Heterogeneous evolution of SARS-CoV-2 seroprevalence in school-age children

Results from the school-based cohort study Ciao Corona in November–December 2021 in the canton of Zurich

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Summary

BACKGROUND: Much remains unknown regarding the evolution of SARS-CoV-2 seroprevalence and variability in seropositive children in districts, schools and classes as only a few school-based cohort studies exist. Vaccination of children, initiated at different times for different age groups, adds additional complexity to the understanding of how seroprevalence developed in the school aged population.

AIM: We investigated the evolution of SARS-CoV-2 seroprevalence in children and its variability in districts, schools and classes in Switzerland from June/July 2020 to November/December 2021.

METHODS: In this school-based cohort study, SARS-CoV-2 antibodies were measured in primary and secondary school children from randomly selected schools in the canton of Zurich in October/November 2020, March/April 2021 and November/December 2021. Seroprevalence was estimated using Bayesian logistic regression to adjust for test sensitivity and specificity. Variability of seroprevalence between school classes was expressed as maximum minus minimum seroprevalence in a class and summarised as median (interquartile range).

RESULTS: 1875 children from 287 classes in 43 schools were tested, with median age 12 years (range 6–17), 51% 12+ vaccinated. Seroprevalence increased from 5.6% (95% credible interval [CrI] 3.5–7.6%) to 31.1% (95% CrI 27.0–36.1%) in unvaccinated children, and 46.4% (95% CrI 42.6–50.9%) in all children (including vaccinated). Earlier in the pandemic, seropositivity rates in primary schools were similar to or slightly higher (<5%) than those in secondary schools, but by late 2021, primary schools had 12.3% (44.3%) lower seroprevalence for unvaccinated (all) subjects. Variability in seroprevalence among districts and schools increased more than two-fold over time, and in classes from 11% (95% CrI 7–17%) to 40% (95% CrI 22–49%).

CONCLUSION: Seroprevalence in children increased greatly, especially in 2021 following introduction of vaccines. Variability in seroprevalence was high and increased substantially over time, suggesting complex transmission chains.

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Introduction

More than two years into the SARS-CoV-2 global pandemic, it remains unclear to what extent transmission takes place in schools [1]. The predominant opinion currently is that children of all ages appear to be equally susceptible to SARS-CoV-2 infection compared to adults and that transmission in children occurs primarily in the community in which the children live, including at school, at home and in other settings. Fortunately, symptomatic or severe disease, hospitalisation and death are much less common in children [1–3]. This pattern holds true even under the higher transmissibility and dominance of the delta and omicron variants of concern (VOCs) over other SARS-CoV-2 strains [4–6]. Yet, studies have shown an elevated risk of SARS-CoV-2 infection for adults living in households with children attending schools in-person [7, 8], especially for higher school grades [8], although this was not a consistent finding [9]. Moreover, the number of reported outbreaks in schools after the summer break of 2021 increased compared with earlier times, in part owing to the greater transmissibility of the delta and omicron VOCs, but possibly also to higher testing rates including repetitive pool testing in the school setting [10, 11]. The infection risk may also have varied depending on control measures in schools, such as wearing masks, social distancing, hygiene, symptomatic or repetitive testing and the vaccination status of families, peers and teachers [8, 12]. Overall, several studies documented a low probability of children getting infected within schools under the delta VOC [13], as reported also during the pre-delta period of the pandemic [14–18].

The rate of previous natural infection in children can be estimated from seroprevalence studies and varies between countries and populations. Several studies show that seroprevalence had risen sharply up to 15–42% in children by summer 2021 [19–22], and is expected to be even higher with the emergence of delta and omicron and the parallel increase in vaccination rates among children, adolescents and adults. Most countries, including Switzerland, started vaccination of adolescents above 12 years from summer 2021 on, whereas the vaccine was not approved for the

5- to 11-year-old group until late 2021 (in Switzerland mid-December 2021). The variability of vaccination rates among parents, teachers and children below and above 12 years combined with the ever-changing transmissibility of new variants, differences in mitigation measures at school as well as in the community, and testing attitudes make surveillance of infection rates in school-age children a major challenge. Specifically, more evidence is needed regarding absolute levels of seroprevalence.

