Children with COVID-19 behaving milder may challenge the public policies: A Systematic Review and Meta-Analysis

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Systematic Review

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Abstract

Background: The emerging virus is rampaging globally. Great efforts are needed to cut down the transmission. Clinical characteristics of infected children have been described previously. No meta-analysis on this subgroup have been published.

Methods: A single-arm meta-analysis was conducted. We searched PubMed, Google Scholar, Web of Science, three preprints websites and other Chinese database for studies presenting characteristics of children confirmed with Coronavirus Disease 2019 (COVID-19) from December 1 2019 to March 28 2020. Quality Appraisal of Case Series Studies Checklist was used to assess quality and publication bias was analyzed by Egger's test. Random-effect model was used to calculate the pooled incidence rate (IR) or mean difference (MD) with 95% confidence intervals (CI), or a fixed model instead when I^2<50%. We conducted subgroup analysis according to geographic region. Additionally, we searched United Nations Educational Scientific and Cultural Organization to see how different countries act to the education disruption in COVID-19.

Results: 14 studies (two unpublished) with 361 pediatric patients were included. The mean age was 5.5 (95% CI: 0.344–0.765) years old. 23.4% of children were asymptomatic (95%CI: 0.112-0.377). 32.3% (95%CI: 0.163-0.503) showed normal computed tomography imaging, besides, four children were admitted in intensive care units (0, 95%CI: 0.000-0.001) and one death was reported (0, 95%CI: 0.000-0.001). Up to 191 countries have implemented nationwide school closures, affecting over 91% of the world's students.

Conclusion: Children were also susceptible to SARS-CoV-2, while critical cases or death were rare. Characterized by mild presentation, the dilemma that children may become a potential spreader in the pandemic, while strict managements like prolonged school closures, may undermine their well-beings. Thus, the public policies are facing challenge.

Background

In December 2019, dozens of pneumonia cases with unknown etiology were reported in Wuhan, Hubei Province of China. Further sequencing analysis on samples of bronchoalveolar lavage fluid from pneumonia patients indicated that a new type of coronavirus, 2019 novel coronavirus (2019-nCoV), later renamed as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was to blame for this outbreak.[1,2] The emerging disease caused by this pathogen, was then named Coronavirus Disease 2019 (COVID-19) officially by the World Health Organization (WHO). Human-to-human transmission has been recognized early onset of the spread of COVID-19[3], and the numbers of confirmed cases keeps surging over the past few months. On 11 Mar 2020, the outbreak of COVID-19 was formally classified as a worldwide pandemic. As of 19 April, altogether 2241778 confirmed cases and 152551 deaths across 210 countries were reported by WHO.[4]

Though the SARS-CoV-2 is, based on current updated knowledge, phylogenetically, different from severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East Respiratory Syndrome-coronavirus (MERS CoV), which were identified as the cause of the two previous epidemics occurred in China and Saudi Arabia, they do share certain similarities.[5] SARS-CoV-2 shares 82% genome sequence similarity to SARS-CoV and 50% genome sequence homology to MERS-CoV. All the three viruses belong to Beta coronavirus and are enveloped positive-strand RNA viruses, patients got infected mainly manifested with respiratory symptoms (e.g. fever and cough)and poor clinical outcomes often associated with older age and underlying diseases.[5,6]Children with SARS or MERS appeared to develop a milder clinical course, thus resulted in a significant low mortality in the two previous outbreaks.[7,8]An earlier study on 2143 pediatric patients by Dong[9] and colleagues found that 3% of laboratory-confirmed cases were severe/critical, while 7.4% in suspected cases.

So far, SARS-CoV-2 infection has aroused grave concern globally, however, it seems that children got less focused due to a milder presentation. Evidence-based data is in an urgent need to make up the gap in understanding clinical spectrum of COVID-19 in children. Therefore, we are going to synthesize and summarize the clinical characteristics and epidemiology of children with COVD-19 based on the latest literatures to provide a systematic view towards pediatric patients.

Methods

The protocol of this review followed recommendations established by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[10] and was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (ID: CRD42020173233).

Search strategy

A systematic search was conducted in the following electronic databases: PubMed/Medline, Google Scholar, Web of Science, three preprints including Medrxiv, Biorxiv and SSRN, China National Knowledge Infrastructure（CNKI）, Wanfang and several Chinese medical journals from December 1, 2019 to March 28,2020, incorporating the terms “COVID-19”, ”SARS-CoV-2”, ”characteristic”, ”epidemiology” etc. No language limitations were applied. The detailed search strategy can be found in Additional File 1.

Additionally, we searched United Nations Educational Scientific and Cultural Organization (UNESCO ,https://zh.unesco.org/) to find out how different countries act to the education disruption in COVID-19.

Study selection

The studies included in this meta-analysis should meet the following criteria：(1) all types of studies either retrospective or prospective (e.g. cohort, cross-sectional study, case report, case series); (2) studies reporting information regarding COVID-19;（3）studies describing clinical characteristics of pediatric patients (0-18 years) diagnosed by RT-PCR; (4) clinical data of more than three cases can be drawn from the articles. Duplicate studies were removed. Studies that select cases from the same hospital were excluded to avoid regional bias and potential redundant report, then articles with maximum cases were retained. We also excluded studies that reported data on both adults and children, where we failed to extract pediatric data.

