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.

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Review

Epidemiology of COVID-19 infection in young children under five years: A systematic review and *meta*-analysis

Mejbah Uddin Bhuiyan [a,1,*], Eunice Stiboy [b,1], Md. Zakiul Hassan [c], Mei Chan [d], Md. Saiful Islam [c,e], Najmul Haider [f], Adam Jaffe [d,g], Nusrat Homaira [d,g]

[a] *Wesfarmers Centre of Vaccines and Infectious Diseases, Telethon Kids Institute, Western Australia, Australia*
[b] *School of Public Health, Faculty of Medicine and Health, The University of Sydney, New South Wales, Australia*
[c] *Program for Emerging Infections, Infectious Diseases Division, icddr,b, Bangladesh*
[d] *School of Women's and Children's Health, Faculty of Medicine, University of New South Wales, Sydney, New South Wales, Australia*
[e] *School of Public Health and Community Medicine, Faculty of Medicine, University of New South Wales, Sydney, New South Wales, Australia*
[f] *The Royal Veterinary College, University of London, Hatfield, Hertfordshire, AL9 7TA, UK*
[g] *Respiratory Department, Sydney Children's Hospital, Sydney, New South Wales, Australia*

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ABSTRACT

Introduction: Emerging evidence suggests young children are at greater risk of COVID-19 infection than initially predicted. However, a comprehensive understanding of epidemiology of COVID-19 infection in young children under five years, the most at-risk age-group for respiratory infections, remain unclear. We conducted a systematic review and *meta*-analysis of epidemiological and clinical characteristics of COVID-19 infection in children under five years.

Method: Following the Preferred Reporting Items for Systematic Reviews and Meta-analyses , we searched several electronic databases (Pubmed, EMBASE, Web of Science, and Scopus) with no language restriction for published epidemiological studies and case-reports reporting laboratory-confirmed COVID-19 infection in children under five years until June 4, 2020. We assessed pooled prevalence for key demographics and clinical characteristics using Freeman-Tukey double arcsine random-effects model for studies except case-reports. We evaluated risk of bias separately for case-reports and other studies.

Results: We identified 1,964 articles, of which, 65 articles were eligible for systematic review that represented 1,214 children younger than five years with laboratory-confirmed COVID-19 infection. The pooled estimates showed that 50% young COVID-19 cases were infants (95% CI: 36% – 63%, 27 studies); 53% were male (95% CI: 41% – 65%, 24 studies); 43% were asymptomatic (95% CI: 15% – 73%, 9 studies) and 7% (95% CI: 0% – 30%, 5 studies) had severe disease that required intensive-care-unit admission. Of 139 newborns from COVID-19 infected mothers, five (3.6%) were COVID-19 positive. There was only one death recorded.

Discussion: This systematic review reports the largest number of children younger than five years with COVID-19 infection till date. Our *meta*-analysis shows nearly half of young COVID-19 cases were asymptomatic and half were infants, highlighting the need for ongoing surveillance to better understand the epidemiology, clinical pattern, and transmission of COVID-19 to develop effective preventive strategies against COVID-19 disease in young paediatric population.

Contents

* Corresponding author at: Wesfarmers Centre of Vaccines and Infectious Diseases, Telethon Kids Institute, Perth Children's Hospital, 15 Hospital Avenue, Nedlands WA 6009, Australia.
E-mail address: Mejbah.Bhuiyan@telethonkids.org.au (M.U. Bhuiyan).
[1] Contributed equally.

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1. Introduction

Globally acute respiratory infection (ARI) including pneumonia is the leading cause of morbidity and mortality in young children aged less than five years. Respiratory viruses such as influenza and respiratory syncytial virus (RSV) remain the leading causes of ARI in under five children [1]. The immature immune system have been linked to increased risk of infectious diseases, particularly respiratory viral infections in infants [1], However, as the research on ongoing pandemic (Corona Virus Disease 2019 (COVID-19)) caused by a novel respiratory virus, Severe Acute respiratory Syndrome- Coronavirus – 2 (SARS-CoV-2) continues to grow, it appears that young children are less susceptible to this SARS-CoV-2 [2]. Current research suggests that the lowered susceptibility in children is likely due to the scarcity of the SARS-CoV-2 angiotensin-converting enzyme 2 (ACE2) receptor in the respiratory tract in children, meaning that the virus has less receptors to bind to and take hold within a child's respiratory tract [3]. It is also hypothesised that higher rates of prior infection with other human coronavirus in children may provide protection against severe SARS-CoV-2 infection in children[4]. Additionally, emerging evidence suggest most laboratory confirmed cases of COVID-19 in children results in mild disease, with severe disease in children considered rare [2]. Limited data are available relating to host immunologic response to COVID-19 infection in young children; nevertheless, it is evident that children do get infected with COVID-19 and around 12–18% of infected children are aged < 12 months [5,6]. Few studies have reported potential of transmission of COVID-19 infection from mothers to newborns, but understanding of vertical transmission of COVID-19 infections is still limited [7–10].

As of 28th July 2020, globally there have been 16,646,987 confirmed cases of COVID-19 with 656,608 deaths [11]. The magnitude of the crisis has led to unprecedented speed in developing an effective vaccine. There are nearly 200 candidate vaccines against SARS-CoV-2 infection at different stages of development with at least two being in advancedd stages of clinical trial [12]. It is possible that a safe and efficacious vaccine may become available for clinical use by late 2020 or early 2021 [13]. The World Health Organisation (WHO) is working with various stakeholders to ensure that when a vaccine is developed, they will facilitate the equitable access and distribution of the vaccine to people globally, prioritizing people at the greatest risk [14]. Often vaccines for respiratory infections, such as influenza and pneumococcal disease are highly recommended to groups of population at increased risk of severe disease including children aged less than five years, pregnant women, people with chronic morbidities and elderly population (aged > 65 years) [15,16].

