Susceptibility to SARS-CoV-2 infection amongst children and adolescents compared with adults: a systematic review and meta-analysis

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Abstract

Background

The degree to which children and young people are infected by and transmit the SARS-CoV-2 virus is unclear. Clinical series and testing cohorts based upon screening of symptomatic cases provide biased estimates of susceptibility in children. The role of children and young people in transmission of SARS-CoV-2 is dependent on susceptibility, symptoms, viral load, social contact patterns and behaviour.

Methods

We undertook a rapid systematic review of contact-tracing studies and population-screening studies to address the question "What is the susceptibility to and transmission of SARS-CoV-2 by children and adolescents compared with adults?" We searched PubMed and medRxiv on 16 May 2020 and identified 6327 studies, with additional studies identified through handsearching of cited references (2) and professional contacts (4). We assessed quality, summarized findings and undertook a random effects meta-analysis of contact-tracing studies.

Results

18 studies met inclusion criteria; 9 contact-tracing, 8 population-screening and 1 systematic-review. Studies were of predominantly low and medium quality. Meta-analysis of contact tracing studies showed that the pooled odds ratio of being an infected contact in children compared with adults for all contact tracing studies was 0.44 (0.29, 0.69) with substantial heterogeneity (63%). Findings from a systematic review of household clusters of COVID-19 found 3/31 (10%) were due to a child index case and a population-based school contact tracing study found minimal transmission by child or teacher index cases. Findings from population-screening studies were heterogenous, included both infection prevalence and seroprevalence studies, and were not suitable for meta-analysis. Large studies from Iceland, the Netherlands and Spain and an Italian municipal study showed markedly lower prevalence amongst children and young people, however studies from Stockholm, England and municipalities in Switzerland and Germany showed no difference in prevalence between adults and children.

Conclusions

There is preliminary evidence that children and young people have lower susceptibility to SARS-CoV-2, with a 56% lower odds of being an infected contact. There is weak evidence that children and young people play a lesser role in transmission of SARS-CoV-2 at a population level. Our study provides no information on the infectivity of children.

Background

The degree to which children and young people are infected by and transmit the SARS-CoV-2 virus is an important but unanswered question.[1 2] It is however vital to assess this to inform plans for when and how countries should reopen schools and relax social other distancing measures and for determining the impacts of this on infections amongst children and on the broader population.

Initial data from China early in the COVID-19 pandemic showed that children comprised a very small proportion of clinical cases.[3] More recent studies show that children and young people account for 1-3% of reported cases across countries[4-7] and an even smaller proportion of severe cases and deaths.[4 8] However virus testing in nearly all countries has been limited to those with symptoms or contacts of with those with symptoms and may be influenced by healthcare-seeking behaviour. Children appear more likely to have asymptomatic infection than adults and symptom- or clinical-based series likely underestimate infections in children. Therefore such data are difficult to use to determine the prevalence, susceptibility, and infectiousness of SARS-CoV-2 amongst children and young people.

The role that children and young people play in transmission of SARS-CoV-2 by is dependent upon multiple factors, including their risk of exposure to potential infection, their probability of being infected upon exposure (susceptibility), the extent to which they develop symptoms upon infection or remain asymptomatic, the extent to which they develop a viral load sufficiently high to transmit and their propensity for making potentially infectious contact with others, dependent upon numbers of social contacts across age-groups and behaviour during those contacts.

Evidence is beginning to emerge on some of these areas. A very early systematic review of transmission in children identified few relevant studies.[9] Different study types may provide useful information on susceptibility and transmission in children compared with adults, yet each is open to various sources of bias. As noted above, data based upon symptomatic screening of populations or on clinical sources will provide only biased assessments of susceptibility amongst children.

Contact-tracing studies where children are the index case can provide evidence on transmission. A systematic review of household cluster studies, available in preprint, suggests that children were the index case in only 3 (10%) of 31 individual cluster studies.[10] Contact-tracing studies with systematic follow-up of all contacts to estimate secondary attack rates in children and adults can provide strong evidence on differential susceptibility. Findings from some contact tracing studies suggest that children are less likely to be secondary cases than adults,[11] although others have found no difference in secondary attack rates.[12] Few studies have examined transmission in school settings.[13] A population-based contact-tracing study from New South Wales, Australia, reported only two secondary cases in students and none in staff from 18 index cases (9 students, 9 staff), although children were rapidly being withdrawn from school during the follow-up[14] and awareness of COVID-19 was high. A preprint report from a high-school outbreak in France occurring before closure of schools reported transmission amongst 15-17 year old students but very few secondary cases amongst younger siblings.[14] National data from the Netherlands thus far report no school-based clusters of transmission.[6]

Population-screening studies may identify infection through viral RNA detection by real-time polymerase chain reaction (RT-PCR) or by serological detection of antibodies indicating response to infection. However the prevalence of SARS-CoV-2 in children in a population is not a direct indicator of susceptibility or transmission as the expected prevalence depends on multiple factors including i) the susceptibility of children; ii) mixing patterns in that population, especially mixing rates between adults and children, mixing between children, and interventions that disrupt mixing, e.g. school

closure or social distancing; iii) numbers of children and adults in the population; and iv) viral load and infectiousness. These are inter-dependent and therefore determining if the observed prevalence in children deviates from the expected prevalence is not straightforward. Conclusions that can be therefore drawn about susceptibility to and transmission of SARS-CoV-2 in children from contact-tracing and population studies are also subject to limitations depending on the definition of the population and the validity of tests used as well as the timing of screening in relationship to infection prevalence and social distancing measures.

There are no published studies addressing the mechanisms of transmission of SARS-CoV-2 in children. Data on viral load in children, a necessary prerequisite for transmission is extremely limited. An non-peer-reviewed report on SARS-CoV-2 viral load by age from Germany noted that some symptomatic children had viral load titres as high as adults and reported finding no relationship of viral load with age,[15] suggested to be evidence that children are as infectious as adults. However a re-analysis of these data has suggested that viral load may be lower in children than adults.[16]

We undertook a systematic review and meta-analysis of published and unpublished literature to assess the susceptibility to and transmission of SARS-CoV-2 in children and adolescents compared with adults. We limited this review to other systematic reviews, contact-tracing studies (other than those focused on single clusters) and population-based studies of prevalence as these are likely to be most informative and least open to bias. This is the first iteration of this review and we plan to update it as additional data become available.

Methods

Our review question was "What is the susceptibility to and transmission of SARS-CoV-2 by children and adolescents compared with adults?"

We undertook a rapid systematic review using two electronic databases searched on 16 May 2020. We included published and preprint studies and unpublished data from national public health websites because much data on COVID-19 are not yet published in the peer-reviewed literature.

Our inclusion criteria were as follows:

1. Data source: any published or preprint article type or data from a national public health website reporting government statistics and studies
2. Study type: contact tracing studies or population prevalence studies of SARS-CoV-2 / COVID-19
3. SARS-CoV-2 infection proven using PCR or serology
4. Outcomes:
    a. Contact tracing studies: study provides data on either i) rate of secondary infections in children and young people compared with adults, after contact with an index case; or ii) rate of secondary infections (of persons of any age) from child index cases compared with that from adult index cases. We only included studies that provided numerical data rather than only associations. We did not formally define age thresholds for children and adolescents as this was likely to exclude studies, but instead used the age-bands provided in each study.
    b. Population prevalence studies: study provides data on SARS-CoV-2 infection prevalence or seroprevalence in children and adolescents separately to adults.