The Ciao Corona study examines SARS-CoV-2 seroprevalence among children in primary and secondary schools in one of the largest cantons of Switzerland [23]. In this school-based prospective cohort study, so far there have been four rounds of antibody testing, in June–July 2020 (T1) [24], October–November 2020 (T2) [17], March–April 2021 (T3) [16] and November–December 2021 (T4), to assess the proportion of seropositive children and adolescents within cantonal districts, and by school, school level and class. Seroprevalence increased from 1.5 to 16.4% from T1 to T3, and clustering of seropositive children within school classes was low and mostly reflected community transmission [16]. Up to T3, seroprevalence in primary schools was similar to or slightly higher than in secondary schools (T2: primary 5.6% vs secondary 5.7%; T3: 19.5% vs 15.1%), possibly due to closer contact with parents [16, 17].

The aim of this study was to describe the evolution of seroprevalence in children and adolescents from randomly selected schools of the canton of Zurich from October 2020 to December 2021, and to assess changes and variability of seropositive children within and across districts, schools, school levels and classes in our cohort. Because of low seroprevalences and recent school closures that may have led to infections more from households than from schools in June–July 2020 and generally a lower positive predictive value in a low seroprevalence setting, we do not report T1 results here.

Materials and methods

The protocol for this school-based cohort study has previously been reported (ClinicalTrials.gov identifier: NCT04448717) [23], as well as the results of the first three rounds of Ciao Corona testing [16, 17, 24]. Ciao Corona, as part of the Swiss-wide research network Corona Immunitas [25], examines a randomly selected cohort of public and private schools and classes in the canton of Zurich, Switzerland. With 1.5 million inhabitants, the canton of Zurich is largest of 26 cantons in Switzerland by population and is home to a linguistically and ethnically diverse population in both urban and rural settings. A similar daily incidence of diagnosed SARS-CoV-2 cases until December 2021 in the canton of Zurich and Switzerland (see appendix) show that the canton of Zurich is quite representative for Switzerland as a whole. The study was approved by the Ethics Committee of the Canton of Zurich, Switzerland (2020-01336). All participants provided written informed consent before being enrolled in the study.

After an initial lockdown period during which schools were closed from March to May 2020 across Switzerland, children have been physically in school without interruption. Preventive measures such as hygiene and social distancing rules, and mask requirements were implemented in public and private schools according to cantonal rules, but with some variation within and among cantons. Children were required to stay at home if they had a fever or other than minor cold symptoms. School personnel were required to wear masks starting in October 2020, whereas secondary school children (7th–9th grades) wore masks from November 2020, and the older primary school children (4th–6th grades) in the early months of 2021, and again from December 2021. School-specific contact tracing was introduced in August 2020, where testing and quarantine recommendations depended on the situation. If at least two children in a class simultaneously tested positive, then the whole class would be quarantined (existing policy from May to February 2022). However, if children were wearing masks, then quarantine was restricted to close contacts. Some schools started to participate in weekly pooled polymerase chain reaction (PCR) testing in spring 2021, with optional participation from children. By the time of T4 testing, approximately 80% of participating schools took part in repetitive testing, with variable participation rates of individual children, but at least 80% in most schools. In the case of a positive pool of up to 10 students, each child in that pool had a second individual test, and students remained at school but wore masks until the results were available. In the case of three or more positive cases in a class, negative-tested children who participated in pool testing could continue to attend school, and children who did not participate in repetitive testing were then required to quarantine for 10 days.

