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Review Paper

Asymptomatic infection and transmission of COVID-19 among clusters: systematic review and meta-analysis

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ABSTRACT

Objectives: Countries throughout the world are experiencing COVID-19 viral load in their populations, leading to potential transmission and infectivity of asymptomatic COVID-19 cases. The current systematic review and meta-analysis aims to investigate the role of asymptomatic infection and transmission reported in family clusters, adults, children and health care workers, globally.
Study design: Systematic review and meta-analysis.
Methods: An online literature search of PubMed, Google Scholar, medRixv and BioRixv was performed using standard Boolean operators and included studies published up to 17 August 2021. For the systematic review, case reports, short communications and retrospective studies were included to ensure sufficient asymptomatic COVID-19 transmission data were reported. For the quantitative synthesis (meta-analysis), participant data from a collection of cohort studies focusing on groups of familial clusters, adults, children and health care workers were included. Inconsistency among studies was assessed using I^2 statistics. The data synthesis was computed using the STATA 16.0 software.
Results: This study showed asymptomatic transmission among familial clusters, adults, children and health care workers of 15.72%, 29.48%, 24.09% and 0%, respectively. Overall, asymptomatic transmission was 24.51% (95% confidence interval [CI]: 14.38, 36.02) among all studied population groups, with a heterogeneity of $I^2 = 95.30\%$ ($P < 0.001$). No heterogeneity was seen in the population subgroups of children and health care workers. The risk of bias in all included studies was assessed using the Newcastle Ottawa Scale.
Conclusions: For minimising the spread of COVID-19 within the community, this study found that following the screening of asymptomatic cases and their close contacts for chest CT scan (for symptomatic patients), even after negative nucleic acid testing, it is essential to perform a rigorous epidemiological history, early isolation, social distancing and an increased quarantine period (a minimum of 14–28 days). This systematic review and meta-analysis supports the notion of asymptomatic COVID-19 infection and person-to-person transmission and suggests that this is dependent on the varying viral incubation period among individuals. Children, especially those of school age (i.e. <18 years), need to be monitored carefully and follow mitigation strategies (e.g. social distancing, hand hygiene, wearing face masks) to prevent asymptomatic community transmission of COVID-19.
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Introduction

Symptomatic COVID-19 viral infection is a significant risk factor for transmission of the disease within the general public. The major signs of COVID-19 infection include fever, dyspnoea, a dry cough and diarrhoea; these symptoms are reported to last up to 14 days, with a median incubation period of 9–12 days. Aerosol transmissions occur through sneezing or coughing and are reported to be the primary route of person-to-person infection.[1] However, simulation studies have also observed asymptomatic COVID-19 person-to-person transmission.[2] Polymerase chain reaction (PCR)-based assays are recommended in managing asymptomatic transmission of the virus.[3] He et al. reported the first case of asymptomatic transmission of

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COVID-19 on 21 February 2020.[4] Asymptomatic infection was reported as 'hidden coronavirus infections' ('infections' or 'covert coronavirus infections').[5] The COVID-19 prevention and control protocol (6th edition) states that asymptomatic COVID-19 cases should remain in quarantine for 14 days and that they should have two negative nucleic acid tests before being discharged. Worldwide, interest in asymptomatic COVID-19 infections and their transmission potential had increased.[6] In China, around 86% of asymptomatic COVID-19 transmission was undocumented before travel restrictions were introduced.[6]

To date, asymptomatic COVID-19 cases have been reported among family clusters,[7–12] pregnant women,[13,14] adults,[15–24] children,[1,25,26] health care workers[27–29] and travellers.[30–34] Considering the potential transmission of asymptomatic COVID-19 within the community, this study aimed to collate data from the general population, as well as vulnerable groups from different backgrounds, and perform a meta-analysis. Previous studies have reported the proportion of COVID-19 infections attributable to asymptomatic transmission to be around 20%, with some variation depending on the population group. In this study, a meta-analysis was performed that considered different population groups.

Methods

Study design

A systematic review and meta-analysis were performed.

Data sources and search strategy

For the systematic review and meta- analysis PRISMA guidelines were followed.[35,36] The following Boolean operators were used to search the PubMed database, Google scholar, medRxiv and BioRixv: 'asymptomatic transmission', '((COVID-19) AND (Coronavirus)) AND (Asymptomatic transmission)', '((COVID-19) OR (Coronavirus)) AND (asymptomatic transmission)', '(SARS-CoV-2) AND (asymptomatic transmission)', '(2019-nCoV) AND (asymptomatic transmission)', '(Wuhan pneumonia) AND (asymptomatic transmission)', '(Wuhan flu) AND (asymptomatic transmission)', '(2019-nCoV acute respiratory disease) AND (asymptomatic transmission)' and '(2019-nCoV respiratory syndrome) AND (asymptomatic transmission)'. This study included published literature in English language up to 17 August 2021..

