RESEARCH LETTER

Neonates are more vulnerable to symptomatic SARS-CoV-2 infection than children: a matched cohort study in Brazil

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As the causative agent of coronavirus disease 2019 (COVID-19), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is one of the seven coronaviruses pathogenic to human and one of the four human coronaviruses that cause acute respiratory disease syndrome. Although it affects people of all age groups, the risk of mortality is age-dependent. As in many other diseases, elderly patients have a higher risk of infection, mortality, and morbidity [1]. While it is a common belief that children fare better than adult and elderly, recent evidence merged that neonates and infants are associated with a higher risk of mortality and morbidity, compared to children and adolescents [2, 3]. For instance, a cross-country study found that the infection–fatality ratio of those aged < 5 years was found to be 0.003, higher than those aged between 5 and 14 years of 0.001 despite lower than those aged between 20 and 59 that vary between 0.006 and 0.323 [4]. However, whether this holds true in the risk of infection is not yet verified. Against this background, the present work aimed to verify whether neonates are more susceptible to COVID-19 using publicly available data of all polymerase chain reaction (PCR) tests performed in the state of São Paulo of Brazil.

Data were gathered on the 29th November 2020 from "e-SUS NOTIFICA", a publicly available online database managed by the Ministry of Health of the Brazilian Government and has been described elsewhere [5]. Reporting of flu-like syndrome is mandatory in Brazil and the database is used for surveillance purposes. It consolidated the data of confirmed and suspected cases from local databases managed by local health authorities. To register cases in the database, certified healthcare professionals reported and verified case information in a pre-determined form. Sociodemographic and clinical data, including results of diagnostic tests for SARS-CoV-2 infection, were included in the database. Clinical endpoints such as death and recovery were recorded. However, we found that they were not reliable metrics, because they were not revised once cases were registered in the database.

Efforts have been made to reduce bias. First, we confined the study to the state of São Paulo, the economic center of Brazil that is also largely responsible for the entry and spread of COVID-19 [6]. Second, it is possible that asymptomatic patients were less likely to be tested. Therefore, only symptomatic patients were included to reduce the selection bias. Finally, only patients with a conclusive PCR-test (nasopharyngeal swab) result were included in the study as it remains the gold standard for SARS-CoV-2 diagnosis. Therefore, cases that met all following criteria were included in the study: (1) conclusive PCR-test results; (2) age is not missing; and (3) symptomatic. Cases that failed to meet any of the inclusion criteria were excluded from the study. The following data were gathered from the database: (1) sex; (2) age at PCR test; (3) signs and symptoms (they were categorized by the database as cough, fever, sore throat, dyspnea, and others); (4) comorbidities; and (5) PCR-test result. Patients were divided into seven different age groups with the corresponding definition in parentheses: neonate (aged 30 days or below), infant (aged above 30 days but below 2 years), young child (aged 2 years or above but below 6 years), child (aged 6 years or above but below 12 years), adolescent (aged 12 years or above but below 18 years), adult (aged 18 years or above but below 60 years), and elderly (aged 60 years or above). Sex and comorbidities were included as they were pre-existing (prior to infection) characteristics of the patient.

The outcome of the study was to assess the risk of positive PCR result in different age groups. To eliminate confounding, a matched cohort was formed by matching sex

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and comorbidities using propensity scores generated by a binary logistic regression model. Because signs and symptoms did not predispose the patient to SARS-CoV-2 infection, they were not predictors of infection, and therefore were not included for matching. Then, a multivariate regression model was used to compute the odds ratios (ORs) in different age groups with adults as the reference group. To summarize the characteristics of the study cohort, statistical comparisons were made between the PCR-positive and PCR-negative group using Fisher's exact tests as Chi-squared test is an approximate test.

All computations were performed on R Version 4.1.1 with package "MatchIt" for propensity score matching. A P value of 0.05 was considered significant. Ethical approval is not required in the UK and Brazil as the data were anonymized and publicly available.