Population

As described elsewhere [23], public and private primary schools in the canton of Zurich were randomly selected in May 2020, and the geographically closest secondary school was also invited. The 55 participating schools (among them 2 private schools) were distributed in each of the 12 geographic districts proportional to the population size. Within participating schools, classes were randomly selected, stratified by school level: lower level (grades 1–3, age 6–9), middle level (grades 4–6, age 9–12), and upper level (grades 7–9, age 12–16). The aim was to invite at least three classes, with at least 40 children in each school level at a school. The invited sample is representative of the school-age population in the canton of Zurich.

Eligible children and adolescents (hereafter, children) in the selected classes could participate in any of the testing rounds and were reinvited to later testing periods. In the fourth round of testing, from November to December 2021, some schools declined to continue, reducing the total number of schools included from 55 to 43. Additional classes within the 43 participating schools were invited with the aim of obtaining a similar sample size to previous rounds. This resulted in 71 classes with only new children at T4 and 119 classes with a mix of new children at T4 or from previous rounds and 97 classes with only previously tested children. The main exclusion criterion was having a suspected or confirmed SARS-CoV-2 infection at the time of testing, which precluded attendance at school.

Serological testing

Venous blood samples were collected at schools from 26 October to 19 November 2020 (T2), 15 March to 16 April

2021 (T3) and 15 November to 14 December 2021 (T4). Blood samples were analysed using the Sensitive Anti-SARS-CoV-2 Spike Trimer Immunoglobulin Serological (SenASTrIS) test [26]. The test uses Luminex technology to detect IgG and IgA antibodies binding to the entire trimeric S protein of SARS-CoV-2, and has 94.0% sensitivity and 99.2% specificity for testing for IgG. It should be noted that previous publications of the Ciao Corona study reported results of a different Luminex-based test (e.g., ABCORA 2.3 binding assay), and therefore they will vary slightly from what is reported here.

At T4, two different definitions of seroprevalence were considered: (a) seroprevalence in tested children without documented vaccination, or (b) Seroprevalence in all tested children (including those reporting vaccination). Because subjects who were both infected and vaccinated are not included in the first definition, seroprevalence will be underestimated. The true infection rate will be somewhere between the two definitions.

Statistical analysis

Statistical analysis included descriptive statistics and Bayesian hierarchical modelling to estimate seroprevalence. The Bayesian approach accounts for the sensitivity and specificity of the SARS-CoV-2 antibody test and the hierarchical structure of cohort (individual and school levels). The model (Bayesian logistic regression) was adjusted for participants' grade and geographic district of the school and included random effects for school levels. We applied poststratification weights, which adjusted for the total population size of the specific school level and the geographic district. The model and weighting procedure are described in detail elsewhere [24].

Variability in seroprevalence among districts, communities, schools, school level and classes was examined using variance partition coefficient, which describes the proportion of total variation that can be attributed to within unit variability[25]. With the introduction of the COVID-19 vaccine to this age group in Switzerland, it is no longer possible to examine clustering as we have done in previous analyses of this study. Official statistics of SARS-CoV-2 infections in children aged 7–17 years of age in the canton of Zurich were retrieved to calculate the cumulative incidence of diagnosed SARS-CoV-2 cases by T2 to T4, and to compare with the proportion of seropositive children by 6 November 2020 (median time point of T2), 29 March 2021 (T3) and 29 November 2021 (T4) [27].

Socioeconomic status of the school was measured with a composite measure, Social Index (SI), which reflects the socioeconomic status (e.g., unemployment, immigrant population) of the location of the school and is provided by the Educational Directorate of Canton Zurich. Scores range from 100 to 120 with lower scores indicating less disadvantaged schools. All statistical analysis was performed using the R programming language [28]. and Bayesian models were fit using the RSTAN package [29].

Results

Participant characteristics for T2, T3 and T4 are presented in table 1.

Among 930 participants aged 12 or older, 51% (n = 472) had been vaccinated at least 2 weeks prior to T4 serological testing. Among seropositive children, 50% in primary and 91% in secondary school were vaccinated. Of the 55 schools participating prior to T4, 43 continued to participate (table 2).