Data extraction

Data were extracted from included studies by two reviewers (CL and LL) using Microsoft Excel 2019 independently, any disagreements were resolved by discussion with a third investigator (YH). We extracted study characteristics including study design, time of enrollment, institutions, sample size, study subject features age, gender, epidemiology, symptoms and signs(e.g., fever, cough, lack of symptom), laboratory findings (e.g. white blood cell counts[WBC] and lymphocyte counts [L], biochemical parameters), computed tomography (CT) images，treatments and outcomes(e.g. discharged, death). Primary presentation described in each study were extracted with no assumptions.

Assessment of methodological quality

Quality assessment of eligible studies was performed by the Quality Appraisal of Case Series Studies Checklist of the Institute of Health Economics (IHE)[11], which is comprised of 20 items. Each item would be scored ‘0’ if it was answered ‘NO’ or ‘UNCLEAR’, if the answer was ‘YES’, the item scored ‘1’. A study with 14 or more scores (≥ 70%) was considered to be of acceptable quality.

Statistical analysis

The statistical software R 3.6.3 (R Foundation) was used to carry out the single-arm meta-analysis. Original data extracted from the literature will be transformed by the double arcsine method if the distribution of the data is not normally distributed. Pooled incidence rates (IR) and 95% confidence intervals (95% CI) were calculated or dichotomous data and mean difference (MD) with 95% CI were used to report continuous data. The χ^2 test and the I^2 statistic were used to assess heterogeneity among studies with the random-effect model and DerSimonian and Laird method, or a fixed model instead when I^2<50% (I^2>50% indicated that heterogeneity was statistically significant). We also conducted a subgroup analysis according to geographic region (Wuhan and outside Wuhan) to explore reasons for heterogeneity. In addition, a sensitivity analysis was followed by.

Publication bias was assessed using funnel plots and Egger's regression asymmetry test for meta-analysis that included at least 10 studies. For meta-analysis that included fewer 10 studies, there might be a high risk of bias due to the poor statistical power. *P*-value of <0.05 indicated the existence of publication bias.

Results

Study search and characteristics

A total of 560 relevant papers were identified after a systematic search. (see Figure 1). For those which were accessible to pediatric data, we conducted a comprehensive screening and comparison according to time of enrollment, institutions and demographic characteristics of subjects, 23 articles were under suspicion of an overlapped data were removed. Of 14 studies incorporating 361 children included in this meta-analysis, six were case series, four cross-sectional, three prospective cohorts and 1 retrospective cohort, none compared cases with controls. two studies were unpublished. Study size ranged from three to 171 participants. All of these researches were conducted in China, among which three were from Wuhan with 181 cases. The detailed characteristics can be found in Supplementary Table 1 (see Additional File 2).

As of 19 April 2020, 191 countries were reported to have implemented nationwide school closures to mitigate the impact of COVID-19 on children, affecting over 91% of the world's student population.

Demographical characteristics and Epidemiology

The mean age of pediatric patients enrolled in the 14 studies was 5.55 years old (95%CI: 3.44–7.65), range from one day to 17 years old, boys accounted for 55.8% (95%CI:0.501–0.614).

A large number of cases were identified as part of family clusters with COVID-19, the pooled incidence rate was up to 83.8% (95%CI:0.708-0.940). Besides, the pooled prevalence of cases who exposed to epidemic area was 33.7% (95%CI:0.029-0.735), contacted with confirmed or suspected cases 24.2% (95%CI:0.005-0.494).

Clinical Manifestations

After a systematic review, we found 12 symptoms and five signs were reported in children infected with SARS-CoV-2. For the features of "sneezing" ，"swollen tonsils", "headache"，"wheeze", "chill/rigor", and "tachycardia", meta-analysis was thought to be unnecessary since only one or two researches presented. As is shown in Table 1, fever (57.2%, 95%CI: 0.431-0.708) and cough (42.7%, 95% CI:0.304-0.555) were the most prevalent. Body temperature of 115 patients in seven researches were extracted and presented in Supplementary Table 2 (see Additional File 3), most children had developed a mild or moderate fever. Lack of symptoms was also relatively common in these included cases, which turned out a proportion of 23.4% (95%CI: 0.112-0.377). Conversely, other symptoms or signs didn't have such a frequent presentation (summarized in Table 1).

Laboratory Findings

WBC in 77 cases were below the normal range, the pooled incidence rate was 17.3% (95%CI: 0.092-0.268), increased WBC were found in 11 of 120 participants, the pooled incidence rate was 4.9% (95%CI: 0.8-11.1)[maximum:16.71×10^9/L,minimum:3.2×10^9/L].Compared to lymphopenia (9.7%, 95% CI: 0.006-0.243), lymphocytosis (25.8%, 95% CI: 0.105-0.441) was more common in pediatric patients[max:13.93×10^9/L,min:0.65×10^9/L]. Increased C-Reactive Protein (CRP) was in 18.3% (95%CI:

0.085-0.302) of subjects with a maximum of 47.1mg/L. The pooled incidence rate of an elevated level of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were 15.71%(95%CI:0.039-0.303), 8.2% (95%CI0.047-0.124) respectively.