We excluded the following studies:

1. reports of single clusters and contact tracing of single household outbreaks
2. studies of hospitalised patients, clinical studies and cohorts defined by symptoms e.g. national testing studies using symptom-based case definition
3. studies of unconfirmed cases i.e. cases based on self-report or symptoms
4. studies of healthcare workers or occupational health studies (as these exclude children)
5. modelling studies unless these also reported new data as above
6. reviews unless these reported summarised data
7. studies of vertical transmission
8. duplicate studies or those reporting from the same population of cases or contacts as other studies.

Search strategy

See Figure 1 for the search flow diagramme. We searched two electronic databases, PubMed and the medical preprint server medRxiv on 16 May. Searches included all studies up to 16 May 2020.

The search terms used for PubMed were:
("COVID-19"[tw] OR "2019-nCoV"[tw] OR "SARS-CoV-2"[tw]) AND ((child* OR infant*) OR ("transmission"[tw] OR "transmission" [mh]) OR ("Disease Susceptibility"[tw] OR "susceptibility"(mh)) OR ("epidemiology"[tw] OR "epidemiology" [mh]) OR ("contact tracing"[tw] or "communicable disease contact tracing"[mh])), with articles restricted to those on humans, in English and with abstracts.

The search terms used in medRxiv were separate searches for 'child and covid-19', 'covid-19 and epidemiology', 'covid-19 and susceptibility' and 'covid-19 transmission' as more complex Boolean search terms are not available.

Searches were undertaken by one researcher (RV) who screened studies on title and abstract to identify potentially eligible studies for full-text review. Full text studies were then reviewed by two researchers for eligibility (RV and OM or CW) and data were extracted independently by two researchers (RV and OM or CW). We handsearched cited references in all potentially eligible studies for additional candidate studies. Additional studies were also identified by the authors and through their professional networks.

From each of the included studies, data on country, study type, study context with regards social distancing measures and school closures at the time of the study, case definition, testing method, sampling method, and infection rates in adults and children were extracted. Where data were incomplete e.g. in preprints and in unpublished studies or online reports, we wrote to authors to request additional data.

Methodological quality of included studies was assessed based on a critical appraisal checklist for prevalence studies.[17] Seven methodological components were assessed: study had clear objectives; appropriateness of case identification; adequacy of sample size; adequate description of study setting (including description of social distancing measures at the time of study); detailed description of study participants; use of valid methods for testing for SARS-CoV-19; use of appropriate statistical methods to address study question. Two authors (OM and CW) critically appraised each study independently and assigned a score of 1 if criteria were met, 0 if not, or U (uncertain) if data were insufficient. We further assessed risk of bias relevant to the review question using two additional criteria: whether symptomatic contacts (in contact-tracing studies) or individuals (population-screening studies) were more likely to participate than asymptomatic ones; and whether the obtained sample was >75% of the intended sample. For population studies we additionally noted

whether the proportion of the population that were children and young people in the sample was >80% of that expected in the national population. We assigned studies an overall assessment of quality including assessment of risk of bias. Studies were categorised as high quality if they met all quality criteria and had low risk of bias on both criteria; medium if they had low risk of bias on 1 or more criteria and met ≥5 of 7 quality criteria; and low if they had met <5 quality criteria. Quality was assigned as Uncertain if multiple domains could not be scored due to lack of information.

Analysis
Summaries of all included studies are presented in the results along with a meta-analysis where data allowed. Contact tracing and population prevalence studies were considered separately. Random effects meta-analysis with restricted maximum likelihood estimation was undertaken using the *meta* commands in Stata 16 (StataCorp; College Station, TX). Odds ratios were used as the primary metric for contact tracing studies to estimate the relative odds of secondary attack rate in children and adolescents as compared to adults. Prevalence ratios were used as the primary metric in population-based studies to estimate the relative prevalence in children as compared to adults. We planned subgroup analyses based upon quality of study and age of children / adolescents where data allowed. Subgroup analysis was undertaken using restricted maximum likelihood.

Ethics
No ethical approvals were required for these secondary analyses of existing datasets.

Funding
No funding was received for this review.

Findings

The PubMed search resulted in 820 articles of which 47 were examined in full text and 6 included in the study (Figure 1). The total number of preprints identified through the separate medRxiv searches were 249, 2180, 1100 and 1978 respectively, totalling 5507 however there was some overlap between these that could not be quantified. Of these, 18 were potentially eligible and screened on full text and 6 were included. We identified a further 2 studies through reference-checking and identified three national prevalence studies and one regional school contact-tracing study through our professional contacts.

In total, 18 studies were included (Table 1) with quality and bias assessments shown in Table 2. Seven were peer-reviewed journal articles, 5 journal preprints, 4 non-peer reviewed reports and 1 was data from as yet unpublished national prevalence study. In terms of study type, 9 studies were contact tracing studies, 1 was a review of household contact studies and 7 were population-screening studies. Six studies were from mainland China, one each from Taiwan, Japan, Iceland, Italy, the Netherlands, Sweden, Germany, Spain, Switzerland, Australia and the UK, and one study was a review of small clusters from multiple countries (with no overlap with the contact-tracing studies). Measures of quality and potential for bias are shown in Table 2.

Web links for included studies (all are open access) are shown in Appendix Table 1.

Contact tracing studies
Of the 9 contract tracing studies (6 published, 2 in preprint, 1 unpublished report), 6 were from mainland China and one each from Taiwan, Japan and Australia. Index cases and secondary cases in all studies were identified by PCR virus testing.

Published studies

Zhang et al[11] undertook a contact tracing study following and testing all close contacts of COVID-19 cases reported in Hunan province to the Hunan Centers for Disease Control, China between January 16, 2020 and March 1, 2020. Contacts were followed for 14 days, and swabbed to find symptomatic and asymptomatic cases. The study included 114 clusters representing 136 index cases and 7193 contacts. One (0.7%) index case was aged <15 years. The authors reported that children aged 0-14 years had a lower risk of secondary infection than those aged 15-64 years (OR=0.34 (95%CI: 0.24-0.49), p-value<0.0001).

Bi et al.[12] undertook a contact tracing study in Shenzhen, China following 391 cases of COVID-19 and 1286 of their close contacts identified by the Shenzhen Center for Disease Control and Prevention between Jan 14 and Feb 12, 2020. Of the index cases, 32 (8.2%) were 0-19 years. Contacts were followed for 14 days. They reported no significant difference in attack rates in children (attack rate 7.4% in <10y, 7.1% in 10-19y) compared with adults.

Wu et al.[18] followed confirmed index cases and their household contacts from the city of Zhuhai, China, from 1 February to 1 March 2020. 35 out of 83 potential index cases participated, along with their 148 household contacts who were followed for 21 days. The study did not report numbers of children who were index cases. The authors found that age was not associated with the secondary attack rate.

Wang et al.[19] undertook a contact tracing study on 85 SARS-CoV-2 positive patients admitted to a hospital in Wuhan City, Hubei Province, China, over two days (13-14 February 2020). They enrolled 85 households corresponding to the 85 patients and identified 155 household contacts who were followed for 14 days. The age definition for children in this study was not reported. The authors reported that only 2/18 (11%) of children in households were positive compared with 130/222 (58.6%) of adults, however this included 8/18 (44%) of children that were not tested compared with 19% of adults. Re-analysis of only tested contacts shows that 2/10 (20%) of children were positive compared with 130/179 (73%) of adults.