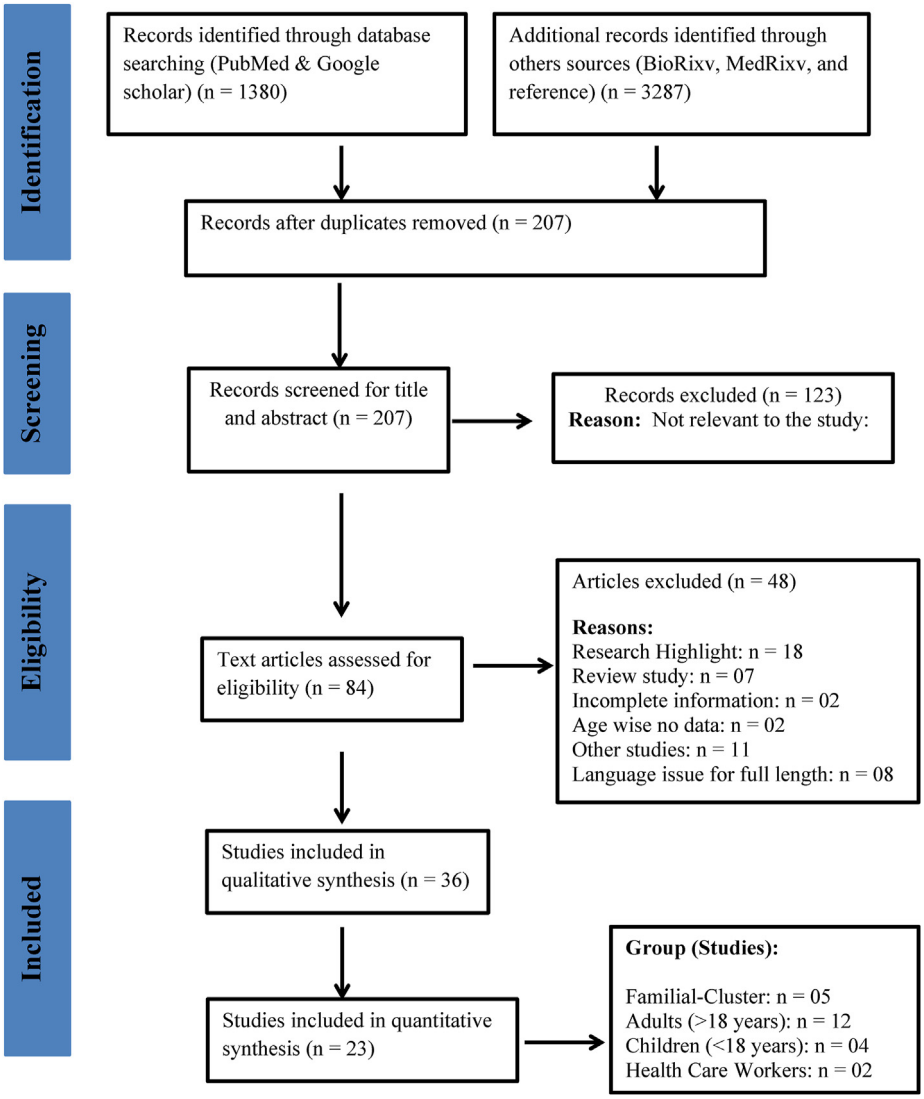

Fig. 1. PRISMA chart.

Table 1
Characteristics of the included studies.