At the time of writing this paper (July 2020) the pandemic had been present for 6 months, with many considering this the first wave of the pandemic. According to the US National Center for Biotechnology Information (NCBI) SARS-CoV-2 literature database [17], >35,200 research studies and case reports have been published which provides updated information relating to how the pandemic has evolved in different sub-groups of people in different parts of the world. However, there is a lack of comprehensive epidemiological data relating to the pandemic specifically in children aged less than five years, the most at-risk paediatric age-population for respiratory infections and a priority population for vaccine globally. The objective of this systematic review and *meta*-analysis was to compile existing literature and analyse published data to provide a robust understanding on epidemiological and clinical pattern of COVID-19 infection in children aged less than five years to inform clinical decisions and guide a road map for prevention strategies including COVID-19 vaccine in young children.

2. Methods

2.1. Search strategy and selection criteria

This systematic review and *meta*-analyses of available literature on epidemiological and clinical features of COVID-19 infection in children aged less than five years was conducted following standard PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) guidelines. The review protocol was registered in PROSPERO (CRD42020181936).

Relevant articles and reports published as of June 4, 2020 in the electronic databases including Pubmed, EMBASE, Web of Science and Scopus reporting epidemiological and clinical data on laboratory confirmed COVID-19 in children of any age were searched. The search strategy included a combination of free search terms and MESH terms with no language restriction. One review author (MUB) with previous experience of searching literature in electronic databases developed the search strategy. The following terms were included but not limited to the database search: "2019 nCoV", "2019ncov", "2019-nCoV", "2019 novel coronavirus", "Novel coronavirus 2019", "COVID 19", "COVID-19", "COVID19", "Wuhan coronavirus", "Wuhan pneumonia", "SARS CoV-2", "SARS-Cov-2" and were limited to "all child (0–18 years)", and "Human". Once the initial search was complete, we also looked into WHO coronavirus database to ensure that no relevant key articles were missed. The detailed search strategies applied for different databases are available in Supplementary table 1. EndNote was used to manage literature search output.

The primary eligibility for inclusion of studies were published studies investigating epidemiology, transmission and clinical features of COVID-19 infection in children confirmed by laboratory

Table 1
Study and demographic characteristics of 1,214 children included from 65 eligible studies*

Study	Country	Data collection month	Study design	Total number of < 5 years children with COVID-19			Age	Male (n)	Reported Source f infection
				N	<1 year	1–5 years			
An P [24]	China	Feb	Case report	1	0	1	36 *m*	0	Family
Cai J [25]	China	Jan – Feb	Observational	4	2	2	3 m – 60 *m*	1	Community
Cai X [26]	China	Jan – Feb	Case report	4	3	1	2 m-15 *m*	3	Family, Community
CDC [27]	USA	Feb – Apr	Observational	689	398	291	0-5y	NA	community
Chen H [28]	China	Jan	Observational	0	0	0	Newborn	NA	Vertical
Chen Y [29]	China	Jan – Feb	Case report	0	0	0	Newborn	NA	Vertical
Cui Y [30]	China	Feb	Case report	1	1	0	55d	0	Community
Dong L [31]	China	Feb	Case report	0	0	0	Newborn	NA	Vertical
Dong Y [5]	China	Feb	Observational	223	86	137	0-5y	NA	Community
Dumpa V [32]	USA	Mar	Case report	1	1	0	22d	NA	Community
Jiang S [33]	China	May	Case report	1	0	1	3.5y	0	Community
Kamali Aghdam M [34]	Iran	Mar	Case report	1	1	0	15d	0	Community
Kan M [35]	USA	Apr	Case report	1	1	0	35d	0	Community
Le H [36]	Vietnam	Mar	Case report	1	1	0	3 *m*	0	Community
Li W [37]	China	Jan – Feb	Observational	4	0	4	10 m-4y	3	Community
Li Y [38]	China	Jan – Feb	Observational	8	0	8	1-5y	3	Community
Li Y [39]	China	Feb	Case report	0	0	0	Newborn	NA	Vertical
Liu H [40]	China	Jan – Feb	Observational	2	2	0	2–11 *m*	2	Community
Liu M [41]	China	–	Case report	2	1	1	7 m-2.4y	1	Community
Liu P [42]	China	Jan – Mar	Observational	0	0	0	Newborn	24	Vertical
Liu W [43]	China	Jan – Feb	Observational	0	0	0	Newborn	NA	Vertical
Liu W [44]	China	Jan	Observational	5	0	5	1-5y	2	Community
Lou X[45]	China	Dec 2019	Observational	1	1	0	6 *m*	1	Family
Lu X[46]	China	Jan – Feb	Observational	71	31	40	1d-5y	NA	Community
Lu Y[47]	China	Jan – Feb	Observational	3	1	2	2 m-3y	2	Community
Ma H[48]	China	Jan – Feb	Observational	50	NA	NA	<2.5y	28	Community
Ma X[49]	China	Feb	Observational	4	1	3	11 m-43 *m*	2	Community
Mansour A[50]	Lebanon	Mar	Case report	1	0	1	16 *m*	0	Community
Mao L[51]	China	Feb	Case report	1	0	1	14 *m*	1	Community
Merza M[52]	Iraq	Mar – Apr	Observational	1	0	1	60 *m*	1	Family
Morand A[53]	France	Mar	Case report	1	0	1	55 *m*	0	Family
Munoz A[54]	USA	–	Case report	1	1	0	21d	1	Community
Ng K[55]	UK	Mar – Apr	Observational	8	8	0	5d-12 *m*	2	Community
Paret M[56]	USA	Mar	Case report	2	2	0	25-56d	2	Community
Peng Z[57]	China	NA	Case report	0	0	0	Newborn	NA	Vertical
Qiu H[58]	China	Jan – Mar	Observational	10	NA	NA	0-5y	6	Family cluster & Community
Rahimzadeh G[59]	Iran	NA	Case report	4	0	4	2-5y	2	Community
See K[60]	Malaysia	Jan – Feb	Case report	2	0	2	20 m-4y	1	Community
Shekerdemian L[61]	USA & Canada	Mar – Apr	Observational	14	8	6	<1-5y	NA	Community
Shen Q[62]	China	Jan – Feb	Observational	2	0	2	1-2y	0	Community
Song Q[63]	China	Jan – Mar	Observational	4	1	3	11 m-3y	4	Community
Su L[64]	China	Jan – Feb	Observational	5	2	3	11–43 *m*	2	Community
Sun D[65]	China	Jan – Feb	Observational	4	2	2	2–25 *m*	3	Community; Family
Tan Y[66]	China	Jan – Mar	Observational	3	0	3	13 m-3y7m	1	Community
Wang J[67]	China	Feb	Case report	1	1	0	23d	1	Community
Wang S [68]	China	Mar	Case report	0	0	0	Newborn	NA	Vertical
Wei M [69]	China	Dec - Feb	Observational	9	9	0	1–11 *m*	2	Community
Wolf G [70]	Germany	Jan – Feb	Case report	1	0	1	2y	1	Family
Xia W [71]	China	Jan – Feb	Observational	14	9	5	<1m-3y	NA	Community
Xing Y [72]	China	Jan – Mar	Observational	1	0	1	1.5y	1	Family
Xu Y [73]	China	Apr	Observational	3	2	1	2–41 *m*	2	Community
Yang H [74]	China	Jan – Mar	Observational	0	0	0	Newborn	NA	Vertical
Yang H [75]	China	Jan – Mar	Observational	0	0	0	Newborn	NA	Vertical
Yang P [76]	China	Jan	Observational	0	0	0	Newborn	NA	Vertical
Zachariah P [77]	USA	Mar – Apr	Observational	12	12	0	<1yr	NA	Community
Zeng H [78]	China	Feb	Observational	0	0	0	Newborn	NA	Vertical
Zeng L [79]	China	Feb – Mar	Case report	1	1	0	<1y	NA	Community
Zhang G[80]	China	Jan	Case report	2	0	2	14 *m*	0	Community
Zhang Y [81]	China	Jan	Case report	1	1	0	3 *m*	1	Community
Zhang ZJ [82]	China	Jan – Mar	Observational	4	4	0	30 h-17d	3	Family
Zheng F [83]	China	Feb	Observational	10	NA	NA	1 m-3y	NA	Community
Zhong Z [84]	China	NA	Observational	3	1	2	3 m-2y	1	Community
Zhou Y [85]	China	Jan – Feb	Observational	9	NA	NA	7 m-3y	4	Community
Zhu H [86]	China	Jan – Feb	Observational	0	0	0	Newborn	NA	Vertical
Zhu L [87]	China	Jan – Feb	Observational	2	0	2	1y7m-4y	2	Community