Radiologic Findings

No abnormal radiologic imaging presentation were reported in 32.3% (95% CI: 0.163-0.503). Apart from that, the most common manifestation in CT imaging was ground-glass opacity (GGO) (28.2%, 95% CI:15.8-42.0), unilateral patchy shadows or GGO were more frequently presented than bilateral (29.2%[95%CI0.154-0.448] vs 17.5% [95% CI: 0.044-0.349]). Additionally, six[12,13] subjects were reported with consolidation on CT, two[21] showed interstitial abnormalities and one asymptomatic infant with pulmonary bulla in Zhou's research[13].

Treatments and clinical outcomes

Approximate 78.7% SARS-CoV-2 infected children were treated with interferon (95% CI: 0.526-0.971), 46.8% (95% CI: 23.6-70.7) were given antiviral agents including ribavirin, oseltamivir, oral lopinavir, and ritonavir. A small number of cases received corticosteroid and immunoglobin therapy, the pooled incidence rate was 1.2% (95% CI: 0.00-0.077) and 2.5% (95% CI: 0.000-0.104). Additionally, four among 361 patients were treated by mechanical ventilation to maintain oxygenation.

We failed to conduct meta-analysis on the severity of disease due to incomplete data. The pooled proportion of patients who got discharged from hospital was 75.1% (95% CI: 0.573-0.898).By reviewing all these studies, however, we found that four children were diagnosed as critical type of COVID-19 and admitted in intensive care units(ICU) (0,95% CI: 0.000-0.001), 3[17]of them were reported to suffer from underlying diseases [hydronephrosis, leukemia(undergoing chemotherapy), and intussusception], unfortunately, a 10-month infant with intussusception died due to multiorgan failure.

Subgroup analysis and sensitivity analysis

There was no significant heterogeneity in nine specific characteristics, publication bias was detected in five groups of meta-analysis ("Exposure to epidemic aera"," Sore throat", "Tachypnea/Dyspnea", "Immunoglobin", and "Death"). (Table 1). The results of subgroup analysis were presented in Table 2, from which we found that geographic region may account for the heterogeneity of "Tachypnea/Dyspnea". A further exploration for between-study heterogeneity by sensitivity analysis showed that none of these studies should be excluded.

Discussion

The unpredictable emergency of SARS-CoV-2 has posed a substantial threat to public health. Implementing efforts on aggregating the existing data about epidemiology, clinical, laboratory, and imaging characteristics to have a better understanding of the virus, its patterns of spread and the spectrum of illness is of critical significance. To our knowledge, this is the first meta-analysis to study presentations in children with COVID-19. Through a comprehensive searching, a total of 14 articles with 361 laboratory-confirmed cases were included.

The general proportion of male to female of this analysis (55.8% *vs* 44.2%) is similar to the gender distribution in an initial investigation[9](57.5% *vs* 42.5% in 731 confirmed cases) and in general population (55.9% *vs* 44.1%) (Table 3). All the results seem to show that male have a slightly higher incidence than female in COVID-19.

According to our results, children got infected with SARS-CoV-2 mainly through family clustering, quite the same as SARS-CoV[7,27] and MERS-CoV[8].While compared to adults, children are more likely to be asymptomatic or present milder symptoms, this reminds us that, whenever there's a family member caught with this virus, it is necessary to conduct a virologic screening test on the child as soon as possible. Otherwise, the infected child may become a threat to other vulnerable populations (e.g. elderly people or people with severe underlying disease), resulting in further extension of ongoing pandemic, as was seen during influenza outbreak.

Fever and cough are the most common symptoms in COVID-19 children, in our study, the pooled incidence of fever is 54.4%, which is lower than that in adults[35], SARS[26] and influenza[38]. (Table 3). Clearly, children with COVID-19 rarely had obvious signs and symptoms of upper respiratory tract (pharyngeal congestion, rhinorrhea, sore throat, stuffy nose). Through a comprehensive review, it's easy to draw the conclusion that SARS-CoV-2 leads to a less aggressive clinical course in children with more asymptomatic and fewer symptoms, compared to that in adults and the other two pathogens. (Table 3).

In terms of laboratory abnormalities, interestingly, the frequency of lymphocytosis is higher than lymphopenia (25.8% vs 9.7%), which is quite different from findings in COVID-19 adults[35]and SARS[26].Besides, leucopenia was found in 17.3% of patients, nevertheless, a research including 80 virologic-confirmed children cited by Henry[32] reported 46% of leukopenia. Theoretically, virus particles primarily spread through the respiratory mucosa, initially using the angiotensin-converting enzyme 2(ACE2) receptor(the cell-entry receptor for SARS-CoV-2) at ciliated bronchial epithelial cells and infect other cells, induce a cytokine storm in the body, generate a series of immune responses, and cause changes in peripheral white blood cells and immune cells such as lymphocytes[33,34,35].Presumptions have been made that children may be protected against SARS-CoV-2 because this enzyme is less mature at a younger age, since the immune system undergoes substantial changes from birth to adulthood. In general, WBC and lymphocyte remained normal in the majority of pediatric patients, suggesting that the newly emerging virus, SARS-CoV-2, may have a marginal influence on the immune function of children.

