The Impact of Childhood and Parental Vaccination on SARS-CoV-2 Infection Rates in Children

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Background: The data on the indirect protection of children via the coronavirus disease 2019 (COVID-19) vaccination of household members are insufficient, and analyses to evaluate the efficacy of COVID-19 vaccines are limited.

Methods: We gathered data on 12,442 patients under the age of 18 regarding the vaccination status of their household members, their vaccine preferences and doses, and their previous history of COVID-19 infection immediately before the patients were administered a real-time reverse transcriptase-polymerase chain reaction (RT-PCR) test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) between September 1, 2021 and December 5, 2021.

Results: A total of 18.4% (2289) were vaccinated, 91.4% with BNT-162b2mRNA vaccine, 8.6% with inactivated COVID-19 vaccine; 48.7% received a single dose, and 51.3% had 2 doses. Real-time RT-PCR positivity proportions were much higher in older children ($P < 0.001$) and were higher in children 12 years of age and older [odds ratio (OR), 1.34; 95% confidence interval (CI): 1.21–1.47] compared with others. SARS-CoV-2 infection was significantly lower in the vaccinated group (fully and incompletely) ($P < 0.001$). Unvaccinated (OR, 4.88; 95% CI: 3.77–6.13) and incompletely vaccinated children (OR, 1.83; 95% CI: 1.52–2.12) had a higher risk of COVID-19 infection compared with fully vaccinated patients No significant association was found between the COVID-19 real-time RT-PCR positivity rates of patients and the vaccination status or vaccine preferences of household members ($P > 0.05$ each).

Conclusions: SARS-CoV-2 infection rates were significantly lower in vaccinated children, especially with mRNA vaccines. The indirect protection of unvaccinated children via the vaccination of household members against COVID-19 seems inadequate. The individual vaccination of children remains crucial.

Key Words: coronavirus disease 2019, vaccine, children, parental vaccination

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Coronavirus disease 2019 (COVID-19) has been the most severe health problem in the world since December 2019. As vaccination campaigns were rapidly being launched around the globe, a COVID-19 immunization campaign with the inactivated vaccine (CoronaVac by Sinovac) was also launched in Turkey, beginning in January 2021, shortly after emergency use approval. The BNT-162b2mRNA vaccine (BioNTech by Pfizer) began to be additionally implemented on April 2, 2021. The Turkish Ministry of Health recommended administering the third booster dose with an optional inactivated or mRNA vaccine as of the beginning of July 2021. CoronaVac for 3–17 year olds and BioNTech for 12–15 year olds were reported to be effective and safe.[1,2] Following these reports, the national vaccination campaign was expanded on September 5, 2021, for both vaccines to include children over 12 years old.

Children and adolescents infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have generally milder disease than older age groups.[3,4] Nevertheless, children and adolescents can experience prolonged clinical symptoms, and severe illness may occur, especially with the presence of some comorbid conditions. Also, the primary infection may lead to multisystem inflammatory syndrome in children.[3,5,6] In addition to the risk of severe disease and related morbidities, the role of children and adolescents in the transmission of SARS-CoV-2 infection remains questionable and uncertain.[7] Seroprevalence studies conducted outside of outbreak settings suggest that infection rates of children and teenagers are similar to those in older age groups.[8] The possibility that viral spread could be occurring from asymptomatic and unvaccinated children to other children and their families and that many could get trapped in a kind of vicious circle between school and home should not be disregarded.[8] Since the role of children in the transmission of SARS-CoV-2 remains inexplicit, the adequacy of parental vaccination in terms of protecting children from SARS-CoV-2 infection as well as the effects of childhood vaccination on the spread of disease should be illuminated. We, therefore, aimed in this study to investigate what impact the vaccination of household members and childhood vaccination had on childhood SARS-CoV-2 infection rates.

