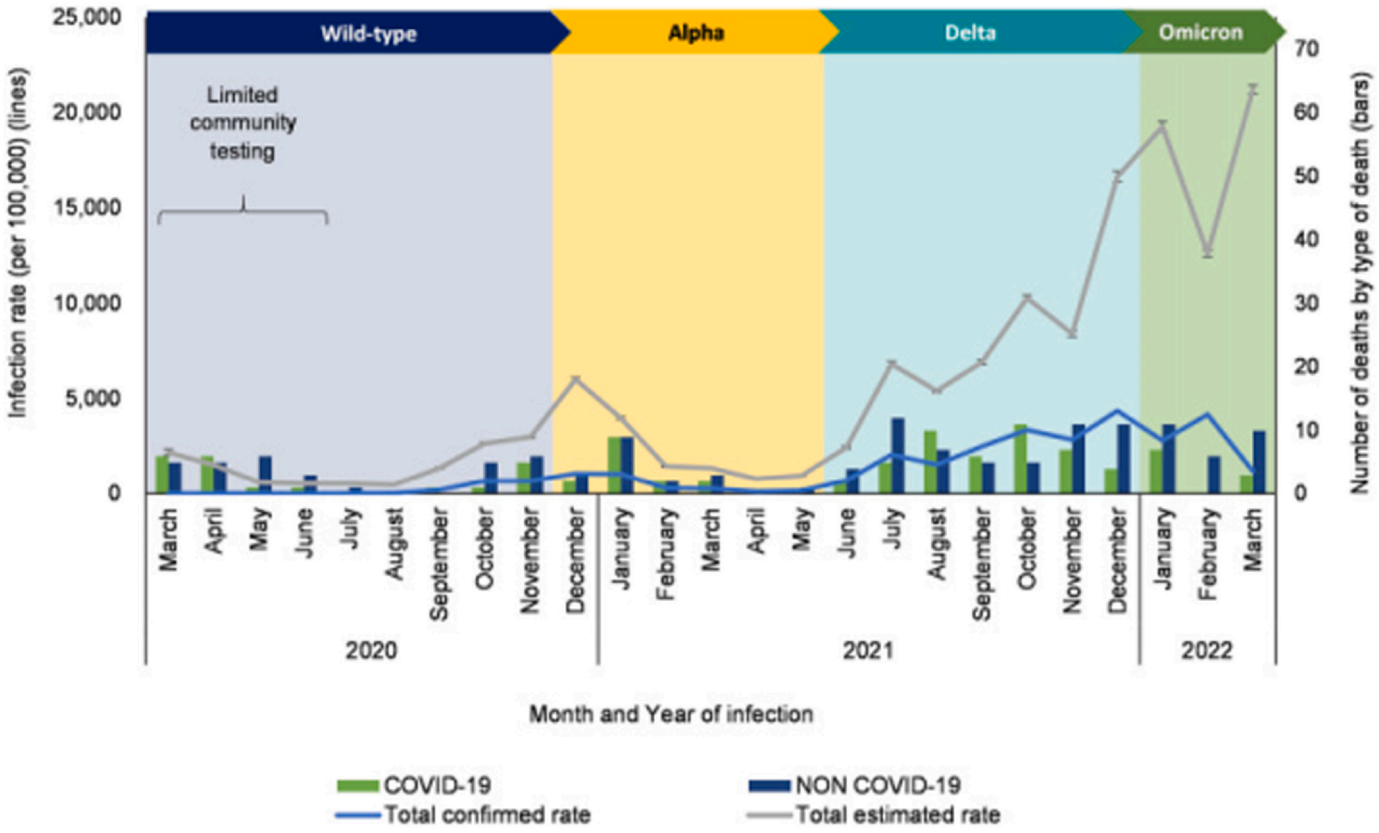

Fig. 2. COVID-19 infection rates by age group and number of deaths by cause of death in CHILDREN aged < 20-years-old (predominant circulating variant shown by coloured chevrons). Graph taken from Hani et al., 2023.

wider national context, which was outside of the remit of the JCVI, ministers were recommended to seek the advice of the Chief Medical Officers, who recommended vaccination with the aim of "*protecting young people from catching COVID-19, reducing transmission in schools and keeping pupils in the classroom*".[52]

A second dose of mRNA vaccine for 16–17-year-olds was subsequently recommended by the JCVI in November 2021, and later, in 12–15-year-olds, when there was greater certainty in the data regarding the risk-benefits of vaccination, as well as emerging data on rapidly waning protection offered by the first dose against Omicron.[52,53]

A lower-dose (10 mcg) mRNA COVID-19 vaccine for 5–11-year-olds was licensed in December 2021 and, in the UK, was initially offered to high-risk children and those with an at-risk family member.[53] In February 2022, this offer was extended to all 5–11 year-olds.[54] Subsequently, children who turned five on or after September 1, 2022 are currently only eligible for vaccination if they are in a clinical risk-group. In April 2023, vaccine eligibility was extended to younger children aged 6 months to 4 years who were in a clinical risk group.[55] In England, by the end of 2022, two-dose COVID-19 vaccine uptake was 63% in 16–17-year-olds, 49% in 12–15-year-olds and 11% in 5–11-year-olds.[56] By comparison, vaccine uptake in Israel was 65% in 12–15-year-olds and 25% for 5–11-year-olds and, in the US by October 2022, was 71% for 12–17-year-olds and 39% for 5–11-year-olds.[57,58]

Overall, in light of high levels of population immunity and low disease severity with Omicron and its subvariants, in November 2022, the JCVI advised the targeting of future COVID-19 vaccine programmes to high-risk groups only, namely older adults and those in a clinical risk group, and moving away from vaccinating healthy children and adults aged < 50 years.[59]

Myocarditis

The rollout of mRNA COVID-19 vaccines was associated with an increase in reports of acute myocarditis, predominantly in adolescent and young adult males.[60] Published studies continue to report an increased risk of myocarditis after mRNA vaccination in males aged 12–39-years, especially young adults aged 18–29 years.[61] In 5–11-year-olds, post-implementation studies reported a much lower risk of post-vaccination myocarditis, potentially because of the lower dose in mRNA vaccines for this age group.[62] Using the Vaccine Adverse Event Reporting System (VAERS), the US Centre for Disease Control and Prevention (CDC) calculated the rates of myocarditis per 1 million doses to be 2.6 for 5–11-year-olds, 46.4 for 12–15-year-olds and 75.9 for 16–17-year-olds.[63] Myocarditis risk was higher in males and after both doses, with higher risks associated with the second mRNA dose; the risk was also higher with the mRNA-1272 (Spikevax, Moderna) vaccine than the BNT-162b2 (Cominarty®, Pfizer) vaccine, possibly because of a higher antigen content in the former.[64]

Initial studies with short follow-up reported favourable outcomes of mRNA vaccine-induced myocarditis. An early study by the CDC found that 87% (577/661) of hospitalised cases had resolved presenting symptoms by hospital discharge. More recent studies with longer follow-up, however, have raised potential long-term complications in a proportion of patients. In Victoria, Australia, 75 cases of vaccine-induced myocarditis (8.3/100,000 doses), predominately in males (n = 62, 82.7%) and after dose two (n = 61, 81.3%).[65] The highest risk was in 16–17-year-olds, and the most common presenting symptoms were chest pain, dyspnoea and palpitations. Females were more likely to have ongoing clinical symptoms at 1-month follow up (p = 0.02). Cardiac MRI abnormalities were identified in 91.7% (31/36) of those who were investigated. In

Canada, follow-up of 20 consecutive patients (median age 23 years, 85% male) with acute myocarditis within 10 days of mRNA vaccination, 18 (90%) had persistence of abnormal late gadolinium enhancement (LGE) consistent with fibrosis, although none of the patients experienced major clinical outcomes which was defined as "*defined as cardiac hospitalisation, new-onset heart failure requiring diuretic use, atrial fibrillation, or ventricular arrhythmia.*"[66] The authors concluded that patients with COVID-19 mRNA vaccine-associated myocarditis showed rapid improvements in cardiac oedema, contractile function and global LGE burden after 3 months, but regional fibrosis following oedema resolution was commonly observed, justifying a need for ongoing surveillance. In a US CDC-funded study, data were collected between Aug 24, 2021 and Jan 12, 2021 for 519 patients who were > 90 days post-myocarditis onset.[67] Of these, 320/393 (81%) were reported by their healthcare provider to have recovered although, at the last follow-up, 104 (26%) were prescribed daily medication related to myocarditis. Additionally, 49/249 (20%) of individuals who completed a quality-of-life questionnaire reported problems with performing usual activities, 74 (30%) reported pain and 114 (46%) reported depression. Most patients had improvements in cardiac investigations at follow-up, including normal or back-to-baseline troponin concentrations (181/200, 91%), echocardiograms (262/279, 94%), ECG (24/311, 77%), exercise stress testing (94/104, 90%, and ambulatory rhythm tests (86/96, 90%). Cardiac MRI identified an abnormality in 81/151 (54%) patients, with 20/151 (13%) having evidence of ongoing myocarditis at follow-up suggested by presence of both LGE and oedema on cardiac MRI. At follow-up, nearly one third of patients (32%, 125/393) has still not been cleared for all physical activity. It is important also to emphasise that published studies focus on adolescents and young adults with symptoms severe enough to seek medical help and that there are no data on the risk or outcomes of less severe vaccine-induced myocardial events in those with no or mild symptoms after vaccination. Finally, a systematic review published in June 2022 found 62 studies, including 218 cases of COVID-19 vaccine-associated myocarditis.[68] The authors reported that troponin levels were consistently elevated in 98.6% of patients and ECG at admission was abnormal in 88.5% of cases. Most patients (92.6%) recovered, but three patients died.

