Risk of adverse events after covid-19 in Danish children and adolescents and effectiveness of BNT162b2 in adolescents: cohort study

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ABSTRACT

OBJECTIVES

To assess the risk of acute and post-acute adverse events after SARS-CoV-2 infection in children and adolescents in Denmark and to evaluate the real world effectiveness of the BNT162b2 mRNA vaccine (Pfizer-BioNTech) among adolescents.

DESIGN

Cohort study.

SETTING

Nationwide Danish healthcare registers.

PARTICIPANTS

All Danish people younger than 18 years who were either tested for SARS-CoV-2 using reverse transcriptase polymerase chain reaction (RT-PCR) or vaccinated with BNT162b2 to 1 October 2021.

MAIN OUTCOME MEASURES

Risk of hospital admissions (any hospital contact of ≥12 hours); intensive care unit (ICU) admissions; serious complications, including multisystem inflammatory syndrome in children (MIS-C), myocarditis, and neuroimmune disorders; and initiating drug treatment and health service use up to six months after being tested. Vaccine effectiveness in vaccine recipients compared with unvaccinated peers was evaluated as one minus the risk ratio at 20 days after the first dose and 60 days after the second dose.

RESULTS

Of 991 682 children and adolescents tested for SARS-CoV-2 using RT-PCR in Denmark, 74 611 (7.5%) were positive. The risk of hospital admission with any variant for ≥12 hours was 0.49% (95% confidence interval 0.44% to 0.54%; 361/74 350), and 0.01% (0.01% to 0.03%; 10/73 187) of participants were admitted to an ICU within 30 days of testing positive. The risk of MIS-C within two months of SARS-CoV-2 infection was 0.05% (0.03% to 0.06%; 32/70 666), whereas no participants had myocarditis outside of MIS-C or encephalitis and fewer than five had Guillain-Barré syndrome. In the post-acute phase (1-6 months after infection), participants who tested positive for SARS-CoV-2 showed a 1.08-fold (95% confidence interval 1.06-fold to 1.10-fold) increase in rate of contacts with general practitioners compared with a reference cohort sampled among all children tested for SARS-CoV-2 during the study period. Overall, 278 649 adolescents received BNT162b2. Compared with unvaccinated adolescents, the estimated vaccine effectiveness among 229 799 adolescents vaccinated with one dose was 62% (95% confidence interval 59% to 65%) after 20 days, and among 175 176 vaccinated with two doses was 93% (92% to 94%) after 60 days during a period when delta was the dominant variant.

CONCLUSIONS

The absolute risks of adverse events after SARS-CoV-2 infection were generally low in Danish children and adolescents, although MIS-C occurred in 0.05% (32/70 666) of participants with RT-PCR confirmed SARS-CoV-2 infection. In adjusted analyses, rates of general practitioner visits were slightly increased in SARS-CoV-2 positive children and adolescents, which could indicate persisting symptoms. BNT162b2 appeared to be effective in reducing the risk of SARS-CoV-2 infection with the delta variant in adolescents.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Rates of hospital and intensive care unit admissions, mortality, and immune mediated complications have varied among studies in children and adolescents with SARS-CoV-2

Variations in setting and data availability could explain these conflicting results, with most studies performed among young people admitted to hospital, who are unrepresentative of most young people with SARS-CoV-2

Evidence suggests that a substantial proportion of young people experience persistent symptoms or sequelae after covid-19, but existing studies have limitations, including low response rates and selection bias

WHAT THIS STUDY ADDS

In this study, children and adolescents showed low risks of serious adverse events after SARS-CoV-2 infection

Rates of visits to a general practitioner were slightly increased, however, and multisystem inflammatory syndrome in children was observed in one of 2200 children with polymerase chain reaction confirmed SARS-CoV-2

The BNT162b2 mRNA vaccine was associated with a substantial reduction in the risk of confirmed SARS-CoV-2 three months after the first dose, when the delta variant was dominant

Introduction

As of 19 January 2022, more than 330 million people have been infected with SARS-CoV-2 worldwide.[1] Although widespread vaccination against SARS-CoV-2 has greatly improved the prognosis of covid-19 among adults in countries with high availability of vaccines and high rates of vaccinations, SARS-CoV-2 continues to spread.[2] During the summer of 2021, many countries initiated mass vaccinations programmes against SARS-CoV-2 in adolescents aged 12 years or older and recently extended these programmes to children aged 5 to 11 years when the BNT162b2 (Pfizer-BioNTech) covid-19 vaccine was authorised for emergency use in this age group. All approved mRNA vaccines against

SARS-CoV-2 are seemingly effective in inducing immunogenicity and reducing the risk of covid-19, yet their ability to prevent immune mediated complications from SARS-CoV-2 infection, including multisystem inflammatory syndrome in children (MIS-C), remains to be determined.[3-5] The decision to offer vaccines against SARS-CoV-2 to children and adolescents has been much debated. Childhood vaccination may be necessary to increase overall population immunity.[6] Studies have, however, consistently reported that SARS-CoV-2 infection in children and adolescents is generally asymptomatic or mild, limiting the benefit of vaccination in individual.[7]

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. Reports of hospital admission and case fatality rates among children and adolescents have varied considerably, seemingly dependent on setting and data availability, and data are scarce among most children and adolescents with asymptomatic or mild disease.

We describe the SARS-CoV-2 epidemic in Danish children and adolescents and provide population based estimates for the risk of adverse outcomes in the acute and post-acute phases after SARS-CoV-2 infection in these groups and for the real world effectiveness of BNT162b2 among adolescents.