As for radiologic aspects, our research found that a proportion of 32.3% of 308 virologic positive cases were in absence of CT abnormalities, and Ground glass opacity, also typical signs of severe acute respiratory syndrome (SARS)[26], was shown in only 28.2% of pediatric patients. In addition, 14 cases in our research underwent chest X-ray, four of them (28.6%) subsequently showed abnormal opacities in the lung. This kind of low sensitivity hints us that routinely radiologic scans should not be over emphasized for screening or early identification of COVID-19 in children in consideration of substantial radiation exposure, especially when the child is lack of symptoms or running a mild clinical course. Therefore, more strict strategies and screening practices are required for the better management of pediatric cases.

It's worth noting that underlying conditions have played a pivotal role in COVID-19. Four of 361 cases included were diagnosed as critical type of novel coronavirus infected pneumonia and required mechanical ventilation, three of them were undergoing hydronephrosis, leukemia, and intussusception respectively. A 10-month-old infant with intussusception had multi-organ failure and died 4 weeks after admission[21].Compared to adults[35], the spread of SARS-CoV-2 yield a much better prognosis in pediatric patients, similar to SARS[7]and Middle East Respiratory Syndrome (MERS)[8]. 75.1% cases were discharged, the discharge rate ought to be higher actually since many children were still in hospital before the submission of the papers. The reasons why children experience a milder COVID-19 disease remain elusive. One possible explanation is that the response of children to SARS-CoV-2 is fundamentally different from that of adults, as demonstrated in earlier reports[30], the frequency of lymphopenia found in adults suggests that SARS-CoV-2 might act on lymphocytes, which is rare in children. Prior exposure to other respiratory virus may exert an influence, making children's immune systems more resilient[26]. Another potential theory is related to differences in the expression of ACE 2 receptor which was thought to be the cell-entry receptor for SARS-CoV-2[33,36].Besides, some researchers proposed that the mild disease in children may be associated with trained immunity, which refers to the use of certain vaccines such as Bacille de Calmette Guerin (BCG). BCG has been proved to provide nonspecific protection of mice against influenza virus infection probably by the induction of trained immunity[39]. In addition, children suffered from fewer comorbidities than adults. Accordingly, further studies in fields of immunology, anatomy and virology are required to ravel out this puzzle.

With massive public health interventions implemented actively and effectively, the spread of SARS-CoV-2 seems to have been under control in several countries. On 18 April 2020, there were only 16 newly confirmed cases across mainland China, nine of which were imported[39]. At present, while some countries are considering enhance control measures, China is planning to lift restrictions, work resumes and school starts are on agenda. Nevertheless, concerns have been proposed that a second wave of cases might occur in light of the absence of herd immunity against COVID-19, escalating case importation or residual infected seeds and resumption of economic activities.[40,41]It's plausible to suggest whether children have to get away from school again to mitigate the revival transmission. School closures can affect the spread of virus during a pandemic through reducing transmission and new cases, while long periods of social distancing interventions in school may put students in a disadvantaged situation. Recently, some scholars are questioning the benefits brought by closing schools. On the one hand, school closures are based on empirical evidence and assumptions from influenza outbreaks, it's hard to say such measures are also effective in coronavirus outbreaks like SARS, MERS and especially COVID-19, for which transmission dynamics appear to be different.[42] A systemic review[42] concluded that school closures in SARS did not contribute to the control of the epidemic and its effectiveness in COVID-19 would be less than other social distancing interventions, with only 2-4% of death prevention. Meanwhile, less comprehensive and deliberate plan can result in a completely converse consequence. Jude Bayham and Eli P Fenichel[43] estimated that school closures could lead to mortality rate increased by 0.35% and a greater number of deaths than they prevent when the health-care workforce declines by 15.0% due to unintended childcare obligations. (Table 4 shows alternative closure strategies in five countries). On the other hand, prolonged school dismissals can be detrimental to children's physical and mental health.[44,45] Out of school means a totally altered lifestyle—for example，fewer physical activities, less interaction with peer groups and longer screen time. Besides, many schools are offering online courses, but this is not available to all, especially to children from low socioeconomic households, and they may be further disadvantaged by nutrition shortfalls. Moreover, with home confinement, communities lockdown and economic recession deepens, family conflicts are rising, children are more likely to be exposed to domestic violence and abuse. Consequently, it is imperative for the policy makers to weigh the benefits of school closure against its costs carefully and deliberately and provide alternative strategies to minimize the adverse impacts of the COVID-19 on children's well-being.