Whether the risk of myocarditis is higher after SARS-Cov-2 infection or after COVID-19 vaccination has proved difficult to establish with any certainty because of inherent biases in the published observational studies.[69] A 2022 systematic review concluded that there was a 7-fold higher risk of myocarditis after confirmed SARS-CoV-2 infection than COVID-19 vaccination.[69] By comparing myocarditis rates in vaccinated persons (where the date of vaccination is known for all vaccinated persons) against confirmed SARS-CoV-2 infection, the risks will be grossly overestimated because the latter will not include those with asymptomatic or mild infection who won't be tested for SARS-CoV-2 or those who choose not to test for the virus. Importantly, too, in a more recent UK study the risk of vaccine-induced myocarditis in 16–39 year-olds was lower in those vaccinated with a second or a booster dose of mRNA vaccine after prior infection than in infection-naïve individuals.[70] Given the vast majority of the population have now been infected, vaccinated or both, it is likely that myocarditis rates after either infection or vaccination will decline but it will be important to monitor this, especially in the context of new SARS-CoV-2 variants and variant vaccines.

COVID-19 vaccine effectiveness

In England, UKHSA has undertaken regular vaccine effectiveness studies since the first COVID-19 vaccines were implemented. The primary aim of the COVID-19 vaccination programme was to prevent severe disease, hospitalisations and death but the vaccine fortuitously also helped protect against infection and transmission during the alpha and delta periods.[71] The emergence of Omicron BA.1 in November 2021, however, was associated with high rates of infection, transmission and disease in both previously-infected and previously-vaccinated individuals. Protection against severe disease, hospitalisation and death however, which has been attributed to the cellular immunity provided by COVID-19 vaccines, remained high.[72]

In adolescents, we observed very short-term vaccine protection against symptomatic infection with Omicron variants in 12–17 year-olds, with vaccine effectiveness falling to 23% by 70 days after the second COVID-19 mRNA vaccine dose (Fig. 3).[73] We also compared protection against symptomatic infection in adolescents after mRNA vaccination or previous SARS-CoV-2 infection in adolescents in a large, national test-negative case-control study up to the end of March 2022, when the UK stopped universal community testing for SARS-CoV-2.[74] We found that prior infection provided enhanced protection against subsequent infection with Omicron (59%; 95% CI 47–69), higher than vaccination alone (30%, 95% CI 25–34) at 15–24 weeks after dose two. The combination of previous infection and vaccination provided the highest protection, irrespective of primary infecting SARS-CoV-2 variant, at the same interval of 15–24 weeks after dose two: 76%, (95% CI 66–82) after prior delta infection and 64% (95% CI 52–73) after prior alpha infection.[74] (Table 1) The highest protection against symptomatic Omicron infection was observed in those with Omicron infection after vaccination, reaching 96.4% (95% CI, 84.4–99.1%) at 15–24 weeks after two doses. This is consistent with studies in adults and in laboratory studies showing that hybrid immunity provides the most robust protection against symptomatic infection.[75–77]

In 5–11 year-olds, a recent US study found that two doses of BNT-162b2 was effective against SARS-CoV-2 infection, with higher effectiveness against Delta than against Omicron but, as in adults, protection waned within a few weeks.[78] (Table 1) In previously-uninfected children, vaccine effectiveness reached 63.2% (95% CI, 61.0–65.2) at 4 weeks after the first dose but decreased to 15.5% (95% CI, 8.1–22.8%) at 16 weeks. This compares with 69.6% (95% CI, 57.4–78.3%) and 22.4% (95% CI, 13.0–30.8), respectively, in previously-infected children. Notably, the effectiveness of omicron infection against reinfection with omicron was 90.7% (95% CI, 89.2–92.0%) at 2 months and 62.9% (95% CI, 58.8–66.6) at 4 months in unvaccinated children compared to 94.3% (95% CI, 91.6 to 96.1) and 79.4% (95% CI, 73.8 to 83.8), respectively in vaccinated children.[78]

Since hospitalisations for severe COVID-19 are rare in children, assessing the impact of COVID-19 vaccination in reducing childhood hospitalisations has been challenging, especially because of the difficulties in distinguishing incidental infections from severe COVID-19 in hospitalised children. Several studies have, however, reported significant reductions in the risk of hospitalisation in vaccinated compared to unvaccinated children. In the US, among 12–18 year-olds during the Omicron period, vaccine effectiveness was 40% (95% CI, 9–60%) against hospitalisation for COVID-19, being 79% (95% CI, 51–91%) against critical COVID-19 compared to 20% (95% CI, −25 to 49%) against noncritical COVID-19.[79] Over the same period, vaccine effectiveness against hospitalisation in 5–11 year-olds was 68% (95% CI, 42–82%).[79] In Italy, vaccine effectiveness against severe Omicron infection, defined as hospitalisation or death, was 41% in 5–11 year-olds.[80] This Italian study, however, highlighted the very low risk of severe COVID-19 in children irrespective of prior infection or vaccination status in 5–11 year-olds, with an estimated hospitalisation risk of 84/100,000 infections, ICU admission of 2/100,000 infections and infection fatality risk of 0.3/100,000 infections.[81] Similar very low risks have been reported in the US and Qatar.[82,83] One US study calculated a risk of 19.1 hospitalisations per 100,000 infections in unvaccinated compared to 9.2 hospitalisations per 100,000 infections among vaccinated 5–11-year-olds during

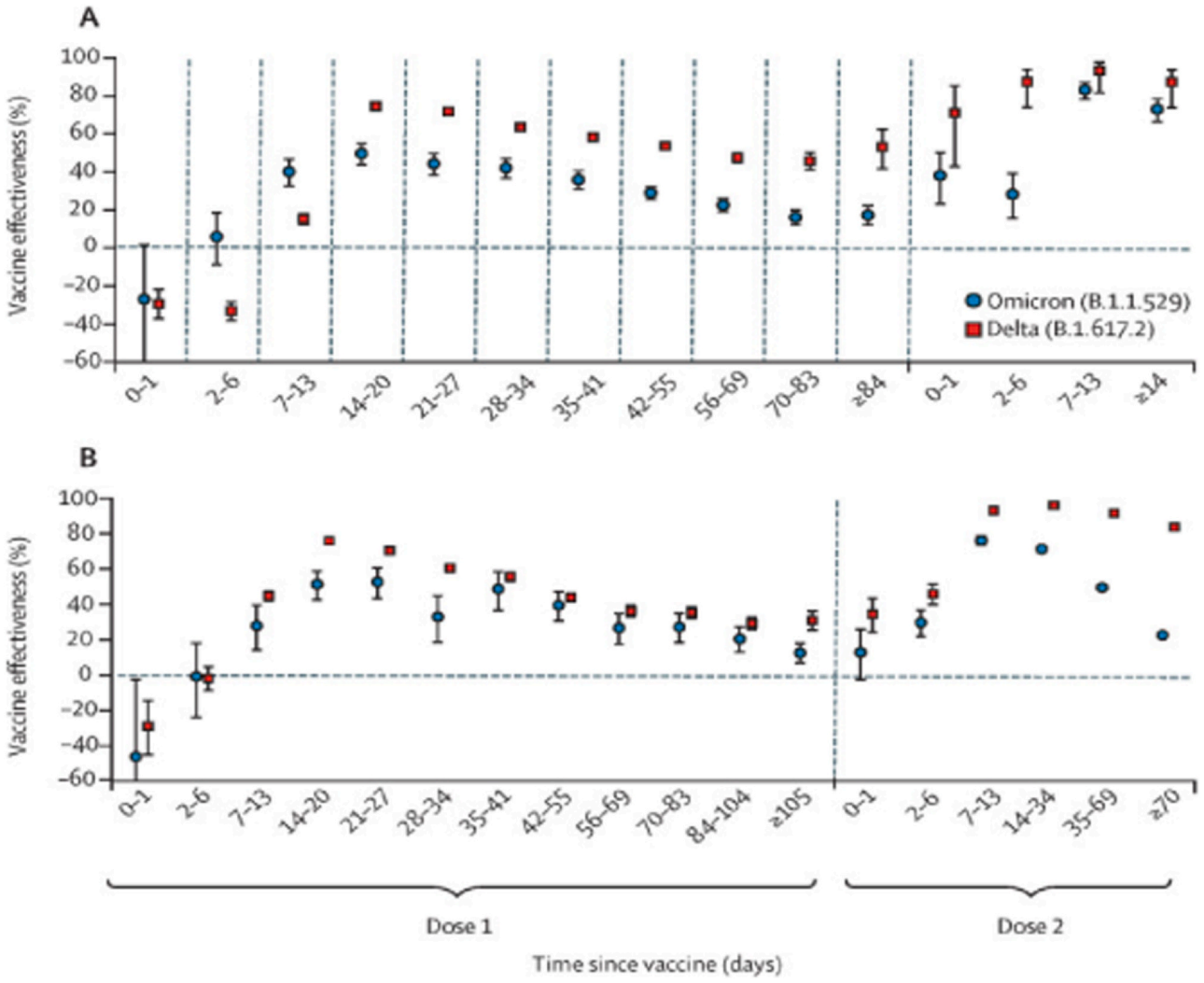

Fig. 3. Vaccine effectiveness in 12–15-year-olds (A) and 16–17-year-olds (B) with symptomatic, PCR-confirmed COVID-19. Graph taken from Powell et al., 2022.

