Comprehensive assessment of paediatric SARS-CoV-2 infection: A Danish population-based cohort study

Journal:	*BMJ*
Manuscript ID	BMJ-2021-068898.R1
Article Type:	Original research
Date Submitted by the Author:	11-Nov-2021
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Keywords:	COVID-19, Pediatrics, Public health

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A Danish population-based cohort study

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Abstract

Objective: To assess the risk of acute and post-acute adverse events following SARS-CoV-2 infection in children and adolescents in Denmark, a high-income country with widespread community-based testing and population-based data capture, and to evaluate real-world effectiveness of the BNT162b2 mRNA vaccine among adolescents.

Design: Cohort study

Setting: Nationwide Danish healthcare registers.

Participants: All Danish children and adolescents below 18 years of age who were either RT-PCR-tested for SARS-CoV-2 until 31 July 2021 or vaccinated with the BNT162b2 mRNA vaccine until 11 August 2021 were eligible for inclusion.

Main outcome measures: In evaluation of acute and post-acute outcomes following SARS-CoV-2 infection, we assessed the risk of hospitalisation, intensive care unit (ICU) admission, serious complications including multisystem inflammatory syndrome in children (MIS-C), myocarditis and neuroimmune disorders, as well as the risk of initiating drug therapy and health service utilisation up to six months after testing. Comparing vaccine recipients to unvaccinated peers, we evaluated the vaccine effectiveness towards SARS-CoV-2 infection as one minus the risk ratio at 20 days after the first dose and 60 days after the second dose.

Results: Among 972,099 children RT-PCR-tested for SARS-CoV-2 in Denmark, 60,692 (6.2%) tested positive for SARS-CoV-2. Among these, 319 (0.5%) were hospitalised for 12 hours or more and 12 (0.02%) received ICU treatment within 30 days of testing. The risk of MIS-C within two months of SARS-CoV-2 infection was 0.05% (N=27), whereas there were no cases of myocarditis outside of MIS-C, encephalitis and <5 cases of Guillain-Barré syndrome. In the post-acute phase from 1 to 6 months after infection, SARS-CoV-2 positive children had a 1.08 times (95% CI, 1.07 to 1.10) increased rate of contacts with general practitioners compared to a reference cohort sampled among all children tested for SARS-CoV-2. The estimated vaccine effectiveness against documented SARS-CoV-2

infection was 65% (62 to 67) 20 days after the first dose and 88% (78 to 94) 60 days after the second dose.

Conclusions: The absolute risks of adverse events after SARS-CoV-2 infection were generally low in Danish children, although MIS-C occurred in 1 of 2000 children with documented SARS-CoV-2 infection. In adjusted analyses, SARS-CoV-2 positive children had slightly increased rates of general practitioner visits which could indicate persisting symptoms to SARS-CoV-2 infection. The BNT162b2 mRNA vaccine was effective in preventing SARS-CoV-2 infection in adolescents.

What is already known on this topic

- Existing studies have reported conflicting rates of hospitalisation, ICU admission, mortality, and immune-mediated complications, such as multisystem inflammatory syndrome (MIS-C), among children infected with SARS-CoV-2.
- The most likely cause of these conflicting results is variations in setting and data availability, with most studies having been conducted among hospitalised children, who do not represent the majority of children infected with SARS-CoV-2.
- Some evidence suggests that a substantial proportion of children experience persisting symptoms or sequelae to SARS-CoV-2 infection, but existing studies have major limitations, including responder bias and lack of control groups.

What this study adds

- In a nationwide setting, children and adolescents have low risks of serious adverse events after SARS-CoV-2 infection, although with slightly increased rates of general practitioner visits and with MIS-C occurring in one of 2000 children with documented SARS-CoV-2 infection.
- The BNT162b2 mRNA vaccine was effective in preventing documented SARS-CoV-2 infection for up to three months after the first dose.

Introduction

One and a half year into the severe respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, more than 250 million cases have been reported worldwide.[1] Widespread vaccination against SARS-CoV-2 has greatly improved the prognosis of coronavirus disease 2019 (COVID-19) among adults in countries with high availability and rates of vaccinations, however, SARS-CoV-2 continues to spread among the younger, largely unvaccinated, population.[2] Many countries have initiated mass vaccinations programs against SARS-CoV-2 in adolescents 12 years of age or older. On 29 October, 2021, the U.S. Food and Drug Administration authorized the emergency use of BNT162b2 in children 5 through 11 years of age, and soon regulators will thus need to decide whether to extend mass vaccination programmes against SARS-CoV-2 to their child populations. All approved messenger RNA vaccines against SARS-CoV-2 are seemingly effective in reducing SARS-CoV-2 transmission and preventing COVID-19 hospitalisations, and are thus also expected to prevent immune-mediated complications to SARS-CoV-2 infection, including multisystem inflammatory syndrome (MIS-C).[3–5] Childhood vaccination may further be necessary to increase overall population immunity.[6] However, studies have consistently found that children have lower susceptibility to SARS-CoV-2 than adults and that infection is generally asymptomatic or mild, limiting the individual child's benefit of vaccination.[7,8]

To inform this decision, it is of major public health importance that the risks of SARS-CoV-2 among children and adolescents are portrayed accurately and in different settings. Among children and adolescents, reports of hospitalisation and case fatality rates have varied considerably, seemingly depending on setting and data availability, and data is scarce among the majority of children that have asymptomatic or mild disease.

In this study, we therefore aimed to provide a thorough description of the SARS-CoV-2 epidemic in Danish children and adolescents and to provide population-based estimates

for the risk of adverse outcomes following SARS-CoV-2 infection in children and the real-world effectiveness of the BNT162b2 mRNA vaccine among adolescents.

Methods

This population-based cohort study used individual-level linkage of data from Danish patient, prescription, health insurance, and vaccination registries. [9–13] We included all reverse-transcriptase polymerase chain reaction (RT-PCR) confirmed SARS-CoV-2 cases in Denmark until 31 July, 2021, and examined clinical characteristics of children needing hospitalisation and the occurrence of acute and post-acute health care outcomes following SARS-CoV-2 infection in children. Furthermore, we estimated the vaccine effectiveness of BNT162b2 against documented SARS-CoV-2 infection. This study was reported according to the Reporting of Studies Conducted Using Observational Routinely Collected Health Data statement. All analytical source code used can be obtained from https://gitlab.sdu.dk/pharmacoepi/sars-cov-2-children/.

Setting

Denmark reported its first case of SARS-CoV-2 on 27 February 2020, and on 11 March 2020, the Danish government imposed a comprehensive lockdown of the country to control community spread. In April 2020, day-care centres and primary schools gradually reopened. An increasing transmission of SARS-CoV-2 was seen in the autumn of 2020, leading to gradual restrictions and new closures of schools from mid-December 2020 until March 2021. In the early phase of the epidemic, RT-PCR testing was limited to individuals with symptoms of COVID-19 and testing of children required referral by a general practitioner to hospital-based testing units. From July 2020, testing without requisition became available for children over 12 years, and in September 2020 this was expanded to all children over 2 years. In December 2020, rapid antigen testing also became available. All tests were provided for free and easily accessible with a high density of testing

locations nationwide. Denmark began mass vaccination programmes against SARS-CoV-2 for adolescents aged 16-17 years in May 2021 and for 12-15 year-olds in July 2021. To date, Danish children and adolescents have almost exclusively been vaccinated with the BNT162b2 mRNA vaccine (99.5% of all vaccine recipients 12-17 years).

Study population

All individuals under 18 years with a reverse-transcriptase polymerase chain reaction (RT-PCR) test for SARS-CoV-2 in Denmark from 27 February 2020, to 31 July 2021, or individuals under 18 years vaccinated with the BNT162b2 mRNA vaccine from 1 May to 11 August 2021 were eligible for inclusion. In all analyses, individuals were included if they completed follow up before or on 31 August 2021. As of July 1, 2021, the Danish population under 18 years consisted of 1,151,399 individuals.

Acute and post-acute effects of SARS-CoV-2 infection

For these analyses, the main cohort comprised all children under the age of 18 with RT-PCR-confirmed SARS-CoV-2 infection. In baseline characterization of SARS-CoV-2 cases, this group was further stratified into children who did and did not require hospitalisation within the first 30 days after their first positive SARS-CoV-2 test. We sampled a reference cohort from the entire cohort of children under the age of 18 who were tested for SARS-CoV-2 during the study period. For each child, we randomly sampled an index date from the distribution of test dates among SARS-CoV-2 positive children. Children who were not living in Denmark during the year prior to the index date or had previously been tested positive for SARS-CoV-2 were excluded from further analyses. As a sensitivity analysis, we also compared SARS-CoV-2 test positive children to children who tested negative for SARS-CoV-2. For each SARS-CoV-2 positive individual, we sampled 10 SARS-CoV-2 negative individuals based on the year of birth, sex, year and week of testing.

Outcomes of SARS-CoV-2 infection were considered in three periods: the acute phase (day 0 to 29), an intermediate period where serious complications related to SARS-

CoV-2 infection were likely to occur (day 0 to 59) and the post-acute phase (day 30 to 179). These periods were chosen to maximize capture of serious complications in all phases of the epidemic. During the acute phase, we examined the risk of hospitalisation, intensive care unit admission and receiving mechanical ventilation. In these analyses, we excluded children who had the outcome of interest during the month preceding sampling. Hospitalisation was defined as any hospital stay longer than 12 hours, a definition adopted from the Danish national COVID-19 surveillance system to distinguish patients with less severe disease requiring short hospital visits from those with treatment-requiring disease.[14] We also explored alternative definitions of hospitalisations as any hospital contact with a duration longer than 24 hours and any hospital contact with a duration longer than 24 hours with a discharge diagnosis of COVID-19.

For the intermediate period, we examined the occurrence of receiving a first ever in- or outpatient hospital diagnosis of potential complications or sequelae to SARS-CoV-2 infection. Included disease entities were venous thromboembolism (VTE), MIS-C, myocarditis, pneumonia, encephalitis, Guillain-Barré syndrome, and other neuroimmune disorders.