MATERIALS AND METHODS

Study Design and Population

The present prospective study was conducted between September 1, 2021 and December 5, 2021, at the Children's Hospital of the Ankara City Hospital, which is among the largest pediatric hospitals in Europe and the pediatric COVID-19 reference center in the Turkish capital of Ankara. The study group consists of outpatient children who have undergone COVID-19 real-time reverse transcriptase-polymerase chain reaction (real-time RT-PCR) testing because of clinical suspicion of SARS-CoV-2 infection, having fever, respiratory symptoms and findings that include cough, tachypnea, wheezing, rales, being in contact with someone who has tested positive for COVID-19 or exhibiting fever and diarrhea. The study did not include patients who did not have any complaints but were requested to have real-time RT-PCR tests for routine control

purposes before traveling abroad or for any surgical operation because they underwent PCR tests in a separate area without a doctor's examination. The Turkish language questionnaire was administered to parents before their children had taken the COVID-19 real-time RT-PCR test. It consisted of 26 questions addressing these topics: (1) sociodemographic characteristics of the patients (age, gender); (2) patients' and their family members' previous history of SARS-CoV-2 infection and (3) the COVID-19 vaccination history and vaccine type (mRNA or inactive vaccine) of patients and their more than 18-year-old household members (parents, siblings and nonparental adults). The parents filled out only one form for each patient. The real-time RT-PCR results were later recorded as positive or negative.

If any of the family members living together in the same household had a SARS-CoV-2 infection, the infection history of each family member was considered and accepted as positive. At the time of the study, in line with ministry procedures when one of the family members was positive for COVID-19, the entire family was quarantined, and other individuals were not tested, so the infection history of other individuals remains suspicious. If one of the members had documented COVID-19 infection history and because the whole family was kept in quarantine for 14 days in the same house and the virus was highly contagious, all family members were considered to have had it. All individuals over the age of 18 in the family were classified as "fully" vaccinated if each had 2 or more doses of COVID-19 vaccines, as "unvaccinated" if they had none. Those who did not comply with these 2 options were evaluated as "incompletely" vaccinated.

Background

The dominant genetic variant circulating in the area during study time was the delta variant. Schools were opened 5 days after our study was initiated, and all school-age children, more than 6 years old, attended their formal education without interruption. Families in quarantine are not included in the study group, as the health care of the families who were followed inhome quarantine due to COVID infection during the study period was given by the filiation and surveillance teams. Throughout the study, wearing masks was obligatory in all public spaces in Turkey.

Statistical Analysis

The Statistical Package for the Social Sciences version 23.0 (IBM Corp., Armonk, NY) was used to analyze the data. Descriptive statistics (including frequencies and means) for all variables were calculated. The Kolmogorov-Smirnov test was used to examine whether the continuous variables showed normal distribution. The results were expressed as mean ± standard deviation, median interquartile range, numbers and percentages (%) depending on whether the data were parametric or not. The difference between the groups in terms of categorical variables was analyzed using the χ^2 test. The Mann-Whitney *U* test investigated differences between the 2 independent groups in terms of binary variables. A power analysis was also conducted for secondary analysis to investigate the association between vaccine type (mRNA or inactivated) and COVID positivity proportion of patients. A logistic regression model was created for assessing factors related to COVID positivity. The model included the vaccination status of patients, personal and household members' previous history of COVID-19 infection, vaccination status of all household members and age groups based on vaccine eligibility. Hosmer-Lemeshow goodness of fit statistics were used to assess model fit. A 5% type-I error level was used to infer statistical significance.

All of the parents provided informed consent prior to participating in the study. This study was conducted in conformity with the principles of the Declaration of Helsinki and approved by the Republic of Turkey Ministry of Health, the Ethics Committee of Ankara City Hospital and the Institutional Review Board of the Children's Hospital of Ankara City Hospital.

RESULTS

Between September 1, 2021 and December 5, 2021, the parents of 14,191 patients of 28,957 to whom the survey had been delivered before COVID-19 real-time RT-PCR testing agreed to participate in the study. The forms, totaling 1769, that were incompletely filled out by the parents or those missing patient identification information were excluded. The study was conducted with 12,442 patients. Of the 12,442 children, 5936 (47.7%) were female, and 6506 (52.3%) were male. The median age was 11 (7–14). While 72.5% (n = 9017) of the patients did not have a more than 18-year-old household member, except for their mother and father, 27.5% had one or more than 18-year-old household members (median: 1, minimum 1 to maximum 4). The demographic and clinical characteristics of children and parents are displayed in Table 1. The vaccination rates of mothers, fathers and other household members were 86.3%, 87.1% and 82.3%, respectively. The most preferred vaccine was the BNT162b2mRNA vaccine among household members, and the majority had received 2 doses. The vaccination status and vaccine types of household members are displayed in Table 2.

