Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Science Bulletin 65 (2020) 2057–2060

Contents lists available at ScienceDirect

Science Bulletin

journal homepage: www.elsevier.com/locate/scib

Science Bulletin
www.scibull.com

Short Communication

Strong immunity against COVID-19 in the early two years of age links to frequent immunization of routine vaccines

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ARTICLE INFO

Article history:
Received 24 May 2020
Received in revised form 9 July 2020
Accepted 28 July 2020
Available online 8 August 2020

Coronavirus disease 2019 (COVID-19) has become a global pandemic, currently affecting 215 countries and regions. Over 5,200,000 confirmed cases, including nearly 340,000 deaths, were reported as of May 24, 2020. COVID-19 severity and mortality are higher in elderly patients with pre-existing chronic diseases [1,2]. Children seem to be less susceptible to COVID-19 than adults. Among the reported cases in China, pediatric patients under 10 years old accounted for only approximately 1% of the total confirmed patients [1]. Similarly, epidemiological studies found that pediatric cases account for 1%–5% of the diagnosed COVID-19 cases in countries that have had large outbreaks, including China, Italy, the United Kingdom, and the United States [3–6]. According to the World Health Organization (WHO) COVID-19 global surveillance database of 715,130 cases from 24 February to 13 April 2020, this proportion has been stable over time [7]. Few severe pediatric COVID-19 cases have been reported [1,8]. It remains unknown why children are at a lower risk for severe manifestations of COVID-19 than adults.

In this retrospective study, 25 patients under 10 years old were selected from a total of 186 laboratory-confirmed COVID-19 patients (Materials and methods, Fig. S1 and Table S1 online). All patients were enrolled at Taihe Hospital in Shiyan city, located in the northwest of Hubei province, 450 km away from Wuhan city. We comprehensively analyzed the factors associated with the disease outcomes of these pediatric patients.

The symptoms displayed by all 25 pediatric COVID-19 patients were mainly mild, e.g., fever, cough, and more sputum than adults (64.0% vs. 24.2%, $P < 0.0001$). These children did not exhibit fatigue, myalgia, chill, shortness of breath, anorexia, or headache. Notably, 24.0% had diarrhea (Table S2 online). Elevated levels of lactate dehydrogenase, aspartate aminotransferase, high-sensitivity C-reactive protein, and serum amyloid A were frequently detected. In contrast with adult patients, lymphocytopenia, thrombocytopenia, leukopenia, anemia, and hypoproteinemia were absent or rarely found in these children (Table S3 online). Radiographic abnormalities were found in 88.0% of the pediatric COVID-19 patients, with 44.0% having both unilateral and bilateral lesions. Most cases (84.0%) displayed patchy shadows, and one case (4.0%) had ground-glass opacities. None of these children required treatment in an intensive care unit (Tables S4 and S5 online).

The patient age distribution revealed that children of all ages are susceptible to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (Fig. 1a). Most children are immunized with routine vaccines, including the tuberculosis vaccine *Bacillus* Calmette-Guérin (BCG), hepatitis B vaccine, polio vaccine, and measles-mumps-rubella vaccine, receiving doses between birth and preschool age. In China, the majority (77%) of vaccine dosages (i.e., 17 dosages of 10 routine vaccines) are administered to children before the age of 2 years, whereas only five dosages of four routine vaccines are given to children over 2 years old (Fig. 1b). To further explore how patient age and vaccination status affect pediatric patient recovery from COVID-19, we analyzed the pediatric COVID-19 patient recovery time after stratifying the patients by age. The two groups with children aged under 2 years tended to have shorter periods between the first positive SARS-CoV-2 detection and subsequent negative SARS-CoV-2 PCR results than the other groups of older children (Fig. 1c). Significant differences in the duration from disease onset to subsequent negative SARS-CoV-2 PCR results were found in both the < 1-year-old group and the 1–2-year-old group as compared with the 2–3-year-old group

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https://doi.org/10.1016/j.scib.2020.08.012
2095-9273/