There are several limitations need to be acknowledged. Firstly, the number of included cases is relatively small, a few researches have reported larger simple size of pediatric patients, whereas sufficient data are unavailable. Secondly, most of articles in this meta-analysis are descriptive and retrospective with a low quality, they highlighted different aspects of the illness, consequently, high heterogeneity was inevitable. Thirdly, all of the studies included are derived from China, many reports from countries outside China like US, Italy, where the pandemic is progressing with a sharp increasing number at present, provide individual cases or only crude epidemiological data, which didn't meet our inclusion criteria. In addition, we have intended to conduct a subgroup analysis based on age stratification and severity of the disease, while enough information was unavailable. Therefore, the findings of this meta-analysis still need to be updated by more relevant studies with more strict design and larger sample size.

Conclusions

In conclusion, our study highlights the epidemiology, clinical characteristics of COVID-19 in pediatric patients. This quantitative analysis provides evidence-based knowledge for the diagnosis and management in pediatric patients in the ongoing pandemic. Children are also susceptible to SARS-CoV-2. Compared to adults, children experience a milder clinical course. The most frequent symptoms were fever and cough, no symptoms were also quite common. Children with no or mild symptoms should be virologic-screened and isolated from immunocompromised populations at once when a family member is diagnosed with COVID-19 to prevent child-driven transmission. Vigilant attention should be paid to children who have underlying disease. A group of children were absent from CT abnormalities, CT scans should not be overemphasized to avoid excessive radiation exposure. Public health officials should attach importance to additional childcare programs to protect the well-being of children in this pandemic context.

Abbreviations

2019-nCoV: 2019 novel coronavirus

ACE2: angiotensin-converting enzyme 2

ALT: alanine aminotransferase

AST: aspartate aminotransferase

BCG: Bacille de Calmette Guerin

COVID-19: Coronavirus Disease 2019

CRP: C-Reactive Protein

CT: computed tomography

GGO: ground-glass opacity

IHE: Institute of Health Economics

L: lymphocyte counts

MERS: Middle East Respiratory Syndrome

MERS-CoV: Middle East Respiratory Syndrome-coronavirus

SARS: severe acute respiratory syndrome

SARS-COV: severe acute respiratory syndrome coronavirus

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

WBC: white blood cell counts

WHO: World Health Organization

Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

Availability of data and materials: Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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Authors' contributions: YS generated the idea, designed the study and participated in the whole process of research. CL and LL conducted literature screening and data extraction, YH was responsible for data analysis and interpretation. CL, YH and LL wrote this manuscript collaboratively, FL and YS contributed to the final revision of the paper. All authors read and approved the final manuscript.

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Tables

Table 1. Results of Meta-analysis on 361 children with COVID-19

Characteristics	Events/ Total	N of studies	Mean(y-old) /Pooled incidence (%)	95% CI	I^2	*P*- value	Publication bias (p-value)
Demographic							
Age	361/361	14	5.5	3.44-7.65			
Male	199/361	14	55.8	50.1-61.4	19%	0.25	0.4046
Epidemiology							
Exposure to epidemic area	212/327	13	33.7	2.9-73.5	97%	<0.01	0.0147
Family cluster	255/317	11	83.8	70.8-94.0	74%	<0.01	0.9747
Contacted with confirmed or suspected cases	54/325	13	24.2	5.0-49.4	92%	<0.01	0.0735
Unclear	32/361	14	3.2	0.0-11.9	77%	<0.01	0.9076
Clinical manifestations							
Asymptomatic	67/318	12	23.4	11.2-37.7	73%	<0.01	0.2137
Fever	176/355	14	57.2	43.1-70.8	73%	<0.01	0.241
Cough	161/355	14	42.7	30.4-55.5	67%	<0.01	0.6794
Pharyngeal erythema	88/361	13	4.2	0.0-18.7	90%	<0.01	0.0363
Diarrhea	24/316	12	3.4	1.0-6.7	0%	0.56	0.4158
Sore throat	15/352	13	3.6	0.0-11.8	72%	<0.01	0.01148
Vomit	22/316	13	2.8	0.7-5.9	25%	0.20	0.7396

Characteristics	Events/ Total	N of studies	Mean(y-old) /Pooled incidence (%)	95% CI	I^2	*P*- value	Publication bias (p-value)
Rhinorrhea	22/352	13	1.8	0.2-4.4	45%	0.04	0.425
Tachypnea/dyspnea	54/352	13	1.8	0.0-10.2	79%	<0.01	0.02327
Fatigue/myalgia	19/352	13	1.5	0.1-3.9	4%	0.41	0.5585
Expectoration	15/352	13	1.5	0.0-8.2	71%	<0.01	0.1136
Stuffy nose	17/352	13	0.9	0.0-4.6	35%	0.10	0.6263
Laboratory findings							
WBC decreased	77/327	13	17.3	9.2-26.8	50%	0.02	0.3354
WBC increased	11/120	11	4.9	0.8-11.1	10%	0.35	0.4624
L decreased	31/322	12	9.7	0.6-24.3	84%	<0.01	0.1609
L increased	44/149	11	25.8	10.5-44.1	74%	<0.01	0.9364
CRP increased	72/358	13	18.3	8.5-30.2	74%	<0.01	0.6414
ALT increased	30/279	9	8.2	4.7-12.4	0%	0.57	0.8605
AST increased	40/278	9	15.1	3.9-30.3	78%	<0.01	0.4548
CT imaging							
Normal	84/308	12	32.3	16.3-50.3	80%	<0.01	0.2071
GGO	101/329	12	28.2	15.8-42.0	70%	<0.01	0.4431

