Baojia Zheng   ORCID iD: 0000-0002-9797-7867

An increasing public health burden arising from children infected with SARS-CoV2: a systematic review and meta-analysis

Baojia Zheng, MD[1], Hui Wang, PhD[1*], and Cuixiang Yu, MD[2*]

1. Department of Microbiology and Immunology, School of Basic Medical Sciences, Jinan University, Guangzhou 510632, China.

2. Nursing Department of the Fifth Affiliated Hospital of Sun Yat-Sen University, Zhuhai 519000, China.

Conflict of interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

* Correspondence to: Cuixiang Yu, MD. Nursing Department of the Fifth Affiliated Hospital of Sun Yat-Sen University, Zhuhai 519000, China. E-mail: yucx@mail.sysu.edu.cn. Hui Wang, PhD. Department of Microbiology and

Immunology, School of Basic Medical Sciences, Jinan University, Guangzhou

510632, China. E-mail: twanghzzm@jnu.edu.cn;

Summary. Background: Severe acute respiratory syndrome coronavirus 2 (SARS-

CoV2) is spreading all over the world and poses a great threat to humans. This

study aimed to systematically review the current situation and public health

burden associated with children infected with SARS-CoV2. Methods: We

searched 4 electronic databases without language limitations. The pooled

proportion or odds ratio (OR) and 95% CI confidence interval (CI) were

calculated for each analysis to explore the prevalence of asymptomatic infection

and coinfection, as well as to assess the sex of SARS-CoV-2-infected children.

Results: We obtained data from 14 eligible studies with 410 patients for the meta-

analysis. The pooled proportion of asymptomatic infection was 40.45% (95%CI:

24.04-56.85), while coinfection was 10.14% (95%CI: 3.97-16.30), of which

Mycoplasma pneumonia (50%, 95%CI: 28.24-71.76) and influenza virus or

parainfluenza virus (22.76%, 95%CI: 4.76-40.77) were the most common

pathogens. Both male and female children were susceptible to SARS-CoV2

infection. And the pooled proportion of family clustering infection was 83.63%

(95%CI: 77.54-89.72). Conclusion: A high proportion of asymptomatic infections

occurs in children infected with SARS-CoV2, who are also susceptible to

coinfection regardless of sex. These data affirm the increasing public health

burden arising from infected children regarding the causation of asymptomatic infection or misdiagnosis and as a significant contributor to virus spread. The public should pay more attention to children during epidemics and conduct multimethod detection to further effectively identify infected children and control the source of infection.

Keywords: SARS-CoV2; children; asymptomatic infection; coinfection

INTRODUCTION

The city of Wuhan in China became the focus of global attention due to an outbreak of pneumonia of unknown etiology in late December 2019 that was epidemiologically linked to a seafood wholesale market, where the sale of live animals also occurred. The pathogen was promptly identified as a novel coronavirus, which is currently designated the 2019 novel coronavirus then officially named SARS-CoV2.[1,2] Although the estimated mortality rate of SARS-CoV2 is approximately 6%,[3] which is lower than that of severe acute respiratory syndrome (SARS) (9.6%), its transmission rate is similar to that of SARS (3%), leading to an increase in mortality. At present, there are no effective medicines, and vaccines against SARS-CoV2 are still in the trial stage. As a result of human-to-human transmission, SARS-CoV2 spread very fast and caused a formidable outbreak in many cities in China and globally. As of April 13th 2020, a total of

1,773,084 cases were confirmed, with 111,562 deaths.[4] The primary reported cases were mainly middle-aged and elderly patients, with fewer cases among children. However, both adults and children are susceptible to infection with this virus.

The first confirmed pediatric case of SARS-CoV2 infection was reported in Shenzhen, China on January 20.[5] This first pediatric case was a ten-year-old asymptomatic child who had a CT scan to determine ground-glassopacity in the lungs after contact with confirmed cases in the family. According to published statistics, there were 44,672 laboratory confirmed cases throughout China as of February 11, of which only 965 (2%) were younger than 19 years.[6] However, the number of infected children is increasing significantly with the peak of the epidemic, and more tests for pathogens are being carried out in communities. Additionally, some children have asymptomatic infections, facilitating virus evasion and diffusion, and this has gradually attracted more public attention.