Methods

In this population based cohort study, we used individual level linkage of data from Danish patient, prescription, health insurance, and vaccination registries.[8-12] The study cohort included all children and adolescents younger than 18 years with a confirmed SARS-CoV-2 infection using reverse-transcriptase polymerase chain reaction (RT-PCR) to 1 October 2021. We examined the clinical characteristics of participants who were admitted to hospital with covid-19 and the occurrence of healthcare outcomes in the acute and post-acute phases of SARS-CoV-2 infection. Using data from Danish large scale genome sequencing of SARS-CoV-2 available from the Global Initiative in Sharing All Influenza Data, we also evaluated the risk of study outcomes across the dominant SARS-CoV-2 variants.[13 14] Furthermore, we estimated the effectiveness of BNT162b2 against confirmed SARS-CoV-2 infection. This study was reported according to the reporting of studies conducted using observational routinely collected health data (RECORD) statement.

Setting

Denmark reported its first resident with SARS-CoV-2 on 27 February 2020, and on 11 March 2020 the Danish government imposed a comprehensive lockdown to control community spread of the virus. In April 2020, day care centres and primary schools gradually reopened. An increase in the transmission of SARS-CoV-2 occurred in the autumn of 2020, leading to gradual restrictions and new closures of schools from mid-December 2020 to 8 February 2021, when children were gradually allowed backed to school, starting with the youngest children. Schools fully reopened on 6 May 2021. In the early phase of the epidemic, RT-PCR testing was limited to people with symptoms of covid-19, and testing of children and adolescents required referral by a general practitioner to hospital based testing units. From July 2020, testing without requisition became available for children older than 12 years, and in September 2020 testing was extended to all children older than 2 years. Throughout the epidemic, the Danish Health Authorities have encouraged RT-PCR testing of children and adolescents with potential symptoms of covid-19 or after their close contact with a SARS-CoV-2 positive individual. From March 2021 to end of the school year in June 2021, twice weekly testing was encouraged in school children aged 12 years or older, and these recommendations were reinstated in August 2021.

Use of antigen testing in children and adolescents was limited until the spring of 2021 and has since been used mainly for children aged 12 years or older, and only for asymptomatic testing. Children with a positive antigen test result were encouraged to have an RT-PCR-test. All tests were provided for free and were easily accessible, with a high density of testing locations nationwide. Denmark began mass vaccination programmes against SARS-CoV-2 for adolescents aged 16 and 17 years in May 2021 and for those aged 12 to 15 years in July 2021. To date, Danish children and adolescents have almost exclusively been vaccinated with BNT162b2 (99.6% of all vaccine recipients aged 12-17 years).

Study population

All children and adolescents were eligible for inclusion if they were younger than 18 years and had undergone RT-PCR testing for SARS-CoV-2 in Denmark from 27 February 2020 to 1 October 2021, or they were younger than 18 years and had received the BNT162b2 vaccine before or on 1 October 2021. In all analyses, we included participants if they completed follow-up before or on 31 October 2021. As of 1 October 2021, the Danish population consisted of 1 151 849 children and adolescents younger than 18 years.

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

The main cohort for the analyses of the acute and post-acute effects of SARS-CoV-2 infection comprised all participants younger than 18 years with RT-PCR confirmed SARS-CoV-2. In baseline characterisation of these participants, we further stratified this group into those who required hospital admission and those did not within the first 30 days after a first positive SARS-CoV-2 test result. For comparison, we sampled a reference cohort from the entire cohort of children younger than 18 years 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 data on drug prescription use,

hospital admissions, and healthcare use before SARS-CoV-2 infection, we excluded children who were not living continuously in Denmark during the year before the index test date. Participants were further excluded from the reference cohort if they had previously tested positive for SARS-CoV-2. As a sensitivity analysis, we also compared children and adolescents who tested positive for SARS-CoV-2 with those who tested negative. For each SARS-CoV-2 positive participant, we sampled 10 SARS-CoV-2 negative participants based on year of birth, sex, and year and week of testing. The test negative comparator group was not used in main analyses, however, as participants might not resemble the background population at the time of their negative test related to reasons for active SARS-CoV-2 testing (eg, symptoms, need of healthcare services, screening before contact with healthcare system).

We considered the outcomes of SARS-CoV-2 infection in three periods: the acute phase (days 0 to 29), an intermediate period when serious complications related to SARS-CoV-2 infection were likely to occur (days 0 to 59), and the post-acute phase (days 30 to 179). We chose these periods to maximise capture of serious complications in all phases of the epidemic, with hospital admissions related to the primary infection most likely to occur within the first month of infection, whereas immune mediated complications such as MIS-C could occur weeks after the primary infection. No outcome was reported across overlapping periods. During the acute phase, we examined the risk of hospital admission, intensive care unit (ICU) admission, and requiring mechanical ventilation. In these analyses, we excluded participants who had the outcome of interest during the month preceding sampling. Hospital admission 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 who required short hospital stays from those with disease that required treatment.[15] We also explored alternative definitions of hospital admission 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 a first ever in-patient or outpatient hospital diagnosis of potential complications or sequelae from SARS-CoV-2 infection. Included diseases were venous thromboembolism, 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 that might not lead to a hospital admission, including short acting β2 agonists, inhaled corticosteroids, paracetamol (acetaminophen), non-steroidal anti-inflammatory drugs, and antibiotics used in Denmark to treat respiratory tract infections. Participants with a redeemed prescription for the drug of interest one year before the index test date, were excluded from the respective analysis. Finally, we assessed differences in health service use by establishing rates of general practitioner visits, visits to specialists in private healthcare, hospital outpatient visits, and hospital admissions (overall and specifically related to paediatrics (<18 years)), allowing for multiple occurrences of each type of visit. In analyses of the intermediate and post-acute phase, we restricted analyses to participants with at least two or six months of follow-up. Supplementary table S1 lists the specific ICD-10 (international classification of diseases, 10th revision) codes and anatomical therapeutic classification codes we used to define diseases and drug groups.

