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SARS-CoV-2 seroprevalence among children in Latvia

A cross-sectional study

Krista Sapronova, MD[a,*], Rūta Kaķe, MD[b], Jana Pavāre, MD, PhD[c], Dagne Grāvele, MD, PhD[b], Ivita Šēla, MD[c], Estere Ērgle, MD[b], Dana Isarova, MD[c], Zanda Grīnberga, MD[b], Dace Zavadska, MD, PhD[c]

Abstract

Coronavirus disease 2019 (COVID-19) is a major global health concern. In contrast to adults, the course of the disease has been observed to be mild or even asymptomatic in children. It is therefore both clinically and epidemiologically important to measure the seroprevalence in children and adolescents to discern the overall morbidity of the disease and to compare these findings with similar data collected globally. We conducted a cross-sectional study between March and July of 2022 at the Children Clinical University Hospital in Riga, Latvia, to evaluate the seroprevalence of antibodies to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Participants aged 0 to 18 years were enrolled during hospitalization for reasons other than COVID-19. The levels of SARS-CoV-2 spike protein and nucleocapsid antibodies were measured in blood samples. The possibility of transplacental antibody transport was evaluated by directly interviewing the mothers of participants aged 18 months and younger. Various demographic and epidemiological risk factors and their association with seroprevalence were analyzed. Positive SARS-CoV-2 nucleocapsid antibodies were designated the main criterion for seropositivity. Of 200 enrolled children, 173 were found to be seropositive, resulting in an overall seroprevalence of 86.5%. The highest seroprevalence was detected in children and adolescents aged 12 to 18 years. With the progression of the COVID-19 pandemic, the seroprevalence in children has increased significantly. We found that almost 1-third of seropositive children in our study population were unaware of being previously infected with SARS-CoV-2 due to an asymptomatic course of the disease. Our study findings pertaining to high seropositivity among children and adolescents might be beneficial for public authorities to adapt epidemiological strategies and prevention measures. The high seroprevalence rate reported here and in many other populations around the world suggests that COVID-19 will likely become one of the many seasonal viral infections.

Abbreviations: COVID-19 = coronavirus disease 2019, N = nucleocapsid protein, S = spike protein, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Keywords: children, COVID-19, Latvia, seroprevalence, vaccination

1. Introduction

On March 11, 2020, the World Health Organization declared the coronavirus disease 2019 (COVID-19) outbreak a global pandemic.[1] COVID-19 is caused by infection with the highly transmissible severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The first COVID-19 case in Latvia was documented on March 2, 2020.[2,3] Since then, COVID-19 has increasingly become the most pertinent public health concern in Latvia and many other countries, affecting health services, education provision and social interaction. Distance learning was implemented in Latvian schools during the 2 national lockdowns (March 12, 2020 to June 9, 2020, and November 9, 2020 to April 6, 2021). Strict restrictions were also placed on interest-related education and to a lesser extent on preschool learning. Subsequently, the format of the provision of education was dependent on the regional epidemiological situation. In general, a partial return to school was permitted, but this was constantly under review (State Education Quality Service Republic of Latvia, unpublished data, September 2022). At the end of 2021 a new SARS-CoV-2 variant Omicron caused further increase in COVID-19 cases which resulted in calls for further unified restrictions across countries.[4]

It is clearly evident that the pandemic has placed a considerable burden on society. Thus, the measurement of COVID-19 epidemiological data is crucial for planning the most effective vaccination strategies and preventive measures in order to achieve successful epidemiological results with a negligible

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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[a] *Riga Stradins University and Children Clinical University Hospital, Riga, Latvia,* [b] *Children's Clinical University Hospital, Riga, Latvia,* [c] *Children Clinical University Hospital and Riga Stradins University, Riga, Latvia.*

** Correspondence: Krista Sapronova, Riga Stradins University and Children Clinical University Hospital, Vienības gatve 45, Riga LV-1004, Latvia (e-mail: kristasapronova@gmail.com).*

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impact on societal processes. Access to most up to date information on seroprevalence levels enables educated decision making to navigate through the post pandemic times when the community immunity is achieved.