* Data presented where available from selected publications included in the review; NA = Not available.

diagnosis for SARS-CoV-2 from any type of biological specimen (e.g. respiratory specimen, stool etc.) through reverse-transcriptase polymerase chain reaction (RT-PCR), as per the case definition from WHO [18,19]. Only infection of COVID-19 in children confirmed by RT-PCR were included to ensure comparability of data extracted from multiple studies conducted in different countries. Details of study inclusion and exclusion criteria are in the Box 1.

Box 1 Inclusion and Exclusion Criteria.

Inclusion criteria.

Study of community-acquired COVID-19 infection.

Enrolment of children <5 years old (studies that include all age children and adults were included only if the data for children <5 years could be extracted)

Laboratory diagnosis of SARS-CoV-2 from any type of biological specimen (e.g. respiratory specimen, stool etc.) through reverse-transcriptase polymerase chain reaction (RT-PCR)

Published on or before June 4, 2015.

Exclusion criteria.

Systematic reviews of COVID-19 in children or policy and case-management guidelines or abstracts only or opinion pieces or editorials or letters to the editor.

Studies of children and/or adults where the data for adults and children >5 years could not be excluded.

2.2. Study selection

Two reviewers conducted the initial search (MUB and NH). MUB compiled all articles identified through literature search. Two reviewers (MUB and ES) independently screened the title and abstract of all publications to confirm eligibility and ensured the screened publication reported data for children younger than five years. All publications in Chinese language were translated by one of the investigators (MC) who is a Native Chinese speaker and a health professional (research nurse) . Any discrepancies in primary screening were initially discussed by two reviewers and resolved by consensus, otherwise a third reviewer (NH) resolved any disagreements. The risk of reviewer publication bias was minimised by involving two independent reviewers and a third reviewer when required, and by using predefined inclusion and exclusion criteria to identify all relevant studies.

2.3. Data extraction

The following information was extracted from each eligible study: the year of publication, location, study year and timeline, total number of children with COVID-19, average age (median or mean, if both reported, then median was preferred over mean), duration of illness, symptoms (including asymptomatic children), number of children who developed severe illness requiring intensive care unit (ICU) admission and number of deaths. For studies which included both adults and/or children of all ages, only data relating to children younger than five years were extracted. Extracted data from each publication was recorded in a spreadsheet.

