



Association between vaccinations and clinical manifestations in children with COVID-19

Shijian Liu^{1,2,3#}, Chunhui Yuan^{4#}, Jianfei Lin^{1,3#}, Wenqi Gao^{5#}, Dan Tian¹, Xiaonan Cai⁵, Jiajun Yuan¹, Feiyan Xiang⁵, Yan Yang¹, Xinru Huang¹, Ruizhen Li⁶, Yun Xiang⁴, Hongmei Shan⁷, Li Zhao⁷, Bin Dong¹, Min Zhou¹, Shilu Tong^{1,8}, Tongxin Chen⁹, Jianbo Shao^{5,10}, Liebin Zhao^{1,2}, Han Xiao⁵

¹Child Health Advocacy Institute, Shanghai Children's Medical Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China; ²School of Public Health, Shanghai Jiao Tong University School of Medicine, Shanghai, China; ³Pediatric Translational Medicine Institute, Shanghai Children's Medical Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China; ⁴Department of Laboratory Medicine, Wuhan Children's Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; ⁵Institute of Maternal and Child Health, Wuhan Children's Hospital, Tongji Medical College, Huazhong University of Science & Technology, Wuhan, China; ⁶Department of Child Healthcare, Wuhan Children's Hospital, Tongji Medical College, Huazhong University of Science & Technology, Wuhan, China; ⁷Department of Special Service Clinic, Shanghai Children's Medical Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China; ⁸School of Public Health, Queensland University of Technology, Brisbane, Australia; ⁹Department of Rheumatology and Immunology, Shanghai Children's Medical Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China; ¹⁰Department of Imaging Center, Wuhan Children's Hospital, Tongji Medical College, Huazhong University of Science & Technology, Wuhan, China

Contributions: (I) Conception and design: JB Shao, LB Zhao, H Xiao; (II) Administrative support: SJ Liu; (III) Provision of study materials or patients: CH Yuan, WQ Gao, D Tian, XN Cai, JJ Yuan, FY Xiang, Y Yang, RZ Li, Y Xiang, XR Huang, HM Shan, L Zhao, B Dong; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: JF Lin, SL Tong, TX Chen; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Han Xiao. Institute of Maternal and Child Health, Wuhan Children's Hospital, Tongji Medical College, Huazhong University of Science & Technology, Wuhan 430016, China, 100 Hong Kong Road, Jiangan District, Wuhan 430016, China. Email: tjxiaohan1980@163.com; Prof. Liebin Zhao. Shanghai Children's Medical Center, Shanghai Jiao Tong University School of Medicine, Shanghai 200127, China. Email: zhaoliebin@scmc.com.cn; Jianbo Shao. Department of Imaging Center, Wuhan Children's Hospital, Tongji Medical College, Huazhong University of Science & Technology, 100 Hong Kong Road, Jiangan District, Wuhan, 430016, China. Email: wchshaojianbo@126.com.

Background: The infection rate of Coronavirus Disease 2019 (COVID-19) in children was less than that in adults. However, the underlining reason is not well known.

Methods: Children with COVID-19 were recruited from two Children's Hospitals in Wuhan and Shanghai in this case-control study. The associations of initial symptoms with age, vaccinations of Bacillus Calmette Guerin (BCG), and influenza and pathogens were determined by Chi-square *t*-test.

Results: We evaluated 248 confirmed cases, and 56 suspected cases with COVID-19. The median age was 6.82 years old, and 118 cases (38.82%) were girls. Furthermore, 30.26% of all patients were asymptomatic cases. The percentage of asymptomatic cases vaccinated with BCG was not significantly higher than that without BCG vaccination [86/280 (30.71%) *vs.* 6/13 (46.15%), *P*=0.203], and initial symptoms were not related with immunized influenza vaccine (*P*=0.267). Compared to parameters in pediatric patients with normal body temperatures, patients with fever had higher C reactive protein (CRP) (*P*<0.001).

Conclusions: Pediatric COVID-19 patients with BCG vaccinations exhibit similar clinical manifestations compared to those without BCG vaccinations, and the severity of symptoms in pediatric patients may be related to the maturity of immune function.

