Pediatric RESEARCH

www.nature.com/pr

SYSTEMATIC REVIEW

Coronavirus disease 2019 (COVID-19) in children and/or adolescents: a meta-analysis

Alessandro Mantovani[1], Elisabetta Rinaldi[1], Chiara Zusi[1,2], Giorgia Beatrice[1], Marco Deganello Saccomani[3] and Andrea Dalbeni[4]

BACKGROUND: To assess the overall prevalence of clinical signs, symptoms, and radiological findings in children and/or adolescents with COVID-19.

METHODS: We systematically researched in PubMed, Scopus and Web of Science databases observational studies describing COVID-19 in children and/or adolescents until April 11, 2020. Data regarding clinical and radiological features were extracted from eligible studies and meta-analysis was performed using random-effects modeling.

RESULTS: We examined 19 eligible studies for a total of 2855 children and/or adolescents with COVID-19. Approximately 47% of subjects had fever (95% confidence interval [CI] 22−72%; $I^2 = 98.6\%$), 37% cough (95%CI 15−63%; $I^2 = 98.6\%$), 4% diarrhea (95%CI 0−12%; $I^2 = 92.2\%$), 2% nasal congestion (95%CI 0−7%; $I^2 = 87.7\%$), 1% dyspnea (95%CI 0−7%; $I^2 = 91.5\%$) and 0% abdominal pain (95%CI 0−1%; $I^2 = 76.3\%$). Subjects presented mild symptoms in 79% (95%CI 65−91%; $I^2 = 93.5\%$) of cases, whereas only 4% (95%CI 1−9%; $I^2 = 76.4\%$) were critical. Among those with pneumonia on computed tomography, 26.4% (95%CI 13−41%; $I^2 = 80.8\%$) presented a unilateral involvement, 16% (95%CI 5−29%, $I^2 = 81.2\%$) had bilateral involvement and 9% (95%CI 0−24%; $I^2 = 88.7\%$) had interstitial pneumonia.

CONCLUSIONS: Children and/or adolescents tend to have a mild COVID-19 course with a good prognosis.

Pediatric Research (2021) 89:733–737; https://doi.org/10.1038/s41390-020-1015-2

IMPACT:

- Compared to adults, children and/or adolescents tend to have a mild COVID-19 course with a good prognosis.
- This study provides new and consistence information on the clinical and radiological characteristics of COVID-19 in pediatrics.
- This study may help to fight COVID-19 in pediatric population.

INTRODUCTION

The novel Coronavirus disease 2019 (COVID-19) is to date a global pandemic, affecting approximately 1,600,000 individuals and with nearly 100,000 deaths and 215 countries, areas, or territories implicated.[1] These data were updated to April 12, 2020.[1] The COVID-19 disease can affect all age groups, although children and/or adolescents seem to be less susceptible to this infection.[2] Furthermore, the reports of severe COVID-19 forms in pediatric populations are rare.[3] At present, however, data regarding COVID-19 in children and adolescents are scarce and, specifically, a systematic description of the clinical spectrum of such disease in this age group is lacking.

Therefore, the aim of this meta-analysis was to assess the overall prevalence of clinical signs, symptoms, and radiological findings in children and/or adolescents with COVID-19 disease by meta-analyzing data from observational studies available so far.

METHODS

Data sources and searches

We searched in PubMed, Scopus and Web of Science databases in order to identify all observational studies, published until April 11, 2020, evaluating COVID-19 in children and/or adolescents. Only studies with a sample size ≥4 were considered. No limitations in terms of race or ethnicity were used. Exclusion criteria were: (i) abstracts, editorials, comments, reviews, guidelines; and (ii) studies that have involved adult populations. Nineteen observational studies were identified with the terms "COVID19" (OR "COVID-19" OR "Coronavirus disease 2019") with filter "Humans" and "English language". Indeed, papers in non-English language were excluded. Given that the eligible studies were observational, we followed the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines for the meta-analysis.[4]

Data extraction and quality assessment

Three investigators (A.M., C.Z. and E.R.) evaluated the abstracts independently and then they achieved the full texts of relevant papers. They read the articles independently and decided if they met the inclusion criteria. Discrepancies were solved by discussion with a fourth investigator (A.D.). For all eligible studies, data on sample size, population, clinical and radiological features, and outcomes were extracted from all eligible studies and meta-analysis was carried out using random-effects modeling.