The outbreak of SARS-CoV2 is catastrophic. There have been many studies on SARS-CoV2 infection in adults, bringing surveillance precautions into much public awareness, whereas studies on infected children are still relatively scarce due to fewer cases or difficulty in conducting full-scale detection. Therefore, it is valuable to perform a comprehensive analysis of the different published SARS-CoV2 pediatric cases recording clinical and epidemiological features, merging and

contrasting results across multiple studies and identifying the current status and public health burden of childhood infection through pooled estimates.

Thus, the present study was undertaken to evaluate the current status of SARS-CoV2 infection in children by performing a meta-analysis to raise awareness and concern about the growing health burden on the public arising from infected children. The findings provide some helpful information for clinicians and the public health sector for developing tracking policies and for preparing intensive strategies against SARS-CoV2 threats.

METHODS

Search strategy

The present review adhered to the Systematic Review and Meta-Analysis's Preferred Reporting Project (PRISMA) statement.[7] In the second week of April 2020, a search was conducted in 4 electronic databases, including PubMed, EMBASE, Web of Science and the Chinese databases China National Knowledge Infrastructure (CNKI), without language limitations. The following search terms (MeSH) were used in "All fields" to identify relevant published articles:

1. "SARS-CoV-2" OR "SARS2" OR "COVID19" OR "COVID-19 pandemic" OR "COVID-19 virus infection" OR "coronavirus disease-19" OR "2019 novel coronavirus infection" OR "2019-nCoV infection" OR "coronavirus

disease 2019" OR "2019-nCoV disease" OR "COVID-19 virus disease" OR

"2019-nCoV" OR "2019 novel coronavirus disease"

2. "child" OR "children" OR "infant" OR "infants"

3. 1 AND 2

Study selection

The published studies were retrieved with no restrictions of language. The

included studies were required to meet the following eligibility criteria: (1) studies

focused on pediatric patients infected with SARS-CoV2 whose nucleic acid test or

CT scan were positive; (2) retrospective observational studies, case reports or

research articles describing the epidemiological, demographic, and clinical

features of confirmed cases, which allowed stratification; and (3) a minimum size

of patients (n>3) to conduct a meta-analysis. Reports published as review articles,

editorials, press, managements or guidance were excluded. We also excluded

repetitive cases by searching the hospitals where the data were collected because

they contained the same information. All titles were independently screened by

two authors in accordance with the search strategy mentioned above (BJ and

HW). A total of 747 records were acquired from the 4 electronic databases. After

removing duplicate records, two authors independently performed an abstract

review of potentially relevant records to assess their eligibility based on the

inclusion/exclusion criteria. Differences were resolved through discussion until a consensus was reached. Then, a full text search of the remaining 27 records was conducted, and 13 records were eliminated due to case repetition and difficulty in stratifying (Fig. 1).

Data extraction and analysis

We stratified the information to evaluate the current status of pediatric infection by asymptomatic infection, sex, coinfection and family clustering. Meta-analysis of proportions was also calculated for asymptomatic infection, coinfection and family clustering in children. Pooled proportions were calculated by single-arm meta-analysis. As sex was considered a dichotomous variable, we used the binomial distribution to calculate odds ratio (OR) and 95% confidence interval (CI) for the included studies. A pooled OR not equal to 1 indicated a difference between subjects. Heterogeneity was assessed with the I^2 statistics for each analysis, with the significance level set at $P<0.05$.[8] If significant heterogeneity between studies was detected, a random effects model was used to combine OR estimates, or the studies were divided into specific subgroups based on different factors.[9] Subgroup analysis was performed based on clinical symptoms and coinfecting pathogens. A forest plot was used to illustrate the distribution of the outcome and effect size obtained from each published study. All statistical analyses were conducted using STATA 12.0 (STATA Corp, College Station, TX).