Author	Country	Age, years [mean (±SD)/median (IRQ)]	Study Type	Type of test	Major findings
Family cluster					
Chan et al., 2020[8]	China	Family: 36-60 Child: 10	Cohort	RT-PCR	Supports person-to-person transmission between family
Chen et al., 2020[9]	China	8.5 ± 0.17	Case report	RT-PCR	The ability of COVID-19 transmission during the asymptomatic period even after negative viral testing
Lu et al., 2019[10]	China	8	Case report	RT-PCR	Supports rigorous investigation in the combination of various testing methods for asymptomatic COVID-19 cases
Qian et al., 2020[11]	China	6	Brief report	RT-PCR	Variation in clinical manifestation across individuals was observed
Ye et al., 2020[12]	China	38 ± 18.38	Cohort	RT-PCR	Possibility of COVID-19 transmission by the asymptomatic carrier during the incubation period
Bai et al., 2020[7]	China	20	Cohort	RT-PCR	Support asymptomatic transmission through a family contact
Xie et al., 2021[56]	China	>18	Cohort	RT-PCR	Handwashing, social distancing should be done
Zhang et al., 2021[57]	China	>18	Cohort	RT-PCR	Asymptomatic patients can transmit the disease and improve protective measures.
Adults					
Tian et al., 2020[21]	China	47.5	Cohort	RT-PCR	Early isolation and quarantine for close contacts to prevent asymptomatic transmission
Kim et al., 2020[17]	Korea	26 (22–47)	Research note	RT-PCR	Supports social distancing to prevent asymptomatic transmission
Kong et al., 2020[8]	China	37.7 (±19)	Cohort	RT-PCR	Suggest rigorous epidemiological history and chest CT scan as a practical tool to identify the asymptomatic COVID-19 cases in the community
Yin et al., 2020[22]	China	–	Cohort	RT-PCR	No difference in the transmission rate of COVID-19 between asymptomatic and symptomatic cases
Meng et al., 2020[55]	China	42.60 (±16.56)	Cohort	RT-PCR	Suggest chest CT scan as a vital tool to screen the asymptomatic COVID-19 cases in the community
Al Hosani et al., 2019[15]	UAE	37 (30–45)	Cohort	RT-PCR	No transmission among household contacts after the implication of strong isolation policies
He et al., 2020[16]	China	–	Cohort	RT-PCR	Significantly smaller transmissibility of asymptomatic cases than symptomatic
Qiu et al., 2020[20]	China	43 (8–84)	Cohort	RT-PCR	Suggested transmission occurred after 14 days quarantine periods
Zhou et al., 2020[24]	China	–	Short communication	RT-PCR	Recommended rigorous epidemiological history and nucleic acid testing
Park et al., 2020[19]	Korea	38 (20–0)	Report	RT-PCR	Supports contact tracing, testing and increasing quarantine to prevent asymptomatic COVID-19 transmission in the community
De laval et al., 2021[61]	France	40 (24–59)	Cohort	RT-PCR	The median incubation day was 4 (1–13) days.
Wong et al., 2020[34]	Brunei	–	Cohort	RT-PCR	Proposes differentiated testing strategies to account for different transmission risk
Huang et al., 2020[60]	China	–	Cohort	RT-PCR	To identify the presence of asymptomatic carriers as early as possible in the community. Infection occurs during the incubation period of asymptomatic cases.
Sugano et al., 2020[58]	Japan	–	Cohort	RT-PCR	Possibility of asymptomatic transmission and the period from exposure to illness ranged from 2 to 17 days.
Nsekye et al., 2021[62]	Rawanda	–	Cohort	RT-PCR	Contact tracing and testing should be done.
Children					
Hu et al., 2020[25]	China	<15	Cohort	RT-PCR	Suggest close contact tracing and nucleic acid testing to identify the asymptomatic COVID-19 tracing the community
Qiu et al., 2019[26]	China	8.3 (±3.5)	Cohort	RT-PCR	Possibility of asymptomatic COVID-19 transmission by close contacts
Tan et al., 2020[1]	China	–	Cohort	RT-PCR	Possibility of asymptomatic COVID-19 transmission by intrafamilial contact
Sun et al., 2020[59]	China	5.8	Cohort	RT-PCR	Both nasopharyngeal and anal swabs should be confirmed negative viral load before declaring full recovery to avoid oral-faecal transmission.
Health care Workers					
Kimball et al., 2020[27]	USA	–	Report	RT-PCR	Reported rapid transmission among health care worker
Schoierzeck et al., 2020[29]	Germany	48	Cohort	RT-PCR	Suggest nucleic acid testing for asymptomatic COVID-19 cases

Table 1 (*continued*)

Author	Country	Age, years [mean (±SD)/median (IRQ)]	Study Type	Type of test	Major findings
Lucar et al., 2020[28]	USA	>18	Cohort	RT-PCR	transmission reported because of prolonged surgery done on asymptomatic COVID-19 case
Traveller aged >18 years					
COVID-19 NERC, 2020[30]	Korea	>18	Cohort	RT-PCR	Supports asymptomatic transmission with minor symptoms
Mizumoto et al., 2020[32]	Japan	>18	Rapid communication	RT-PCR	Support social distancing to prevent the asymptomatic transmission
Wan et al., 2020[33]	China	>18	Short communication	RT-PCR	Possibility of asymptomatic transmission after 14 days quarantine from asymptomatic COVID-19 case
Wong et al., 2020[34]	Brunei	–	Rapid communication	RT-PCR	Support social distancing & nucleic acid testing of asymptomatic COVID-19 case
Le et al., 2020[54]	China	–	Abstract	–	Support asymptomatic COVID-19 viral transmissibility in the absence of signs and symptoms

Note: - Missing values (mean/median values were not reported).
IQR, interquartile range; RT-PCT, reverse transcription-polymerase chain reaction.