[1]Section of Endocrinology, Diabetes and Metabolism, Department of Medicine, University and Azienda Ospedaliera Universitaria Integrata of Verona, Verona, Italy; [2]Pediatric Diabetes and Metabolic Disorders Unit, Department of Surgical Sciences, Dentistry, and Pediatrics, and Gynaecology, University Hospital of Verona, Verona, Italy; [3]Department of Pediatrics, Woman's and Child's University Hospital of Verona, Verona, Italy and [4]Section of General Medicine, Hypertension and Liver Unit, University and Azienda Ospedaliera Universitaria Integrata of Verona, Verona, Italy

Correspondence: Alessandro Mantovani (alessandro.mantovani@univr.it)

Received: 23 April 2020 Revised: 3 June 2020 Accepted: 3 June 2020
Published online: 17 June 2020

Two authors (A.M. and A.D.) evaluated the risk of bias independently. Given that the eligible studies were observational, we used the Newcastle−Ottawa Scale (NOS) adapted for cross-sectional study.

Data synthesis and analysis

The primary outcomes of the study were the percentage of children and/or adolescents with fever, cough, nasal congestion, dyspnea, diarrhea, or abdominal pain as well as the percentage of children and/or adolescents with mild or severe symptoms. In addition, we assessed the percentage of children and/or adolescents with evidence of pneumonia at computed tomography (CT) scan. The pooled prevalence of children and/or adolescents with clinical signs and symptoms was calculated with a random-effects model.[5] The confidence intervals (CIs) were calculated with the method described by Wilson et al.[6,7] Seeing that some eligible studies had prevalences of various clinical signs and symptoms and radiological findings equal to zero, we computed the pooled estimates also after the Freeman−Tukey double arcsine transformation.[6,7]

In order to assess the heterogeneity, we firstly used visual examination of the forest plots. The heterogeneity among eligible studies was also investigated by the I^2-statistics. According to Higgins and Thompson,[8] interpretation of I^2-statistics is as follows: I^2 values of nearly 25% show low heterogeneity; I^2 values of roughly 50% show medium heterogeneity; and I^2 values of roughly 75% show high heterogeneity. The publication bias was evaluated by the funnel plots and the Egger's regression asymmetry tests for each primary outcome measure.[9]

In order to investigate the possible sources of heterogeneity among eligible studies, we also performed subgroup analyses. Specifically, in relation to the data observed in the eligible studies, the pooled prevalences of various signs and symptoms were evaluated stratifying the studies by study country (i.e., Asian countries vs. non-Asian countries). All statistical analyses were made with STATA® 14.2 (Stata, College Station, TX).

RESULTS

Supplementary Fig. S1 reports the flow diagram of the study selection. As summarized in Table 1, we considered 19 eligible observational studies,[10–28] including a total of 2855 (mainly Chinese) children and/or adolescents (mean age 6.9 ± 7.0 years; 50.3% males) with confirmed diagnosis of COVID-19 disease by nasopharyngeal swabs. Eighteen of the eligible studies provided data on major adverse events,[10–16,18–28] whereas one described only the severity of the disease.[17] Overall, as reported from Supplementary Tables S1–S6, ~47% of children had fever (95%CI 22−72%; $I^2 = 98.6\%$), 37% cough (95%CI 15−63%; $I^2 = 98.6\%$), 4% diarrhea (95%CI 0−12%; $I^2 = 92.2\%$), 2% nasal congestion (95%CI 0−7%; $I^2 = 87.7\%$), 1% dyspnea (95%CI 0−7%; $I^2 = 91.5\%$) and 0% abdominal pain (95%CI 0−1%; $I^2 = 76.3\%$). Children and adolescents presented mild symptoms in 79% (95%CI 65−91%; $I^2 = 93.5\%$) of cases, whereas only 4% (95%CI 1−9%; $I^2 = 76.4\%$) of patients were considered critical. Fifteen studies[10–18,20–24,27,28] described also the radiological findings at chest CT (Table 2). As reported in Supplementary Table S7, no evidence of pneumonia at CT scan was observed in 26% (95%CI 8−48%; $I^2 = 92.4\%$) of children and/or adolescents. Among those with pneumonia, confirmed by CT, 26.4% (95%CI 13−41%; $I^2 = 80.8\%$) presented a unilateral involvement (Supplementary Table S8), 16% (95%CI 5−29%, $I^2 = 81.2\%$) had bilateral involvement (Supplementary Table S9) and 9% (95%CI 0−24%; $I^2 = 88.7\%$) had interstitial pneumonia (Supplementary Table S10).