The total number of included classes increased from 275 to 287, and the median number of classes per school increased from five to seven (range 2–10). The number of participants per school remained fairly constant, but participation at the class level was lower at T4 than during previous rounds. Socioeconomic status was comparable between schools that did participate and those that no longer participated in T4 (median 105 among schools not participating vs 107 among participating schools, p = 0.33).

Evolution of seroprevalence

Seroprevalence at T2 was 5.6% (95% credible interval [CrI] 3.5–7.6%) and at T3 18.4% (95% CrI 15.1–21.9%) (table 1). At T4, it was 31.1% (95% CrI 27.0–36.1%) in non-vaccinated children and 46.4% (95% CrI 42.6–50.9%) in all children (including vaccinated). Based on an overall PCR-positivity rate of 133 positive tests per 1000 inhabitants in the canton of Zurich aged 6–17 years, we estimate a ratio of diagnosed to seropositive children in late 2021

Table 1:
Characteristics of study participants over time.

		Oct-Nov 2020, T2	Mar-Apr 2021, T3	Nov-Dec 2021, T4
N total		2500	2450	1875
N (%) primary school (grades 1–6)		1594 (64%)	1606 (66%)	1050 (56%)
N (%) secondary school (grades 7–9)		906 (36%)	837 (34%)	825 (44%)
Age (years), median (range)		12 (7–17)	12 (7–17)	12 (7–17)
Sex male, n (%)		1211 (48%)	1166 (48%)	882 (47%)
Socioeconomic status, n (%)	High	1621 (70%)	1616 (72%)	1211 (73%)
	Low–medium	687 (30%)	633 (28%)	443 (27%)
Vaccinated, aged 12+		0	0	472/930 (51%)
Seroprevalence adjusted*	Infected only	5.6% (3.5–7.6)	18.4% (15.1–21.9)	31.1% (27.0–36.1)
	Vaccinated ± infected			46.4% (42.6–50.9)
Ratio of diagnosed to seropositive		1:5.8	1:3.5	1:3.5

Numbers denote participants (%). Seroprevalences are means (95% credible interval). Socioeconomic status was based on parental educational level with high denoting at least one parent with preparatory high school or university.

*Adjusted for school level, sex, and district, as well as test sensitivity and specificity. Seroprevalence due to infection only describes the total number of infected children with SARS-CoV-2 antibodies out of all unvaccinated children. Similarly, seroprevalence due to vaccination and/or infection is the total number of children with SARS-CoV-2 antibodies, regardless of vaccination status, out of all tested children.

Table 2:

Participation rates and school-level characteristics of the Ciao Corona study at T2, T3 and T4.

	Oct-Nov 2020, T2	Mar-Apr 2021, T3	Nov-Dec 2021, T4
Number of schools	55	55	43
Number of classes	276	275	287
Median number of classes per school (min–max)	5 (2–10)	5 (2–10)	8 (3–18)
– IQR	3–6	3–6	5–8
Median number of participants per school (min–max)	41 (13–101)	37 (15–102)	39 (16–94)
– IQR	31–56	30–59	[27–58
Median number of participants per class (min–max)	9 (1–20)	9 (1–21)	6 (1–17)
– IQR	5–12	5–12	2–8
% Participation within a class, median (min–max)	47% (5–94%)	50% (4–96%)	33% (4–89%)
– IQR	30–62%	32–63%	22–47%
Number of classes with five or more participants	222	221	203

IQR: interquartile range

of 1: 3.5 which was similar to March to April 2021 (T3), though T2 had a higher proportion of children undiagnosed, 1:5.8.

At T2 seroprevalence was similar across school levels (primary 5.5%, 95% CrI 3.4–7.8% vs secondary 5.6%, 95% CrI 2.8–8.7%), whereas at T3, primary school children had a higher seroprevalence (19.5%, 95% CrI 16.0–23.7%) than secondary school children (15.1%, 95% CrI 10.7–19.6). At T4, when only children with SARS-CoV-2 antibodies due to infection were counted and vaccinated subjects excluded, primary students had lower seroprevalence than secondary school students (28.7% vs 41.0%).