Characteristics	Events/ Total	N of studies	Mean(y-old) /Pooled incidence (%)	95% CI	I^2	*P*- value	Publication bias (p-value)
Unilateral compromised	63/258	8	29.2	15.4-44.8	61%	0.01	-
Bilateral compromised	44/258	8	17.5	4.4-34.9	74%	<0.01	-
Therapy							
Interferon	148/177	10	78.7	52.6-97.1	91%	<0.01	0.1378
Antiviral agents	97/177	10	46.8	23.6-70.7	88%	<0.01	0.3747
Antibiotic	50/168	9	27.9	3.2-61.6	94%	<0.01	-
Corticosteroid	9/183	11	1.2	0.0-7.7	60%	<0.01	0.3779
Immunoglobin	8/177	10	2.5	0.0-10.4	65%	<0.01	0.04036
Outcome							
Discharged	262/320	11	75.1	57.3-89.8	85%	<0.01	0.1203
ICU admission	4/361	14	0	0.0-0.1	0	0.97	0.119
Death	1/361	14	0	0.0-0.1	0	1	0.000

Note: WBC: white blood cell counts, L: lymphocyte counts, CT: computed tomography, GGO: ground-glass opacity; ICU: intensive care unit.

If the observed index wasn’t reported in a research, 0 cases were calculated as occurred.

Exposure to epidemic area referred to children who resided in Wuhan or travelled to Wuhan.

Contacted with confirmed or suspected cases: cases here didn’t include family members.

Table 2 Subgroup analysis on the characteristics of children with COVID-19.

Characteristics	Wuhan			Outside Wuhan		
	R (95%CI)	I2	p-value	R (95%CI)	I2	p-value
Epidemiology						
Exposure to epidemic area	71.5% (0.019-1.000)	94%	<0.01	22.2% (0.069-0.415)	78%	<0.01
Family cluster	76.6% (0.699-0.827)	NA	NA	84.2% (0.675-0.964)	74%	<0.01
Contacted history	21.4% (0.000-0.881)	92%	<0.01	25.7% (0.057-0.516)	87%	<0.01
Unclear	4.6% (0.011-0.094)	0%	0.66	2.7% (0.000-0.151)	82%	<0.01
Clinical manifestations						
Asymptomatic	10.8% (0.056-0.169)	0%	0.43	32.4% (0.149-0.523)	74%	<0.01
Fever	83.8% (0.270-1.000)	89%	<0.01	52.4% (0.372,0.674)	64%	<0.01
Cough	75.3% (0.319-1.00)	80%	<0.01	35.4% (0.223-0.493)	57%	<0.01
Pharyngeal erythema	42.4% (0.000-0.805)	75%	0.02	0% (0.000-0.018)	0%	0.77
Diarrhea	4% (0.008-0.087)	0%	0.82	2.6% (0.000-0.080)	11%	0.34
Sore throat	0% (0.000-0.000)	0%	0.54	6.3% (0.005-0.158)	57%	0.01
Vomit	16% (0.000-0.609)	82%	<0.01	2.2% (0.000-0.068)	0%	0.93
Rhinorrhea	3.5% (0.005-0.080)	0%	0.61	0.2% (0.000-0.087)	50%	0.03
Tachypnea/dyspnea	24.9% (0.179-0.324)	6%	0.34	0.1% (0.000-0.022)	0%	0.83
Fatigue/myalgia	3.4% (0.005-0.079)	0%	0.42	0.2% (0.000-0.026)	0%	0.62
Expectoration	0% (0.000-0.000)	0%	0.54	3.4% (0.000-0.111)	53%	0.02
Stuffy nose	1.1% (0.000-0045)	0%	0.98	0.13% (0.000-0.075)	50%	0.03
Laboratory findings						
WBC decreased	24.9% (0.179-0.324)	48%	0.15	14.6% (0.084-0.219)	44%	0.07
WBC increased	0% (0.000-0.185)	0%	0.9	5.9% (0.012-0.126)	24%	0.23
L decreased	28.8% (0.000-0.987)	94%	<0.01	6.1% (0.000-0.194)	72%	<0.01
L increased	15.7% (0.000-0.803)	73%	0.05	27.9% (0.112-0.477)	77%	<0.01
CRP increased	38.7% (0.031-0.821)	81%	<0.01	14.6% (0.041-0.286)	73%	<0.01
ALT increased	9.9% (0.052-0.155)	0%	0.57	5.8% (0.012-0.123)	0%	0.49
AST increased	33.4% (0.000-0.860)	86%	<0.01	11.7% (0.003-0.316)	77%	<0.01
CT imaging						
Normal	12.0% (0.066-0.185)	0%	0.71	37.8% (0.187-0.587)	74%	<0.01
GGO	30% (0.226-0.378)	0%	0.79	29.3% (0.116-0.502)	77%	<0.01
Unilateral compromised	21.3% (0.000-0.580)	70%	0.04	34.4% (0.228-0.467)	0%	0.57
Bilateral compromised	22.4% (0.000-0.694)	81%	<0.01	16.1% (0.01-0.397)	68%	0.01
Therapy						

