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The SARS-CoV-2 pandemic in Germany may represent the sum of a large number of local but independent epidemics each initiated by individuals aged 10–19 years, middle-aged males, or elderly individuals

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Abstract

Many epidemiological aspects of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemics, particularly those affecting children, are still sparsely elucidated. Data on the first pandemic phase during the year 2020 indicated that children might serve as a virus reservoir. We now analyzed data on more than 530 000 SARS-CoV-2 polymerase chain reaction (PCR) and 12 503 anti-SARS-CoV-2 antibody tests performed in the west of Germany until Week 4 of 2021. We show that children of at least 10 years of age may play a prominent role in the pandemic showing highest PCR-positive rates in the first (Weeks 28–35), second (Weeks 42–48), and third wave (Week 50 of 2020–Week 2 2021) of the second pandemic phase, although the waves were not mainly initiated by children. The waves' kinetics differed even in nearby cities. Low PCR-positive rates were confined to areas of lower population density. PCR-positive rates were higher among middle-aged males compared with women and among very old females compared with males. From Week 25, seroprevalence rates slowly increased to 50%, indicating ongoing virus activity. In conclusion, the SARS-CoV-2 pandemics is characterized by many local but interacting epidemics, initiated and driven by different social groups. Children may not be the main initiators of virus spreading but older children may significantly affect the course of the pandemic. High population density is associated with higher SARS-CoV-2 incidence.

KEYWORDS

children, epidemiology, gender, polymerase chain reaction, population density, SARS-CoV-2, SARS-CoV-2 antibodies

1 | INTRODUCTION

The impact of children for the course of the pandemic is still a matter of discussion.[1,2] This concerns the general susceptibility of children towards severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),[3] their impact on viral transmission,[3–5] the viral loads in pediatric respiratory specimen compared with adults,[6–11] and the time spans of viral shedding compared with adults[9,12] or within different pediatric age groups.[13] Hereby, during the first phase of the pandemic, transmission rates from children to further contact persons have been reported to range from 0.5% to 20%.[5,14]

Although longitudinal epidemiological data are important to understand the course of the SARS-CoV-2 pandemic, only few studies have provided longitudinal data spanning a longer period of time. Mensah et al.[15] reported on SARS-CoV-2 infection rates among British school children between July and December 2020, based on polymerase chain reaction (PCR) data. They found an increase of overall positive rates with age. Although low in summer, infection rates increased from August, before school reopening. Young adults were affected earlier than younger children. Despite keeping schools open during the British national lockdown in November 2020, infection rates decreased in school-age children so that schools might not be responsible for driving the pandemic. Leeb et al.[16] described pediatric SARS-CoV-2 incidence rates in the United States as proven by PCR testing. Higher incidences were found among adolescents of 12–17 years compared with 5- to 11-year-old-children. From March 2020 to July 2020, incidences increased continuously, followed by a plateau in August and a decrease in September 2020.[16] Lim et al.[17] studied seroprevalence rates in different regions of the United States between March and August 2020, showing marked time- and region-specific differences. As antibody titers decreased over time, they suggested that seroprevalence estimates might underestimate the true cumulative incidence of SARS-CoV-2 infections.[17] Based on longitudinal antibody studies performed between January 2020 and February 2021 among German children between 1 and 10 years, Hippich et al.[18] reported on positive rates of up to 8%, which was higher than during PCR studies and explained by frequently asymptomatic pediatric infections. Based on serological studies from children below 18 years of age in Missisippi (USA), Hobbs et al.[19] calculated a continuous increase of seroprevalence rates between April and September 2020 to about 18% with no difference between boys and girls.

People of color,[19–23] people with low socioeconomic status,[22–25] families with many members,[26] middle-aged men,[27] and people from areas with higher population densities[28,29] seem to have higher infection rates. A low socioeconomic status[25,30,31] and male gender[27] may further be associated with a poorer prognosis.

