Diploma Thesis

The incidence of a SARS-CoV-2 infection amongst children and adolescents in a primary care setting using rapid antigen tests in comparison to a tertiary health care centre between November 1st, 2020, and February 28th, 2021, in Graz, Austria

submitted by

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Graz, 26.07.2023

Affidavit

I declare on my honour that I have written this thesis independently and without outside help, that I have not used any sources other than those indicated, and that I have marked the passages taken verbatim or in substance from the sources used as such.

Graz, 26.07.2023 Pia Katharina Winkler eh

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Abbreviations and acronyms

Ag-RDT	antigen-detecting rapid diagnostic test
ARDS	acute respiratory distress syndrome
bpm	beats per minute
CDC	Centre for Disease Control and Prevention
CFR	case-fatality rate
CI	confidence interval
COVID-19	coronavirus disease 2019
CRP	C-reactive protein
Ct	Cycle threshold
ED	Emergency Department
GCS	Glasgow Coma Scale
GGO	ground-glass opacity
GI	gastro-intestinal
i.e.	id est
ICU	intensive care unit
IQR	interquartile range
MERS CoV	middle east respiratory syndrome coronavirus
MIS-C	multisystem inflammatory syndrome in children
NAAT	nucleic acid amplification test
PCT	procalcitonin
RDT	rapid diagnostic tests

RNA	Ribonucleic acid
RT-PCR	reverse transcription-polymerase chain reaction
SARS-CoV	severe acute respiratory syndrome coronavirus
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
vs	versus
WHO	World Health Organisation
h	hours
d	days
y, yrs	years
mg	milligrams
ng	nanograms
µm	micrometres
mL	millilitres
>	more than
≥	more or as much as than
<	less than
≤	less or as less as

Figures and tables

Kurzfassung

Hintergrund Seit Oktober 2020 kam es aufgrund der besseren Verfügbarkeit und Praktikabilität zur Etablierung von Antigentests zur Diagnostik von SARS-CoV-2 Infektionen im niedergelassenen Bereich. Ziel der vorliegenden Studie ist Daten der Primärversorgung mit einem Tertiärversorgungszentrum zu vergleichen.

Methode Bei klinischem Verdacht auf eine SARS-CoV-2 Infektion bei Kindern und Jugendlichen wurde im Primärversorgungszentrum ein SARS-CoV-2 Antigentest mit einer nasopharyngealen Probe durchgeführt. Im Falle eines positiven Antigentests wurde das Ergebnis mit einem PCR-Test überprüft. Im Tertiärzentrum erfolgte im selben Zeitraum bei klinischem Verdacht auf eine SARS-CoV-2 Infektion eine PCR-Testung. Die Häufigkeit von SARS-CoV-2 Infektionen wurde mittels retrospektiver Datenanalyse der aufgezeichneten Fälle zwischen 01.11.2020 und 28.02.2021 sowohl im pädiatrischen Primärversorgungzentrum als auch im Tertiärversorgungszentrum erhoben.

Ergebnisse Im untersuchten Zeitraum wurde im Primärversorgungszentrum bei 412 symptomatischen Patient*innen und im Tertiärversorgungszentrum wurden im selben Zeitraum 1454 Patient*innen mit Symptomen auf SARS-CoV-2 getestet. Die Posititvitätsrate im pädiatrischen Primärversorgungszentrum betrug 2.2% (neun Tests waren positiv); in den anschließenden PCR-Tests zeigten sich ct-Werte unter 33. Das Tertiärversorgungszentrum testete im selben Zeitraum 5.4% der Fälle positiv auf SARS-CoV-2. Dies entspricht einem statistisch signifikanten Unterschied in der Posititvitätsrate ($p=0.01$) zwischen den medizinischen Versorgungszentren. Im Tertiärversorgungszentrum war bei SARS-CoV-2 infizierten Patient*innen Fieber, Husten, Schnupfen und der Verlust des Geschmacks-/Geruchssinns signifikant häufiger als bei negativ getesteten Patient*innen ($p<0.05$).

Conclusio Aus ambulant-pädiatrischer Sicht waren im untersuchten Zeitraum SARS-CoV-2 Infektionen bei Kindern und Jugendlichen insgesamt selten und wiesen mildere Verläufe auf als bei Erwachsenen. Hier zeigt sich im Vergleich eine niedrigere Positivitätsrate im niedergelassenen Bereich. Dies könnte einerseits durch die

gegenüber den PCR-Tests geringere Sensitivität der im Primärzentrum verwendeten Antigentests erklärt werden. Andererseits könnte es an der Tatsache liegen, dass Patient*innen mit ausgeprägter Symptomatik oder dem konkreten Verdacht auf eine SARS-CoV-2 Infektion primär eher das Tertiärzentrum aufsuchten.

Abstract

Background Since October 2020, rapid antigen-based tests for the diagnosis of SARS-CoV-2 infections were established in the primary care setting due to better availability and practicability. The aim of the present study is to compare data from primary health care with a tertiary health care centre.

Patients and Methods In case of suspicion of a SARS-CoV-2 infection in children and adolescents, a SARS-CoV-2 antigen test was performed with a nasopharyngeal specimen at the primary health care centre. In case of a positive antigen test, the result was verified with a PCR test. At the tertiary centre, PCR testing was performed during the same period. The frequency of SARS-CoV-2 infections was collected by retrospective data analysis of the recorded cases between 01.11.2020 and 28.02.2021 in both medical health care centres.

Results During the period studied, 412 symptomatic patients in the primary health care centre were tested with a rapid SARS-CoV-2 antigen-based test. In the tertiary health care centre, 1,454 patients with symptoms were tested for SARS-CoV-2 by PCR during the same period. The positivity rate in the primary care centre was 2.2% (9 tests were positive); subsequent PCR tests showed CT values below 33. The tertiary health care centre tested 5.4% of the cases positive for SARS-CoV-2 in the same period, representing a statistically significant difference in positivity rate ($p=.01$) between the medical centres. In the tertiary health care centre, fever, cough, rhinitis, and ageusia/anosmia were significantly more common in SARS-CoV-2 infected patients than in negatively tested patients ($p<0.05$).

Conclusion From an outpatient paediatric point of view, SARS-CoV-2 infections in children and adolescents were rare overall in the period studied and had milder courses than in adults. In comparison, a lower positivity rate is found in the primary health care centre. On the one hand this could be explained by the lower sensitivity of the antigen-based tests used compared to the PCR tests. On the other hand the fact that patients with pronounced symptoms or the concrete suspicion of a SARS-CoV-2 infection could have preferred to directly go to the tertiary health care centre.

1. Introduction

Coronavirus disease 2019 (COVID-19) initially was recognised as a cluster of atypical cases of pneumonia in late December 2019, in Wuhan, Hubei province, China. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) could be identified as the causative agent of this disease. From there on the novel virus spread fast beyond the borders of China and all over the world. First cases in Europe were recorded on January 24th, 2020, in France. (1) Because of the rapid human-to-human transmission, COVID-19 quickly progressed to a global problem.

On March 11th, 2020, the World Health Organisation (WHO) declared COVID-19 as a pandemic. (2) Since the beginning of the pandemic to end of January 2022, more than 340 million confirmed infections with SARS-CoV-2 and 5.5 million deaths due to the infection have been registered globally. Concerning Austria 1.5 million confirmed cases of COVID-19 and 13.5 thousand deaths have been recorded. (3) However, the given numbers are probably significantly underestimated because of the large number of oligosymptomatic and asymptomatic courses of disease, and limitations in diagnostic test availability. (4–6)

To date, numerous studies exist about transmission patterns of SARS-CoV-2, clinical and laboratory features in adults, but children and adolescents were rarely investigated, as they only represented a small percentage of those infected. Hence, studies are either lacking or have shown variable results in case studies depending on the observed country. (7–9)

The first relevant study identifying the epidemiological characteristics of COVID-19 among Chinese children and adolescents was carried out by Dong et al. During the study period from January 16th, 2020, to February 8th, 2020, 2135 SARS-CoV-2 infected children and adolescents younger than 18 years were reported to the Chinese Centre for Disease Control and Prevention (CDC). The conclusion of this study was that children and adolescents of all ages are vulnerable to a SARS-CoV-2 infection, thus particularly infants are susceptible for COVID-19. Furthermore no significant sex difference was reported. (7) There is a noticeable difference between virulence and pathogenicity of COVID-19 in Asian and European populations. Especially the mortality rate of COVID-19 in Italy (7.2%) was considerably higher than compared to China (2.3%). (10) Most studies were carried out in China, but nevertheless the data cannot necessarily be applied to the European population, as evidenced by the incidence of the SARS-CoV-2 infection and fatality rate in Italy. (11)

In Austria 530.844 cases of COVID-19, caused by SARS-CoV-2 have been reported since February 27th, 2020 until March 27th, 2021. As children under 15 years make up 14.4% of the Austrian population, they account for 7.9% of the reported cases. (12) The role of children and adolescents contributing to the transmission of SARS-CoV-2 still remains unclear. Early studies from the beginning of the pandemic have shown that children may be infected less frequently, do have milder symptoms, or have a greater number of asymptomatic infections compared to adults. (13–15)

The aim of this thesis is to retrospectively analyse the incidence of SARS-CoV-2 infections amongst symptomatic children and adolescents under the age of 18 years in a primary health care centre in Graz, Austria during November 2020 until February 2021. In addition, the characteristics as well as clinical signs and symptoms of this population will be compared to the population during the same time in a tertiary health care institution (Department of Paediatrics and Adolescent Medicine of the Medical University of Graz, Austria).

1.1 SARS-CoV-2

The SARS-CoV-2 is a new member of the coronavirus family. The coronaviruses are a group of various viruses; all of them causing mild to severe respiratory infections in humans. Nevertheless, they often originate from different kind of animals. In 2002 and 2012 there have been fatal respiratory diseases. Both causative agents belonged to the family of coronaviruses. In 2002 it was the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV); and in 2012 the Middle East respiratory syndrome coronavirus (MERS-CoV). (16) At the end of December 2019 the outbreak of an unusual pneumonia was registered in Wuhan, China. Chinese scientist confirmed that the causative virus isolated from bronchoalveolar lavage fluids must be a novel one.

(17,18) This time, the virus was designated as SARS-CoV-2, which is a single stranded RNA betacoronavirus with a potential zoonotic origin. The novel virus derived the name from SARS-CoV, as they share 79% of the genome sequence. 50% of the genome identity is similar to MERS-CoV. (16,19,20) The highly transmissible virus quickly spread all over the world, causing an extraordinary threat to the global public health. (21,22)

In course of the pandemic arose variants due to amino acid substitutions in the spike protein as a selective advantage. (23,24) An increase in SARS-CoV-2 cases at the end of December 2020 indicated the spread of the highly transmissible variant Alpha (B.1.1.7). in South Africa and Beta (B.1.351) in the UK. (25,26) The subsequent mutation Delta (B.1.617.2) has become the one of importance for the European region since December 2021. (27) Variant Delta has been followed by variant Omicron (B.1.1.529) which spread even quicker and caused mild infections. The Omicron variant remains the predominant one since the beginning of 2022 and shows an increased transmission rate and reduced effectiveness of vaccines. (24,28)

1.2 COVID-19

SARS-CoV-2 is susceptible to all age groups based on currents studies. (14) In adults a SARS-CoV-2 infection manifests itself by various symptoms after an incubation period of 1-14 days (median 5-6 days). (29) The Cochrane review about the accuracy of symptoms identifies 16 studies comprising 7706 patients, who were infected with SARS-CoV-2. They determine 27 symptoms, which can be subclassified in four categories: systematic, gastrointestinal, respiratory, and cardiovascular manifestations. The main clinical signs varied between each study, so no characteristic combination of symptoms can be described. The analysed symptoms have a high specificity but a very low sensitivity. Myalgia or arthralgia, fever, headache, and fatigue increase the likelihood of COVID-19. These symptoms are considered as red flags for a SARS-CoV-2 infection as their specificity is reported to be above 90%. (30)

Chen et al carried out a first representative descriptive study of SARS-CoV-2 infected adult patients in Wuhan, China. The study group consisted of 99 adults with a median age of 55.5 years. The patients were hospitalized between January 1st, 2020, and January 20th, 2020. The SARS-CoV-2 infection was detected via reverse transcription-polymerase chain reaction (RT-PCR). Half of the patients had chronic diseases. By the end of the study period 11 out of 99 patients (11%) died because of the SARS-CoV-2 infection. The first two deaths had no pre-existing comorbidities, but a long history of smoking. The study concludes that old men with an underlying chronic disease are highly susceptible to COVID-19. Vulnerable people are very likely to develop an acute respiratory distress syndrome (ARDS) or a septic shock followed by multi-organ failure. The case fatality rate displays the high pathogenicity and virulency of SARS-CoV-2 in humans. (31)

The SARS-CoV-2 infection in children and adolescents may develop a wide range of clinical manifestations in children and adolescents. Fever is the most common symptom, followed by respiratory symptoms such as cough, rhinorrhoea, and a sore throat. Especially in the young age group (2 - 15 years) gastrointestinal symptoms may indicate the beginning of a SARS-COV-2 infection. (32) Additional signs of infection are headache, tachypnoea, and tachycardia. Fatigue and myalgia are also often reported. (33) Anosmia or ageusia are only rarely occurring in this age group. (34,35) However, the loss of sense of smell or taste, similar to adults, seems to be a specific sign of a SARS-CoV-2 infection. (36) This summarises why the diagnosis of a SARS-CoV-2 infection is challenging to make in paediatric-adolescent patients.