Li et al.[20] undertook a contact tracing study of all index cases identified from two hospitals outside Wuhan in Hubei Province, China, from 1 January to 13 February 2020. They recruited 105 index patients with their households (n=105) and all family contacts (n=392). Family contacts were quarantined immediately for 14 days after their index was confirmed. The proportion of index cases who were children was not reported. Secondary infection with SARS-CoV-2 was detected in 64 of 392 household contacts (16.3%), with a lower infection rate in children <18 years (4%; 4/100) compared with 17.1% in adults.

Cheng et al.[21] undertook a prospective contact tracing study through the Taiwan Centers for Disease Control that enrolled all of the initial 100 confirmed COVID-19 cases in Taiwan (identified between 15 January and 18 March 2020) together with their 2761 close contacts (household and otherwise). Contacts were quarantined at home for 14 days after their last exposure to the index case. The youngest index case was age 11 years although the proportion of index cases that were children was not reported. They reported an overall secondary attack rate of 0.8%, lower in children <20y (0.4%) than in adults (0.9%).

Unpublished studies

Jing et al.[22] undertook a contact tracing study of all confirmed cases of COVID-19 reported to the Gangzhou Municipal Center for Disease Control (CDC) before 17 February 2020. Contact tracing was

undertaken by municipal CDC officers, with all household and other contacts quarantined and followed for 14 days. They identified 195 unrelated clusters with 212 primary cases and 137 nonprimary cases. Ten (4.7%) of index cases were aged <20 years. They reported that the odds of infection among those <20 years old compared with those 60+ was 0.27 (95% CI: 0.13-0.55).

Mizumoto et al.[23] in a brief report outlined the age distribution of secondary cases amongst the first 313 domestically acquired cases of COVID-19 in Japan before 7 March 2020 and their 2496 close contacts. Detail of type of contacts and on how long close contacts were followed for are lacking, however the total number of contacts (8 per index case) suggests these are likely household and non-household contacts. The authors reported that the secondary attack rate was 7.2% (95%CI: 3.0, 14.3) in males and 3.8% (0.8, 10.6) amongst females under age 20 years, compared with 22.2% (16.3, 29.0) amongst males and 21.9% (14.4, 31.0) amongst females 50-59 years.

The National Centre for Immunisation Research and Surveillance in Australia[14] undertook a contact-tracing survey of all SARS-COV-2 cases identified in schools in the state of New South Wales from 5 March to 21 April 2020. All school-related close contacts (n=863) of 18 positive cases (9 student; 9 staff cases) from 15 schools were followed up at 5-10 days after contact. Some contacts also received antibody testing (details are lacking). They reported that only 2 students and 0 staff cases were identified over the following 4 weeks (by positive serology). The 12 high school cases (8 students; 4 staff) from 10 schools had a total of 695 contacts (598 students; 97 staff), with 1 student secondary case identified. The risks of secondary infection in secondary schools were therefore 1/598 (0.2%) for students and 0/97 for staff. The 6 primary school cases (1 student; 5 staff) from 5 schools had a total of 168 contacts (137 student; 31 staff) and resulted in 1 student case. The risk of secondary infection in primary schools was therefore 1/137 (0.7%) for students and 0/31 for staff.

Meta-analysis of contact tracing studies

We undertook a random effects meta-analysis of secondary infection rates in children and young people compared with adults using data from the eight contact-tracing studies that included household or all close contacts. Data from the schools contact tracing study were not considered comparable as social contact matrices in schools were likely to be very different from households or the general population included in other studies. For these analyses we combined data on all children and young people <20 years and all adult age-groups >20 years, thus odds ratios (OR) and prevalence rates for adults may differ from those reported for particular age-groups.

The pooled OR estimate for all contact-tracing studies of being an infected contact in children compared with adults was 0.44 (0.29, 0.69) with substantial heterogeneity (63%) (Figure 2). We repeated this analysis grouping studies by quality (low compared with medium; Figure 3). The pooled estimate for medium quality (low risk of bias) studies was 0.51 (0.31, 0.83). The test for subgroup differences between low and medium quality studies was not significant (between group variance; df=1, chi2= 1.03, p=0.311).

Some of the contact-tracing studies included only household contacts whereas others traced all close contacts. We hypothesised that household studies might provide a clearer indication of the relative susceptibility to infection of children versus adults because all contacts within households might be assumed to receive a similar exposure to infection from index cases. We therefore undertook a post-hoc analysis which grouped studies by type of contacts (only household contacts or all contacts) (Figure 4). Studies of household contacts gave a lower pooled odds ratio (0.41 (0.23, 0.73) than did studies of all contacts (0.67 (0.52, 0.86) (between group variance; df=1, chi2= 12.66, p<0.001). The study by Mizumoto et al. was excluded from this analysis as data on type of contacts were not included. However the total number of contacts in this study made it unlikely these were household contacts only and sensitivity analysis including Mizumoto et al. in the all contacts

category did not substantially change these findings (Appendix Figure A1). There were insufficient data to undertake sensitivity analyses separating children and adolescents as few studies reported these separately.

Household cluster studies

None of the included contact-tracing studies reported secondary attack rates for child index cases separately to those for all index cases, and thus we were unable to examine the impact of transmission from child index cases from these studies. However we identified one systematic review (in preprint) of household cluster contact studies which addresses this question. Zhu et al[10] undertook a systematic review of household transmission clusters of COVID-19 from studies from China, Singapore, Vietnam, Japan, South Korea and Iran published up to March 2020. They combined a systematic review of online databases with information provided by public health news systems from China, Europe, France, Germany, Italy, Japan, South Korea and the USA. None of the contact-screening studies we report above were included in Zhu et al.'s review. The authors identified 31 household transmission clusters with sufficient data, defined as ≥ 2 confirmed COVID-19 cases occurring within 2 weeks of each other. Three of 31 (9.7%) household clusters identified to have a child (<18 years) as the index case. In sensitivity analyses to account for potential asymptomatic index children, the authors noted that if a child with asymptomatic infection in any household was presumed to be the asymptomatic index case, then potentially up to 6/28 (21%) of clusters could be due to child index cases. A third analysis excluding index cases with a travel history identified 2/23 (9%) with a child as the index case. The authors separately identified publications on household clusters of H5N1 influenza transmission and noted that children were the index case 54% (30/56) of such clusters. The review concluded that children have not played a substantive role in the intra-household transmission of SARS-Cov-2, although the study design could not establish whether children are less frequent among index cases because they are less infectious than adults or because they are less susceptible to infection in the first place.

Population screening studies

Of the 8 population prevalence studies, there was one published study of national prevalence of SARS-CoV-2 infection in Iceland, 3 preprint studies of municipalities with high prevalence (Vo, Italy; Gangelt, Germany; Geneva, Switzerland), 1 unpublished preliminary report from a nationally-representative prevalence study (Netherlands) and 3 non-peer reviewed reports of prevalence studies (Stockholm, Sweden; and national prevalence studies from Spain and England).

The study from Vo was undertaken before and immediately after the imposition of strict social distancing measures and primarily likely reflects transmission before 'lockdown', whilst moderate social distancing measures were instituted during data collection for the national Icelandic study and the Stockholm study. All other studies reflect the prevalence of SARS-Cov-2 infection during and after the imposition of significant social distancing measures.

Gudbjartsson et al.[24] report the detected prevalence of SARS-CoV-2 in the Icelandic population from 13 March to 6 April 2020. During this time primary schools were open however many but not all secondary schools were closed and there were moderate restrictions on social contacts. PCR was used to identify cases from nasopharyngeal and oropharyngeal samples. An additional targeted testing group was assessed however those data are not considered here as sampling was not population-based. In the population screening sample, no cases were identified in 848 children under 10 years compared with 100/12,232 (0.8% (0.7, 1.0) amongst those over 10 years. However, participation in the study was primarily by request of participants rather than by random sampling, which may have introduced biases in participation.