December 2021 to February 2022, when Omicron was predominant.[84] Recently, a Canadian study involving 62 hospitalised and 27,674 non-hospitalised SARS-CoV-2 cases found that two mRNA vaccine doses resulted in an 85% (aOR = 0.15; 95% CI%, 0.04–0.53) lower likelihood of hospitalisation in 12–17 year-olds, and a 79% (aOR = 0.21; 95%CI, 0.03–0.77) lower likelihood of hospitalisation after one dose in 4–11 year-olds.[85] With regards to the effects of prior infection, a US study reported that prior Omicron infection provided 98% (95%CI, 53–100%) protection against hospitalisation compared to 76% (95% CI, 28–92) after two BNT162b2 doses over the same time period.[78]

In summary, published studies report a very low risk of COVID-19 hospitalisations in children irrespective of SARS-CoV-2 variant and, among previously uninfected children, COVID-19 vaccination helped protect against their very low risk of hospitalisation. At the same time, prior infection especially with Omicron, also protected against hospitalisation with subsequent reinfection. Interestingly, the conclusions drawn from these studies have varied in different countries. Some countries such as the US, Italy and Israel have continued to recommend regular COVID-19 vaccine boosters for children because of the rapid decline in protection against infection.[48,78,86] A recent study from Singapore reported 94% (95%CI, 86–97) protection against hospitalisation after one booster dose, remaining above 80% > 60 days later, suggesting that booster may provide longer protection that primary vaccination in children, but this needs to be confirmed in other studies.[87] On the other hand, other countries, such as the UK and Qatar, have concluded that current evidence "suggest the need to reconsider the value and strategies of vaccinating healthy children in the Omicron era with the use of currently available vaccines,"[59] and that "these data question the need for additional boosters vaccine doses for adolescents with already high protection against SARS-CoV-2 infection."[74,83] In the UK, the priority for vaccinating against COVID-19 has always been to prevent severe disease, hospitalisation and death, which is rare in children. This, in addition to the fact that since nearly all children have now already been infected with SARS-CoV-2,[18] which in and of itself will help protect against reinfection and severe disease, has led the UK to recommend against further COVID-19 vaccination for healthy persons under the age of 50 years.[59]

Ongoing surveillance of hospitalised cases, however, remains critical, with the emergence of newer variants, especially in young children who have never been offered COVID-19 vaccination in countries such as the UK. Given that most children hospitalised with severe COVID-19 had significant underlying conditions across the different SARS-CoV-2 variant waves,[37] further studies are needed to describe changing characteristics of hospitalised children in populations with high immunity through prior infection and vaccination,[36] especially in the context of co-circulating respiratory viruses,[38] so that effective interventions can be implemented to protected those who remain most at risk of severe COVID-19.

Table 1
Summary of vaccine effectiveness in infection naïve and previously infected individuals against Delta and Omicron variants in children aged > 5-years-old.

Study	Age group (years)	Vaccine	Variant	Event	Time period since event	VE
Castelli et al., 2022	12–17	mRNA-1273	Delta	Second dose	Median 66 (IQR 40) days	70.2 (66.8–73.1)
Castelli et al., 2022	12–17	BNT162b2	Delta	Second dose	Median 66 (IQR 40) days	64.1 (60.5–67.3)
Florentino (Brazil), 2022	12–17	BNT162b2	Delta	Second dose	56–69 days	26·6 (4·1–43·9)
Florentino (Scotland), 2022	12–17	BNT162b2	Delta	Second dose	56–69 days	86·5 (72·2–93·4)
Powell et al., 2022	12–17	BNT162b2	Delta	Second dose	15–24 weeks	80.9 (79.4–82.3)
Powell et al., 2022	12–17	mRNA* + previous Alpha infection	Delta	Second dose	15–24 weeks	97.0 (97.2–98.8)
Powell et al., 2022	12–17	mRNA* + previous Delta infection	Delta	Second dose	15–24 weeks	98.3% (87.9–99.8)
Chemateilly et al., 2022	12–17	BNT162b2	Pre-Omicron	Second dose	Median 45 (IQR (16–88)	87.6 (84.0–90.4)
Sacco et al., 2022	5–11	BNT162b2	Omicron	Second dose	43–84 days	21.2 (19.7–22.7)
Chemateilly et al., 2022	5–11	BNT162b2	Omicron	Second dose	Median 69 (IQR 31–97)	25.7 (10.0–38.6)
Yung et al., 2023	5–11	BNT162b2 + previous infection	Omicron	Second dose	> 180 days	78.7 (70.4–84.7)
Lin et al., 2023	5–11	mRNA*	Omicron	Second dose	6 months	28.6% (27.3–29.9)
Lin et al., 2023	5–11	mRNA* + previous infection	Omicron	Second dose	6 months	10.6% (4.4–16.4)
Lin et al., 2023	5–11	mRNA*	Omicron	Omicron reinfection	6 months	59.9 (55.8–63.5)
Lin et al., 2023	5–11	Previous Omicron infection	Omicron	Omicron reinfection	6 months	53.4% (51.6–55.1)
Castelli et al., 2022	12–17	mRNA-1273	Omicron	Second dose	Median 66 (IQR 40) days	17.9 (14.0–21.5)
Castelli et al., 2022	12–17	BNT162b2	Omicron	Second dose	Median 66 (IQR 40) days	28.1 (25.2–30.8)
Chemateilly et al., 2022	12–17	BNT162b2	Omicron	Second dose	Median 162 (IQR 48-205)	30.6 (26.9–34.1)
Powell et al., 2022	12–17	BNT162b3	Omicron	Second dose	15–24 weeks	29.8 (24.9–34.2)
Powell et al., 2022	12–17	BNT162b4	Omicron	Third dose	15–24 weeks	33.6 (14.6–48.3)
Florentino (Brazil), 2022	12–17	BNT162b2	Omicron	Second dose	56–69 days	32·0 (30·0–33·9)
Florentino (Scotland), 2022	12–17	BNT162b2	Omicron	Second dose	56–69 days	65·4 (61·9–68·7)
Yung et al., 2023	12–17	BNT162b2 + previous infection	Omicron	Third dose	> 180 days	92.6 (82.1–96.9)
Powell et al., 2022	12–17	mRNA* + previous Omicron infection	Omicron	Second dose	15–24 weeks	96.4 (84.4–99.1)
Powell et al., 2022	12–17	mRNA* + previous Delta infection	Omicron	Third dose	2–14 weeks	80.7 (71.1–87.1)
Powell et al., 2022	12–17	mRNA* + previous Delta infection	Omicron	Second dose	15–24 weeks	75.5 (65.6–82.5)

* mRNA is written where the mRNA vaccine is unspecified.

Immune responses after SARS-CoV-2 infection

Prior to the pandemic, coronavirus infections were estimated to be responsible for around 7% of respiratory tract infections in hospitalised children annually.[88–92] Coronaviruses generally cause mild disease, but rare outbreaks of more severe disease have been reported, as in the case of SARS (Severe acute respiratory syndrome) and MERS (Middle East respiratory syndrome).[1,93] Despite this disease burden, comparatively little research attention was given to the natural dynamics of immune responses to coronavirus infections. Exposure to coronavirus was known to produce relatively weak antibody responses in children, with IgG responses progressively accumulating during childhood through repeated rounds of re-infection, thus suggesting that coronaviruses are relatively poorly immunogenic in children.[94] However, studies assessing cellular immunity to coronavirus suggested that, despite weaker antibody responses, children rapidly developed cellular immunity, which was comparable to healthy adults, and, in contrast to antibody responses, cellular responses to seasonal coronaviruses were lower in the elderly, hinting at a potential cause of the age-associated severity of COVID-19.[95–97]

Early in the pandemic, because of the age-associated risk of severe disease, little attention was focused on childhood responses to SARS-CoV-2 infection. We undertook multiple studies to assess cellular and serum antibody responses in primary school-aged children compared to adults with prior SARS-CoV-2 infection. In contrast to seasonal coronaviruses, we found that the early SARS-CoV-2 variants were highly immunogenic in children, driving high levels of spike-specific antibody response compared to those produced to seasonal coronaviruses and also higher than the adult response to SARS-CoV-2 natural infection.[98] Curiously, nucleocapsid-specific antibody responses were lower in SARS-CoV-2 infected children than adults, despite studies showing comparable viral loads in children.[99] This indicates that children may have a differential response to specific antigens compared to adults, although the reasons for this remain undefined. The cellular response was likewise focused towards the spike protein, with robust spike-specific responses in children that were again higher than seen in naturally-infected adults.[98]

Surprisingly we also identified cross-reactive cellular responses, albeit at lower levels, in around half of unexposed children - those with responses had evidence of recent seasonal coronavirus infection, indicating cross-reactive coronavirus cellular immunity in children. Further exploration has indeed shown the presence of cross-reactive responses in children which diminish in adulthood,[95] and there was indication pre-existing cellular responses may have offered limited protection from infection.[100] These observations are consistent with studies showing that children possess greater diversity in immune responses to infection, generating less-focused responses, thus allowing broader responses to be developed to an initial antigenic challenge which can then be recruited to unseen future encounters. This may partially underly the age-associated severity of COVID-19.