In general, affected children without underlying chronic disease exhibit mild symptoms and have a low risk of hospitalisation or life-threatening complications. (37,38) Risk factors for more severe COVID-19 outcomes, which are present at the older age group, do not apply for children and adolescents. (39) Using the example of adult SARS-CoV-2 cases in Italy, these risk factors are most commonly arterial hypertension (68.3%), type II diabetes mellitus (3.,1%), or in 28.2% ischemic heart disease. (40)

Hence to the mild clinical presentation the number of unreported cases must not be disregarded. Depending on the structure and design of the studies, a percentage of 16%-35% of asymptomatic courses was considered. (41–43) However, the actual prevalence is probably higher, as younger children without symptoms are barely tested.

(44) Indeed, serological studies revealed that half of the children tested positive for SARS-CoV-2 has never shown clinical signs of an infection. (32)

A retrospective case study of 74 children infected with SARS-CoV-2 in Wuhan gave a delineation of the progression of COVID-19 in children at the beginning of the pandemic. (45) The children were all hospitalized in one health care centre between January 28th, 2020, and March 3rd, 2020. The age of the paediatric patients ranged from 2 months up to 15.3 years. The SARS-CoV-2 infection was confirmed by RT-PCR assays of nasal or nasopharyngeal swab samples. 22 out of 74 children (29.7%) were asymptomatic but were hospitalized as they had contact with infected family members or were in hospital care because of other reasons and then were diagnosed with a SARS-CoV-2 infection. The children with symptoms initially manifested in 55.4% by cough and in 51.4% by fever. Cough with sputum (28.8%) and diarrhoea (13.5%) were observed upon admission. Furthermore, poor appetite, vomiting, fatigue, myalgia, and abdominal pain were stated but in rare cases. Laboratory indices on admission showed neither a lymphopenia nor a thrombocytopenia in any case. 17 children (23.0%) demonstrated elevated levels of aspartate aminotransferase. The highly sensitive C-reactive protein was elevated in 14 children (18.9%). None of the 74 studied children was positive for Influenza virus A and B in the collected nasopharyngeal specimens. Upon admission computed tomography (CT) scans of the chest were taken from each child. Half of them (40 patients, 54.1%) showed a pathologic CT with unilateral or bilateral pulmonary infiltrates. Predominant findings were multifocal ground-glass opacities (35.1%) or a patchy consolidation (18.9%). More abnormal CT manifestations were observed in symptomatic children than in asymptomatic children. 5 children (6,7%) displayed abnormal CT findings without any concomitant respiratory or digestive symptoms proofing the SARS-CoV-2 infection. (45)

Italy was the first European country with exploding numbers of SARS-CoV-2 infections. Since February 20th, 2020, the incidence of COVID-19 multiplicated with originally confirmed cases in the Lombardy region. As the mortality of COVID-19 in Italian adults was the highest compared to the global numbers, children and adolescents under the age of 18 years represented only 1% of the total number of the SARS-CoV-2 infections in Italy. (46) The author of The Coronavirus Infection in Paediatric Emergency Departments (CONFIDENCE) study illustrated in a letter to the editor of The New England Journal of Medicine the following condition in 17 paediatric emergency departments in Italy in a representative study. The cohort consisted of 100 Italian children with a median age of 3.3 years who were diagnosed with a SARS-CoV-2 infection via nasal or nasopharyngeal swabs analysed with RT-PCR. The study period was from March 3rd, 2020, to March 27th, 2020. Contrary to the retrospective case study of 74 children in Wuhan (45) the majority of Italian children (55%) contracted the infection outside of the child's family. The most common symptoms upon admission were increased temperature with temperature levels above 37.6°C (54%) and cough (44%). Putting the symptoms of COVID-19 in perspective of the classification by Dong et. (Table 1) (7) 21% of the children were asymptomatic, 58% had mild symptoms, 19% moderate, 1% severe, and 1% showed critical symptoms of disease. Both severe and critical cases had underlying health conditions. (47)

Simultaneously to the Italian study (47), research was done on the epidemiology and clinical presentation of SARS-CoV-2 infected children in Geneva, Switzerland by Posfay-Barbe et al (48). This Swiss study involved all patients younger than 16 years with a confirmed SARS-CoV-2 infection between March 10th to April 10th, 2020 identified by the Geneva University Hospital´s surveillance network. During this period in total 4310 patients tested positive with SARS-CoV-2 infection. Out of these 40 patients were younger than 16 years, which represents 0.9% of this population. The nasopharyngeal swabs were analysed for SARS-CoV-2 by RT-PCR. 18% (7 children) were hospitalized. None of the observed children required intensive care unit (ICU) admission or specific therapies. Most common symptoms of SARS-CoV-2 infection were cough (82%) and fever (67%). More than half of the cases reported atypical manifestations like headache and nasal discharge. Diarrhoea was reported in 18% of the cases. (48)

On June 25th, 2020, the first European multinational, multicentre cohort study (41) was published with 582 participating children and adolescents under the age of 19 years in 82 health-care institutions across 25 European countries. The median age was 5 years.

The study period was from April 1st to April 24th, 2020 – a time when COVID-19 was spread all over Europe for the first time. The diagnosis of a SARS-CoV-2 infection was made through RT-PCR analysis of samples at any anatomical site of the patient (respiratory tract, blood, stool, or cerebrospinal fluid). In this study 60% of children got infected by parents or siblings. For the remaining 40% the source of infection was not by a family member or of unknown origin. In this study not only tertiary and quaternary health-care institutions but also secondary or primary health-care institutions diagnosed the SARS-CoV-2 infection. The clinical presentation of COVID-19 was in 65% of the cases pyrexia with a body temperature level at 38°C or above. Furthermore, 50% showed symptoms of an upper respiratory tract infection. 25% presented with lower respiratory tract infection. Gastrointestinal symptoms were reported in 22% of the children. 7% had gastrointestinal symptoms because of the SARS-CoV-2 infection without having signs of a typical respiratory infection. Asymptomatic children, who never developed any symptoms of illness, accounted for 16% in this cohort study. Co-infections with other viral agents were determining factors for requiring admission to the ICU. Four deaths were reported during the study. Accordingly, the case-fatality rate was 0.7%. (41)

1.3 Epidemiology and Transmission

One year after the first SARS-CoV-2 infection was confirmed, the epidemiology and transmission of SARS-CoV-2 infections in children and adolescents has yet to be fully delineated. (49,50) Initially, the comparison to the transmission patterns of the SARS outbreak in 2003 was drawn. (51,52) In Europe, early public interventions in order to limit the viral shedding, closures of the education system and day care facilities initially reduced the transmission of SARS-CoV-2. (53) By autumn 2020, the infection rate increased drastically in the European countries. (54) Still, the role of children in the transmission of SARS-CoV-2 remained unclear as the majority of the young age group showed asymptomatic or mild symptoms after infection. In a systematic review by Viner et al. patients younger than 20 years have a lower susceptibility to get infected by SARS-CoV-2 with a probability of 56% compared to patients older than 20 years. (50)

Nevertheless, asymptomatic children do spread the virus. (42,44,55) However, the viral load of asymptomatic children is usually lower than that of children with symptoms. (56)

The main transmission route happens via droplets with a diameter ≥5µm, which are reaching distances of one meter by sneezing or coughing. In aerosol droplets the virus is estimated to stay active for up to three hours. (51) Direct and indirect paths of transmission are possible due to the stability of the virus for 48h on stainless steel and 72h on plastic surfaces. (52) Faecal viral shedding has been proven in both children and adults. (57) From today's perspective vertical transmission is possible but can be neglected as the clinical relevance is not given. (58,59)

A potent driver of transmission is the respiratory tract. Therefore, a study was carried out to determine the correlation between the viral load of SARS-CoV-2 RNA analysed via RT-PCR and the severity of symptoms in adults and children. Early case reports from Italy stated an inversed association between Ct (Cycle threshold) values and the probability of a positive SARS-CoV-2 extraction of the specimen. The lower the Ct value, the higher the viral load in the respiratory tract, but with no significant difference between symptomatic and asymptomatic patients. (60) A recent study from North America concludes that ct-levels are significantly lower in symptomatic patients regardless of the age. Additionally, asymptomatic children do not have significant different levels of SARS-CoV-2 RNA in comparison to asymptomatic adults. This also applies to symptomatic children and adults. The specimen of this study were taken in the in mid-turbinate or anterior nares regions. (61)

By analysing epidemiological patterns of COVID-19 a division into asymptomatic, mild, moderate, severe, and critical patients allows a more detailed delineation. The first epidemiological study by Dong et al. in March 2020 (7) classifies patients depending on their clinical presentation. "Asymptomatic" SARS-CoV-2 patients do not develop any clinical, radiological or laboratory signs but show a positive SARS-CoV-2 nucleic acid test result. "Mild" symptoms include a sore throat, cough, rhinitis, fever, or fatigue. In the physical examination of a mild infection are signs of an acute upper respiratory tract infection but no pathologic findings in the auscultation of the lungs. Additionally, children presenting only digestive abnormalities with or without fever are also classified as “mild”. “Moderate” infections show on the one hand no signs of hypoxemia but on the other hand symptoms of pneumonia with fever and cough. On top, subclinical lung lesions in the computed tomography (CT) of the chest allocate to the “moderate” classification. “Severe” SARS-CoV-2 infections present any kind of respiratory and digestive symptoms combined with dyspnoea and central cyanosis (oxygen saturation <92%). Patients who risk progressing to the acute respiratory distress syndrome belong to the “critical” cohort. Shock, coagulation dysfunction, encephalopathy, acute kidney, or myocardial injury are signs of a critical SARS-CoV-2 infection. This classification of Dong et al. does not take laboratory findings into consideration (Table 1). (7)

TABLE 1 Severity of Disease Classification Based on Associated Signs and Symptoms

Leading Signs and Symptoms	Asymptomatic	Mild	Moderate	Severe[a]	Critical[b]
Cough	−	+	+[c]	+	+
Fever	−	±	+	+	+
Fatigue	−	+	+	NR	NR
Myalgia	−	+	+	NR	NR
Sore throat	−	+	+	NR	NR
Runny nose	−	+	NR	NR	NR
Sneezing	−	+	NR	NR	NR
Congestion of the pharynx	−	+	NR	NR	NR
Chest auscultatory findings	−	−	±	+	+
Nausea	−	+[d]	NR	NR	NR
Vomiting	−	+[d]	NR	NR	NR
Abdominal pain	−	+[d]	NR	NR	NR
Diarrhea	−	+[d]	NR	+	NR
Wheezing	−	−	±	NR	NR
Dyspnea	−	−	NR	+	+
Hypoxemia	−	−	−	+	+
Central cyanosis	−	−	−	+	+
Acute respiratory distress syndrome	−	−	−	−	+
Respiratory failure	−	−	−	−	+
Shock	−	−	−	−	+
Encephalopathy	−	−	−	−	+
Myocardial injury or heart failure	−	−	−	−	+
Coagulation dysfunction	−	−	−	−	+
Acute kidney injury	−	−	−	−	+
Chest imaging	−	−	+[e]	+	+
SARS-CoV-2 PCR	+	+	+	+	+

NR indicates not reported in the classification of Dong et al.[2] + indicates the presence of a symptom, whereas − indicates the absence; ± indicates that symptom may come with other symptoms or not be present. PCR, polymerase chain reaction.