RESULTS

Characteristics of the included studies

The flow diagram of the search and study selection process was shown in Fig. 1. A total of 14 eligible studies[10-23] with 410 patients (Table 1) were included. Of the 14 selected studies, 1 was from Spain and 13 from China, two of which were from the same hospital (Wuhan Children's Hospital); however, they were included because the cases were collected at different times. There were 7 retrospective studies, 6 case reports and 1 research study. All the included studies were published from January to April 2020, after the initial outbreak of SARS-CoV2 occurred at the end of December 2019. The numbers of cases in the included studies ranged from 5 to 115 cases, with 232 males and 178 females. The overall average age (±standard error (SE)) of the pediatric patients was 5.27±2.4 years (Table 1).

The manifestations of SARS-CoV2 infection in children

After infection, the children might appear to be asymptomatic, though with a positive result using nucleic acid diagnosis with a nasopharyngeal or rectal swab. The estimated proportion of asymptomatic patients ranged from 10% to 80%, with the pooled proportion reaching 40.45% (95%CI: 24.04-56.85, Fig. 1a), with significant heterogeneity. Subgroup analysis of the clinical manifestations in the

symptomatic children is shown in Fig. 2b, revealing that the most prevalent

clinical symptoms were fever (48.70%, 95%CI: 36.77-60.63) and dry cough

(35.09%, 95%CI: 23.62-46.57), followed by sore throat (12.24%, 95%CI: 4.02-

20.45), diarrhea or/and vomiting(11.30%, 95%CI: 4.82-17.79). Heterogeneity

among the estimated clinical symptoms was significant, with I^2 values ranging

from 50.40% to 80.9%.We also analyzed the risk of sex in the pediatric patients,

showing that males did not tend to be more susceptible to infection than females,

with a pooled OR among males compared with females of 1.15 for the line

crossing the null hypothesis (95%CI: 0.63-2.08, Fig. 3); the I^2 value was 59.8%.

Coinfection situation in SARS-CoV2**-infected children**

There were 4 articles demonstrated the coinfection situation of children infected

with SARS-CoV2. As shown in Fig. 4a, the proportion of coinfection ranged from

4.88% to 24%, with a pooled estimated of 10.14% (95%CI: 3.97-16.30, Fig. 4a).

Furthermore, subgroup analysis of types of coinfected diseases showed the pooled

proportion of *M. pneumonia* coinfection to be as high as 50% (95%CI:28.24-

71.76, Fig. 4b), followed by influenza virus or parainfluenza virus

(22.76%,95%CI: 4.76-40.77). The heterogeneity in the estimated coinfected

pathogen was insignificant, with an I^2 value of 0.

The source of infection in SARS-CoV2-infected children

As reported, in adults the routes of infection were diverse, however, the presentation of symptoms in most of the infected children started after a confirmed diagnosis in family members. As shown in Fig. 5, the proportion of family clustering in children highly ranged from 64% to 91.30%, with a pooled estimated of 83.63% (95%CI: 77.54-89.72, Fig. 5).

DISCUSSION

SARS-CoV2 is a newly discovered coronavirus with a genetic structure that is 82% similar to SARS-CoV.[24] This origin of this new coronavirus is wild animals, and it can be transmitted through droplets or contact or through the fecal-oral route, with high incidence and rapid spread, posing a huge threat to global public health.[25]

Children are also susceptible to viral infection because of their immature immune system. Although the number of infected cases in children is comparably fewer than that in adults, there is no doubt that the number of confirmed pediatric cases is showing a tendency to increase significantly as the epidemic continues. However, the current status and characteristics of pediatric infections have not been fully described due to the small number of scattered cases. Hence, we collected qualified reported cases of children for systematic review and meta-

analysis, aiming to evaluate the features and situation of the children infected with SARS-CoV2 and their possibly increasing health burden on the public.