Lavezzo et al.[25] collected viral PCR data from 86% of the eligible resident population of the municipality of Vo, Veneto region, Italy, between 21 and 29 February 2020, in study undertaken close to the imposition of very strict social distancing measures in the region (from 23 February). We present data only from this first survey although the paper also reports a second survey undertaken during 'lockdown'. The authors reported that amongst those 0-20 years the secondary infection rate was 0.6% (3/467) compared with 3.0% amongst adults.

The Swedish Public Health Agency, Folkhälsomyndigheten,[26] undertook viral screening in the population of the capital Stockholm between 30 March and 6 April 2020. Sweden had instituted voluntary social distancing measures since 16 March 2020, with primary schools kept open although secondary schools were only teaching online. There were 18 positive cases from 707 valid tests in 738 participants (67% of those invited) who performed home self-sampling using nasopharyngeal swabs. The proportion of positive cases was below that needed to detect associations. The authors reported no significant differences in positivity between age groups; amongst 0-15 year olds there were 4 of 147 positive (2.8% (0.7, 7.0)) compared with 2.6% (1.1, 5.1) of 30-59 year olds.

The UK Office for National Statistics (ONS) published preliminary analyses of the nationally-representative Coronavirus (COVID-19) Infection Survey of the prevalence of PCR-positive SARS-CoV-2 amongst 10,705 individuals in England between 27 April and 10 May 2020.[27] We were unable to rate the quality of this study due to insufficient information. Cases were identified by home self-sampling using nasopharyngeal swabs with carers swabbing young children. 33 individuals in 30 households tested positive and that 0.32% (0.11, 0.72) of 2-19 year olds were positive, similar to 0.26% (0.12, 0.50) of 20-49 year olds and 0.32% (0.13, 0.66) of 50-69 year olds.

Streek et al.[28] conducted a sero-epidemiological study in a small German municipality (Gangelt) which was exposed to a super-spreading event (a carnival on 15 February 2020) with a high local infection rate followed by strict local social distancing measures from 28 February. The authors collected serology samples 6 weeks later (between 30 March and 7 April) whilst national social distancing was in place. A random sample of 600 households was invited to participate and 1007 individuals from 405 households participated and 919 provided serology data. They reported no association of age with the seropositivity rate although the seropositivity amongst 5-14 year olds was 9.1% compared with 15.4% for those 15 years or more. Note that 62% of the 88 participants who could not be assessed were children not assessed for technical reasons.

Stringhini et al.[29] undertook a seroprevalence study in Geneva canton from 6 April to 27 April 2020, Switzerland and report preliminary data from the first 3 weeks of planned 12 week study. 31% (1335) participated of those invited. Children and young people 5-19y made up 16% of the sample. They reported that that 13/214 of 5-19 year olds (6.0%, 95% CI 2.3-10.2%) were seropositive, similar to 20-49 year olds (8.5%, 95% CI 4.9-11.7) but with lower seroprevalence among those 50 and older (3.7%, 95%CI 0.9-6.0).

The Spanish Ministry of Health published the preliminary findings of the ENE-COVID-19 study, a nationally representative sero-prevalence study which collected data from 27 April to 11 May 2020.[30] We were unable to rate the quality of this study due to insufficient information. Participants were selected by random sampling of households in municipalities across Spain. Data reported here were from a rapid immunochromatography test (Orient Gene IgG, from Zhejiang Orient Gene Biotech) which did not require venepuncture. Comparison of the rapid test IgG with SARS-CoV-2 serology in 16,953 of the study sample found 97.3% agreement between tests. 60,897 participants provided samples out of 102,803 approached. Those 0-19 years (n=11,464) made up 23% of the sample. Prevalence by age-group was 1.1% in infants, 2.2% for 1-4 year olds, 3.0% for 5-9 year olds,

3.9% for 10-14 year olds and 3.8% for 15-19 year olds compared with 5.5% amongst adults aged 20 or over.

The Netherlands National Institute for Public Health and the Environment (RIVM) is conducting the Pienter Corona study, a nationally representative sero-prevalence survey of antibodies to SARS-CoV-2.[6] Population-based sampling was undertaken in a random sample of a randomly chosen subset of municipalities across the Netherlands. Preliminary data based upon samples taken between 31 March and 13 April 2020 was provided by the study principal on 13 May 2020[31] showing that in a total sample of 2096, seropositivity was found in 1% (0.3-2.3) of 0-19 year olds and 4.2% (3.3-5.3) of adults.

We did not undertake a meta-analysis of population-screening studies, given the important differences in the populations (including demography and exposure history), epidemic time-points and methodologies involved and because some of the studies only provided preliminary results. Figure 5 shows a forest plot of prevalence ratios for infection in children compared with adults, with studies grouped as: a) virus prevalence studies undertaken before institution of strict social distancing measures (Iceland; Vo; Stockholm); 2) late virus prevalence studies undertaken entirely during 'lockdown' (UK ONS); 3) national seroprevalence studies (Netherlands; Spain); and 4) municipal seroprevalence studies (Streek et al; Stringhini et. al). The viral-detection studies from Iceland and Italy, together with the Netherlands and Spanish national seroprevalence studies suggest markedly lower prevalence amongst children compared with adults. However the viral-detection studies from Stockholm and England and the serological surveys from Geneva and Gangelt showed no difference in prevalence / sero-prevalence between adults and children.

Discussion

We identified a rapidly growing literature on the susceptibility to SARS-CoV-2 in children and adolescents. However data on transmission by children and adolescents were very sparse and inconclusive.

Data from contact-tracing studies suggest there is preliminary evidence that children and young people have lower susceptibility for SARS-CoV-2 infection. Meta-analysis of these studies found the pooled odds ratio for testing positive in children compared with adults was 0.44 (0.29, 0.69), meaning those under approximately age 18-20 years had a 56% lower odds of infection than adults. The contact-tracing studies were largely consistent in finding children and adolescents had lower odds of being secondary cases when in contact with an index case than adults, and only the study by Bi et al. found an odds ratio close to one. There was little difference in the pooled estimate when only medium quality studies with low risk of bias were included. This pooled estimate is similar to an estimate analysis by Davies et al.,[32] who fitted a transmission model to data from 6 countries accounting for reduced social contacts during school closures and estimated that those under 20 years were approximately half as susceptible to SARS-CoV-2 as adults. In a post-hoc subgroup analysis we found that estimates of susceptibility were lower in studies of household contacts only compared with studies including all traced contacts. Such subgroup analyses are exploratory and this could reflect confounding by shielding of children within families. Data were insufficient to explore differences in susceptibility between younger children and adolescents and adults.

Data from population-screening studies are more heterogenous and were not suitable for meta-analysis. Using these data to determine the susceptibility of children to infection requires comparison of observed and expected prevalence, and determining expected prevalence depends on the dynamics of the epidemic prior to the sampling time. Two early viral-detection studies

(Iceland, Vo) and the Dutch and Spanish national seroprevalence study all show notably lower virus prevalence amongst children. In contrast, two infection prevalence studies, the Stockholm study and the recent UK ONS study, show infection rates in children similar to those in adults. There are a number of possible explanations for this discrepancy, but it is notable that there were 5 or fewer child infections in each of the population-screening studies aside from the Spanish national study, highlighting the great uncertainty in many of these estimates. It is important to note that the studies in the UK and Sweden have been done whilst social contacts have been reduced, to a lesser extent in Sweden and more markedly in the UK where little virus is now circulating. It is possible that the earlier viral-detection studies (Vo, Iceland) better reflect normal (pre-'lockdown') social contact patterns for children and adults, although they may also reflect the effects of travel amongst adults in spreading virus.