In the post-acute phase, we identified initiation of prescription drugs representing possible complications and persistent symptoms of SARS-CoV-2 infection which may not lead to a hospital admission, including short-acting β2-agonists, inhaled corticosteroids, paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), and antibiotics used in Denmark to treat airway infections. Children who had redeemed a prescription for the drug of interest one year prior to the index date, were excluded from the respective analysis. Finally, we assessed differences in health service utilization by establishing rates of general practitioner visits, visits at private practicing specialists, hospital outpatient visits and hospital admissions (overall and specifically related to paediatrics), allowing for multiple occurrences of each type of visit. In analyses of the intermediate and post-acute phase, we restricted analyses to individuals with at least 2 or 6 months of follow-up. For the specific international classification of disease, 10th revision (ICD-10) codes and

anatomical therapeutical classification (ATC) codes used to define disease entities and drug groups, please see supplementary table S1.

Statistical analysis

To characterize the differences in baseline characteristics among assumed asymptomatic or mild cases compared to more severe cases of SARS-CoV-2 infection, we described demographics, temporality, and medical history, stratified on whether SARS-CoV-2 positive cases were hospitalised within the first month of testing or not. In assessment of outcomes in the predefined acute and intermediate phase, we calculated absolute risks among children with and without a positive RT-PCR test for SARS-CoV-2. To address potential confounding, we estimated propensity score-weighted risk differences and risk ratios with robust 95% confidence intervals (CIs) using binomial regression. The propensity score model included age, sex, calendar time, gestational age, comorbidities, and current drug use as defined in supplementary table S2. Age was modelled using restricted cubic splines with four knots.

To identify potential post-acute effects or complications to SARS-CoV-2 infection, we assessed the risk of initiation of new medication from 30-179 days after a SARS-CoV-2 test and estimated risk differences comparing SARS-CoV-2 positive children to the reference cohort. Rates of health care visits were assessed monthly from 30-179 days after a SARS-CoV-2 test. To control for underlying differences in baseline health-care use among SARS-CoV-2 positive children and children in the reference cohort, we estimated prior-event rate ratio (PERR) adjusted rate ratios.[16] We calculated rate ratios of health service utilization among SARS-CoV-2 positive children and the reference cohort during a pre-baseline period from day -179 to -30 before testing and the post-acute follow-up period from day +30 to +179 after testing. PERR-adjusted rate ratios were calculated as $RR_{Post\text{-}acute}$ / $RR_{Baseline}$ and normal based 95% CIs were obtained using bootstrapping techniques with 200 replications.

Vaccine effectiveness

We investigated the vaccine effectiveness of BNT162b2 in regards to preventing laboratory-confirmed SARS-CoV-2 infection in adolescents aged 12-17 years who were vaccinated between 1 May 2021 and 11 August 2021. For comparison, we matched 10 unvaccinated individuals to each vaccinated individual based on birthyear, sex and municipality on the date of vaccination. Vaccinated and unvaccinated individuals were followed during two periods: 0 to 20 days after the first dose, and 0 to 60 days after the second dose. We excluded adolescents who tested positive for SARS-CoV-2 or were vaccinated with any other COVID-19 vaccine prior to the beginning of follow up. Adolescents in the comparator cohorts were censored if vaccinated during follow up. We estimated vaccine effectiveness as one minus the risk ratio for each period. Risk ratios were obtained using log-binomial regression adjusted for matching factors and immigration status. Only individuals with complete follow up were included. In sensitivity analyses, we explored whether informative censoring affected our results, by estimating vaccine effectiveness while weighting the comparator cohorts in the inverse probability of censoring.

Public and patient involvement

Owing to both the nature and urgency of this study, no patients or members of the public were involved in study design, conduct or reporting.

Results

Between 27 February 2020 and 31 July 2021, 972,099 Danish children and adolescents were tested for SARS-CoV-2 in Denmark, and 60,692 tested positive, corresponding to 84% and 5.3% of the total Danish population under 18 years. The incidence of SARS-CoV-2 among children showed two peaks in December 2020 and August 2021 with 63 and 36 new daily cases per 100,000 children (Figure 1A). The daily number of tests were largely influenced

by test availability and governmentally issued restrictions and recommendations. Thus, the number increased in the fall of 2020 along with the peak in the epidemic and again in the spring of 2021 when schools reopened and school children were encouraged to undergo weekly testing (Figure 1B). The number of COVID-19 related hospitalisations peaked in December 2020 and summer of 2021 (Figure 1C). Due to data protection regulations, data on whole genome sequencing of RT-PCR SARS-CoV2 tests was not stratified on age, however, the distribution of variants was assumed to be similar in children and adults. During the SARS-CoV-2 peak in December 2020, the B.1.1.7 lineage variant of SARS-CoV-2 dominated but was replaced by the alpha lineage in the spring of 2021, and by July 2021 the delta lineage had become the dominant strain in Denmark (supplementary Figure S1). Vaccine uptake increased rapidly during the early summer of 2021, and by end July 37% of adolescents aged 12-15 years and 82% of 16-17 year-olds had begun vaccination against SARS-CoV-2 (Figure 1D).

Of the 60,692 SARS-CoV-2 positive children in Denmark, 319 were hospitalised within the first month of testing (0.5%). The risk of hospitalisation was highest among the 0-1 year-olds (3.4%), and lower in the remaining age groups (0.3 to 0.5%) (Table 1). The risk of hospitalisation was similar in the second and third part of the pandemic, regardless of the predominant SARS-CoV-2 strain (supplementary table S3). Hospitalised SARS-CoV-2 positive children were more likely than non-hospitalised cases to have a medical history of the selected comorbidities, with 39% having at least one recorded comorbid disease, most often a history of psychiatric disorders (16%), prematurity (11%) and asthma (9.1%). Likewise, hospitalised children had a higher prevalence of prescription drug use one year prior to infection, particularly of asthma medication and systemic antibiotics, and 43% had redeemed prescriptions of at least two unique drugs. Characteristics of the reference cohort are included in the supplementary (table S4).

When applying stricter definitions of hospital admission, the overall rate of hospitalisation among SARS-CoV-2 cases was reduced from 0.5% to 0.3% (N=206/60,692)

when requiring a visit longer than 24 hours, and to 0.1% (N=77/60,692), when requiring both a visit longer than 24 hours and a hospital diagnosis of either COVID-19 or MIS-C. Compared to the reference cohort sampled among all SARS-CoV-2 tested children, SARS-CoV-2 positive children had a higher risk of any hospitalisation within the first month, with an adjusted risk difference (RD) of 0.22% (95% CI, 0.16 to 0.28) (Figure 2). ICU admissions occurred in 0.02% of SARS-CoV-2 positive cases, which was similar to the frequency in the reference cohort.

Among the cohort with at least two months of follow-up, we observed 27 cases of MIS-C (0.05%). There were no cases of encephalitis, myocarditis outside of MIS-C, or neuroimmune disorders among SARS-CoV-2 positive children two months after testing and less than five cases of Guillain-Barre syndrome (Figure 2).

In the post-acute phase from day 30 to 179 after testing, 0.13% of SARS-CoV2 test positive children received a diagnosis code for persisting symptoms of SARS-CoV-2 infection ("long COVID") (Figure 2). Overall, initiation of prescription drugs was similar in SARS-CoV-2 positive children and the reference cohort. Of those who tested positive, 2.61% initiated antibiotics used to treat respiratory infections, 1.23% initiated treatment with short-acting β2-agonists, and 0.77% and 0.94% with paracetamol and NSAIDs. Compared with the reference cohort, the adjusted risk difference was marginally increased for initiation of treatment with inhaled corticosteroids (RD +0.08, 0.00 to 0.16) (Figure 2).

Within the post-acute phase, 16,368 (41.7%) of children and adolescents with SARS-CoV-2 infection and 183,645 (40.6%) of comparators had visited their general practitioner, 1523 (3.9%) and 18,364 (4.1%) at paediatric outpatient clinics and 613 (1.6%) and 7077 (1.6%) were admitted to a hospital (supplementary Table S5). When comparing baseline and overall post-acute health care utilisation between SARS-CoV-2 positive children and comparators, we only observed increased PERR-adjusted rate ratios for general practitioner visits (1.08 [95% CI; 1.07 to 1.10]) (Table 2). SARS-CoV-2 positive cases only had increased rates of hospital admissions during the second month after infection,

while they continued to have increased rates of general practitioner visits throughout the observation period (supplementary figure S2).

In sensitivity analyses using a cohort of SARS-CoV-2 test-negative children as comparators, SARS-CoV-2 positive children were no longer at increased risk of hospitalisation within the first month of testing and the signals indicating increased initiation of bronchodilating agents during the post-acute phase was also attenuated (supplementary table S7).

Among Danish adolescents, 321,467 were vaccinated against SARS-CoV-2. Of these, 83%(n=265,520) had completed the vaccination programme and the median time between doses for BNT162b2 was 35 days (IQR 25 to 36) (supplementary table S9). 219,776 individuals vaccinated with BNT162b2 were eligible for the first dose vaccine effectiveness analysis with 2,454,727 adolescents sampled as unvaccinated comparators (supplementary table S10). Figure 3 shows the cumulative incidence for documented SARS-CoV-2 infection. The estimated vaccine effectiveness against documented SARS-CoV-2 infection was 65% (95% CI; 62 to 67) 20 days after the first dose and 88% (95% CI; 78-94) 60 days after the second dose (supplementary Table S11).