A total of 2,012,765 suspected and confirmed cases were found in the database, including all cases dated between February and November 2020. Of these, 1,765,415 (88%) cases had a conclusive PCR-test result. After the removal of 44,012 (2.5%) cases with age missing, 1,721,403 (97.5%) cases were left, consisting of 75,469 (4.4%) asymptomatic patients and 1,645,934 (95.6%) symptomatic patients. The latter was eligible for inclusion. Of the included, 647,028 (39%) were tested positive for SARS-CoV-2 infection (Table 1).

A summary of the characteristics between PCR-positive and -negative groups before matching is shown in column (1) and (2) of Table 1. Due to the very large sample, all measures were found significant. Nevertheless, these figures do not provide useful information because of the presence of confounding. A summary of the characteristics between the groups after matching is shown in column (3) and (4). Due to matching, there was no significant difference in sex and comorbidities. All age group variables remained significant.
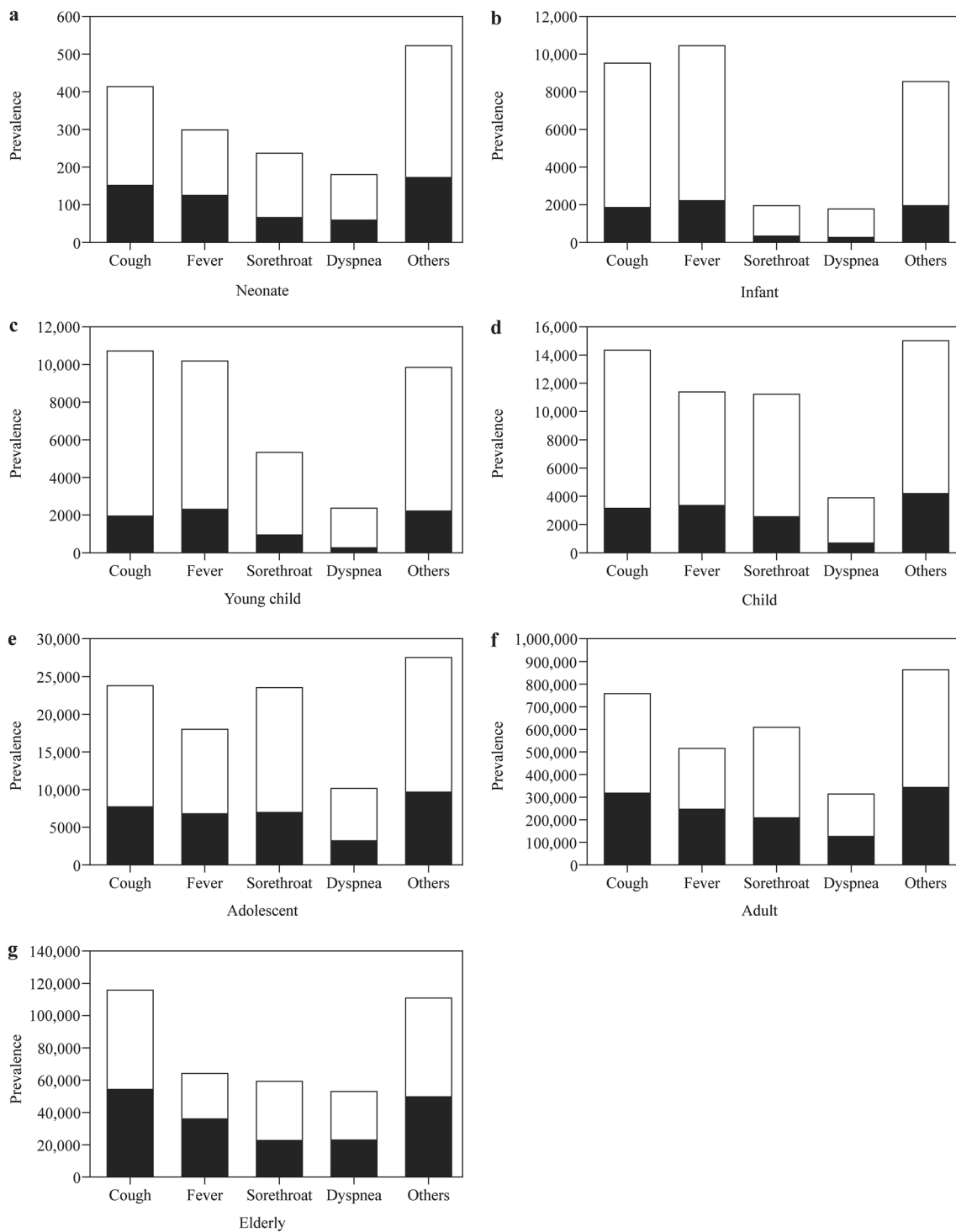
The prevalence of signs and symptoms by age group is shown in Fig. 1. For almost all age groups, higher prevalence of signs and symptoms was seen in the PCR-positive group. The difference in prevalence between PCR-positive and PCR-negative group, however, appeared to be more salient in infants, young children, children, and adolescents. Moreover, sore throat and dyspnea were less prominent in pediatrics.