We found few data that were informative on the onward transmission of SARS-CoV-2 from children to others. Data from the systematic review of household cluster studies and from the large Australian school contact-tracing study suggest that, at a population level, children and young people might play only a limited role in transmission of this pandemic. This is consistent with the data on susceptibility noted above, i.e. suggesting that lower rates of secondary infection mean that children and young people have less opportunity for onward transmission. The strength of this evidence is however very weak and these data do not allow us to come to a conclusion about the infectivity of children and adolescents. It is worthwhile noting however that even those studies which found no differential effects by age do not suggest that SARS-CoV-2 is spread more by children than adults, unlike pandemic influenza.[33]

Limitations

Our study is subject to a number of limitations. Overall the number of studies in each category was low and quality was very mixed. We elected to include all studies regardless of quality due to the very high policy relevance of findings, however this limits our ability to make stronger conclusions.

We did not considered the impact of susceptibility by age for adults nor the impact of the shielding of older age groups on infection rates. . The demography of a population, as well as mixing rates within and between age groups is critical to determining the expected prevalence in each age group at the time of sampling. All the studies occurred at time of profound change in number and nature of social contacts that people have, and especially the effect of school closure. These changes and their timings have been different in different places and can alter the age-specific prevalence, as can geographic heterogeneity in transmission, meaning comparisons both within and between populations must be made with care.[34]

All included studies were open to bias. The secondary infection rate in some of the contact tracing studies was low, e.g. Bi et al., Cheng et al., and this may represent an underestimate of the unmitigated household attack rate of SARS-CoV-2 as transmission chains were cut short because of strict control measures.[33] Most of the contact-tracing studies were undertaken when strict social distancing measures had been introduced, e.g. closures of schools and workplaces, restriction of travel. This would have reduced contacts outside the home, especially contacts between children, but it may have increased contacts between children and adults by increasing the household contact rate. All the included contact-tracing studies are from East Asia with the exception of the Australian schools study. This does not necessarily reduce their generalisability, although more studies are needed from different regions. We have assumed that cases identified in contact-tracing studies are due to exposure to the index case. In the early stage of the epidemic, when most of these studies were done, this is reasonable, but at higher levels of community transmission it is possible that some cases amongst contacts are due to contact with other cases. It is not clear if exposure to other cases may differ by age and thus potentially bias the findings.

The numbers of children in these analyses was small in most of the studies, and was frequently less than the 15-25% of the population that children and adolescents under 18 years make up in most countries. This likely reflects lower recruitment of children and may be a source of bias, although the direction of this bias is unclear. Issues with the identification of virus or antibodies in young children may also be a source of bias; there may be technical issues with nasopharyngeal swab samples by carers in very young children. Age-differentials in mounting antibody responses to SARS-CoV-2 may also confound findings in seroprevalence studies.

A number of the population-screening studies reported only preliminary estimates (Netherlands Pienter, UK ONS, Stockholm and Spanish ENE-COVID-19 studies), and it is possible that the balance of child to adult positive cases will change with further recruitment. However we felt it was important to include these data in this review given the importance of the question and given that many of the preliminary studies were conducted by national public health agencies.

Findings from population-screening studies were inconsistent and may reflect a range of biases, even in large apparently well-conducted studies. In the national Iceland survey by Gudbjartsson et al., 57% of those in the population-screening group reported having some upper respiratory tract infection symptoms, interpreted as upper respiratory tract infections common in the Icelandic population. However this could have introduced bias if those with COVID-19 symptoms were more likely to respond to the screening invitation, inflating case positivity amongst adults but not amongst children. There were very small numbers of children and adolescents in all the population-screening studies with the exception of the Spanish ENE-COVID-19 study. Additionally, many of these studies consisted of preliminary reports, and conclusions must await further data.

We excluded from our review a large contact tracing study from Guangzhou, China, Luo et al.,[35] as: a) nearly one-third of the contacts were from a cruise ship in which the proportion of children in the population was likely low; and b) there was likely some overlap with an included study also from Guangzhou in which recruitment dates overlapped (Jing et al.). However Luo et al. reported that the secondary infection rate amongst 0-17 year olds was 1.8% (14/783) compared with 2.8% (115/4159) amongst those 18 or older. We also excluded the study by Fontanet et al.[36] of an outbreak in a French high school, as our criteria excluded single cluster studies.

Summary and implications

There is preliminary evidence that children and adolescents under 18-20 years have lower susceptibility to SARS-CoV-2 infection than adults. There is weak evidence that children and young people play a lesser role in transmission of SARS-CoV-2 at a population level, however our study provides no information on the infectivity of children per se. Further data are urgently needed to answer these questions. These include further large, high quality contact tracing studies with repeated swabbing and high-quality virus-detection studies. Studies which investigate secondary infections from child or adolescent index cases in comparison to secondary infections from adult index cases are particularly needed. Monitoring of infection rates and contact-tracing studies within child-care and school settings will also be important. A range of serological studies are planned in many countries and these need to be sufficiently powered to assess infection across different age groups and include repeated sampling at different time periods as social distancing restrictions are lifted. We will continue to update this review, including further data as available and updating preliminary data from some included studies.

References

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Figure 1. PRISMA flow diagramme for search