Statistical analysis

To characterise the differences in baseline characteristics among assumed asymptomatic participants or those with mild SARS-CoV-2 infection compared with more severe infection, we described personal characteristics, time periods (27 February to 31 July 2020, 1 August 2020 to 31 January 2021, 1 February to 20 June 2021, and 1 July to 31 October 2021), and medical history, stratified on whether SARS-CoV-2 positive participants were admitted to hospital or were not within the first month of testing. In assessment of outcomes in the predefined acute and intermediate phases, we calculated absolute risks among children with and without a positive RT-PCR test result for SARS-CoV-2. To deal with potential confounding, we estimated propensity score weighted risk differences and risk ratios with robust 95% confidence intervals using binomial regression with an identity and log link.[16] 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 from SARS-CoV-2 infection, we assessed the risk of initiation of new drugs from 30 to 179 days after a SARS-CoV-2 test result and estimated risk differences comparing SARS-CoV-2 positive participants with the reference cohort. We also assessed the rates of healthcare visits monthly from 30 to 179 days after a SARS-CoV-2 test. To control for underlying differences in baseline healthcare use among SARS-CoV-2 positive participants and participants in the reference cohort, we estimated the prior event rate ratio (PERR) adjusted rate ratios.[17] We calculated rate ratios of health service use among SARS-CoV-2 positive participants and the reference cohort during a pre-baseline period from days −179 to −30 before testing and the post-acute follow-up period from days 30 to 179 after testing. PERR adjusted rate ratios were calculated as rate ratios in the post-acute phases divided by the rate ratios at baseline, and we obtained normal based 95% confidence intervals using bootstrapping techniques with 200 replications.

Vaccine effectiveness

We investigated the effectiveness of BNT162b2 for preventing laboratory confirmed SARS-CoV-2 infection in adolescents aged 12-17 years who were vaccinated before or on 1 October 2021. For comparison, we matched 10 unvaccinated participants to each vaccinated participant based on birth year, sex, and municipality on the date of vaccination. Vaccinated and unvaccinated participants 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 received any other covid-19 vaccine before 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 immigration status. Only those with complete follow-up for 21 days after the first dose or 60 days after the second dose 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.

Patient and public involvement

Owing to the nature of this study and data privacy constraints, no patients or members of the public were involved in the study design, analysis, interpretation of data, or revision of the manuscript.

Results

Overview of the Danish SARS-CoV-2 epidemic

Between 27 February 2020 and 1 October 2021, 991 682 Danish children and adolescents were tested for SARS-CoV-2 using RT-PCR in Denmark of whom 74 611 (7.5%) tested positive, corresponding to 86.1% and 6.5% of the total Danish population younger than 18 years, respectively. The incidence of SARS-CoV-2 among children and adolescents showed two peaks, in December 2020 and August 2021, with 78 and 47 new daily cases per 100 000 individuals, respectively (fig 1). The daily number of tests was largely influenced by test availability and government issued restrictions and recommendations. Thus, the number of daily tests increased in the autumn of 2020 along with the peak in the epidemic and again in the spring of 2021 when schools reopened and weekly testing was encouraged in school children (fig 1). The number of covid-19 related admissions to hospital peaked in December 2020 and August 2021 (fig 1). Owing to data protection regulations, data on whole genome sequencing of RT-PCR SARS-CoV2 tests were not stratified on age; however, the distribution of variants was assumed to be similar between young people and adults. During the SARS-CoV-2 peak in December 2020, the B.1.177 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.[14] Vaccine uptake increased rapidly during June to August 2021, and by the end October vaccination against SARS-CoV-2 had started in 72% of adolescents aged 12-15 years and 88% aged 16-17 years (fig 1).

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

Of the 74 611 SARS-CoV-2 positive children and adolescents in Denmark, 391 were admitted to hospital within the first month of being tested (0.52%, 95% confidence interval 0.47% to 0.58%). The proportion of hospital admissions was highest among infants aged 0-1 years (3.5%, 2.9% to 4.1%; 119/3369), and in the remaining age groups ranged from 0.29% (0.22% to 0.35%; 76/26 641) among those aged 6-11 years to 0.51% (0.39% to 0.64%; 68/13 247) among those aged 16-17 years (table 1). The risk of hospital admission was similar across periods when the B.1.177, alpha, and delta variants predominated (see supplementary table S4). SARS-CoV-2 positive participants admitted to hospital were more likely than SARS-CoV-2 positive participants not admitted to hospital to have a medical history of comorbidities, with 39.1% (153/391) having at least one recorded comorbid disease—most often a history of psychiatric disorders (14.1%; 55/391), premature birth (10.2%, 40/391), and asthma (7.7%, 30/391). Likewise, participants admitted to hospital had a higher prevalence of prescription drug use one year before infection, particularly for asthma drugs and systemic antibiotics, and in 40.2% (157/391) of participants prescriptions were redeemed for at least two different drugs. Participants with SARS-CoV-2 infection were slightly older than participants in the reference cohort and were more likely to be first and second generation immigrants, but on all other variables participants in the reference cohort resembled participants positive for SARS-CoV-2 (table 1).

When stricter definitions of hospital admission were applied, the overall rate of hospital admissions among SARS-CoV-2 positive participants decreased from 0.52% to 0.33% (95% confidence interval 0.29% to 0.38%; 249/74 611) when requiring a visit longer than 24 hours, and to 0.11% (0.09% to 0.14%; 88/74 611) when requiring a visit longer than 24 hours and having a hospital diagnosis of either covid-19 or MIS-C.

Compared with the reference cohort sampled among all SARS-CoV-2 tested participants, SARS-CoV-2 positive participants had a higher risk of any hospital admission within the first month, with an adjusted risk difference of 0.20% (95% confidence interval 0.15% to 0.25%; fig 2). The risk of ICU admission among SARS-CoV-2 positive participants was 0.01% (0.01% to 0.03%), similar to the frequency in the reference cohort.