Keywords: Coronavirus Disease 2019 (COVID-19); pediatric cases; Bacillus Calmette Guerin (BCG); immunoglobulins; cytokines

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1 Introduction

2 A novel coronavirus outbreak occurred in December 2019
3 (1-4). As of May 30, 2020, a total of 5,817,385 Coronavirus
4 Disease 2019 (COVID-19) cases and 362,705 related
5 deaths have been confirmed (5). Common symptoms at
6 onset of illness include fever, cough, myalgia, and fatigue
7 (6-8), whereas less common symptoms include shortness
8 of breath, dizziness, headache, pharyngalgia, chest pain,
9 abdominal pain, diarrhea, nausea, vomiting, loss of appetite,
10 and weakness (1,2). COVID-19 is more likely to affect
11 older patients with comorbidities (9), as only 889 of 72,314
12 (1.2%) such adult cases were asymptomatic cases (10,11). In
13 contrast, 12.9% of pediatric cases have been asymptomatic
14 cases (12).

15 It has remained unclear as to why the infection rate of
16 COVID-19 in children has been less than that in adults. One
17 possible reason is that children have less exposure and more
18 protection by their guardians; another possibility is that
19 children have more active innate immune responses (13).
20 Most infants have received regular immunizations in China
21 and other Asian countries, including Bacillus Calmette
22 Guerin (BCG), which has been demonstrated to provide
23 non-specific protection against influenza infections,
24 possibly via the induction of trained innate immunity (14).
25 However, the underlying features of such BCG-mediated
26 protection and the association of BCG vaccinations
27 and clinical manifestations in children with COVID-19
28 have remained largely unknown (15,16). Therefore, in
29 the present study, we explored the associations of BCG
30 vaccination and clinical manifestations in pediatric patients
31 with COVID-19.

32 We present the following article in accordance with the
33 STROBE reporting checklist (available at <http://dx.doi.org/10.21037/tp-20-225>).
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37 Methods

38 Patient and data selection

39 All pediatric patients with COVID-19 were recruited from
40 two hospitals during the specific period from January 28
41 to March 12, including 240 laboratory-confirmed cases
42 from Wuhan Children's Hospital, 56 suspected cases and
43
44

8 imported confirmed cases from Shanghai Children's
45 Medical Center. Wuhan Children's Hospital represents the
46 only hospital in Wuhan for treating pediatric patients under
47 16 years with COVID-19, as designated by the Chinese
48 central government. We collected data on demographics
49 (age, gender), epidemiological histories, clinical symptoms,
50 results of clinical pathogen examinations from hospital
51 information system or laboratory information system.
52 The vaccination status (influenza vaccines and Bacillus
53 Calmette Guerin vaccines) was checked in the vaccination
54 management system and information of unavailable patients
55 in the system was collected from the parents by telephone,
56 however the type and vaccinating time of influenza virus
57 were not collected. The total vaccination times for BCG
58 were calculated from the time of initial vaccination time to
59 the time of confirmation of diagnosis.
60

61 Diagnostic criteria

62 Suspected and confirmed cases were diagnosed based on
63 the Novel Coronavirus 2019 Diagnosis and Treatment
64 Protocol, seventh version (17). Nasopharyngeal swabs from
65 suspected children younger than two years, as well as throat
66 swabs from children two years or older, were obtained for
67 detection of severe acute respiratory syndrome coronavirus
68 2 (SARS-CoV-2). According to the protocol of the Chinese
69 Center for Disease Control and Prevention (CDC) for
70 detection of SARS-CoV-2, a duplex one-step real-time
71 reverse-transcription PCR (RT-PCR) was performed to
72 confirm SARS-CoV-2 infection at the local designated
73 laboratory, for which positive detection determined
74 a confirmed case. Suspected cases were determined
75 based on one of the following two criteria: (I) having an
76 epidemiological link to adult cases; or (II) an exposure to
77 Wuhan or other epidemic areas in the Hubei province
78 within the previous 14 days and presenting with acute fever
79 and/or respiratory symptoms (18). Further pathogens tests
80 were needed for other respiratory viruses in the following,
81 asymptomatic case is positive for SARS-CoV-2 infection
82 and not any symptoms at the initial admission to the
83 outpatient, serologic tests in the suspected cases were not
84 conducted since it was not available. We compared the
85 infection rate between patients with and without vaccinated
86
87