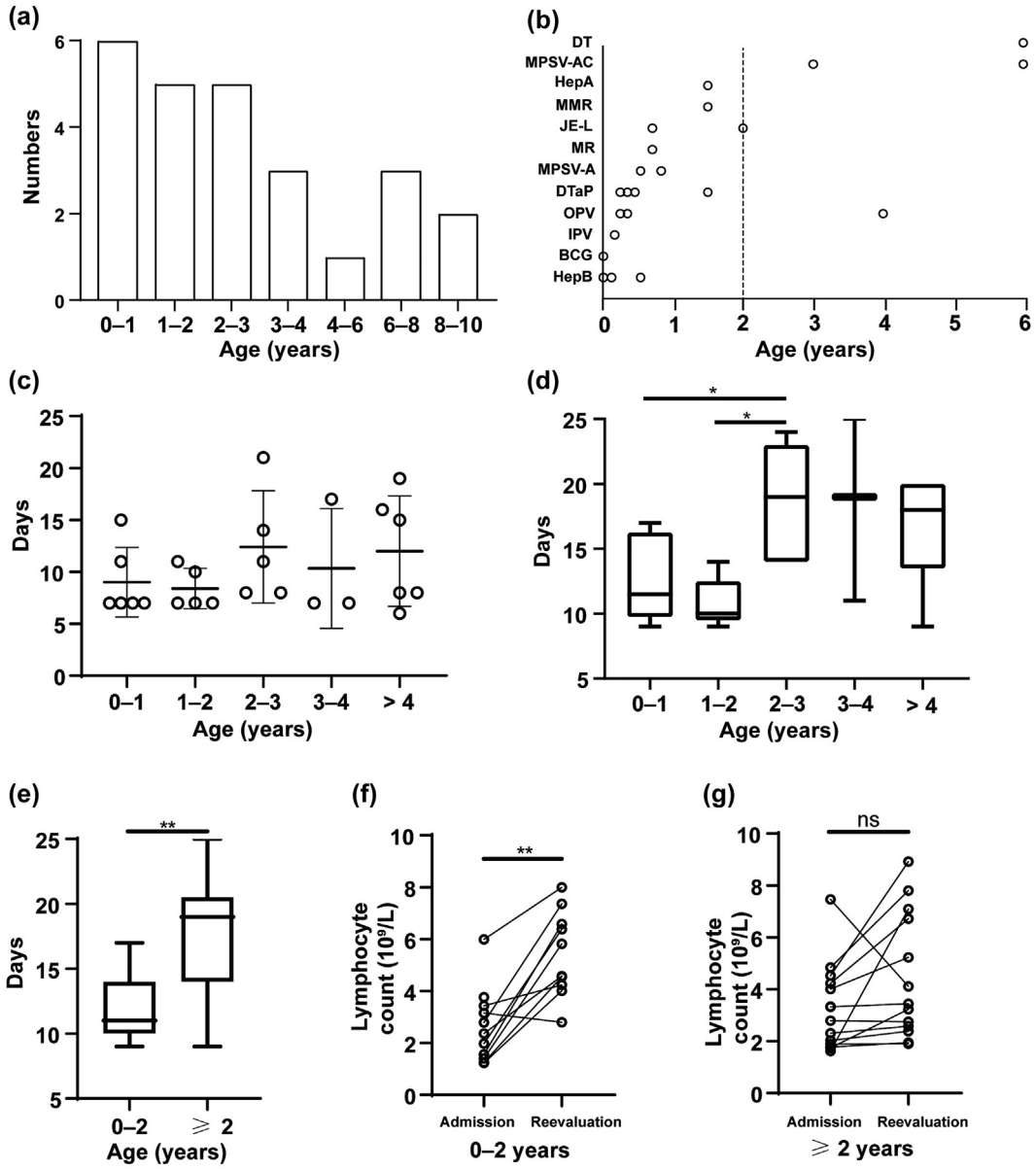

Fig. 1. Potential factors that determine the better COVID-19 outcomes in children under 2 years old. (a) Age distribution of 25 pediatric patients under 10 years old. (b) Immunization schedules of pre-school children in China. (c) Duration from SARS-CoV-2 RNA-positive detection to subsequent negative SARS-CoV-2 PCR results for patients with the indicated ages. Data are presented as the medians and IQRs (interquartile ranges); empty circles represent individual patients. (d) Duration from disease onset to subsequent negative SARS-CoV-2 PCR results for patients with the indicated ages. Data are presented as the medians and IQRs; *P*-values were calculated by a Mann-Whitney nonparametric *t*-test. (e) Duration from disease onset to subsequent negative SARS-CoV-2 PCR results for patients under and over 2 years old. Data are presented as the medians and IQRs; *p*-value was calculated by a Mann-Whitney nonparametric *t*-test. (f) Lymphocyte counts at admission and at the time of subsequent negative SARS-CoV-2 PCR results for patients under 2 years old. Empty circles represent individual lymphocyte counts; *P*-value was calculated by a paired *t*-test. (g) Lymphocyte counts at admission and at the time of subsequent negative SARS-CoV-2 PCR results for patients over 2 years old. Empty circles represent individual lymphocyte counts; *P*-value was calculated by a paired *t*-test. All the *P*-values from statistical tests were from two-sided evaluations. *: $P < 0.05$; **: $P < 0.01$; ns: non-significant. HepB: Hepatitis B vaccine; BCG: *Bacillus* Calmette-Guerin vaccine; IPV: Inactivated polio vaccine; OPV: Oral polio vaccine; DTaP: Diphtheria and tetanus toxoid with acellular pertussis vaccine; MPSV-A: Meningococcal polysaccharide vaccine A; MR: Measles and rubella vaccine; JE-L: Live attenuated Japanese encephalitis vaccine; MMR: Measles, mumps and rubella vaccine; HepA: Hepatitis A vaccine; MPSV-AC: Meningococcal polysaccharide vaccine A + C; DT: Diphtheria and tetanus toxoid children's dose.