MIS-C was observed in 32/70 666 participants (0.05%, 95% confidence interval 0.03% to 0.06%) with at least two months of follow-up. No encephalitis, myocarditis outside of MIS-C, or neuroimmune disorders were observed among SARS-CoV-2 positive

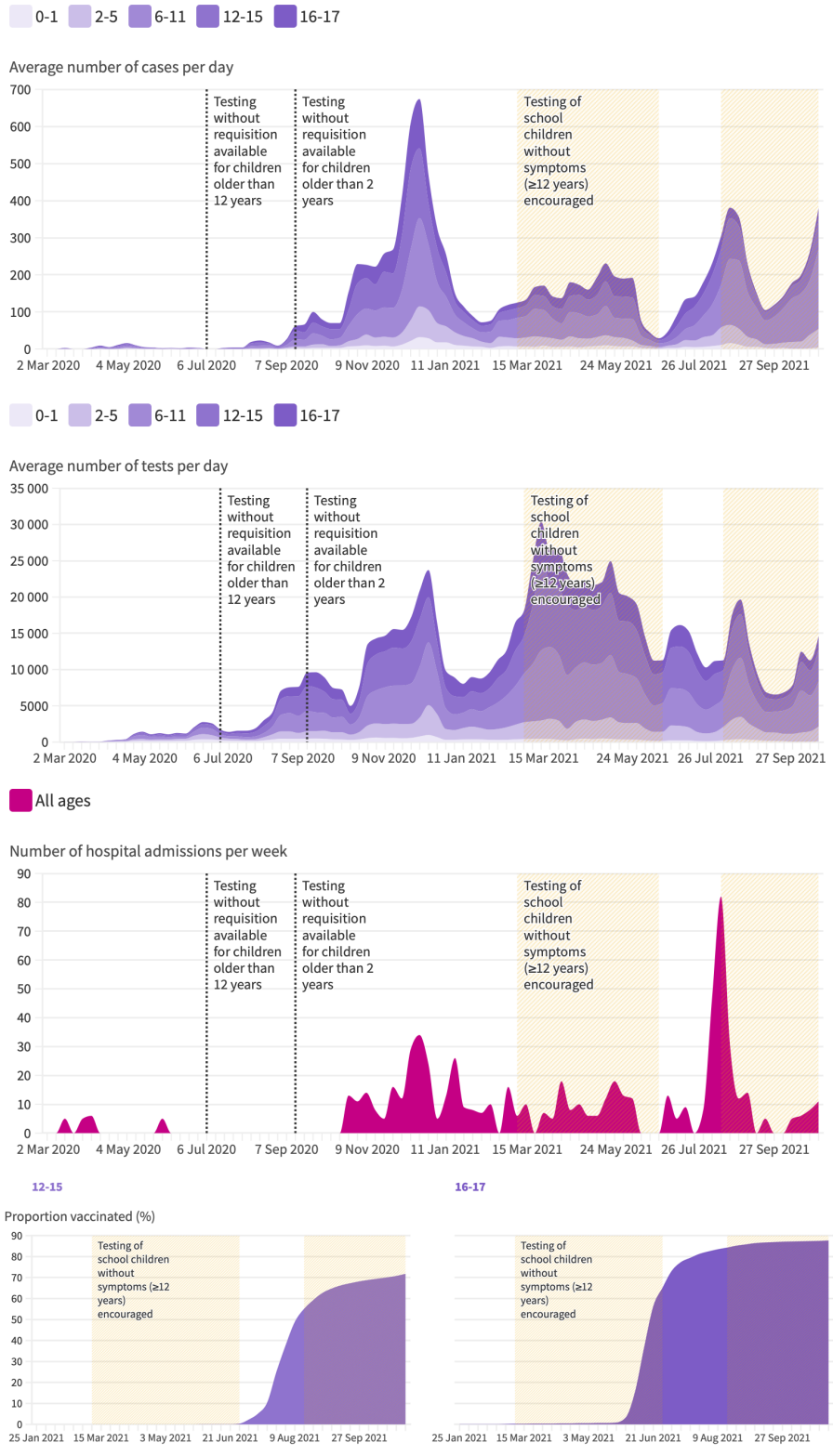


Fig 1 | Average daily number of SARS-CoV-2 positive children and adolescents younger than 18 years during the epidemic in Denmark, stratified on age; average daily number of reverse transcriptase polymerase chain reaction tests among those younger than 18 years, stratified on age; number of weekly hospital admissions among those younger than 18 years, stratified on age; and vaccination uptake in adolescents aged 12-15 and 16-17 years. Denmark had national lockdowns, including school closures, in spring 2020 and from mid-December 2020 to 6 May 2021.The first and second dotted lines represent the dates when testing without requisition became available for children older than 12 years and older than 2 years, respectively. Throughout the epidemic, testing of children has mainly been recommended in the presence of symptoms and after close contacts with someone with known covid-19. Shaded bars indicate periods when asymptomatic testing of school children (≥12 years) was encouraged. An interactive version of this graphic is available at https://public.flourish.studio/visualisation/8865344

Table 1 | Baseline characteristics of children and adolescents (<18 years) admitted or not admitted to hospital within the first month after a positive SARS-CoV-2 reverse-transcriptase polymerase reaction test result. Values are numbers (percentages) unless stated otherwise