The relatively high heterogeneity ($I^2 > 80\%$) observed in the overall primary analyses of our study may reflect important differences among the main characteristics of study populations, including age (from some days to 13 years), country (i.e., China, USA, and Spain), and different care setting. In fact, heterogeneity was partly attenuated stratifying the studies by country.

The Egger's regression tests showed a significant asymmetry of the funnel plots for some primary outcome measures (i.e., fever, cough, diarrhea, and nasal congestion), indicating a possible publication bias (Supplementary Table S11). For this reason, we then did the nonparametric trim and fill analysis[29] that have indicated that the impact of publication bias was very little (data not shown).

DISCUSSION

The principal results of our meta-analysis are as follows: (a) in children and/or adolescents with COVID-19, the most important symptoms are fever and cough, although a relatively small number of individuals also had diarrhea; (b) mild symptoms were observed in most cases; and (c) no children and/or adolescents died.

Subjects of any age can gain severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (Table 2). In a systematic review, Ludvigsson[30] also reported that in children and/or adolescents symptomatic infection appears to be uncommon, although severe cases have been reported. Our meta-analysis substantially confirmed the results by Ludvigsson,[30] but it adds further information regarding the prevalence of various clinical signs and symptoms, as well as the percentage of children and/or adolescents with specific alterations on CT by the meta-analysis of data reported in 19 observational studies available so far. In particular, our meta-analysis suggests that fever and cough, but also diarrhea, are the most frequent clinical characteristics that can be observed in children and/or adolescents with COVID-19. In addition, very recently, in a systematic review of 18 studies involving pediatric cohorts, Castagnoli et al.[31] also confirmed that children and/or adolescents undergo less severe COVID-19 infection when compared to adults, thus having mild symptoms and a good prognosis.

The number of cases with COVID-19 observed in children and/or adolescents is scarcely reported in the daily reports of most non-Asian countries, but are, instead, commonly described in the Asian reports. For this reason, in our meta-analysis, we found 17 studies conducted in Chinese children and/or adolescents, only one conducted in the US population and one performed in Spain. In addition, it is important to note that more recently in a large Chinese report, only 2% of infections were observed in individuals younger than 20 years old.[32] Similarly, in South Korea, 6.3% of 8000 infections were observed in individuals under the age of 20 years.[33] Importantly, the majority of the studies reported hospitalization and symptoms at the event. Our report also documented that mild symptoms were observed in approximately 80% of cases, whereas more than 4% of children were considered critical. However, no one has died from COVID-19 in eligible studies of our systematic review and meta-analysis.

Along with other authors[30,31] we believe that children and/or adolescents may have a better prognosis for COVID-19, when compared to adults, for the following reasons: (a) seeing that the SARS-CoV-2 S protein attaches the angiotensin-converting enzyme (ACE) 2[30,31,34] children and/or adolescents may be protected, as this enzyme may be less developed at a younger age[35]; and (b) the percentage of children and/or adolescents affected by COVID-19 having an exaggerated inflammatory response against the virus are not commonly described in the reports available so far.[30,36] However, it is important to underline that in the middle of May 2020, the Centers for Disease Control and Prevention (CDC)[37] and World Health Organization (WHO)[38] have communicated the existence of a hyperinflammatory syndrome in children, also defined as Multisystem Inflammatory Syndrome in Children (MIS-C). Indeed, this is an emerging syndrome characterized by fever, many signs and symptoms,

Table 1. Main characteristics of children and/or adolescents with COVID-19.