Looking at the COVID-19 real-time RT-PCR results of patients, 2004 (16.1%) patients were positive, 10,438 (83.9%) were negative. The positivity proportion in our study was in parallel with the daily Ankara city positivity proportion given by the Ministry of Health. Clinical features and characteristics of children are displayed in Table 1. The median age of positives was 12 years (9–14 years), whereas the median age of negatives was 11 years (6–14 years). There was a statistically significant association between real-time RT-PCR positivity proportions and age ($P < 0.001$); real-time RT-PCR positivity was much higher in older children, but no association was found with gender ($P > 0.05$). Additionally, a subgroup analysis stratifying patients into 2 groups by age less than 12 years (vaccine ineligible) and age greater than or equal to 12 years (vaccine eligible) was performed since the age was not normally distributed. While the real-time RT-PCR positivity proportion was 18.2% in children 12 years of age and older with vaccine eligibility, it was 14.2% in children under 12 years of age ($P < 0.001$). Compared with children under the age of 12, COVID-19 real-time RT-PCR positivity proportion was higher in children 12 years old and older (OR, 1.34; 95% CI: 1.21–1.47) (Table 3).

The positivity proportion was found to be lower in those who were vaccinated (fully vaccinated and incompletely vaccinated) compared with others ($P < 0.001$). Since the vaccination of children under the age of 12 has not yet been initiated in Turkey, children 12 years of age and over having the right to be vaccinated were also evaluated, and the positivity was lower in vaccinated children 12 years and older ($P < 0.001$). Comparing fully vaccinated and incompletely vaccinated children, more positive patients were detected in the incompletely vaccinated group ($P < 0.001$). Additionally, unvaccinated patients (OR, 4.88; 95% CI: 3.77–6.13) and incompletely vaccinated patients (OR, 1.83; 95% CI: 1.52–2.12) had a higher risk of COVID-19 infection compared with fully vaccinated patients (Table 3).

There was no association among the children between vaccine type and real-time RT-PCR positivity rates ($P > 0.05$). But there was insufficient power to avoid type II error (ß > 0.20). And also, the BNT162b2mRNA group comprised approximately 92% of the patients, and there was a significant size difference between

TABLE 1. Clinical Features and Characteristics of Patients Based on Real-Time RT-PCR Results

Variables	COVID-19 Real-Time RT-PCR Positive	COVID-19 Real-Time RT-PCR Negative	*P*
Number (%)	2004 (16.1%)	10438 (83.9%)	
Age (yr) (median, IQR)	12 (9–14)	11 (6–14)	<0.001
Age groups depending on vaccine eligibility			
<12 yr	963 (46.7%)	5634 (54.0%)	<0.001
≥12 yr	1068 (53.3%)	4804 (46.0%)	
Gender			
Female	991 (49.5%)	4945 (47.4%)	>0.05
Male	1013 (50.5%)	5493 (52.6%)	
Vaccination status of patients			
Vaccinated	230 (11.5%)	2059 (19.7%)	<0.001
Unvaccinated	1174 (88.5%)	8379 (80.3%)	
Vaccine doses of vaccinated patients			
Fully vaccinated	160 (69.6%)	955 (46.4%)	<0.001
Incompletely vaccinated	70 (30.4%)	1104 (53.6%)	
Vaccine type of patients			
BNT162b2mRNA	205 (89.1%)	1887 (91.6%)	>0.05
Inactivated vaccine	25 (10.9%)	172 (8.6%)	
Personal and household members' previous history of COVID-19 infection			
Yes	501 (25.0%)	2580 (24.7%)	>0.05
No	1503 (75.0%)	7858 (75.3%)	
Vaccination status of household members			
Fully vaccinated	1247 (62.2%)	6694 (64.1%)	>0.05
Incompletely vaccinated	752 (37.6%)	3724 (35.7%)	
Unvaccinated	5 (0.2%)	20 (0.2%)	

IQR indicates interquartile range.