[a] Mild or moderate clinical patterns and any manifestations suggesting rapid disease progression (ie, tachypnoea, hypoxemia with oxygen saturation <92%, neurologic deterioration, dehydration, myocardial injury, coagulation dysfunction, or rhabdomyolysis).

[b] Quick progression of disease with respiratory failure with need for mechanical ventilation (ie, acute respiratory distress syndrome or persistent hypoxia), septic shock, or multiple organ failure.

[c] Mostly dry cough, followed by productive cough.

[d] Some cases may have only digestive symptoms such as nausea, vomiting, abdominal pain and diarrhea.

[e] Pneumonia is the leading criteria to classify a patient into the moderate severity of disease. Some cases may have no clinical signs and symptoms, but chest CT shows lung lesions, which are subclinical.

Table 1 Primary symptoms related to COVID-19 by Dong et al. (in Pediatrics 2020, June, Volume 145, Issue 6)

1.4 Complications

Regardless of the severity of the infection, two long-term consequences following a SARS-CoV-2 infection are of concern: multisystem inflammatory syndrome in children (MIS-C) and long-COVID.

1.4.1 MIS-C

In the course of the pandemic, there has been an increased occurrence of school-aged children and adolescents with prolonged fever, abdominal pain, and cardiac dysfunction in combination with a confirmed SARS-CoV-2 infection in the previous 2 - 6 weeks. The clinical signs and a cluster of reported cases in a British hospital pointed to the occurrence of a paediatric multisystem inflammatory syndrome associated with a previous SARS-CoV-2 infection. (62,63) The Centre for Disease Control and

Prevention (CDC) named the new medical condition MIS-C. (64) According to current knowledge MIS-C, also known as paediatric inflammatory multisystem syndrome-temporally associated with SARS-CoV-2 (PIMS-TS), a post-infectious hyperinflammatory immune reaction. (65–68) According to the CDC COVID-19 response team, MIS-C is more frequent in school aged children, with a median age of 8 years. Male patients are affected slightly more often (55%). (63,69)

Usually, children diagnosed with MIS-C present 2 - 6 weeks after being infected with SARS-CoV-2 with fever and at least one of the following symptoms: rash, conjunctivitis, gastrointestinal symptoms, neurologic symptoms, oral mucosal changes, cervical lymphadenopathy and peripheral oedema. (70) These manifestations are overlapping with symptoms of the Kawasaki's disease, the toxic shock syndrome, and the acute abdominal condition. An existing SARS-CoV-2 infection can usually be detected serologically or suspected on the basis of a proven exposure. (71) Immunoglobulins and, if necessary, corticosteroids and acetylsalicylic acid are used therapeutically. In the majority of cases intensive care treatment is necessary with the need of catecholamines and artificial ventilation. Complete healing occurs predominately, but complications such as cardiovascular symptoms might remain. (72,73)

1.4.2 Long-COVID in children

Similar to other infectious diseases (e.g., EBV), there are more and more reports of persistent medical conditions after an acute SARS-CoV2 infection. Fatigue is the most common symptom associated with long-COVID. Sleep disturbances, concentration difficulties, myalgia, nasal obstruction, and headache often occur together with fatigue. Chest pain, nausea, persistent cough, palpitations, gastrointestinal distress, arthralgia, or exanthema are less common symptoms. Highly variable data exists about sore throat or anosmia. (74,75) These symptoms beyond a period of four weeks after infection are called long-COVID or post-acute sequelae of COVID-19. If they persist for more than twelve weeks, they are referred as post-COVID syndrome. (76–78)

Studies analysing long-COVID symptoms in comparison between seropositive and seronegative children and adolescents were carried out in Switzerland and the United

Kingdom. In the Swiss study, 1.355 children and adolescents (of whom 109 were seropositive) aged 6 and 16 years were interviewed 6 months after serological testing reporting long-COVID matching symptoms. (79) In the British analysis, 1.734 confirmed SARS-CoV-2 infected 5 - to 17 - years old children and adolescents were consulted regularly in comparison with a matched control group. (80) In contrast, data without inclusion of a control group were published from Italy (consisting of follow-ups of 123 children and adolescents at a mean of 5 months after SARS-CoV-2 infection), the Netherlands (retrospective analysis of 89 long-COVID cases in paediatric departments) and Australia (follow-ups of 151 children 3-6 months after SARS-CoV-2 infection), as well as in a small Swedish case series (on 5 children and adolescents with long-COVID symptoms). (74,75,81–83)

The incidence of long-COVID syndromes ranges from 4 – 9 % in British, Swiss, and Australian studies. (81) Medical conditions persisting for more than 4 weeks are significantly more frequent in seropositive children (4 %) compared to the control group (1 %) in the British study. (80) In the Swiss study, prolonged symptoms (>12 weeks) affected seropositive (4 %) participants more frequently than seronegative (2 %) participants. (79) In the Italian cohort analysis, 58 % of the children and adolescents correspond to the medical condition of long-COVID. (74) In the British and Australian studies, there was a high tendency for the symptoms to regress over time. While 4 % of the COVID-19 convalescents in the British analysis reported symptoms for ≥4 weeks, only 2 % were symptomatic for ≥8 weeks. In the Australian cohort, symptoms completely regressed within the follow-up period (3 - 6 months). (80,81)

1.5 Situation in Austria during the study period

At the beginning of October 2020, the peak value of daily confirmed new infections since the start of the pandemic was exceeded for the first time and the beginning of a second wave of infections was announced. (84) To prevent the human-to-human transmission of SARS-CoV-2 the Federal Government of Austria took various actions during the study period between November 1st, 2020, and February 28th, 2021.

By November 3rd, 2020, Austria moved into “lockdown light” due to the accelerated transmission rate. Social interactions were limited by cancelling all public gatherings, closing the gastronomy, the hotel industry, and all non-essential businesses. With COVID-19 precautions only supermarkets, pharmacies, clinics, petrol stations remained open. Initially, educational facilities and childcare centres remained open too. There was a curfew to stay at home between 8 p.m. and 6 a.m. (85)

On November 11th, 2020, a peak of infections was recorded with 3,1 % of the Austrian population older than 16 years being tested positive with SARS-CoV-2. Due to a national prevalence study, 55 % of the infected people presented mild to no symptoms of illness. (86,87) Consequently, stricter measurements were imposed on November 14, 2020: the lockdown expanded to the entire day, social contacts were restricted to the minimum, educational facilities were instructed to close, and health services were re-prioritised.

With December 6th, 2020, first steps of reopening were performed by opening the retail market and establishing COVID-19 precautions, e.g., using masks, keeping one meter distance to everybody. It took until February 8th, 2021, to lift many of the measures that had been in place until then, such as the closure of shops and schools.

1.6 SARS-CoV-2 detection tests

Tests to diagnose SARS-CoV-2 infections are widely used to detect the disease at an early stage and to prevent transmission of the disease. (88) There are two diagnostic tests available: RT-PCR and rapid antigen-based detection tests, with RT-PCR being the gold standard. The use of antigen-based detection tests is crucial to provide rapid and broad screening in primary health care centres. These two techniques represent direct methods to detect the virus during an active infection. A SARS-CoV-2 infection can also be confirmed indirectly by testing for the corresponding immunoglobin antibodies. However, only previous infections can be detected by this method. (89)

RT-PCR requires some time of operation by well-trained staff at the local laboratory, Diagnostic & Research Institute of Hygiene, Microbiology and Environmental Medicine, Medical University of Graz. Hence, accurate and timely SARS-CoV-2 test devices are fundamental in case of emergency, for screening purposes and to expedite disease prevention and control.

1.6.1 RT-PCR

The gold standard in the diagnostic of SARS-CoV-2 is the real-time reverse-transcription polymerase chain reaction. (90,91) The principle of this nucleic acid amplification testing is the denaturation of the ribonucleic acid into fragments in the initial cycle. Then the priming and the exponential multiplication of the material takes place in several cycles. Depending on the concentration of SARS-COV-2 RNA in the specimen, the multiplication of the RNA happens more quickly, and the cut-off level is surpassed, which implies a positive result. Therefore, the circle threshold-value (ct-value) represents the measure of the SARS-CoV-2 RNA concentration in the sample. (92) The cut-off value in this study is 33, with lower values indicating actual infection and transmission of SARS-COV-2.

1.2.1 Antigen-based rapid diagnostic tests

Since September 11th, 2020, the WHO advised using rapid diagnostic tests (RDTs), especially antigen-based test devices (Ag-RDTs). This procedure is based on the detection of SARS-CoV-2 viral proteins in respiratory secretions. In a cassette a lateral flow assay is performed with a visual result after 15 minutes. (93)

The WHO sets the standards for the requirement of at least 80 % sensitivity and 97 % specificity to detect SARS-CoV-2, compared to a nucleic acid amplification test (NAAT), like the RT-PCR. In addition, the WHO proposes the use of rapid SARS-CoV-2 tests in remote areas, for screening purposes, and to monitor the incidence in communities. Ultimately, shortage of RT-PCR test capacity during an outbreak requires the use of RDTs. (94–96)

In the primary health care centre in Graz tests by Panbio™ COVID-19 Ag Rapid Test Device were used since November 2020 for the quick point-of-care diagnosis of symptomatic children. This test device was used due to its sensitivity of 91.7 % (95% CI 85.8 – 93.4) and its specificity of 98.9% (95% CI 97.5 – 99.6). Especially in terms of the sensitivity in case identification (92.6%) and contact tracing (94.2%) this test device has its strengths. The asymptomatic screening with this rapid diagnostic test has a hit rate of 79.5%. (97) At ct-values below 25 the sensitivity is particularly high with 98.2%. The capacity of effective transmission at Ct levels above 25 is discussed. (98)

1.6.2 Antibody-based tests

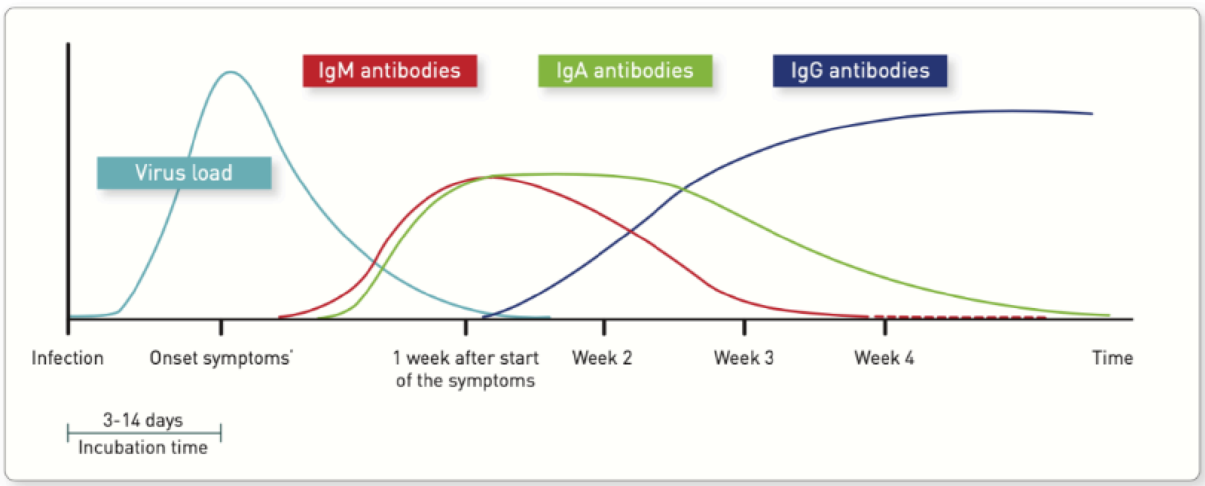

Table 2 Development of the antibody response (IMD Berlin,2020,p. 1 (128)*)*

detection of a SARS-CoV-2 infection by antibody-based test assays have limited potential, as neutralising antibodies cannot be detected at the onset of infection. (Table 2) (99) Respectively, the mean seroconversion time of IgM and IgG rages from 18 to 20 days after infection. (100,101) Therefore, antibody-based tests are applicable at the ending of the disease for epidemiological studies, and for the confirmation of neutralising antibodies in the blood for individuals. (102)

2. Methods

2.1 Study design and participants

This retrospective study was approved by the ethic committee of the Medical University Graz (ethic committee approval number 33-449 ex 20/21).