	SARS-CoV-2 positive		
	Admitted to hospital (n=391)	Not admitted to hospital (n=74 220)	Reference* (n=920 893)
Personal characteristics			
Median (IQR) age (years)	8 (1-14)	11 (7-15)	10 (5-14)
Age category (years):			
0-1	119 (30.4)	3250 (4.4)	59 481 (6.5)
2-5	49 (12.5)	9616 (13.0)	181 411 (19.7)
6-11	76 (19.4)	26 565 (35.8)	315 599 (34.3)
12-15	79 (20.2)	21 610 (29.1)	243 994 (26.5)
16-17	68 (17.3)	13 179 (17.8)	120 408 (13.1)
Female sex	191 (48.8)	36 297 (48.9)	449 017 (48.8)
Immigration status:			
1st generation	15 (3.8)	4831 (6.5)	29 941 (3.3)
2nd generation	92 (23.5)	15 479 (20.9)	81 428 (8.8)
Time period			
27 Feb 2020 31 Jul 2020	32 (8.2)	889 (1.2)	11 646 (1.3)
1 Aug 2020 to 31 Jan 2021	159 (40.7)	34 868 (47.0)	437 076 (47.5)
1 Feb to 30 Jun 2021	106 (27.1)	20 595 (27.7)	257 486 (28.0)
1 Jul to 31 Oct 2021	94 (24.0)	17 868 (24.1)	214 685 (23.3)
Perinatal history			
Prematurity (28-37 weeks)	40 (10.2)	3142 (4.2)	44 277 (4.8)
Immaturity (<28 weeks)	n<5	156 (0.2)	2152 (0.2)
Small for gestation age	11 (2.8)	857 (1.2)	13 000 (1.4)
Low birth weight (<2500 g)	30 (7.7)	2130 (2.9)	28 502 (3.1)
Medical history			
Asthma	30 (7.7)	4010 (5.4)	50 568 (5.5)
Other chronic respiratory diseases	10 (2.6)	460 (0.6)	6488 (0.7)
Chronic cardiac disease	8 (2.0)	354 (0.5)	4046 (0.4)
Diabetes mellitus	n<5	190 (0.3)	2664 (0.3)
Autoimmune disorders	14 (3.6)	840 (1.1)	9991 (1.1)
Epilepsy or convulsions	35 (9.0)	3124 (4.2)	40 062 (4.4)
Congenital malformations and chromosomal abnormalities	34 (8.7)	1937 (2.6)	25 127 (2.7)
Malignancy or immunodeficiency	13 (3.3)	330 (0.4)	4179 (0.5)
Psychiatric disorders	55 (14.1)	4509 (6.1)	63 844 (6.9)
No of comorbidities:			
0	238 (60.9)	57 896 (78.0)	706 834 (76.8)
1	85 (21.7)	12 169 (16.4)	156 760 (17.0)
≥2	68 (17.4)	4155 (5.6)	57 299 (6.2)
Hospital admissions in past year:			
0	361 (92.3)	73 989 (99.7)	917 118 (99.6)
1	NR	221 (0.3)	3543 (0.4)
≥2	n<5	10 (0.0)	232 (0.0)
Current drug use†			
Short acting β2 agonists	38 (9.7)	2985 (4.0)	44 040 (4.8)
Inhaled corticosteroids	24 (6.1)	2477 (3.3)	33 142 (3.6)
Leukotriene D4 receptor antagonists	5 (1.3)	428 (0.6)	6000 (0.7)
Nasal corticosteroids	14 (3.6)	3395 (4.6)	38 766 (4.2)
Systemic antihistamines	18 (4.6)	3490 (4.7)	42 929 (4.7)
Systemic corticosteroids	n<5	160 (0.2)	1661 (0.2)
No of systemic antibiotics:			
0	296 (75.7)	65 524 (88.3)	813 554 (88.3)
1	56 (14.3)	6074 (8.2)	74 262 (8.1)
≥2	39 (10.0)	2622 (3.5)	33 077 (3.6)
Paracetamol (acetaminophen)	35 (9.0)	1670 (2.3)	22 634 (2.5)
NSAIDs	19 (4.9)	1591 (2.1)	18 990 (2.1)
No of different drugs:			
0	143 (36.6)	41 474 (55.9)	506 281 (55.0)
1	91 (23.3)	16 320 (22.0)	208 584 (22.7)
≥2	157 (40.2)	16 426 (22.1)	206 028 (22.4)

IQR=interquartile range; NR=not reported because of Danish data protection law; NSAIDs=non-steroidal anti-inflammatory drugs.
Data on race and socioeconomic status not available from study data sources.
*Reference cohort was sampled among all children and adolescents tested for SARS-CoV-2 during study period.
†Defined as redeemed prescription for drug of interest during one year before start of follow-up.

participants two months after testing, and fewer than five cases of Guillain-Barré syndrome occurred (fig 2). When the risk of MIS-C was evaluated by the dominant SARS-CoV-2 variant as a post hoc analysis, results were similar across periods dominated by the B.1.177 (0.04%, 0.02% to 0.06%), alpha (0.04%, 0.02% to 0.08%), and delta variants (0.04%, 0.01% to 0.09%) (see supplementary table S4).