SARS-CoV-2 infection in children was also observed to significantly enhance seasonal coronavirus antibody responses, which was shown in part to be composed of cross-reactive antibody responses between SARS-CoV-2 and the seasonal beta-coronaviruses. However, boosting of antibody responses was also observed to the distantly-related alpha-coronaviruses which demonstrated that early SARS-CoV-2 variants were highly immunogenic in children, which may underly the rare inflammatory syndrome (PIMS-TS) discussed separately in this review.

As the pandemic progressed effective vaccines were rolled out to children, as with adults, the vaccines were highly immunogenic and induces higher circulating antibody titres than natural infection, comparable with those of vaccinated adults.[101–103] In a small-scale study, we also found that cellular responses were also induced by vaccination in children and were comparable to that seen in natural infection.[47]

The immune responses generated by natural infection or vaccination protected children from reinfection through the delta wave but the emergence of Omicron variants with higher infectivity, enhanced immune evasion and high circulation in schools resulted in most school-aged children experiencing a primary Omicron infection, while many who were previously-infected experienced a secondary infection with Omicron. [78,104,105]

In contrast to pre-Omicron variants, we and others identified significantly lower antibody levels, and consequently lower neutralisation activity, following Omicron primary infection, consistent with those reported in adults.[77,106,107] Whereas, secondary infection, following infection with a pre-Omicron variant, resulted in marked boosting of the antibody response, to both Omicron and to the pre-Omicron variants. Such preference for the initial antigenic challenge (antigenic seniority) has been observed following influenza infection, although not for seasonal coronavirus infection, indicating that similar antigenic seniority exists following pre-Omicron SARS-CoV-2 infection. Following primary Omicron infection, however, either re-infection with an Omicron sub-variant or vaccination with the Wu-Hu-1- spike antigen boosted antibody responses to all SARS-CoV-2 variants with little bias. Regardless of the antibody response, the cellular response was robust irrespective of initial variant infection, and importantly, there was no evidence of evasion of the cellular response by Omicron.

These data suggest that SARS-CoV-2 has evolved to immunologically become similar to seasonal coronaviruses, with lower immunogenicity, consistent with a significantly reduced risk of PIMS-TS, but may in the short-term result in increased frequency of reinfection, comparable to frequent reinfections with seasonal coronaviruses.

PIMS-TS

PIMS-TS is a rare and unexpected, severe outcome of SARS-CoV-2 infection in children. In England, we have been undertaking PIMS-TS surveillance since the first cases were identified in April 2020, initially through the British Paediatric Surveillance Unit (BPSU),[108] and subsequently using national administrative databases.[86] Early surveillance identified a high risk of severe clinical presentations in children with PIMS-TS, with 118/268 (44%) requiring intensive care, 30% (80/268) requiring inotropic support and three children (1.1%) died.[108] Cases typically presented around 2–6 weeks after SARS-CoV-2 infection, with an estimated risk of 45/100,000 SARS-CoV-2 infections in England for children < 15-years, similar to US estimates of 32/100,000 in < 20 year-olds.[86] PIMS-TS shares many clinical features with Kawasaki disease (an acute childhood febrile systemic vasculitis), but the median age of PIMS-TS cases was 8.2 years compared to 2.7 years for Kawasaki disease.[109]

Recent studies *albeit* with small case numbers have shown that mRNA vaccination is effective in preventing PIMS-TS cases, certainly through prevention of infection (mainly before the Omicron wave) but potentially also lowering absolute risk of PIMS-TS in children with breakthrough infection after vaccination. In one Danish study, (n = 51), PIMS-TS incidence was one in 3400 unvaccinated individuals (95%CI, 2600–4600) with the delta variant and one in 9900 vaccinated individuals (95% CI, 1800–390000) with breakthrough infection after vaccination.[110] In England, six month follow-up of 46 children with PIMS-TS in 2020 found that systemic inflammation had resolved in all but one patient and few-organ specific sequalae were observed, although 45% (18/40) of patients had a 6-minute walk test below the third centile for their demographic and 40% (15/38) reported severe emotional difficulties.[111]

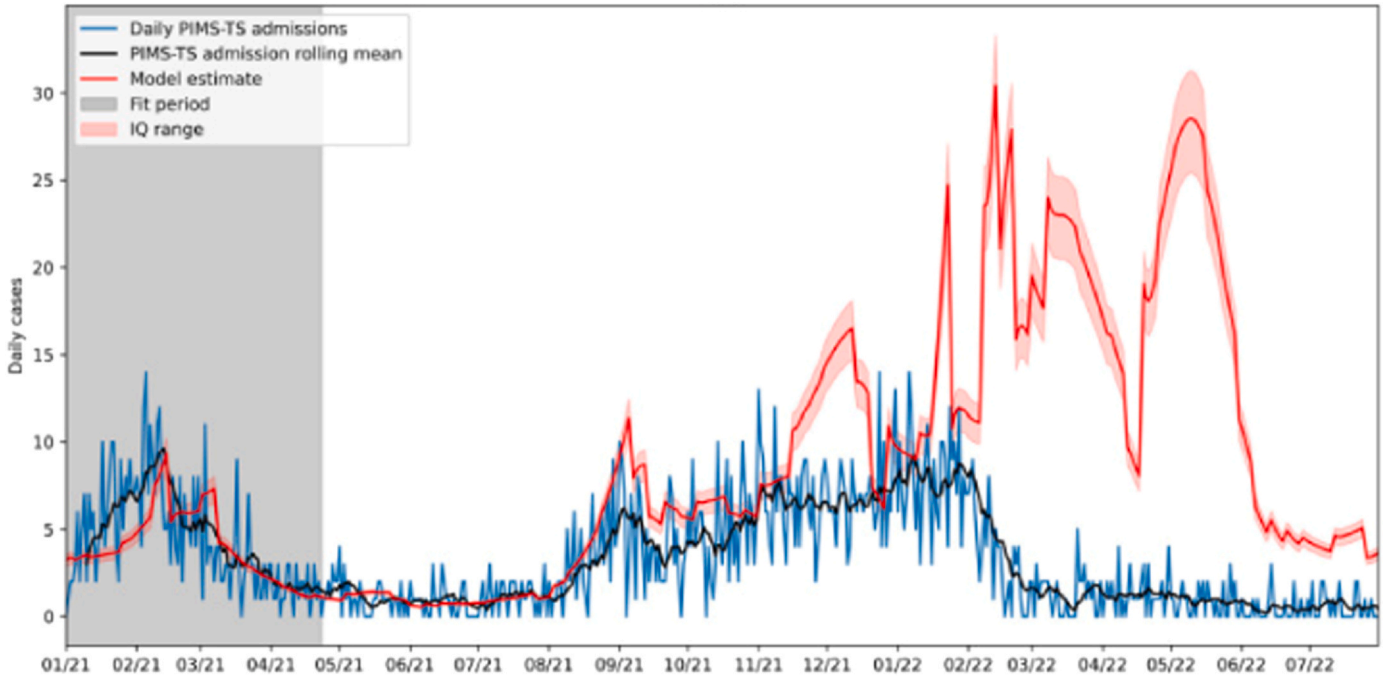

Fig. 4. Forecasted PIMS-TS admissions based on a model fitted to the alpha variant wave of COVID-19, alongside observed PIMS-TS admissions in < 15-year-olds. Graph taken from Shingleton et al., 2022.

Using computer modelling with data from the first pandemic wave, we predicted regional and national PIMS-TS rates based on community infection rates during the alpha variant wave in England.[86] With the emergence of the delta wave, PIMS-TS risk after SARS-CoV-2 infection dropped significantly from 0.038% during the alpha variant wave to 0.026%.[86] Despite the very high case numbers associated with the Omicron variants, we identified a much lower risk of PIMS-TS, initially in children in the South-East of England,[112] and subsequently nationally by comparing hospitalised case numbers with expected case numbers predicted through modelling (Fig. 4).[113] It has been suggested that this could be due to the more recent variants harbouring key genetic mutations in surface antigens postulated to trigger the PIMS-TS hyper-inflammatory response.[112] The risk of PIMS-TS has also been proposed to be was associated with a lack of prior exposure to seasonal coronaviruses.[114]

Now that the majority of children have immunity against SARS-CoV-2 through a combination of previous infection and vaccination, the risk with PIMS-TS with subsequent variant waves is likely to be very low, as already observed after the Omicron wave (Fig. 4).[113] We have also observed that the age of children with PIMS-TS has been declining over the course of the pandemic, making it likely that the condition will become similar to Kawasaki disease, affecting mainly infants and toddlers, who are likely to be unexposed to SARS-CoV-2 or other potential infectious triggers of Kawasaki disease.