The calculated ORs are graphically illustrated in Fig. 2, with adults as the reference group. Except for neonates whose sample size was relatively small ($n = 870$, 0.13% of all cases in the matched cohort), the 95% confidence intervals (CIs) for other age groups were narrow. Not surprisingly, elderly (OR = 1.65, 95% CI 1.63–1.67) had the highest risk of infection compared to other age groups. Pediatrics had a lower risk of infection than adults. Neonates, infants, young children, children, and adolescents had 53%, 75%, 73%, 64%, and 50% decrease in the odds of risk of infection than adults, respectively. However, the risk of infection was not linear but U-shaped with neonates being significantly more vulnerable to SARS-CoV-2 (OR = 0.47, 95% CI 0.41–0.54).

Table 1 Summary of the studied cohort before (1 & 2) and after (3 & 4) matching

Variables	(1) PCR-positive ($n = 647,028$)	(2) PCR-negative ($n = 998,906$)	P (1) vs. (2)	(3) PCR-positive ($n = 647,011$)	(4) PCR-negative ($n = 647,011$)	P (3) vs. (4)
Baseline characteristics, %						
Neonate	0.04 (284)	0.06 (591)	< 0.001	0.04 (284)	0.09 (586)	< 0.001
Infant	0.51 (3296)	1.25 (12,532)	< 0.001	0.51 (3296)	1.92 (12,446)	< 0.001
Young child	0.62 (4021)	1.46 (14,633)	< 0.001	0.62 (4021)	2.23 (14,415)	< 0.001
Child	1.09 (7044)	1.97 (19,676)	< 0.001	1.09 (7044)	2.92 (18,924)	< 0.001
Adolescent	2.40 (15,552)	3.09 (30,818)	< 0.001	2.40 (15,552)	4.60 (29,766)	< 0.001
Adult	82.41 (533,219)	81.56 (814,725)	< 0.001	82.41 (533,209)	80.11 (518,351)	< 0.001
Elderly	12.92 (83,612)	10.60 (105,931)	< 0.001	12.92 (83,605)	8.12 (52,523)	< 0.001
Male[a]	45.37 (293,564)	40.58 (405,338)	< 0.001	45.37 (293,564)	45.30 (293,118)	0.432
Comorbid conditions, %						
Immunodeficiency	0.85 (5467)	0.96 (9612)	< 0.001	0.85 (5467)	0.85 (5489)	0.840
Diabetes	5.01 (32,413)	3.87 (38,642)	< 0.001	5.01 (32,413)	5.01 (32,401)	0.965
Chronic heart disease	8.24 (53,324)	7.03 (70,256)	< 0.001	8.24 (53,323)	8.28 (53,544)	0.482
Chronic kidney disease	0.46 (2964)	0.40 (3949)	< 0.001	0.46 (2964)	0.45 (2905)	0.448
Chronic respiratory disease	3.01 (19,490)	4.13 (41,296)	< 0.001	3.01 (19,489)	3.01 (19,488)	> 0.999
Obesity	0.30 (1964)	0.38 (3816)	< 0.001	0.30 (1964)	0.30 (1960)	0.962
Pregnant	0.41 (2618)	0.56 (5556)	< 0.001	0.40 (2617)	0.40 (2607)	0.901
Chromosomal disease	0.29 (1869)	0.35 (3509)	< 0.001	0.29 (1869)	0.29 (1865)	0.961

PCR polymerase chain reaction. [a]$n = 998,901$ and 647,011 for PCR-positive and PCR-negative, respectively

Fig. 1 Prevalence of signs and symptoms by age groups. **a** Neonate; **b** infant; **c** young child; **d** child; **e** adolescent; **f** adult; **g** elderly. Black: PCR-positive; white: PCR-negative. *PCR* polymerase chain reaction

They had similar susceptibility to adolescents (OR = 0.50, 95% CI 0.49–0.51).