Inclusion criteria:

All children 18 years or younger who took either a SARS-CoV-2 rapid antigen-based test or a nucleic acid amplification test (RT-PCR) with symptoms of illness and who sought admission to the primary health care centre of MD Peter Fritsch in Graz or to the Emergency Department of the Paediatric and Adolescent Medicine, Medical University Graz were included during the study period between November 1st, 2020, and February 28th, 2021. Additionally, patients were included with a high risk of exposure, exposure to a person tested positive with SARS-CoV-2 within the last 14 days and signs of illness.

Exclusion criteria:

Children and adolescents were excluded from this study who performed a test without any signs of illness. Patients with insufficient data were also excluded from the analysis.

Test procedures:

The used tests at primary health care centre were Panbio™ COVID-19 Ag Rapid Test Devices or nucleic acid amplification tests, namely based on real-time reverse transcriptase-polymerase chain reaction (RT-PCR), in the event of a positive result. At the tertiary health care system all children were tested with RT-PCR using the in vitro diagnostics / Conformité Européenne (IVD/CE) - labeled Cobas R SARS-CoV-2 test (Roche Molecular Systems, Branchburg, NJ, USA) for use on the Cobas R 6800/8800 system (Roche Molecular Diagnostics, Rotkreuz, Switzerland). (103)

2.2 Study definitions

A SARS-CoV-2 confirmed case was a patient in whom the SARS-CoV-2 RNA was detected in a specimen of the respiratory tract via RT-PCR with a ct-value below 33.

RT-PCR testing was conducted as part of routine clinical care according to the COVID-19 guidelines. The day, when the first symptom occurred is considered as the date of onset of symptoms. Date of diagnosis is defined as the day of the first positive SARS-CoV-2 RT-PCR test. Pyrexia was defined as a body temperature of at least 37.5°C.

Data was acquired with a standardised data collection form (enclosed in the Appendix) and obtained from records of outpatients' and hospitalised patients' medical assessments in the electronic hospital information system 'Medocs' at the Emergency Department of Paediatrics and Adolescent Medicine, Medical University Graz. The same procedure was performed at the primary health care system where the data was obtained from records on its electronical information system.

In this study the following symptoms of each patient were evaluated: pyrexia, tonsilitis, coughing, pharyngitis, rhinitis, conspicuous or accelerated respiratory sounds, sudden anosmia or ageusia, gastrointestinal symptoms including vomiting and diarrhoea. In addition, the risk of exposure was evaluated. The chaperone was asked the identical questionnaire to evaluate the exposure to SARS-CoV-2 infected persons.

The numbers were analysed in subgroups according to measures of disease prevention and control which were summarized in 'lockdown'. Applicable throughout Austria and thus also for the primary and tertiary health care centre. At the beginning of the study period, "light" lockdown measurements were applied. In this study, '**Lockdown light I**' covered the period from 1st November 2020 to November 16th, 2020. As the incidence of SARS-CoV-2 increased rapidly in Austria, more rigorous prevention measures were introduced by November 17th, 2020. The lockdown that followed, called **Lockdown 1** in this study, lasted from November 17th, 2020, to December 7th, 2020. The strict prevention measures were loosened on December 8th, 2020. From this day until Christmas Day, December 25th, 2020, lockdown light measurements were applied again. This period is summarised in the present study by **'Lockdown light II'**. By December 26th, 2020, the Austrian Government implemented stricter measures for disease prevention and control. The second strict lockdown during this study period followed: '**Lockdown 2**' started on December 26th, 2020 and ended on February 7th, 2021. On February 8th, 2021, until the end of the study period on 28th

February 2021, the strict measures were lifted and ‘lockdown light’ restrictions were reinstated – called ‘**Lockdown light III**’ in this study.

3. Statistics

The collected data was anonymised and subsequently registered in an Excel-file. The statistical analysis was either performed using Excel, or the statistical program SPSS (version 27; IBM). For a detailed analysis, the study population was divided into groups according to their characteristic value.

The Shapiro-Wilk test was used to assess the distribution of the data. Depending on the distribution, the data were summarised as followed: Normally distributed quantitative data with continuous variables were summarised according to by its mean, range and or ± standard deviation (SD) as required. The 2-sample t-test was applied to explore the difference between continuous normally distributed variables. Non-normally distributed figures were presented by the median and the interquartile range (IQR). Non-normally distributed characteristics were compared with each other using the Mann-Whitney U test. The analysis of qualitative data was outlined by frequencies in absolute and relative numbers. Percentages of clinical characteristics were calculated from the number of children included in that specific characteristic. Categorical data were compared by the Pearson or Spearman test. To identify the reasons for heterogeneity, subgroup analysis was performed.

The strength of evidence is represented by the p-value, with $p<0.05$ indicating a statistically significant difference.

4. Results

The study population is described in the first section of this chapter (4.1) with respect to the demographic characteristics. The subsequent section (4.2) summarises the primary health care centre, followed by the tertiary health care centre in 4.3. The characteristics of the children infected with SARS-CoV-2 in the two centres are then compared in chapter 4.4. Finally, in 4.5, a case study of a particularly severe course of the disease is presented.

4.1 Characteristics of the study population

Study population	**Primary health care centre**	**Tertiary health care centre**	**p value**
n	**412**	**1454**	
Lockdown light I (16d)	56	204	
Lockdown 1 (21d)	83	237	
Lockdown light II (18d)	59	204	
Lockdown 2 (44d)	118	508	
Lockdown light III (21d)	96	301	
Gender			
Female (n(%))	203 (49.3%)	669 (46.0%)	**n.s.**
Age (in yrs; median [IQR])	2.9 (1.6-6.2)	2.6 (1.1-6.4)	**.04**
Time to diagnosis (in d; median [IQR])	2 (1-3)	**1 (1-4)**	**0.01**
Pre-existing conditions (n(%))	54 (13.1%)	179 (12.3%)	**n.s.**
Clinical symptoms (n(%))			
Temperature >37.5°C	200 (48.5%)	**820 (56.4%)**	**.01**
Sore throat	**103 (25.0%)**	223 (15.3%)	**<.01**
Coughing	**160 (38.8%)**	453 (31.2%)	**<.01**
Rhinitis	**153 (37.1%)**	427 (29.4%)	**<.01**
Dyspnoea	35 (8.5%)	**289 (19.9%)**	**<.01**
Tachypnoea	17 (4.1%)	**102 (7.0%)**	**.04**
Anosmia/Ageusia	0	7 (0.5%)	**n.s.**
GI symptoms	74 (18.0%)	**583 (40.1%)**	**<.01**
Earache	**23 (5.6%)**	38 (2.6%)	**<.01**
Headache	13 (3.2%)	**105 (7.2%)**	**<.01**
Contact to an infected person	**40 (9.7%)**	68 (4.7%)	**<.01**

Table 3 Basic characteristics of the population

First of all, during the entire study period between November 1st, 2020, and February 28th, 2021, a total of 1866 children and adolescents with symptoms (described in table 1.2) were tested for SARS-CoV-2 in two different health care centres in Graz, Austria.

412 children and adolescents took a SARS-CoV-2 detection test at the primary health care centre. In case of a positive outcome, the result was confirmed with RT-PCR. 1454 children and adolescents were registered during the same time at the tertiary health care centre. Those were only tested by RT-PCR.

In the primary health care centre, this means an average testing-frequency of about 3 (IQR 3 – 4) children per day during the study period of 120 days (412/120d). In comparison, 12 (IQR 11 – 13) symptomatic children were tested per day at the tertiary health centre (1454/120d). There were no significant differences between the gender ratios. The study populations of the two health care centres were also comparable in terms of patients with underlying health conditions (13.1% at the primary vs.12.3% at the tertiary health care centre), with correlating numbers listed in Table 3 according to the health care centres.

Regarding the age, the study population at the tertiary health care centre was younger compared to the primary health care centre. The median age of the study population at the tertiary health care centre was 2.6 years (IQR 1.1 – 6.4 y). At the primary health care system, the median age was 2.9 years (IQR 1.6 – 6.2 y; p=0.04). The time to diagnosis varied between the two health care centres: the study population at the tertiary health care centre sought help 1 day after onset of symptoms (IQR 1 – 4 d), whereas patients at the primary health care centre presented after a median time of 2 days (IQR 1 – 3 d; p=0.01). This tendency was also seen in terms of symptom severity: fever, tachypnoea and gastrointestinal symptoms were more likely to be treated at the tertiary health centre.

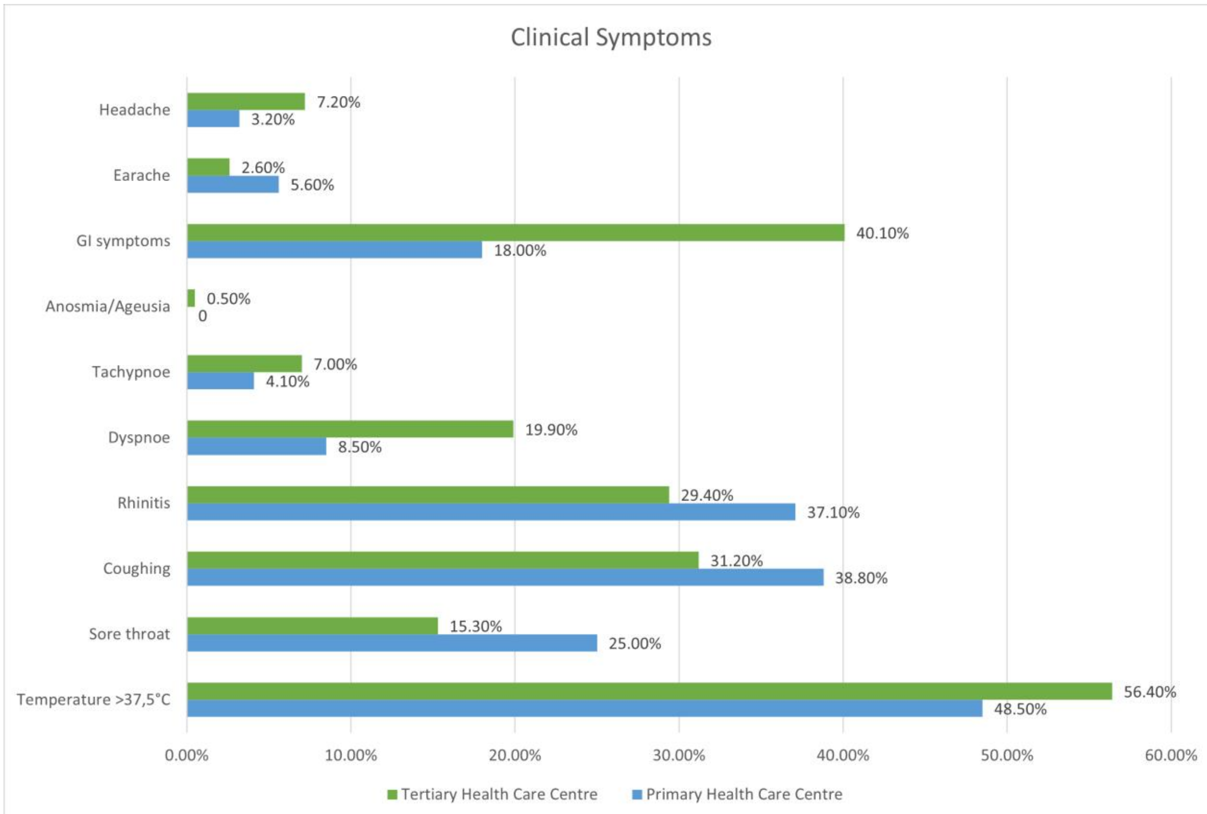

Table 4 Comparison of the symptoms

Parents chose to attend a primary or tertiary health centre for their children for a variety of reasons. A higher percentage of children with mild symptoms including a sore throat, cough, rhinitis, or earache visited the primary health care centre to determine the cause of the disease ($p=<0.01$ for each symptom compared to the other health care centre). Children with fever ($p=0.01$), shortness of breath ($p=<0.01$), accelerated breath ($p=0.04$), gastrointestinal symptoms ($p=<0.01$), or headache ($p=<0.01$) were more likely to visit the tertiary health care centre. The risk factor of a close contact to a SARS-CoV-2 infected person was more frequent (9.7% at the primary vs. 4.7% at the tertiary health care centre) at the primary health care centre ($p=<0.01$).