Long COVID

Persistent symptoms following SARS-CoV-2 infection, affecting both physical and mental health, has been widely reported across all age groups. Whilst multiple definitions were proposed for long COVID since the first year of the pandemic, it was only as recently as February 2023 that an international definition was formally agreed by the WHO for children.[115] This was defined as a "*Post COVID-19 condition in children and adolescents occurs in individuals with a history of confirmed or probable SARS-CoV-2 infection, when experiencing symptoms lasting at least 2 months which initially occurred within 3 months of acute COVID-19. Current evidence suggests that symptoms more frequently reported in children and adolescents with post-COVID-19 condition compared with controls are fatigue, altered smell/anosmia and anxiety. Other symptoms have also been reported. Symptoms generally have an impact on everyday functioning such as changes in eating habits, physical activity, behaviour, academic performance, social functions (interactions with friends, peers, family) and developmental milestones. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. They may also fluctuate or relapse over time. Workup may reveal additional diagnoses, but this does not exclude the diagnosis of post COVID-19 condition.*"

Initial national estimates of long COVID prevalence, based on asking parents if their child was suffering from long COVID, were reported by the Office for National Statistics as 12.9% for 2–11 year-olds and 14.5% for 12–16 year-olds.[116] These data were experimental and were provided without a comparator group, therefore, potentially leading to misinterpretation. Over time, statistical analysis methods were improved, including the use of control groups, which reduced the long COVID risk estimates. In March 2023, the difference is prevalence of the most common persistent symptoms between cases and controls was 0.20% for 2–11-year-olds and 1.01% for 12–16-year-olds.[117]

Throughout the pandemic, well-controlled studies reporting post-COVID symptoms have shown a small but significant excess in prevalence of physical symptoms, as well as the proportion with > 3 post-COVID symptoms, among confirmed/probable COVID-19 cases compared to uninfected controls.[118,119] The clinical significance of this small increase, however, is not yet fully understood; at the same time studies with appropriate control groups has also reported similar mental health, fatigue and well-being scores between cases and controls.[118]

In the UK, the CLoCk study has assessed persistent symptoms in SARS-CoV-2 PCR-positive teenagers compared to age, sex and geographically matched PCR-negative controls across England for 24 months.[120] At the 12-month follow-up, the CLoCk study found that the symptoms reported at 6 months had generally resolved with a new cohort of teenagers reporting the same symptoms at the subsequent timepoint.[121] Therefore, while the overall prevalence of specific symptoms may vary up to 12 months after SARS-CoV-2 infection, the cohorts of teenagers reporting those specific symptoms

will have changed several times during that period. A similar pattern was observed for the same symptoms reported by test-negative teenagers (control group) *albeit* at lower prevalence, raising questions about causality of reported post-COVID symptoms in relation to the initial acute infection.[118]

The UK CLoCk study developed a model to predict which adolescents may be most likely to experience at least one physical symptom three months after a positive SARS-CoV-2 test. They found that an impairing, persisting symptom was associated with a higher number of symptoms at the time of testing, worse physical and mental health (self-rated) and feelings of loneliness before their SARS-CoV-2 test; additionally, females and older adolescents were also more likely to experience persisting symptoms.[122] On-going longitudinal follow-up studies of the CLoCk cohort continue to report common, non-pathological symptoms in children over the course of the pandemic, with no significant impact on their physical or mental well-being, irrespective of the SARS-CoV-2 variant, number of infections or vaccination status.[123–127] Elsewhere, a Norwegian cohort study assessing prevalence and risk factors of "post-COVID condition" (PCC) in 12–25-year-olds found almost identical point prevalence estimates between those who tested SARS-CoV-2 positive and the negative control group, with a risk difference of 1.5% (95% CI, −10.2% to 13.1%). SARS-CoV-2 status was found to not be associated with PCC at 6 months, whereas symptom severity was (RR, 1.41; 95% CI, 1.27 to 1.56), as was loneliness (RR, 1.01; 95% CI, 1.00–1.02) and low-levels of physical activity (RR, 0.96; 95% CI, 0.92–1.00).

Taken together, given the broad inclusive criteria that are still in place and often interpreted without context or comparison with appropriate control groups, the current long COVID definitions are not fit for purpose. Most importantly, they fail to identify the small group of children who are genuinely experiencing adverse complications of SARS-CoV-2 infection, such as chronic fatigue, respiratory compromise, and cognitive difficulties. Better definitions are needed, including distinct clinical syndromes encompassed within the current broad definition, so that we can develop appropriate referral, diagnostic and management pathways. Better outcome studies are also needed to inform clinicians, parents and policy makers.[128]

Conclusions

The epidemiology and clinical characteristics of COVID-19 in children have changed progressively over the course of the pandemic. Reassuringly, disease severity in children has always been mild but currently, given that almost all children have antibodies to SARS-CoV-2, primarily through infection but also vaccination, the small proportion of more severe outcomes of SARS-CoV-2, including myocarditis, hospitalisation, PIMS-TS, and death, has continued to decline over time. This review highlights the importance of continued research and research-driven policymaking for appropriate and balanced public health actions. This is especially important in order to address health inequalities and provide targeted support for clinically vulnerable children and those disproportionately affected by COVID-19, as well as in the context of new SARS-CoV-2 variants and future vaccines.

Funding information

None.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors would like to acknowledge Suzanne Elgohari for her support in accessing historic SARIwatch data.

Appendix

sKIDs Investigation team includes: (i) UKHSA: Shazaad Ahmad, Felicity Aiano, Frances Baawuah, Joanne Beckmann, Andrew Brent, Bernadette Brent, Joanna Garstang, Ifeanyichukwu O Okike, Kevin Brown, Mary Ramsay.

References

1. Hilgenfeld R, Peiris M. *From SARS to MERS: 10 years of research on highly pathogenic human coronaviruses. Antivir Res* 2013;**100**(1):286–95.
2. Ladhani SN, Amin-Chowdhury Z, Davies HG, et al. *COVID-19 in children: analysis of the first pandemic peak in England. Arch Dis Child* 2020;**105**(12):1180–5.
3. Viner R, Russell S, Saulle R, et al. *School closures during social lockdown and mental health, health behaviors, and well-being among children and adolescents during the first COVID-19 wave: a systematic review. JAMA Pedia* 2022;**176**(4):400–9.
4. Rajmil L, Hjern A, Boran P, Gunnlaugsson G, Kraus de Camargo O, Raman S. *Impact of lockdown and school closure on children's health and well-being during the first wave of COVID-19: a narrative review. BMJ Paediatr Open* 2021;**5**(1):e001043.
5. Hoffman JA, Miller EA. *Addressing the consequences of school closure due to COVID-19 on children's physical and mental well-being. World Med Health Policy* 2020;**12**(3):300–10.
6. Viner RM, Russell SJ, Croker H, et al. *School closure and management practices during coronavirus outbreaks including COVID-19: a rapid systematic review. Lancet Child Adolesc Health* 2020;**4**(5):397–404.
7. Viner RM, Mytton OT, Bonell C, et al. *Susceptibility to SARS-CoV-2 infection among children and adolescents compared with adults: a systematic review and meta-analysis. JAMA Pedia* 2021;**175**(2):143–56.
8. Li B, Zhang S, Zhang R, Chen X, Wang Y, Zhu C. *Epidemiological and clinical characteristics of COVID-19 in children: a systematic review and meta-analysis. Front Pedia* 2020;**8**:591132.
9. Molteni E, Sudre CH, Canas LS, et al. *Illness duration and symptom profile in symptomatic UK school-aged children tested for SARS-CoV-2. Lancet Child Adolesc Health* 2021;**5**(10):708–18.
10. Dawood FS, Porucznik CA, Veguilla V, et al. *Incidence rates, household infection risk, and clinical characteristics of SARS-CoV-2 infection among children and adults in Utah and New York City, New York. JAMA Pedia* 2022;**176**(1):59–67.
11. Waterfield T, Watson C, Moore R, et al. *Seroprevalence of SARS-CoV-2 antibodies in children: a prospective multicentre cohort study. Arch Dis Child* 2021;**106**(7):680–6.
12. Ladhani SN, Baawuah F, Beckmann J, et al. *SARS-CoV-2 infection and transmission in primary schools in England in June-December, 2020 (sKIDs): an active, prospective surveillance study. Lancet Child Adolesc Health* 2021;**5**(6):417–27.
13. Mensah AA, Sinnathamby M, Zaidi A, et al. *SARS-CoV-2 infections in children following the full re-opening of schools and the impact of national lockdown: prospective, national observational cohort surveillance, July-December 2020, England. J Infect* 2021;**82**(4):67–74.
14. UK Health Security Agency. Coronavirus (COVID-19) in the UK. 2022. Accessed May 8, 2023 https://coronavirus.data.gov.uk/details/cases?areaType=nation&areaName=England.
15. Ratcliffe H, Tiley KS, Andrews N, et al. *Community seroprevalence of SARS-CoV-2 in children and adolescents in England, 2019–2021. Arch Dis Child* 2022.
16. Hoschler K, Ijaz S, Andrews N, et al. *SARS antibody testing in children: development of oral fluid assays for IgG measurements. Microbiol Spectr* 2022;**10**(1):e0078621.
17. Powell AA, Ireland G, Leeson R, et al. *National and regional prevalence of SARS-CoV-2 antibodies in primary and secondary school children in England: the School Infection Survey, a national open cohort study, November 2021. J Infect* 2023;**86**(4):361–8.
18. Office for National Statistics. COVID-19 Schools Infection Survey, England: pupil antibody data and vaccine sentiment, March to April 2022. 2022. Accessed May 8, 2023 https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/covid19schoolsinfectionsurveyengland/pupilantibodiesandvaccinesentimentmarch2022.
19. Oeser C, Whitaker H, Borrow R, et al. *Following the Omicron wave, the majority of children in England have evidence of previous COVID infection. J Infect* 2023;**86**(3):256–308.
20. Clarke KEJJ, Deng Y, et al. *Seroprevalence of infection-induced SARS-CoV-2 antibodies—United States, September 2021–February 2022. MMWR Morb Mortal Wkly Rep* 2022;**71**:606–8.
21. Ludvigsson JF. *Children are unlikely to be the main drivers of the COVID-19 pandemic—a systematic review. Acta Paediatr* 2020;**109**(8):1525–30.
22. Miller E, Waight PA, Andrews NJ, et al. *Transmission of SARS-CoV-2 in the household setting: a prospective cohort study in children and adults in England. J Infect* 2021;**83**(4):483–9.