Using the data collected in the state of São Paulo, the present work found a U-shaped relation between age and the risk of infection with neonates having a higher risk of infection than infants and children. Increased susceptibility in neonates and/or infants had previously been demonstrated, although no attention was paid. For instance, studies reporting the incidence of COVID-19 cases that have a more detailed breakdown of age groups, such as increments of
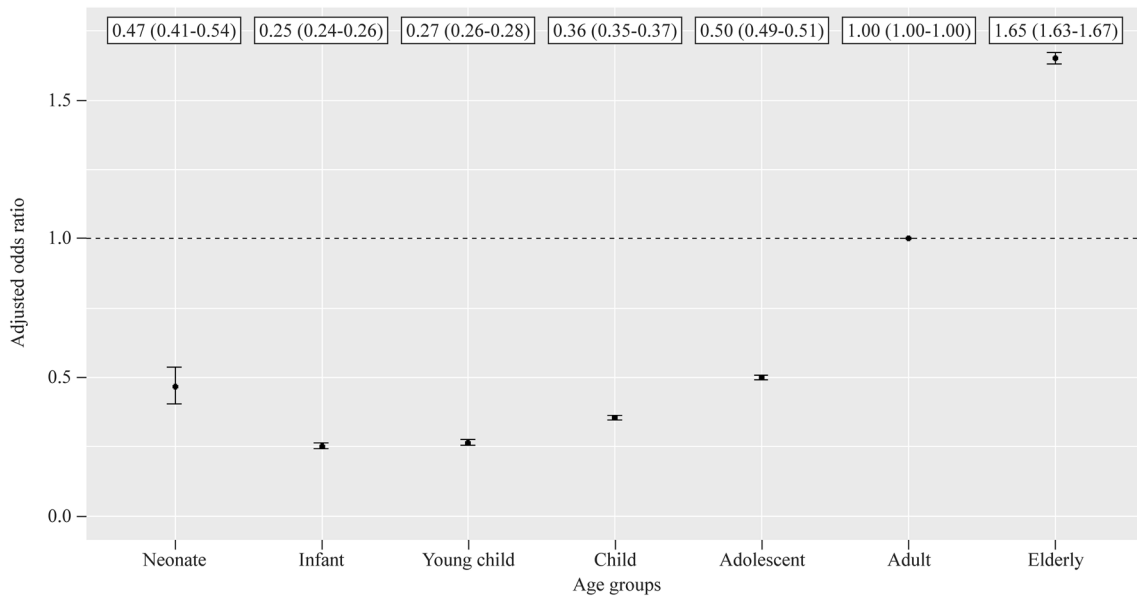
Fig. 2 Adjusted odds ratio of severe acute respiratory syndrome coronavirus 2 infection (95% confidence intervals)

4 years, have shown more cases in those aged below 5 years than those between 5 and 9 (Fig. 3a, based on data from [7]). In contrast, studies that does not have a detailed breakdown of age groups, such as age groups by increment of 9 years, fail to show this pattern (Fig. 3b, based on data from [8]), compared with other age groups. Similar patterns have also been observed in the other studies [9, 10].

There are still no explanations to the U-shaped relationship, albeit hypotheses have been proposed. Here, we discussed these hypotheses with reference to our findings. First, biomarkers that are linearly associated with age alone cannot explain the reduced susceptibility in children, lymphocyte count for instance. If it is associated with the susceptibility

to SARS-CoV-2 infection, the prevalence of COVID-19 should be lower in infants than in children, because lymphocyte count decreases with age [11].