Author [Ref.]	PMID	Country	Sample size	Age	*n* of boys (%)	Fever, *n* (%)	Nasal congestion, *n* (%)	Cough, *n* (%)	Dyspnea, *n* (%)	Abdominal pain, *n* (%)	Diarrhea, *n* (%)	Mild cases, *n* (%)	Critical cases, *n* (%)	NOS
Zheng et al.[10]	32207032	China	25	3 years (from 2 to 9 years)	14 (56)	13 (52)	2 (8)	11 (44)	2 (8)	2 (8)	3 (12)	15 (60)	2 (8)	5
Sun et al.[11]	32193831	China	8	7 years (from 2 months to 15 years)	6 (75)	6 (75)	0 (0)	6 (75)	8 (100)	0 (0)	3 (37.5)	0 (0)	8 (100)	5
Lu et al.[12]	32187458	China	171	7 years (from 1 day to 15 years)	104 (60)	71 (42)	9 (5)	83 (48)	0 (0)	0 (0)	15 (9)	168 (98.2)	3 (1.8)	5
Liu et al.[13]	32171865	China	4	4 years (from 1 month to 9 years)	2 (50)	3 (75)	0 (0)	3 (75)	0 (0)	0 (0)	0 (0)	3 (75)	1 (25) RSV + SARS CoV-2	5
Liu et al.[14]	32163697	China	6	3 years (from 1 to 7 years)	2 (33)	6 (100)	0 (0)	6 (100)	0 (0)	0 (0)	0 (0)	0 (0)	1 (16)	5
Xia et al.[15]	32134205	China	20	2 years (from 1 day to 14 years)	13 (65)	12 (60)	3 (15)	13 (65)	2 (10)	0 (0)	3 (15)	NA	0 (0)	5
Cai et al.[16]	32112072	China	10	6 years (from 1 to 11 years)	4 (40)	8 (80)	4 (40)	6 (60)	0 (0)	0 (0)	0 (0)	10 (100)	0 (0)	5
Dong et al.[17]	32179660	China	2146	7 years (from 2 to 13 years	1213 (56)	NA	NA	NA	NA	NA	NA	1904 (89.7)	125 (5.8)	5
Liu et al.[18]	32217900	China	5	6 years (from 7 months to 13 years)	4 (80)	2 (40)	0 (0)	2 (40)	0 (0)	0 (0)	1 (20)	5 (100)	0 (0)	5
Wei et al.[19]	32058570	China	9	6 months (from 56 days to 11 months)	2 (22)	4 (44)	1 (11)	2 (22)	0 (0)	0 (0)	0 (0)	6 (67)	0 (0)	5
Su et al.[20]	32208917	China	9	3.5 years (from 11 months to 9 years)	3 (33)	2 (22)	0 (0)	1 (11)	0 (0)	0 (0)	0 (0)	9 (100)	0 (0)	5
Zhou et al.[a][21]	32204756	China	9	From 1 to 3 years	Not reported in the Abstract	4 (44)	1 (11)	2 (22)	0 (0)	0 (0)	0 (0)	9 (100)	0 (0)	5
Qiu et al.[22]	32220650	China	36	8.3 (from 1 to 16 years)	23 (64)	13 (36)	0 (0)	7 (19)	1 (3)	NA	2 (6)	17 (47)	7 (19)	5
Shen et al.[23]	32259403	China	9	7.5 (from 1 to 12 years)	3 (33)	3 (33)	0 (0)	1 (11)	0 (0)	0 (0)	2 (22)	9 (100)	0 (0)	5
Zhu et al.[24]	32270592	China	10	9.2 (from 1 to 18 years)	5 (50)	4 (40)	NA	3 (30)	0 (0)	NA	0 (0)	9 (100)	0 (0)	5
CDC COVID-19 Response Team[25]	32271728	USA	291	NA (<18 years)	NA	163 (56)	21 (7)	158 (54)	39 (13)	17 (6)	37 (13)	NA	NA	5
Tagarro et al.[26]	32267485	Spain	41	1 year (1 month to 15 years)	18 (44)	11 (27)	NA	14 (34)	NA	NA	2 (5)	37 (90)	4 (10)	5
Feng et al.[27]	32061200	China	15	8 years (from 4 to 14 years)	5 (33)	5 (33)	NA	1 (7)	NA	NA	NA	15 (100)	0 (0)	5
Wang et al.[28]	32118389	China	31	7 years (from 6 months to 17 years)	15 (48.4)	20 (65)	2 (6.5)	14 (45)	0 (0)	NA	3 (9)	31 (100)	0 (0)	5

NA not available, *NOS* Newcastle–Ottawa Quality Assessment Scale.
[a]Article in Chinese, but most data were available in the abstract that was written in English.

Table 2. Main chest computed tomography (CT) findings of children and/or adolescents with COVID-19.