The course of SARS-CoV-2 infection in children is known to be primarily mild or even asymptomatic. Studies have shown that the most common COVID-19 symptoms are fever, cough and gastrointestinal symptoms such as nausea, vomiting and diarrhea. Other reported symptoms include runny nose, pharyngitis, dyspnea, rash, conjunctivitis, fatigue, and neurologic signs, etc.[5] As the manifestations of COVID-19 are nonspecific and are practically indistinguishable from other acute viral infections of childhood, seroprevalence studies are essential to measure the incidence in a research population. Furthermore, as asymptomatic and subclinical cases could be underestimated, these types of cases should be identified using molecular testing or other laboratory methods of SARS-CoV-2 surveillance. In Latvia, vaccination of children against COVID-19 was initiated on June 2, 2021 and targeted the age group 12 to 17 years. On December 16, 2021, vaccination of those aged 5 to 11 years was started. By August 2022, 21% of Latvian children had received the full vaccination course against COVID-19, comprising of 2% of children aged 11 years and younger, 55% of children aged 12 to 15 years, and 73% of children aged 16 to 17 years.[6,7]

The amount of seroprevalence data collected from the pediatric population is limited. However, a recent seroprevalence study conducted in the United States has reported that in February 2022, approximately 75% of the pediatric population had evidence of a previous COVID-19 infection, with about 1-third of cases seropositive since December 2021. Furthermore, the study also reported an increased infection rate with the SARS-CoV-2 Omicron variant among children and adolescents, and the most significant increase in seroprevalence occurred in the age group with the lowest vaccination coverage.[8] A seroprevalence study from Poland with a smaller research population demonstrated that 57% of 686 children were seropositive during the analysis period of June 1, 2021 to April 30, 2022. Similarly, an increase in seroprevalence was detected during the Delta and Omicron COVID-19 variant "waves," with the highest seroprevalence of 87.5% of respondents during April 2022.[9]

The present study reports the SARS-CoV-2 seroprevalence among children in Latvia. The study population was comprised of children who were hospitalized or received treatment in the emergency department of the Children Clinical University Hospital in Riga, Latvia, for health issues other than COVID-19. Moreover, we compare our findings with similar data collected globally.

2. Materials and methods

2.1. Study design

The SARS-CoV-2 seroprevalence of Latvian children was evaluated from a single-center cross-sectional epidemiological study conducted between March and July of 2022 at the Children Clinical University Hospital in Riga, Latvia. The study was approved by the Ethics Committee of Riga Stradins University, Latvia (No. 22-2/569/2021).

2.2. Data collection settings

Study participants were randomly selected from patients who were hospitalized at the Children Clinical University Hospital or received treatment in the emergency department. The eligibility criteria were age between 0 and 18 years and no indication of acute SARS-CoV-2 infection nor contact person status at the time of enrollment in the study. The exclusion criteria were acute SARS-CoV-2 infection and noncompliance with the defined age category. Parents, legal guardians or the participants themselves (aged 14 years and older) were informed of the study purpose and protocol and informed consent for participating in the study was obtained. Each study participant was surveyed to gather information about their demographic features (age, gender, and region of residence), COVID-19 epidemiological risk factors (preschool/school attendance, known contact with COVID-19-positive person, etc) and potential symptoms of COVID-19 from acute infection episodes since March 2020. Serum samples which were taken for other diagnostic or treatment purposes were tested for SARS-CoV-2 infection antibodies. Additional telephone interviews were conducted with the mothers of children aged 18 months and younger to obtain more specific information about their vaccination status against COVID-19. Raw data of the study can be found as the Supplemental Digital Content 1, Supplemental Digital Content, http://links.lww.com/MD/I404.

2.3. Laboratory methods

Total anti-SARS-CoV-2 nucleocapsid protein (N) and anti-SARS-CoV-2 spike protein (S) antibodies in human serum samples were determined using an electrochemiluminescence immunoassay with a fully automated system (cobas e601, Roche). All tests were conducted in the Children Clinical University Hospital laboratory and were performed according to the manufacturer instructions and under strict quality control assessment. The anti-SARS-CoV-2 S assay used a recombinant protein representing the receptor-binding domain of the S antigen in a double-antigen sandwich assay format. A value ≥ 0.80 U/mL was considered a positive result. According to the manufacturer, the assay has a specificity of 100% and a sensitivity of 98.8%.[10,11] The anti-SARS-CoV-2 N assay used a recombinant protein representing the N antigen in a double-antigen sandwich assay format. A cutoff index value ≥ 1.0 (COI; signal sample/cutoff) was considered a positive result. According to the manufacturer, the assay has an analytical specificity of 99.5%, a clinical specificity of 99.8%, and a sensitivity of 60.2% to 99.5% (0–14 days post PCR confirmation test).[12]

