



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

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Comprehensive assessment of paediatric SARS-CoV-2 infection
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 (Pfizer-BioNTech) 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 October 2021 or vaccinated with the BNT162b2 mRNA vaccine until 02 October 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 961,977 children RT-PCR-tested for SARS-CoV-2 in Denmark, 74,611 (7.8%) tested positive for SARS-CoV-2. Among these, 0.49% (95% CI, 0.44 to 0.54) were hospitalised for 12 hours or more and 0.01% (0.01 to 0.03) received ICU treatment within 30 days of testing. The risk of MIS-C within two months of SARS-CoV-2 infection was 0.05% (0.03 to 0.06), 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, 1.06 to 1.10) increased rate of contacts with general practitioners compared to a reference cohort sampled among all children tested for SARS-CoV-2. Among 229,799 adolescents

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immunised with BNT162b2, the estimated vaccine effectiveness against documented SARS-CoV-2 infection was 62% (59 to 65) 20 days after the first dose and 93% (92 to 94) 60 days after the second dose, compared to unvaccinated adolescents.

Conclusions: The absolute risks of adverse events after SARS-CoV-2 infection were generally low in Danish children, although MIS-C occurred in 0.05% of children with PCR-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 with the delta variant 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 limitations, including low response rates and selection bias..

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 around 1 of 2200 children with PCR-documented SARS-CoV-2 infection.
- The BNT162b2 mRNA vaccine was effective in preventing documented SARS-CoV-2 infection three months after the first dose in the period where delta was the dominating SARS-CoV-2 strain.

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Introduction

One and a half year into the severe respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, more than 330 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.[2] Many countries initiated mass vaccinations programs against SARS-CoV-2 in adolescents 12 years of age or older during the summer of 2021, and recently extended these programmes for children 5 through 11 years of age when the BNT162b2 (Pfizer-BioNTech) COVID-19 vaccine was authorized for emergency use in this age group. All approved messenger RNA vaccines against SARS-CoV-2 are seemingly effective in inducing immunogenicity and preventing COVID-19, however, their ability to prevent immune-mediated complications to SARS-CoV-2 infection, including multisystem inflammatory syndrome (MIS-C), remains to be determined.[3–5] The decision to offer vaccines against COVID-19 to children and adolescents has been much debated. Childhood vaccination may be necessary to increase overall population immunity.[6] However, studies have consistently reported that SARS-CoV-2 infection in children is generally asymptomatic or mild, limiting the individual child’s benefit of vaccination.[7]

In this debate, 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. [8–12] We included all reverse-transcriptase polymerase chain reaction (RT-PCR) confirmed SARS-CoV-2 cases in Denmark until 31 October, 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. Using data from Danish large-scale genome sequencing of SARS-CoV-2 available from the Global Initiative in Sharing All Influenza Data (GISAID), we also evaluated the risk of study outcomes across dominating SARS-CoV-2 strains. [13,14] 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.

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. Throughout the epidemic, children and adolescents have been encouraged by the Danish Health Authorities to undergo PCR-testing in case of symptoms that could be related to SARS-CoV-2 or if they had been in close contact with individuals

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positive for SARS-CoV-2. From March 2021 to end of the school year in June 2021, school children 12 years of age or older were encouraged to undergo testing twice weekly, and these recommendations were reinstated in August 2021.

Use of antigen testing was very limited in children and adolescents until the spring of 2022 and has since been used mainly for children aged 12 years or above and only for asymptomatic testing. If tested positive on an antigen test, children were encouraged to undergo subsequent PCR-testing. 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 (99.6% 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 October 2021, or individuals under 18 years vaccinated with the BNT162b2 mRNA vaccine from 1 May to 02 October 2021 were eligible for inclusion. In all analyses, individuals were included if they completed follow up before or on 31 October 2021. As of October 1, 2021, the Danish population under 18 years consisted of 1,151,849 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. For comparison, we sampled a reference cohort from the entire cohort of children under the age of 18 who were tested for SARS-CoV-2 at some point 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 to ensure that the two cohorts were temporally aligned. To ensure full preexposure data on drug prescription use, hospitalisations and health care utilisation, children who were not living continuously in Denmark during the year prior to the index date were excluded. Children were further excluded from the reference cohort if they had previously been tested positive for SARS-CoV-2. 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. The test-negative comparator group was, however, not used in main analyses as children at the time of their negative test may not resemble the background population due to reasons for active testing for SARS-CoV-2 (e.g. symptoms, need of health care services, screening before contact to the health care system).

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 with hospitalisations related to the primary infection most likely to occur with the first month of infection, while immune-mediated complications such as MIS-C may occur weeks after the primary infection. No outcome was, however, reported across overlapping time periods. 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.[15] We also explored alternative definitions of hospitalisations as any hospital

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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 β 2-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 with an identity link. The propensity score model included age, sex, calendar time, immigration status, gestational age, comorbidities, and current drug use as defined in supplementary table S2. Age was modelled using restricted cubic splines with four knots. None of the included covariates had missing data.

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.[17] 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 $RR_{\text{Post-acute}} / RR_{\text{Baseline}}$ 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 59 days after the second dose. We excluded adolescents who tested positive for SARS-CoV-2 or were

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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 21 days or 60 days of follow-up after the first and second doses 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 the nature of this study, no patients or members of the public were involved in study design, conduct or reporting.

Results

Overview of the Danish SARS-CoV-2 epidemic

Between 27 February 2020 and 31 October 2021, 961,977 Danish children and adolescents were tested for SARS-CoV-2 in Denmark, and 74,611 tested positive, corresponding to 84% and 6.5% 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 78 and 47 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 October 72% of adolescents aged 12-15 years and 88% of 16-17 year-olds had begun vaccination against SARS-CoV-2 (Figure 1D).

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

Of the 74,611 SARS-CoV-2 positive children in Denmark, 391 were hospitalised within the first month of testing (0.5%). The proportion of hospitalisation was highest among the 0-1 year-olds (3.5%), and lower in the remaining age groups (0.3 to 0.5%) (Table 1). The risk of hospitalisation was similar across periods where the B.1.1.7, alpha and delta variant was predominant (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 (14%), prematurity (10%) and asthma (7.7%). Likewise, hospitalised children had a higher prevalence of prescription drug use one year prior to infection, particularly of asthma medication and systemic antibiotics, and 40% had redeemed prescriptions of at least two unique drugs. Children with SARS-CoV-2 infection were slightly older than children in the reference cohort and more likely to be immigrants, but on all other parameters children in the reference cohort resembled SARS-CoV-2 infected children (Table 1).

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=249/74,611) when requiring a visit longer than 24 hours, and to 0.1% (N=88/74,611), 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,

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with an adjusted risk difference (RD) of 0.20% (95% CI, 0.15 to 0.25) (Figure 2). The risk of ICU admission among SARS-CoV-2 positive cases was 0.01% (95% CI, 0.01 to 0.03) 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 32 cases of MIS-C (0.05% [95% CI, 0.03 to 0.06]). 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). As a post hoc analysis, we evaluated the risk of MIS-C by SARS-CoV-2 dominating variant and found that the risk of MIS-C was similar across periods dominated by the B.1.1.7 (0.04% [95% CI, 0.02 to 0.06]), alpha (0.04% [95% CI, 0.02 to 0.08]) and delta strain (0.04% [95% CI, 0.01 to 0.09]) (Supplementary Table S4)

In the post-acute phase from day 30 to 179 after testing, 0.12% (95% CI; 0.09 to 0.15) 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, 2.96% (95% CI, 2.81 to 3.13) initiated antibiotics used to treat respiratory infections, 1.30% (95% CI, 1.20 to 1.41) initiated treatment with short-acting β 2-agonists, and 0.91% (95% CI, 0.82 to 0.99) and 0.71% (95% CI, 0.64 to 0.79) with paracetamol and NSAIDs. Compared with the reference cohort, the adjusted risk difference was increased for initiation of treatment with antibiotics used for respiratory tract infections (RD +0.33, 0.17 to 0.49), short-acting β 2-agonists (RD +0.16, 0.05 to 0.27) and inhaled corticosteroids (RD +0.08, 0.00 to 0.15) (Figure 2).