(Fig. 1d). Further age stratification revealed that the < 2-year-old group recovered an average of 6 days earlier than the older group (11.73 ± 2.76 vs. 17.71 ± 4.71, $P = 0.0011$, Fig. 1e and Table S6 online). Together, these results suggest that young age and frequent vaccine immunization are related to the fast recovery of pediatric patients.

Because pediatric COVID-19 patients aged under 2 years were found to have shorter recovery times, we next further analyzed the clinical differences between children under and over 2 years old; several variables were compared between these two groups (Table S7 online). The levels of gamma globulin, one class of globulins, decrease soon after birth and then gradually rise to near-adult levels by 2 years of age [9]. As expected, those under 2 years old had lower average gamma globulin levels (19.8 g/L vs. 24.9 g/L, $P = 0.0065$) than the patients aged over 2 years. In addition, a higher proportion of these younger patients (54.5% vs. 14.3%, $P = 0.0322$) had gamma globulin levels below the reference level. Similarly, a prolonged activated partial thromboplastin time

(APTT) and shortened prothrombin time (PT) are normally observed during the first 6 months after birth [10]. As expected, a higher percentage of the children under 2 years old had a prolonged APTT (50.0% vs. 8.3%, P = 0.029) and a lower percentage of them had a prolonged PT (0 vs. 41.7%, P = 0.020) compared with the older children, reflecting their immature hematopoiesis status. There were no differences in any of the symptoms, abnormal laboratory indicators, or CT signs between the two groups. Most noticeably, the patients under 2 years old had significantly elevated lymphocyte counts upon recovery ($(2.9 \pm 1.8)\times10^9$ cells/L, 95% CI: $(1.7–4.2)\times10^9$ cells/L; P = 0.0006, Fig. 1f). In contrast, the older group had no significant change in their lymphocyte counts (Fig. 1g). These results indicate that children aged under 2 years respond to SARS-CoV-2 infection better than the older children, despite their immature hematopoiesis.

A number of the pediatric COVID-19 patients (72.0%) had comorbidities, including myocardial damage, liver function damage, electrolyte disorders, or sepsis (Table S5 online). Co-infections with parainfluenza virus, respiratory syncytial virus, adenovirus, influenza viruses, coxsackievirus, Epstein-Barr virus, and mycoplasma were occasionally identified in some patients. Surprisingly, mycoplasma infection was absent in the children under 2 years old, whereas it was present in 75% (9/12) of the patients over 2 years old (P = 0.0002, Table S6 online). Thus, in addition to antiviral treatment, inhaled glucocorticoids, antibiotics (intravenously or orally administrated), and traditional Chinese medicine (TCM) were given to the patients for treating symptoms and co-infections. There was no difference in the proportion or duration of treatments, except for TCM and oral antibiotics; TCM treatment (18.2% vs. 78.6%, P = 0.0027) and oral antibiotics (0.0% vs. 42.9%, P = 0.013) were used less in children under 2 years old (Table S6 online).

In summary, children with COVID-19 exhibited mild symptoms and abnormalities, though comorbidities were common. The pediatric patients under 2 years old controlled SARS-CoV-2 infection and mycoplasma co-infection better and recovered faster than the older patients. Antibiotic and traditional Chinese medicine treatment did not significantly contribute to infection control. Rather, younger age and strong immunity were the factors that determined faster recovery.

It remains unclear why children contract COVID-19 less often and experience less severe cases than adults. One possible explanation is that children have a less intense immune response to the virus than adults [11]. Unlike adult COVID-19 patients who frequently development lymphocytopenia, most of the children in this study had normal leukocyte counts, and neutropenia and lymphocytopenia were rare [1,2,12]. Another possibility is that the angiotensin converting enzyme 2 (ACE2) receptor, which is the binding site for SARS-CoV-2 entry, may be expressed differently in pediatric airways from that of adults [13,14]. Notably, our study found that children under 2 years old appeared to have stronger immunity against COVID-19 than older children. One possible cause is the contribution of maternal immunity. However, this is unlikely given that there was no difference between the infant (<1-year-old) group and the toddler (1–2-year-old) group. Another possibility is that seasonal coronavirus infection in early life may provide some pre-existing cross-reactive adaptive immunity against SARS-CoV-2 infection. However, a previous epidemiological study revealed that the incidence of seasonal coronavirus infection in children under one year old is not significantly different from that in older children [15]. An additional potential explanation for the strong immunity in children under 2 years old is the frequent administration of routine vaccines because children in China receive the majority of vaccinations during this period.