Inclusion and exclusion criteria

For the meta-analysis, the present study included cohort studies that reported asymptomatic person-to-person transmission among clusters. Studies that were published in the English language were included.

Data collection and study selection

Details of authors, sample size and numbers reported for the asymptomatic infection of COVID-19 were extracted and recorded independently. Data extraction was done separately by two independent reviewers, and disagreement was settled by a joint discussion. The data were carefully checked to minimise the risk of duplication.

Quality assessment

The Newcastle Ottawa scale (cohort studies) was used to evaluate the selected studies in the current systematic review and meta-analysis.[35,37]

Publication bias

Possible publication bias in this study was assessed for the included cohort studies.[38]

Statistical analyses and data synthesis

After extracting the results, studies were pooled and the effect of asymptomatic COVID-19 transmission was examined through the random effects method. For continuous outcomes, the standard error (SE) with 95% confidence intervals (CIs) were calculated. Heterogeneity between studies was assessed using the I^2 statistic (I^2 values indicating the existence of heterogeneity were assessed according to Higgins and colleagues).[35,39,40] Data for the meta-analysis were collated.[35,41] Data synthesis was conducted using the STATA 16.0 software.

Patient and public involvement

There was no direct patient or public involvement in this systematic review and meta-analysis.

Results

Literature search

The literature search and screening were performed according to the PRISMA chart (Fig. 1). Initially, 4667 published research articles were identified using the online database search. After removing 4460 duplicate publications, 207 research articles were shortlisted. After screening the title and abstracts, 123 articles were excluded and 84 full-text articles were assessed for eligibility. A further 48 studies were excluded because they were research highlight reports, review studies, had incomplete information, reported no age-specific data, were classified as 'other' non-relevant studies or had language issues. For the qualitative synthesis, 36 articles were selected and 23 studies were included in the meta-analysis. Studies were grouped into the following population subgroups: family clusters (n = 5), adults (n = 12), children (n = 4) and health care workers (n = 2).

Characteristics of the study participants

The main components of the included studies are summarised in Table 1. All published research articles were cohort (observational) study designs. Most of the studies are from China, Korea, the US, Japan and Germany. The current research includes articles published/available online up to 17 August 2021. The current systematic review reports data from 23 studies with a total of 1905 asymptomatic participants. The forest plots of asymptomatic positivity for COVID-19 among the study population (Fig. 2) and among different subgroups (Fig. 3) are shown.

Quality assessment

The Newcastle Ottawa Scale (for cohort studies) was used for qualitative evaluation of the studies included in the meta-analysis.[35,37] The risk of bias was assessed based on three domains (selection, comparability and outcome), as highlighted in Table 2.

Publication bias

The bubble plot (see Fig. 4) shows the study-specific effect size, where the size of each bubble is proportional to the precision of

each study. Asymptomatic participants' funnel plot (standard error) showed no obvious publication bias (Fig. 5).

Meta-analysis

The outcomes of the current meta-analysis (Table 3), and forest plots of asymptomatic positivity for COVID-19 among the study population (Fig. 2) and different subgroups (Fig. 3) are shown. A random-effects model was used for the different levels of reported asymptomatic COVID-19 transmission in the community. The current meta-analysis observed heterogeneity among familial clusters ($I^2 = 59.02\%$, $P = 0.04$, with a proportion of 15.72% [95% CI: 1.88, 36.10]) and adults aged ≥18 years ($I^2 = 97.47\%$, $P < 0.001$, with a proportion of 29.48% [95% CI: 15.56, 45.58]). This study did not observe any heterogeneity among children and health care workers, although the random effect model showed the proportion of asymptomatic transmission to be 24.09% (95% CI: 17.23, 31.62) and 0% (95% CI: 0.00, 3.17), respectively. We observed a significant difference ($P = 0.005$) of heterogeneity between groups ($I^2 = 95.30\%$).

Discussion

The current study summarised available literature reporting asymptomatic transmission of COVID-19 as retrospective studies and case reports from family clusters, adults, children, health care workers and travellers. The person-to-person asymptomatic transmission was observed among familial clusters in an asymptomatic COVID-19 child (aged 10 years old) who had an abnormal chest CT and in another asymptomatic child with mild chest CT manifestation; family members of these children showed signs of fever and respiratory issues and had a positive COVID-19 test result.[8,9] The current study suggests that thorough epidemiological investigations, in combination with multiple detection methods (e.g. reverse transcription PCR [RT-PCR], chest CT, rapid IgM-IgG and serum C-reactive protein [CRP] level), asymptomatic carriers in the community who are displaying different (or no) clinical manifestations can be identified.[10,11] Another study supports the possibility of asymptomatic transmission among familial clusters during the incubation period.[12] In addition, in a familial cluster of five COVID-19-positive patients, it was observed that they had contact with other asymptomatic family members who had returned from Wuhan, China, suggesting asymptomatic transmission.[7]