Whereas PCR studies detect acute infections, antibody studies may mirror the general course of the pandemic and the effect of vaccinations. IgM and IgG anti-SARS-CoV-2 antibodies may already be detectable within 1 week after symptom onset and show an increase of detection rates until Weeks 2–4 (IgM) or Weeks 4–8 (IgG), which is followed by a decrease during the following months.[32–34] More severely affected patients seem to develop antibodies earlier.[35,36] Typically, IgG anti-SARS-CoV-2 becomes positive before the disappearance of viral shedding.[13,37] Similar to IgM, IgA-type antibodies may become detectable before IgG-type antibodies and may decrease more rapidly.[36] Heterogeneous positive rates for anti-SARS-CoV-2 antibodies have been described at similar times in different countries, which may mirror local particularities of the pandemic and the use of different test systems.[38] As different test systems do not show identical results, simultaneous application of different test systems has been recommended to achieve highest detection rates.[33]

Based on PCR data of a large private laboratory and of the University Hospital RWTH Aachen laboratory, we have recently shown for the first phase of the SARS-CoV-2 pandemic that children, although not driving spreading of the virus, might serve as viral reservoirs, as they did not show a similar marked decline of positive rates compared with adults.[39] We also found that these data were representative of the situation in Germany. We now wanted to know whether differences regarding the SARS-CoV-2 infection between children and adults were also present in the second phase of the pandemic focusing on an even larger cohort of patients. We further focused on differences between males and females, different regions and different population densities.

2 | METHODS

Data sets on 540 587 studies on SARS-CoV-2 PCR tests performed by the laboratory MVZ Dr. Stein + Kollegen, Möchengladbach, Germany, between January 27, 2020 and January 31, 2021 were included into this study. These data sets contained the PCR result, patient age at investigation, patient gender the ZIP code of the proband´s home town, and/or of the institution where the specimen had been drawn. If both ZIP codes were available, the ZIP code of the proband´s home town was used for further analyses. The vast majority (81%) of the patients derived from the western part of the German state of North Rhine-Westphalia, 16% from the eastern part of North Rhine-Westphalia, a small number from further cities from all over Germany (1%), and from two areas in the Netherlands and Belgium (2%), respectively. The data available included the first phase (calendar Weeks 8–16 in 2020) and the second phase (calendar Week 28 in 2020 to 4 in 2021) where most SARS-CoV-2 infections in North Rhine-Westphalia were still caused by strains of the wild-type variant of SARS-CoV-2, whereas the α-variant was just about to emerge (share of the α-variant at the end of January 2022: 11.7%; source: Gisaid.org).

PCR studies were performed as reported previously.[39] Antibody data were available from studies performed on 12 503 samples in the same area and during the same period of time. The Elecsys® Anti-SARS-CoV-2 S kit (Roche) targeting IgM/IgA/IgG antibodies to nucleocapsid protein was used for determination of total antibody levels and the Anti-SARS-CoV-2-ELISA test (Euroimmun) was used for determination of IgG and IgA antibodies. Application of both test systems has repeatedly been reported in the literature.[33,37]

The study was approved by the Ethics committee of the Medical Faculty of RWTH Aachen University (CTC-A 20-295).

3 | RESULTS

3.1 | Results from SARS-CoV-2 PCR testing

PCR data derived from 236 548 male and 297 596 female patients studied between calendar Week 7 in 2020 and calendar Week 4 in 2021. The time course of overall positive rates depicts the initial phase of the pandemic in spring 2020 (around calendar Week 12), a decrease of positive rates until Week 27 of 2020, and a second phase with three waves of increasing positive rates with peaks at Weeks 32, 45, and 52 in 2020, respectively (Figures S1). Absolute numbers of tests did not correlate with the corresponding positive rates

Considerably, more tests were performed among middle-aged adults than among younger and older persons (Figure 1). Overall positive rates were lowest among children between 1 and 7 years of age and highest among older children and adults around 50 years of age.