Outcome	SARS-CoV-2 positive cohort		Reference cohort		Risk difference (95% CI)	Relative risk (95% CI)
	No of events	Risk (%)	No of events	Risk (%)		
Follow-up: 30 days						
Hospital admission	361/74 350	0.49 (0.44 to 0.54)	2895/917 118	0.32 (0.30 to 0.33)	0.20 (0.15 to 0.25)	1.71 (1.53 to 1.91)
Intensive care unit admission	10/73 187	0.01 (0.01 to 0.03)	100/899 432	0.01 (0.01 to 0.01)	0.00 (-0.00 to 0.01)	1.54 (0.80 to 2.95)
Mechanical ventilation	n<5	-	41/911 582	0.00 (0.00 to 0.01)	-	-
Renal replacement therapy	n<5	-	n<5	-	-	-
Follow-up: 60 days						
MIS-C*	32/70 666	0.05 (0.03 to 0.06)	6/875 881	0.00 (0.00 to 0.00)	0.04 (0.03 to 0.06)	62.65 (25.28 to 155.23)
Myocarditis	0/70 693	0.00 (0.00 to 0.01)	n<5	-	-	-
Venous thromboembolism	n<5	-	n<5	-	-	-
Pneumonia	13/66 682	0.02 (0.01 to 0.03)	224/832 378	0.03 (0.02 to 0.03)	0.00 (-0.01 to 0.01)	1.05 (0.60 to1.84)
Guillian-Barré syndrome	n<5	-	n<5	-	-	-
Encephalitis	0/70 669	0.00 (0.00 to 0.01)	7/875 999	0.00 (0.00 to 0.00)	-	-
Other neuroimmune disorders	0/70 681	0.00 (0.00 to 0.01)	n<5	-	-	-
Follow-up: 1-6 months						
Long covid	58/48 948	0.12 (0.09 to 0.15)	32/607 990	0.01 (0.00 to 0.01)	0.11 (0.08 to 0.14)	18.61 (12.31 to 28.12)
Short acting β2 agonists	608/46 728	1.30 (1.20 to 1.41)	8033/577 096	1.39 (1.36 to 1.42)	0.16 (0.05 to 0.27)	1.14 (1.05 to 1.24)
Inhaled corticosteroids	292/47 163	0.62 (0.55 to 0.69)	3861/585 285	0.66 (0.64 to 0.68)	0.08 (0.00 to 0.15)	1.14 (1.01 to 1.29)
Paracetamol (acetaminophen)	338/47 620	0.71 (0.64 to 0.79)	4067/590 889	0.69 (0.67 to 0.71)	-0.01 (-0.09 to 0.07)	0.98 (0.88 to 1.10)
NSAIDs	433/47 821	0.91 (0.82 to 0.99)	5065/594 724	0.85 (0.83 to 0.88)	0.01 (-0.08 to 0.09)	1.01 (0.91 to 1.11)
Antibiotics for respiratory tract infections	1306/44 072	2.96 (2.81 to 3.13)	15 922/546 159	2.92 (2.87 to 2.96)	0.33 (0.17 to 0.49)	1.13 (1.06 to 1.19)
Other antibiotics	790/46 701	1.69 (1.58 to 1.81)	7918/584 800	1.35 (1.32 to 1.38)	0.17 (0.05 to 0.29)	1.11 (1.04 to 1.20)

Fig 2 | Absolute risks, adjusted risk differences, and risk ratios for hospital based outcomes, diagnosis based outcomes, and initiation of new drugs during follow-up in SARS-CoV-2 positive children and a reference cohort sampled among children tested for SARS-CoV-2 in Denmark. Because of Danish legislation, counts fewer than five cannot be reported. Risk differences and risk ratios are propensity score weighted estimates adjusted for age, sex, calendar time, gestational age, comorbidities, and current drug use, as specified in the appendix. *Multisystem inflammatory syndrome in children (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 SARS-CoV-2 epidemic. Therefore, children with Kawasaki disease occurring within two months of SARS-CoV-2 infection were considered to have MIS-C. NSAIDs=non-steroidal anti-inflammatory drugs

In the post-acute phase from days 30 to 179 after testing, 0.12% (0.09% to 0.15%) of SARS-CoV-2 positive children and adolescents received a diagnosis code for persisting symptoms of infection (ie, long covid) (fig 2). Overall, initiation of prescription drugs was similar in SARS-CoV-2 positive participants and the reference cohort. Of those who tested positive, 2.96% (2.81% to 3.13%) received antibiotics used for respiratory tract infections, 1.30% (1.20% to 1.41%) received short acting β2 agonists, 0.71% (0.64% to 0.79%) received paracetamol, and 0.91% (0.82% to 0.99%) received NSAIDs. Compared with the reference cohort, the adjusted risk difference was increased for antibiotics for respiratory tract infections (0.33, 95% confidence interval 0.17 to 0.49), short acting β2 agonists (0.16, 0.05 to 0.27), and inhaled corticosteroids (0.08, 0.00 to 0.15) (fig 2).

Within the post-acute phase, 20 616 (42.1%, 95% confidence interval 41.7% to 42.5%) of participants with SARS-CoV-2 infection and 247 620 (40.7%, 40.6% to 40.8%) of the reference cohort had visited a general practitioner, 1910 (3.9%, 3.7% to 4.1%) and 23 954 (3.9%, 3.9% to 4.0%) had visited a paediatric outpatient clinic, and 775 (1.6%, 1.5% to 1.7%) and 9369 (1.5%, 1.5% to 1.6%) were admitted to a hospital (see supplementary table S6). When baseline and overall post-acute healthcare use was compared between SARS-CoV-2 positive participants and the reference cohort, the PERR adjusted rate ratios were observed to increase for general practitioner visits (1.08, 95% confidence interval 1.06 to 1.10) and hospital admissions (1.15, 1.02 to 1.28; table 2). SARS-CoV-2 positive participants only showed increased hospital admissions rates until four months after infection, whereas increased rates of general practitioner visits continued throughout the observation period (see supplementary figure S2).

In sensitivity analyses using a cohort of SARS-CoV-2 test negative participants as comparators, SARS-CoV-2 positive participants were no longer at increased risk of hospital admission within the first month of testing, and the signals indicating increased initiation of bronchodilators and antibiotics during the post-acute phase were also observed to be attenuated (see supplementary table S8).

Vaccine effectiveness

Among Danish adolescents, 278 649 received BNT162b2, with a median time between doses of 28 days (interquartile range 22-35). Of these participants, vaccine effectiveness was assessed in 229 799 after a first dose and 175 176 after a second dose (see supplementary table S11). Figure 3 shows the cumulative incidence for confirmed SARS-CoV-2 infection. The estimated vaccine effectiveness against documented SARS-CoV-2 infection was 62% (95% confidence interval 59% to 65%) 20 days after the first dose and 93% (92% to 94%) 60 days after the second dose (see supplementary table S12). In sensitivity analyses, informative censoring showed no effect on results (see supplementary table S12). The frequency of RT-PCR testing for SARS-CoV-2 during follow-up was higher in unvaccinated adolescents than in vaccinated adolescents (1114 *v* 874 tests per 1000 individuals per month) (post hoc analysis, supplementary table S13).