To assess the risk of a SARS-CoV-2 infection, the reason for presentation at the health care centre was registered. At the primary health care centre 372 out of 412 children (90.3%) and at the tertiary health care centre 1526 out of 1454 (81.8%) visited the health care centre due to symptoms of illness. A small proportion (40/412; 9.7% at the primary, and 68/1454; 4.7% at the tertiary health care centre) were symptomatic children with a history of being a close contact to an infected person. Milder symptoms like a sore throat, cough, rhinitis, or earache were more often treated at the primary health care centre.

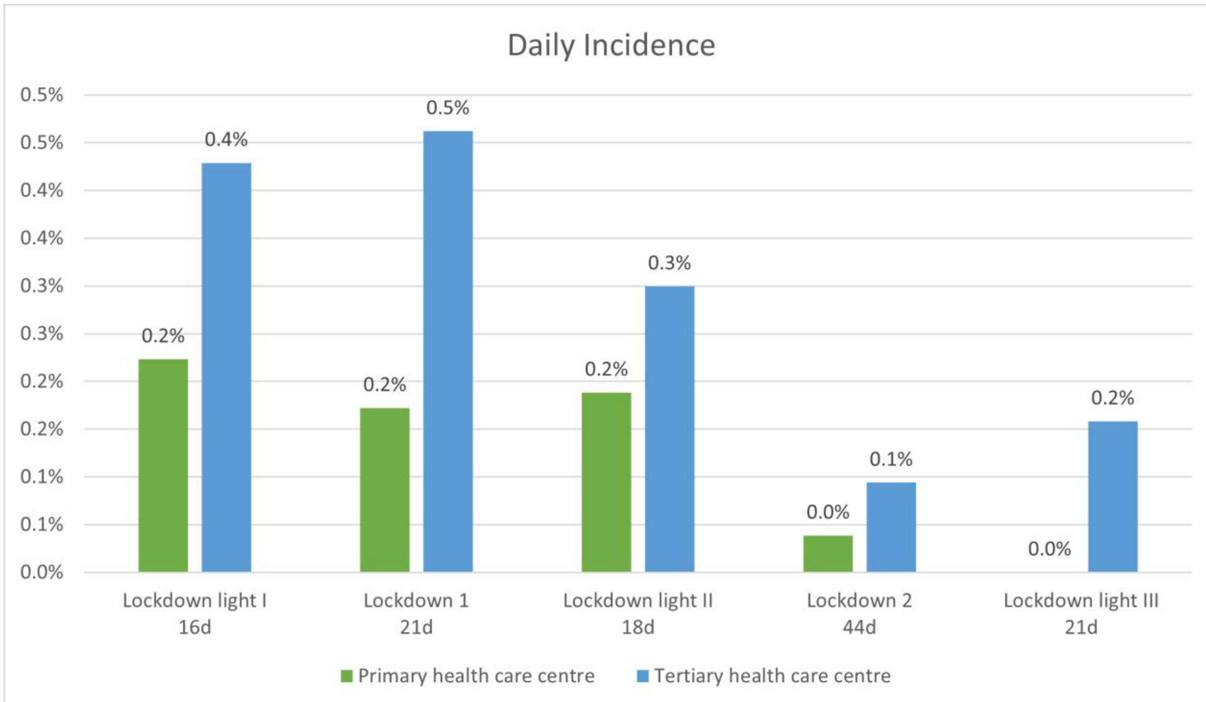

Table 5 Daily incidence during the various lockdowns

To calculate the daily incidence, the number of children infected with SARS-CoV-2 compared to all children tested during the lockdown was related to the duration of the lockdown. The duration of each lockdown is given in Table 5. Looking at the incidence of the two centres separately, the numbers are the following.

The incidence of SARS-CoV-2 infected children varied at each health care centre: During 'Lockdown light I', 0.2% (2/56/16) of the children at the primary and 0.4% (14/204/16) at the tertiary health care centre were confirmed SARS-CoV2 infected children. During the strict 'Lockdown 1', 0.2% (3/83/21) at the primary and 0.5% (23/237/21) of the children at tertiary health care centre were found infected with SARS-CoV-2. Respectively, 0.2% (2/5918) at the primary and 0.3% (11/204/18) at the tertiary health care was the frequency of children infected during 'Lockdown light II'. During the long 'Lockdown 2' the incidence at the primary health care centre decreased to 0.0% (2/118/44). At the tertiary health care centre, the difference was not that striking with an incidence of 0.1% (21/508/44) during 'Lockdown 2'. At the end of the study, during

‘Lockdown light III’ no infected (0/96/21) children were registered at the primary health care centre. At the tertiary health care centre 0.2% (10/301/21) of the children were found infected during the same period. In summary, the positivity rate was significantly higher at the hospital, but overall, there was a decrease after the period of ‘lockdown light 2’ in both health care centres.

4.2 Results of the primary centre

4.2.1 Study population

During the study period, 412 children (50.7% male, and 49.3% female) visited the primary health care centre. The median age was 2.9 years (IQR 1.0 – 3.0 years). The youngest patient tested was 66 days old; the oldest patient aged 18.2 years. The majority of patients (91.3%) was 10 years old or younger, 69.4% of the study population were 5 years old or younger. 9 out of the 412 (2.2%) tested children have been infected with SARS-CoV-2.

54 patients (54/412; 13.1%) had an underlying disease (Table 6). The main condition was premature birth (15/412; 3.6%), followed by allergies of any kind (11/412; 2.7%). 8 children (8/412; 1.9%) had diseases of the urinary tract. 6 children (6/412; 1.5%) had bronchial asthma. The risk factor “obesity” applied to 5 children (5/412; 1.2%). 4 children (4/421; 1.0%) had known immune deficiencies (periodic fever syndrome, autoinflammatory disorder). 2 children had a heart disease (2/412, 0.5%). One child (1/412; 0.2%) suffered from type I diabetes. Finally, two patients (2/412; 0.2%) had a genetic disease (Bardet-Biedl-Syndrome, Medium-chain acyl-coenzyme A dehydrogenase deficiency).

None of the 9 SARS-CoV-2 infected children detected at the primary health care centre had an underlaying health condition.

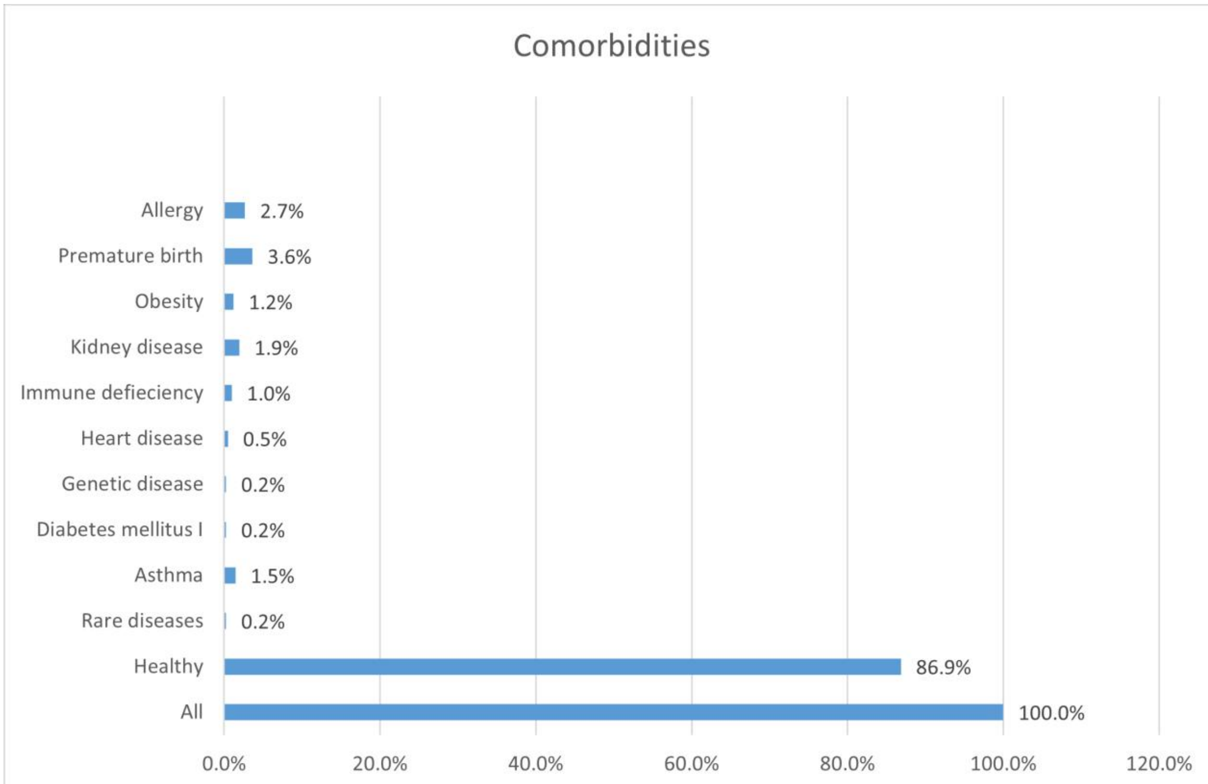

Table 6 Comorbidities in the primary health care centre

The **main reasons for visiting a primary health care centre** were signs of an illness. 40 out of the 412 tested children (9.7%) showed not only signs of an illness but in addition reported close contact to an infected person. 5 out of these 40 (12.5%) children with close contact in their medical history were tested positive by rapid SARS-CoV-2 antigen-based tests and showed ct-levels between 15 and 25 units in the performed RT-PCR. The information about the **onset of symptoms** was provided by 232 out of 412 patients (56.3%). The median time between the onset of symptoms until the visit at the primary health care centre was 2 (IQR 1-3) days with an average of 2 reported symptoms. Here, the most **common symptoms** were fever (200/412; 48.5%), and milder symptoms like cough (160/412; 38.8%) and rhinitis (153/412; 37.1%). The most frequent symptom of SARS-CoV-2 infected children was fever (6/9; 66.7%), followed by cough (5/9; 55.6%). During the study period no patient reported anosmia or ageusia.