During the initial phase of the pandemic, the shares of specimens tested positive for SARS-CoV-2 had been lower among children compared with adults but the ensuing decrease was retarded in children compared with adults.[39] To analyze the kinetics of positive rates during the further course of the pandemic, data were grouped into 5-year age groups, focusing on the weeks until January of 2021 in 1-week-intervals (Figure 2). As already indicated above, this second phase of the pandemic was characterized by three waves of increasing positive rates: between calendar Weeks 28 and 35 of 2020, between calendar Weeks 42 and 48 of 2020, and between calendar Week 50 of 2020 and Week 2 of 2021, respectively. During these three waves children and adolescents between 10 and 19 years of age always showed the highest positive rates, whereas children between 0 and 9 years were among those groups with the lowest positive rates. The third wave was preceded by high positive rates observed among persons between 90 and 99 years of age.

For further investigating the infection kinetics, we analyzed cumulative positive results in three different town areas (Aachen, Heinsberg, and Möchengladbach; distances between 40 and 65 km) between calendar Weeks 9 and 25 of the year 2020. Infection kinetics during this first phase of the pandemic differed between these cities and infection numbers increased at different time points (Figure S2). Therefore, the general kinetics of the SARS-CoV-2 pandemic in Germany represents the sum of a large number of local but interacting epidemics.

To find out whether peak infections in children showed similar characteristics as in adults, we determined the week with the highest infection rate (Figure S3) and the peak infection rates (Figure 3) for every 1-year age group, and for each of the three waves of the second phase. During the first wave of Phase 2 (around calendar Week 32) peak infection rates occurred at similar times in different
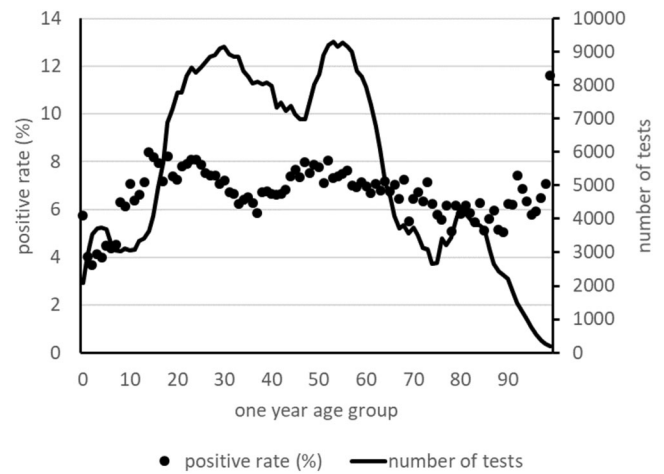

FIGURE 1 Number of tests performed in different 1-year age groups between Week 7 of 2020 and Week 4 of 2021. Comparison with the corresponding overall positive rates of the respective age groups
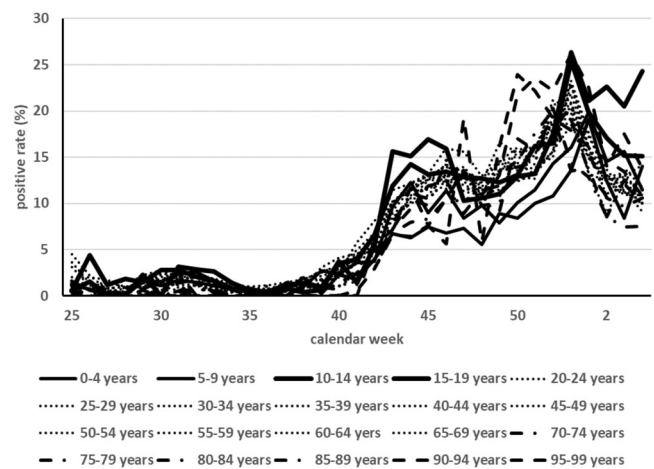