Discussion

Principal findings

In this study, we present nationwide data on all 60,692 RT-PCR-confirmed paediatric cases of SARS-CoV-2 in Denmark, finding that 0.5% of cases were admitted to a hospital and 0.02% required admission to an intensive care unit. The absolute risk of serious complications to SARS-CoV-2 was generally low, although MIS-C occurred in one out of 2000 children with documented SARS-CoV-2 infection. Further, SARS-CoV-2 positive children were slightly more likely to visit their general practitioner for up to six months after infection compared to a reference cohort, possibly indicating persistent symptoms after SARS-CoV-2 infection. Finally, BNT162b2 vaccine effectiveness was high in

adolescents between 12 and 17 years with an estimated effectiveness against documented infection of 88% 60 days after the second dose.

Strengths and limitations

A major strength of our study is the nationwide coverage of the data sources used, allowing us to identify and follow all Danish children and adolescents tested for SARS-CoV-2 without restricting to e.g. children seen in the hospital setting. This increases the generalizability of our results, as the majority of children with SARS-CoV-2 infection do not require hospital admission. Further, we had complete individual-level ascertainment of all previous hospital-contacts, prescription drug use, and contacts in the Danish primary health care system, and we were able to follow study individuals for up to six months. However, our study also has important limitations. SARS-CoV-2 infection status was established by highly sensitive and specific RT-PCR tests, however, the number of SARS-CoV-2 cases is likely underestimated decreasing the denominator in risk estimates. [17,18] Some asymptomatic or mild cases may not undergo testing, and although encouraged, a proportion of SARS-CoV-2 positive individuals detected on rapid antigen testing may not undergo subsequent RT-PCR-testing. Second, we did not have access to medical records and could therefore not verify hospital diagnoses or reasons for contacts to primary care physicians at the individual level. Further, the ICD-10 diagnosis code for MIS-C was not implemented in Denmark until 1 April, 2021, and until then cases of MIS-C received a discharge diagnosis code for Kawasaki disease. We therefore considered Kawasaki disease occurring within two months of SARS-CoV-2 infection as MIS-C, which may have led to misclassification, although the reported risk was similar to a previous count of MIS-C cases from the Danish paediatric COVID-19 network.[19] Finally, due to the observational nature of our study, residual differences in the comparison of the SARS-CoV-2 positive children to the reference cohort cannot be ruled out despite our attempts to adjust for such differences using PERR-adjustment and propensity score methods.

Comparisons with other studies

The reported risks associated with SARS-CoV-2 infection in children are highly dependent on setting and often affected by being limited to hospital-based databases or claims data. There are also substantial geographic disparities in outcomes, possibly related to differences in national management of the epidemic, access to health care, testing capacity and issues of race, social inequality, and underlying child health. Data from a systematic review report that the paediatric case fatality rate of SARS-CoV-2 is only 0.01% in high income countries compared to 0.24% in low- and middle-income countries.[20] In Denmark, two child fatalities have been registered within 30 days of a positive SARS-CoV-2 test, corresponding to a case fatality rate of 0.003%, however, it is unknown whether these cases were directly caused by SARS-CoV-2 infection.[21] Compared to the few previous studies providing population-based data on the risk of hospitalisation following SARS-CoV-2 infection, the reported risks was similar to that of Israel and Spain (0.2 to 0.5%) , but lower than those reported from the UK (1.3%), and the US (5.7%).[8,22–24] Both the case fatality rate and risk of hospitalisation are, however, influenced by access to testing for SARS-CoV-2 and are likely to be overestimates of the true risk. A Danish SARS-CoV-2 seroprevalence study have estimated that the true prevalence of SARS-CoV-2 infection among adolescents is 3-5 fold higher than that detected by national RT-PCR tests.[18] Assuming that the vast majority of undetected cases are asymptomatic or mild, the true risk of hospitalisation following SARS-CoV-2 infection could be considerably lower than the 0.5% reported in this study. When using registry data or other surveillance databases, there is also an issue of distinguishing between children hospitalised for COVID-19 and children hospitalised with a pre-admission screening test positive for SARS-CoV-2. Previous studies reported that 40-45% of hospitalisations registered to COVID-19 were not related to diseases caused by SARS-CoV-2.[25] Of note, when we restricted our definition of COVID-19 related hospitalisations to those who were admitted for at least 24 hours and had a discharge diagnosis of COVID-19, the risk of hospitalisations was reduced five-fold.

Generally, we observed low risks of serious outcomes to SARS-CoV-2 infection in our high-income setting with low health and socioeconomic inequalities. We found that neuroimmune complications were exceedingly rare while MIS-C occurred in 0.5 per 1000 documented SARS-CoV-2 infections, which is similar to other population-based estimates. [26–28] Previous studies have identified obesity and Black and Hispanic race as important risk factors for severe COVID-19 and MIS-C.[23,24,28] This needs to be considered when generalizing our results, as Denmark is a predominantly ethnic white society with a low prevalence of childhood obesity.[29]

The long-term consequences of COVID-19 in children and adolescents are still largely unknown and much debated. There is an increasing amount of literature reporting on persisting symptoms following infection, such as fatigue, headache, myalgia, cough and sleep disturbances persisting in anywhere from 4 to 66% of children with SARS-CoV-2 infection.[30] Recently released data from a UK Office of National Statistics survey, report a prevalence of persisting symptoms in 0.12 to 0.62% of children after 12 weeks.[31] However, case definitions vary and studies are limited by small numbers, highly selected populations, low response rates, or lack of control groups. The discussion on persisting symptoms after SARS-CoV-2 infection is further complicated by the lack of similar data on persisting symptoms after other common respiratory virus infections and by these symptoms being highly prevalent in childhood, which may have been exaggerated by the negative effects of lockdown measures on children's well-being.[30,32–34] We did not have information on symptom-based outcomes, but we observed, that SARS-CoV-2 positive children visited their general practitioner more often during follow-up compared to the reference cohort, possibly indicating persistent symptoms, although absolute differences in risk were small. Likewise, we identified an increased risk one to six months after SARS-CoV-2 infection of initiating treatment with inhaled corticosteroids, which could be related to persistent dyspnoea and cough. However, when we compared SARS-CoV-2 positive cases to children who were also tested for SARS-CoV-2, likely often due to respiratory symptoms, the association diminished, which could imply that the observed

signals are not specifically related to SARS-CoV-2 , but to respiratory infections in general. Future studies are, however, needed to elucidate whether post-infectious complaints are more frequent after SARS-CoV-2 infection compared to other endemic respiratory viruses.

In a non-controlled setting where the delta variant was predominant, this study estimated a high effectiveness of the BNT162b2 vaccine of preventing documented SARS-CoV-2 infection in adolescents. Our estimates were similar to those reported from Israeli data of 90% (95% CI, 88 to 92) 7 to 21 days after the second dose, and we also showed that vaccine effectiveness remained high for up to 90 days after vaccination.

Policy implications

The implications of our study results for regulators are complex. Our data adds to the existing evidence that SARS-CoV-2 infection in children and adolescents is generally mild with low risks of adverse events, although MIS-C occurs in 1 of 2000 children with RT-PCR documented SARS-CoV-2 infection. However, we also demonstrate that BNT162b2 is highly effective in preventing SARS-CoV-2 infection in adolescents. Importantly, while the risk of adverse events to SARS-CoV-2 infection is low in children, vaccination can be indirectly beneficial by providing families with a sense of security and by contributing to a normalization of children's everyday life without testing requirements, risk of isolation, school closures and other restrictions. From a public health perspective, childhood vaccination against SARS-CoV-2 may also be favourable in order to reduce transmission and reach the desired level of herd immunity. The benefits of vaccination should, however, be considered in the context of multiple factors including adverse events, availability of vaccines, regional control of the epidemic, and emerge of new SARS-CoV-2 variants.

Conclusion

In conclusion, we found that the absolute risks of hospitalisation, ICU admission and serious post-acute complications to SARS-CoV-2 infection in children and adolescents

were generally low in a high-income country as Denmark with free access to health care. Children with documented SARS-CoV-2 infection had a slightly increased risk of initiating therapy with inhaled corticosteroids one month to six months after SARS-CoV-2 infection, and they visited their general practitioner more often, which could indicate persistent symptoms following infection. While our findings are generally reassuring, further large, population-based studies are still urgently needed to provide additional data on both short- and long-term morbidity following SARS-CoV-2 among children and adolescents. Real-world effectiveness of the BNT162b2 vaccine among adolescents was high in our setting. Such information is important to ensure a qualified discussion of future protective measures including the value of mass vaccination programmes against SARS-CoV-2 among children and adolescents.

Ethical approval

According to Danish law, patient consent or approval by an ethics review board are not required for studies based entirely on registry data. However, the study was approved by the institutional data protection board at the University of Southern Denmark (11/247) and by the Danish Health Data Authority (FSEID-00005447).

Transparency

The lead author (HK) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained. The study was registered in the Real World Evidence Registry (https://osf.io/7ejh5) prior to the commencement of statistical analyses and amendments to the analysis plan are also provided at this site.

Role of funding source

The authors received no specific funding for this work.

Contributors

HK, LCL and AP conceptualised the study, and MH and LGS provided important input to the methodology and data interpretation. LCL performed the data analysis, and LCL and AP verified the underlying data and code. HK drafted the original manuscript, and all authors critically revised the manuscript and approved the final version for publication. HK and AP are the guarantors. The corresponding author attests that all listed authors meet authorship criteria.

Competing interests

AP report funds paid to his institution for participation in research projects funded by Alcon, Almirall, Astellas, AstraZeneca, Boehringer Ingelheim, Novo Nordisk, Servier, and

LEO Pharma, outside the the current work. LCL reports funds paid to his institution for participation in research projects funded by Menarini Pharmaceuticals and LEO Pharma, outside the current work. HK, MH and LGS declare no competing interests.

Data sharing

Data on the prevalence of SARS-CoV-2 variants are available from "Our World in Data" (https://github.com/owid/covid-19-data/tree/master/public/data), which are based on genome sequencing data from GISAID (https://www.gisaid.org/). Individual level data cannot be shared by the authors due to Danish data protection regulations. De-identified data can be made available for authorized researchers after application to Forskerservice at The Danish Health Data Authority.

