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Short Communication

Association of contact to small children with a mild course of COVID-19

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\textbf{A B S T R A C T}

It is known that severe COVID-19 cases in small children are rare. If a childhood-related infection were protective against a severe course of COVID-19, it would be expected that adults with intensive and regular contact with small children may also have a mild course of COVID-19 more frequently. To test this hypothesis, a survey among 4010 recovered COVID-19 patients was conducted in Germany. 1186 complete answers were collected. 6.9\% of these patients reported frequent and regular job-related contact with children below ten years of age, and 23.2\% had their own small children, which was higher than expected. In the relatively small subgroup with intensive care treatment (n = 19), patients without contact with small children were overrepresented. These findings are not well explained by age, gender, or BMI distribution of those patients and should be validated in other settings.

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\textbf{I n t r o d u c t i o n}

The coronavirus disease 2019 (COVID-19) pandemic has affected millions of people worldwide. In contrast to many other infectious diseases, children have diagnostic findings similar to adults, but fewer children seem to have developed severe pneumonia (Ludvigsson, 2020). At present, this phenomenon is not well understood. One of several explanations might be that other infections that are frequent in childhood are protective against a severe course of COVID-19.

There are recent reports about cross-reactivity regarding COVID-19. For instance, it was shown that T cell reactivity to SARS-CoV-2 epitopes is also detected in non-exposed individuals (Grifoni et al., 2020). In principle, cross-reactivity might contribute to the heterogeneity of COVID-19 infections: the majority of patients can be treated in an outpatient setting, but some patients require long-term intensive care.

If a childhood-related infection were protective against a severe course of COVID-19, it would be expected that adults with intensive and regular contact with small children also may have a mild course of COVID-19 more frequently because these adults are more exposed to those childhood-related infections. To test this hypothesis, a survey of recovered COVID-19 patients was conducted.

\textbf{M e t h o d s}

In the context of the Coronaplasma Project (local ethics committee approval: AZ 2020-220-f-S) at the University Hospital of Münster, Germany, an online-survey of 4010 persons who recovered from a confirmed COVID-19 infection was performed. This cohort volunteered to donate plasma with antibodies against COVID-19. Most of these persons live in the state of North Rhine-Westphalia in Germany. Because only a few cases with a severe course of the disease are represented in this cohort, an additional nine COVID-19 patients requiring intensive care therapy at the University Hospital in Münster were included in this survey. The main question was: Did You have frequent and regular contact with children below ten years? Answer options were: Yes, due to my job (in particular, kindergarten, primary school, pediatric practice); Yes, due to my own children; No. In this context, “frequent and regular contact” refers to staying in the same room with close physical proximity on a near-daily basis. These data were combined with basic demographic data (age, gender), body mass index (BMI), and type of COVID-19 treatment (outpatient only; inpatient; inpatient with intensive care).

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Results

2112 answers were collected with the online survey (response rate of 52.7%). 1186 records (effective response rate of 29.6%) contained all required data items and were further analyzed. The median age of participants was 46 years (range 17–77). 56% were females, 44% males. The median body mass index was 24.7. Eighty-two percent (6.9%) reported frequent and regular contact with children below ten years due to their job. 276 persons (23.2%) answered frequent and regular contact with their own children below ten years of age. Fifty-nine percent (5.0%) reported inpatient treatment, and 19% (1.6%) were admitted to intensive care units (ICU). Eighteen of 19 (95%) ICU patients were males.

Age in the group with regular contact with children (n = 358, “child group”) was lower compared to the group without this type of contact (n = 828, “no child group”): median 41 versus 49 years (p = 0.002). BMI was slightly higher in the child group (median 25.2 versus 24.6). The proportion of females was 60% in the child group and 54% in the no child group. Regarding inpatient treatment, there was no difference between both groups: 19% (0.5%) in the child group, 40% (4.8%) in the no child group. Of note, intensive care treatment was reported by three of 19% (16%) inpatients in the child group and by 16 of 40 inpatients (40%) in the no child group (p = 0.056, exact Fisher test, one-sided). The median age of ICU patients in the child group was 55, in the no child group 95.5 years.

Discussion

Two findings of this survey are noteworthy: First, 6.9% of a large cohort with a predominantly mild course of COVID-19 (no fatalities, only 1.6% with intensive care treatment) reported frequent and regular job-related contact with children below ten years of age. According to the German national statistics agency, there are approximately 650,000 kindergarten teachers, 230,000 primary school teachers, and 15,000 pediatricians for a country with 83 million people (Statista GmbH, 2020a, 2020b, 2020c), i.e., approximately 1% of the population has frequent job-related contact with small children. Our COVID-19 cohort is not a representative sample of the general population, but the rate of job-related contacts with small children seems to be elevated, which is not well explained by the age, gender, or BMI distribution of this cohort. Altogether, approximately 30% of our cohort report frequent contact with small children, which is higher than in the general population.

Second, in the relatively small subgroup with intensive care treatment, patients without contact with small children were overrepresented. Again, this is not well explained by age, gender, or BMI distribution for this subgroup.

This survey has several limitations: Our cohort is not a representative sample of the general population. Like in many surveys, the response rate is limited, and relevant data was only available for about 30% of the contacted persons. Data were provided by laypersons and are not validated by medical professionals. And importantly, association is not causation.

What can be concluded from this survey, and what are the possible next steps? It is known that severe COVID-19 cases in small children are rare. There seems to be an association between contact with small children and with a mild course of COVID-19 in adults. This finding needs to be validated in other settings. An obvious hypothesis derived from this data is that certain childhood infections might provide partial immunity against COVID-19 and potentially reduce the need for ICU therapy in adults. To test this hypothesis, laboratory tests for relevant pathogens should be performed, preferably with biomaterial collected before a COVID-19 infection. Candidates for such pathogens include endemic coronaviruses like HCoV-NL63 and -229E, which are commonly found in children. From a public health perspective, specific biomarkers to predict the course of COVID-19 before an infection would be highly valuable to identify patients at risk, because even healthy young and middle-aged adults can die from COVID-19. If cross-reactivity with relatively harmless pathogens like endemic coronaviruses could be demonstrated, this might even become a vaccination strategy – like vaccination with cowpox, which helped to eradicate smallpox in the last century.

Conflict of interest

The authors declare no conflict of interest.

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Ethical approval

Approved by Ethik-Kommission der Ärztekammer Westfalen-Lippe und der Westfälischen Wilhelms-Universität Münster (AZ 2020–220-F-S)

References

Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. Acta Paediatr. 2020;109(6):1088–95, doi:http://dx.doi.org/10.1111/apa.15276.
Grifoni A, Weiskopf D, Ramirez SI, et al. Targets of T cell responses to SARS-CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals. Cell 2020;181(7). doi:http://dx.doi.org/10.1016/j.cell.2020.05.015 1489–1501.e15.
Statista GmbH. https://de.statista.com/statistik/daten/studie/1011406/umfrage/fachraeume-in-der-kinderbetreuung-in-deutschland/ [Accessed 16 July 2020].
Statista GmbH. https://de.statista.com/statistik/daten/studie/162263/umfrage/anzahl-der- Lehrkraeaeften-nach-schularten/ [Accessed 16 July 2020].
Statista GmbH. https://de.statista.com/statistik/daten/studie/158849/umfrage/aeltere-nach-taetigkeitsbereichen-in-deutschland/ [Accessed 16 July 2020].