Figure 1: Proportion of ever-seropositive children in the canton of Zurich among districts (upper), schools (middle) and classes (lower) at T2 (October-November 2020), T3 (March-April 2021) and T4 (November-December 2021). Each district has an individual colour in the upper panels, primary school children (grades 2–6) in light blue and secondary school children in dark blue (medium and lower panels). Boxplots in the lower panels denote median and describe variability of seroprevalence on a school level expressed as maximum seroprevalence in a class minus minimum seroprevalence and summarised as median (interquartile range). Whiskers of boxplots denote ± 1.5 standard deviation (SD).

Proportion of ever-seropositive children in the canton of Zurich among districts (upper), schools (middle) and classes (lower) at T2 (October-November 2020), T3 (March-April 2021) and T4 (November-December 2021). Each district has an individual colour in the upper panels, primary school children (grades 2–6) in light blue and secondary school children in dark blue (medium and lower panels). Boxplots in the lower panels denote median and describe variability of seroprevalence on a school level expressed as maximum seroprevalence in a class minus minimum seroprevalence and summarised as median (interquartile range). Whiskers of boxplots denote ± 1.5 standard deviation (SD).

However, when both infected and vaccinated participants were included, secondary school students had an average seroprevalence of 75.8% (95% CrI 69.6–82.4%), compared with 31.5% (95% CrI 27.1–36.1%) among primary school students (grades 1–6) (see table 1).

Variability of seroprevalence within and across districts, schools, and school classes

District level seroprevalence ranged from 30.4% to 88.5% at T4 (fig. 1a-c) indicating a substantial increase in variability over both T2 (2.1–18.0%) and T3 (11.1–27.2%).

At T2 and T3, we observed only small differences between the school-level seroprevalence rates of primary and secondary schools (T2: primary 5.6% vs secondary 5.7%; T3: 19.5% vs 15.1%) (fig. 1d-f). However, by T4 in the full sample (infected and/or vaccinated), all secondary schools had a higher seroprevalence than all but one of the primary schools (fig. 1d-f). Within schools there was large variation between seroprevalence of classes (fig. 1g-i). At T2, median between-class variability was 11% (IQR 7–17%), at T3, 24% (IQR 17–37%), and at T4 median between-class variability had increased to 40% (IQR 22–49%). For example, in the primary school with the lowest seroprevalence at T4 (fig. 1i, leftmost bar), had classes with a minimum of 0% and a maximum of 40% seropositive subjects, thus a between class variability of 40%. Results were similar with a range of different inclusion criteria of classes in the analysis (two or three children tested per class; two participants per class and at least two classes per school; at least three participants and at least 50% participation in class). Even within a single geographic district, seroprevalence varied widely between and within schools (fig. 2).

The overall explained variance was at most 25% (fig. 3, supplementary table S1 in the appendix).

Among unvaccinated children only, explained total variance and variance explained by community, school and class were fairly similar but waned over time from T2 to T4. When the vaccinated children were also included, explained variability increased markedly from T3 to T4 with most variability explained by school level, i.e., primary versus secondary school level.

Discussion

In this school-based cohort study of more than 1800 school children from randomly selected schools of the most populous canton in Switzerland, SARS-CoV-2 seroprevalence in children and adolescents increased from 6% in October/ November 2020 to 46% in November/December 2021. The ratio of diagnosed to seropositive children in late 2021 (T4) of 1:3.5 was similar to March to April 2021 (T3).