Discussion

This study presents nationwide data on all 74 611 children and adolescents younger than 18 years with RT-PCR confirmed SARS-CoV-2 in Denmark to 1 October 2021 and found that 0.5% (361/74 350) required hospital admission and 0.01% (10/73 187) required ICU admission. The absolute risk of serious complications from SARS-CoV-2 was observed to be generally low, although MIS-C was diagnosed in 0.05% (32/70 666) of children within two months of confirmed SARS-CoV-2 infection. Furthermore, SARS-CoV-2 positive children and adolescents were slightly more likely to visit their general practitioner for up to six months after infection compared with a reference cohort (selected from the entire cohort of children younger than 18 years who were tested for SARS-CoV-2 at some point during the study period), possibly indicating persisting symptoms of SARS-CoV-2 infection. Finally, the effectiveness of BNT162b2 was observed to be high in adolescents aged 12 to 17 years, with an estimated effectiveness of 93% against confirmed SARS-CoV-2 infection 60 days after the second dose.

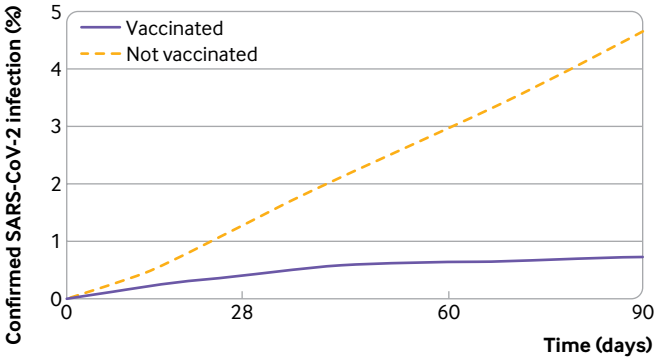
Strengths and limitations of this study

A major strength of our study is the nationwide coverage of the data sources used, allowing us to identify and

Table 2 | Rates of healthcare service use per 1000 individuals* from six months to one month before and from one month to six months after the index date. Values in brackets are total number of visits unless stated otherwise

	SARS-CoV-2 positive		Reference†		
Visit type	Baseline	Follow-up	Baseline	Follow-up	PERR (95% CI)
Hospital admission‡	22 (1094)	19 (947)	25 (15 056)	19 (11 323)	1.15 (1.02 to 1.28)
Paediatric admission	10 (506)	10 (469)	11 (6622)	9 (5356)	1.15 (0.99 to 1.30)
General practitioner	913 (44 722)	800 (39 163)	932 (566 365)	754 (458 286)	1.08 (1.06 to 1.10)
Outpatient	366 (17 929)	369 (18 064)	373 (226 938)	363 (220 525)	1.02 (0.98 to 1.07)
Paediatric outpatient	57 (2783)	54 (2654)	56 (34 202)	53 (32 414)	1.01 (0.95 to 1.06)
Private specialist	159 (7783)	164 (8038)	160 (97 153)	161 (97 992)	1.04 (1.01 to 1.07)

PERR=prior event rate ratio adjusted rate ratio; CI=confidence interval.
*Rates are reported in children younger than 18 years during baseline period from days −179 to −30 before testing and post-acute follow-up period from days 30 to 179 after testing.
†Reference cohort was sampled among all children and adolescents tested for SARS-CoV-2 during study period.
‡Admissions are defined as any hospital contact lasting 12 hours or more.



Individuals at risk:

Vaccinated			
229 799	228 867	217 695	165 493
Not vaccinated			
2 296 231	1 262 169	876 689	481 224

Fig 3 | Cumulative incidence of reverse transcriptase polymerase chain reaction test confirmed SARS-CoV-2 infection. Cumulative incidence curve for confirmed SARS-CoV-2 infection in adolescents aged 12-17 years vaccinated with mRNA vaccine BNT162b2 and matched unvaccinated adolescents, from the day the first vaccine dose was administered

follow all Danish children and adolescents tested for SARS-CoV-2 without being restricted to, for example, patients seen in the hospital setting. This increases the generalisability of our results, as most of the children and adolescents with SARS-CoV-2 infection do not require hospital admission. Furthermore, we had complete individual level ascertainment of all previous hospital contacts, prescription drug use, and contacts in the Danish primary healthcare system, and we were able to follow study participants for up to six months. However, our study also has important limitations. Firstly, SARS-CoV-2 infection status was established using highly sensitive and specific RT-PCR tests; however, the number of children and adolescents positive for SARS-CoV-2 is probably underestimated, decreasing the denominator in risk estimates.[18 19] Some young people with asymptomatic or mild infection might not undergo testing, and, although encouraged, a proportion with SARS-CoV-2 positivity detected using rapid antigen testing might not undergo subsequent RT-PCR testing. Secondly, we did not have access to medical records and therefore could not verify hospital diagnoses or reasons for contacts with primary care doctors at the individual level. Moreover, the ICD-10 diagnosis code for MIS-C was not implemented in Denmark until 1 April 2021, and until then young people with MIS-C received a discharge diagnosis code for Kawasaki disease. We therefore considered Kawasaki disease that occurred within two months of SARS-CoV-2 infection as MIS-C, which could 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, owing to the observational nature of our study, residual differences in the comparison of the SARS-CoV-2 positive participants with 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. Substantial geographical disparities in outcomes also exist, possibly related to differences in national management of the epidemic, access to healthcare, testing capacity, and issues of race, social inequality, and underlying child health. A systematic review reported that the paediatric case fatality rate of SARS-CoV-2 is only 0.01% in high income countries compared with 0.24% in low and middle income countries.[21] In Denmark, two deaths in children 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 due to SARS-CoV-2 infection.[22] Compared with the few previous studies providing population based data on the risk of hospital admission after SARS-CoV-2 infection, the reported risks were similar to those of Israel and Spain (0.2% to 0.5%), but lower than those reported from the UK (1.3%) and US (5.7%).[7 23-25] Both the case fatality rate and the risk of hospital admissions 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 threefold higher than that detected by national RT-PCR tests.[26] Assuming that the majority of undetected infections are asymptomatic or mild, the true risk of hospital admission after 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 a problem of distinguishing between children and adolescents admitted to hospital with covid-19 and those admitted with a preadmission screening test positive for SARS-CoV-2. Previous studies reported that 40-45% of hospital admissions registered to covid-19 were not related to diseases caused by SARS-CoV-2.[27] When we restricted our definition of covid-19 related hospital admissions to those of children and adolescents who were admitted for at least 24 hours and had a discharge diagnosis of covid-19, the risk of hospital admissions reduced fivefold.