FIGURE 2 Time course of positive rates for different age groups, starting just after the end of the first phase of the pandemic in Germany
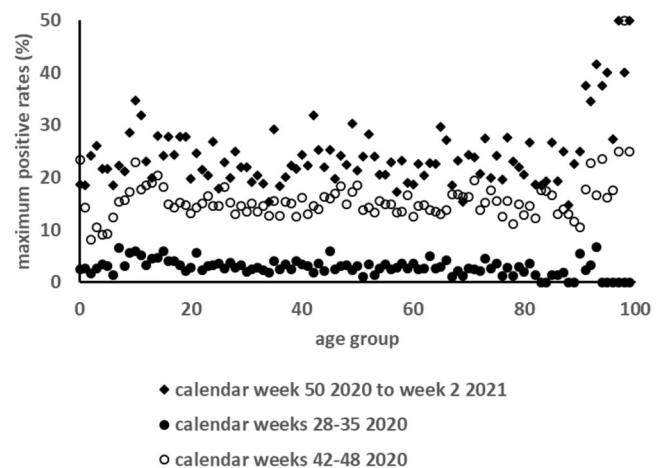

FIGURE 3 Maximum positive rates in different one year age groups during the three waves of the second phase of the pandemic

age groups, whereas peak infection rates of persons below 25 and above 75 years of age occurred somewhat earlier during the second wave (around calendar Week 46; Figure S3). In patients from 65 years of age, the second wave evolved into the third wave. In this third wave, peak infections among middle-aged adults (around Week 53) occurred later than among most older adults, followed by peak infections among children. After the first phase (Weeks 22–27), results from all age groups showed weeks with negative PCR findings. After the first wave of Phase 2 (Weeks 36–41), weeks with negative findings were quite confined to persons below 20 and above 65 years of age, respectively. Thereafter, weeks with negative findings were nearly absent from all age groups.

Maximum positive rates itself differed between the three waves of Phase 2, showing values between 2% and 4% in Wave 1 (Weeks 28–35), 10% and 20% in Wave 2 (Weeks 42–48 of 2020), and 20% and 30% in Wave 3 (Weeks 50 of 2020 to 4 of 2021), respectively (Figure 3). Maximum positive rates among children between 0 and 9 years were among the lowest ones, whereas maximum positive rates among children between 10 and 19 years were among the highest of all age groups in all three waves of Phase 2. Highest positive rates were observed among very old patients (Figure 1).

Men have been reported to be more seriously affected by SARS-CoV-2 infections.[40] We therefore compared overall positive rates among 278 753 females and 218 726 males in different 1-year age groups (Figure 4). Overall positive rates were similar among male and female children up to 19 years of age but higher among males compared with females between 20 and 70 years of age. From 90 years of age, overall positive rates among women were higher than those among men.

During the first phase of the pandemic, positive rates observed in ambulatory and hospital settings differed markedly.[39] Including a much larger number of investigations performed between Week 7 of 2020 and Week 4 of 2021 (Figure 5), we found that irrespective of age, positive rates were always lower in patients tested in hospitals compared with ambulatory settings. Within the ambulatory or hospital group, respectively, positive rates among different age groups showed very similar patterns with lower rates among young children. When additionally distinguishing between male and female patients (Figure S4), we found that only males of 20–60 years of age tested in ambulatory settings showed markedly higher overall positive rates than women. They even showed highest positive rates compared with nearly all other age or gender groups. In addition, only men of about 60–80 years of age studied in hospitals showed higher positive rates than women.

To study whether higher positive rates among male adults were consistent throughout the pandemic, we calculated the positive rates for 50- to 54-year-old males and females, not differentiating between ambulatory or not ambulatory patients (Figure S5). During most weeks of the pandemic, 50- to 54-year-old males showed higher positive rates than females.

To evaluate whether higher overall positive rates might also be related to higher population densities, we compared the population densities of those 100 postal regions where at least 1000 SARS-CoV-2
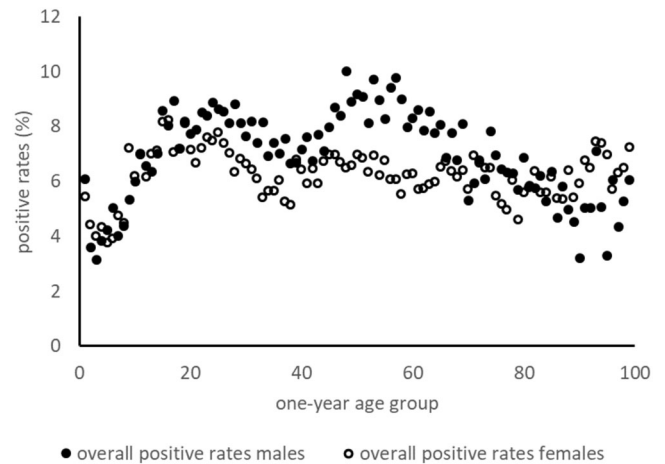