These key points will be discussed in further detail below. Secondary school children had much higher seroprevalence rates than primary school children by the end of 2021, a difference which was not previously observed and only partially explained by higher vaccination rates. Variability of seroprevalence between districts, schools and classes within the same school increased substantially between the end of 2020 and the end of 2021 two- to fourfold. Explained variability over time decreased among unvaccinated subjects. This evolution mirrors an increasingly complex system of SARS-CoV-2 spread and transmission,

Figure 2: Variability of seroprevalence of children and adolescents at T4 (November–December 2021) among 11 districts (grey bars, mean), 43 schools (triangles, mean) and 200 classes (boxplots) within the same schools and districts. Along the horizontal axis, schools are displayed without names for reasons of confidentiality. Only classes where more than five children participated were included. Boxplots describe variability of seroprevalence on a school level, with middle bar indicating median seroprevalence, box representing the interquartile range (middle 50% of classes) and whiskers the more extreme classes.
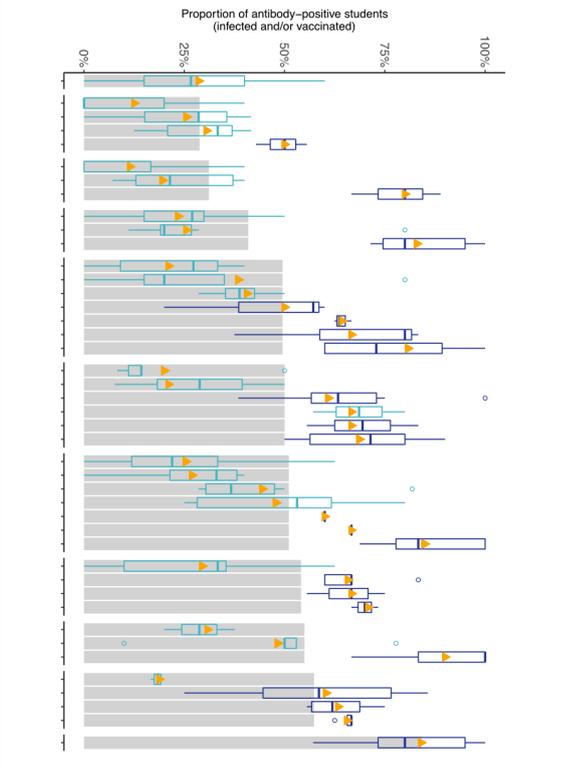

Figure 3: Composite variability in seroprevalence of children and adolescents at T2 (October–November 2020), T3 (March–April 2021) and T4 (November–December 2021) using variance partition coefficients. The total length of the bars shows the total proportion of variance in seroprevalence explained by class, school level (primary versus secondary), school (ID), community, and district. The remaining residual variation is attributable to unmeasured factors.
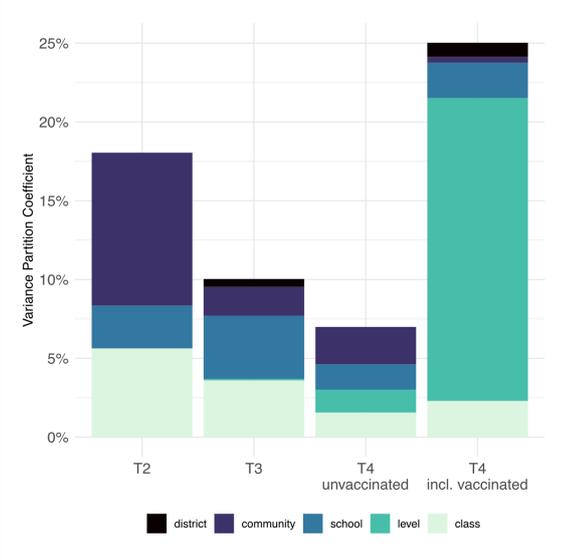
which is highly variable both in and outside of the school system, even in a relatively small part of the same country.

The increase in seroprevalence in children and adolescents in our study from 6% in October/November 2020 (T3) to 46% in November/December 2021 (T4) is consistent with other seroprevalence studies of Europe and the USA [20–22]. Yet between-country variability is substantial and is driven by multiple processes: vaccination status of children, adolescents and adults [1], some youth being vaccinated despite infection, heterogeneity of immune responses to SARS-CoV-2 with occasional failure to seroconvert after infection [30], and background community transmission [31].