During any disease outbreak, the unborn babies of pregnant women are at high risk. It has been reported that pregnant women with asymptomatic COVID-19 infection have delivered babies who are negative for the COVID-19 nucleic acid test, suggesting no vertical transmission among neonates born to COVID-19-infected mothers.[14,42–49]

In Wuhan, a lower COVID-19 fatality rate and higher discharge rate were observed than in Beijing, China. It is essential to identify asymptomatic individuals and implement necessary control measures to prevent transmission.[21] In South Korea, 41 COVID-19 asymptomatic adults were identified (confirmed by RT-PCR) out of 213 individuals.[17] In another study among 100 asymptomatic cases, 60% developed delayed symptoms and none of the asymptomatic patients died, suggesting that asymptomatic transmission could take place during the incubation period.[18] Another study did not observe any difference in the symptomatic and asymptomatic COVID-19 transmission rates among patients.[22] In adults, CT imaging of asymptomatic COVID-19 individuals has advantages in highly suspicious cases with negative nucleic acid test results.[17] A serological investigation among 31 of 34 adult cases with

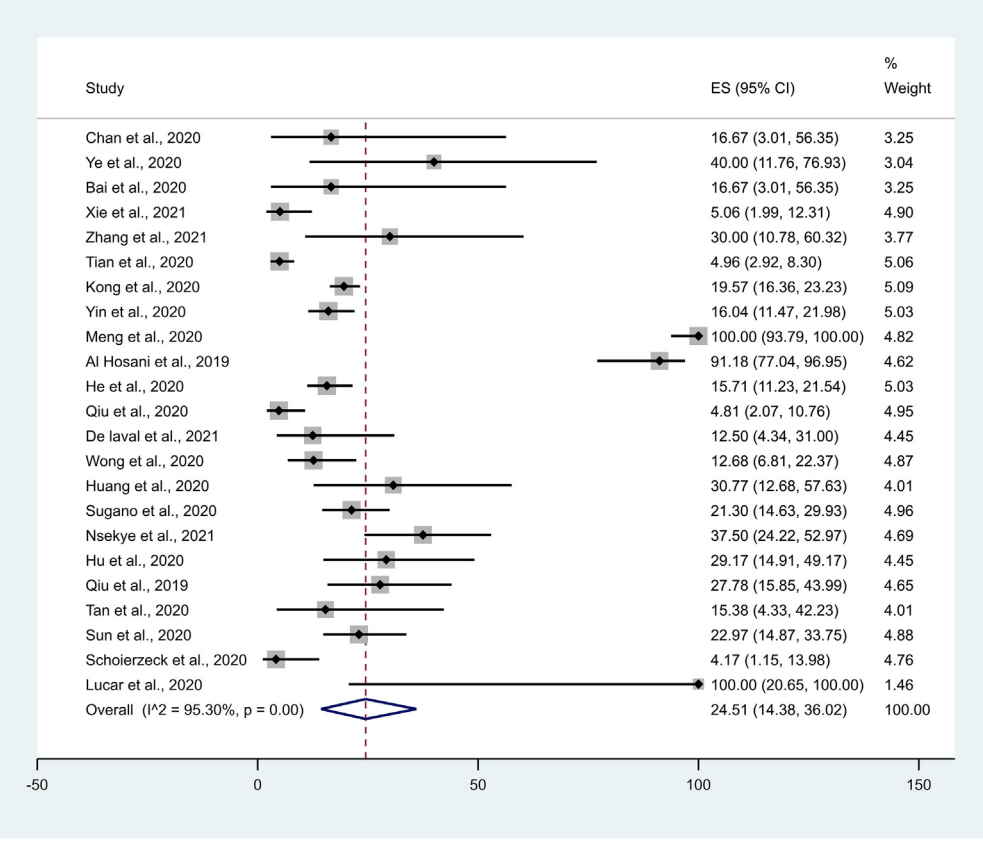

Fig. 2. Forest plot of asymptomatic positivity for COVID-19 among the study population. CI, confidence interval.