Table 1 Characteristics of confirmed and suspected cases with COVID-19

Demographics	All cases (n=304)	Confirmed cases (n=248)	Suspected cases (n=56)	χ^2	P
Sex, n (%)				0.15	0.701
Male	186 (61.18)	153 (61.69)	33 (58.93)		
Female	118 (38.82)	95 (38.31)	23 (41.07)		
Age (years), n (%)				21.38	<0.001
<1	51 (16.78)	45 (18.15)	6 (10.71)		
1–3	40 (13.16)	28 (11.29)	12 (21.43)		
3–6	46 (15.13)	30 (12.10)	16 (28.57)		
6–9	66 (21.71)	53 (21.37)	13 (23.21)		
9–12	48 (15.79)	41 (16.53)	7 (12.50)		
≥12	53 (17.43)	51 (20.56)	2 (3.57)		
Median age, years (interquartile range)	6.82 (2.08, 10.20)	7.18 (2.24, 10.89)	4.92 (1.82, 7.48)		0.025
Initial symptoms, n (%)				34.15	<0.001
Asymptomatic	92 (30.26)	92 (37.10)	0 (0.00)		
Fever and/or respiratory symptoms*	203 (66.78)	147 (59.27)	56 (100.00)		
Other symptoms [#]	9 (2.96)	9 (3.63)	0 (0.00)		
Vaccination, n (%)					
BCG vaccine	280 (92.10)	239 (96.37)	41 (73.21)		
Influenza vaccine	70 (23.03)	46 (18.55)	24 (42.86)		

*, respiratory symptoms: cough, pharyngalgia, and shortness of breath; [#], other symptoms: dizziness, headache, abdominal pain, diarrhea, nausea, vomiting, loss of appetite, and weakness.

88 BCG or flu vaccine.

89

90 **Statistical analysis**

91

92 We first described the demographic characteristics of
 93 patients, including gender and age. Subsequently, we
 94 focused on the association of initial symptoms with age,
 95 vaccinations. Chi-square tests and Fisher’s exact tests were
 96 used for categorical variables when appropriate, and Mann-
 97 Whitney U tests were used for comparing median values
 98 of non-normally distributed variables. All analyses were
 99 conducted using Statistical Product and Service Solutions
 100 (SPSS 25.0) software and R 3.6.2. The criterion for
 101 statistical significance was P<0.05 via two-tailed tests.

102

103 **Ethics statement**

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105 The study was conducted in accordance with the
 106 Declaration of Helsinki (as revised in 2013), and was

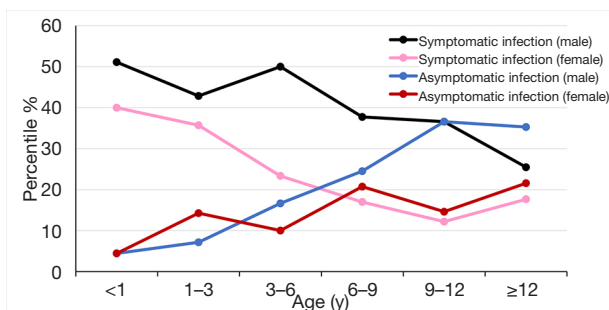
approved by the Institutional Review Board of Wuhan
 Children’s Hospital (IEC-2020R003-E01) and Shanghai
 Children’s Medical Center (SCMCIRB-K2020019-1).
 Individual consent for this retrospective analysis was waived.

Results

A total of 304 pediatric patients with COVID-19 were
 included in this study (Table 1), including 56 suspected and
 248 laboratory-confirmed cases. Among these cases, 240
 (97.17%) children with COVID-19 were recruited from
 Wuhan Children’s Hospital, and there were also eight
 imported cases (2.83%, Table 2). All suspected cases were
 collected from the Shanghai Children’s Medical Center.
 Among them, 153 (61.69%) confirmed and 33 suspected
 (58.93%) male patients were included, which were more
 than those of female cases. The median age (interquartile
 range) was 7.18 (2.24–10.89) years for confirmed cases and
 4.92 (1.82–7.48) years for suspected children. Furthermore,

Table 2 Characteristics of imported cases.