FIGURE 4 Overall positive rates in males and females of different 1-year age groups based on data from Week 7 of 2020 to Week 4 of 2021
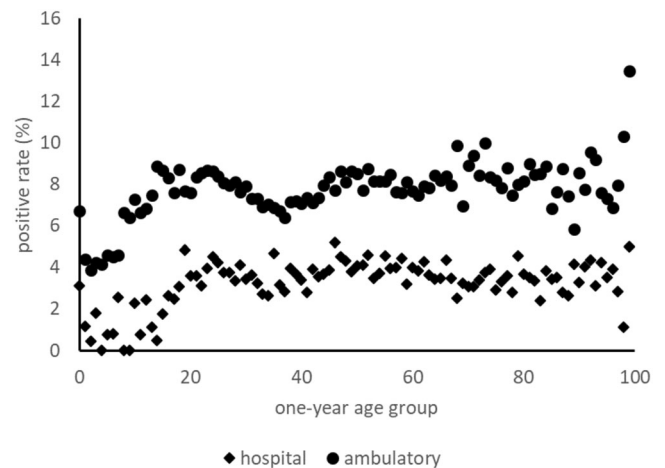

FIGURE 5 Overall positive rates of patients tested in hospital or ambulatory settings. Data displayed for different 1-year age groups
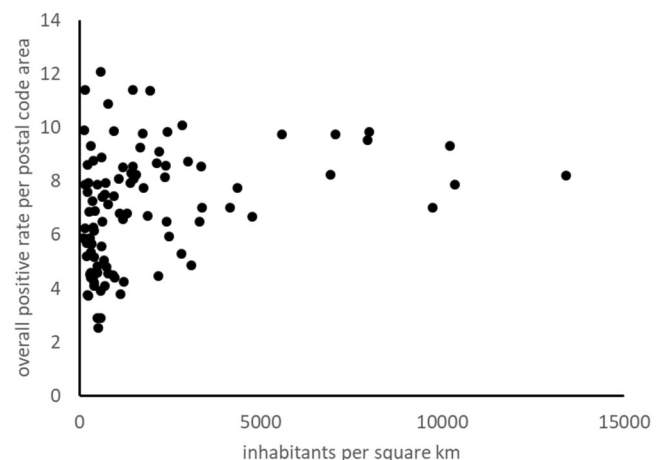

FIGURE 6 Overall positive rates in different postal regions compared with the population densities in the respective regions

PCR analyses had been performed during the whole observation period with the overall positive rates in the respective postal regions (Figure 6). Whereas high overall positive rates were also observed in regions with low population densities, all regions with population densities of at least 4000 inhabitants per km^2 showed overall positive rates of at least 6%.

3.2 | Anti-SARS-CoV-2 antibody findings

Data from three different antibody tests were available, for example, studies for IgG and IgA anti-SARS-CoV-2 antibodies, as well as for total anti-SARS-CoV-2 antibodies.

To evaluate whether testing for one antibody could substitute testing for another type of antibody, we first analyzed 151 data sets where data from all three assay types were available for each patient (Table S1). In this analysis, total antibody tests were always positive when IgG-type antibodies were positive. Total antibodies, however, proved positive more frequently than IgG antibodies, which for part may be due to the additional presence of IgA and/or IgM type antibodies.