TABLE 2. Vaccination Status and Vaccine Types of Household Members

	Mothers	Fathers	Other Household Members
Vaccination Status and Vaccine Types	n (%)	n (%)	n (%)
Vaccination status of parents			
Vaccinated (incompletely and fully vaccinated)	10733 (86.3)	10832 (87.1)	3644 (82.3)
Unvaccinated	1709 (13.7)	1610 (12.9)	783 (17.7)
Vaccine type of parents			
Inactivated	1567 (12.6)	1433 (11.5)	589 (13.3)
BNT162b2mRNA	8302 (66.7)	8500 (68.3)	2639 (59.6)
Both	864 (6.9)	899 (7.2)	416 (9.4)
None	1709 (13.7)	1610 (12.9)	783 (17.7)
Vaccine doses			
Single (incompletely)	1274 (11.9)	996 (9.2)	493 (13.5)
Two (fully)	8402 (78.3)	8581 (79.2)	2566 (70.4)
Three and more (fully)	1057 (9.8)	1255 (11.6)	585 (16.1)

the inactivated and mRNA vaccine groups. While the RT-PCR positivity rate was 9.8% in the mRNA group, it was 12.7% in the inactivated vaccine group.

No statistical association was found between the vaccination status and vaccine types of household members and the COVID-19 real-time RT-PCR positivity rates of the patients ($P > 0.05$ each). The previous history of SARS-CoV-2 infection in household members and patients was also not associated with COVID-19 real-time RT-PCR positivity ($P > 0.05$).

DISCUSSION

This study evaluated what effect the vaccination of household members and childhood vaccination had on childhood SARS-CoV-2 infection rates. To the best of the authors' knowledge, this is one of the very first studies showing that the vaccination of household members does not provide significant protection for children against SARS-CoV-2 infection, but that vaccination is efficient and protective in children, even with a single dose.

The BNT162b2mRNA COVID-19 vaccine, BioNTech by Pfizer, was the first vaccine approved for emergency use by the United States Food and Drug Administration.[9] In the ongoing process, it was shown that BioNTech is immunogenic, first in 12–15-year-old children and then in 5–11-year-old children, and that it has a favorable safety profile and is highly effective (effectivity, 90.7%) against COVID-19 (20,21). CoronaVac is an inactivated aluminum-adjuvant vaccine developed by Sinovac Life Science Company, Beijing, China.[10] It was reported later that 2 doses of the CoronaVac were safe and well-tolerated and induced humoral responses in 3–17-year-old children and adolescents.[2] The COVID-19 real-time RT-PCR positivity in our study was found to be much higher in unvaccinated children, which supports the finding that both vaccines are effective in children.

The safety and efficacy of the CoronaVac and BioNTech vaccines in adults have been investigated in different clinical trials, but there are limited data on the superiority of these 2 vaccines over each other. Mok et al[11] found that the levels of antibodies elicited by CoronaVac were significantly lower than BNT162b2mRNA

TABLE 3. Factors That are Associated With COVID-19 Infection in Children

Variable	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age groups		
Vaccine ineligible(<12 y)	Reference	Reference
Vaccine eligible(≥12 y)	1.34 (1.21–1.47)	1.84 (1.66–2.04)
Vaccination status of patients		
Fully	Reference	Reference
Incompletely	1.26 (1.06–1.50)	1.83 (1.52–2.12)
Unvaccinated	3.34 (2.61–4.27)	4.88 (3.77–6.13)
Personal and household members' previous history of COVID-19 infection		
No	Reference	Reference
Yes	(0.91–1.13)	0.98 (0.87–1.08)
Vaccination status of all household members		
Fully	Reference	Reference
Incompletely	1.23 (0.46–3.30)	0.98 (0.36–2.62)
Unvaccinated	1.34 (0.50–3.58)	1.01 (0.38–2.73)

in adults. Rotshild et al[12] reported that the BioNTech vaccine was associated with the highest efficacy in preventing symptomatic COVID-19 compared with other vaccines, including CoronaVac. Murt et al[13] found that seropositivity rates and antibody levels were lower in hemodialysis patients who received an inactivated vaccine, but while mRNA vaccine had better immunogenicity, both vaccines protected from symptomatic infection when seropositivity was achieved in hemodialysis patients. In our study, children vaccinated with BioNTech or CoronaVac had less SARS-CoV-2 infection rates compared with unvaccinated children, regardless of vaccine type, and no difference was found between the 2 vaccines. On the other hand, there was a reasonably significant difference between the 2 groups; the BioNTech group was about 10.6 times larger. In addition, the positivity rate was lower in the BioNTech group, although there was no statistical difference. In the light of these data, although there is no statistical difference in the RT-PCR positivity proportions between the mRNA vaccine and the inactivated vaccine groups, we consider that the efficacy could not be said to seem to be similar due to the difference in the RT-PCR positivity rate for each group and the significant size difference between the groups.