This review included 14 studies encompassing 410 pediatric cases. In all the included articles, there is no record of the prognosis of pediatric patients, but according to the statistics, the prevalence of infected children ranged from 1.2% to 5% in different countries, and children constituted less than 1% of all US hospitalisations. Additionally, the prevalence of severe and critical disease was 10.6% in children aged <1 at diagnosis, 1-5 years (7.3%), 6-10 years (4.2%), 11-15 years (4.1%) and 16-17 years (3.0%), indicating that children under one year old have a high incidence of severe illness.[26] We conducted a single-arm meta-analysis to analyze the prevalence of clinical symptoms in infected children. However, we found that the clinical manifestations of the infected children were not as typical as those of adults, which might include asymptomatic, fever and dry cough, or upper respiratory tract symptoms such as stuffy nose, runny nose and sore throat. Gastrointestinal symptoms such as abdominal discomfort, nausea, vomiting, abdominal pain, and diarrhea might also occur. Furthermore, gastrointestinal symptoms are the first manifestation in neonates.[27] These symptoms of SARS-COV2 are similar to SARS with the predominant and most consistent symptom is fever. Other symptoms include rhinitis, cough and diarrhea[28]. While children infected by Middle East Respiratory Syndrome

Coronavirus (MERS-CoV) with more typical symptoms, ranging from asymptomatic infection to severe respiratory distress leading to death.[29]

In our study, most cases were of preschool age, and the prevalence of asymptomatic cases highly reached 40%. Additionally, the most common clinical symptoms of children with manifestations were fever and dry cough, followed by sore throat and diarrhea or vomiting, but few children experienced symptoms of dyspnea and chest tightness, as adults do. Compared with adult cases, the condition of pediatric cases was mostly mild, which maybe related to the underdeveloped respiratory system. One study showed that SARS-CoV2 can utilize multiple homologous isoforms of angiotensin-converting enzyme II (ACE2) to effectively enter human respiratory tract cells.[30] The weak function of ACE2 receptors or their low expression in the underdeveloped respiratory system can limit viral invasion to some extent. Nonetheless, a concern is that many infected children were asymptomatic but positive for viral nucleic acid, and they might become the most dangerous group of virus transmission in the public. Du et al.[31] estimated that the basic reproduction number (R0) of SARS-CoV2 was 2.56. Adam Kucharski et al. [32] believed that R0 fluctuated between 1.5 and 4, suggesting that SARS-CoV2 has a strong ability to spread. Furthermore, the viral load of the upper respiratory tract in asymptomatic patients is roughly equivalent to that in patients with obvious pneumonia.[33] Collectively, as found from our

study, the proportion of asymptomatic children was surprisingly large, suggesting that infected children are an important source of virus spread leading to outbreaks and difficulty in control, as children are easily overlooked by the public due to their social status and stereotype.

Based on our findings, sex was not a risk factor associated with these SARS-CoV2-infected children because the pooled OR of males compared to females was close to 1 and crossed the invalid line, indicating that boys are not more susceptible than girls. As shown in Fig. 4, approximately 10% of confirmed pediatric cases had coinfections, and the most common coinfecting pathogens were *M. pneumonia* (50%) and influenza virus or parainfluenza virus (22%), according to our statistics. Moreover, we found some other coinfecting viruses, such as adenovirus, syncytial virus and Epstein-Barr virus, but statistics were missing due to the small number of cases or few hospitals conducted coinfection detection. We believed that this number would increase if attention had not been just focused on SARS-CoV2 detection and ignored the detection of other pathogens. It is unknown whether children with coinfection are more likely to be immunologically susceptible to coronavirus infection. Considering the early stages of the outbreak, if the contact history of suspicious child cases was unclear, along with the routine respiratory pathogen test being conducted and found to be positive, it was easy to overlook the detection of SARS-CoV2 nucleic acid,

resulting in misdiagnosis as ordinary bronchopneumonia and a large amount of viral transmission among the public. Additionally, whether coinfections with SARS-CoV2 result in sequelae and their effects on subsequent growth and public burden are still unknown.

It is worth noting that one of the included studies revealed real-time RT–PCR positivity using rectal swabs for eight of ten pediatric patients, which remained detectable well after nasopharyngeal swabs became negative,[22] suggesting that the gastrointestinal tract may shed virus and that fecal–oral transmission between children and adults is possible. Positive results of rectal swabs lasting for 13 days in one of the eight patients, a 12-year-old girl, suggests that the discharge standard of infected children cannot rely only on nasopharyngeal swabs; it needs to be combined with rectal swab detection and prolonged detection time.