Within the post-acute phase, 20,616 (42.1%) of children and adolescents with SARS-CoV-2 infection and 247,620 (40.7%) of comparators had visited their general practitioner, 1910 (3.9%) and 23,954 (3.9%) at paediatric outpatient clinics and 775 (1.6%) and 9369 (1.5%) were admitted to a hospital (supplementary Table S6). When comparing baseline and overall post-acute health care utilisation between SARS-CoV-2 positive children and comparators, we observed increased PERR-adjusted rate ratios for general

practitioner visits (1.08 [95% CI; 1.06 to 1.10]) and hospital admissions (1.15 [95% CI; 1.02-1.28]) (Table 2). SARS-CoV-2 positive cases only had increased rates of hospital admissions until four months 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 and antibiotics during the post-acute phase was also attenuated (supplementary table S8).

Vaccine effectiveness

Among Danish adolescents, 278,649 were vaccinated against COVID-19 with BNT162b2 with a median time between doses of 28 days (IQR 22 to 35). 229,799 individuals vaccinated with BNT162b2 were eligible for the first dose vaccine effectiveness analysis and 175,176 individuals were eligible for analysis of effectiveness after full immunisation (supplementary table S11). Figure 3 shows the cumulative incidence for documented SARS-CoV-2 infection. The estimated vaccine effectiveness against documented SARS-CoV-2 infection was 62% (95% CI; 59 to 65) 20 days after the first dose and 93% (95% CI; 92 to 94) 60 days after the second dose (supplementary Table S12). Sensitivity analyses showed no impact of informative censoring on results (supplementary Table S12). The frequency of PCR-testing for SARS-CoV-2 during follow-up was higher in unvaccinated adolescents than in vaccinated adolescents (1114 vs. 874 tests per 1000 persons per month) (post hoc analysis, Supplementary Table S13).

Discussion

Principal findings

In this study, we present nationwide data on all 74,611 RT-PCR-confirmed paediatric cases of SARS-CoV-2 in Denmark, finding that 0.5% of cases were admitted to a hospital and

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0.01% 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 0.05% of 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 93% 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. [18,19] 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.[20] 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.[21] 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.[22] 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%).[7,23–25] 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. Recent Danish SARS-CoV-2 seroprevalence studies have estimated that the true prevalence of SARS-CoV-2 infection among adolescents is up to 3 fold higher than that detected by national RT-PCR tests.[26] 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

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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.[27] 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 0.05% of documented SARS-CoV-2 infections, which is similar to other population-based estimates. [28–30] Previous studies have identified obesity and Black and Hispanic race as important risk factors for severe COVID-19 and MIS-C.[24,25,30] This needs to be considered when generalizing our results, as Denmark is a predominantly ethnic white society with a low prevalence of childhood obesity.[31]

The long-term consequences of COVID-19 in children and adolescents are still much debated. There is an increasing amount of literature reporting on persisting symptoms following infection, such as fatigue, headache, cognitive difficulties, myalgia, and cough persisting in anywhere from 4 to 66% of children with SARS-CoV-2 infection.[32] Because these symptoms are highly prevalent in childhood and adolescence and may have been exaggerated by the negative effects of lockdown measures on children’s well-being, comparison with non-SARS-CoV-2 infected individuals is crucial in order not to overestimate the prevalence of “long-COVID”. Emerging controlled studies on persistent symptoms after SARS-CoV-2 infection, all report increased risk of symptoms after both four and twelve weeks, but with wide ranges of prevalence and risk differences ranging from 0.8% to 13.1% among SARS-CoV-2 infected children and controls. [33–38] 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 with some

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4 impact of daily functioning, although absolute differences in risk were small. Likewise,
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6 we identified an increased risk one to six months after SARS-CoV-2 infection of initiating
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8 treatment with bronchodilating agents, which could be related to persistent dyspnoea and
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10 cough. However, when we compared SARS-CoV-2 positive cases to children who were
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12 also tested for SARS-CoV-2, likely often due to respiratory symptoms and required testing
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14 prior to contact with the health care system, the association diminished, which could
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16 imply that the observed signals are not specifically related to SARS-CoV-2, but to
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18 respiratory infections in general. Future studies are, however, needed to elucidate whether
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20 post-infectious complaints are more frequent after SARS-CoV-2 infection compared to
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22 other endemic respiratory viruses.
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25 In a non-controlled setting where the delta variant was predominant, this study
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27 estimated a high effectiveness of the BNT162b2 vaccine of preventing documented SARS-
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29 CoV-2 infection in adolescents. Our estimates were similar to those reported from Israeli
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31 data of 90% (95% CI, 88 to 92) 7 to 21 days after the second dose, and we also showed that
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33 vaccine effectiveness remained high 90 days after vaccination. [5]. Unvaccinated children
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35 had a higher frequency of PCR-testing for SARS-CoV-2 during follow-up, which is in part
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37 explained by recommendations that limited asymptomatic testing to unvaccinated
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39 adolescents during the fall of 2021, however, the vaccine effectiveness may be
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41 overestimated due to this limitation.
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45 Policy implications

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47 The implications of our study results for regulators are complex. Our data adds to the
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49 existing evidence that SARS-CoV-2 infection in children and adolescents is generally mild
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51 with low risks of adverse events, although MIS-C occurs in 0.05% of children with RT-PCR
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53 documented SARS-CoV-2 infection. However, we also demonstrate that BNT162b2 is
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55 highly effective in preventing SARS-CoV-2 infection in adolescents, and like in adults,
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57 vaccination may prevent COVID-19 related hospitalisations, although we did not observe
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59 enough hospitalisations during the study period to obtain meaningful risk estimates.
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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 normalisation 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 bronchodilating agents and antibiotics 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/xv8pt/?view_only=) prior to the commencement of statistical analyses and amendments to the analysis plan are also provided at this site. All analytical source code used can be obtained from <https://gitlab.sdu.dk/pharmacoepi/sars-cov-2-children/>.

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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

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Data sharing

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.

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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.

Denmark had national lock-downs including school closures in the spring of 2020 and from mid-December 2020 until March 2021. The first dotted line represents the date where testing without requisition became available for children over 12 years of age; the second dotted line when it came available to all children over 2 years. Throughout the epidemic, testing of children has mainly been recommended in case of symptoms and for close contacts of COVID-19. Marked areas indicate periods, where asymptomatic testing of school children (≥ 12 years) was encouraged.

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=Multisystem inflammatory 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.

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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 study individuals. Children and adolescents with documented SARS-CoV-2 infection are stratified by whether the infection led to hospitalization within the first month after a positive SARS-CoV-2 RT-PCR test.