In a second approach, we focused on data sets where only two antibody assays had been performed for each patient (IgG vs. IgA, IgG vs. total antibodies, and IgA vs. total antibodies; Table S2). Similar to the findings in Table S1, testing for total antibodies proved positive in 98% of studies where IgG-type antibodies proved positive, whereas testing for total antibodies in general proved positive more frequently than testing for IgG antibodies. This also could be for part explained by the presence of IgA-type antibodies. In a small proportion of patients, IgA-type antibodies were positive, whereas total antibodies were not. Therefore, testing for total antibodies may, for a large extent, substitute for testing for IgG but not for IgA antibodies. The different tests were not interchangeable completely in any constellation.

To calculate overall positive rates for different 1-week intervals, patients who were antibody positive in at least one of the three tests were defined antibody-positive (Figure 7). We included data from calendar Week 7 of 2020 to calendar Week 4 of 2021 and from 12 503 patients, differentiating between males and females but not between different age groups. The resulting course of positive rates over time mirrors a continuous increase of anti-SARS-CoV-2 seropositivity in the population starting from Week 25. No difference between males and females was observed.

We also studied antibody-positive rates among different age groups differentiating between men and women. Overall positive rates of females and males were similar between age 0 and 74 years of age (Figure S6). From age 75 years, positive rates increased. In 9 of the 11 5-year age groups describing the age period from 20 to 74 years, men showed higher antibody-positive rates than women, which complies with the above-described PCR data. No male predominance was found below 15 years and above 75 years of age.

To evaluate whether distinct antibody subtypes were predominant in distinct age groups positive rates for IgA-type, IgG-type, and
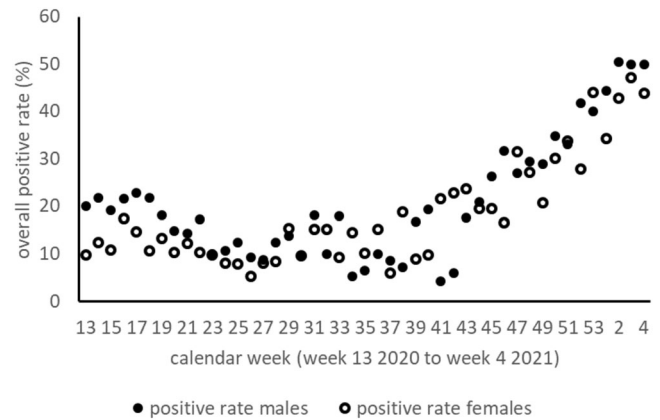

FIGURE 7 Overall antibody-positive rates over time resulting from antibody testing, differentiating between males and females

total antibodies were plotted against different 5-year age groups and compared with the number of tests performed in these age groups. As shown in Figure S7, younger patients tended to show lower positive rates for IgA-type antibodies than for IgG-type or total antibody studies. From age 30 to 79 years, positive rates of the three different antibody test were very similar. Highest positive rates in general were observed among patients from 75 years of age. Children and older persons had been tested considerably less frequently for anti-SARS-CoV-2 antibodies than middle-aged patients.

To study whether different age groups differed with regard to the distribution of their antibody titers, positive antibody titers were classified in a semiquantitative fashion, leading to titers of <10, 10–19, 20–29, 30–39, and so on. Then the cumulative proportions of these groups were depicted for each age group and for the three tests. Due to the low test numbers in young and old persons, reliable data were available between 15 and 84 years of age only. For all three tests, young age groups showed low antibody titers more frequently than older age groups (Figure S8a–c).

We finally compared samples for which both PCR and antibody data were available (Table S3). In the majority of PCR-positive samples, antibodies to SARS-CoV-2 were also detected. This share was 78% of the PCR-positive samples for the total antibody test, 76% for the IgG antibody test, and 64% for the IgA antibody test.

4 | DISCUSSION

We recently described a particular role of children during the first phase of the SARS-CoV-2 pandemic, showing a delayed decrease of infection rates compared with adults.[39] Focusing on a longer period of time, we now focused on ongoing differences between children and adults, males and females, or patients living in different postal regions. The study period ends with January 2021, when the SARS-CoV-2 α-variant had just started to emerge and before the introduction of routine antigen tests and of vaccinations.