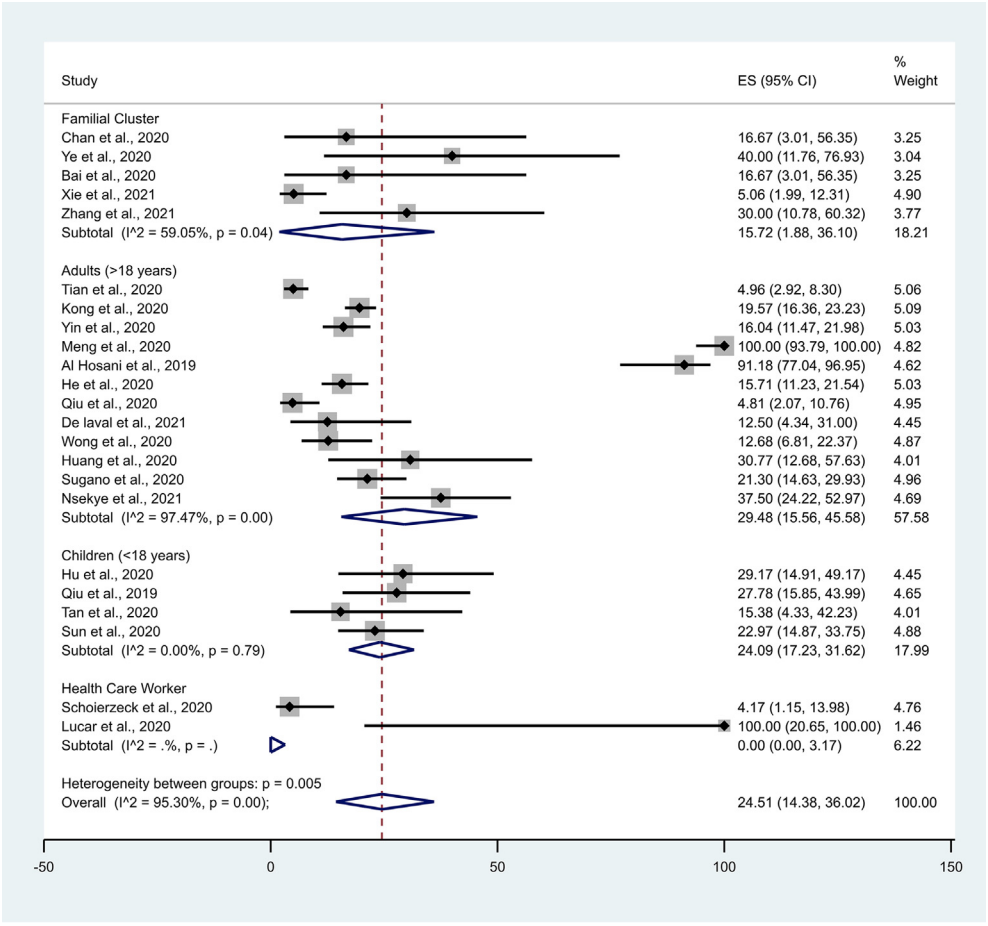

Fig. 3. Forest plot of asymptomatic positivity for COVID-19 among different population subgroups. CI, confidence interval.

asymptomatic COVID-19 infection did not require oxygen support during hospitalisation.[15] Theoretically, the quantified infection transmission rate shows the estimated risk ratio (RR) of infectivity of symptomatic against asymptomatic to be 3.9% (95% CI: 1.5, 11.8). In asymptomatic adults, the transmission was significantly smaller than in symptomatic cases.[16] No gender difference was observed for asymptomatic transmission.[20]

Further longitudinal surveillance using nucleic acid testing is warranted to identify and assess viral load among asymptomatic COVID-19 adults.[24] In one study, four asymptomatic cases were quarantined for 14 days; thus, these individuals were unable to transmit the infection due to proper isolation management.[19]

Asymptomatic COVID-19 transmission has been observed in children.[26] In one study, 24 asymptomatic cases were identified from close contacts of asymptomatic COVID-19 patients.[25] Another study supports multiple-site sampling of close contacts[1] among children. In a review, it was observed that adults with COVID-19 infection are more likely to show clinical symptoms and radiological manifestations than children, which is in line with previous reports for severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) coronaviruses.[50]

In a study investigating health care workers in a nursing facility, rapid transmission of COVID-19 was reported in 76 residents; 23 (30.3%) had positive test results, and 13 were asymptomatic on the day of testing, suggesting the possibility of asymptomatic transmission of COVID-19.[27] Establishing effective infection control strategies to prevent COVID-19 transmission among frontline health care workers and patients should be addressed urgently and as a priority. In another study, including 48 participants (healthcare worker), two asymptomatic cases become positive, suggesting appropriate testing strategies are essential to prevent outbreaks of COVID-19 within hospital settings.[29] In the United States, health care workers who were not wearing respirators were exposed to an asymptomatic COVID-19 patient without developing clinical illness.[28]