Generally, we observed low risks of serious outcomes from SARS-CoV-2 infection in our high income setting with low health and socioeconomic inequalities. We found that neuroimmune complications were exceedingly rare, whereas MIS-C occurred in 0.05% of confirmed 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 generalising our results, as Denmark is predominantly a society of white ethnicity with a low prevalence of childhood obesity.[31]

The long term consequences of covid-19 in children and adolescents are still much debated. An increasing amount of literature reports on persisting symptoms after infection, such as fatigue, headache, cognitive difficulties, myalgia, and cough persisting in anywhere from 4% to 66% of young people 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 young people's wellbeing, comparison with non-SARS-CoV-2 infected individuals is crucial so as 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 12 weeks, but with wide ranges of prevalence and risk differences, ranging from 0.8% to 13.1% among SARS-CoV-2 infected children and adolescents and controls.[33-38] We did not have information on symptom based outcomes, but we observed that SARS-CoV-2 positive children and adolescents visited a general practitioner more often during follow-up than the reference cohort, possibly indicating persistent symptoms with some impact on daily functioning, although absolute differences in risk were small. Likewise, we identified an increased risk of initiating treatment with bronchodilators one to six months after SARS-CoV-2 infection, which could be related to persistent dyspnoea and cough. However, when we compared SARS-CoV-2 positive children and adolescents with those who were also tested for SARS-CoV-2, often because of respiratory symptoms and the required testing before contact with the healthcare system, the association diminished, which could imply that the observed signals are not specifically related to SARS-CoV-2 but to respiratory tract infections in general. Future studies are, however, needed to elucidate whether post-infectious symptoms are more common after SARS-CoV-2 infection than after other endemic respiratory viral infections.

In a non-controlled setting where the delta variant was predominant, this study estimated a high effectiveness of BNT162b2 in reducing the risk of confirmed SARS-CoV-2 infection in adolescents. Our estimates were similar to those reported from Israel (90%, 95% confidence interval 88% to 92%) seven to 21 days after the second vaccine dose, and we also showed that vaccine effectiveness remained high 90 days after vaccination.[5] Unvaccinated children and adolescents had a higher frequency of RT-PCR testing for SARS-CoV-2 during follow-up, which is in part explained by recommendations that asymptomatic testing be limited to unvaccinated adolescents during the autumn of 2021; however, vaccine effectiveness may be overestimated because of this limitation.

Policy implications

The implications of our findings for regulators are complex. Our data add to the existing evidence that SARS-CoV-2 infection in children and adolescents is generally mild and the risk of adverse events is low, although MIS-C was observed in 0.05% of children with RT-PCR confirmed SARS-CoV-2 infection. However, we also found that BNT162b2 is highly effective in reducing the risk of SARS-CoV-2 infection in adolescents, and, as with adults, vaccination might prevent covid-19 related hospital admissions—although we did not observe enough admissions during the study period to obtain meaningful risk estimates. Importantly, while the risk of adverse events related to SARS-CoV-2 infection is low in children and adolescents, vaccination can be indirectly beneficial by providing families with a sense of security and by contributing to a normalisation of young people'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 might also be favourable 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 the emergence of new SARS-CoV-2 variants.

Conclusion

We found that the absolute risks of hospital admission, ICU admission, and serious post-acute complications from SARS-CoV-2 infection in children and adolescents were generally low in a high income country such as Denmark with free access to healthcare. Children and adolescents with confirmed SARS-CoV-2 infection had a slightly increased risk of requiring bronchodilators and antibiotics one month to six months after SARS-CoV-2 infection, and they visited a general practitioner more often, which could indicate persistent symptoms after infection. Although our findings are generally reassuring, further large, population based studies are still urgently needed to provide additional data on both the short term and the long term morbidity after SARS-CoV-2 infection among children and adolescents. Real world effectiveness of BNT162b2 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.

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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. The study was, however, approved by the institutional data protection board at the University of Southern Denmark (11/247) and by the Danish Health Data Authority (FSEID-00005447).

Data sharing: Individual level data cannot be shared by the authors owing to Danish data protection regulations. Deidentified data can be made available for authorised researchers after application to Forskerservice at the Danish Health Data Authority. The analytical source code can be obtained from https://gitlab.sdu.dk/pharmacoepi/sars-cov-2-children/.

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) before the commencement of statistical analyses, and amendments to the analysis plan are also provided at this site.

Dissemination to participants and related patient and public communities: Study findings will be disseminated directly to Danish regulators and to the Danish Paediatric Society. Further, study findings will be provided to the public through press releases and via social media postings.

Provenance and peer review: Not commissioned; externally peer reviewed.

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Supplementary information: figures S1 and S2 and tables S1-S13