2.4. Data analysis

Risk of bias in the included studies was evaluated using a methodological quality assessment tool formulated by Murad et al. [20] for case series and case reports, and by Hoy et. al [21] for all retrospective and prospective studies included in the review. The study characteristics including study design and country were tabulated. The clinical signs and symptoms were categorised under broad clinical headings: a) Upper respiratory included rhinorrhoea, cough and blocked or stuffy nose; b) Lower respiratory included tachypnoea and dyspnoea; c) Gastrointestinal included vomiting, diarrhoea, abdominal pain and abdominal distention and, d) Other signs and symptoms that included, headache, poor feeding/decreased oral intake, hypothermia, tachycardia, paroxysmal crying, fatigue/drowsiness and hypotension. Disease severity was classified as mild (no hospitalisation required or discharged from emergency room), moderate (required hospitalisation) or severe (required admission at ICU or high-dependency care unit (HDU) or mechanical ventilation support). Descriptive analysis with available data, was performed on socio-demographic characteristics for children aged less than five years with laboratory-confirmed COVID-19 infection, clinical signs and symptoms, disease severity and outcomes and transmission of SARS-CoV-2 from COVID-19 positive mothers.

The *meta*-analysis included all studies with the exception of case reports and case series and where n = 1.Pooled estimates on key demographic (age, sex) and clinical characteristics (upper respiratory symptoms, lower respiratory symptoms, other symptoms, disease duration and severity, treatment received) were assessed using Freeman-Tukey double arcsine method, with a random effects model in R statistical software [22]. We intended to estimate the proportion of children aged < 5 years positive among all children who were tested for SARS-CoV-2 infection; however, as there were very few publications where the denominator (total number of children tested for SARS-CoV-2) was reported, proportion positive could not be calculated Heterogeneity was assessed by Pearson χ^2 (Q statistic) test and I^2 statistics was used to report variations [23]. An I^2 value of < 25% was taken to indicate low heterogeneity, 26%-74% moderate heterogeneity, and > 75% high heterogeneity [23].

3. Results:

3.1. Search outcome and study characteristics

We identified 1,964 articles from electronic databases and manual search (Fig. 1). After removing duplicates (n = 844), titles and abstracts were screened for 1,120 articles and 185 were eligible for full-text examination. Of 185 full-text articles, 65 articles including 39 which were observational studies (retrospective medical record review and prospective cross-sectional studies) and 26 case studies and case reports were included in this review. The main characteristics of the studies are presented in Table 1.

The included 65 studies were conducted in 11 different countries: China (n = 49), United States (n = 6), Iran (n = 2), Vietnam (n = 1), Lebanon (n = 1), Iraq (n = 1), France (n = 1), United Kingdom (n = 1), Malaysia (n = 1), Canada (n = 1), and Germany (n = 1) (Table 1), and from four different WHO regions (European region, n = 3; Western Pacific region, n = 52 Pacific American region, n = 6; Eastern Mediterranean region, n = 4). Risk of bias was assessed separately for case-reports and case-studies (n = 26) (Fig. 2) and observational studies (n = 39) (Fig. 3). Given the

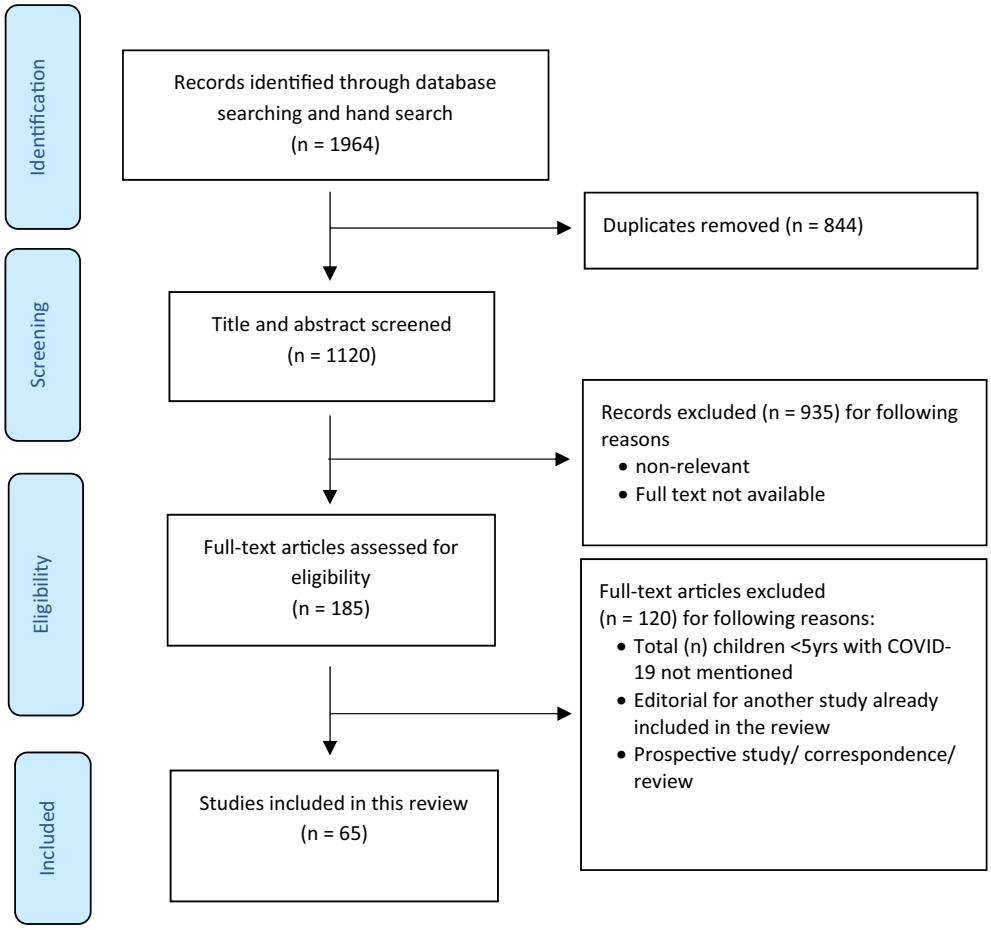

Fig. 1. Flow diagram for study screening for the systematic review and *meta*-analysis

majority of observational studies included only COVID-19 confirmed children, there was low risk in regard to generalisability to similar paediatric population.