Besides eliciting immunity to specific pathogens, vaccines also have nonspecific protective effects on unrelated infections [16], known as heterologous immunity. There are two types of heterologous immunity: classical heterologous immunity and trained immunity. Classic heterologous immunity mainly results from the cross-reactivity of T-cell responses to epitopes from different pathogens [17,18]. Pre-existing cross-reactive T-cell immunity to infections or vaccinations alters subsequent T-cell responses to antigens of unrelated pathogens [18–20], thus frequently contributing to a protective or pathogenic role in infectious diseases [18,20]. Trained immunity mediated by primed innate immune cells can last up to 1 month and is able to boost beneficial immune responses to infections [21]. Trained immunity can also last for a relatively long period and protect the host from an unrelated infection [21,22]. For example, healthy volunteers who received the BCG vaccine 1 month before receiving the yellow fever vaccination had significantly lower yellow fever virus titers than the volunteers who received a placebo vaccination [22]. BCG immunization protects mice from infections of viruses, including influenza virus and rodent coronavirus [23]. Furthermore, consecutive BCG vaccination in humans for 3 months reduced the incidence of acute upper tract respiratory infections by 80% [24]. It is plausible that immunization with routine vaccines, such as BCG [25], in infants generates relatively long-lasting trained immunity. Consistent with this presumption, some scientists are also recommending the use of other live attenuated vaccines, such as OPV (oral polio vaccine) [26] and MMR (measles, mumps and rubella) vaccine [27], as a preventive strategy for COVID-19. These vaccines have been testing in clinical trials (NCT04328441, NCT04327206, NCT04348370, NCT04445428, NCT04357028, etc.) to enhance human immunity against SARS-CoV-2 and mitigate COVID-19 illness. Thus, our present findings provide the first evidence to support the clinical trials.

This study is mainly based on the clinical data of patients in one hospital. Thus, it has some limitations including its sample size, lack of critical severe cases, inability to effectively analyze how different treatments influence patient outcomes. In addition, the low rate of treatment with traditional Chinese medicine in children under two years old may be related to their lower treatment compliance than the older. All these issues are warranted to further being investigated. Nevertheless, we did have a substantial number of patients under 2 years old, who had fewer drug treatments but yet recovered faster. This circumvents at least part of limitations.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgments

This work was supported by the Hubei Provincial Department of Science and Technology Innovation Group Programme (2019CFA034), the Foundation for Free Exploration of Hubei University of Medicine (FDFR201802), the Shiyan Municipal Guided Emergent Scientific Research Programme for the Prevention and Control of New Coronavirus Pneumonia (20Y12), the National Natural Science Foundation of China (81972668) and the National Key Research and Development Program of China (2018ZX10301-208). We sincerely acknowledge all the health-care workers in the diagnosis and treatment of patients in Taihe Hospital (New Coronavirus Pneumonia Consultation Expert Panel, Department of Pediatrics, Department of Infectious Disease, Fever Clinic, New Coronavirus Pneumonia Medical Emergency Team, Laboratory Department, Department of Radiology, Nursing Department, and Material Supply Department).

Author contributions

Qibin Leng and Zhiguo Luo conceived the idea and directed the entire study. Qibin Leng, Zhiguo Luo and Li Qiu designed the clinical study. Zhiguo Lou and Li Qiu provided financial and ethical supports. Jie Lou provided administrative support. Junbo Wu retrieved the literature. Li Qiu and Junbo Wu did the data entry. Chengdong Zhang and Jie Luo double-checked the data entry. Li Qiu did the statistical analysis. Chengdong Zhang audited the analysis. Qibin Leng and Zhiguo Luo had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Qibin Leng, Li Qiu, and Chengdong Zhang drafted the manuscript. Mihai G. Netea and Chengdong Zhang provided further data interpretation and edited the manuscript. All authors critically revised the manuscript for important intellectual content and gave the final approval for the version to be published. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the integrity or accuracy of any part of the work were appropriately investigated and resolved.

Appendix A. Supplementary materials

Supplementary materials to this article can be found online at https://doi.org/10.1016/j.scib.2020.08.012.

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