Acknowledgments

We thank Morten Olesen from the University of Southern Denmark for review of the source code used in this study.

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Figure legends

Figure 1: Overview of the SARS-CoV-2 epidemic in Danish children and adolescents.

Panel (A) Average daily number of SARS-CoV-2 positive individuals under 18 years during the epidemic, stratified on age. Panel (B) Average daily number of RT-PCR tests among individuals under 18 years during the epidemic, stratified on age. Panel (C) Number of weekly hospitalizations among individuals under 18 years during the epidemic, stratified on age. Panel (D) Vaccination uptake in adolescents ages 12 to 15 and 16 to 17 years.

Figure 2: Absolute risks and adjusted risk differences and risk ratios for hospital-based, diagnosis-based outcomes, and initiation of new medication during follow-up in SARS-CoV-2 positive children and a reference cohort sampled among children tested for SARS-CoV-2.

Because of Danish legislation, counts less than five cannot be reported. Risk differences (RD) and risk ratios (RR) are propensity-score weighted estimates adjusted for age, sex, calendar time, gestational age, comorbidities and current drug use as specified in appendix.

MIS-C=Multiinflammatory syndrome in children. NSAIDs= non-steroidal anti-inflammatory drugs.

†MIS-C is reported as a combined endpoint of MIS-C and Kawasaki disease. The ICD-10 diagnosis code for MIS-C was not implemented in Denmark until late in the epidemic. Therefore, cases of Kawasaki disease occurring within two months of SARS-CoV-2 infection were considered as MIS-C.

Figure 3: Cumulative incidence of RT-PCR test confirmed SARS-CoV-2 infection

Cumulative incidence curve for documented SARS-CoV-2 infection in adolescents aged 12-17 years vaccinated with BNT162b2 and matched unvaccinated adolescents, starting from the day of administration of the first vaccine dose.

Tables

Table 1: Baseline characteristics of children and adolescents with documented SARS-CoV-2 infection, stratified one whether the infection led to hospitalization within the first month after a positive SARS-CoV-2 RT-PCR test.

	Non-hospitalised (n=60,373)	Hospitalised (n=319)
Demographics		
Median age (IQR)	11 (7-15)	9 (1-15)
Age category (years)		
0-1	2,784 (4·6)	98 (31)
2-5	7,890 (13)	37 (12)
6-11	19,786 (33)	59 (18)
12-15	17,828 (30)	64 (20)
16-17	12,085 (20)	61 (19)
Female sex	29,337 (49)	160 (50)
Temporality		
First wave	889 (1·5)	32 (10)
Second wave	34,869 (58)	159 (50)
Alpha-dominant	20,596 (34)	106 (33)
Delta-dominant	4,019 (6·7)	22 (6·9)
Perinatal history		
Prematurity (28-37 weeks)	2,914 (4·8)	35 (11)
Immaturity (<28 weeks)	134 (0·2)	n<5
Small for gestational age	767 (1·3)	9 (2·8)
Low birth weight (<2500g)	1,936 (3·2)	25 (7·8)
Medical history		
Asthma	3,588 (5·9)	29 (9·1)
Other chronic respiratory diseases	387 (0·6)	8 (2·5)
Chronic cardiac disease	314 (0·5)	7 (2·2)
Diabetes mellitus	148 (0·2)	n<5
Autoimmune disorders	717 (1·2)	12 (3·8)
Epilepsy or convulsions	2,861 (4·7)	31 (9·7)
Congenital malformations and chromosomal abnormalities	1,649 (2·7)	30 (9·4)
Malignancy or immunodeficiency	278 (0·5)	9 (2·8)
Psychiatric disorders	3,867 (6·4)	51 (16)
Number of comorbidities		
0	46,075 (76)	194 (61)
1	10,517 (17)	64 (20)
2+	3,781 (6·3)	61 (19)
Hospital admissions within the last year		
0	60,181 (100)	294 (92)
1	184 (0·3)	NR
2+	8 (0·0)	n<5
Current drug use†		
Short-acting beta-2 agonists	2,489 (4·1)	32 (10)
Inhaled corticosteroids	2,083 (3·5)	20 (6·3)
Leukotriene D4-receptor antagonists	363 (0·6)	5 (1·6)

Nasal corticosteroids	2,827 (4·7)	11 (3·4)
Systemic antihistamines	2,909 (4·8)	16 (5·0)
Systemic corticosteroids	134 (0·2)	n<5
Systemic antibiotics		
0	52,854 (88)	239 (75)
1	5,210 (8·6)	45 (14)
2+	2,309 (3·8)	35 (11)
Paracetamol	1,476 (2·4)	32 (10)
NSAIDs	1,356 (2·2)	17 (5·3)
Number of unique drugs		
0	32,970 (55)	107 (34)
1	13,478 (22)	74 (23)
2+	13,925 (23)	138 (43)

Data are n(%) unless stated otherwise. Data on race and socioeconomic status are not available from our data sources. NR=not reported because of Danish data protection law. NSAIDs=non-steroidal anti-inflammatory drugs. †Defined as having redeemed a prescription for the drug of interest during one year prior to the start of follow-up.

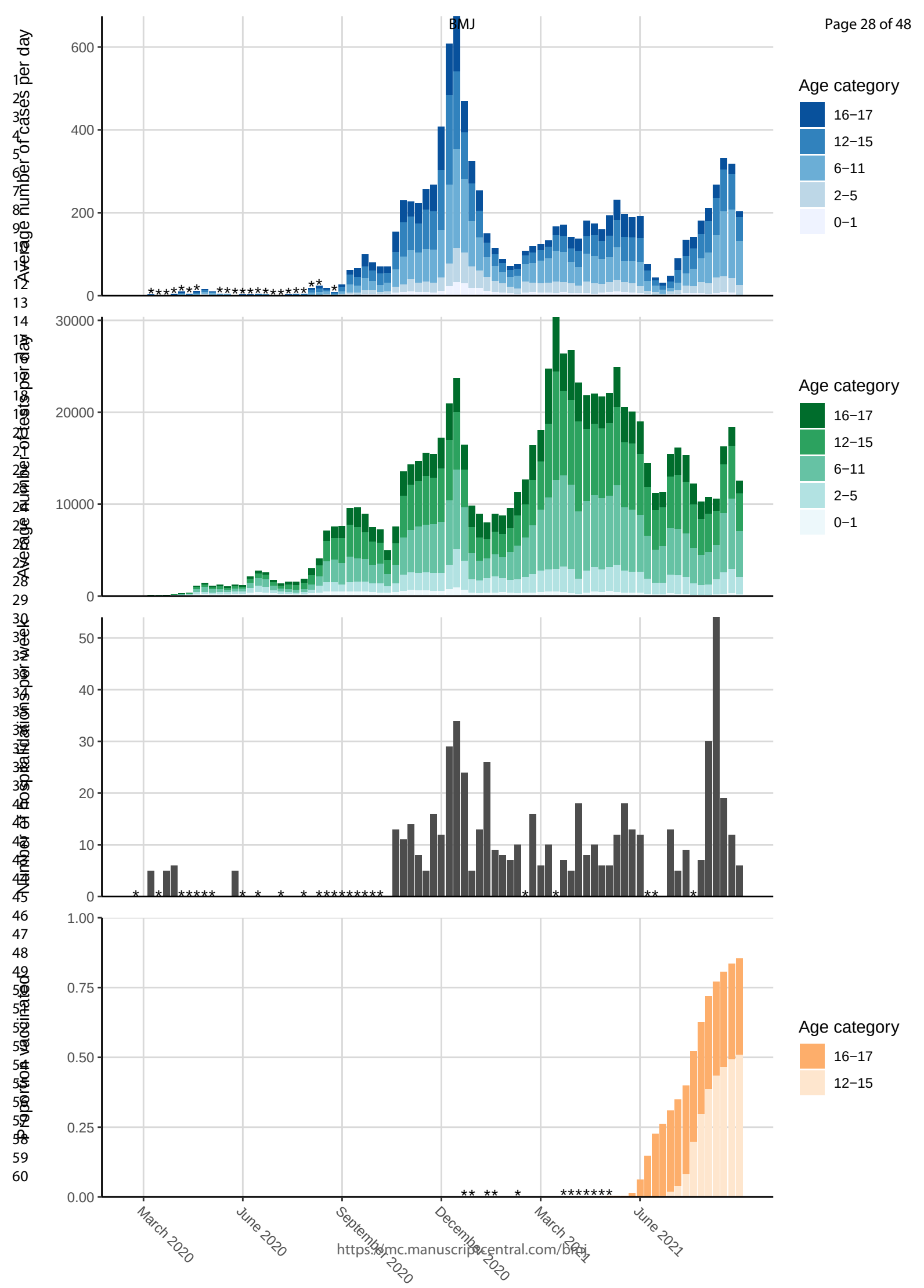
Table 2: Rates of health care services 6 months to 1 month before and 1 to 6 months after the index date.