	SARS-CoV-2 positive		Reference
	Hospitalised (n=391)	Non-hospitalised (n=74,220)	(n=920,893)
Demographics			
Median age (IQR)	8 (1-14)	11 (7-15)	10 (5-14)
Age category (years)			
0-1	119 (30)	3,250 (4.4)	59,481 (6.5)
2-5	49 (13)	9,616 (13)	181,411 (20)
6-11	76 (19)	26,565 (36)	315,599 (34)
12-15	79 (20)	21,610 (29)	243,994 (26)
16-17	68 (17)	13,179 (18)	120,408 (13)
Female sex	191 (49)	36,297 (49)	449,017 (49)
Immigration status			
1st generation	15 (3.8)	4,831 (6.5)	29,941 (3.3)
2nd generation	92 (24)	15,479 (21)	81,428 (8.8)
Temporality			
27 Feb 2020 to 31 Jul 2020	32 (8.2)	889 (1.2)	11,646 (1.3)
01 Aug 2021 to 31 Jan 2021	159 (41)	34,868 (47)	437,076 (47)
01 Feb 2021 to 30 Jun 2021	106 (27)	20,595 (28)	257,486 (28)
01 Jul 2021 to 31 Oct 2021	94 (24)	17,868 (24)	214,685 (23)
Perinatal history			
Prematurity (28-37 weeks)	40 (10)	3,142 (4.2)	44,277 (4.8)
Immaturity (<28 weeks)	n<5	156 (0.2)	2,152 (0.2)
Small for gestation<51 age	11 (2.8)	857 (1.2)	13,000 (1.4)
Low birth weight (<2500g)	30 (7.7)	2,130 (2.9)	28,502 (3.1)
Medical history			
Asthma	30 (7.7)	4,010 (5.4)	50,568 (5.5)
Other chronic respiratory diseases	10 (2.6)	460 (0.6)	6,488 (0.7)
Chronic cardiac disease	8 (2.0)	354 (0.5)	4,046 (0.4)
Diabetes mellitus	n<5	190 (0.3)	2,664 (0.3)
Autoimmune disorders	14 (3.6)	840 (1.1)	9,991 (1.1)
Epilepsy or convulsions	35 (9.0)	3,124 (4.2)	40,062 (4.4)
Congenital malformations and chromosomal abnormalities	34 (8.7)	1,937 (2.6)	25,127 (2.7)
Malignancy or immunodeficiency	13 (3.3)	330 (0.4)	4,179 (0.5)
Psychiatric disorders	55 (14)	4,509 (6.1)	63,844 (6.9)
Number of comorbidities			
0	238 (61)	57,896 (78)	706,834 (77)
1	85 (22)	12,169 (16)	156,760 (17)
2+	68 (17)	4,155 (5.6)	57,299 (6.2)
Hospital admissions within the last year			

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0	361 (92)	73,989 (100)	917,118 (100)
1	NR	221 (0.3)	3,543 (0.4)
2+	n<5	10 (0.0)	232 (0.0)
Current drug use			
Short-acting beta-2 agonists	38 (9.7)	2,985 (4.0)	44,040 (4.8)
Inhaled corticosteroids	24 (6.1)	2,477 (3.3)	33,142 (3.6)
Leukotriene D4-receptor antagonists	5 (1.3)	428 (0.6)	6,000 (0.7)
n<5sal corticosteroids	14 (3.6)	3,395 (4.6)	38,766 (4.2)
Systemic antihistamines	18 (4.6)	3,490 (4.7)	42,929 (4.7)
Systemic corticosteroids	n<5	160 (0.2)	1,661 (0.2)
Systemic antibiotics			
0	296 (76)	65,524 (88)	813,554 (88)
1	56 (14)	6,074 (8.2)	74,262 (8.1)
2+	39 (10.0)	2,622 (3.5)	33,077 (3.6)
Paracetamol	35 (9.0)	1,670 (2.3)	22,634 (2.5)
NSAIDs	19 (4.9)	1,591 (2.1)	18,990 (2.1)
Number of unique drugs			
0	143 (37)	41,474 (56)	506,281 (55)
1	91 (23)	16,320 (22)	208,584 (23)
2+	157 (40)	16,426 (22)	206,028 (22)

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.

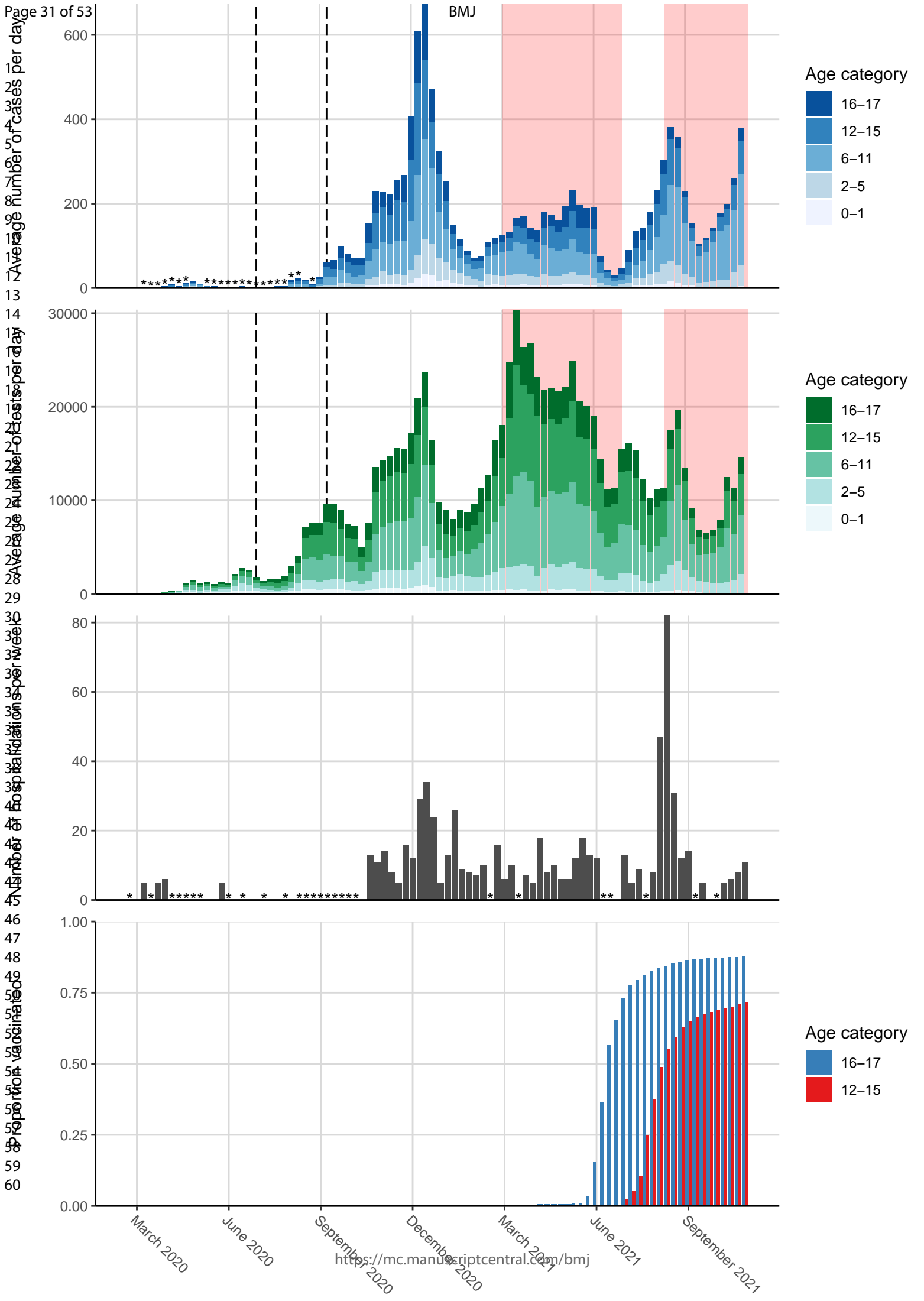
Table 2: Rates of health care services 6 months to 1 month before and 1 to 6 months after the index date.