3.2. Demographic features of COVID-19 cases

A total of 1,214 children younger than five years with RT-PCR confirmed COVID-19 infection (further mentioned as COVID-19 cases) were included in this systematic review (Table 1). There were 474 COVID-19 cases from China, 720 from United States of America and Canada, eight from United Kingdom, five from Iran, two from Malaysia and one each from Vietnam, Lebanon, Iraq, France, and Germany. Of 1,214 COVID-19 cases, age-distribution data were available for 1,135 (93%) cases. The age of 1,135 COVID-19 cases ranged from zero days to less than five years: 596 (53%) were less than one year (infant) (Table 1). Among the 596 COVID-19 infant cases, five (1%) were newborns. Of the included 65 studies, 45 studies reported gender distribution for 179 COVID-19 cases: 117 (65%) were male. Source of infection was reported for 1,211 cases, of which 1,186 (98%) cases had a community acquired source.

3.3. Clinical Symptoms, therapeutic management of COVID-19 cases and disease outcome

Of 1,214 COVID-19 cases, symptomatic status was reported for 880 (72%) of children: 834/880 (95%) were symptomatic and 46 (5%) were asymptomatic (Table 2). Where data available, detailed clinical symptoms were extracted for 196 children: fever (75/196, 38%) was the most frequently reported symptom followed by any upper respiratory symptoms (69/196, 35%), gastrointestinal (GI) symptoms were reported in 7.7% (15/196). Disease severity (mild, moderate or severe) were extractable for 345 children: the majority were mild illness (n = 155, 44.9%); 22 cases required simply oxygen therapy and 4 cases required invasive ventilator support. Treatment information was reported for 102 COVID-19 cases. A total of 64 (63%) of COVID-19 cases (20 studies) received at least one antiviral treatment, the most common medications reported were Interferon (includes both interferon beta-1b and interferon alfa-2b) (n = 31, 47.7%) and Oseltamivir (n = 20, 30.8%). Similarly, antibiotic treatments were reported in 17 studies and 29 COVID-19 cases (29%) received at least one antibiotic, with the most commonly reported antibiotic being Azithromycin (n = 8, 27.6%). Steroid treatment was reported in nine cases: all received Methylprednisone.

Disease outcome was reported for 121 cases (43 publications), of these cases 120 cases were discharged from hospital or recovered with one death. The deceased case was a 10 month-old female infant with no underlying medical conditions or no history of preceding exposure to a known COVID-19 case [26].

3.4. COVID-19 infection in newborns from COVID-19 infected mothers

Of the 65 publications included in the review, 14 reported SARS-CoV-2 status in 151 newborns from 149 laboratory-confirmed or clinically-confirmed COVID-19 positive mothers, all

Table 2
Descriptive clinical characteristics of 1,214 RT-PCR confirmed COVID-19 cases for all 65 articles included in review.

		Number of children (N)	(%)
Symptomatic status		880	
	Symptomatic	834	94.7
	Asymptomatic	46	5.2
Symptoms reported [a]		196	
	Fever	75	38.2
	Upper Respiratory	69	35.2
	Lower Respiratory	10	5.1
	Gastrointestinal	15	7.7
	Other	27	13.8
Disease Severity [b]		345	
	Mild	155	44.9
	Moderate	173	50.1
	Severe	17	4.9
Medications		102	
	Antivirals [c]	64	62.7
	Antibiotics [d]	29	28.4
	Steroids	9	8.8
Disease Outcomes		121	
	Recovered/ Discharged	120	99.2
	Dead	1	0.8
Source		1211	
	Community	1186	97.9
	Family	12	0.9
	Vertical	13	1.2

[a] Upper respiratory symptoms included rhinorrhoea, cough and blocked or stuffy nose; Lower respiratory symptoms included tachypnoea and dyspnoea; Gastrointestinal symptoms included vomiting, diarrhoea, abdominal pain and abdominal distention; Other symptoms that were reported in few cases included, headache, poor feeding/decreased oral intake, hypothermia, tachycardia, paroxysmal crying, fatigue/drowsiness and hypotension;

[b] Mild Disease = non-hospitalised, Moderate Disease = hospitalised, Severe Disease = HDU/ICU admission/mechanical ventilation.

[c] Interferon (n = 31), Oseltamivir (n = 20), Ritonavir (n = 9), Lopinavir (n = 7), Ribavirin (n = 7), Chloroquine (n = 4) and Ioponavir (n = 2).

[d] Azithromycin (n = 8), Meropenem (n = 5),Vancomycin (n = 4), Linezolid (n = 2), Augmentin (n = 2), Gentamicin (n = 2), Ampicillin (n = 1), Cefepime (n = 1), Penicillin (n = 1), Ceftriaxone (n = 1), Amikacin (n = 1), Cefotaxime (n = 1), Amoxicillin (n = 1), Ceftazidime (n = 1, 3.4%).

were diagnosed with COVID-19 prior to delivery [28,29,31,39,42,43,57,68,74–76,78,82,86]. Of the 149 deliveries, 133 (89%) were caesarean section (C-section) (Supplementary table 2). Of the 151 babies born, 25 (16.5%) were born preterm (gestational age < 37 weeks) and 15 (10%) had low-birth weight (<2500 g). Five (3.3%) newborns were COVID-19 positive by RT-PCR at age 30 h to 17 days. All the five mothers completed at least 40 weeks of gestation and all five newborns were delivered by C-section. All but one mother developed respiratory symptoms before delivery. Of five newborns, three of them showed at least one respiratory symptom including fever, cough, shortness of breath and vomiting. None of them required intensive care unit admission or mechanical ventilation. The hospital stays of newborns ranged from 16 days to 30 days.