	SARS-CoV-2 positive		Reference cohort†		
	Rate/1000 individuals (total visits)				
Visit type	**Baseline**	**Follow-up**	**Baseline**	**Follow-up**	**PERR (95% CI)**
Hospital admission‡	22 (876)	19 (753)	25 (11410)	19 (8670)	1.13 (0.99-1.27)
Paediatric admission	10 (399)	10 (375)	11 (5142)	9 (4161)	1.16 (0.97-1.35)
General practitioner	949 (37247)	802 (31469)	978 (442146)	763 (345058)	1.08 (1.07-1.10)
Outpatient	373 (14638)	364 (14276)	379 (171441)	363 (164196)	1.03 (0.98-1.08)
Paediatric outpatient	57 (2230)	55 (2143)	57 (25925)	55 (24787)	1.01 (0.95-1.06)
Private practicing specialist	155 (6099)	167 (6551)	158 (71527)	165 (74716)	1.02 (0.98-1.05)

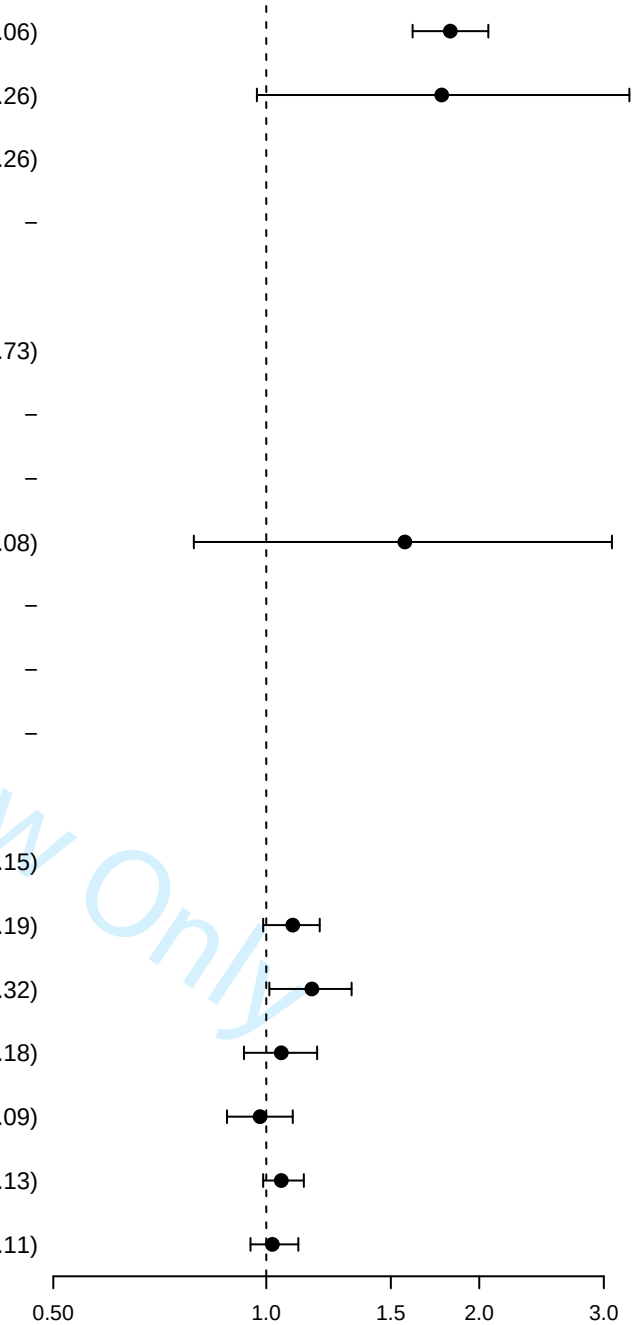
Rates are reported as the number of events per 1000 individuals under 18 years during the baseline period and follow-up. PERR=prior event rate ratio adjusted rate ratio.

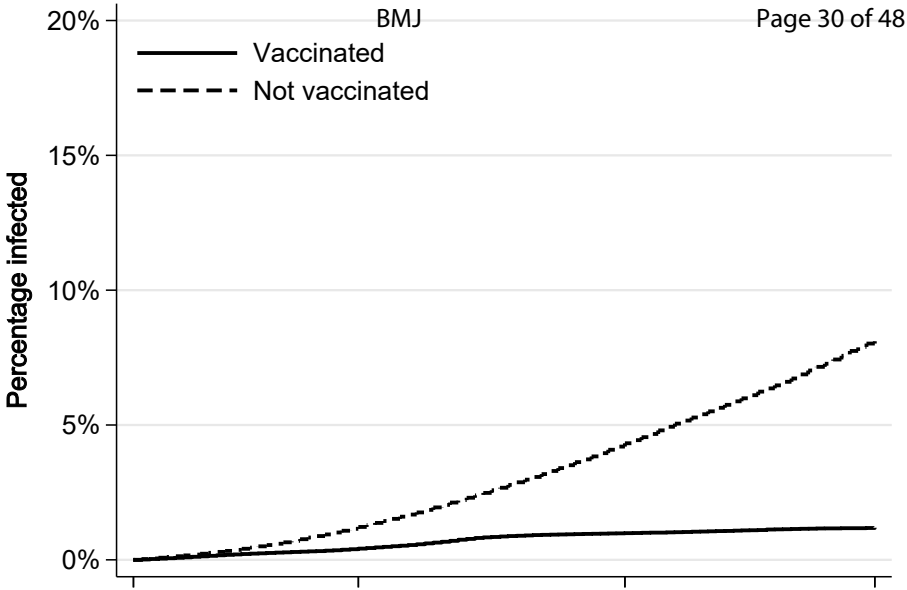
† Children sampled from the entire cohort of children tested for SARS-CoV-2 during the study period.

‡ Admissions are defined as any physical hospital contact with a duration of 12 hours or more.


Average number of cases per day
600
400
200
0
Age category
16–17
12–15
6–11
2–5
0–1
Average number of tests per day
30000
20000
10000
0
Age category
16–17
12–15
6–11
2–5
0–1
Number of hospitalisations per week
50
40
30
20
10
0
Proportion vaccinated
1.00
0.75
0.50
0.25
0.00
Age category
16–17
12–15
March 2020
June 2020
September 2020
December 2020
March 2021
June 2021

Outcome	Events	Risk (%)	Events	Risk (%)	RD (95% CI)	RR 95% CI
Follow up: 30 days						
Hospital admission	294/60475	0.49	2044/700908	0.29	0.22 (0.16, 0.28)	1.82 (1.61, 2.06)
Intensive care unit admission	12/60521	0.02	85/701062	0.01	0.01 (−0.00, 0.02)	1.77 (0.97, 3.26)
Mechanical ventilation	5/60642	0.01	20/702761	0.00	0.01 (−0.00, 0.01)	3.81 (1.41, 10.26)
Renal replacement therapy	n<5	–	0/703763	0.00	–	–
Follow up: 60 days						
MIS−C	27/56780	0.05	9/655493	0.00	0.05 (0.03, 0.06)	37.42 (19.25, 72.73)
Myocarditis	0/NR	0.00	n<5	–	–	–
Venous thromboembolism	n<5	–	n<5	–	–	–
Pneumonia	9/53193	0.02	97/618586	0.02	0.01 (−0.01, 0.02)	1.57 (0.79, 3.08)
Guillian−Barré syndrome	n<5	–	n<5	–	–	–
Encephalitis	0/56783	0.00	n<5	–	–	–
Other neuroimmune disorders	0/56797	0.00	n<5	–	–	–
Follow up: 1−6 months						
Long−COVID	51/39244	0.13	32/452192	0.01	0.12 (0.09, 0.16)	19.01 (12.84, 28.15)
Short−acting beta−2 agonists	460/37438	1.23	5751/428285	1.34	0.10 (−0.01, 0.21)	1.09 (0.99, 1.19)
Inhaled corticosteroids	231/37775	0.61	2778/434859	0.64	0.08 (0.00, 0.16)	1.16 (1.01, 1.32)
Paracetamol	295/38183	0.77	2961/439457	0.67	0.03 (−0.06, 0.12)	1.05 (0.93, 1.18)
NSAIDs	362/38330	0.94	3739/442280	0.85	−0.02 (−0.12, 0.08)	0.98 (0.88, 1.09)
Antibiotics for respiratory tract infections	916/35083	2.61	10493/402844	2.60	0.14 (−0.04, 0.31)	1.05 (0.99, 1.13)
Other antibiotics	625/37433	1.67	5877/434591	1.35	0.04 (−0.09, 0.18)	1.02 (0.95, 1.11)





Individuals at risk:

Vaccinated	219776	218911	119015	9587
Not vaccinated	2454727	1099770	340635	22325

Supplementary material

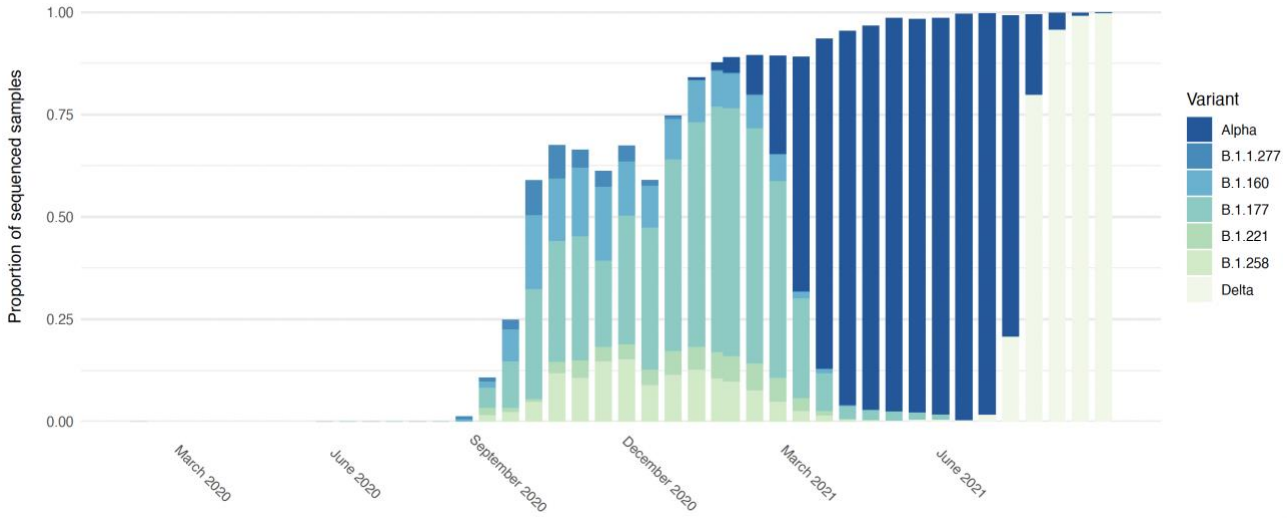
Supplement to: Kildegaard H, Lund LC, Højlund M, Stensballe LG, Pottegård A. Comprehensive assessment of paediatric SARS-CoV-2 infection: a Danish population-based cohort study.