Characteristics	Wuhan			Outside Wuhan		
	R (95%CI)	I2	p-value	R (95%CI)	I2	p-value
Interferon	0% (0.000-0.268)	NA	NA	86.3% (0.643-0.995)	89%	<0.107
Antiviral agents	1. (0.732-1.000)	NA	NA	40.4% (0.179-0.649)	88%	<0.01
Antibiotic	1.0 (0.732-1.000)	NA	NA	19.4% (0.002-0.517)	94%	<0.01
Corticosteroid	66.7% (0.236,0.987)	NA	NA	0.1% (0.000-0.023)	16%	0.30
Immunoglobin	16.7% (0.000-0.586)	NA	NA	1.9% (0.000-0.096)	66%	<0.01
Outcome						
Discharged	90.3% (0.847-0.949)	0%	0.38	67.7% (0.421-0.893)	87%	<0.01
ICU admission	0 (0.000-0.001)	31%	0.24	0 (0.000-0.001)	0	1
Death	0 (0.000-0.000)	0	0.75	0 (0.000-0.001)	0	1

Note: WBC: white blood cell counts, L: lymphocyte counts, CT: computed tomography, CRP: C-Reactive Protein, ALT: alanine aminotransferase, AST: aspartate aminotransferase, GGO: ground-glass opacity; ICU: intensive care unit. NA: not applicable, only one study in the subgroup.

Table 3 Comparison of incidence of clinical characteristics between children with COVID-19, general population with COVID-19, children with SARS and children with H1N1 influenza

	Children with COVID-19	General population with COVID-19[35]	Children with SARS[28]	Children with H1N1 influenza[38]
Age(y-old)	5.5(3.44-7.65)	51.97 (46.06-57.89)	12.2	5
Male	55.8% (50.1-61.4)	55.9% (51.6-60.1)	20 (45.5%)	81(54.7%)
Asymptomatic	23.4% (11.2-37.7)	-	0	<6.1%
Fever	57.2% (43.1-70.8)	88.7% (84.5-92.9)	100%	93.9%
Cough	42.7% (30.4-55.5)	57.6% (40.8-74.4)	63.6%	88.5%
Sore throat	3.6% (0.0-11.8)	11.0% (2.8-19.2)	13.6%	19.6%
Diarrhea	3.4% (1.0-6.7)	6.1% (2.4-9.7)	20.5%	6.1%
Tachypnea/Dyspnea	1.8% (0.0-10.2)	45.6% (10.9-80.4)	9.1%	-
Leucopenia	17.3% (9.2-26.8)	18.7% (8.5-28.8)	34.1%	16.9%
Lymphopenia	9.7% (0.6-24.3)	43.1% (18.9-67.3)	77.3%	34.5%
Ground-glass opacity	28.2% (15.8-42.0)	68.5% (51.8-85.2)	-	-
Comorbidities	3% (11/361)	36.8% (24.7-48.9)	11.4%	14.9%
ICU admission	0 (0.0-0.1)	20.3% (10.0–30.6%)	11.4%	19.6%
Death	0 (0.0-0.0)	13.9% (6.2-21.5)	0	2%
N	361	2874	44	148

Note: The results of characteristics of COVID-19 in children and general population were presented with pooled incidence and 95% CI, characteristics of "comorbidities" in children with COVID-19 were presented with incidence(n/N) due to insufficient data.

No meta-analysis results of characteristics of children with SARS and H1N1 influenza were found, incidence(n/N) was presented as a substitute.

"-": not available.

Table 4 School strategies in different countries in response to COVID-19.

UK[46]	Localized closures have been implemented since 28 Feb. All educational settings are closed to everyone except the children of critical workers and vulnerable children* since 20 March and will stay closed until further notice.
US[47]	School-based strategies (e.g., short-term or extended dismissals, event cancellations, social distancing measures) are adopted locally in collaboration with local health officials based on level of community transmission of COVID-19 and presence of COVID-19 cases within the school, combined with open child care programs# like private child care centers for essential service providers. The majority of States have mandated school closures since 10 April, including until the end of the academic year in June. Some States, however, have recommended but not mandated the school closures.
Italy[48]	Some schools in the heaviest hit area have been shut down since 24 Feb. Mandatory closure of all schools and universities across the country were implemented from 10 March and will remain shut until 3 May.
France[49]	All nurseries, schools, colleges, high schools and universities are closed from 16 March and will gradually reopen from 11 May with the exception of universities, which will not reopen until the summer. Childcare services are established for staff who are essential to the management of the health crisis.
German[50]	Temporarily closing kindergartens and schools and postponing restart of colleges were implemented in state levels since mid-March are to be extended until 3 May 2020. Schools remain open for those who are willing to continue classes in some states. Daycare centres are available and will continue and will be extended to other occupational and needed groups.