Author [Ref.]	Sample size	Normal findings on chest CT, *n* (%)	Unilateral involvement on chest CT, *n* (%)	Bilateral involvement on chest CT, *n* (%)	Interstitial involvement on chest CT, *n* (%)
Zheng et al.[10]	25	8 (32)	5 (20)	12 (48)	0
Sun et al.[11]	8	0 (0)	2 (25)	6 (75)	0
Lu et al.[12]	171	0	32 (19)	21 (12)	2 (2)
Liu et al.[13]	4	1 (25)	2 (50)	1 (25)	0
Liu et al.[14]	6	1 (17)	0 (0)	1(17)	3 (50)
Xia et al.[15]	20	4 (20)	6 (30)	10 (50)	12 (60)
Cai et al.[16]	10	0	4 (10)	0	0
Dong et al.[17]	2146	NA	NA	NA	NA
Liu et al.[18]	5	1 (20)	3 (60)	1 (20)	0 (0)
Wei et al.[19]	9	NA	NA	NA	NA
Su et al.[20]	9	7 (78)	2 (22)	0	0
Zhou et al.[21]	9	0	9 (100)	0	6 (67)
Qiu et al.[22]	36	17 (47)	0	0	19 (53)
Shen et al.[23]	9	7 (78)	2 (22)	0	0
Zhu et al.[24]	10	5 (50)	3 (30)	2 (20)	0
CDC COVID-19 Response Team[25]	291	NA	NA	NA	NA
Tagarro et al.[26]	41	NA	NA	NA	NA
Feng et al.[27]	15	6 (40)	NA	NA	2 (13)
Wang et al.[28]	30	16 (52)	5 (17)	9 (30)	0

CT computed tomography, *NA* not available.

such as conjunctivitis, rash, edema, shock, and/or gastrointestinal syndrome, and also multiorgan failure.[37,38] By study design, however, we were unable to capture this syndrome across eligible studies.

The principal limitations are that all the studies were mainly conducted in Asian countries (i.e., China). Another limitation is the sample size of each study that had collected few cases. In addition, we were not able to include the current manuscripts published in non-English language. Thus, it is plausible to suppose that some important pediatric cohorts were not included in our meta-analysis, given that at present the main data from studies and clinical cases involving children and adolescents come from China. However, in this context, it is also important to underline that other authors have made a similar choice in conducting meta-analyses on various aspects of COVID-19 outbreak. Lastly, even though we used a random-effects model, the interpretation of the results may require caution, given the heterogeneity observed in the analyses. However, the heterogeneity observed in our meta-analysis may reflect a mix of patients from different countries (i.e., China, USA, and Spain), with different ages ranging from some days to 13 years, and treated in different settings.

In conclusion, our report shows that children and/or adolescents tend to have a mild COVID-19 course with a good prognosis.

AUTHOR CONTRIBUTIONS

A.M. and A.D. conceptualized and designed the study, carried out the initial analyses, drafted the initial manuscript, and reviewed and revised the manuscript. E.R., C.Z., G.B. and M.D.S. designed the data collection instruments, collected data, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

ADDITIONAL INFORMATION

The online version of this article (https://doi.org/10.1038/s41390-020-1015-2) contains supplementary material, which is available to authorized users.

Competing interests: The authors declare no competing interests.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

REFERENCES

1. World Health Organization. Coronavirus disease 2019. https://www.who.int/emergencies/diseases/novel-coronavirus-2019 (2020).
2. Cruz, A. & Zeichner, S. COVID-19 in children: initial characterization of the pediatric disease. *Pediatrics* https://doi.org/10.1542/peds.2020-0834 (2020).
3. Rothan, H. A. & Byrareddy, S. N. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *J. Autoimmun.* https://doi.org/10.1016/j.jaut.2020.102433 (2020).
4. Stroup, D. F. et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* **283**, 2008–2012 (2000).
5. Higgins, J. P. T. & Green, S. (eds). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* (The Cochrane Collaboration, 2011).
6. Newcombe, R. G. Two-sided confidence intervals for the single proportion: comparison of seven methods. *Stat. Med.* **17**, 857–872 (1998).
7. Nyaga, V. N., Arbyn, M. & Aerts, M. Metaprop: a STATA command to perform meta-analysis of binomial data. *Arch. Public Health* **72**, 39 (2014).
8. Higgins, J. P. & Thompson, S. G. Quantifying heterogeneity in a meta-analysis. *Stat. Med.* **21**, 1539–1558 (2002).
9. Egger, M., Smith, G. D. & Phillips, A. N. Meta-analysis: principles and procedures. *BMJ* **315**, 1533–1537 (1997).
10. Zheng, F., et al. Clinical characteristics of children with coronavirus disease 2019 in Hubei, China. *Curr. Med. Sci.* https://doi.org/10.1007/s11596-020-2172-6 (2020).
11. Sun, D. et al. Clinical features of severe pediatric patients with coronavirus disease 2019 in Wuhan: a single center's observational study. *World J. Pediatr.* https://doi.org/10.1007/s12519-020-00354-4 (2020).
12. Lu, X. et al. SARS-CoV-2 infection in children. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMc2005073 (2020).
13. Liu, H. et al. Clinical and CT imaging features of the COVID-19 pneumonia: focus on pregnant women and children. *J. Infect.* https://doi.org/10.1016/j.jinf.2020.03.007 (2020).