Appendix

Figures

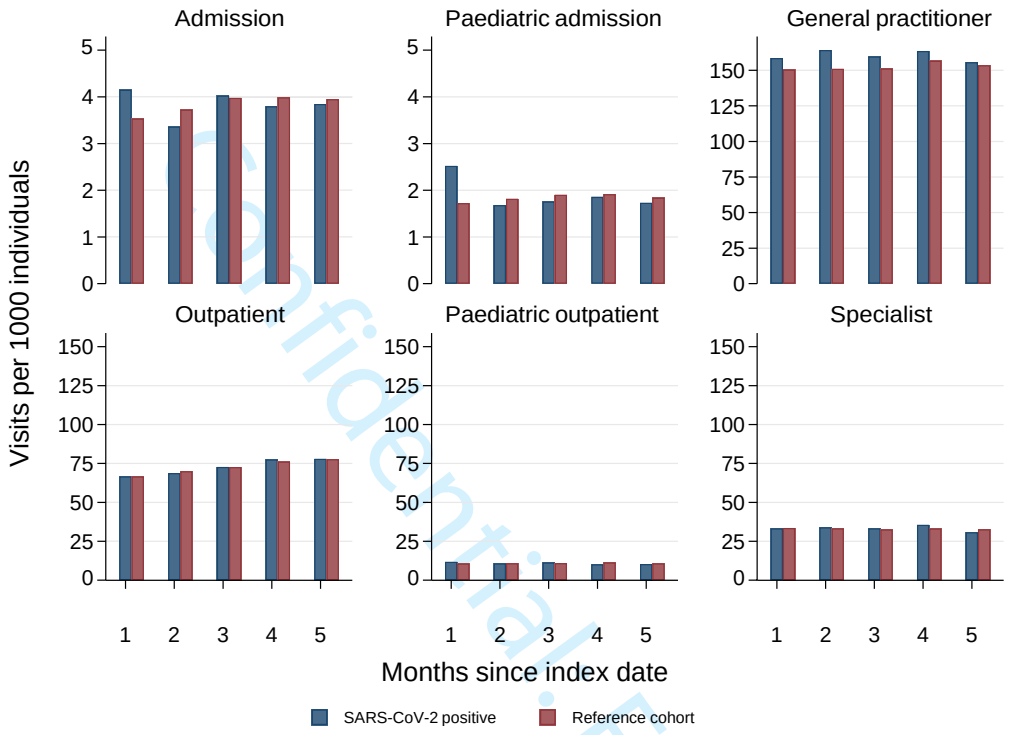
Tables

Figure S1: Distribution of SARS-CoV-2 variants during the epidemic



Data on the prevalence of SARS-CoV-2 variants over time were based on data from the Global Initiative on Sharing All Influenza Data (GISAID). [1]

Figure S1. Bar chart of health care utilisation



The figure illustrates the monthly rates for six types of healthcare visits during follow up among SARS-CoV-2 positive children and the reference cohort. Each bar illustrates the monthly rate, e.g. month 1 is day 30-59, month 2 day 60-89.
Specialist = Visit at a primary care dermatologist, ENT-specialist or ophthalmologist.
Outpatient = Physical hospital contact with a duration of less than 6 hours.
Admission = Physical hospital contact with a duration of 12 hours or more.

Table S1. ICD-10 and ATC codes used to define outcomes

	Coding system	Codes
Diagnosis-based outcomes		
Myocarditis	ICD-10	I40, I41, I514
MIS-C†	ICD-10	B972B, M303
Venous thromboembolism	ICD-10	I26, I801, I802, I803, I808. I809, I822, I823, I829
Pneumonia	ICD-10	A481, B012, J12-J18, J100
Guillian-Barré syndrome	ICD-10	G610
Encephalitis	ICD-10	A858, A869, G04-05
Other neuroimmune disorders	ICD-10	G35, G360, G368, G369, G373, G378, G379, H46
Hospital referral for suspicion of sequelae after COVID-19 infection	ICD-10	B948A, Z038Q
Medication outcomes		
Short-acting beta2-agonists	ATC	R03AC02-4, R03AL01-02, R03CC02
Inhaled corticosteroids	ATC	R03BA, R03AK, R03AL08, R03AL09
Paracetamol	ATC	N02BE01
NSAIDs	ATC	M01 excl. M01AX
Antibiotics for respiratory tract infections	ATC	J01CA04, J01CE02, J01CR02, J01FA
Other antibiotics	ATC	J01 excl. J01CE02, J01CA04, J01CR02, J01FA

Information on diagnoses representing possible complications from SARS-CoV-2 infection was obtained from inpatient and outpatient hospital diagnoses recorded in the Danish National Patient Registry.[2] Use of prescription drugs was identified from the Danish National Prescription Registry.[3] †MIS-C is a combined endpoint of MIS-C and Kawasaki disease. The ICD-10 diagnosis code for MIS-C was not implemented in Denmark until April 1, 2021. Therefore, cases of Kawasaki disease occurring within two months of SARS-CoV-2 infection were considered as MIS-C.

Abbreviations:
ICD-10 = International Classification of Diseases and Health Related Problems, 10th revision
ATC = Anatomical Therapeutical Chemical Classification
NSAIDs = Non-steroidal anti-inflammatory drugs.
COVID-19 = Coronavirus disease 2019.
MIS-C = Multisystem inflammatory syndrome in children

Table S2. ICD-10 and ATC codes used to define baseline covariates

	Coding system	Codes
Perinatal history		
Prematurity	ICD-10	P073
Immaturity	ICD-10	P072
Small for gestational age	ICD-10	P050
Low birth weight	ICD-10	P070, P071
Comorbidities		
Asthma	ICD-10	J45-46
Other chronic respiratory diseases	ICD-10	E84, J41-44, J47, J84, P27
Chronic cardiac disease	ICD-10	I05-08, I20-28, I34-37, I42-49, I50-51
Renal disease	ICD-10	N03, N05, N07, N18, N19, N25-27
Diabetes	ICD-10	E10-14
Autoimmune disease, not including diabetes	ICD-10	D510, D590, D591, D690, D693, D86 E035, E039, E050, E055, E059, E063, E065, E271, E272, E310 G04, G131, G35, G36, G61, G700 H20 I00-I02 K50, K51, K732, K743, K900 L10, L12, L130, L40, L63, L80 M05-06, M08, M30, M311, M313, M315-7, M32-34, M350-M353, M358-M359, M45, M60
Epilepsy or convulsions	ICD-10	G40, R56
Congenital malformations and chromosomal abnormalities	ICD-10	Q00-07, Q20-28, Q30-34, Q60-64, Q90-99
Malignancy or immunodeficiency	ICD-10	C00-96, D70-72, D730, D81-84
Psychiatric disorder	ICD-10	Any chapter F diagnosis
Current drug use		
Short-acting beta2-agonists	ATC	R03AC02-4, R03AL01-02, R03CC02
Inhaled corticosteroids	ATC	R03BA, R03AK, R03AL08, R03AL09
Leukotrine D4-receptor antagonists	ATC	R03DC
Nasal corticosteroids	ATC	R01AD
Systemic antihistamines	ATC	R06A
Systemic corticosteroids	ATC	H02AB
Systemic antibiotics, no. of prescription fills (0,1,+2)	ATC	J01
Paracetamol	ATC	N02BE01
NSAIDs	ATC	M01 excl. M01AX

Information on medical history was obtained from inpatient and outpatient hospital diagnoses recorded in the Danish National Patient Registry.[2] Use of prescription drugs was identified from the Danish National Prescription Registry.[3]
Abbreviations:
ICD-10 = International Classification of Diseases and Health Related Problems, 10th revision
ATC = Anatomical Therapeutical Chemical Classification
NSAIDs = Non-steroidal anti-inflammatory drugs.

Table S3 Number of hospitalisations during the different stages of the epidemic among children tested positive for SARS-CoV-2

	SARS-CoV-2 positive		
	Admissions	N	Risk (%)
Period			
First wave	32	921	(3.5)
Second wave	159	35,028	(0.5)
Alpha variant	106	20,702	(0.5)
Delta variant	22	4041	(0.5)

First wave = 27 February 2020 to 31 July 2020
Second wave = 1 August 2020 to 28 February 2021
Alpha variant dominating period = 1 March 2021 to 30 June 2021
Delta variant dominating period = 1 July 2021 to 31 August 2021
Information on hospital visits was obtained from the Danish National Patient Registry.[2]

Table S4. Baseline characteristics of SARS-CoV-2 tested children and adolescents before and after propensity score weighting.