2.4. Case definition criteria

A case was interpreted as seropositive when a level of anti-SARS-CoV-2 S antibodies ≥ 0.80 U/mL and a level of anti-SARS-CoV-2 N antibodies ≥ 1.0 COI were detected. Study participants who had anamnesis data of a previous COVID-19 infection and had positive anti-SARS-CoV-2 S antibodies without anti-SARS-CoV-2 N antibodies were considered as seropositive if there were no data of having received vaccination against COVID-19.

2.5. Statistical analysis

Data were compiled and statistically analyzed using the REDCap system and IBM SPSS Statistics platform (version 27.0). Data were collected and exported from the REDCap system to the SPSS platform for the following analysis. Descriptive statistical data analysis was performed, grouping participants into 3 age groups. Categorical variables such as age group, gender, etc. Were compiled as frequencies and percentages. 95% confidence interval for frequencies was calculated. Different categorical variables and their association with seroprevalence were analyzed.

3. Results

3.1. Study population descriptive characteristics

This study recruited 200 patients from different departments of the Children's Clinical University Hospital in Riga, Latvia. All included patients met the eligibility criteria. Data were collected

between March and July of 2022. Children under the age of 5 years accounted for 40.5% (n = 81) of the study sample, 33.0% (n = 66) were 5 to 11 years old, and 26.5% (n = 53) were 12 to 18 years old. Of note, 24 children were 18 months old or younger, which can affect the interpretation of seroprevalence results in this age group due to potential transplacental transfer of maternal antibodies.[13] Therefore, this age group underwent a more thorough analysis. The study participants were 50% female and 50% male. The vast majority of participants attended either school (43%, n = 86) or preschool (38%, n = 76) on a daily basis. Furthermore, 40% (n = 80) also attended extracurricular activities, thus resulting in close contact with other children. The questionnaire issued to each participant covered the time period from the beginning of the COVID-19 pandemic. At least 1 chronic condition was reported by 27.5% (n = 55) of the patients. These included asthma, different types of allergies, congenital heart disease and diabetes. Most of the participants (79%, n = 158) reported at least 1 known close contact with a SARS-CoV-2 laboratory-confirmed person. Specifically, 49.5% (n = 99) stated this contact was inside their family, 16.0% (n = 32) was outside their family, and 13.5% (n = 27) was both. Additionally, 60.5% (n = 121) of the participants disclosed that they had had close contact with a person with symptoms of an acute infection but no laboratory confirmation of COVID-19 infection.

Table 1

Descriptive characteristics of the study population and seroprevalence.

Variable	Seropositive for SARS-CoV-2 nucleocapsid protein antibodies*	
	No.	% (95% CI)
All participants	173	86.5 (81.8–91.2)
Age group:		
<5 yr	63	77.8 (68.7–86.8)
5–11 yr	60	90.9 (84.0–97.8)
12–18 yr	50	94.3 (88.1–100.6)
Gender:		
Female	90	90.0 (84.1–95.9)
Male	83	83.0 (75.6–90.4)
Children with chronic conditions	49	89.1 (80.9–97.3)
Children with known close contact with a SARS-CoV-2 laboratory-confirmed person:	144	91.1 (86.7–95.6)
Contact inside family	89	89.9 (84.0–95.8)
Contact outside family	29	90.6 (80.5–100.7)
Contact both inside and outside family	26	96.3 (89.2–103.4)
Children with known close contact with a person with acute infection symptoms but no laboratory confirmation of COVID-19 infection	103	85.1 (78.8–91.5)

CI = confidence interval, COVID-19 = coronavirus disease 2019, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

* Data include 3 patients with only spike protein antibodies detected.

3.2. Seroprevalence of SARS-CoV-2 antibodies

We detected 173 seropositive children out of a total of 200, giving an overall seroprevalence of 86.5%. In the group of children under the age of 5 years, the seroprevalence was 77.8%, whereas it was 90.9% in the group of children aged 5 to 11 years. The highest seroprevalence, 94.3%, was found in the group of children and adolescents aged 12 to 18 years. Of the 100 girls in the study population, 90 (90%) were seropositive. Of the 100 boys in the study population, 83 (83%) were seropositive. Thus, 52% of the seropositive children were girls. The various characteristics of the study population and their association with seroprevalence are shown in Table 1. Further details of the table can be found attached as Supplemental Digital Content 2, Supplemental Digital Content, http://links.lww.com/MD/I405.