Family cluster is one of the epidemic characteristics of SARS-CoV2. In our analysis, up to 80% of infected children come from family clustering infections, indicating close contact with the confirmed members in family is the key to a cluster of outbreaks. As reported, most cases of mortality involved children under 1 year old or newborns.[10] Interestingly, SARS-CoV2 was not detected in serum or throat swab by RT-PCR in any of the newborns of 6 mothers with confirmed SARS-CoV2. However, virus-specific antibodies were detected in neonatal blood sera samples.[34] One of the possible explanations is antibody-dependent

enhancement (ADE) of SARS-CoV2 because ADE can induce the immune response and elicit sustained inflammation, lymphopenia, and/or cytokine storms, one or all of which have been documented in severe cases and deaths. It has been also reported in the literature that the cytokine storm may be related to the severity of COVID-19.[36]

Our study had some limitations. We did not analyze the incubation period of children because it was difficult to stratify for meta-analysis due to different descriptions in some different studies. As of February 11, 2020, after analyzing 44,672 laboratory confirmed cases, a study reported that 965 cases were younger than 19. However, only 410 pediatric cases were enrolled in our study because we deleted some duplicate cases, which also resulted in a reduction in case number. Only four articles were selected for analyzing coinfection because it was not assessed or reported in the remaining studies. Most clinicians directly detected coronavirus and ignored other coinfections if they found suspicious symptoms early in the outbreak. It was estimated that the proportion of coinfection in children maybe increase once the implementation of multiple detection technologies. Even thought the number of published articles was limited, we would like to alert the public to coinfection in children based on our findings. Whether the coinfected virus will cause increased coronavirus virus virulence or facilitate mutation or severe unknown complications is still unclear.

CONCLUSIONS

In our study, we found that the proportion of asymptomatic infections in children was high; both males and females were susceptible to SARS-CoV2. Children may have coinfection, and the pathogens of coinfection were diverse; of which *M. pneumoniae* and influenza virus or parainfluenza virus were the main coinfecting pathogens, implying that early misdiagnosis or a single detection method would overlook the virus and facilitate rapid spread in the public. Overall, an increasing public health burden indeed arises from the infected children, and we cannot ignore this. Nucleic acid detection of both nasopharyngeal swabs and rectal swabs along with lung CT examination should be actively conducted for children with unknown contact history or in families with diagnosed cases. In addition, misdiagnosis at the early stage should be avoided, which is of great significance for controlling the epidemic.