In Korea, COVID-19 was transmitted by 16 infected travellers from other countries; the disease was infectious at this stage, which resulted from close contact with asymptomatic carriers.[30] Most of the infections on board the Diamond Princess Cruise ship highlight the asymptomatic transmission of COVID-19 in confined settings. To further mitigate the transmissibility of COVID-19, it may be advised to minimise the number of individuals gathering in confined settings.[32] A 36-year-old traveller who returned from Wuhan tested positive for COVID-19 positive and health care workers who were in close contact with this patient also tested positive; however, the patient initially had no symptoms.[33] A high proportion of asymptomatic COVID-19 infection (12%) was reported among travellers returning to Brunei. Similarly, an asymptomatic COVID-19 patient showed viral transmissibility without showing any signs or symptoms after travelling in China.[31] In another study, it was suggested that testing facilities should be increased to help identify asymptomatic COVID-19 cases.[34]

Although this study recommends early isolation and social distancing for asymptomatic COVID-19 cases, it is important to recognise that this may lead to psychological and emotional distress (as reported in a qualitative study from the United

Table 2
Quality Assessment: Cohort study quality according to the Newcastle Ottawa scale.

Study	Selection******				Comparability**	Outcome*****			Total Quality Score
	1	2	3	4	5	6	7	8	
Family cluster									
Chan et al., 2020[8]	*	0	*	0	*	*	0	0	4
Ye et al., 2020[12]	*	0	*	0	0	*	0	0	3
Bai et al., 2020[7]	*	0	*	0	0	*	0	0	3
Xie et al., 2021[56]	*	0	*	0	0	*	0	0	3
Zhang et al., 2021[57]	*	0	*	0	0	*	0	0	3
Adults									
Tian et al., 2020[21]	*	0	*	0	0	*	0	0	3
Kong et al., 2020[8]	*	0	*	0	0	*	0	0	3
Yin et al., 2020[22]	*	0	*	0	0	*	0	0	3
Meng et al., 2020[55]	*	0	*	0	0	*	0	0	3
Al Hosani et al., 2019[15]	*	0	*	0	0	*	0	0	3
He et al., 2020[16]	*	0	*	0	0	*	0	0	3
Qiu et al., 2020[20]	*	0	*	0	0	*	0	0	3
De laval et al., 2021[61]	*	0	*	0	0	*	0	0	3
Wong et al., 2020[34]	*	0	*	0	*	*	0	0	4
Huang et al., 2020[60]	*	0	*	0	0	*	0	0	3
Sugano et al., 2020[58]	*	0	*	0	0	*	0	0	3
Nsekye et al., 2021[62]	*	0	*	0	0	*	0	0	3
Children									
Hu et al., 2020[25]	*	0	*	0	0	*	0	0	3
Qiu et al., 2019[26]	*	0	*	0	0	*	0	0	3
Tan et al., 2020[1]	*	0	*	0	0	*	0	0	3
Sun et al., 2020[59]	*	0	*	0	0	*	0	0	3
Health care Workers									
Schoierzeck et al., 2020[29]	*	0	*	0	0	*	0	0	3
Lucar et al., 2020[28]	*	0	*	0	0	*	0	0	3

Note: Selection; 1) Representativeness of the exposed cohort, 2) Selection of the non-exposed cohort, 3) Ascertain exposure, 4) Demonstration that outcome of interest was not present at the start of the study; **Comparability;** 5) Comparability of cohorts based on the design or analysis controlled for confounders; **Outcome:** 6) Assessment of outcome, 7) Was follow-up long enough for outcomes to occur, 8) Adequacy of follow-up of cohorts.
*Newcastle-Ottawa Scale contains 8 items within 3 domain and the total maximum score is 9. A study with score from 7-9, has high quality, 4-6, high risk, and 0-3 very high risk of bias.

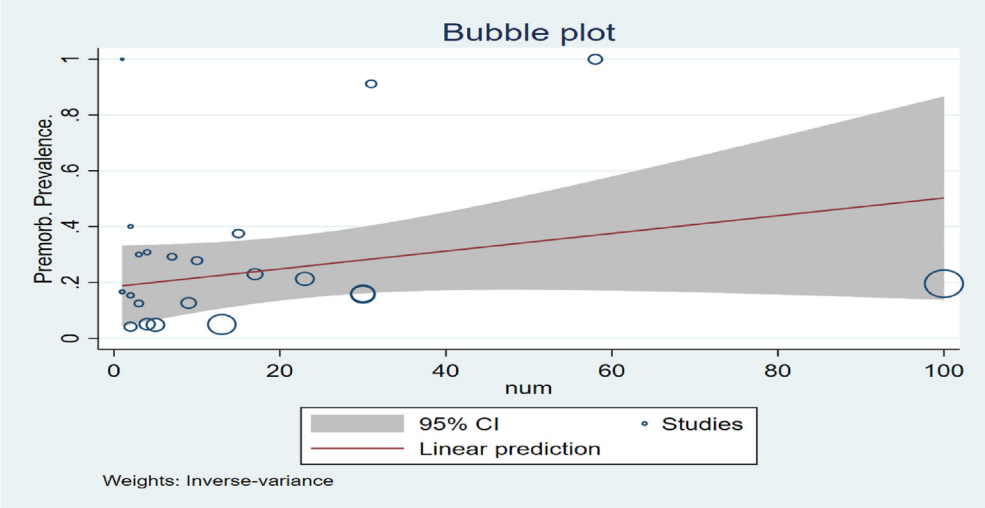

Fig. 4. Bubble Plot.