Patient ID	Gender	Age (years)	Nationality	Date of diagnosis	Initial symptoms	Epidemiological history	BCG vaccine	Influenza vaccine
Case 1	Male	8	Spain	2020/3/18	Asymptom	2020/3/16 from Spain to Qatar, 2020/3/17 to Thailand, 2020/3/18 to Shanghai	No	No
Case 2	Male	8	United Kingdom	2020/3/22	Asymptom	2020/3/20 from United Kingdom to Shanghai	No	No
Case 3	Female	10	United Kingdom	2020/3/22	Cough (2 days)	2020/3/20 from United Kingdom to Shanghai	Yes	No
Case 4	Female	17	China	2020/3/23	Fever (1 day)	2020/3/17 from United Kingdom to Shanghai	Yes	No
Case 5	Male	17	Canada	2020/3/23	Asymptom	2020/3/21 from Canada to Shanghai	Yes	Yes
Case 6	Male	13	United Kingdom	2020/3/23	Cough (1 day)	2020/3/23 from United Kingdom to Shanghai	Yes	No
Case 7	Female	15	United States	2020/3/23	Asymptom	2020/3/16 from the United States to Sweden, 2020/3/23 to Shanghai	No	Yes
Case 8	Female	8	China	2020/3/25	Asymptom	2020/3/24 from the Philippines to Shanghai	Yes	No

**Figure 1** Association of age and clinical symptoms in children with COVID-19.

126 92 of 304 (30.26%) cases consisted of asymptomatic
 127 patients. The percentages of initial symptoms were
 128 significantly different ($P < 0.001$) between confirmed and
 129 suspected cases. Total 181/240 (75.42%) vaccination status
 130 was founded in the vaccination management system, that
 131 of 59/240 (24.58%), 8 imported confirmed cases and all
 132 56 suspected cases was collected from the guardians by
 133 telephone.

134 The percentage of asymptomatic children increased with
 135 age; in contrast, the percentage of symptomatic patients
 136 with COVID-19 decreased with age among both boys and

girls ($P < 0.001$) (Figure 1). The median age (interquartile
 137 range) was 9.28 (6.31–12.54) years for asymptomatic
 138 confirmed children and 4.57 (0.95–9.33) years for
 139 symptomatic children ($P < 0.001$), which was not significantly
 140 different from suspected cases.
 141

The percentage of asymptomatic patients vaccinated
 142 with BCG was not significantly lower than the percentage
 143 of those without BCG vaccination [86/280 (30.71%) vs.
 144 6/13 (46.15%), $P = 0.203$]. Similarly, the percentage of
 145 patients with fever and/or respiratory symptoms who had
 146 been immunized with BCG was also not significantly higher
 147 than the percentage of those without BCG vaccination
 148 [187/280 (66.79%) vs. 5/13 (38.46%), $P = 0.033$]. There was
 149 no significant difference in the percentage of asymptomatic
 150 patients given influenza vaccine compared to the percentage
 151 of those who did not receive an influenza vaccination
 152 ($P = 0.267$) (Table 3).
 153

Using correlational analysis, we found that hs-
 154 CRP was correlated with the symptom of fever ($r = 0.31$,
 155 $P < 0.001$). Different ages were significantly associated
 156 with fever ($P = 0.004$), cough ($P = 0.003$), and diarrhea
 157 ($P = 0.012$) in confirmed cases (Table 4). We have compared
 158 the eight imported cases with Chinese cases in Wuhan,
 159 the percentage of BCG vaccination (5/8) for imported
 160

Table 3 Association between vaccinations and initial symptoms

Initial symptoms	BCG vaccine				Influenza vaccine			
	Yes, n (%)	No, n (%)	χ^2	P	Yes, n (%)	No, n (%)	χ^2	P
Asymptomatic	86 (30.71)	6 (46.15)	Fisher	0.203 ^a	17 (24.29)	75 (34.25)	2.64	0.267
Fever and/or respiratory symptoms*	187 (66.79)	5 (38.46)	Fisher	0.033 ^b	50 (71.43)	138 (63.01)		
Other symptoms [#]	7 (2.50)	2 (15.38)	Fisher	0.149 ^c	3 (4.29)	6 (2.74)		

*, respiratory symptoms: cough, pharyngalgia, and shortness of breath; [#], Other symptoms: dizziness, headache, abdominal pain, diarrhea, nausea, vomiting, loss of appetite, and weakness; ^a, comparison of asymptom vs. fever and/or respiratory symptoms; ^b, comparison of fever and/or respiratory symptoms vs. other symptoms; ^c, comparison of asymptom vs. other symptoms.