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Figures

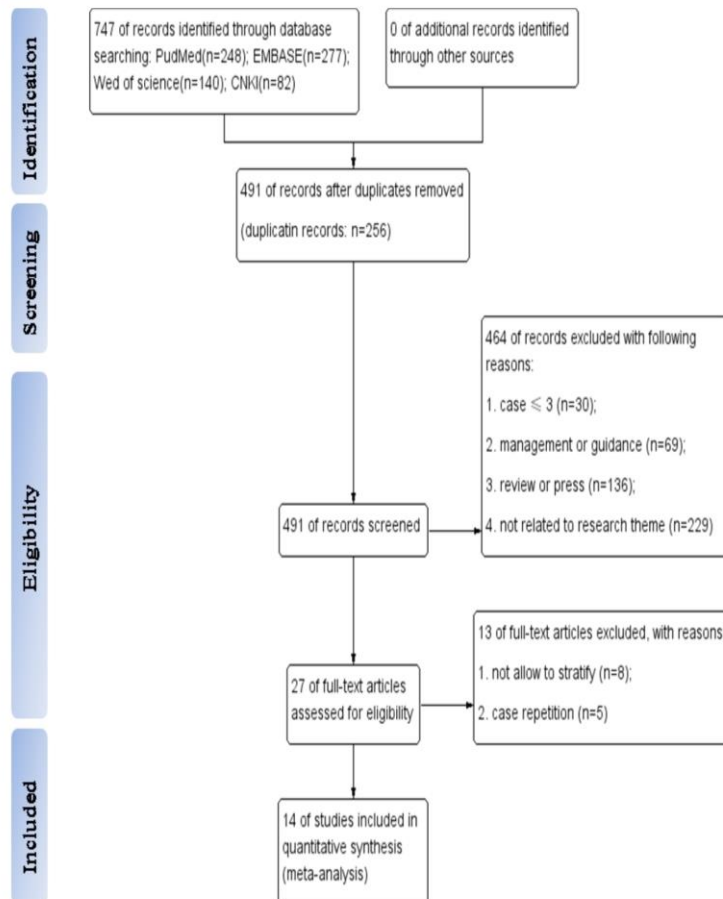Fig. 1. Flow diagram of study selection

Fig. 1. Flow diagram of study selection

Fig. 2. Estimated asymptomatic infection and clinical symptoms in children by SARS-CoV2. (a) Single-arm meta-analysis of the proportion of asymptomatic infection in enrolled cases. (b) Single-arm meta-analysis of the proportion of clinical symptoms in enrolled cases.
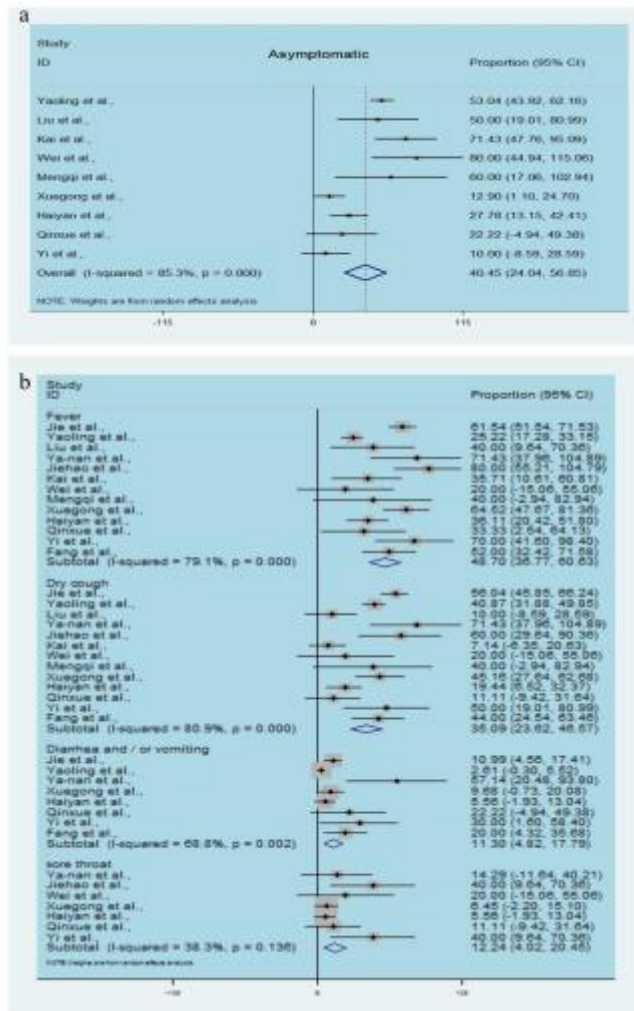
Fig. 3. Odds ratio (OR) of SARS-CoV2-infected children among male compared with female.