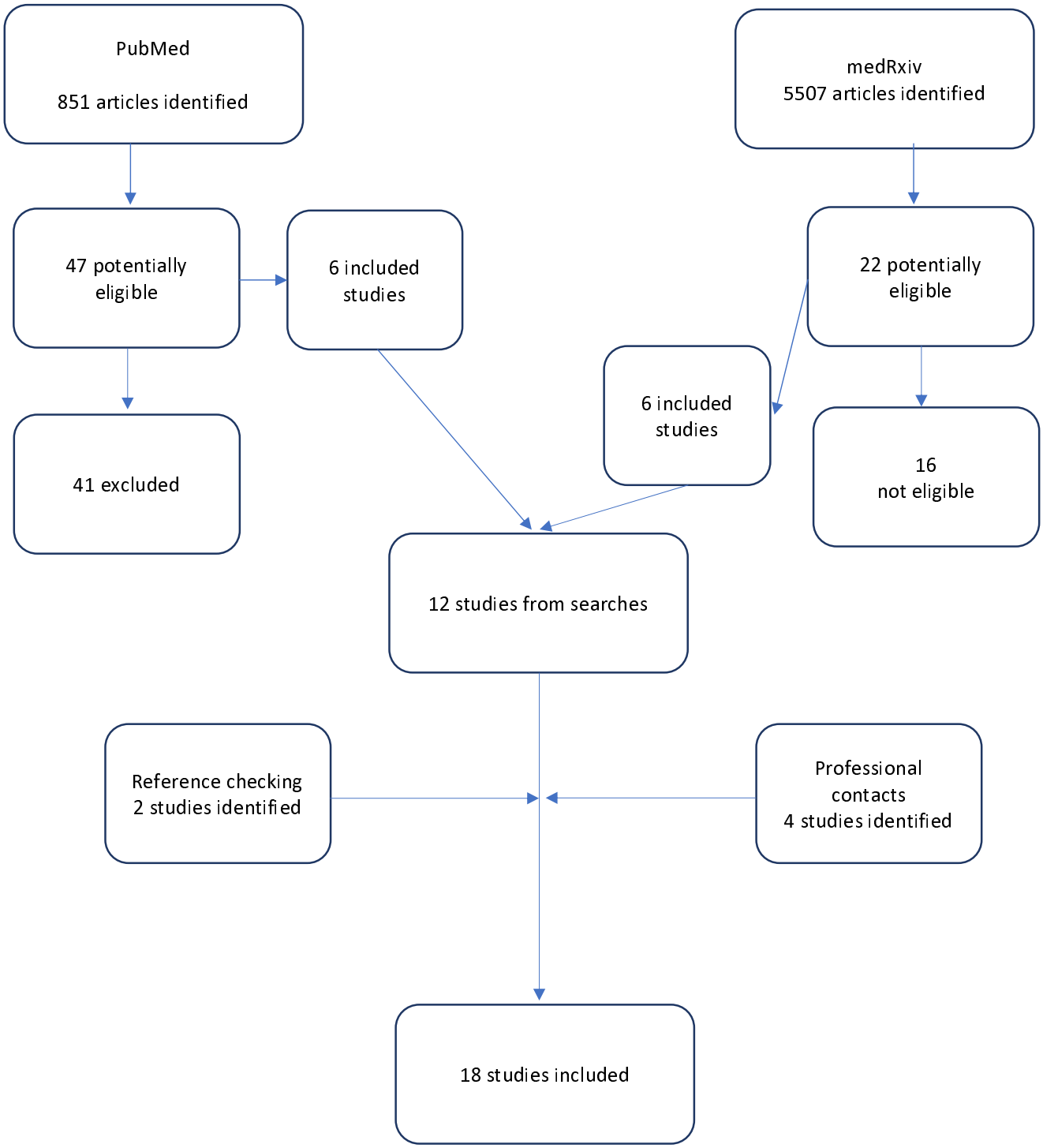

Figure 2. Pooled estimate of odds of being an infected contact in children compared adults for all contact tracing studies

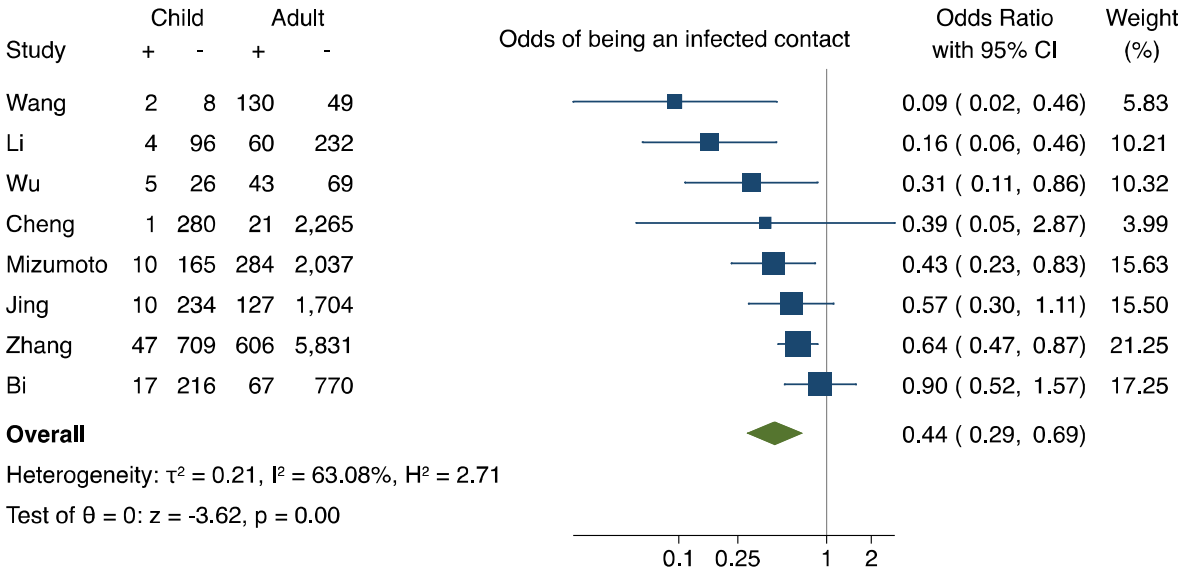

Figure 3. Pooled estimate of odds of being an infected contact in children compared with adults for in medium- compared with low-quality contact tracing studies (Quality defined in Table 2).

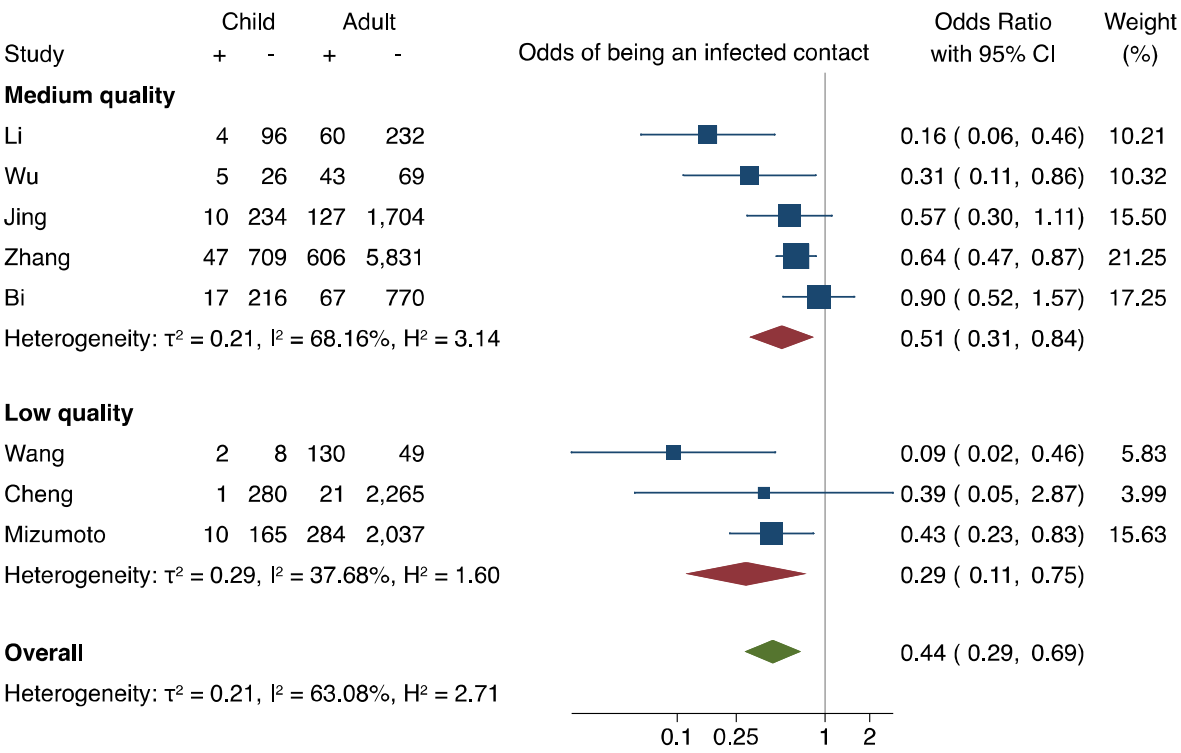

Figure 4. Pooled estimate of odds of being an infected contact in children compared with adults for in studies including all close contacts compared with household-only contact tracing studies