4.2.2 Lockdowns

Primary Health Care Centre	Lockdown light I	Lockdown 1	Lockdown light II	Lockdown 2	Lockdown light III
Duration (in d)	16	21	18	44	21
n	56	83	59	118	96
Age (in yrs; median [IQR])	2.3 (1.3-6.5)	2.5 (1.6-4.2)	3.6 (1.6-7.0)	3.4 (1.5-6.7)	2.8 (1.7-6.2)
Time to diagnosis (in d; median [IQR])	2 (1-3.5)	2 (1-6)	2 (1-3.25)	1 (1-4)	2 (1-3)
SARS-CoV-2 infected (n (%))	2 (3.6%)	3 (3.6%)	2 (3.4%)	2 (1.7%)	0
Contact to an infected person (n (%))	7 (12.5%)	25 (30.1%)	5 (8.5%)	2 (1.7%)	1 (1.0%)
Comorbidities (n (%))	2 (3.6%)	12 (14.5%)	6 (10.2%)	20 (16.9%)	14 (14.6%)
Hospitalisation (n (%))	0	0	0	1 (0.8%)	0
Duration as inpatient (in d; median [IQR])	-	-	-	3	-
Admission to ICU (n (%))	-	-	-	-	-
Clinical symptoms (n (%))					
Temperature >37.5°C	33 (58.9%)	34 (41.0%)	28 (47.5%)	65 (55.1%)	40 (41.7%)
Sore throat	15 (26.8%)	15 (18.1%)	26 (44.1%)	27 (22.9%)	20 (20.8%)
Coughing	18 (32.1%)	38 (45.8%)	18 (30.5%)	43 (36.4%)	43 (44.8%)
Rhinitis	18 (32.1%)	34 (41.0%)	25 (24.4%)	47 (39.8%)	29 (30.2%)
Dyspnoe	3 (5.4%)	11 (13.3%)	6 (10.2%)	9 (7.6%)	6 (6.3%)
Tachypnoe	1 (1.8%)	4 (4.8%)	5 (8.5%)	6 (5.1%)	1 (1.0%)
Anosmia/Ageusia	0	0	0	0	0
GI Symptoms	5 (8.9%)	14 (16.9%)	15 (25.4%)	28 (32.7%)	12 (12.5%)
Earache	0	6 (7.2%)	1 (1.7%)	6 (5.1%)	10 (10.4%)
Headache	0	2 (2.4%)	1 (1.7%)	6 (5.1%)	4 (4.2%)

Table 7 Study population at the primary health care system

Primary Health Care Centre	Lockdown light I	Lockdown 1	Lockdown light II	Lockdown 2	Lockdown light III
Duration (in d)	16	21	18	44	21
SARS-CoV-2 infected children	2	3	2	2	0
Daily incidence	0.2%	0.2%	0.2%	0.0%	0.0%
Age (in yrs; median [IQR])	6.0 (2.4-6.0)	2.1 (0.4-2.1)	3.0 (2.9-3.0)	0.9 (0.2-0.9)	-
Time to diagnosis (in d; median [IQR])	1 (1-1)	-	4.5 (1-4.5)	1	-
SARS-CoV-2 infected (n)	0	0	0	0	-
Contact to an infected person (n %))	1	1	1	1	-
Comorbidities (n %))	0	0	0	1	-
Hospitalisation (n)	-	-	-	3	-
Duration as inpatient (in d; median [IQR])	-	-	-	0	-
Clinical symptoms (n %))					-
Temperature >37.5°C	1	0	2	2	-
Sore throat	2	0	1	1	-
Coughing	2	2	0	1	-
Rhinitis	0	1	1	0	-
Dyspnoe	0	0	0	1	-
Tachypnoe	0	0	1	0	-
Anosmia/Ageusia	0	0	0	0	-
GI symptoms	0	1	0	1	-
Earache	0	0	0	0	-
Headache	0	0	0	0	-
Number of symptoms (n)	3	2	3.5	3.5	-

Table 8 Basic characteristics of the infected children of the primary health care centre

During '**Lockdown light I**', 56 children performed a rapid SARS-CoV-2 antigen-based test at the primary health care centre. 2 out of 56 children (incidence = 3.6%) had positive results during 'Lockdown light I'. The following RT-PCR tests showed ct-values of 15 and 23 units. Detailed characteristics of the study population at the primary health care centre in regard to time to diagnosis, comorbidities and clinical symptoms are listed in Table 7. Characteristics of the children infected with SARS-CoV-2 are shown in Table 8.

During **Lockdown 1**, 83 children with signs of an illness sought help at the primary health care centre. 25 children had a positive contact history, out of these only one child was tested positive for SARS-CoV-2 (4.0%). Overall, during 'Lockdown 1', 3 children were tested positive (3/83; 6.3%), with ct-levels ranging from 15 – 28 units. Table 7 and Table 8 provide further information about the study population.

For the 59 children who visited the primary health care centre during **'Lockdown light II'** the main symptom was an elevated temperature level above 37,5°C (28/59; 47.5%), followed by a sore throat (26/59; 44.1%). SARS-CoV-2 was detected in 2 children (2/59; 3.4%) during 'Lockdown light II'. Both of them had contact to an infected person. One child with three mild symptoms took a rapid antigen-based detection test 8 days after onset of symptoms. Further information about the clinical symptoms and time to diagnosis in Table 7 and Table 8.

Common symptoms during **Lockdown 2** were fever (65/118; 55.1%) and rhinitis (47/118; 39.8%). The consequences of the restrictions were reflected in the low rate of SARS-CoV-2 infections. The primary health care centre treated 118 symptomatic children during this period - which implied an average number of 3 presentations at the primary health care centre per day (118/44d). In one child, the fever was associated with gastrointestinal symptoms. Due to the gastrointestinal symptoms and the young age, the patient was admitted as a precautionary measure for 3 days in order to monitor the fluid balance closely.

In the **'Lockdown light III'** period, 96 children were tested of which none was found to be infected by SARS-CoV-2 (0/96, 0%). The effect of the strict measures was still evident at the end of the study period, as only 5 symptomatic children were treated per day and none of them tested positive with SARS-CoV-2.

Throughout the study period, there was a low positivity rate, which decreased over time due to the reinstated lockdown measures. All the SARS-CoV-2 infected children, who were screened at the primary health care centre, did not have any underlaying health conditions. No severe course of disease was registered. Only one child was admitted to hospital for 3 days as a precautionary measure. There was no statistically significant difference between the symptoms of children infected by SARS-CoV-2 or not (Table 7 and Table 8).

4.3 Results of the tertiary centre

4.3.1 Study population

Table 9 Reasons for visiting the tertiary health care centre

During the study period, 1454 children in the tertiary health care system were tested for SARS-CoV-2 based on their signs of illness. The proportion of female patients was 46.0%. The **age** ranged from the day of birth (0 days) to 18.0 years at the time of the SARS-CoV-2 detection test. The median age was 2,6 years (IQR 1,1 – 6.4 years). The time from the onset of symptoms to the presentation at the tertiary health care system was on average one day (IQR 1 – 4 days). 79 (5.4%) children were **infected** by SARS-CoV-2 during the study period in the tertiary health care centre in Graz, Austria.

Patients visited the tertiary health centre for various reasons. Most patients admitted themselves to the tertiary health centre due to an onset of symptoms. The following reasons for presentation were given in the tertiary health care centre (Table 9): referral from a specialist (194/1454; 13.7%), 37 in-hospital-referrals (37/1454; 2.5%), and one patient was admitted after taking a rapid SARS-CoV-2 antigen-based self-test at home (1/1454; 0.1%). The proportion of children with a known contact to an infected person was 4.7% (68/1454). This number included contact to infected family members (4.5%) and non-family members (0.2%). It can be stated that the contact with an infected family member (65/68; 95.6%) was more frequent than to a non-family member. In only 3 patients (3/68; 4.4%) a non-family member could be identified as the origin of the infection.

179 (12.3%) of the tested patients had **underlying disease**. These underlying health conditions consisted of illnesses described in the following. The most common health conditions were urinary tract diseases (28/1454; 1.9%). 20 children (20/1454; 1.4%) of the study population had a heart disease. The categories 'asthma' and 'premature birth' were equally frequent (17/1454; 1.2%). 14 children (14/1454; 1.0%) were oncologic patients at the time of testing. Genetic diseases (DYRK or MCAD mutations, Down syndrome) were reported in 13 children (13/1454; 0.9%). 11 children (11/1454; 0.8%)

had an underlying immune deficiency. Other rare underlying diseases are listed in Table 10.

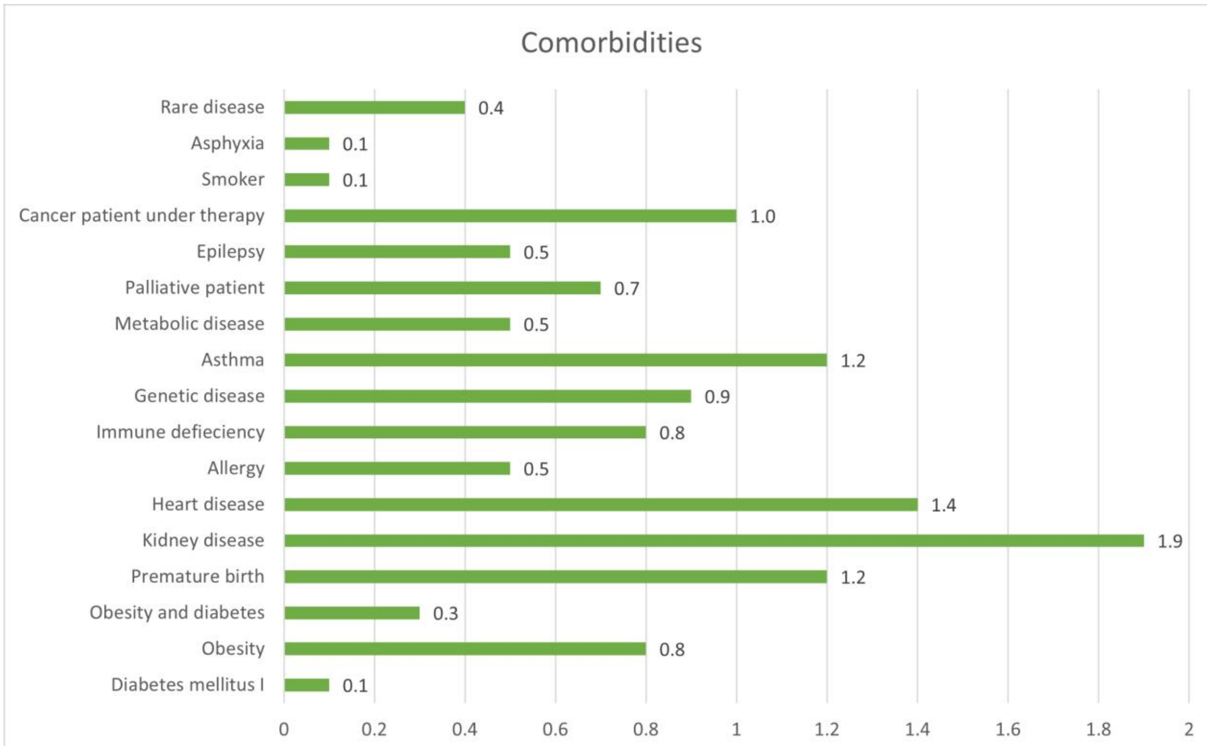

Table 10 Comorbidities of the patients at the tertiary health care centre

The analysis of the reasons for undertaking a SARS-CoV-2 detection test at the tertiary health care centre were the following (Table 3): The most frequent reason was fever (820/1454; 56.4%). The second most common symptoms were gastrointestinal symptoms including vomiting, diarrhoea, or abdominal pain (583/1454; 40.1%). Also coughing (453/1454; 31.2%) and rhinitis (427/1454; 29.4%) were reasons for performing a SARS-CoV-2 detection test. Other symptoms in descending order of frequency were dyspnoea (289/1454; 19.9%), sore throat (223/1454; 15.3%), headache (105/1454; 7.2%), and tachypnoea (102/1454; 7.0%). Anosmia or ageusia was reported by 7 people (7/1454; 0.5%), but this was not a direct indicator for a subsequent positive SARS-CoV-2 test result. A close contact to an infected person within the last 14 days was reported in 4.7% (68/1454) of the study population.