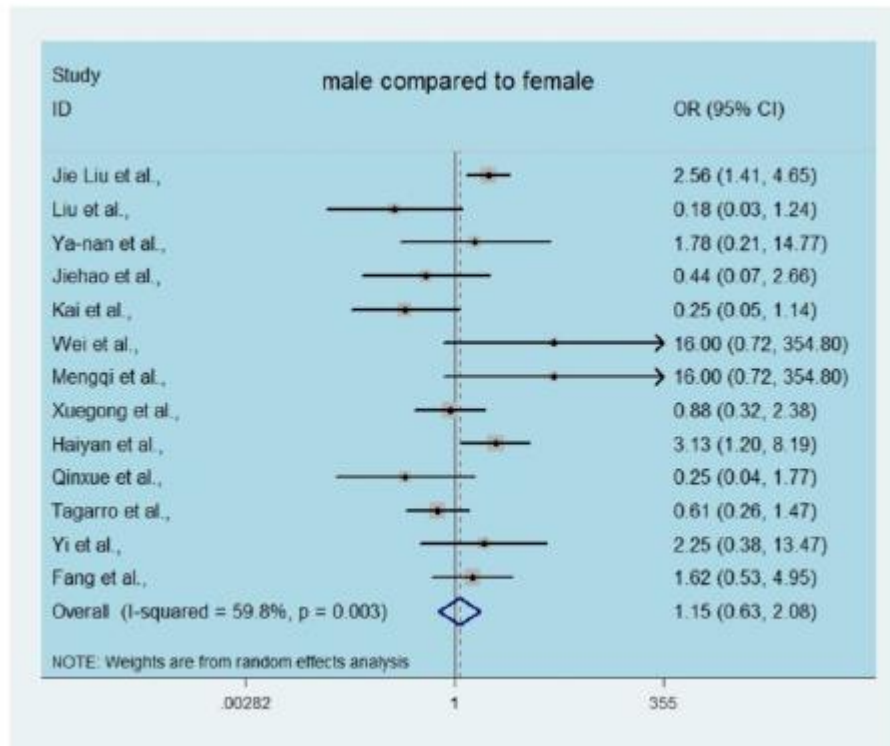
Fig. 4. Estimated coinfection and coinfected pathogens in children by SARS-CoV2. (a) Single-arm meta-analysis of the proportion of coinfection in enrolled cases. (b) Single-arm meta-analysis of the proportion of coinfected pathogens in enrolled cases.
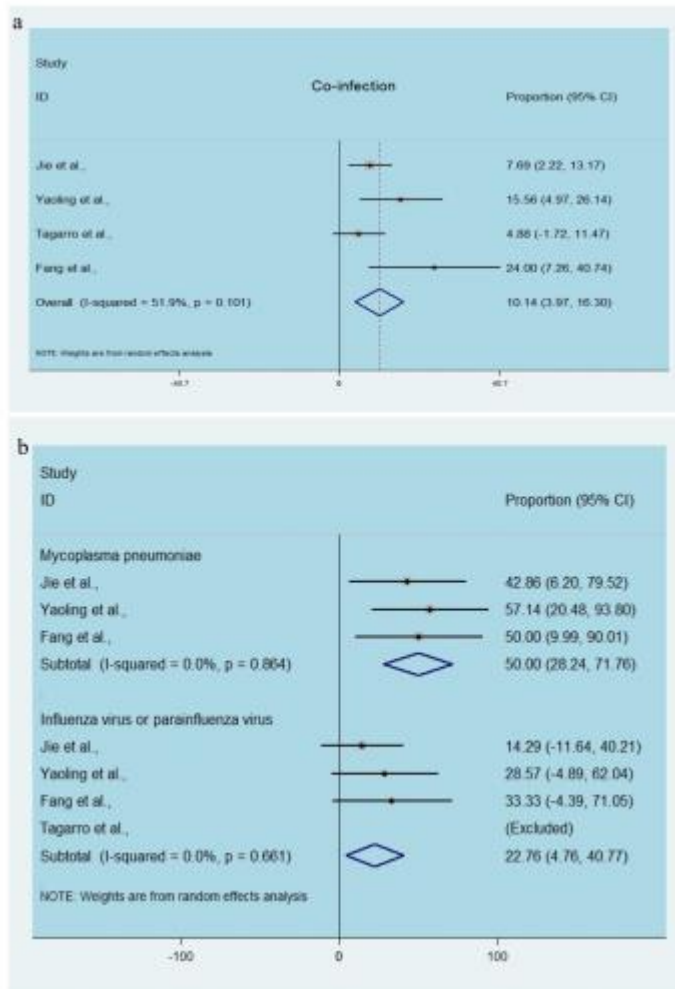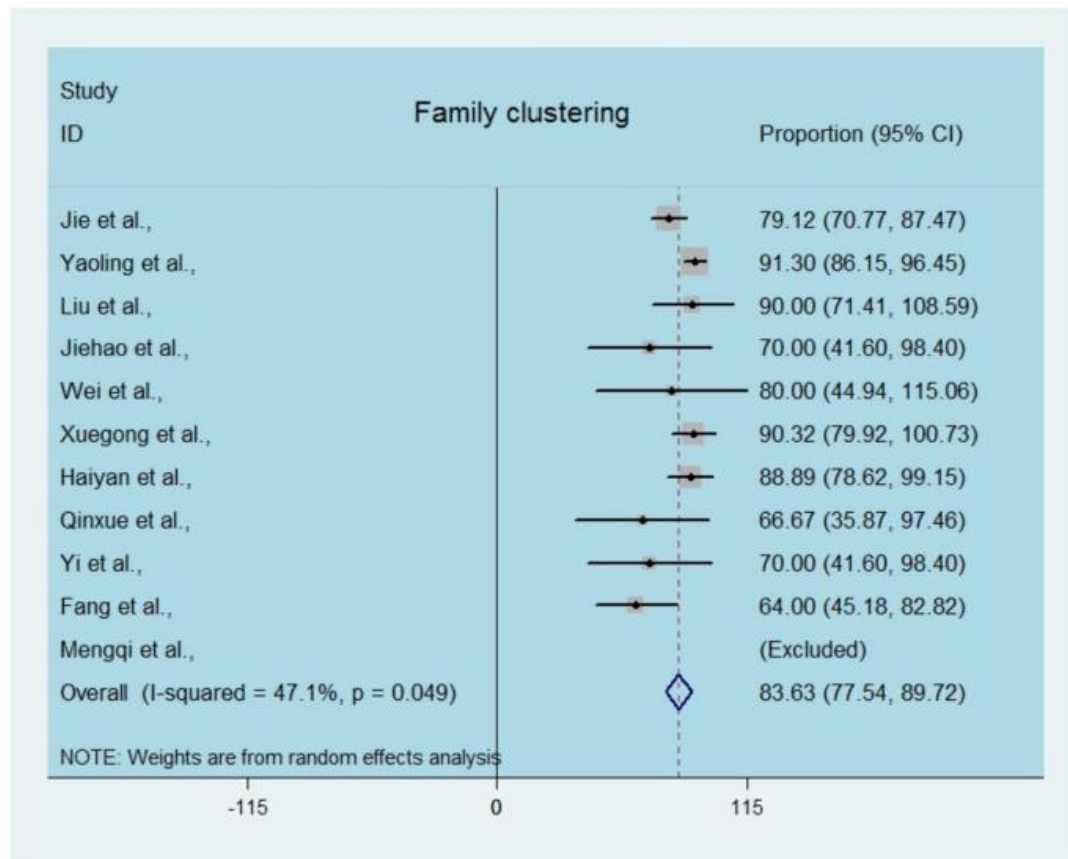
Fig. 5. Estimated family clustering infection in children by SARS-CoV2. Single-arm meta-analysis of the proportion of family cluster in enrolled cases.