3.5. Meta-analysis

A total of 31 studies (COVID-19 cases, n = 1,181) (excluding case-reports and case-studies) were eligible for *meta*-analysis, studies excluded from the *meta*-analysis included studies were n = 1. Using data, when available, the outputs from *meta*-analysis are presented in Table 3. The pooled estimate showed that among children aged less than five years with COVID-19 infection, 50% (95% CI: 36% to 63%) of children were aged less than one year (Fig. 4) and 53% (95% CI: 41% to 65%,) were male (supplementary Fig. 1). Using studies that reported both symptomatic and asymptomatic COVID-19 cases, the pooled prevalence showed 43% (95% CI: 15% to 73%) were asymptomatic. We estimated 40% (95% CI: 6% to 78%) required no hospitalisation. Of the children who required hospitalisation (moderate/severe disease), 49% (95% CI: 12% to 86%) required oxygen therapy (not inclusive of mechanical ventilation). The pooled prevalence for antiviral treatment was 99% (95% CI: 92% to 100%) using data from 10 studies comprising 48 COVID-19 cases and similarly, for antibiotics was 71% (95% CI: 46% to 92%) using data from 5 studies comprising 14 COVID-19 cases, many cases reported combined treatments

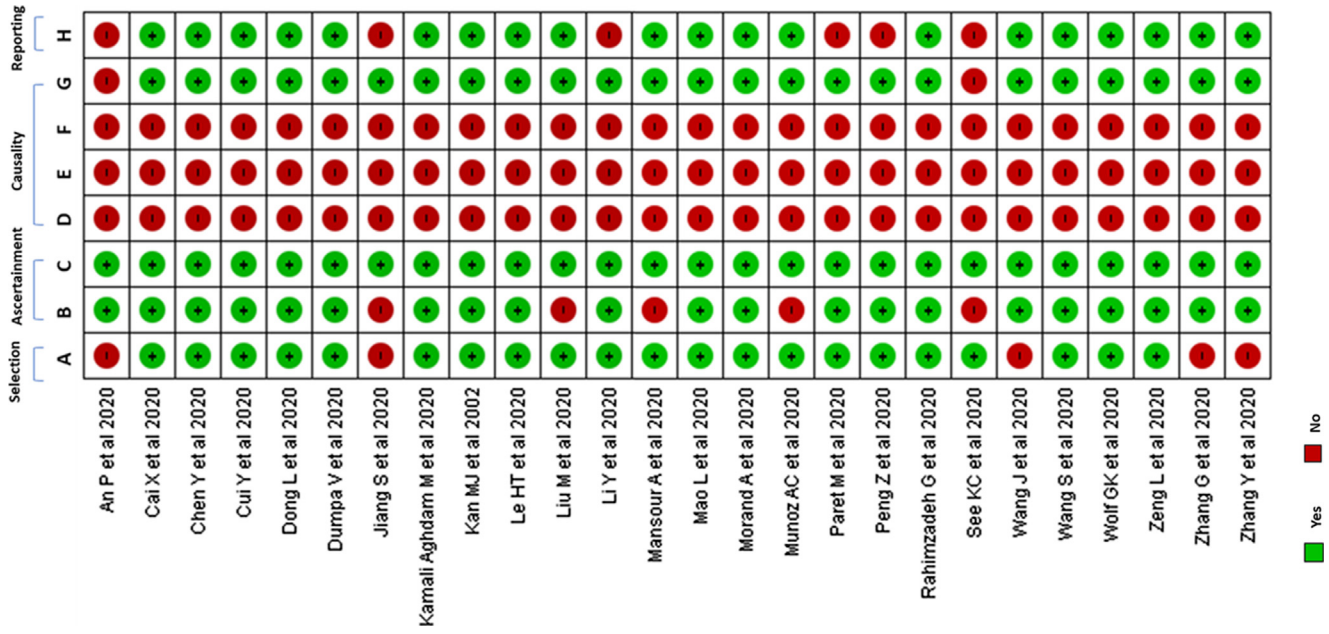

Fig. 2. Risk of bias assessment for case-reports and case-studies included in the review

Fig. 3. Risk of bias assessment for observational studies included in the review (excluding case-reports and case- studies)

for patients. We were unable to extract data on transmission source and death for the *meta*-analysis.

4. Discussion:

To our knowledge this is the most comprehensive systematic review and *meta*-analysis of the literature, specific for children aged less than five years with laboratory confirmed COVID-19 infection. Our systematic review suggests that the prognosis of COVID-19 in children aged less than five years aligns with current published research, with >90% of children developing mild to moderate disease. These results are similar to recent reviews by Castagnoli et al [88] and Hoang et al [89] in all children < 18 years. This also follows trends that only 7% of cases in our review were severe cases requiring ICU or HDU admission, compared to 53% of adults recorded with severe COVID-19 disease requiring ICU admission [90]. This is a particularly important finding given that infants and young children aged less than five years are already at high risk of severe disease associated with other respiratory infections including influenza and RSV. It is likely that many COVID-19 infections in young children were classified as moderate illness (requiring hospital admission), were in fact mild disease, as those reported to have a hospital admission were due to isolation requirements only, not necessarily due to severity of clinical condition. This is also likely that many asymptomatic children were not tested and thus only the children with clinical manifestations were included in this study. Thus, the proportions we reported for severe and moderate cases could be higher than the true proportions.