Kingdom).[51] Further studies are warranted based on the 'one health' approach to tackle asymptomatic transmission.[52] A study by Tao et al. suggested the inclusion of infection fatality rate (IFR) in surveillance data to minimise asymptomatic COVID-19 cases in the community.[53]

Limitations

There are some limitations in the current systematic review and meta-analysis. A mixed population, a continuous variable, variation in clinical conditions and use of different statistical methods may result in heterogeneity among studies included in the current meta-analysis. Furthermore, the current study only included reported cases of asymptomatic COVID-19 transmission.

Study importance

This is the first study to review the possibility of asymptomatic COVID-19 transmission among different population subgroups in the community. This study also identifies the potential role of

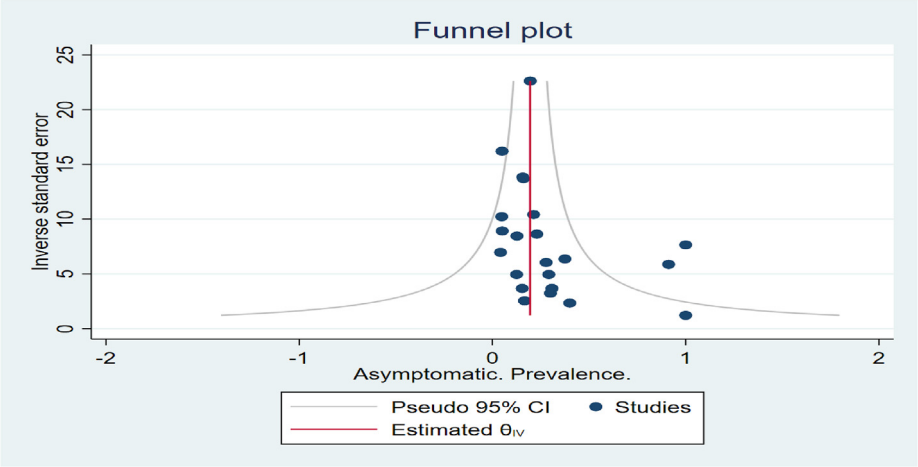

Fig. 5. Funnel Plot.

Table 3
The meta-analysis of asymptomatic transmission for COVID-19 among different population subgroups.

Risk factor (Asymptomatic) Group	Studies	Asymptomatic Population (n)	Total Sample Size (N)	Proportion (95% CI)	I^2, *P*-Value
Family Cluster	5	11	106	15.72 (1.88, 36.10)	59.02%, $P = 0.04$
Adults (≥18 years age)	12	321	1603	29.48 (15.56, 45.58)	97.47%, $P < 0.001$
Children (<18 years age)	4	36	147	24.09 (17.23, 31.62)	0.00%, $P = 0.79$
Health care Workers	2	3	49	0.00 (0.00, 3.17)	–
Combined (groups)	23	71	1905	24.51 (14.38, 36.02)	95.30%, $P < 0.001$

CI, confidence interval.

isolation, identification of close contacts, social distancing, and testing asymptomatic COVID-19 cases with chest CT scan and nucleic acid testing to minimise the spread of the virus in the community.

Conclusions

Currently, there is no evidence that COVID-19 can be transmitted in the asymptomatic stage; however, results suggest that asymptomatic infections are not limited to one population group (e.g. neonates, children, adults). In young people, it has been suggested that their strong immune status protects against COVID-19 severity. We hypothesise that asymptomatic carriers, either children or adults, should be vigilant as they are capable of transmitting COVID-19 during the incubation period without showing any signs or symptoms. As previous reports support the involvement of lung function in asymptomatic COVID-19 cases, we recommend chest CT scans among symptomatic cases, which is a convenient tool to monitor and track patients in their incubation period.

Author statements

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Ethical approval

Not required.

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Competing interests

None declared.

Contributors

Dr Khaiwal Ravindra: Concept design, data extraction, interpretation, final correction and writing the first draft. Mr Vivek Singh Malik: Data extraction, interpretation and writing the first draft. Dr Bijaya K Padhi: Interpretation, internal review of data, review and editing. Dr Sonu Goel: Discussion, review and editing. Dr Madhu Gupta: Internal review of data, review and editing.

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