Table

Table 1-Characteristics of the included studies.

Author	Country, city/province	Year/mouth	All	Male	Female	Age (Mean,year)	Study type
Jie et al.,[10]	China, Wuhan	2020/3	91	56	35	4	Retrospective study
Yaoling et al.,[11]	China, Wuhan	2020/4	115	73	42	-	Retrospective study

Liu et al.,[12]	China, Shandong	2020/3	10	3	7	5.1	Cases report
Ya-nan et al.,[13]	China, Xian	2020/2	7	4	3	1.3	Cases report
Jiehao et al.,[14]	China, Shanghai	2020/2	10	4	6	6.1	Cases report
Kai et al.,[15]	China, Shenzhen	2020/4	15	5	10	7	Retrospective study
Wei et al.,[16]	China, Zhuhai	2020/3	5	4	1	3.4	Cases report
Mengqi et al.,[17]	China, Chongqing	2020/2	5	4	1	6.6	Cases report
Xuegong et al.,[18]	China, Autonomous region	2020/4	31	15	16	7.1	Retrospective study
Haiyan et al.,[19]	China, Zhejiang	2020/3	36	23	13	8.3	Retrospective study
Qinxue et al.,[20]	China, Changshao	2020/3	9	3	6	7.5	Cases report
Tagarro et al.,[21]	Spain, Madrid	2020/3	41	18	23	1	Retrospective study
Yi et al.,[22]	China, Guangzhou	2020/3	10	6	4	8.1	Research study

| Fang et al.,[23] | China, Hubei | 2020/3 | 25 | 14 | 11 | 3 | Retrospective study |
| Total | | | 410 | 232 | 178 | 5.27±2.4 | |