161 confirmed cases is much lower than that of China (239/248),
 162 and the asymptomatic rate (5/8) is higher than that of
 163 Chinese cases (92/248). Meanwhile, age was found to be
 164 significantly associated with mycoplasma (P<0.001) and
 165 cytomegalovirus (P=0.040) infection in confirmed cases, co-
 166 infection was associated with hs-CRP between COVID-19
 167 alone and in combination with MP (Table S1).

169 **Discussion**

170
 171 To the best of our knowledge, this is the first study on the
 172 association of vaccinations and clinical manifestations in
 173 children infected with COVID-19. A previous study of 2,143
 174 pediatric patients indicated that clinical manifestations in
 175 children infected with COVID-19 were less severe than
 176 those in adult patients (10,12). However, the underlying
 177 features of this phenomenon have not been well identified.
 178 In the present study, we found that pediatric patients with
 179 BCG vaccinations exhibited clinical features similar to
 180 those of patients who did not receive BCG vaccinations.
 181 Furthermore, the percentage of asymptomatic patients was
 182 positively correlated with age, suggesting that the severity
 183 of pediatric patients was related to the maturity of immune
 184 function.

185 In the current study, asymptomatic cases accounted
 186 for 37.10% of all confirmed cases, which is higher than
 187 the 12.90% reported among 2,143 pediatric patients
 188 in a previous study, since some clinical cases were also
 189 included in this previous study (12). The symptoms that
 190 children are more likely to be fever and/or cough than
 191 adults (19,20). We found that slightly more boys than girls
 192 (61.69% vs. 38.31%) were affected by COVID-19 and
 193 that the median age of all pediatric COVID-19 cases was
 194 6.82 years (interquartile range: 2.08–10.20), which is similar
 195 to the findings of two recent epidemiological studies (4,12).
 196 Hence, these findings suggest that boys may be more exposed

to family members and/or other children with COVID-19. 197

198 Although it remains unclear as to why symptoms in
 199 pediatric cases are milder than those in adult cases of
 200 COVID-19, this phenomenon may be related to both
 201 host and exposure factors. ACE2 or TMPRSS2 DNA
 202 polymorphisms were likely associated with genetic
 203 susceptibility of COVID-19 (21,22). The immune system of
 204 children is still developing and may respond to pathogens
 205 differently compared to that in adults. In the present study,
 206 we found that the percentage of asymptomatic COVID-19
 207 infections increased with age, whereas the percentage of
 208 symptomatic COVID-19 infections decreased with age
 209 (Figure 1). It suggests that immune function gradually
 210 matures with age, and the more vigorous immune response
 211 mounted by adults may also explain the detrimental
 212 immune response associated with acute respiratory distress
 213 syndrome (13). Furthermore, since children often
 214 experience respiratory infections in the winter, we found
 215 that positive results of mycoplasma IgM were related to
 216 age in children with COVID-19. Children are also usually
 217 well cared for at home and might have relatively fewer
 218 opportunities to expose themselves to pathogens and/or
 219 sick patients, and girls are generally less exposed to outdoor
 220 activities than boys.