14. Liu, W. et al. Detection of Covid-19 in children in early January 2020 in Wuhan, China. *N. Engl. J. Med.* **382**, 1370–1371 (2020).
15. Xia, W. et al. Clinical and CT features in pediatric patients with COVID-19 infection: different points from adults. *Pediatr. Pulmonol.* https://doi.org/10.1002/ppul.24718 (2020).
16. Cai, J. et al. A case series of children with 2019 novel coronavirus infection: clinical and epidemiological features. *Clin. Infect. Dis.* https://doi.org/10.1093/cid/ciaa198 (2020).
17. Dong, Y. et al. Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in China. *Pediatrics* https://doi.org/10.1542/peds.2020-0702 (2020).
18. Liu, M., Song, Z. & Xiao, K. High-resolution computed tomography manifestations of 5 pediatric patients with 2019 novel coronavirus. *J. Comput. Assist. Tomogr.* https://doi.org/10.1097/RCT.0000000000001023 (2020).
19. Wei, M. et al. Novel coronavirus infection in hospitalized infants under 1 year of age in China. *JAMA* https://doi.org/10.1001/jama.2020.2131 (2020).
20. Su, L. et al. The different clinical characteristics of corona virus disease cases between children and their families in China—the character of children with COVID-19. *Emerg. Microbes Infect.* **9**, 707–713 (2020).
21. Zhou, Y. et al. Clinical features and chest CT findings of coronavirus disease 2019 in infants and young children. *Zhongguo Dang Dai Er Ke Za Zhi* **22**, 215–220 (2020).
22. Qiu, H. et al. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. *Lancet Infect. Dis.* https://doi.org/10.1016/S1473-3099(20)30198-5 (2020).
23. Shen, Q. et al. Novel coronavirus infection in children outside of Wuhan, China. *Pediatr. Pulmonol.* https://doi.org/10.1002/ppul.24762 (2020).
24. Zhu, L. et al. Clinical characteristics of a case series of children with coronavirus disease 2019. *Pediatr. Pulmonol.* https://doi.org/10.1002/ppul.24767 (2020).
25. C. D. C. COVID-19 Response Team. Coronavirus disease 2019 in children—United States, February 12−April 2, 2020. *MMWR Morb. Mortal. Wkly. Rep.* **69**, 422–426 (2020).
26. Tagarro, A. et al. Screening and severity of coronavirus disease 2019 (COVID-19) in children in Madrid, Spain. *JAMA Pediatr.* https://doi.org/10.1001/jamapediatrics.2020.1346 (2020).
27. Feng, K. et al. Analysis of CT features of 15 Children with 2019 novel coronavirus infection. *Zhonghua Er Ke Za Zhi* **58**, E007 (2020).
28. Wang, D. et al. Clinical analysis of 31 cases of 2019 novel coronavirus infection in children from six provinces (autonomous region) of northern China. *Zhonghua Er Ke Za Zhi* **58**, E011 (2020).
29. Duval, S. & Tweedie, R. A nonparametric "trim and fill" method of accounting for publication bias in meta-analysis. *J. Am. Stat. Assoc.* **95**, 89–98 (2000).
30. Ludvigsson, J. F. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. *Acta Paediatr.* https://doi.org/10.1111/apa.15270 (2020).
31. Castagnoli, R. et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children and adolescents: a systematic review. *JAMA Pediatr.* https://doi.org/10.1001/jamapediatrics.2020.1467 (2020).
32. Wu, Z. & McGoogan J. M. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA* https://doi.org/10.1001/jama.2020.2648 (2020).
33. KCDC. Updates on COVID-19 in Korea. https://www.cdc.go.kr/board/board.es?mid=a30402000000&bid=0030 (2020).
34. Wrapp, D. et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science* **367**, 1260–1263 (2020).
35. Simon, A. K., Hollander, G. A. & McMichael, A. Evolution of the immune system in humans from infancy to old age. *Proc. Biol. Sci.* **282**, 20143085 (2015).
36. Henry, B. M., Lippi, G. & Plebani, M. Laboratory abnormalities in children with novel coronavirus disease 2019. *Clin. Chem. Lab. Med.* https://doi.org/10.1515/cclm-2020-0272 (2020).
37. https://www.cdc.gov/coronavirus/2019-ncov/daily-life-coping/children/mis-c.html (2020).
38. https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19 (2020).