Note: *Vulnerable children include children who are supported by social care, those with safeguarding and welfare needs, including child in need plans, on child protection plans, ‘looked after’ children, young carers, disabled children and those with education, health and care (EHC) plans.

#Other open child care programs are home-based child care, pre-kindergarten programs, Head Start and Early Head Start programs, temporary child care centers, and child care centers that partner with healthcare facilities to support healthcare workers who need child care.

Additional File Legend

Additional File 1.pdf SEARCH STRATEGY: This file describes the search strategy of this meta-analysis.

Additional File 2.doc Supplementary Table 1. Characteristics of the included studies

Additional File 3.doc Supplementary Table 3. The distribution features of 115 children with fever in 7 researches.

Figures

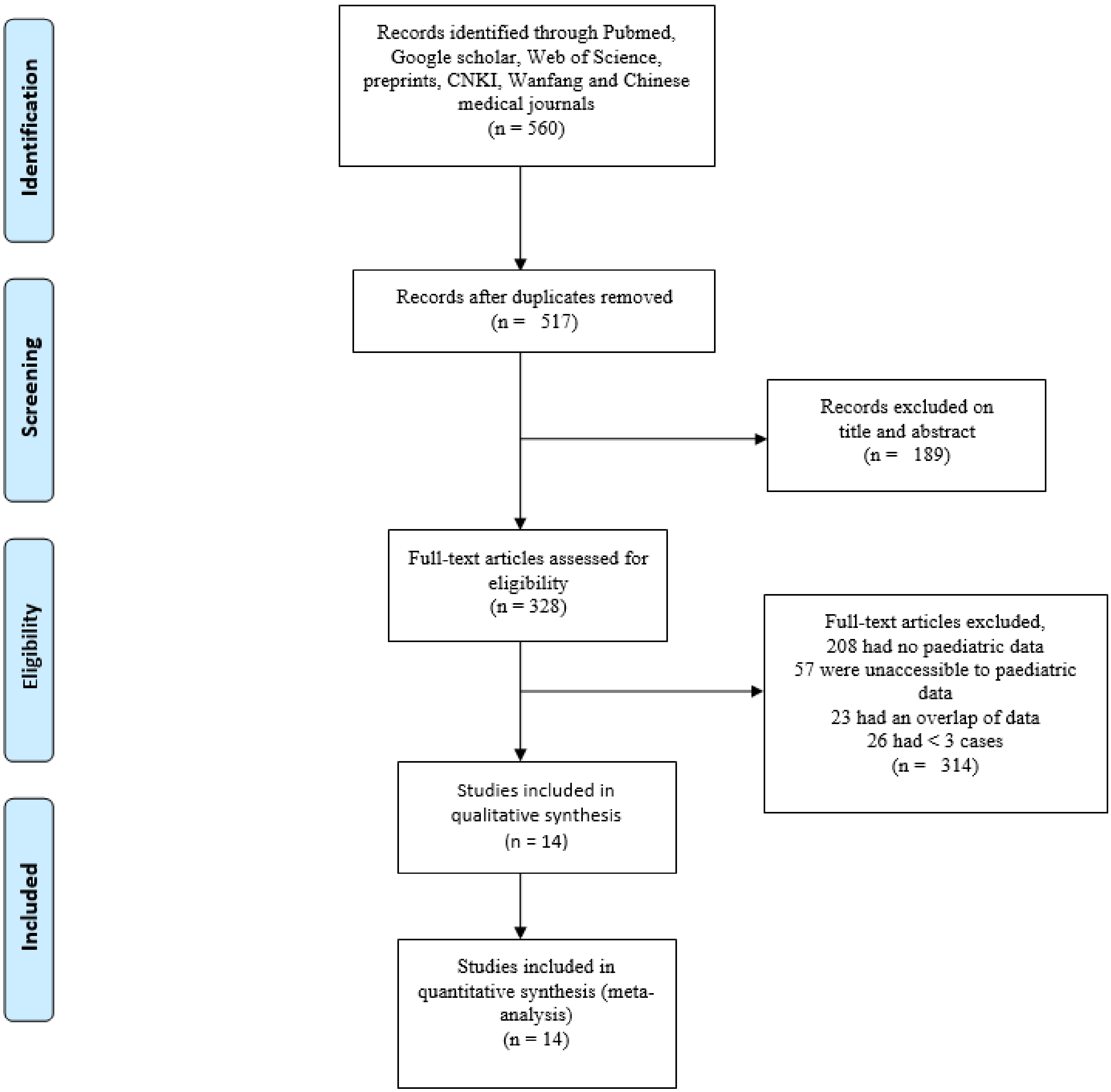

Figure 1

PRISMA 2009 flow diagram of the included studies

Supplementary Files

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- AdditionalFile1.pdf
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