221 BCG has been identified to induce trained immunity
 222 that protects against unrelated pathogens (23,24). An
 223 analysis of infant immunization with BCG in 33 countries
 224 suggested BCG vaccination may reduce the incidence of
 225 acute lower respiratory infection by 17–37% (25). Children
 226 have a more active innate immune response and fewer
 227 underlying disorders. In the present study, we observed
 228 that the percentage of asymptomatic patients vaccinated
 229 with BCG was not significantly lower than those without
 230 BCG vaccination. This finding may be related to the
 231 trained immunity of BCG and any cross-protective non-
 232 specific effects: the immune system learns more than

Table 4 Association of age with symptoms in pediatric COVID-19 patients

Characteristics	Suspected cases												Confirmed cases															
	<1 year	%	1–3 years	%	3–6 years	%	6–9 years	%	9–12 years	%	≥12 years	%	P	<1 year	%	1–3 years	%	3–6 years	%	6–9 years	%	9–12 years	%	≥12 years	%	P		
Fever																												
Yes	5	83.33	11	91.67	15	93.75	9	69.23	7	100.00	2	100.00	0.380	20	44.44	19	67.86	12	40.00	18	33.96	11	26.83	13	25.49	0.004		
No	1	16.67	1	8.33	1	6.25	4	30.77	0	0.00	0	0.00		25	55.56	9	32.14	18	60.00	35	66.04	30	73.17	38	74.51			
Cough																												
Yes	5	83.33	9	75.00	13	81.25	10	76.92	5	71.43	0	0.00	0.353	26	57.78	9	32.14	13	43.33	13	24.53	10	24.39	13	25.49	0.003		
No	1	16.67	3	25.00	3	18.75	3	23.08	2	28.57	2	100.00		19	42.22	19	67.86	17	56.67	40	75.47	31	75.61	38	74.51			
Cough																												
Expectoration	1	16.67	2	16.67	5	31.25	2	15.38	0	0.00	0	0.00	0.575	24	92.31	9	100.00	12	92.31	11	84.62	10	100.00	13	100.00	0.656		
Dry cough	4	66.67	7	58.33	8	50.00	8	61.54	5	71.43	0	0.00		2	7.69	0	0.00	1	7.69	2	15.38	0	0.00	0	0.00			
Pharyngalgia																												
Yes	0	0.00	0	0.00	1	6.25	0	0.00	1	14.29	0	0.00	0.561	0	0.00	0	0.00	0	0.00	1	1.89	1	2.44	1	1.96	0.952		
No	6	100.00	12	100.00	15	93.75	13	100.00	6	85.71	2	100.00		45	100.00	28	100.00	30	100.00	52	98.11	40	97.56	50	98.04			
Shortness of breath																												
Yes	0	0.00	1	8.33	0	0.00	0	0.00	0	0.00	0	0.00	0.482	1	2.22	1	3.57	0	0.00	0	0.00	1	2.44	1	1.96	0.730		
No	6	100.00	11	91.67	16	100.00	13	100.00	7	100.00	2	100.00		44	97.78	27	96.43	30	100.00	53	100.00	40	97.56	50	98.04			
Dizziness																												
Yes	0	0.00	0	0.00	0	0.00	0	0.00	2	28.57	1	50.00	0.006	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	–
No	6	100.00	12	100.00	16	100.00	13	100.00	5	71.43	1	50.00		45	100.00	28	100.00	30	100.00	53	100.00	41	100.00	51	100.00			
Headache																												
Yes	0	0.00	0	0.00	0	0.00	1	7.69	0	0.00	0	0.00	0.714	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	1.96	0.786		
No	6	100.00	12	100.00	16	100.00	12	92.31	7	100.00	2	100.00		45	100.00	28	100.00	30	100.00	53	100.00	41	100.00	50	98.04			
Abdominal pain																												
Yes	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	–	0	0.00	0	0.00	1	3.33	1	1.89	1	2.44	0	0.00	0.631		
No	6	100.00	12	100.00	16	100.00	13	100.00	7	100.00	2	100.00		45	100.00	28	100.00	29	96.67	52	98.11	40	97.56	51	100.00			
Diarrhea																												
Yes	0	0.00	1	8.33	0	0.00	0	0.00	0	0.00	0	0.00	0.482	1	2.22	3	10.71	1	3.33	0	0.00	0	0.00	1	1.96	0.012		
No	6	100.00	11	91.67	16	100.00	13	100.00	7	100.00	2	100.00		44	97.78	25	89.29	29	96.67	53	100.00	41	100.00	50	98.04			
Nausea																												
Yes	0	0.00	0	0.00	0	0.00	0	0.00	1	14.29	0	0.00	0.268	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	–
No	6	100.00	12	100.00	16	100.00	13	100.00	6	85.71	2	100.00		45	100.00	28	100.00	30	100.00	53	100.00	41	100.00	51	100.00			
Vomiting																												
Yes	0	0.00	0	0.00	1	6.25	0	0.00	2	28.57	1	50.00	0.026	4	8.89	0	0.00	0	0.00	2	3.77	1	2.44	0	0.00	0.124		
No	6	100.00	12	100.00	15	93.75	13	100.00	5	71.43	1	50.00		41	91.11	28	100.00	30	100.00	51	96.23	40	97.56	51	100.00			
Loss of appetite																												
Yes	1	16.67	1	8.33	0	0.00	0	0.00	1	14.29	1	50.00	0.040	2	4.44	0	0.00	1	3.33	1	1.89	0	0.00	0	0.00	0.421		
No	5	83.33	11	91.67	16	100.00	13	100.00	6	85.71	1	50.00		43	95.56	28	100.00	29	96.67	52	98.11	41	100.00	51	100.00			
Weakness																												
Yes	0	0.00	0	0.00	1	6.25	1	7.69	1	14.29	1	50.00	0.232	3	6.67	0	0.00	0	0.00	0	0.00	1	2.44	0	0.00	0.077		
No	6	100.00	12	100.00	15	93.75	12	92.31	6	85.71	1	50.00		42	93.33	28	100.00	30	100.00	53	100.00	40	97.56	51	100.00			