Similar to the first phase of the pandemic, less PCR (and antibody) tests had been performed among children and older persons (Figures S1 and S7),[39] and absolute test numbers decreased in January 2021, although overall positive rates were still high in different age groups (Figure S1) and viral mutations were emerging.

The here described second phase of the pandemic consisted of three different waves, which showed increasing infection rates and were each followed by an only partial decrease of positive rates (Figure 2). The waves' kinetics were not equal for different regions or different age groups. As depicted in Figure S2, even in nearby cities maximum infection rates occurred at different points of time. Moreover, whereas overall positive rates among children below 10 years were particularly low, those of 10- to 19-year-old patients were particularly high (Figure 2) and peak infection rates among preschool children were lower than those among school children (Figure 3). This different involvement indicates that different pediatric age groups may require different infection control interventions. PCR and serological literature data from various countries confirm lower infection rates for younger children[16,21,26,28,41,42] and higher positive rates among older children also compared with adults.[26,41–43]

Despite higher positive rates, older children do not necessarily account for virus spreading. During the first wave of Phase 2 showing low overall positive rates (Figure S3 and 3), pediatric and adult infections emerged together as peak positive rates of children and adults occurred simultaneously. During the second wave, when overall positive rates were still low, peak infection rates of children and older people preceded those of middle-aged adults. Therefore, children may well have contributed to virus spreading. During the third wave, peak infections in older people preceded those of all other age groups. Therefore, children may not have initiated this wave, which caused extensive contact restrictions in Germany.

Men have been reported to be more severely affected by Sars-CoV-2. In line with these data, overall positive rates were higher among 20- to 65-year-old men than among age-matched women.[27] Endocrine and immunological gender-specific differences have been discussed in this context.[44,45] Among the here reported patients, however, lower female infection rates did not only affect the premenopausal but the entire working lifetime which argues against this hypothesis. According to the literature, the pattern of social contacting may also affect viral transmission. Hereby highest transmission rates are frequently predicted for respiratory infections in school children and young adults.[46,47] The patterns of social contact may differ between different age groups, with regard to the involvement of family or nonfamily members, the presence of physical contact, and whether contacts occur during school, work, or leisure times.[47–50] Men, for example, show higher employment rates than women (for details, browse eurostat.ec.europa.eu) but experience a decrease of social [51] and of physical activities [52] after retirement. In general, from age 65 years, the number of contacts involving several persons (clustering) drops.[53] Whereas the rate of social contacting is stable throughout the life span for family members, it continuously decreases for nonfamily members with an accelerated decrease after 70 years of age.[48] Therefore, differences in social contacting between working life and retirement may be one further cause for differences between male and female infection rates.

High male positive rates were restricted to ambulatory tests and overall positive rates in hospitals were generally lower than those from ambulatory settings. This may be related to the fact that hospitals preferentially harbor noninfected persons plus selected persons with severe SARS-CoV-2 infections. Moreover, during this phase of the pandemic, SARS-CoV-2 infection rarely led to hospital admission of middle-aged men compared with older persons. These biases must be considered when including hospital data into epidemiological studies.

Socioeconomic factors[25] and higher population densities[28,29] may also affect infection rates. According to the here reported findings, population density alone does not determine spreading of the virus as high SARS-CoV-2 infection rates were also present in regions of low population densities (Figure 7). All areas with population densities above 4000 inhabitants per km^2, however, showed overall infection rates above 6% so that living closely together may promote virus spreading.

Whereas PCR studies detect acute infections, antibody studies may provide a view on the general course of the pandemic. For this study, data for a total antibody test and for an IgA- and IgG-antibody test were available. Whereas the total antibody test detected quite all persons tested positive by the IgG test, the IgA test did not substitute for the IgG test or the total antibody test, respectively (Tables S1 and S2). Therefore, a panel of tests should be used for optimum detection of past SARS-CoV-2 infections.

At a first glance, overall antibody-positive rates of children and middle-aged adults were quite similar (Figure S6). This contrasts the low overall positive rates among younger children tested by PCR (Figure 1) and indicates that the pandemic may have involved children with a similar frequency as adults. In line with PCR data (Figure 1), boys of 15–19 years of age showed particularly high antibody-positive rates (Figure S6), and 20- to 74-year-old males showed slightly higher positive rates than females (Figure 4). Older patients, finally, showed highest positive rates among all age groups (Figure S6).