Positive SARS-CoV-2 N antibodies were used as the main criterion to define seropositivity. However, one of the participants who was 4 years old tested positive for S antibodies but negative for N antibodies, with no history of vaccination against COVID-19. This patient was regarded as seropositive. In addition, 2 other participants who were vaccinated against COVID-19 and had a history of positive SARS-CoV-2 also tested positive for S antibodies but negative for N antibodies. These 2 patients were also regarded as seropositive.

A PCR- or rapid antigen test-confirmed COVID-19 infection at least once in the previous 2 years was reported by 61.5% (n = 123) of the participants. Therefore, based on the seroprevalence data, 50 of the 173 seropositive children (28.9%) were unaware they had been infected with SARS-CoV-2. A total of 175 (87.5%) children reported at least 1 known episode of acute respiratory infection since February 2020. The most common symptoms recorded were cough (67.0%, n = 134), fever (78.0%, n = 156), sore throat (42.5%, n = 85) and rhinorrhea (67.0%, n = 134). Fourteen (7.0%) children complained about a loss of taste and 13 (6.5%) complained about a loss of smell.

3.3. Vaccination status

We found that 19.0% (n = 38) of the participants were vaccinated against COVID-19. Specifically, 9.1% (n = 6) were vaccinated in the group of children aged 5 to 11 years, whereas it was 60.4% (n = 32) in the group of children and adolescents aged 12 to 18 years. Of the 38 children and adolescents vaccinated, 36 received Comirnaty and 2 received Spikevax. Regarding the family members of the participants, 91.5% (n = 183) had received at least 1 vaccination against COVID-19. Specifically, 87.0% (n = 174) of the mothers were vaccinated, while it was 78.0% (n = 156) of the fathers. Furthermore, 86.8% (n = 33) of the 38 vaccinated children were found to be seropositive with N antibodies.

3.4. Children aged 18 months and younger and seropositivity

Twenty-four of our study participants were 18 months old or younger. In addition to completing the questionnaire, telephone interviews were conducted with the mothers (21 of the 24 mothers responded) to obtain more specific information about their vaccination status against COVID-19. It was determined that 8 of the mothers started vaccination against COVID-19 immediately before or during pregnancy, 10 started vaccination after pregnancy, and 3 were not vaccinated. Figure 1 shows the association between the vaccination status of the mothers and the seropositivity of their children. One child who was 5 months old and had no history of a positive SARS-CoV-2 test tested positive for S antibodies only. As the child's mother was vaccinated against COVID-19 during pregnancy, we surmised that this child was immunized with maternal antibodies and so did not include this patient in the seropositive group. Five other children of mothers vaccinated immediately before or during pregnancy were seropositive with both N and S antibodies, with only 2 of them having a history of a positive SARS-CoV-2 test. All 5 of these patients were included in the seropositive group. Two children of mothers vaccinated immediately before or during pregnancy were found to be seronegative.

4. Discussion

This is the first study to report the seroprevalence of SARS-CoV-2 among children in Latvia. As we recruited the 200 study participants from the Children Clinical University Hospital in Riga – Latvia only tertiary pediatric hospital that provides