	SARS-CoV-2 positive (n=60,692)	Reference cohort (n=703,786)	SMD	Reference cohort (weighted) (n=60,688)	SMD
Demographics					
Median age (IQR)	11 (7-15)	10 (5-14)	0·24	12 (7-15)	0·00
Age category (years)					
0-1	2,882 (4·7)	46,044 (6·5)	0·08	2,486 (4·1)	0·03
2-5	7,927 (13)	135,048 (19)	0·17	8,681 (14)	0·04
6-11	19,845 (33)	241,193 (34)	0·03	19,104 (31)	0·03
12-15	17,892 (29)	187,859 (27)	0·06	18,543 (31)	0·02
16-17	12,146 (20)	93,642 (13)	0·18	11,875 (20)	0·01
Female sex	29,497 (49)	342,741 (49)	0·00	29,493 (49)	0·00
Temporality					
First wave	921 (1·5)	10,717 (1·5)	0·00	905 (1·5)	0·00
Second wave	35,028 (58)	404,373 (57)	0·01	34,768 (57)	0·01
Alpha-dominant	20,702 (34)	238,772 (34)	0·00	20,674 (34)	0·00
Delta-dominant	4,041 (6·7)	49,924 (7·1)	0·02	4,342 (7·2)	0·02
Perinatal history					
Prematurity (28-37 weeks)	2,9494·9)	38,011 (5·4)	0·02	3,178 (5·2)	0·02
Immaturity (<28 weeks)	NR	1,778 (0·3)	-	144 (0·2)	-
Small for gestational age	776 (1·3)	10,897 (1·5)	0·02	777 (1·3)	0·00
Low birth weight (<2500g)	1,961 (3·2)	24,280 (3·4)	0·01	1,964 (3·2)	0·00
Medical history					
Asthma	3,617 (6·0)	42,388 (6·0)	0·00	3,615 (6·0)	0·00
Other chronic respiratory diseases	395 (0·7)	5,135 (0·7)	0·01	395 (0·7)	0·00
Chronic cardiac disease	321 (0·5)	3,239 (0·5)	0·01	321 (0·5)	0·00
Diabetes mellitus	NR	2,067 (0·3)	-	151 (0·2)	-
Autoimmune disorders	729 (1·2)	7,965 (1·1)	0·01	729 (1·2)	0·00
Epilepsy or convulsions	2,892 (4·8)	33,732 (4·8)	0·00	2,890 (4·8)	0·00
Congenital malformations and chromosomal abnormalities	1,679 (2·8)	20,202 (2·9)	0·01	1,681 (2·8)	0·00
Malignancy or immunodeficiency	287 (0·5)	3,340 (0·5)	0·00	287 (0·5)	0·00
Psychiatric disorders	3,918 (6·5)	49,108 (7·0)	0·02	3,922 (6·5)	0·00
Number of comorbidities					
0	46,269 (76)	530,807 (75)	0·02	46,154 (76)	0·00
1	10,581 (17)	124,598 (18)	0·01	10,609 (17)	0·00
2+	3,842 (6·3)	48,381 (6·9)	0·02	3,926 (6·5)	0·01
Hospital admissions within the last year					
0	60,475 (100)	700,908 (100)	0·01	60,474 (100)	0·00
1	NR	2,647 (0·4)	-	198 (0·3)	-
2+	NR	231 (0·0)	-	17 (0·0)	-
Current drug use					
Short-acting beta-2 agonists	2,521 (4·2)	33,765 (4·8)	0·03	2,516 (4·1)	0·00
Inhaled corticosteroids	2,103 (3·5)	25,579 (3·6)	0·01	2,101 (3·5)	0·00
Leukotriene D4-receptor antagonists	368 (0·6)	4,661 (0·7)	0·01	368 (0·6)	0·00
Nasal corticosteroids	2,838 (4·7)	30,056 (4·3)	0·02	2,837 (4·7)	0·00
Systemic antihistamines	2,925 (4·8)	32,998 (4·7)	0·01	2,923 (4·8)	0·00
Systemic corticosteroids	NR	1,328 (0·2)	-	136 (0·2)	-
Systemic antibiotics					
0	53,093 (87)	618,953 (88)	0·01	53,094 (87)	0·00

1	5,255 (8·7)	58,650 (8·3)	0·01	5,254 (8·7)	0·00
2+	2,344 (3·9)	26,183 (3·7)	0·01	2,341 (3·9)	0·00
Paracetamol	1,508 (2·5)	18,335 (2·6)	0·01	1,510 (2·5)	0·00
NSAIDs	1,373 (2·3)	14,648 (2·1)	0·01	1,373 (2·3)	0·00
Number of unique drugs					
0	33,077 (54)	383,707 (55)	0·00	32,917 (54)	0·01
1	13,552 (22)	159,769 (23)	0·01	13,620 (22)	0·00
2+	14,063 (23)	160,310 (23)	0·01	14,151 (23)	0·00

Data are n(%) unless stated otherwise. Data on race and socioeconomic status are not available from our data sources. SMD=standardized mean difference. IQR=Interquartile range. NR=not reported because of Danish data protection laws. NSAIDs=non-steroidal anti-inflammatory drugs. †Defined as having redeemed a prescription for the drug of interest during one year prior to the start of follow-up.

Table S5 Risk of health care utilisation

The table provides the number of individuals with six types of healthcare visits during one to six months of follow up among SARS-CoV-2 positive children and the reference cohort.

	SARS-CoV-2 positive (N=39255)		Reference cohort (N=452206)	
Visit type	**Events**	**Risk, %**	**Events**	**Risk, %**
Admission	613	1.6	7077	1.6
Paediatric admission	317	0.8	3547	0.8
General practitioner	16368	41.7	183645	40.6
Outpatient	7127	18.2	82298	18.2
Paediatrc outpatient	1523	3.9	18364	4.1
Specialist	4266	10.9	49618	11.0

Admission = Physical hospital contact with a duration of 12 hours or more.
Outpatient = Physical hospital contact with a duration of less than 6 hours.
Specialist = Visit at a primary care dermatologist, ENT-specialist or ophthalmologist.
Information on inpatient and outpatient hospital visits was obtained from the Danish National Patient Registry.[2] Data on visits at general practitioners and private practicing specialists was obtained from the Danish National Health Service Register.[4]

Table S6. Baseline characteristics of SARS-CoV-2 positive and test-negative children and adolescents before and after propensity score weighting.

	SARS-CoV-2 positive (n=60,692)	SARS-CoV-2 negative (n=606,435)	SMD	SARS-CoV-2 negative (weighted) (n=60,642)	SMD
Demographics					
Median age (IQR)	11 (7-15)	12 (7-15)	0·03	11 (7-15)	0·00
Age category (years)					
0-1	2,882 (4·7)	20,915 (3·4)	0·07	2,436 (4·0)	0·04
2-5	7,927 (13)	78,479 (13)	0·00	8,639 (14)	0·03
6-11	19,845 (33)	197,826 (33)	0·00	19,369 (32)	0·02
12-15	17,892 (29)	195,650 (32)	0·06	18,100 (30)	0·01
16-17	12,146 (20)	113,565 (19)	0·03	12,099 (20)	0·00
Female sex	29,497 (49)	307,037 (51)	0·04	29,472 (49)	0·00
Temporality					
First wave	921 (1·5)	9,334 (1·5)	0·00	945 (1·6)	0·00
Second wave	35,028 (58)	349,622 (58)	0·00	35,122 (58)	0·00
Alpha-dominant	20,702 (34)	207,042 (34)	0·00	20,560 (34)	0·00
Delta-dominant	4,041 (6·7)	40,437 (6·7)	0·00	4,014 (6·6)	0·00
Perinatal history					
Prematurity (28-37 weeks)	2,949 (4·9)	32,063 (5·3)	0·02	3,133 (5·2)	0·01
Immaturity (<28 weeks)	NR	1,494 (0·2)	-	139 (0·2)	-
Small for gestational age	776 (1·3)	8,473 (1·4)	0·01	775 (1·3)	0·00
Low birth weight (<2500g)	1,961 (3·2)	20,502 (3·4)	0·01	1,958 (3·2)	0·00
Medical history					
Asthma	3,617 (6·0)	41,233 (6·8)	0·03	3,614 (6·0)	0·00
Other chronic respiratory diseases	395 (0·7)	4,244 (0·7)	0·01	395 (0·7)	0·00
Chronic cardiac disease	321 (0·5)	3,290 (0·5)	0·00	321 (0·5)	0·00
Diabetes mellitus	NR	2,051 (0·3)	-	151 (0·2)	-
Autoimmune disorders	729 (1·2)	8,440 (1·4)	0·02	729 (1·2)	0·00
Epilepsy or convulsions	2,892 (4·8)	30,761 (5·1)	0·01	2,891 (4·8)	0·00
Congenital malformations and chromosomal abnormalities	1,679 (2·8)	17,576 (2·9)	0·01	1,678 (2·8)	0·00
Malignancy or immunodeficiency	287 (0·5)	3,507 (0·6)	0·01	287 (0·5)	0·00
Psychiatric disorders	3,918 (6·5)	46,369 (7·6)	0·05	3,915 (6·5)	0·00
Number of comorbidities					
0	46,269 (76)	448,845 (74)	0·05	46,116 (76)	0·00
1	10,581 (17)	113,933 (19)	0·04	10,638 (18)	0·00
2+	3,842 (6·3)	43,657 (7·2)	0·03	3,888 (6·4)	0·00
Hospital admissions within the last year					
0	60,475 (100)	603,375 (99)	0·02	60,347 (100)	0·02
1	NR	2,731 (0·5)	-	265 (0·4)	-
2+	NR	329 (0·1)	-	31 (0·1)	-
Current drug use					
Short-acting beta-2 agonists	2,521 (4·2)	29,415 (4·9)	0·03	2,520 (4·2)	0·00
Inhaled corticosteroids	2,103 (3·5)	23,883 (3·9)	0·03	2,103 (3·5)	0·00
Leukotriene D4-receptor antagonists	368 (0·6)	4,783 (0·8)	0·02	368 (0·6)	0·00
Nasal corticosteroids	2,838 (4·7)	33,774 (5·6)	0·04	2,836 (4·7)	0·00
Systemic antihistamines	2,925 (4·8)	33,250 (5·5)	0·03	2,923 (4·8)	0·00
Systemic corticosteroids	NR	1,631 (0·3)	-	136 (0·2)	-
Systemic antibiotics					
0	53,093 (87)	526,571 (87)	0·02	53,048 (87)	0·00

1	5,255 (8·7)	53,443 (8·8)	0·01	5,257 (8·7)	0·00
2+	2,344 (3·9)	26,421 (4·4)	0·02	2,338 (3·9)	0·00
Paracetamol	1,508 (2·5)	16,050 (2·6)	0·01	1,506 (2·5)	0·00
NSAIDs	1,373 (2·3)	16,307 (2·7)	0·03	1,372 (2·3)	0·00
Number of unique drugs					
0	33,077 (54)	392,539 (65)	0·21	39,722 (66)	0·23
1	13,552 (22)	107,650 (18)	0·11	10,883 (18)	0·11
2+	14,063 (23)	106,246 (18)	0·14	10,037 (17)	0·17

Data are n(%) unless stated otherwise. Data on race and socioeconomic status are not available from our data soruces. SMD=standardized mean difference. IQR=Interquartile range. NR=not reported because of Danish data protection laws. NSAIDs=non-steroidal anti-inflammatory drugs. †Defined as having redeemed a prescription for the drug of interest during one year prior to the start of follow-up.