4.3.2 Lockdowns

Tertiary Health Care Centre	Lockdown light I	Lockdown 1	Lockdown light II	Lockdown 2	Lockdown light III
Duration (in d)	16	21	18	44	21
n	204	237	204	508	301
Age (in yrs; median [IQR])	3 (1.1-8.0)	2.1 (0.9-5.5)	2.9 (1.2-6.4)	2.4 (1.0-6.3)	2.8 (1.3-6.6)
Time to diagnosis (in d; median [IQR])	2 (1-3)	2 (1-4)	1 (1-3)	1 (1-3.75)	1 (1-3.75)
SARS-CoV-2 infected (n (%))	14 (6.9%)	23 (9.7%)	11 (5.4%)	21 (4.1%)	10 (3.3%)
Contact to an infected person (n (%))	16 (7.8%)	24 (10.1%)	4 (2.0%)	21 (4.1%)	7 (2.3%)
Comorbidities (n (%))	32 (15.7%)	36 (15.2%)	22 (10.8%)	47 (9.3%)	42 (14.0%)
Hospitalisation (n (%))	82 (40.2%)	96 (40.5%)	86 (42.2%)	237 (46.7%)	123 (40.9%)
Duration as inpatient (in d; median [IQR])	3 (2.5-5.5)	3 (3-10)	4 (4-4)	3 (3-6)	2 (2-2)
Admission to ICU (n (%))	0	2 (0.8%)	1 (0.5%)	0	0
Clinical symptoms (n (%))					
Temperature >37.5°C	103 (50.5%)	138 (58.2%)	121 (59.3%)	291 (57.3%)	167 (55.5%)
Sore throat	37 (18.1%)	36 (15.2%)	34 (16.7%)	70 (13.8%)	46 (15.3%)
Coughing	71 (34.8%)	86 (36.3%)	46 (22.5%)	135 (26.6%)	115 (38.2%)
Rhinitis	68 (33.3%)	72 (30.4%)	58 (28.4%)	129 (25.4%)	100 (33.2%)
Dyspnoe	42 (20.6%)	52 (21.9%)	39 (19.1%)	92 (18.1%)	64 (21.3%)
Tachypnoe	19 (9.3%)	24 (10.4%)	15 (7.4%)	30 (5.9%)	14 (4.7%)
Anosmia/Ageusia	1 (0.5%)	1 (0.4%)	3 (1.5%)	0	2 (0.7%)
GI Symptoms	91 (44.6%)	78 (32.9%)	76 (37.3%)	219 (43.1%)	119 (39.5%)
Earache	4 (2.0%)	12 (5.1%)	5 (2.5%)	14 (2.8%)	3 (1.0%)
Headache	17 (8.3%)	10 (4.2%)	11 (5.4%)	43 (8.5%)	24 (8.0%)

Table 11 Characteristics of the tertiary health care centre

Tertiary Health Care Centre	Lockdown light I	Lockdown 1	Lockdown light II	Lockdown 2	Lockdown light III
Duration (in d)	16	21	18	44	21
SARS-CoV-2 infected children	14	23	11	21	10
Daily incidence	0.4%	0.5%	0.3%	0.1%	0.2%
Age (in yrs; median [IQR])	4.0 (0.3-11.4)	2.1 (0.4-11.7)	2.6 (0.6-7.2)	1.4 (0.5-3.9)	2.2 (1.0-12.8)
Time to diagnosis (in d; median [IQR])	1.5 (1-4)	1.5 (1-3)	1 (1-3)	1 (1-5)	3 (0.5-4.5)
SARS-CoV-2 infected (n)	4 (28.6%)	6 (26.1%)	0	4 (19.0%)	3 (30.0%)
Contact to an infected person (n %))	8 (50.0%)	15 (65.2%)	3 (27.3%)	17 (81.0%)	5 (50.0%)
Comorbidities (n %))	5 (35.7%)	11 (47.8%)	3 (27.3%)	11 (52.4%)	3 (30.0%)
Hospitalisation (median [IQR])	3 (2.5-5.5)	3 (3-10)	4 (4-4)	3 (3-6)	2 (2-2)
Duration as inpatient (in d; median [IQR])	0	2 (8.7%)	1 (9.1%)	0	0
Clinical symptoms (n %))					
Temperature >37.5°C	8 (57.1%)	18 (78.3%)	10 (90.9%)	18 (85.7%)	5 (50.0%)
Sore throat	2 (14.3%)	3 (13.0%)	2 (18.2%)	2 (9.5%)	2 (20.0%)
Coughing	7 (50.0%)	16 (69.6%)	4 (36.4%)	5 (23.8%)	5 (50.0%)
Rhinitis	3 (21.4%)	12 (52.2%)	6 (54.5%)	8 (38.1%)	4 (40.0%)
Dyspnoe	1 (7.1%)	6 (26.1%)	1 (9.1%)	2 (9.5%)	4 (40.0%)
Tachypnoe	2 (14.3%)	1 (4.3%)	1 (9.1%)	2 (9.5%)	2 (20.0%)
Anosmia/Ageusia	0	1 (4.3%)	1 (9.1%)	0	1 (10.0%)
GI symptoms	8 (57.1%)	6 (26.1%)	4 (36.4%)	8 (38.1%)	1 (10.0%)
Earache	0	2 (8.7%)	0	0	0
Headache	1 (7.1%)	1 (4.3%)	1 (9.1%)	3 (14.3%)	1 (10.0%)
Number of symptoms (n)	2	3	3	3	3

Table 12 Characteristics of the SARS-CoV-2 infected children at the tertiary health care centre

During **‘Lockdown light I’** which lasted 16 days, 204 children were tested at tertiary health care centre. An average of 13 children per day (204/16d) presented with signs of an illness at the Emergency Department during ‘Lockdown light I’. 6.9% (14/204) had an infection with SARS-CoV-2 during this period under review. The hospitalisation rate was 40.2% (82/204) which is the lowest number throughout the study period. The median duration as inpatient was 3 days (IQR 2.5 – 5.5 days). No patient needed ICU treatment during this time. Further details are shown in Table 11 and Table 12.

During ‘**Lockdown 1**’, 237 children were tested at the tertiary health care centre. The median time to diagnosis was comparable to the previous lockdown with a median time of 2 days (IQR 1 – 4 days). The most frequent symptoms are listed in Table 11 and Table 12. As in the preceding period, 40.5% of the children were admitted to the hospital as inpatients (96/237) with an average stay of 3 days (IQR 3 – 10 days) on the ward. 2 children (2/237; 0.8%) needed treatment at the ICU to monitor the oxygen saturation. By the end of the period under review all children could be discharged healthy again.

The ‘Lockdown 1’ was followed by ‘**Lockdown light II**’. 204 children sought help at the tertiary health care centre. Mostly fever (121/204; 59.3%) followed by gastrointestinal symptoms (76/204; 37.3%) were the reasons for presentation (Table 11 and Table 12). The daily incidence during ‘lockdown light II’ was 0.3% with 11 children being infected by SARS-CoV-2 (11/204). As inpatients 42.2% of the children (86/204) were admitted. The median time at hospital was 4 days (IQR 4 – 4 d). One child was admitted at the ICU (1/204; 0.5%).

508 children were tested by RT-PCR during **‘Lockdown 2’** at the tertiary health care centre. Over half of the children had fever (291/508; 57.3%) followed by gastrointestinal symptoms (219/508; 43.1%). 21 children (21/508; 4.1%) had contact to a SARS-CoV-2 infected person and 21 children were found to be infected with SARS-CoV-2 during ‘lockdown 2’. The daily incidence is the lowest during this strict lockdown with 0.1% of the children being tested positive with SARS-CoV-2. Almost half of the visiting children (46.7%) were hospitalized with a median time of 3 days (IQR 3 – 6 d). None needed ICU admission to the ICU.

During **‘Lockdown light III’**, 301 children were tested at the tertiary health care centre. In this study population, 3.3% (10/301) children were found infected with SARS-CoV-2. 123 children (123/301; 40.9%) were admitted to the ward with a median time of 2 days (IQR 2 – 2 d). No child needed treatment at the ICU during ‘lockdown light III’. More detailed characteristics of the study population is listed in Table 11 and Table 12.

4.4 Comparison of SARS-CoV-2 infected children

SARS-CoV-2 infected patients	**Pimary health care centre**	**Tertiary health care centre**	**p value**
n	9	79	
Incidence (%)	2.2	5.4	**.01**
Age (in yrs; median [IQR])	2.4 (1.0-3.0)	1.7 (0.5-10.0)	**n.s.**
Gender			
Female (n(%))	4 (44.4%)	36 (45.6%)	**n.s.**
Ct-level (median [IQR])	22.9 (15-28)	20.0 (13-32)	**n.s.**
Pre-existing conditions (n (%))	0	17 (21.5%)	
Asthma bronchiale	0	4 (23.5%)	**<.01**
Kidney disease	0	4 (23.5%)	**<.01**
Heart disease	0	3 (17.6%)	**<.01**
Contact to an infected person (n (%))	5 (55.6%)	47 (59.5%)	**n.s.**
tested positive after contact	12.5%	65.3%	**<.01**
Symptoms (n (%))			
Temperature >37.5°C	6 (66.7%)	59 (74.7%)	**n.s.**
Sore throat	3 (33.3%)	11 (13.9%)	**n.s.**
Coughing	5 (55.6%)	37 (46.8%)	**n.s.**
Rhinitis	2 (22.2%)	33 (41.8%)	**n.s.**
Dyspnoe	1 (11.1%)	14 (17.7%)	**n.s.**
Tachypnoe	1 (11.1%)	8 (10.1%)	**n.s.**
Anosmia/Ageusia	0.0%	3 (3.8%)	**n.s.**
GI symptoms	2 (22.2%)	27 (34.2%)	**n.s.**
Earache	0.0%	2 (2.5%)	**n.s.**
Headache	0.0%	7 (8.9%)	**n.s.**
Hospitalisation (n (%))	1 (11.1%)	33 (41.8%)	**n.s.**
ICU (n (%))	0	3 (9.1%)	**.05**

Table 13 Comparison of SARS-CoV-2 infected patients

There was a statistically significant difference between the incidence of SARS-CoV-2 infected children between the two health care centres (p=0.01). During the study time, 9 children (9/412; 2.2%) were found infected with SARS-CoV-2 at the primary health care centre. In contrast 79 children (79/1454; 5.4%) were infected with the virus at the tertiary health care centre. With regard to the median age (2.4 y at the primary vs. 1.7 y at the tertiary health care centre), gender ratio (44.4% female patients at the primary vs. 45.6% female patients at the tertiary health care centre), median ct-levels (22.9 units at the primary vs. 20.0 units at the tertiary health care centre), and the symptoms of the infected children compared between the two health care centres, no statistically significant difference could be found.

Remarkably, none of the SARS-CoV-2 infected children in the primary health care centre had an underlying chronic disease, although the study populations of the two centres were comparable in terms of underlying health conditions. At the tertiary health care centre 17 children out of the SARS-CoV-2 infected children (17/79; 21.5%) had an underlying chronic disease (most commonly asthma, urinary tract diseases or a heart disease). All these infected children recovered without any adverse outcomes.

In the study population of infected children 55.6% (5/9) children at the primary and 59.5% (47/79) children at the tertiary health care centre had acquired the virus through a close contact to a SARS-CoV-2 infected person within the previous 14 days: 50 children were likely to have contracted the virus within family clusters, 2 children were infected by non-family members. 8.9% (7/79) of the children at the tertiary health care centre were referred by a medical specialist with strong suspicion for COVID-19 and the request for admission to the ward. One child was tested at home by a rapid SARS-CoV-2 antigen-based test and then visited the tertiary health care system. Thus, no statistically significant difference in the prevalence of contact was found in the two study populations, with the main source of infection being within the family. But there was a statistically significant difference in the frequency of children tested positive after contact to a confirmed case (p=<0.01). 12.5% were tested positive after contact at the primary health care centre. Whilst 65.3% of the children were found infected with

SARS-CoV-2 at the tertiary health care centre after known contact to an infected person.

Although no statistically significant difference was found in the comparison between the two health centres in general, there were differences between SARS-CoV-2 infected and not infected children looking at each health care centre separately. In both health care centres, the risk factor of contact to an infected person was significantly more frequent in the group of SARS-CoV-2 infected children than to not infected children (p=<0.01). Fever, cough, and rhinitis occurred significantly more frequent in SARS-CoV-2 infected children than to not infected ones (p=<0.01 for all three symptoms) at the tertiary health care centre.

The majority of the SARS-CoV-2 infected children at the tertiary health care centre could be managed ambulatory. 41.8% (33/79) SARS-CoV-2 infected children were admitted to the ward. The hospitalisation rate at the primary health care centre was 11.1% (1/9). The median time of hospitalisation was 3 days (IQR 3 – 5.5 d) with the longest time at the hospital being 34 days. Due to their course of illness, 3 children (3/33; 3.4% of hospitalized children) needed intensive care monitoring. No child from the primary health care centre required admission to the ICU. None of the children with specific SARS-CoV-2 treatment at the ICU had an underlying health disease. 5 out of the hospitalized children (5/33; 15.2%) had comorbidities but did not need admission to the ICU at any time.

4.5 Case study of MIS-C

During the study period, one 12-years old child with no underlying health conditions was admitted to the ICU due to rapid deterioration of the general condition. Four weeks after being infected by SARS-COV-2 the child needed intensive care treatment at the tertiary health care centre. The primary SARS-CoV-2 infection four weeks earlier was oligosymptomatic with a rhinorrhoea and a mild ageusia.