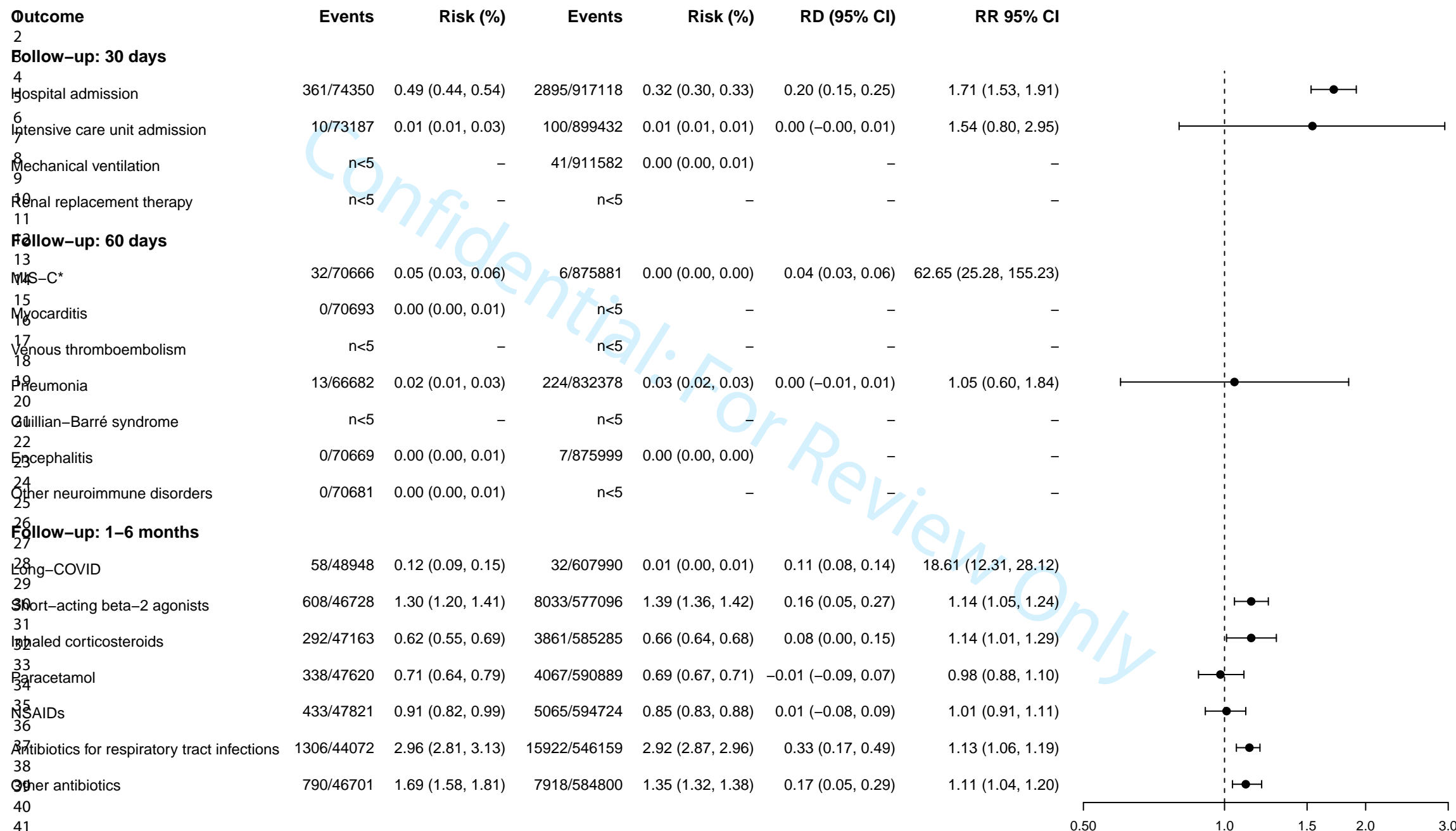
Visit type	SARS-CoV-2 positive		Reference		
	Rate/1000 individuals (total visits)				
	Baseline	Follow-up	Baseline	Follow-up	PERR (95% CI)
Admission	22 (1094)	19 (947)	25 (15056)	19 (11323)	1.15 (1.02-1.28)
Paediatric admission	10 (506)	10 (469)	11 (6622)	9 (5356)	1.15 (0.99-1.30)
General practitioner	913 (44722)	800 (39163)	932 (566365)	754 (458286)	1.08 (1.06-1.10)
Outpatient	366 (17929)	369 (18064)	373 (226938)	363 (220525)	1.02 (0.98-1.07)
Paediatric outpatient	57 (2783)	54 (2654)	56 (34202)	53 (32414)	1.01 (0.95-1.06)
Private practicing specialist	159 (7783)	164 (8038)	160 (97153)	161 (97992)	1.04 (1.01-1.07)

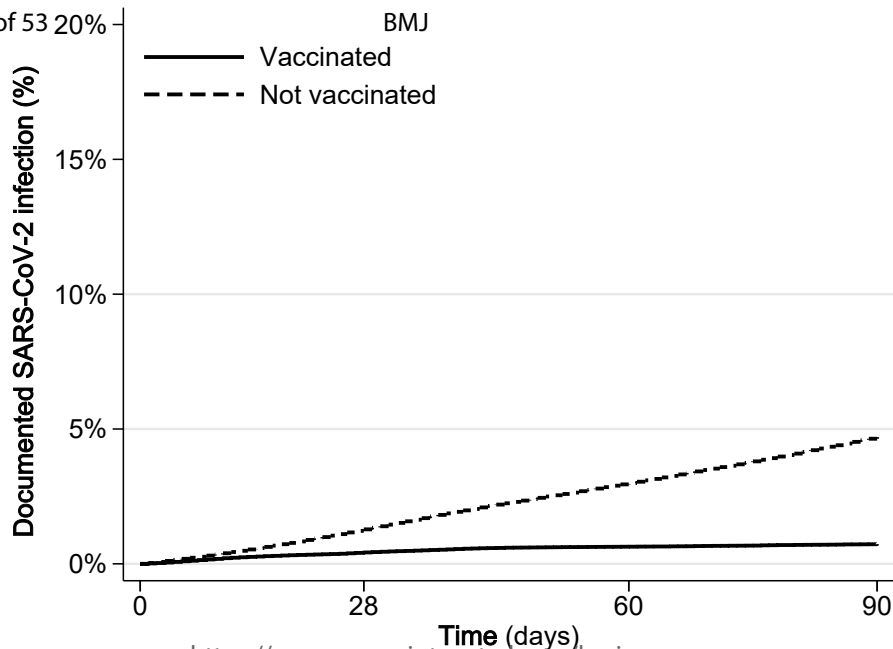
Rates are reported as the number of events per 1000 individuals under 18 years during the baseline period from day -179 to -30 before testing and the post-acute follow-up period from day +30 to +179 after testing. PERR=prior event rate ratio adjusted rate ratio.

† 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.







Individuals at risk:

Vaccinated 229799
Not vaccinated 2296231

<https://mc.manuscriptcentral.com/bmj>

228867
1262169

217695
876689

165493
481224

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.