23. 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;**21**(3):344–53.
24. Irfan O, Li J, Tang K, Wang Z, Bhutta ZA. *Risk of infection and transmission of SARS-CoV-2 among children and adolescents in households, communities and educational settings: a systematic review and meta-analysis. J Glob Health* 2021;**11**:05013.
25. Viner R, Waddington C, Mytton O, et al. *Transmission of SARS-CoV-2 by children and young people in households and schools: a meta-analysis of population-based and contact-tracing studies. J Infect* 2022;**84**(3):361–82.
26. Akaishi T, Ishii T. *Coronavirus disease 2019 transmission and symptoms in young children during the severe acute respiratory syndrome coronavirus 2 Delta variant and Omicron variant outbreaks. J Int Med Res* 2022;**50**(5):3000605221102079.
27. Clifford S, Waight P, Hackman J, et al. *Effectiveness of BNT162b2 and ChAdOx1 against SARS-CoV-2 household transmission: a prospective cohort study in England. Wellcome Open Res* 2023;**8**:96.
28. Singanayagam A, Hakki S, Dunning J, et al. *Community transmission and viral load kinetics of the SARS-CoV-2 delta (B.1.617.2) variant in vaccinated and unvaccinated individuals in the UK: a prospective, longitudinal, cohort study. Lancet Infect Dis* 2022;**22**(2):183–95.
29. Braeye T, Catteau L, Brondeel R, et al. *Vaccine effectiveness against transmission of Alpha, Delta and Omicron SARS-COV-2-infection, Belgian contact tracing, 2021-2022. Vaccine* 2023;**41**(20):3292–300.
30. Koirala A, Winkler NE, Quinn HE, et al. *Understanding SARS-CoV-2 Delta and Omicron variant transmission and vaccine impact in schools and child-care settings in Australia: a population-based study. Lancet Reg Health West Pac* 2023;**35**:100736.
31. Andrews N, Tessier E, Stowe J, et al. *Duration of protection against mild and severe disease by Covid-19 vaccines. N Engl J Med* 2022;**386**(4):340–50.
32. Zsigmond B, Breathnach AS, Mensah A, Ladhani SN. *Very low rates of severe COVID-19 in children hospitalised with confirmed SARS-CoV-2 infection in London, England". J Infect* 2022;**85**(1):90–122.
33. Powell AA, Amin-Chowdhury Z, Mensah A, Ramsay ME, Saliba V, Ladhani SN. *Severe acute respiratory syndrome coronavirus 2 infections in primary school age children after partial reopening of schools in England. Pedia Infect Dis J* 2021;**40**(6):243–5.
34. Cloete J, Kruger A, Masha M, et al. *Paediatric hospitalisations due to COVID-19 during the first SARS-CoV-2 Omicron (B.1.1.529) variant wave in South Africa: a multicentre observational study. Lancet Child Adolesc Health* 2022;**6**(5):294–302.
35. Torjesen I. *Covid-19: Omicron variant is linked to steep rise in hospital admissions of very young children. BMJ* 2022;**376**:o110.
36. Jelic M, Silveira L, Lang S, et al. *Changing characteristics of children with COVID-19 in Colorado admitted during different variant periods. Pedia Infect Dis J* 2023;**42**(8):679–84.
37. Wilde H, Tomlinson C, Mateen BA, et al. *Hospital admissions linked to SARS-CoV-2 infection in children and adolescents: cohort study of 3.2 million first ascertained infections in England. BMJ* 2023;**382**:e073639.
38. Rao S, Armistead I, Tyler A, Lensing M, Dominguez SR, Alden NB. *Respiratory syncytial virus, influenza, and coronavirus disease 2019 hospitalizations in children in Colorado during the 2021-2022 respiratory virus season. J Pedia* 2023;**260**:113491.
39. UK Health Security Agency. Weekly national Influenza and COVID-19 surveillance report; 2022.
40. Bertran M, Amin-Chowdhury Z, Davies HG, et al. *COVID-19 deaths in children and young people in England, March 2020 to December 2021: an active prospective national surveillance study. PLoS Med* 2022;**19**(11):e1004118.
41. Roessler M, Tesch F, Batram M, et al. *Post-COVID-19-associated morbidity in children, adolescents, and adults: a matched cohort study including more than 157,000 individuals with COVID-19 in Germany. PLoS Med* 2022;**19**(11):e1004122.
42. Hani E, Bertran M, Powell A, et al. *Significantly lower infection fatality rates associated with SARS-CoV-2 Omicron (B.1.1.529) infection in children and young people: active, prospective national surveillance, January-March 2022, England. J Infect* 2023;**86**(4):397–8.
43. Sorg AL, Hufnagel M, Doenhardt M, et al. *Risk for severe outcomes of COVID-19 and PIMS-TS in children with SARS-CoV-2 infection in Germany. Eur J Pedia* 2022;**181**(10):3635–43.
44. Harwood R, Yan H, Talawila Da Camara N, et al. *Which children and young people are at higher risk of severe disease and death after hospitalisation with SARS-CoV-2 infection in children and young people: a systematic review and individual patient meta-analysis. eClinicalMedicine* 2022;**44**:101287.
45. Department of Health and Social Care. Policy paper: UK COVID-19 vaccines delivery plan. 2021. Accessed May 8, 2023. https://www.gov.uk/government/publications/uk-covid-19-vaccines-delivery-plan/uk-covid-19-vaccines-delivery-plan.
46. Wong BLH, Ramsay ME, Ladhani SN. *Should children be vaccinated against COVID-19 now? Arch Dis Child* 2021;**106**(12):1147–8.
47. Dowell AC, Powell AA, Davis C, et al. *mRNA or ChAd0×1 COVID-19 vaccination of adolescents induces robust antibody and cellular responses with continued recognition of Omicron following mRNA-1273. Front Immunol* 2022;**13**:882515.
48. Aiano F, Campbell C, Saliba V, Ramsay ME, Ladhani SN. *COVID-19 vaccine given to children with comorbidities in England, December 2020–June 2021. Arch Dis Child* 2022;**107**(3).
49. Nguyen KH, Nguyen K, Mansfield K, Allen JD, Corlin L. *Child and adolescent COVID-19 vaccination status and reasons for non-vaccination by parental vaccination status. Public Health* 2022;**209**:82–9.
50. Medicines and Healthcare products Regulatory Agency. Regulatory approval of Pfizer/BioNTech vaccine for COVID-19; 2021.