Vaccination is an essential intervention to prevent many infectious diseases, but the degree of indirect protection provided by vaccinating household members is not evident.[14] In studies with different vaccines in the past, while it was found that pediatric rotavirus vaccination protects adults from rotavirus, it was also shown that a decrease in the infection probability for unvaccinated household members was not enough for influenza vaccines.[14,15] Unfortunately, there are not enough data on the indirect protection of children with the vaccination of household members against COVID-19. Salo et al[16] found that the indirect effect of COVID-19 vaccines is smaller and less precise for unvaccinated children 3–18 years old than for adults in a real-world setting. In the present study, we did not find an association between the vaccination status and vaccine types of household members and the COVID-19 real-time RT-PCR positivity rates of children, which led us to consider that parental COVID-19 vaccination with inactivated or mRNA vaccines does not have enough of a protective impact on unvaccinated children. There may be some factors affecting this situation. Lockdown policies, restrictions and nonpharmacologic public health interventions, which were applied more strictly in the early stages of the pandemic, were more flexible during the period when the study was conducted. As described in the literature, increased social contact during this period may have affected household transmission.[17–19] The increase in other respiratory virus infections in the same period may support this. Second, it has been observed in recent studies that humoral response substantially decreased after the receipt of the second dose for both vaccines.[20–22] The decrease in the effects of vaccination on the parents who were vaccinated 4 or 5 months ago and the delta variant, which is more contagious and was the predominant variant during the study period, may have decreased the indirect protection of the parental vaccination.[23,24] Some studies on the Delta variant reported that transmission rates are higher, particularly within households, but transmission from adult source cases remains higher than from children.[25] Additionally, the possibility of asymptomatic nasal viral shedding from vaccinated individuals should be considered.[26] Therefore, the individual vaccination of children remains crucial in terms of preserving the continuity of herd immunity even though all household members are vaccinated. It should also be noted that although parental vaccination was not found effective in protecting the children living in the same household, vaccination of both adults and children is of great importance and indispensable in reducing community transmission and decreasing the burden of COVID-19.

In many comprehensive studies from numerous different countries, authors have reported that children, particularly children less than 10 years old, have much lower rates of infection than adolescents, and adults and children have reduced susceptibility and infectivity compared with adults.[27–31] Similarly, young children were less likely to test positive for COVID-19 than adolescents in our study. There may be some factors and mechanisms responsible for this difference between adolescents and children. First of all, schools continued in-person education in almost all of our study period, which lasted longer than 3 months. Furthermore, the fact that older children spend more time outside the home and have more social interactions than younger children may have increased viral transmission in the older age group. Second, clinical manifestations of infected children are generally less severe than those of adult and adolescent patients, and lower respiratory tract symptoms or loss of taste or smell are less likely reported in children.[31–33] Since our study group consisted of pediatric patients admitted to the hospital and younger children were more likely to be asymptomatic and were admitted less frequently due to COVID-19 symptoms, fewer positive tests may have been detected in young children in the analyses. Additionally, it is hypothesized that the lower prevalence of COVID-19 in younger children may be related to lower nasal gene expression of angiotensin-converting enzyme, because compared with younger children, angiotensin-converting enzyme 2 gene expression is significantly higher in older children and adults.[34]

The present study had several limitations. First, the time between the vaccination of parents and children and real-time RT-PCR testing could not be standardized. Second, the vaccination status of other children under 18 living in the same household

and prior health history/immunosuppression of the patients were not questioned. Although our sample size was entirely satisfactory, about half of those invited to the study agreed to participate. The ethnicity, vaccination status and COVID history of those who did not participate are unknown. So, the effect of nonresponder bias should be considered. Additionally, this was a single-site study. Another limitation could be that additional confounders were present that were not measured, so residual confounding is probable.

CONCLUSIONS

The key findings of this study were that SARS-CoV-2 infection rates were significantly lower in vaccinated children, especially with mRNA vaccines. Furthermore, the indirect protection of unvaccinated children via the vaccination of household members against COVID-19 seems inadequate. As a consequence, we suggest that parents should be informed of the safety and efficacy results of recent childhood COVID-19 vaccine clinical trials and that childhood COVID-19 vaccination programs should be encouraged and expanded, even when other household members are vaccinated. It is apparent that childhood vaccination deserves merit for preserving the continuity of herd immunity.

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