233 specific prevention from an intervention. Such training may
234 enhance or reduce susceptibility to unrelated infections (26).

235 The present study has several strengths. First, this is the
236 first study on the association of vaccinations with symptoms
237 in children with COVID-19. Our findings demonstrate
238 that, compared with symptoms in pediatric cases without
239 BCG vaccination, the severity of symptoms in COVID-19
240 pediatric cases with BCG vaccination was similar. Second,
241 we detected common pathogens of respiratory diseases,
242 such that we were able to analyze the relationship between
243 coinfection status and the severity of COVID-19 cases.
244 Finally, we included both confirmed and suspected
245 COVID-19 cases from two different centers, which may
246 help to reveal a comprehensive picture of pediatric patients
247 with COVID-19.

248 This study also has a number of limitations. First, the
249 number of children without BCG vaccination was limited
250 because it is free and mandatory to vaccinate BCG at birth in
251 China according to the Chinese policy (27), the comparison
252 with children in other countries should be increased and the
253 results will be more credible, we will try our best to look
254 up the potential cooperation pediatric hospital in future.
255 Thirteen children were not vaccinated in the present study.
256 Three cases in the present study were imported from Spain,
257 the United Kingdom, and the United States of America. As
258 an important issue, clinical features of COVID-19 in such
259 children require further analysis in future studies. Finally,
260 this was a retrospective study from two hospitals, and the
261 epidemic of COVID-19 is ongoing, however in the current
262 retrospective study, the symptoms and age were recorded in
263 the electronic health record, and the vaccination status was
264 recorded in the specific vaccine management system, the
265 deviation is relatively low. To gain a better understanding
266 of COVID-19 in children, more detailed information
267 on patient vaccinations and clinical outcomes should be
268 collected in future studies.

269 Children with COVID-19 play an important role in
270 family clusters and in community transmission, especially
271 within kindergartens, as well as primary and middle
272 schools (28). Since vaccination plans are different between
273 Asian and Western countries, more comparative studies
274 on protection via vaccinations (e.g., BCG) in COVID-19
275 patients are needed in future studies, it may be helpful to
276 control the COVID-19 epidemic in the global situation.

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Conclusions

In conclusion, pediatric COVID-19 patients with BCG

vaccinations exhibit clinical manifestations similar to those
of patients who had not been vaccinated for BCG, and the
severity of symptoms in pediatric patients may be related to
the maturity of immune function.

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332 aspects of the work in ensuring that questions related
333 to the accuracy or integrity of any part of the work are
334 appropriately investigated and resolved. The study was
335 conducted in accordance with the Declaration of Helsinki
336 (as revised in 2013), and was approved by the Institutional
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