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Appendix

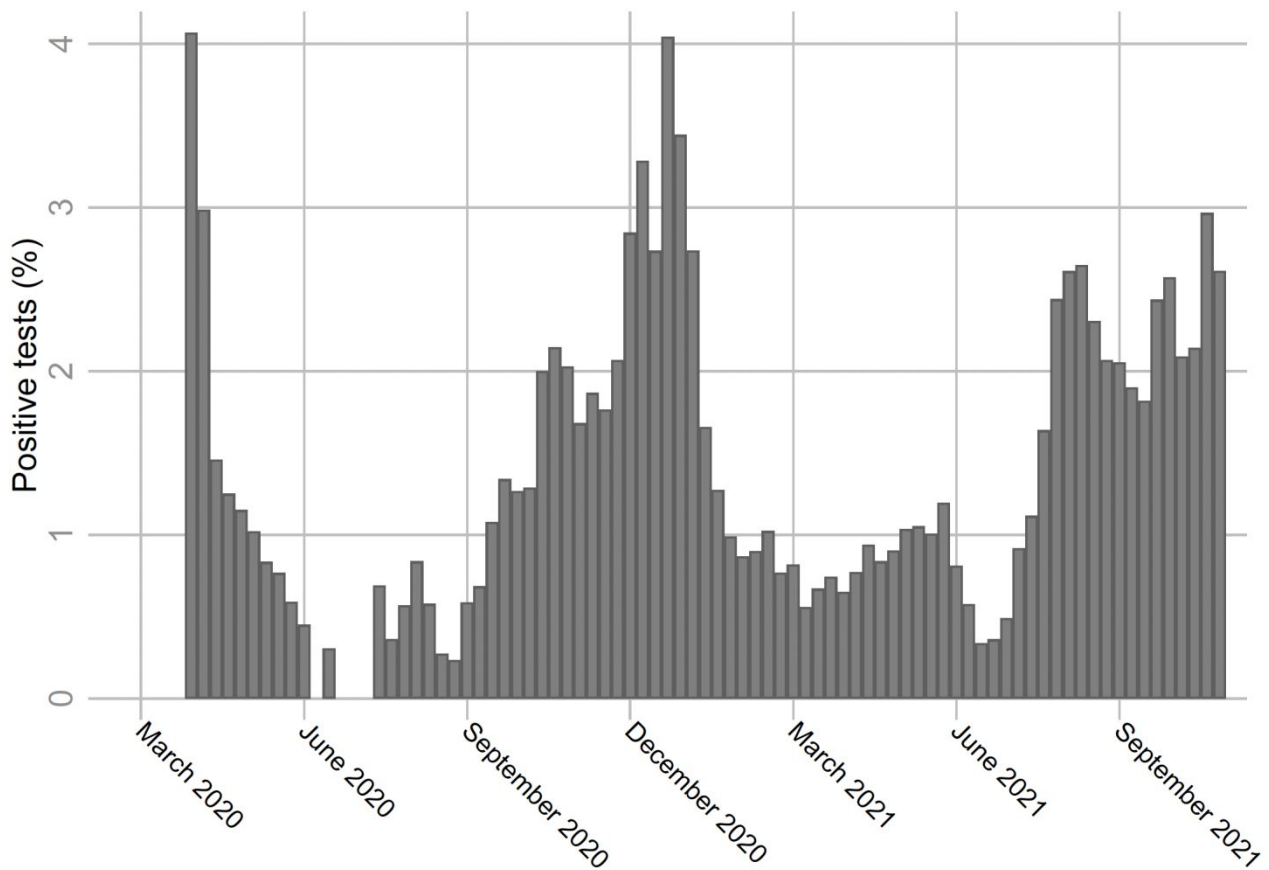
Figures

Figure S1: Weekly share of total SARS-CoV-2 tests that were positive during the epidemic
Figure S2: Bar charts of health care utilization 1 to 6 months following SARS-CoV-2 infection

Tables

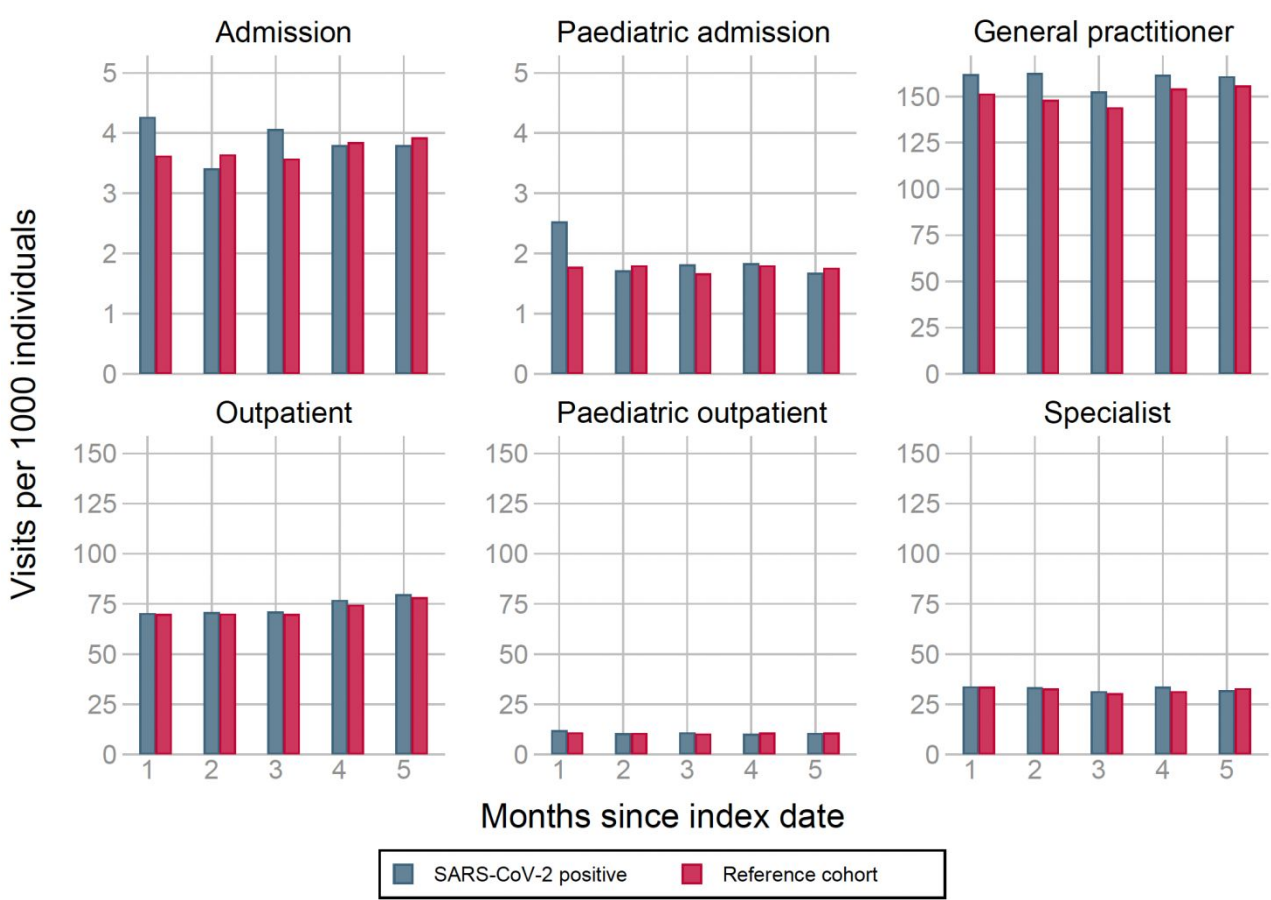
- Table S1. ICD-10 and ATC codes used to define outcomes
- Table S2. ICD-10 and ATC codes used to define baseline covariates
- Table S3. Number and percentage of individuals tested for SARS-CoV-2 of the total Danish child population, stratified on age.
- Table S4. Absolute risks of main study outcomes stratified by SARS-CoV-2 variant
- Table S5. Baseline characteristics of SARS-CoV-2 positive cases and children and adolescents in the reference cohort before and after propensity score weighting.
- Table S6. Rates of health care utilisation
- Table S7. Baseline characteristics of SARS-CoV-2 positive and test-negative children and adolescents before and after propensity score weighting.
- Table S8. Absolute risks, adjusted risk differences and risk ratios for outcomes during follow-up in SARS-CoV-2 positive children and a comparator cohort of SARS-CoV-2 test-negative children and adolescents.
- Table S9. 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.
- Table S10. Demographic characteristics of overall Danish vaccine recipients aged 12 to 17 years
- Table S11. Demographic characteristics of BNT162b2 vaccine recipients included in analyses
- Table S12. Effectiveness of the BNT162b2 vaccine among adolescents 12 through 17 years.
- Table S13. Rates of PCR-testing against SARS-CoV-2 in vaccinated and unvaccinated adolescents.

Figure S1: Weekly share of total SARS-CoV-2 tests that were positive during the epidemic



The weekly number of PCR-test confirmed paediatric SARS-CoV-2 cases as a share of the total number of PCR-tests performed in individuals <18 years.

Figure S2. 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 and so forth.

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.

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
Guillain-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.¹ Use of prescription drugs was identified from the Danish National Prescription Registry.² †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 Therapeutic Chemical Classification

MIS-C = Multisystem inflammatory syndrome in children

COVID-19 = Coronavirus disease 2019.

NSAIDs = Non-steroidal anti-inflammatory drugs.

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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 G40, R56 Q00-07, Q20-28, Q30-34, Q60-64, Q90-99
Epilepsy or convulsions	ICD-10	
Congenital malformations and chromosomal abnormalities	ICD-10	
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.¹ Use of prescription drugs was identified from the Danish National Prescription Registry.²

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 and percentage of individuals tested for SARS-CoV-2 of the total Danish child population, stratified on age.