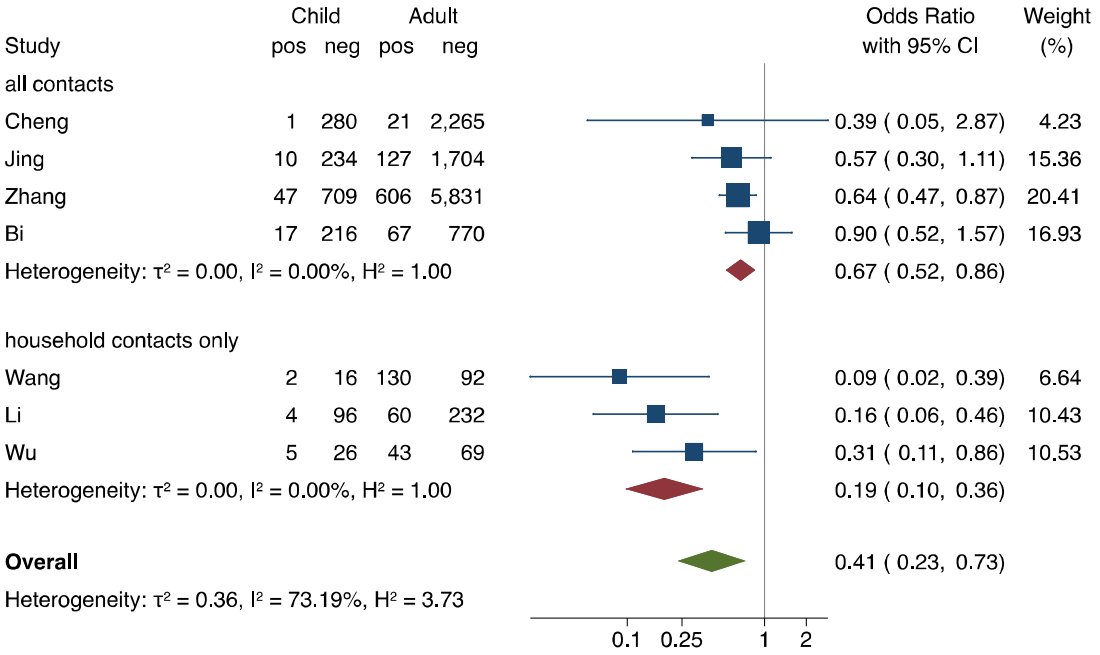

Figure 5. Ratios of the prevalence of SARS-CoV-2 infection in children and young people compared with adults in population-screening studies

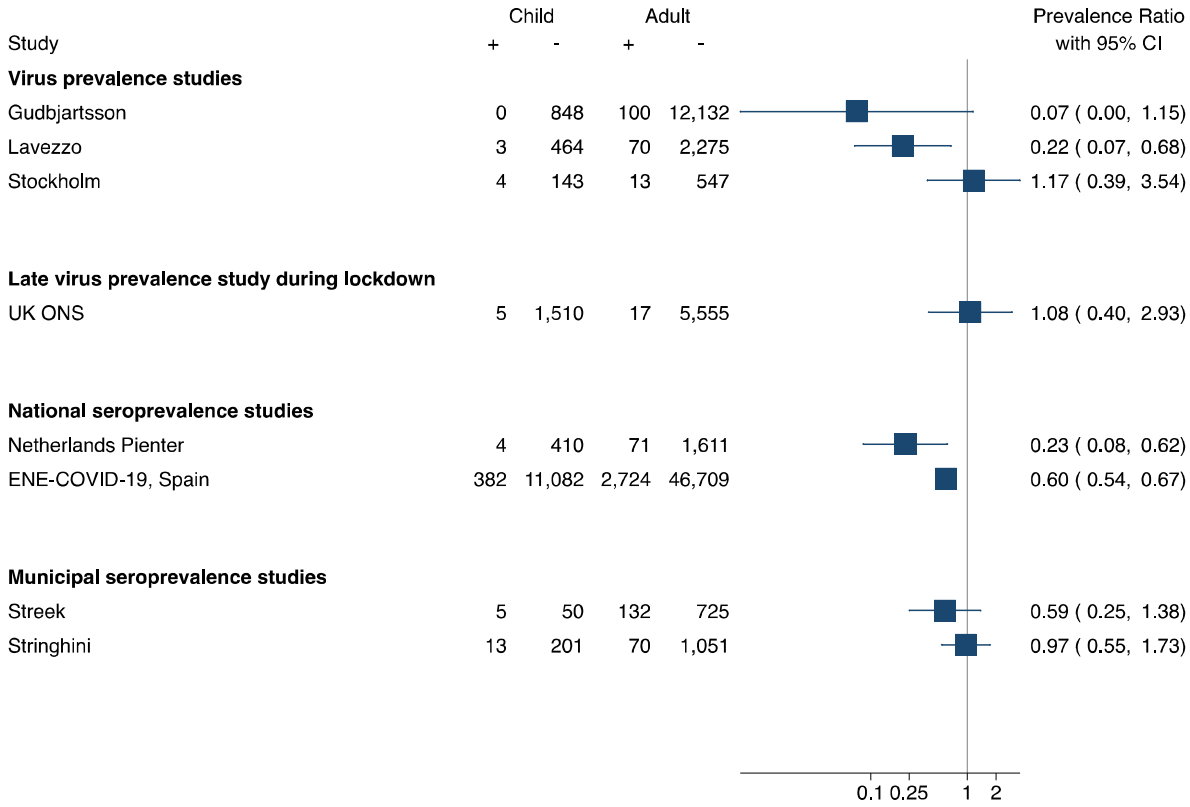

Table 1. Characteristics of included studies

A. Contact-tracing studies							
Author	**Status**	**Place**	**Recruitment of index cases**	**Recruitment and isolation of contacts**	**Contact type**	**Case definition/testing**	**Age: child / adult**
Bi et al.[12]	Published & peer reviewed	Shenzen City, Guangdong, China	Laboratory confirmed cases (n=391) identified by Shenzhen Centre for Disease Control and Prevention by 9 Feb 2020.	Close contacts were identified through contact tracing of a confirmed case and were defined as those who lived in the same apartment, shared a meal, travelled, or socially interacted with an index case 2 days before symptom onset. Recruited regardless of symptoms.	All contact types.	RT-PCR positive, nasal swabs Contacts tested regardless of whether they showed symptoms. 95% of contacts tested after 12 days.	0-19y / 20+y
Zhang et al.[11]	Published & peer reviewed	Hunan, China	All confirmed cases identified by Hunan CDC between 16 January and 1 March 2020 (n=136).	Close contacts were identified through contact tracing of a confirmed cases and placed under medical observation for 14 days. A close contact is defined as an individual who had unprotected close contact (within 1 meter) with a confirmed case or an asymptomatic infection within 2 days before their symptom onset or sample collection.	All contact types	RT-PCR positive All close contacts were tested in accordance with local policy regardless of symptoms. % of contacts tested not stated.	0-14y / 15+y
Jing et al.[22]	Preprint	Guangzhou City, Guangdong, China	Laboratory confirmed cases identified by Guangzhou Municipal CDC by 17 February that had contacts (n=335).	Close contacts were identified through contact tracing and all were quarantined and followed for 14 days. A close contact is defined as an individual who had unprotected close contact (within 1 meter) with a confirmed case or an asymptomatic infection within 2 days before their symptom onset or sample collection.	All contact types	RT-PCR positive All close contacts were followed up in accordance with local protocols. All contacts quarantined regardless of symptoms.	0-19y / 20+y
Li et al.[20]	Published & peer reviewed	Hubei, China (Hospitals in Zaoyang City and Chibi City)	Index cases identified from two hospitals (in Zaoyang City and Chibi City) (n=115) to 13 February 2020. Index cases were excluded if members of their family had links to Wuhan. Not clear if all cases from hospital were sampled or just a sub-set.	All household contacts were quarantined immediately for 14 days by the local government and monitored daily.	Household contacts	RT-PCR positive Nasopharyngeal swab samples were collected at the beginning and the middle of quarantine. 100% of contacts tested 2-4 times.	0-17y / 18+y
Cheng et al.[21]	Published & peer reviewed	Taiwan	The initial 100 confirmed cases in Taiwan between 15 January and 18 March 2020.	Close contacts were identified through epidemiological investigation and defined as a person who did not wear appropriate personal protection equipment (PPE) while having face-to-face contact with a confirmed case for more than 15 minutes during the investigation period (defined by epidemiological investigation and typically up to four days prior to symptom onset or test date	All contact types	RT-PCR positive. Routine testing for household and healthcare worker contacts (30.7%). Other contacts (69.3%) were only tested if symptomatic.	0-19y / 20+y