For analyzing overall antibody-positive rates, a patient was defined antibody-positive if at least one antibody test proved positive. Similar to PCR results, positive rates of antibody tests showed a strong and continuous increase from calendar Week 25 in 2020, which indicates continuous virus activity within the population. The maximum positive rate of about 50% observed at the end of our observational period suggests that a considerable share of persons may have contracted SARS-CoV-2 infections during the preceding months (Figure 7). Due to a preselection bias, this share might be higher than the true positive rates in the general population. The physiological decrease of antibody titers over time, in turn, may have counteracted this effect. No sustained increase of antibody-positive rates was observed during the first phase of the pandemic, which complies with a rapid decrease of antibodies after wild-type Sars-Cov-2 infections. With exception from IgA antibodies, showing somewhat lower positive rates in the age groups from 5 to 39 years,

similar positive rates for all three antibody tests were found for the different age groups (Figure S7).

Because of the number of data available, reliable conclusions for antibody titers could be drawn for patients between 15 and 84 years only (Figure S8a–c). With age, the proportion of patients with low total, IgG, and IgA anti-SARS-CoV-2 antibody titers decreased. As lower antibody titers may mirror less severe SARS-CoV-2-related clinical disease[35,37] or a weaker antibody response this may be of relevance for immunization strategies.

We finally compared samples from which both PCR and antibody data were available (Table S3). Independently from the test system used, the majority of PCR-positive samples also proved antibody positive, which confirms that seroconversion occurs early after primary infection[32,34,36,54] and may be necessary for viral clearance.[13,37] In contrast to literature data, the share of IgA antibodies was not higher during this early phase of the infection than of IgG antibodies.

5 | LIMITATIONS

Our results indicate that the general kinetics of the SARS-CoV-2 pandemic in Germany represents the sum of a large number of local but interacting epidemics. Molecular data of whole genome sequencing of SARS-CoV-2 is available for Germany (e.g., Gisaid. org). Such data could be used to verify our observation on the molecular level. Unfortunately, the sequences are only available on the federal and state level. For the time period investigated by us up to the end of January 2021, <2000 sequences are available for the state of North Rhine-Westphalia. This is not enough data to investigate the clonal expansion of SARS-CoV-2 strains on county or city level. Thus, our observation could not be verified based on molecular data due to the lack of available sequences. However, serological data on state level support the hypothesis of interacting local epidemics, as the prevalence of positive antibody findings differed significantly between regions of Bavaria (tests performed between April to July 2020; prevalence range 0.15%–1.63%).[55] Further, the data were collected retrospectively, not prospectively. This results in an overrepresentation of symptomatic patients, as asymptomatic individuals were probably tested less frequently.

6 | CONCLUSIONS

For a long period of time, the discussion on the impact of children for the SARS-Cov-2 pandemic in Germany was characterized by two contradictory positions: the one led to long-term school closures, the other questioned the necessity of school closures assuming a negligible role of children for infection spread. Both positions proved disadvantageous: the one led to psychosocial and educative problems, the other one questioned the need for studies in the pediatric population. The here reported data indicate that children, although not strongly driving the spread of the virus, may yet relevantly contribute to the pandemic with clear differences between children of different ages. For future pandemics, from the very beginning and irrespective from the infectious agent, pediatric aspects should be addressed as consequently as those from adults, together with aspects of gender and of social contacting. This will enable to develop more precise pediatric recommendations, to avoid extensive social restrictions and to provide more effective infection control.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ETHICS STATEMENT

The study was approved by the Ethics committee of the Medical Faculty of RWTH Aachen University (CTC-A 20-295).

AUTHOR CONTRIBUTIONS

Both authors contributed to the conceptualization of the study, data curation, data analysis, data validation, data visualization, writing of the original draft, revision and editing of the manuscript, and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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