Emerging data suggest that children with confirmed and suspected COVID-19 infection can present with Kawasaki-like syndrome which has been termed as multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2 [91–93]. While such inflammatory syndrome has been documented in paediatric population in the United States, United Kingdom and also Italy, in our systematic review we did not find any reports of Kawasaki disease like syndrome or MIS-C in COVID-19 cases < 5 years to be included in this systematic review.

This systematic review of >1,200 children aged less than five years with COVID-19 infection showed half of these cases were aged less than one year. Infants are particularly at higher risk of infectious disease during the first few months of their lives due to the inadequately developed immune system and are often targeted for prevention strategies. We also found that a handful of newborns (<4%) from COVID-19 infected mothers had laboratory confirmed COVID-19 infection within several hours to days of birth. Nonetheless, the vertical transmission of COVID-19 remains unclear as none of those studies could persuasively claim mother to neonate transmission. Recent reviews addressing immunological assessment, concluded with no evidence of intrauterine transmission during delivery from mothers to their fetuses [9,42,94]. These findings are analogous to data reported during previous influenza pandemics and novel coronavirus strains, associated with Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-Cov) epidemics [95,96]. Vaccine remains one of the most effective public health interventions to prevent transmission of infectious diseases. However, the immature immune system of newborns also

Table 3
Meta-analysis of outcomes (random effects model)[a].

	No. of Studies	Proportion	95%CI [b]	Total no. of cases (n)	I^2	t^2	Q	P-value [c]
Age								
<1yr	27	0.50	0.36 – 0.63	580	78.9%	0.0379	123.17	<0.0001
1–5 yr	27	0.50	0.37 – 0.64	523	78.9%	0.0379	123.17	<0.0001
Sex								
Male	24	0.53	0.41 – 0.65	78	20.4%	0.0104	28.88	0.1844
Clinical Characteristics								
Asymptomatic Cases	9	0.43	0.15 – 0.73	42	82.7%	0.1152	46.24	<0.0001
Symptomatic Cases	11	0.56	0.008 – 1.00	714	99.4%	0.7045	1588.73	0
Symptoms reported								
Fever	18	0.76	0.61 – 0.89	43	0.0%	0	14.70	0.6171
Upper Respiratory Symptoms	13	0.75	0.55 – 0.91	37	25.3%	0.0182	16.05	0.1887
Lower Respiratory Symptoms	2	0.34	0.03 – 0.72	4	0.0%	0	0.0	0.9545
Gastrointestinal Symptoms	3	0.73	0.20 – 1.00	7	48.7%	0.0772	5.85	0.1192
Other Symptoms	2	0.97	0.54 – 1.00	10	32.5%	0.0399	2.96	0.2272
Treatment								
Antibiotics	5	0.71	0.46 – 0.92	14	5.4%	0.0032	4.23	0.3757
Antivirals	10	0.99	0.92 – 1.00	48	0.0%	0	6.11	0.7291
Steroids	3	0.65	0.30 – 0.93	7	0.0%	0	0.88	0.6438
Oxygen Therapy [d]	7	0.49	0.11 – 0.87	14	78.2%	0.1489	27.58	0.0001
Disease Severity								
Mild	4	0.40	0.06 – 0.78	132	84.1%	0.0990	18.91	0.0003
Moderate	7	0.51	0.16 – 0.85	98	87.9%	0.1449	49.75	<0.0001
Severe	5	0.07	0.00 – 0.30	9	73.5%	0.0545	15.08	0.0045
Disease duration (days)						**Mean** [e]	**Min**	**Max**
Duration of illness	8			30		6.51	10	33.1
Duration between symptom onset to detection	9			43		2.06	1.79	7.02
Duration of hospital stay	5			24		4.08	8	22.27

[a] Data presented in *meta*-analysis is only from 31 studies with available data (excluded case reports).
[b] 95%CI = 95% Confidence Interval.
[c] P-value correspondsto Q test stastic and heterogeneity assessment of studies.
[d] Not inclusive of mechanical ventilation.
[e] Mean calculated as weighted average.