Age	Tested (N)	Residents (N)	Tested (%)
0	8374	62551	13
1	32363	61708	52
2	44883	61819	73
3	45794	62628	73
4	47796	62063	77
5	49783	62658	79
6	50009	59239	84
7	51959	58674	89
8	53991	59497	91
9	56265	60761	93
10	59857	63632	94
11	63418	66795	95
12	64665	67160	96
13	66613	69256	96
14	65552	67691	97
15	66891	68881	97
16	67019	68548	98
17	66745	68288	98
Total	961977	1151849	84

Number of individuals < 18 years of age RT-PCR-tested for SARS-CoV-2 at some point until 30 October 2021 as a percentage of the total number of Danish residents < 18 years of age, evaluated on 01 October 2021. The total number of Danish residents < 18 years of age was obtained from Statistics Denmark.³

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Table S4: Absolute risks of main study outcomes stratified by SARS-CoV-2 variant

Outcome	Any variant		B.1.177		Alpha variant		Delta variant	
	Events	Risk (%)	Events	Risk (%)	Events	Risk (%)	Events	Risk (%)
Hospital admission	361/74350	0.49 (0.44, 0.54)	153/30798	0.50 (0.42, 0.58)	98/20102	0.49 (0.40, 0.59)	80/16649	0.48 (0.38, 0.60)
MIS-C†	32/70666	0.05 (0.03, 0.06)	11/30888	0.04 (0.02, 0.06)	9/20164	0.04 (0.02, 0.08)	5/12778	0.04 (0.01, 0.09)
Long-COVID	58/48948	0.12 (0.09, 0.15)	44/30894	0.14 (0.10, 0.19)	7/13009	0.05 (0.02, 0.11)	-	-
Initiation of prescription drugs								
Short-acting beta-2 agonists	608/46728	1.30 (1.20, 1.41)	328/29498	1.11 (1.00, 1.24)	202/12434	1.62 (1.41, 1.86)	-	-
Inhaled corticosteroids	292/47163	0.62 (0.55, 0.69)	169/29741	0.57 (0.49, 0.66)	79/12573	0.63 (0.50, 0.78)	-	-
Paracetamol	338/47620	0.71 (0.64, 0.79)	248/30099	0.82 (0.72, 0.93)	61/12648	0.48 (0.37, 0.62)	-	-
NSAIDs	433/47821	0.91 (0.82, 0.99)	280/30146	0.93 (0.82, 1.04)	104/12731	0.82 (0.67, 0.99)	-	-
Antibiotics for respiratory								
Tract infections	1306/44072	2.96 (2.81, 3.13)	679/27604	2.46 (2.28, 2.65)	493/12011	4.10 (3.76, 4.47)	-	-
Other antibiotics	790/46701	1.69 (1.58, 1.81)	510/29381	1.74 (1.59, 1.89)	200/12479	1.60 (1.39, 1.84)	-	-

Absolute risks of 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, stratified by dominating SARS-CoV-2 variant. Periods of dominating SARS-CoV-2 strain was defined based on Danish large-scale genome sequencing of SARS-CoV-2 provided by the Global Initiative in Sharing All Influenza Data to <https://covariants.org/per-country>.⁴ Because of limited number of events, stratification on SARS-CoV-2 variant was not possible for all study outcomes. Evaluation of Long-COVID and initiation of prescription drugs required six months of follow-up and was therefore not possible for the period dominated by the delta variant. MIS-C=Multisystem inflammatory syndrome in children. NSAIDs= non-steroidal anti-inflammatory drugs.

Table S5. Baseline characteristics of SARS-CoV-2 positive cases and children and adolescents in the reference cohort before and after propensity score weighting.

	SARS-CoV-2 positive (n=74,611)	Reference (n=920,893)	SMD	Reference (weighted) (n=74,559)	SMD
Demographics					
Median age (IQR)	11 (7-15)	10 (5-14)	0,22	11 (7-15)	0
Age category (years)					
0-1	3,369 (4.5)	59,481 (6.5)	0,09	2,759 (3.7)	0,04
2-5	9,665 (13)	181,411 (20)	0,18	10,984 (15)	0,05
6-11	26,641 (36)	315,599 (34)	0,03	25,229 (34)	0,04
12-15	21,689 (29)	243,994 (26)	0,06	22,735 (30)	0,03
16-17	13,247 (18)	120,408 (13)	0,13	12,853 (17)	0,01
Female sex	36,488 (49)	449,017 (49)	0	36,474 (49)	0
Immigration status					
1st generation	4,846 (6.5)	29,941 (3.3)	0,15	4,847 (6.5)	0
2nd generation	15,571 (21)	81,428 (8.8)	0,34	15,497 (21)	0
Temporality					
27 Feb 2020 to 31 Jul 2020	921 (1.2)	11,646 (1.3)	0	938 (1.3)	0
01 Aug 2021 to 31 Jan 2021	35,027 (47)	437,076 (47)	0,01	35,364 (47)	0,01
01 Feb 2021 to 30 Jun 2021	20,701 (28)	257,486 (28)	0	20,827 (28)	0
01 Jul 2021 to 31 Oct 2021	17,962 (24)	214,685 (23)	0,02	17,430 (23)	0,02
Perinatal history					
Prematurity (28-37 weeks)	3,182 (4.3)	44,277 (4.8)	0,03	3,320 (4.5)	0,01
Immaturity (<28 weeks)	NR	2,152 (0.2)	NR	172 (0.2)	NR
Small for gestational age	868 (1.2)	13,000 (1.4)	0,02	865 (1.2)	0
Low birth weight (<2500g)	2,160 (2.9)	28,502 (3.1)	0,01	2,159 (2.9)	0
Medical history					
Asthma	4,040 (5.4)	50,568 (5.5)	0	4,031 (5.4)	0
Other chronic respiratory diseases	470 (0.6)	6,488 (0.7)	0,01	471 (0.6)	0
Chronic cardiac disease	362 (0.5)	4,046 (0.4)	0,01	360 (0.5)	0
Diabetes mellitus	NR	2,664 (0.3)	NR	192 (0.3)	NR
Autoimmune disorders	854 (1.1)	9,991 (1.1)	0,01	854 (1.1)	0
Epilepsy or convulsions	3,159 (4.2)	40,062 (4.4)	0,01	3,152 (4.2)	0
Congenital malformations and chromosomal abnormalities	1,971 (2.6)	25,127 (2.7)	0,01	1,966 (2.6)	0
Malignancy or immunodeficiency	343 (0.5)	4,179 (0.5)	0	340 (0.5)	0
Psychiatric disorders	4,564 (6.1)	63,844 (6.9)	0,03	4,569 (6.1)	0
Number of comorbidities					
0	58,134 (78)	706,834 (77)	0,03	58,091 (78)	0
1	12,254 (16)	156,760 (17)	0,02	12,192 (16)	0
2+	4,223 (5.7)	57,299 (6.2)	0,02	4,276 (5.7)	0
Hospital admissions within the last year					
0	74,350 (100)	917,118 (100)	0,01	74,295 (100)	0
1	NR	3,543 (0.4)	NR	248 (0.3)	NR
2+	NR	232 (0.0)	NR	16 (0.0)	NR
Current drug use					
Short-acting beta-2 agonists	3,023 (4.1)	44,040 (4.8)	0,04	3,020 (4.1)	0
Inhaled corticosteroids	2,501 (3.4)	33,142 (3.6)	0,01	2,501 (3.4)	0
Leukotriene D4-receptor antagonists	433 (0.6)	6,000 (0.7)	0,01	433 (0.6)	0
Nasal corticosteroids	3,409 (4.6)	38,766 (4.2)	0,02	3,410 (4.6)	0
Systemic antihistamines	3,508 (4.7)	42,929 (4.7)	0	3,510 (4.7)	0

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Systemic corticosteroids	NR	1,661 (0.2)	NR	163 (0.2)	NR
Systemic antibiotics					
0	65,820 (88)	813,554 (88)	0	65,776 (88)	0
1	6,130 (8.2)	74,262 (8.1)	0,01	6,124 (8.2)	0
2+	2,661 (3.6)	33,077 (3.6)	0	2,659 (3.6)	0
Paracetamol	1,705 (2.3)	22,634 (2.5)	0,01	1,704 (2.3)	0
NSAIDs	1,610 (2.2)	18,990 (2.1)	0,01	1,605 (2.2)	0
Number of unique drugs					
0	41,617 (56)	506,281 (55)	0,02	41,753 (56)	0
1	16,411 (22)	208,584 (23)	0,02	16,385 (22)	0
2+	16,583 (22)	206,028 (22)	0	16,422 (22)	0

Data are n(%) unless stated otherwise. 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 S6 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.