Until March–April 2021, primary school children consistently showed similar or slightly higher seroprevalence (<5%) than secondary school students, but this pattern had clearly changed by November-December 2021. The 44% higher seropositivity rates among secondary school compared with primary school children are certainly explained by the introduction of the SARS-CoV-2 vaccination. In our analysis, 49% of those eligible to be vaccinated had completed the two-dose regimen, and close to 100% of those were seropositive. It is not possible to determine which of these children also had antibodies due to infection from COVID-19. Considering that some of the vaccinated children were seropositive prior to vaccination (reflecting the seroprevalence of unvaccinated-infected children), the true seroprevalence in infected children would be expected to be higher than what was measured (extrapolating from the infected only children by about 10% to 15%). Not even N-antibodies (reflecting natural infection rather than vaccination) specifically found in infected individuals would have helped to estimate seroprevalence in infected children, as they wane after a few months, much faster than our 8-month time window between T3 and T4 [32, 33]. Even after those vaccinated were excluded, the higher seroprevalence in secondary school children was also documented in other countries [1, 12, 33] and was among the highest among age groups under the delta variant. Adolescents of this age group show social behaviour different from their younger counterparts, with more social contacts outside the home and school setting, and they may also have been weary of the mitigation measures that were constantly in place since the beginning of the pandemic. In previous rounds, seroprevalence was higher in primary than secondary schools, but this was partially explained by differences in mask-wearing policies [16]. Masks were initially required only for the older age group, which was associated with a 5% lower seroprevalence in adolescents than in younger children in early 2021 [16]. The reversed trend in seroprevalence between primary and secondary school in late 2021 with the mask mandate changed to a general masking rule at school during most of the period between testing in 2021 reinforces this previous result [16] and could also be supported by a different social behaviour of adolescents and a higher susceptibility compared with the younger age group in and outside school [34].

Interestingly, explained variability was rather low and decreased over time when vaccinated children were excluded, but increased when all children, including the vaccinated children, were considered. In the unvaccinated group, the dominant part of explained variance at T2 was the community where the child lived and his or her class [17, 24]. School became more important at T3, [16] whereas at T4 neither community, nor school, school level or class explained much variability. With the vaccination of 48% of participating secondary school children, school level became the dominant factor, as the age of children in secondary school corresponded well to the age group where vaccination was available, 12 years and older. Even though the spread in school increased with the more infectious variants, variation was not explained by school or class identity. Other factors such as the household or close contacts outside class and school could still be more important in the infection spread [34].

From a public health perspective, Ciao Corona is unique as it repeatedly measures seroprevalence, an important variable to document the spread of infection in children and adolescents in the school setting, as well to assess the impact of children's seroprevalence and vaccination on SARS-CoV-2 spread in schools. Ciao Corona is one of the few large studies reporting variation in seroprevalence over time in children within districts, schools and school classes from randomly selected schools in a country where the general lock-down at a population level was mild and short (6 weeks in 2020), and school closure lasted only for 2 months at the start of the pandemic. We were able to perform four assessments covering the major SARS-CoV-2 variants (wild type at T1/T2, alpha in T3, delta in T4). The overall retention rate remained comparatively high through March/April 2021 (89% and 87%) although it decreased by T4 (34%), which mainly reflected decisions not to participate in T4 on a school rather than individual level. Use of serological testing implies that children with asymptomatic infections were also detected.