51. Department of Health and Social Care. JCVI statement on COVID-19 vaccination of children aged 12 to 15 years: 3 September 2021. 2021. https://www.gov.uk/government/publications/jcvi-statement-september-2021-covid-19-vaccination-of-children-aged-12-to-15-years/jcvi-statement-on-covid-19-vaccination-of-children-aged-12-to-15-years-3-september-2021#annex-a-jcvi-advice-on-vaccination-of-children-aged-12-to-15-years-with-underlying-health-conditions-31-august-2021.
52. Department of Health and Social Care. Universal vaccination of children and young people aged 12 to 15 years against COVID-19. 2021. https://www.gov.uk/government/publications/universal-vaccination-of-children-and-young-people-aged-12-to-15-years-against-covid-19/universal-vaccination-of-children-and-young-people-aged-12-to-15-years-against-covid-19.
53. Department of Health and Social Care. JCVI statement on COVID-19 vaccination of children and young people: 22 December 2021. 2021. https://www.gov.uk/government/publications/jcvi-update-on-advice-for-covid-19-vaccination-of-children-and-young-people/jcvi-statement-on-covid-19-vaccination-of-children-and-young-people-22-december-2021.
54. Department of Health and Social Care. JCVI statement on vaccination of children aged 5 to 11 years old. 2022. https://www.gov.uk/government/publications/jcvi-update-on-advice-for-covid-19-vaccination-of-children-aged-5-to-11/jcvi-statement-on-vaccination-of-children-aged-5-to-11-years-old.
55. Department of Health and Social Care. COVID-19 vaccination of children aged 6 months to 4 years: JCVI advice, 9 December 2022 (updated 26 April 2023). Accessed May 14, 2023 2023. https://www.gov.uk/government/publications/covid-19-vaccination-of-children-aged-6-months-to-4-years-jcvi-advice-9-december-2022.
56. GOV.UK. Vaccinations in England. 2022. Accessed December 21, 2022. https://coronavirus.data.gov.uk/details/vaccinations?areaType=nation&areaName=England.
57. Isreal Ministry of Health. Coronavirus in Isreal - A General Picture of the Situation. 2022. Accessed November 11, 2022. https://datadashboard.health.gov.il/COVID-19/general.
58. Centre for Disease Control and Prevention. Data.CDC.gov. 2022. Accessed December 14, 2022. https://data.cdc.gov/Vaccinations/Archive-COVID-19-Vaccination-and-Case-Trends-by-Ag/gxj9-t96f/explore/query/SELECT%0A%20%20%60cdc_case_earliest_dt%60%2C%0A%20%20%60agegroupvacc%60%2C%0A%20%20%60_7_day_avg_group_cases_per%60%2C%0A%20%20%60administered_dose1_pct%60%2C%0A%20%20%60series_complete_pop_pct%60/page/filter.
59. Department of Health and Social Care. JCVI statement on the COVID-19 vaccination programme for 2023: 8 November 2022. 2023. https://www.gov.uk/government/publications/covid-19-vaccination-programme-for-2023-jcvi-interim-advice-8-november-2022/jcvi-statement-on-the-covid-19-vaccination-programme-for-2023-8-november-2022.
60. Ali M, Shiwani HA, Elfaki MY, et al. *COVID-19 and myocarditis: a review of literature. Egypt Heart J* 2022;**74**(1):23.
61. Massari M, Spila Alegiani S, Morciano C, et al. *Postmarketing active surveillance of myocarditis and pericarditis following vaccination with COVID-19 mRNA vaccines in persons aged 12 to 39 years in Italy: a multi-database, self-controlled case series study. PLOS Med* 2022;**19**(7):e1004056.
62. Hause AMBJ, Marquez P, et al. *Safety monitoring of Pfizer-BioNTech COVID-19 vaccine booster doses among children aged 5–11 years—United States, May 17–July 31, 2022. MMWR Morb Mortal Wkly Rep* 2022;**71**:1047–51.
63. Shimabukuro T.T. Update on myocarditis following mRNA COVID-19 vaccination. 2022. Accessed July 12, 2023. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-06-22-23/03-COVID-Shimabukuro-508.pdf.
64. Karlstad Ø, Hovi P, Husby A, et al. *SARS-CoV-2 vaccination and myocarditis in a nordic cohort study of 23 million residents. JAMA Cardiol* 2022;**7**(6):600–12.
65. Cheng DR, Clothier HJ, Morgan HJ, et al. *Myocarditis and myopericarditis cases following COVID-19 mRNA vaccines administered to 12-17-year olds in Victoria. Australia, BMJ Paediatr Open* 2022;**6**(1):e001472.
66. Mustafa Alhussein M, Rabbani M, Sarak B, et al. *Natural history of myocardial injury after COVID-19 vaccine-associated myocarditis. Can J Cardiol* 2022;**38**(11):1676–83.
67. Kracalik I, Oster ME, Broder KR, et al. *Outcomes at least 90 days since onset of myocarditis after mRNA COVID-19 vaccination in adolescents and young adults in the USA: a follow-up surveillance study. Lancet Child Adolesc Health* 2022;**6**(11):788–98.
68. Ahmed SK, Mohamed MG, Essa RA, et al. *Global reports of myocarditis following COVID-19 vaccination: a systematic review and meta-analysis. Diabetes Metab Syndr* 2022;**16**(6):102513.
69. Voleti N, Reddy SP, Ssentongo P. *Myocarditis in SARS-CoV-2 infection vs. COVID-19 vaccination: a systematic review and meta-analysis. Front Cardiovasc Med* 2022;**9**:951314.
70. Stowe J, Miller E, Andrews N, Whitaker HJ. *Risk of myocarditis and pericarditis after a COVID-19 mRNA vaccine booster and after COVID-19 in those with and without prior SARS-CoV-2 infection: a self-controlled case series analysis in England. PLOS Med* 2023;**20**(6):e1004245.
71. Eyre DW, Taylor D, Purver M, et al. *Effect of Covid-19 vaccination on transmission of alpha and delta variants. N Engl J Med* 2022;**386**(8):744–56.
72. Jacobsen H, Cobos Jiménez V, Sitaras I, et al. *Post-vaccination T cell immunity to Omicron. Front Immunol* 2022;**13**:944713.
73. Powell AA, Kirsebom F, Stowe J, et al. *Effectiveness of BNT162b2 against COVID-19 in adolescents. Lancet Infect Dis* 2022;**22**(5):581–3.
74. Powell AA, Kirsebom F, Stowe J, et al. *Protection against symptomatic infection with delta (B.1.617.2) and Omicron (B.1.1.529) BA.1 and BA.2 SARS-CoV-2 variants after previous infection and vaccination in adolescents in England, August,*