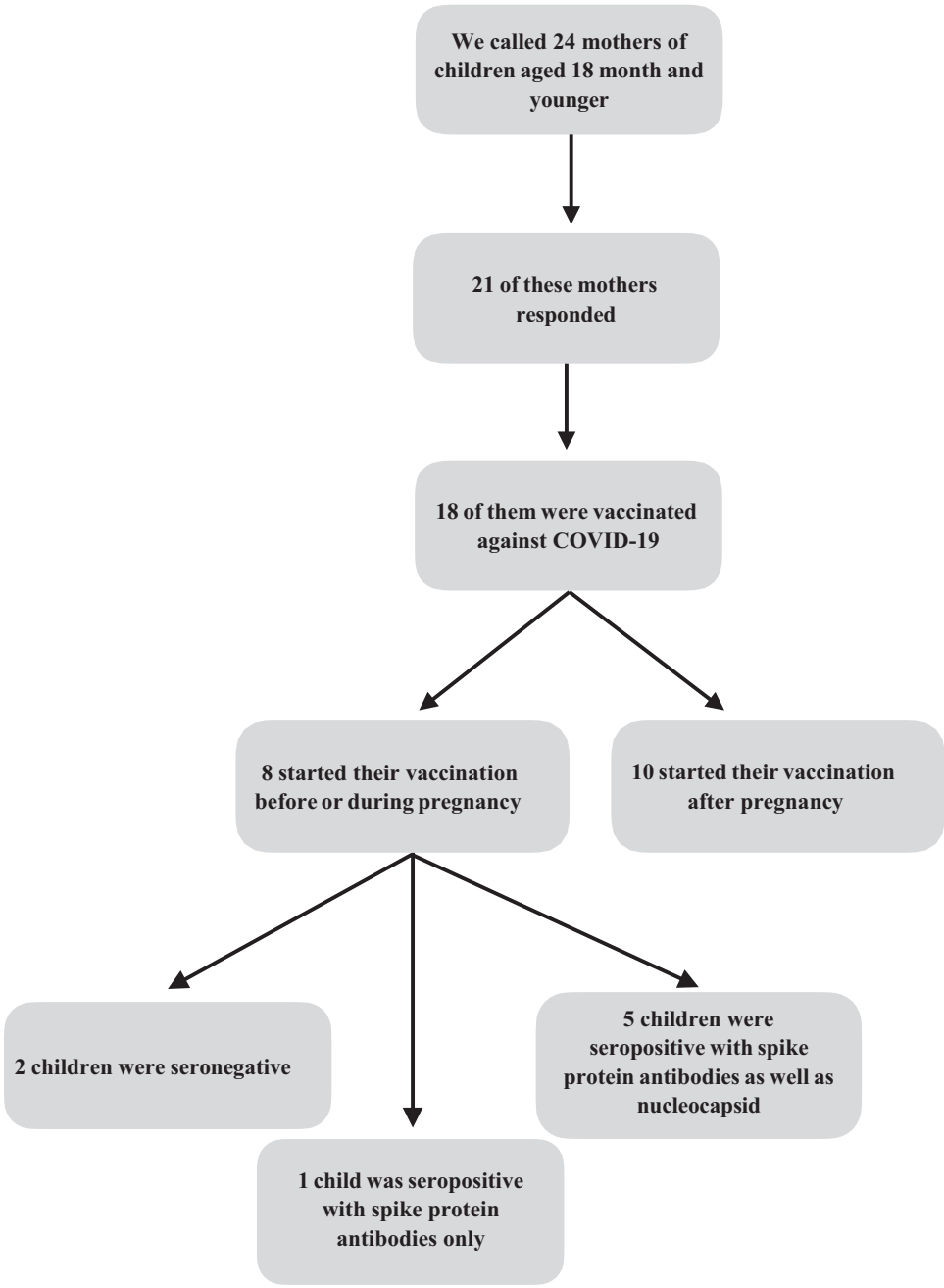

Figure 1. Flowchart of association between vaccination status of mothers and seroprevalence of children aged 18 month and younger. COVID-19 = coronavirus disease 2019.

healthcare for more than 160,000 patients every year from all regions of Latvia[14]–we speculate that our data are likely representative of the whole country.

This study was initiated midway through the Omicron COVID-19 variant wave in Latvia,[15] which hit its peak in February 2022.[16] This might explain why we detected such a high seroprevalence, 86.5%, in our pediatric population. Of the 200 participants, 102 (51%) reported a positive COVID-19 test between January and March of 2022, the same time period during which the Omicron variant started to spread and become the dominant variant of SARS-CoV-2 in most European countries, including Latvia.[17] During this time period, COVID-19 testing was a prerequisite for access to various public services, including attending schools.