It has also been suggested by Wong et al. [12] that the previous exposure to other coronaviruses might provide cross-protection to children, because seroconversion to human coronavirus (HCoV)-NL63 and HcoV-229E, another two strains of human coronavirus, may produce antibodies to coronaviruses that have some degree of neutralizing and cross-protective activity against infection to another coronavirus. If this hypothesis is correct, an inverted U-shaped relation between seroprevalence and age should be observed, because the present work suggested increased
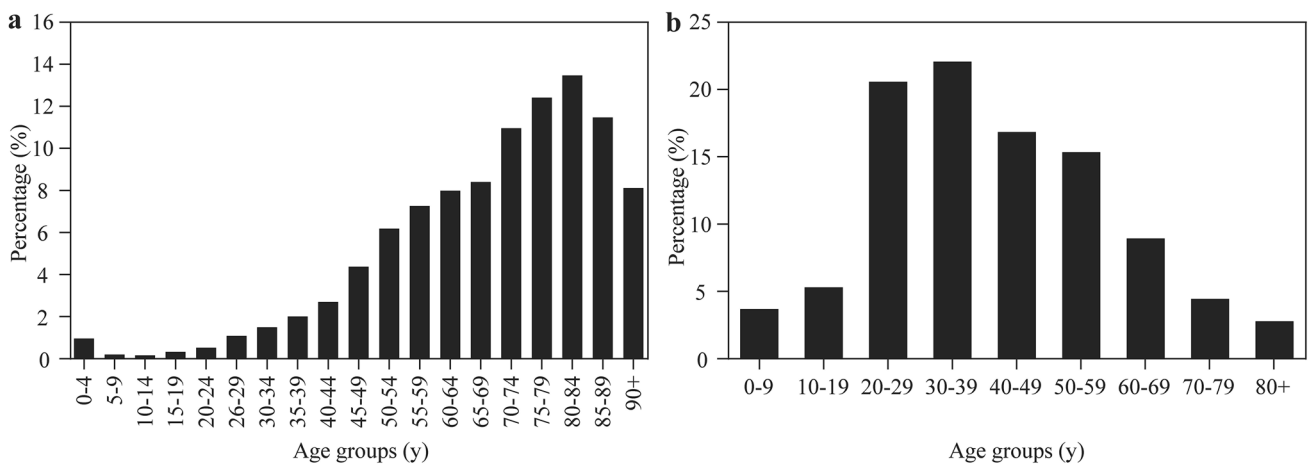
Fig. 3 Incidence of severe acute respiratory syndrome coronavirus 2 infection by age groups in UK (**a**) and Chile (**b**)

infection risk in neonates. However, studies [13, 14] cited by the authors rather found a U-shaped relation, implying that previous exposure to other coronaviruses increases susceptibility to SARS-CoV-2 infection. We speculated that this may be attributed to antibody-dependent enhancement (ADE) in which the binding of non-neutralizing antibodies promotes viral invasion into host cells. ADE has been well documented for a number of viruses including SARS-CoV and Middle East respiratory syndrome-CoV. Furthermore, albeit less likely, the increased susceptibility stemming from ADE may also be attributed to the decline of maternal antibodies against SARS-CoV-2 in which infants born by mothers with antibodies against SARS-CoV-2 possess subneutralizing levels of immunoglobulin G that can enhance SARS-CoV-2 infection [15]. If the hypothesis of ADE is true, it may explain the similar infection risk between neonates and adolescents. Of note, a recent study demonstrated that plasma infected with an early SARS-CoV-2 strain elicited ADE of infection against other SARS-CoV-2 strains [16]. However, whether infection with other human coronaviruses can elicit ADE infection with SARS-CoV-2 remains not known.

While symptoms do not predict the risk of infection, it is worth to note that certain symptoms are less prominent in neonates and infants. This is likely attributed to the fact that they may not be able to verbally describe symptoms such as sore throat. In this case, for instance, the presence of sore throat may be justified when inflammation of the pharynx is observed. Therefore, symptoms that cannot be verbally described by neonates and infants should not be used as a predictor for mortality and morbidity. Research on independent factors of mortality in these population groups is warranted.

The major strength of the present work is the very large sample size. Selection bias is the major limitation of the study. Neonates whose mothers have been tested positive are more likely to be tested. However, this unlikely translates to the increased risk of infection observed in the present work, because the likelihood of vertical transmission remains very low [17].

Declarations

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