Visit type	SARS-CoV-2 positive (N=48,962)		Reference (N=608,013)	
	Events	Risk, %	Events	Risk, %
Admission	775	1,6	9369	1,5
Paediatric admission	400	0,8	4584	0,8
General practitioner	20616	42,1	247620	40,7
Outpatient	9062	18,5	111810	18,4
Paediatric outpatient	1910	3,9	23954	3,9
Specialist	5271	10,8	65348	10,7

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.¹ Data on visits at general practitioners and private practicing specialists was obtained from the Danish National Health Service Register.⁵

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Table S7. Baseline characteristics of SARS-CoV-2 positive and test-negative children and adolescents before and after propensity score weighting.

	SARS-CoV-2 positive (n=74,611)	SARS-CoV-2 negative (n=745,540)	SMD	SARS-CoV-2 negative (weighted) (n=74,563)	SMD
Demographics					
Median age (IQR)	11 (7-15)	11 (7-15)	0,04	11 (7-15)	0,01
Age category (years)					
0-1	3,369 (4.5)	24,051 (3.2)	0,07	2,644 (3.5)	0,05
2-5	9,665 (13)	100,168 (13)	0,01	11,171 (15)	0,06
6-11	26,641 (36)	252,231 (34)	0,04	25,560 (34)	0,03
12-15	21,689 (29)	239,924 (32)	0,07	22,155 (30)	0,01
16-17	13,247 (18)	129,166 (17)	0,01	13,034 (17)	0,01
Female sex	36,488 (49)	376,509 (51)	0,03	36,447 (49)	0
Immigration status					
1st generation	4,846 (6.5)	17,020 (2.3)	0,21	4,847 (6.5)	0
2nd generation	15,571 (21)	51,364 (6.9)	0,41	15,567 (21)	0
Temporality					
27 Feb 2020 to 31 Jul 2020	921 (1.2)	9,315 (1.2)	0	926 (1.2)	0
01 Aug 2021 to 31 Jan 2021	35,027 (47)	349,707 (47)	0	35,656 (48)	0,02
01 Feb 2021 to 30 Jun 2021	20,701 (28)	206,934 (28)	0	19,735 (26)	0,03
01 Jul 2021 to 31 Oct 2021	17,962 (24)	179,584 (24)	0	18,246 (24)	0,01
Perinatal history					
Prematurity (28-37 weeks)	3,182 (4.3)	34,884 (4.7)	0,02	3,272 (4.4)	0,01
Immaturity (<28 weeks)	NR	1,699 (0.2)	NR	172 (0.2)	NR
Small for gestational age	868 (1.2)	9,248 (1.2)	0,01	865 (1.2)	0
Low birth weight (<2500g)	2,160 (2.9)	22,458 (3.0)	0,01	2,162 (2.9)	0
Medical history					
Asthma	4,040 (5.4)	46,211 (6.2)	0,03	4,028 (5.4)	0
Other chronic respiratory diseases	470 (0.6)	5,167 (0.7)	0,01	470 (0.6)	0
Chronic cardiac disease	362 (0.5)	3,790 (0.5)	0	359 (0.5)	0
Diabetes mellitus	NR	2,490 (0.3)	NR	192 (0.3)	NR
Autoimmune disorders	854 (1.1)	9,889 (1.3)	0,02	853 (1.1)	0
Epilepsy or convulsions	3,159 (4.2)	33,897 (4.5)	0,02	3,159 (4.2)	0
Congenital malformations and chromosomal abnormalities	1,971 (2.6)	20,205 (2.7)	0	1,967 (2.6)	0
Malignancy or immunodeficiency	343 (0.5)	4,112 (0.6)	0,01	340 (0.5)	0
Psychiatric disorders	4,564 (6.1)	55,279 (7.4)	0,05	4,575 (6.1)	0
Number of comorbidities					
0	58,134 (78)	564,033 (76)	0,05	58,076 (78)	0
1	12,254 (16)	133,309 (18)	0,04	12,240 (16)	0
2+	4,223 (5.7)	48,198 (6.5)	0,03	4,247 (5.7)	0
Hospital admissions within the last year					
0	74,350 (100)	741,852 (100)	0,02	74,179 (99)	0,03
1	NR	3,316 (0.4)	NR	346 (0.5)	NR
2+	NR	372 (0.0)	NR	38 (0.1)	NR
Current drug use					
Short-acting beta-2 agonists	3,023 (4.1)	35,912 (4.8)	0,04	3,033 (4.1)	0
Inhaled corticosteroids	2,501 (3.4)	29,379 (3.9)	0,03	2,506 (3.4)	0
Leukotriene D4-receptor antagonists	433 (0.6)	5,790 (0.8)	0,02	435 (0.6)	0
Nasal corticosteroids	3,409 (4.6)	40,617 (5.4)	0,04	3,403 (4.6)	0

Systemic antihistamines	3,508 (4.7)	40,253 (5.4)	0,03	3,514 (4.7)	0
Systemic corticosteroids	NR	1,867 (0.3)	NR	164 (0.2)	NR
Systemic antibiotics					
0	65,820 (88)	652,595 (88)	0,02	65,751 (88)	0
1	6,130 (8.2)	62,433 (8.4)	0,01	6,150 (8.2)	0
2+	2,661 (3.6)	30,512 (4.1)	0,03	2,663 (3.6)	0
Paracetamol	1,705 (2.3)	18,371 (2.5)	0,01	1,703 (2.3)	0
NSAIDs	1,610 (2.2)	19,145 (2.6)	0,03	1,602 (2.1)	0
Number of unique drugs					
0	41,617 (56)	391,948 (53)	0,06	40,882 (55)	0,02
1	16,411 (22)	168,331 (23)	0,01	16,739 (22)	0,01
2+	16,583 (22)	185,261 (25)	0,06	16,942 (23)	0,01

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.

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Table S8. Absolute risks, 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	361/74350	0.49 (0.44, 0.54)	6294/741852	0.85 (0.83, 0.87)	-0.38 (-0.44, -0.33)	0.56 (0.50, 0.62)
Intensive care unit admission	10/73187	0.01 (0.01, 0.03)	268/729013	0.04 (0.03, 0.04)	-0.03 (-0.04, -0.01)	0.35 (0.18, 0.66)
Mechanical ventilation	n<5	NR	93/737835	0.01 (0.01, 0.02)	-	-
Renal replacement therapy	n<5	NR	n<5	NR	-	-
Follow-up: 60 days						
MIS-C†	32/70666	0.05 (0.03, 0.06)	22/706031	0.00 (0.00, 0.00)	0.04 (0.03, 0.06)	11.55 (5.73, 23.28)
Myocarditis	0/70693	0.00 (0.00, 0.01)	11/706372	0.00 (0.00, 0.00)	-	-
Venous thromboembolism	n<5	NR	5/706324	0.00 (0.00, 0.00)	-	-
Pneumonia	13/66682	0.02 (0.01, 0.03)	304/667536	0.05 (0.04, 0.05)	-0.03 (-0.04, -0.02)	0.39 (0.22, 0.68)
Guillian-Barré syndrome	n<5	NR	n<5	NR	-	-
Encephalitis	0/70669	0.00 (0.00, 0.01)	8/706104	0.00 (0.00, 0.00)	-	-
Other neuroimmune disorders	0/70681	0.00 (0.00, 0.01)	n<5	NR	-	-
Follow-up: 1-6 months						
Long-COVID	58/48948	0.12 (0.09, 0.15)	35/489318	0.01 (0.00, 0.01)	0.11 (0.08, 0.14)	18.15 (11.46, 28.74)
Short-acting beta-2 agonists	608/46728	1.30 (1.20, 1.41)	5892/462410	1.27 (1.24, 1.31)	0.03 (-0.08, 0.14)	1.02 (0.94, 1.11)
Inhaled corticosteroids	292/47163	0.62 (0.55, 0.69)	3197/468427	0.68 (0.66, 0.71)	-0.06 (-0.14, 0.02)	0.91 (0.81, 1.03)
Paracetamol	338/47620	0.71 (0.64, 0.79)	3965/474248	0.84 (0.81, 0.86)	-0.07 (-0.16, 0.01)	0.90 (0.81, 1.01)
NSAIDs	433/47821	0.91 (0.82, 0.99)	5288/474683	1.11 (1.08, 1.14)	-0.11 (-0.20, -0.02)	0.90 (0.81, 0.99)
Antibiotics for respiratory tract infections	1306/44072	2.96 (2.81, 3.13)	12507/435225	2.87 (2.82, 2.92)	0.11 (-0.06, 0.28)	1.04 (0.98, 1.10)
Other antibiotics	790/46701	1.69 (1.58, 1.81)	8341/463979	1.80 (1.76, 1.84)	0.04 (-0.08, 0.17)	1.03 (0.95, 1.10)