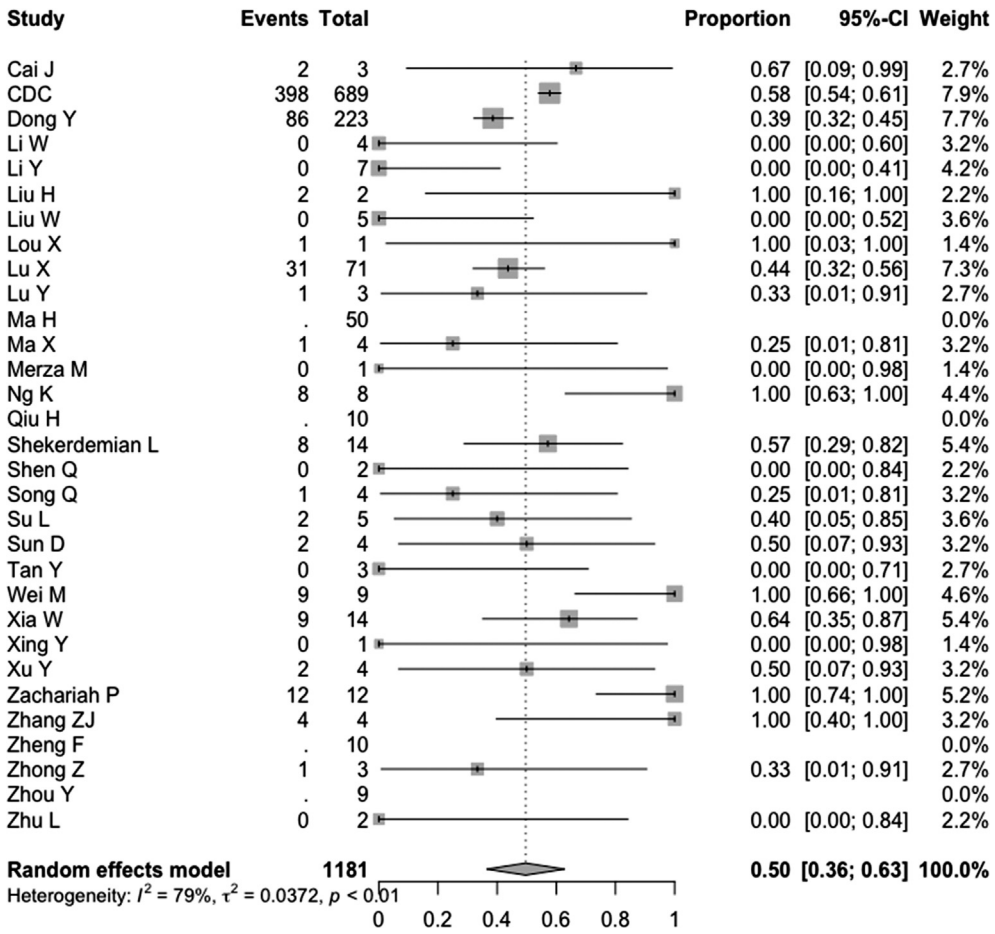

Fig. 4. Forest plot of proportion of all COVID-19 positive children (aged < 5 years) who were aged less than one year from 31 studies included in *meta*-analysis

makes them unsuitable for many vaccines. Maternal immunization during pregnancy has been proven to be an effective strategy in providing protection to infants, against many vaccine-preventable diseases including pertussis, tetanus and influenza during the first few months of life. Maternal immunization during pregnancy has two benefits, it protects the mother and fetus and it also protects the newborn through transplacental transfer of maternal antibody [97]. To date, we do not have an effective vaccine against COVID-19, but there are several vaccines in advanced clinical stages that may become available for clinical use within next 6–12 months [12]. In a situation where the COVID-19 vaccination is deemed to be unsuitable for infants, maternal immunisation could be a viable preventive approach.

We found the majority (>95%) of the COVID-19 infections in children reportedly had a community source of infection, however, familial clusters were common in four case reports included in the review. Young adults and children have a high likelihood of developing COVID-19 due to household transmission, once a family member tests positive to COVID-19 [24]. However, there is limited evidence of secondary infection from children to others, suggesting that the role children play in the transmission pathways of COVID-19 remains unclear. Longer duration of virus shedding through the gastrointestinal tract can play a role in potential faecal-oral transmission of the virus, however this is yet to be confirmed [72,73].

Our systematic review suggests while many children younger than five years were treated with antivirals, 71% were treated with antibiotics, despite having a confirmed diagnosis of COVID-19. This is a concerning proportion of antibiotic use as a treatment for the viral disease in children, given the inappropriate use of antibiotics in under five children is a significant contributor to the emergence and spread of antimicrobial resistance globally [101,99]. While prophylactic treatment with antibiotics in infants with unknown source of infection, is routine in preventing bacteraemia, urinary tract infection (UTI) or pneumonia, this still has limitations in populations of increased antimicrobial resistance [100,101].

4.1. Strengths and limitations

The major strength of our study is it provides comprehensive epidemiological and clinical data on COVID-19 infection in a very specific age-group of children considered to be at highest risk of morbidity and mortality associated with ARIs including pneumonia. We were able to include available and eligible literature that were published in Chinese language (n = 17) during the very early stage of pandemic and inclusion of these articles added to the evidence base of this systematic review. Additionally, this allowed us to include a large number of young children (n = 1,214) in our analysis further strengthening the review.

However, our review had some important limitations as well. The final search of the databases was concluded in early June, which meant that many geographical regions such as the United States and Europe that had resurgence of COVID-19 cases during a second wave were not included in our review. Nevertheless, as more literature become available, our systematic review will provide a comprehensive evidence base to further investigate epidemiological and clinical pattern of COVID-19 in children aged < 5 years. We had 26 case reports and hence the data could not be used in our *meta*-analysis which might have impacted the generalisability of the results. Additionally, only few studies provided detailed information on clinical outcome of the disease, which could be extracted for the pooled analysis. Hence, high level of heterogeneity was observed for some of the key clinical variables in the *meta*-analysis. In order to incorporate the between-study variations, random effect models were used to estimate the summary effect size. There were only two studies from two European countries other than United Kingdom and none from Italy, Sweden, or Spain where the impact of pandemic has been extensive. In our search, we could not find any eligible studies from any country in the South East Asian Region (SEARO) region, where the response to the pandemic capacities remain insufficient. These areas are of particular concern as they tend to have a higher burden of childhood ARI. Additionally, we did not find articles reporting COVID-19 in Indigenous or ethnic minority paediatric populations although these groups of children have higher risk of respiratory infections. Lastly, even though we used comprehensive mesh terms for searching, it is possible we missed some articles.

4.2. Conclusions

Our systematic review has shown that young children aged less than five years generally develop mild COVID-19 disease and these infections are often acquired through community sources. Half of the children aged less than five years with COVID-19 infection were infants. Additionally, a large proportion of the young children with COVID-19 infection are asymptomatic, underpinning the need for ongoing surveillance to monitor COVID-19 disease epidemiology in this paediatric population, strengthening prompt laboratory identification for case isolation and clinical management. Future research to understand risk of vertical transmission of COVID-19 infection will help guide policy decisions around maternal vaccination when an effective vaccine becomes available.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2020.11.078.

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