With the progression of the COVID-19 pandemic, the seroprevalence in children has increased significantly. For instance, a study from Poland detected a significant difference in the SARS-CoV-2 seroprevalence in children between November 2021 (about 40%) and April 2022 (87.5%).[9] In comparison, a cross-sectional study conducted a year earlier (between July and October of 2020) in the United States found the SARS-CoV-2 seroprevalence in children to be 8.5%, illustrating the major surge in the seroprevalence in children with time.[18] These data show that the Omicron variant is more contagious and spreads more easily in the pediatric population than earlier variants of SARS-CoV-2. With regard to different age groups within the pediatric population, a cross-sectional seroprevalence study conducted in Germany between June 2020 and May 2021 observed a significantly higher seroprevalence in children under 3 years of age compared with older children.[19] In the present study, the highest seroprevalence was found in the group of children and adolescents aged 12 to 18 years. This finding may be

due to more frequent social contacts with peers and variable school attendance in the first months of 2022.

Our questionnaire data revealed that the participants complained about different nonspecific symptoms. Most of the participants who had experienced a previous episode of COVID-19 described the course of the disease as mild or even asymptomatic; none of them were admitted to the intensive care unit during the course of the disease. Data collected in Italy in 2020 during the first months of the pandemic documented several nonspecific symptoms in children infected with SARS-CoV-2. The most common ones were fever, dry or productive cough, and rhinorrhea.[20] Although the loss of smell and taste is one of the most specific symptoms of COVID-19, it is not a common symptom in the pediatric population. Indeed, a study conducted in Greece between February 26 and June 30, 2020 found that only 9.8% of children and adolescents with SARS-CoV-2 infection experienced a loss of smell and/or taste.[21]

Our analysis of children aged 18 months and younger examined the association between seropositivity and maternal vaccination status. We found that the seropositivity of children of mothers who started vaccination against COVID-19 immediately before or during pregnancy was variable, for example they were either seropositive with both N and S antibodies, seropositive with S antibodies only, or seronegative. Currently, the number of studies investigating passive immunization of fetuses to SARS-CoV-2 is small and their findings are inconsistent. Thus, this is an important area that warrants further research.

4.1. Limitations

The present study has the following limitations. Our study population comprised of 200 participants. It is likely that a larger study population would have generated more indicative data. However, as our participants were recruited from the only pediatric hospital serving all of Latvia, we believe that our data are representative of the whole country. The participant numbers in the 3 age groups were not equal; however, as they were relatively similar, we regard this as acceptable. Another possible limitation of our study is the length of the time period covered in the questionnaire. As the questions spanned a 2-year time period, the participants/parents/legal guardians may have found it difficult to remember everything correctly. Lastly, it is possible that seropositive participants aged 18 months and younger were inappropriately included in the seropositive group if it was the case that they had received maternal antibodies and had not actually been infected with SARS-CoV-2.

5. Conclusions

This is the first study to report the seroprevalence of SARS-CoV-2 among children in Latvia. Our results show that a significant proportion of Latvian children are seropositive for SARS-CoV-2 N and S antibodies, with almost 1-third unaware of being previously infected with SARS-CoV-2. Studies from different countries documenting the increasing SARS-CoV-2 seroprevalence illustrate that the Omicron variant is more contagious and spreads more easily in the pediatric population than earlier variants of SARS-CoV-2.

Prior to the COVID-19 pandemic, several types of coronaviruses caused infections in children. The increasing morbidity of COVID-19 suggests that it will likely become one of the many seasonal viral infections.

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Author contributions

Conceptualization: Krista Sapronova, Rūta Kaķe, Jana Pavāre, Dagne Grāvele, Ivita Šēla, Estere Ērgle, Dana Isarova, Zanda Grīnberga, Dace Zavadska.
Data curation: Krista Sapronova, Rūta Kaķe, Estere Ērgle, Dana Isarova, Zanda Grīnberga, Dace Zavadska.
Formal analysis: Krista Sapronova, Rūta Kaķe, Dace Zavadska.
Investigation: Krista Sapronova, Rūta Kaķe, Estere Ērgle, Dana Isarova, Zanda Grīnberga, Dace Zavadska.
Project administration: Jana Pavāre, Dana Isarova, Dace Zavadska.
Resources: Dagne Grāvele, Ivita Šēla.
Supervision: Jana Pavāre, Dace Zavadska.
Validation: Dagne Grāvele, Ivita Šēla.
Visualization: Krista Sapronova.
Writing – original draft: Krista Sapronova, Rūta Kaķe.
Writing – review & editing: Krista Sapronova, Jana Pavāre, Dagne Grāvele, Ivita Šēla, Dana Isarova, Dace Zavadska.

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