Table S7. Absolute risks and adjusted risk differences and risk ratios for hospital-based, diagnosis-based outcomes, and initiation of new medication during follow-up in SARS-CoV-2 positive children and a comparator cohort of SARS-CoV-2 test-negative children and adolescents.

	SARS-CoV-2 positive		SARS-CoV-2 negative			
Outcome	**Events**	**Risk (%)**	**Events**	**Risk (%)**	**RD (95% CI)**	**RR 95% CI**
Follow up: 30 days						
Hospital admission	294/60475	0.49	5268/603375	0.87	-0.39 (-0.45, -0.33)	0.56 (0.50, 0.63)
Intensive care unit admission	12/60521	0.02	216/604543	0.04	-0.02 (-0.03, -0.00)	0.56 (0.31, 1.01)
Mechanical ventilation	5/60642	0.01	73/605690	0.01	-0.00 (-0.01, 0.00)	0.68 (0.27, 1.70)
Renal replacement therapy	n<5	-	n<5	-	-	-
Follow up: 60 days						
MIS-C†	27/56780	0.05	21/567754	0.00	0.04 (0.03, 0.06)	12.00 (6.53, 22.04)
Myocarditis	0/NR	0.00	5/568077	0.00	-	-
Venous thromboembolism	n<5	-	7/568038	0.00	-	-
Pneumonia	9/53193	0.02	192/532318	0.04	-0.02 (-0.03, -0.01)	0.44 (0.22, 0.86)
Guillian-Barré syndrome	n<5	-	0/568061	0.00	-	-
Encephalitis	0/56783	0.00	7/567801	0.00	-	-
Other neuroimmune disorders	0/56797	0.00	7/567974	0.00	-	-
Follow up: 1-6 months						
Long-COVID	51/39244	0.13	28/392118	0.01	0.12 (0.09, 0.16)	19.19 (12.00, 30.69)
Short-acting beta-2 agonists	460/37438	1.23	4599/369373	1.25	-0.04 (-0.16, 0.08)	0.97 (0.88, 1.07)
Inhaled corticosteroids	231/37775	0.61	2548/375158	0.68	-0.06 (-0.15, 0.02)	0.90 (0.79, 1.03)
Paracetamol	295/38183	0.77	3194/379473	0.84	-0.04 (-0.14, 0.05)	0.95 (0.84, 1.07)
NSAIDs	362/38330	0.94	4193/380081	1.10	-0.13 (-0.23, -0.03)	0.88 (0.79, 0.98)
Antibiotics for respiratory tract infections	916/35083	2.61	8999/344854	2.61	-0.04 (-0.21, 0.14)	0.99 (0.92, 1.05)
Other antibiotics	625/37433	1.67	6872/371102	1.85	-0.14 (-0.28, -0.00)	0.92 (0.85, 1.00)

Because of Danish legislation, counts less than five cannot be reported. Risk differences (RD) and risk ratios (RR) are propensity-score weighted estimates adjusted for age, sex, calendar time, gestational age, comorbidities and current drug use as specified in appendix.

MIS-C=Multiinflammatory syndrome in children. NSAIDs= non-steroidal anti-inflammatory drugs.

†MIS-C is reported as a combined endpoint of MIS-C and Kawasaki disease. The ICD-10 diagnosis code for MIS-C was not implemented in Denmark until late in the epidemic. Therefore, cases of Kawasaki disease occurring within two months of SARS-CoV-2 infection were considered as MIS-C.

Table S8. Rates of health care services 6 months to 1 month before and 1 to 6 months after the index date in SARS-CoV-2 positive and test-negative children and adolescents.

	SARS-CoV-2 positive		SARS-CoV-2 negative		
	Rate/1000 individuals (total visits)				
Visit type	**Baseline**	**Follow-up**	**Baseline**	**Follow-up**	**PERR (95% CI)**
Admission	22 (876)	19 (753)	25 (9947)	22 (8691)	0.98 (0.87-1.09)
Paediatric admission	10 (399)	10 (375)	12 (4664)	10 (3941)	1.11 (0.92-1.31)
GP	949 (37247)	802 (31469)	1,057 (414653)	838 (328773)	1.07 (1.05-1.09)
Outpatient	373 (14638)	364 (14276)	427 (167463)	428 (167800)	1.03 (0.97-1.08)
Paediatric outpatient	57 (2230)	55 (2143)	62 (24499)	63 (24600)	0.96 (0.89-1.02)
Specialist	155 (6099)	167 (6551)	165 (64657)	173 (67738)	0.97 (0.94-1.01)

Rates are reported as the number of events per 1000 individuals under 18 years during the baseline period and follow-up. PERR=prior event rate ratio adjusted rate ratio. Admissions are defined as any physical hospital contact with a duration of 12 hours or more.

Table S9. Demographic characteristics of Danish vaccine recipients aged 12 to 17 years

	Vaccine recipients N=321,467
Vaccine	
ChAdOx1-S	255 (0.1%)
BNT162b2	319,769 (99.5%)
Ad26.COV2-S	40 (0.0%)
mRNA-1273	1,403 (0.4%)
Completed vaccination programme*	265,520 (82.6%)
Birthyear	
2002	13,913 (4.3%)
2003	54,500 (17.0%)
2004	55,648 (17.3%)
2005	52,856 (16.4%)
2006	46,023 (14.3%)
2007	41,115 (12.8%)
2008	37,595 (11.7%)
2009	19,791 (6.2%)
2010 or later	26 (0.0%)
Male sex	162,534 (50.6%)
Region	
Capital	92,211 (28.7%)
Mid Jutland	78,142 (24.3%)
Northern Jutland	33,835 (10.5%)
Zealand	47,184 (14.7%)
Southern Denmark	70,095 (21.8%)
Immigration status	
First generation	9,306 (2.9%)
Second generation	13,881 (4.3%)

Characteristics of all Danish vaccine recipients vaccinated against SARS-CoV-2 before or on 31 august 2021. Data on vaccination status was obtained from The Danish Vaccination Register.[5]
* Received two vaccine doses for all vaccines, except Ad26.COV2-S.

Table S10. Demographic characteristics on BNT162b2 vaccine recipients included in analyses

	1st dose of BNT162b2 (N=219,776)	Unvaccinated (N=2,454,727)	2nd dose of BNT162b2 (N=1,979	Unvaccinated N=22,306
Birthyear				
2002	10,728 (4.9%)	123,689 (5.0%)	244 (12.3%)	2,790 (12.5%)
2003	45,475 (20.7%)	523,264 (21.3%)	638 (32.2%)	7,427 (33.3%)
2004	47,604 (21.7%)	534,790 (21.8%)	559 (28.2%)	6,145 (27.5%)
2005	43,791 (19.9%)	485,573 (19.8%)	501 (25.3%)	5,554 (24.9%)
2006	25,651 (11.7%)	280,978 (11.4%)	17 (0.9%)	170 (0.8%)
2007	20,941 (9.5%)	228,491 (9.3%)	7 (0.4%)	70 (0.3%)
2008	17,758 (8.1%)	193,137 (7.9%)	8 (0.4%)	90 (0.4%)
2009	7,812 (3.6%)	84,625 (3.4%)	n < 5	NR
2010 or later	16 (0.0%)	180 (0.0%)	n < 5	NR
Male sex	110,763 (50.4%)	1,233,989 (50.3%)	922 (46.6%)	10,451 (46.9%)
Region				
Capital	60,830 (27.7%)	692,754 (28.2%)	1,040 (52.6%)	11,933 (53.5%)
Mid Jutland	53,379 (24.3%)	591,464 (24.1%)	377 (19.1%)	4,190 (18.8%)
Northern Jutland	24,465 (11.1%)	270,332 (11.0%)	111 (5.6%)	1,119 (5.0%)
Zealand	32,037 (14.6%)	360,759 (14.7%)	208 (10.5%)	2,352 (10.5%)
Southern Denmark	49,065 (22.3%)	539,418 (22.0%)	243 (12.3%)	2,712 (12.2%)
Immigration status				
First generation	4,951 (2.3%)	137,733 (5.6%)	39 (2.0%)	1,219 (5.5%)
Second generation	7,888 (3.6%)	227,010 (9.2%)	92 (4.6%)	2,955 (13.2%)

Characteristics of BNT162 recipients and unvaccinated peers included in analyses. Recipients of the first dose were included until 11 August 2021. Recipients of the second dose were included until 2 July 2021 to ensure a follow-up of minimum 60 days.

Table S11. Effectiveness of BNT162b2 vaccine among adolescents 12 thorough 17 years.

	Vaccinated		Unvaccinated		Vaccine effectiveness* (95% CI)		
Follow up	**Events (no. at risk)**	**Risk, %**	**Events (no. at risk)**	**Risk, %**	**ITT**	**Censoring****	**IP-weighted**
Days 0-20 after first dose	665/219776	0.3	15178/2454727	0.6	45 (40-49)	65 (62-67)	66 (63-68)
Days 0-60 after second dose	10/1979	0.5	707/22306	3.2	81 (65-90)	88 (78-94)	88 (78-94)

* Vaccine effectiveness was calculated as 1 – risk ratio.
** Unvaccinated individuals who were vaccinated during follow up were excluded from the analysis.
ITT: Follow up emulated the intention to treat principle, i.e. individuals were followed according to the exposure status at the start of follow up, regardless of changes in the exposure status (unvaccinated individuals being vaccinated during follow up).
IP-weighted: Inverse probability of censoring weighted, i.e. individuals who completed follow up were weighted based on selected covariates to also represent censored individuals.

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