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, immigration status, gestational age, comorbidities and current drug use as specified in appendix.

NR= not reported. MIS-C=Multisystem inflammatory 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 S9. 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.

Visit type	SARS-CoV-2 positive		SARS-CoV-2 negative		PERR (95% CI)
	Rate/1000 individuals (total visits)				
	Baseline	Follow-up	Baseline	Follow-up	
Admission	22 (1094)	19 (947)	24 (11876)	22 (10610)	0.97 (0.88-1.06)
Paediatric admission	10 (506)	10 (469)	11 (5497)	10 (4674)	1.09 (0.95-1.23)
General practitioner	913 (44722)	800 (39163)	1,005 (491742)	826 (404059)	1.07 (1.05-1.08)
Outpatient	366 (17929)	369 (18064)	421 (205813)	429 (209946)	1.01 (0.97-1.05)
Paediatric outpatient	57 (2783)	54 (2654)	61 (29758)	61 (29696)	0.96 (0.90-1.01)
Specialist	159 (7783)	164 (8038)	163 (79979)	167 (81871)	0.99 (0.96-1.02)

Rates are reported as the number of events per 1000 individuals under 18 years during the baseline period from day -179 to -30 before testing and the post-acute follow-up from day +30 to +179 after testing. PERR=prior event rate ratio adjusted rate ratio. Admissions are defined as any physical hospital contact with a duration of 12 hours or more.

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Table S10. Demographic characteristics of Danish vaccine recipients aged 12 to 17 years

Vaccinated adolescents (N=279,655)	
Vaccine	
BNT162b2	278,649 (99.6%)
mRNA-1273	973 (0.3%)
Other*	33 (0.0%)
Completed immunisation	268,508 (96.0%)
Year of birth	
2004	56,811 (20.3%)
2005	54,866 (19.6%)
2006	50,255 (18.0%)
2007	46,224 (16.5%)
2008	42,945 (15.4%)
2009	28,554 (10.2%)
Male sex	142,632 (51.0%)
Region	
Hovedstaden	80,233 (28.7%)
Midtjylland	67,773 (24.2%)
Nordjylland	29,254 (10.5%)
Sjælland	41,336 (14.8%)
Syddanmark	61,059 (21.8%)
Immigration status	
First generation	8,827 (3.2%)
Second generation	12,211 (4.4%)

Characteristics of all Danish vaccine recipients vaccinated against SARS-CoV-2 before or on 31 October 2021. Data on vaccination status was obtained from The Danish Vaccination Register.⁶

* AZD1222 or Ad26.CoV2-S

Table S11. Demographic characteristics on BNT162b2 vaccine recipients included in analyses

	BNT162b2 (first dose)	Unvaccinated	BNT162b2 (second dose)	Unvaccinated
	N=229,799	N=2,296,231	N=175,176	N=1,748,086
Year of birth				
2004	47,377 (20.6%)	473,207 (20.6%)	44,590 (25.5%)	444,038 (25.4%)
2005	45,985 (20.0%)	459,393 (20.0%)	41,740 (23.8%)	416,571 (23.8%)
2006	41,580 (18.1%)	415,537 (18.1%)	30,146 (17.2%)	301,067 (17.2%)
2007	38,334 (16.7%)	383,109 (16.7%)	25,725 (14.7%)	256,894 (14.7%)
2008	35,295 (15.4%)	352,802 (15.4%)	22,458 (12.8%)	224,414 (12.8%)
2009	21,228 (9.2%)	212,183 (9.2%)	10,517 (6.0%)	105,102 (6.0%)
		1,174,089		
Male sex	117,491 (51.1%)	(51.1%)	89,331 (51.0%)	891,943 (51.0%)
Region				
Hovedstaden	64,928 (28.3%)	649,121 (28.3%)	47,764 (27.3%)	476,761 (27.3%)
Midtjylland	56,365 (24.5%)	563,194 (24.5%)	43,586 (24.9%)	435,121 (24.9%)
Nordjylland	24,240 (10.5%)	242,077 (10.5%)	19,031 (10.9%)	189,963 (10.9%)
Sjælland	33,665 (14.6%)	336,630 (14.7%)	25,315 (14.5%)	253,107 (14.5%)
Syddanmark	50,601 (22.0%)	505,209 (22.0%)	39,480 (22.5%)	393,134 (22.5%)
Immigration status				
First generation	6,263 (2.7%)	131,410 (5.7%)	3,918 (2.2%)	155,533 (8.9%)
Second generation	9,045 (3.9%)	208,059 (9.1%)	5,881 (3.4%)	237,565 (13.6%)

Characteristics of BNT162 recipients and unvaccinated peers included in analyses. Recipients of the first dose were included until 02 October 2021. Recipients of the second dose were included until 02 September 2021 to ensure a follow-up of minimum 60 days.

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Table S12. Effectiveness of BNT162b2 vaccine among adolescents 12 thorough 17 years.

	BNT162b2 vaccine recipients		Unvaccinated comparators		Vaccine effectiveness (VE)	
	Events (n/N)	Risk, % (95% CI)	Events (n/N)	Risk, % (95% CI)	VE (95% CI)	IPW-VE (95% CI)
First dose (day 0-29)						
ITT	778/229799	0.34 (0.32, 0.36)	17544/2296231	0.76 (0.75, 0.78)	48 (44-51)	
Complete case**	778/229799	0.34 (0.32, 0.36)	15571/1429266	1.09 (1.07, 1.11)	62 (59-65)	62 (59-65)
Second dose (day 0-59)						
ITT	359/175176	0.20 (0.18, 0.23)	50977/1748086	2.92 (2.89, 2.94)	91 (90-92)	
Complete Case	359/175176	0.20 (0.18, 0.23)	47427/1184197	4.00 (3.97, 4.04)	93 (92-94)	93 (93-94)

Vaccine effectiveness was calculated as 1 – risk ratio. Risk ratios were obtained using log-binomial regression adjusted birth year, sex, municipality and immigration status.

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).

Complete case analysis: Unvaccinated individuals who were vaccinated during follow up were excluded from the analysis.

IPW=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.

Table S13. Rates of PCR-testing against SARS-CoV-2 in vaccinated and unvaccinated adolescents

	Tests (N)	Person time (months)	Monthly test rate (per 1000 individuals)
Vaccinated	120087	137334	874
Unvaccinated	1258490	1129408	1114

The number of PCR-tests for SARS-CoV-2 performed per 1000 persons per month during follow-up in unvaccinated and vaccinated adolescents aged 12 through 17 years.

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