Four weeks after the initial infection, the child presented at the emergency ambulance with a tonsillitis, cervical lymphadenopathy, fever up to 39.9°C, an icteric complexion, and vomiting. Five days after onset of the symptoms during the examination at the hospital, the child deteriorated, became hypotonic and developed severe respiratory distress. On admission to the ICU, the child kept dawning away but was orientated in all qualities (therefore scoring 12 by the Glasgow Coma Scale). With an increased breathing rate of 43 breaths per minute, additionally 6 litres of oxygen per minute through the nasal cannula, the peripheral oxygen saturation reached 92%. At the same time, the patient was tachycardic, the mean arterial pressure was 55 mmHg (standard range 70 – 105 mmHg for a sufficient organ perfusion). The initial blood test showed extremely high levels of inflammation. The CRP (C-reactive protein) was 445.4 mg/L (physiologically below 5mg/L). The PCT (procalcitonin) reached a level of 10.6 ng/mL (physiologically below 0.5 ng/mL). Ferritin, the other acute phase protein was 2151 ng/mL (physiologically below 101 ng/mL). Interleukin 6 measured 3223.0 pg/mL with its physiological benchmark below 7.0 pg/mL. All the gathered findings pointed at an acute respiratory distress syndrome (ARDS) with a local and systemic cytokine storm that trigged rapid clinical deterioration and multiorgan failure of the liver, kidneys and respiratory system. The child had to be intubated due to the respiratory decompensation. At the same time, there was a high need for catecholamines for circulatory support. The metabolic derailment with a severe acidosis as well as the anuria quickly led to the need for continuous haemodialysis including a cytosorb-filter for the elimination of cytokines in the blood. As synopsis of the health condition of the child, the diagnosis of the multisystem inflammatory syndrome in children (MIS-C) was made. The therapy started with high dose methylprednisolone, intravenous immunoglobulins, accompanied by antibiotic therapy.

On the day of admission, the SARS-CoV-2 result of the RT-PCR was negative but intermittently positive in further laboratory controls. After 6 days of invasive ventilation, the patient was extubated without complications. The cortisone therapy was gradually decreased and stopped after 16 days. Finally, the patient could be discharged in good general health condition, cardio-respiratory stable and neurologically clear. The sense of tase was also present again.

5. Discussion

This Covid-19 pandemic has been the severest threat to the global health in this century so far. SARS-COV-2 is the third pathogenic human coronavirus to date after SERS and MERS. We know that the fatality rate is lower compared to those two, but nevertheless the rapid spread and the ability to be easily transmitted is a characteristic of this virus. (16) That is why the pandemic has already lasted two years and is likely to become endemic and will coexist with us for a long time. (104)

In this section the results of this study are discussed in the context of the current state-of-the-art in literature. In this highly dynamic evolution of COVID-19, there are now a number of new developments.

The number of children included in comparable studies in literature ranges from small case studies up to multinational cohort studies including 55.270 children. (105) Our study population consisted of 1866 children and adolescents. In this study the positivity rate ranged from 2.2% at the primary health care centre to 5.4% at the tertiary health care centre. The positivity rate is reported in different study populations with different results, but it is only correctly presented in the epidemiological records by the WHO without study-related limitations. (106) Unfortunately, the WHO record cannot be viewed subdivided by age group and the detailed data of the Austrian record system does not start until 27th February 2020 and is thus outside the study period. (54) This is exactly the reason why we conducted this study, as the aim was to show the early onset of the pandemic in the two health care centres. In addition, SARS-CoV-2 antigen-detecting rapid diagnostic tests were only launched shortly prior to the study period and therefore the indications for this test had yet to be definitively proven at the time of the study.

With this study, it is possible to reflect on the course of infection as well as on the course of disease in children and adolescents during the second lockdown in Graz, Austria. The two health care centres represent a broad cross-section of the population in and around Graz. The study populations between the two health care centres are alike with regard to age, gender ratio, and underlying health conditions with no relevant statistical difference for all three categories. Since the two population sizes and the study protocol are nevertheless different, the incidence can only be calculated and compared to a limited extent. The direct inter-centre comparison is not statistically valid, but a statement can be made about the trend in the incidence in context of the Austrian numbers at that time: Both centres follow the same trend with the overall number of cases increasing at the end of November 2020. After ‘lockdown 1’ the strict measures start to show an effect and the numbers decrease steadily until the end of the study period in February 2021. These figures are in line with the general incidence in Austria at that time. (54)

As made clear in this study, the primary health care centre covers the oligosymptomatic children presenting with rhinitis, sore throat, and coughing, while the tertiary health care centre covers children with more pronounced symptoms as fever, respiratory and gastrointestinal symptoms as well as headache. However, this becomes evident not only in terms of the symptoms, but also in terms of the low hospitality rate in the primary health care centre (1/9 at the primary vs 33/79 at the tertiary health care centre) and the need of intensive care treatment due to the SARS-CoV-2 infection (0/9 at the primary vs 3/79 at the tertiary health care centre).

There were statistically significant differences between the two health care centres regarding the following characteristics: The patients at the tertiary health care centre were significantly younger (p=0.04), with a median age of 2.6 years in comparison with 2.9 years at the primary health care centre. Patients sought admission at the tertiary health care centre significantly quicker (p=0.01) compared to the primary health care centre. The median time from the onset of symptoms to the time of diagnosis was 1 day at the tertiary health care centre respectively 2 days at the primary health care centre. The reasons for the visits varied between the health care centres: A child with more severe symptoms (fever, gastrointestinal symptoms, or conspicuous breathing) was more likely to consult the tertiary health care centre.

The comparison with the tertiary health care centre shows the advantages and disadvantages of the rapid antigen-based test devices. In comparison, a lower positivity rate is found in the primary health care centre. On the one hand, this could be explained by the lower sensitivity of the antigen-based tests used, compared to the PCR tests. On the other hand, the fact that patients with pronounced symptoms or the concrete suspicion of a SARS-CoV-2 infection could have preferred to directly go to the tertiary health care centre.

As indicated by the numbers (12.5% at the primary vs. 65.3% at the tertiary health care centre), the sensitivity of the RT-PCR test is higher with a positive contact history based on a previously performed rapid antigen test. On the one hand, this could be explained by the lower sensitivity of the antigen tests used compared to the RT-PCR. On the other hand, it could also be due to the fact that patients with known symptoms and reasonable suspicion of a COVID infection decided to directly visit the tertiary health care centre.

In the first year of the pandemic, studies indicated that children and adolescents had a lower rate of symptomatic infection than adults, with the majority developing no or mild symptoms. This can be illustrated by the example of the tertiary health care system: The relatively frequent inpatient admissions (624/1454; 42.9%) combined with a very short mean length of stay (3d) could indicate a cautious approach with little experience with SARS-CoV-2 infected children during this study period and at the beginning of the pandemic. This observation is supported by the fact that only a very small percentage (3/624; 0.5%) of hospitalised children actually required intensive monitoring or specific therapy in the intensive care unit.

Before case studies on MIS-C emerged, it was said that severe cases are generally rare in children. Severe courses of infection have only been observed in children with previous illnesses and a weakened immune system. (7,8,47,64,107–110) With this study, the consequences of the delayed immune response to the SARS-CoV-2 infection becomes evident, as MIS-C is also reported during our study period and described in the chapter Case study of MIS-C (4.5).

At the time the study was conducted, no mutations of the RNA have yet occurred, so they are not addressed in this present study. One year later, in January 2022, three dominant variants of SARS-CoV-2 have been registered to be circulating in Austria. In April 2021, B.1.1.7 (a, Alpha) was responsible for the high incidence of infection. During the of summer 2021, B.1.1.7 was replaced by a more infectious variant, classified as

B.1.617 (δ, Delta). Until the end of 2021 the mutation delta was the absolutely dominant variant in many countries of the world including Austria. Since the turn of the year 2021/22, B.1.1.529 (θ, Omicron) is the predominant variant until today. (111) Omicron shows a decoupling of the number of infections from the number of severe courses. (112) Thus the fear of an overload of intensive care capacities is diminishing despite a reduced efficacy of the currently admitted vaccines. However, the overall efficacy of these vaccines against severe courses of the disease has been registered to persist. (113,114)

A new case study by *Ludvigsson J* (115) claims that an infection by the new variants of SARS-COV-2 may exhibit slightly different symptoms. For example, ageusia or anosmia have not been reported in combination with the more recent variants. Furthermore, this study reports on an unusual frequency of convulsions in children who are infected with the Omicron variant of SARS-CoV-2 in Sweden and South Africa. (113,115) A British study clarifies that Omicron is likely to manifest itself by rhinitis, sore throat, headache, sneezing, or fatigue. (116)

Regarding transmission patterns, even asymptomatic children are able to spread the virus. (42,55) However, the viral load of asymptomatic children is usually lower than that of children with symptoms. (117) Moreover, it can be assumed that children are not super spreaders. (33,118–120) Nation-wide school and day-care centre closures are of negligible efficacy compared to general social distancing and hygiene regulations. (43,121–125) However, for children and young adults harmful side effects of social distancing in the context of the containment measures have been reported. (126,127)

This study is limited by its retrospective approach. To be able to answer the research question precisely, a prospective study with an equally large study population and the same enrolment in the sampling procedure would be helpful. In addition, the recording of the Austria-wide incidence by age group, which corresponds to the period under investigation, is missing. However, as this is the first pandemic of its kind, science is of course not the main focus in the beginning and so this retrospective data analysis shows the real outbreak of the pandemic and illustrates the effect of the "lockdowns" with its contact restrictions.

In addition, the different test methods are a limitation of the study. However, due to lack of resources and availability of PCR diagnostics at the time of the study, there was no other possibility of providing adequate care for the children in the primary health care system. The number children who made use of the services offered in the primary health care system at an early stage of the disease, even with mild symptoms, speaks for the use of the tests. In this way, the primary health care systems were able to guarantee their health care services and easy access to the health care system even during the lockdowns. That the strict measures of the different lockdowns were effective is shown by the fact that also in this study the most frequent cause of infection was the family, i.e. the household environment. Moreover, in favour of the strict contact restrictions as well as the face masks speaks the low number of sick children as an average daily number of only 3 consultations at the primary (412/120d) and 12 consultations at the tertiary health care system (1454/120d) has never been so low since.

Considering the pace at which the research in this area is moving forward, it is likely that the findings of the publications described in this study will be quickly complemented by further research.

5.2 Conclusion

From an outpatient paediatric point of view, SARS-CoV-2 infections in children and adolescents were rare over the studied period and had milder courses than in adults. In comparison to tertiary centres, a lower positivity rate is found in the primary health care centre. On the one hand this could be explained by the lower sensitivity of the antigen-based tests used compared to the PCR tests. On the other hand, it can be due to the fact that patients with pronounced symptoms or the concrete suspicion of a SARS-CoV-2 infection tend to primarily go to the tertiary health care centre.

Nevertheless, the use of rapid antigen-based SARS-COV-2 detection tests is useful in the field of point-of-care testing in the primary health care centre setting. During the study period there were no vaccinations and thus no prevention options other than tests to protect against infection. Hence, a safe visit to the doctor could only be ensured by means of screening. So, the rapid test had its justification in this context. A direct comparison of the two test methods is only possible to a limited extent, as sampling is not a standardised procedure. Despite its limitations and retrospective character this study with its discussed publications will hopefully pave the way for a more consistent and predictive plan for future pandemics and viral outbreaks.

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7. Appendix

Checkliste für Covid-19

Fragen betreffend Patient*in

Bekannte Vorerkrankung:

	JA	NEIN
Kontakt mit Covid-19 Fall innerhalb der letzten 14 Tage		
Temperatur > 37,5°C		
Halsschmerzen		
Husten		
Schnupfen		
Auffälliges Atemgeräusch oder Atemnot		
Beschleunigte Atmung		
Plötzlicher Verlust des Geschmack-/Geruchsinnes		
Erbrechen / Durchfall bei Kindern <10 Jahre		
Krankheitsbeginn		

Begleitperson

	JA	NEIN
Kontakt zu gesichertem Covid-19 Fall innerhalb der letzten 14 Tage		
Husten/Atemnot/Halsschmerzen/Verlust von Geruchs- oder Geschmacksinn		