This study also has limitations. Due to the nature of serological testing, exact timing of infections cannot be determined. Therefore, examination of associated infections, in the sense of outbreaks or temporal clusters of infections, is not possible. We used a highly accurate serological test and adjusted for inaccuracy using Bayesian models on a population level, but it is not possible to avoid some false positive or false negative results on an individual level. Additionally, there were likely vaccinated children and adolescents who were also infected, and therefore some underestimation of seroprevalence of the infected-only cohort is likely. Including these children also as infected would increase the estimates of seroprevalence due to infection rather than vaccination. Moreover, the addition of anti-N IgG antibodies that document natural infection with SARS-CoV-2 also in vaccinated children might have helped to tease out the percentage of vaccinated children who also had a natural infection, although children seem to develop lower levels of anti-nucleocapsid IgG antibodies with a faster decline than adults and the temporal sequence of natural infection and vaccination would still be missing [30, 35]. Participation bias in studies like Ciao Corona can occur at the individual level of the child, or on the class or school level; it can be balanced over time or differential non-participation at some time periods might have occurred. Due to the nature of repetitive testing with fear of venous blood sampling in mind, possible participation bias is unavoidable. Yet we managed to have much higher participation rates than other similar studies (33 vs 9%) [36].

Overall, we had comparable study populations of higher socioeconomic status than the general Swiss population at each round, potentially leading to some underestimation of seroprevalence in each testing round as more disadvantaged populations show higher SARS-CoV-2 seroprevalence [36, 37]. Selective non-participation of children with known previous infections compared with previously seronegative children did not occur (e.g., 66 vs 62% of seropositive and seronegative children at T3 participated again at T4), but some misclassification could have taken place as antibody levels may wane over time [38]. Yet, based on the relatively higher participation of secondary compared to primary school children and lower participation rates on the class level at T4 compared to previous rounds (see table 2), some overestimation of seroprevalence is not excluded. On the school level, we examined the social index of the schools, a composite measure which reflects socioeconomic status (e.g., unemployment, immigrant population, parental support by the social system) of the location of the school provided by the Educational Directorate of Canton Zurich. The social index was representative for the canton of Zurich, did not change over time and was comparable among those schools which participated at T4 and those that did not. Because of a lower participation on the class level, with about half of classes newly entering the study at T4 (with unknown previous serological status of these children) and a high number of vaccinated children in whom concurrent natural infections could not be defined with our design, clustering as indication of intra-class or intra-school transmission could no longer be determined.

Conclusion

We observed a large increase in seroprevalence from October 2020 through November 2021, especially between March 2021 and November 2021 following introduction of the vaccine for children 12 years and older. Up to March 2021, primary school children had higher seroprevalence, but by November 2021, secondary school children were more likely to be seropositive. This shift was in part due to introduction of the COVID-19 vaccine, but possibly also due to different behaviour, with more social contacts of older children outside schools and households. Variability in seroprevalence among districts, schools and classes was high and increased over time, even between different schools of the same district and among classes in the same school. Since this variability was not explained by school or class, other factors not captured (e.g., family members and other close contacts outside of the school setting) could still be more important in the spread of infection.

Data sharing statement

Data are still being collected for the longitudinal cohort study Ciao Corona. Upon study completion in 2023, de-identified and potentially aggregated participant data, together with required data dictionaries, will be available on reasonable request by email to the corresponding author. The purpose and methods of data analysis will be evaluated by the study team first to ensure that it complies with the ethics approval.

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Appendix: Supplementary data

Table S1:
Proportion of variance in seroprevalence explained by geographic district, community, school, school level and class, expressed using variance partition coefficient (percent of total variation explained by within cluster variation).

		Oct–Nov 2020 (T2)	Mar–Apr 2021 (T3)	Nov–Dec 2021, unvaccinated* (T4)	Nov–Dec 2021, vaccinated or unvaccinated* (T4)
Regional	district	0%	0.5%	0%	0.9%
	community	9.7%	1.9%	2.4%	0.4%
School	School ID	2.7%	4.0%	1.6%	2.3%
	School level	0%	1.0%	1.4%	19.2%
	class	5.6%	3.6%	1.6%	2.3%
Total		18.0%	10.0%	7.0%	25.1%

* T4 unvaccinated denotes the cohort with only unvaccinated children, T4 vaccinated or unvaccinated denotes the full cohort with vaccinated and unvaccinated children. School ID denotes the individual school.

Figure S1: Average daily cases per 100,000 inhabitants in the canton of Zurich (blue) and across Switzerland (red).