2021–March, 2022: a national, observational, test-negative, case-control study. Lancet Infect Dis 2023;**23**(4):435–44.

75. Goldberg Y, Mandel M, Bar-On YM, et al. *Protection and waning of natural and hybrid immunity to SARS-CoV-2. N Engl J Med* 2022;**386**(23):2201–12.
76. Altarawneh HN, Chemaitelly H, Ayoub HH, et al. *Effects of previous infection and vaccination on symptomatic Omicron infections. N Engl J Med* 2022;**387**(1):21–34.
77. Dowell AC, Lancaster T, Bruton R, et al. *Immunological imprinting of humoral immunity to SARS-CoV-2 in children. Nat Commun* 2023;**14**(1):3845.
78. Lin D-Y, Gu Y, Xu Y, et al. *Effects of vaccination and previous infection on Omicron infections in children. N Engl J Med* 2022;**387**(12):1141–3.
79. Price AM, Olson SM, Newhams MM, et al. *BNT162b2 protection against the Omicron variant in children and adolescents. N Engl J Med* 2022;**386**(20):1899–909.
80. Sacco C, Del Manso M, Mateo-Urdiales A, et al. *Effectiveness of BNT162b2 vaccine against SARS-CoV-2 infection and severe COVID-19 in children aged 5-11 years in Italy: a retrospective analysis of January-April, 2022. Lancet* 2022;**400**(10346):97–103.
81. Ladhani SN. *COVID-19 vaccination for children aged 5-11 years. Lancet* 2022;**400**(10346):74–6.
82. Dorabawila V, Hoefer D, Bauer UE, Bassett MT, Lutterloh E, Rosenberg ES. *Effectiveness of the BNT162b2 vaccine among children 5-11 and 12-17 years in New York after the emergence of the Omicron variant. medRxiv* 2022.
83. Chemaitelly H, AlMukdad S, Ayoub HH, et al. *Covid-19 vaccine protection among children and adolescents in qatar. N Engl J Med* 2022;**387**(20):1865–76.
84. Shi DS, Whitaker M, Marks KJ, et al. *Hospitalizations of children aged 5-11 years with laboratory-confirmed COVID-19—COVID-NET, 14 states, March 2020-February 2022. MMWR Morb Mortal Wkly Rep* 2022;**71**(16):574–81.
85. Simmons AE, Amoako A, Grima AA, et al. *Vaccine effectiveness against hospitalization among adolescent and pediatric SARS-CoV-2 cases between May 2021 and January 2022 in Ontario, Canada: a retrospective cohort study. PLoS One* 2023;**18**(3):e0283715.
86. Shingleton J, Burton L, Williams HE, et al. *Risk of paediatric multisystem inflammatory syndrome (PIMS-TS) during the SARS-CoV-2 alpha and delta variant waves: national observational and modelling study, 2020-21, England. Front Pedia* 2022;**10**:1034280.
87. Chiew CJ, Premikha M, Chong CY, et al. *Effectiveness of primary series and booster vaccination against SARS-CoV-2 infection and hospitalisation among adolescents aged 12-17 years in Singapore: a national cohort study. Lancet Infect Dis* 2023;**23**(2):177–82.
88. Gerna G, Percivalle E, Sarasini A, et al. *Human respiratory coronavirus HKU1 versus other coronavirus infections in Italian hospitalised patients. J Clin Virol* 2007;**38**(3):244–50.
89. Chiu SS, Chan KH, Chu KW, et al. *Human coronavirus NL63 infection and other coronavirus infections in children hospitalized with acute respiratory disease in Hong Kong, China. Clin Infect Dis* 2005;**40**(12):1721–9.
90. Heimdal I, Moe N, Krokstad S, et al. *Human coronavirus in hospitalized children with respiratory tract infections: a 9-year population-based study from Norway. J Infect Dis* 2019;**219**(8):1198–206.
91. Jevšnik M, Uršič T, Žigon N, Lusa L, Krivec U, Petrovec M. *Coronavirus infections in hospitalized pediatric patients with acute respiratory tract disease. BMC Infect Dis* 2012;**12**(1):365.
92. Zeng Z-Q, Chen D-H, Tan W-P, et al. *Epidemiology and clinical characteristics of human coronaviruses OC43, 229E, NL63, and HKU1: a study of hospitalized children with acute respiratory tract infection in Guangzhou, China. Eur J Clin Microbiol Infect Dis* 2018;**37**(2):363–9.
93. Pustake M, Tambolkar I, Giri P, Gandhi C. *SARS, MERS and CoVID-19: an overview and comparison of clinical, laboratory and radiological features. J Fam Med Prim Care* 2022;**11**(1):10–7.
94. Edridge AWD, Kaczorowska J, Hoste ACR, et al. *Seasonal coronavirus protective immunity is short-lasting. Nat Med* 2020;**26**(11):1691–3.
95. Humbert M, Olofsson A, Wullimann D, et al. *Functional SARS-CoV-2 cross-reactive CD4(+) T cells established in early childhood decline with age. Proc Natl Acad Sci USA* 2023;**120**(12):e2220320120.
96. Taira N, Toguchi S, Miyagi M, et al. *Altered pre-existing SARS-CoV-2-specific T cell responses in elderly individuals. Clin Immunol Commun* 2022;**2**:6–11.
97. Jo N, Hidaka Y, Kikuchi O, et al. *Impaired CD4+ T cell response in older adults is associated with reduced immunogenicity and reactogenicity of mRNA COVID-19 vaccination. Nat Aging* 2023;**3**(1):82–92.
98. Dowell AC, Butler MS, Jinks E, et al. *Children develop robust and sustained cross-reactive spike-specific immune responses to SARS-CoV-2 infection. Nat Immunol* 2022;**23**(1):40–9.
99. Madera S, Crawford E, Langelier C, et al. *Nasopharyngeal SARS-CoV-2 viral loads in young children do not differ significantly from those in older children and adults. Sci Rep* 2021;**11**(1):3044.
100. Dowell AC, Ireland G, Zuo J, Moss P, Ladhani S, Team sI. *Association of spike-specific T cells with relative protection from subsequent SARS-CoV-2 Omicron infection in young children. JAMA Pediatr* 2023;**177**(1):96–7.
101. Muñoz FM, Sher LD, Sabharwal C, et al. *Evaluation of BNT162b2 Covid-19 vaccine in children younger than 5 years of age. N Engl J Med* 2023;**388**(7):621–34.
102. Frenck Jr. RW, Klein NP, Kitchin N, et al. *Safety, immunogenicity, and efficacy of the bNT162b2 Covid-19 vaccine in adolescents. N Engl J Med* 2021;**385**(3):239–50.
103. Walter EB, Talaat KR, Sabharwal C, et al. *Evaluation of the BNT162b2 Covid-19 vaccine in children 5 to 11 years of age. N Engl J Med* 2022;**386**(1):35–46.
104. Elliott P, Eales O, Steyn N, et al. *Twin peaks: the Omicron SARS-CoV-2 BA.1 and BA.2 epidemics in England. Science* 2022;**376**(6600):eabq4411.
105. Elliott P, Bodinier B, Eales O, et al. *Rapid increase in Omicron infections in England during December 2021: REACT-1 study. Science* 2022;**375**(6587):1406–11.
106. Toh ZQ, Mazarakis N, Nguyen J, et al. *Comparison of antibody responses to SARS-CoV-2 variants in Australian children. Nat Commun* 2022;**13**(1):7185.
107. Tubiana J, Xiang Y, Fan L, et al. *Reduced B cell antigenicity of Omicron lowers host serologic response. Cell Rep* 2022;**41**(3):111512.
108. Flood J, Shingleton J, Bennett E, et al. *Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 (PIMS-TS): prospective, national surveillance, United Kingdom and Ireland, 2020. Lancet Reg Health Eur* 2021;**3**:100075.
109. Tulloh RMR, Mayon-White R, Harnden A, et al. *Kawasaki disease: a prospective population survey in the UK and Ireland from 2013 to 2015. Arch Dis Child* 2019;**104**(7):640–6.
110. Nygaard U, Holm M, Hartling UB, et al. *Incidence and clinical phenotype of multisystem inflammatory syndrome in children after infection with the SARS-CoV-2 delta variant by vaccination status: a Danish nationwide prospective cohort study. Lancet Child Adolesc Health* 2022;**6**(7):459–65.
111. Penner J, Abdel-Mannan O, Grant K, et al. *6-month multidisciplinary follow-up and outcomes of patients with paediatric inflammatory multisystem syndrome (PIMS-TS) at a UK tertiary paediatric hospital: a retrospective cohort study. Lancet Child Adolesc Health* 2021;**5**(7):473–82.
112. Cohen JM, Carter MJ, Ronny Cheung C, Ladhani S. *Lower risk of multisystem inflammatory syndrome in children (MIS-C) with the Delta and Omicron variants of SARS-CoV-2. Clin Infect Dis* 2022;**76**(3):e518–21.
113. Shingleton J, Williams H, Oligbu G, et al. *The changing epidemiology of PIMS-TS across COVID-19 waves: prospective national surveillance, January 2021 to July 2022, England. J Infect* 2022;**85**:702–69.
114. Consiglio CR, Cotugno N, Sardh F, et al. *The immunology of multisystem inflammatory syndrome in children with COVID-19. Cell* 2020;**183**(4):968–981.e7.
115. World Health Organisation. A clinical case definition for post COVID-19 condition in children and adolescents by expert consensus, 16 February 2023. 2023. https://www.who.int/publications/i/item/WHO-2019-nCoV-Post-COVID-19-condition-CA-Clinical-case-definition-2023-1.
116. Office for National Statistics. Updated experimental estimates of the prevalence of long COVID symptoms. 2021. Accessed July 12, 2023 https://www.google.com/url?sa=i&rct=j&q=&esrc=s&source=web&cd=&cad=rja&uact=8&ved=0CAIQw7AJahcKEwjAqvzI5JeAAxUAAAAAHQAAAAQAg&url=https%3A%2F%2Fwww.ons.gov.uk%2Ffile%3Furi%3D%2Fpeoplepopulationandcommunity%2Fhealthandsocialcare%2Fhealthandlifeexpectancies%2Fadhocs%2F12788updatedestimatesoftheprevalenceoflongcovidsymptoms%2Fcovid19symptomsprevalence.xlsx&psig=AOvVaw2WmsBEenbt0a8uqGtVCXTl&ust=1689753526466223&opi=89978449.
117. Office for National Statistics. Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK; 2023.
118. Stephenson T, Pinto Pereira SM, Shafran R, et al. *Physical and mental health 3 months after SARS-CoV-2 infection (long COVID) among adolescents in England (CLoCk): a national matched cohort study. Lancet Child Adolesc Health* 2022;**6**(4):230–9.
119. Lopez-Leon S, Wegman-Ostrosky T, Perelman C, et al. *More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. Sci Rep* 2021;**11**(1):16144.
120. Stephenson T, Shafran R, De Stavola B, et al. *Long COVID and the mental and physical health of children and young people: national matched cohort study protocol (the CLoCk study). BMJ Open* 2021;**11**(8):e052838.
121. Pinto Pereira SM, Shafran R, Nugawela MD, et al. *Natural course of health and well-being in non-hospitalised children and young people after testing for SARS-CoV-2: a prospective follow-up study over 12 months, 25,Lancet Reg Health. Eur* 2022:100554.
122. Nugawela MD, Stephenson T, Shafran R, et al. *Predictive model for long COVID in children 3 months after a SARS-CoV-2 PCR test. BMC Med* 2022;**20**(1):465.
123. Pinto Pereira SM, Nugawela MD, McOwat K, et al. *Symptom profiles of children and young people 12 months after SARS-CoV-2 testing: a national matched cohort study (The CLoCk Study). Children* 2023;**10**(7).
124. Pinto Pereira SM, Mensah A, Nugawela MD, et al. *Long COVID in children and young after infection or reinfection with the Omicron variant: a prospective observational study. J Pedia* 2023;**259**:113463.
125. Newlands F, Rojas NK, Nugawela M, et al. *A cross-sectional study of the health of emerging young adults in England following a COVID-19 infection. J Adolesc Health* 2023;**73**(1):20–8.
126. Stephenson T, Pinto Pereira SM, Nugawela MD, et al. *Long COVID-six months of prospective follow-up of changes in symptom profiles of non-hospitalised children and young people after SARS-CoV-2 testing: a national matched cohort study (The CLoCk) study. PLoS One* 2023;**18**(3):e0277704.
127. Pinto Pereira SM, Nugawela MD, Rojas NK, et al. *Post-COVID-19 condition at 6 months and COVID-19 vaccination in non-hospitalised children and young people. Arch Dis Child* 2023;**108**(4):289–95.
128. Stephenson T, Shafran R, Ladhani SN. *Long COVID in children and adolescents. Curr Opin Infect Dis* 2022;**35**(5):461–7.