				for asymptomatic cases). All close contacts were quarantined at home for 14 days.			
Wang et al.[19]	Published & peer reviewed	Wuhan, China	Patients hospitalized in Union Hospital (n=85) on 13 and 14 February. Not clear if all cases from hospital were sampled or just a sub-set.	Household contacts of the hospitalised patients	Household contacts	RT-PCR positive Throat swabs. Process for testing household members not stated, but 33% of household contacts were not tested for SARS-CoV-2	Child age not defined.
Mizumoto et al.[37]	Preprint	Japan	Cases that were domestically acquired and confirmed by RT-PCR by 7 March 2020	Contacts of index cases, definition and method of ascertainment not given. No details on isolation of contacts.	Not stated	RT PCR positive. Process and eligibility for testing of contacts not described.	0-19y / 20+y
Wu et al.[18]	Published & peer reviewed	Zhuhai, China	All consecutive patients with probable or confirmed COVID-19 admitted to the Fifth Affiliated Hospital of Sun Yat-sen University from January 17 to February 29, 2020, who gave consent, did not live alone and tested positive (n=83).	Household members of the index cases and who gave consent were followed up for 21 days. No details on isolation of contacts.	Household contacts	RT PCR positive. Process and eligibility for testing of contacts not described, but followed local protocols. All contacts tested.	0-18y / 19+y
NCIRS[14]	Online report	New South Wales, Australia	Followed up all close contacts of COVID-19 cases in all 15 schools for which a person with proven COVID-19 had attended while infectious. Schools remained open but students dismissed from 23 March.	Followed up all close contacts (a person who has been in face to face contact for at least 15 minutes or in the same room for two hours with a case while infectious). All close contacts: a) symptom questionnaire; b) swabbed for COVID-19 testing at between 5-10 days after the last contact; c) had serology.	School-related contacts	RT PCR or serology positive. Swabs taken from 235/863 contacts (30.7%). Number with serology not stated.	5-18y / 20y+
B. Population-screening studies							
Author	**Status**	**Place**	**Context**	**Recruitment**	**Timing of survey**	**Case definition/testing**	**Age: child / adult**
Gudbjartsson et al.[24]	Published & peer reviewed	Iceland	First infection diagnosed on 28 February 2020; Containment measures put in place. Primary schools open but some secondary schools closed and moderate restrictions on social contacts from 13 March.	National population screening. Open invitation for 87% of participants through online portal but with collection of sample from one location (Reyjkavik), and random invitation for a sub-sample (13%). Children <10y made up 6.4% of sample.	13 March to 6 April.	RT-PCR on nasopharyngeal and oropharyngeal samples.	0-9y / 10+y
Lavezzo et al.[25]	Preprint	Vo, Veneto Region, Italy	Quarantined community in an area of Italy that was affected early and severely in the epidemic; area was 'locked down' from the 23 February for two weeks	All age groups were homogeneously sampled with age-specific percentages ranging from 70.8% to 91.6%. Two surveys undertaken; first survey only included here. Those <21y made up 17% of sample.	21-29 February 2020	RT-PCR on nasopharyngeal samples.	0-20y / 21+y
Pienter[6]	Unpublished	Netherlands	Social distancing measures introduced gradually from 11 March 2020. Schools closed	Population-based sampling was undertaken in a random sample of a randomly chosen subset of municipalities	31 March - 13 April 2020	Serology (IgG)	0-19y / 20+y

			from 15 March.	across the Netherlands. Those <20y made up 20% of sample.			
Streek et al.[28]	Preprint	Gangelt, Germany	Carnival held on 15 February. Strict local social distancing measures introduced on 28 February due to local outbreak and deaths.	A random sample of 600 households was invited to participate and 1007 individuals from 405 households participated. 5-14y olds made up 6.0% of sample.	30 March – 7 April	Serology (IgG)	5-14y / 15+y
Stringhini et al.[29]	Preprint	Geneva canton, Switzerland	First case on 26 Feb 2020. Schools closed on 16 March and strict social distancing measures introduced 20 March. Seroprevalence initiated using a population-based sample in canton.	Population-based but not fully random sample. 1300 randomly selected adults approached each week for 3 weeks and invited to bring all household aged 5+ for serology. Only non-symptomatic individuals studied. Total participation was 1335 from 633 households, 31% of invited in first 3 weeks. 16% aged <20y.	6 April to 27 April 2020	Serology (IgG)	5-19y / 20+y
UK ONS[27]	Online report	England	Strict national social distancing measures enacted 20 March 2020.	Representative sample of 10,705 individuals in England. These represent preliminary data from a larger national study of virus prevalence and (future) sero-prevalence. Those 2-19y made up 21.4% of the population.	27 April – 10 May 2020	RT-PCR on nasopharyngeal samples.	2-19y / 20+y
Stockholm[26]	Online report	Stockholm, Sweden	First death reported in Stockholm on 11 March 2020. Voluntary social distancing measures recommended from 16 March 2020, with secondary schools recommended to teach virtually. Primary schools remained open.	Representative sample of population of Stockholm invited. 738 (67% of invited) responded.	30 March - 6 April 2020	RT-PCR on nasopharyngeal samples.	0-15y / 16+y
ENE-COVID-19	Online report	Spain	Strict social distancing was imposed on 14 March 2020. Some restrictions were lifted on 27 April and further restrictions lifted on 11 May.	National representative sample obtained from random sampling of households in municipalities across Spain. 60,897 participants provided samples out of 102,803 approached.	27 April - 11 May 2020	rapid immunochromatography IgG: Orient Gene, Zhejiang Orient Gene Biotech	0-19y / 20+y
C. Household contact studies			**Methods**	**Timing**		**Case definition/testing**	**Age: child / adult**
Zhu et al[10]	Preprint	Studies from China, Europe, France, Germany, Italy, Japan, South Korea and the USA	Review through electronic databases and national public health news reporting: 31 household transmission clusters	Data accessed from 1 Dec 2019 to 18 March 2020		Household cluster defined as ≥ 2 confirmed COVID-19 cases occurring within 2 weeks of each other. Cases defined by national criteria in each cluster.	0-17y / 18+y

Table 2. Quality and bias assessments of included studies

Studies were assigned a score of 1 if criteria were met, 0 if not or U if unknown/Uncertain.

Quality Assessment of Contact Tracing Studies

Author	Clear objectives	Were the participants identified suitable for the objectives of the study?	Adequate sample size	Setting clearly described	Description of participants	Use of RT-PCR to test all contacts	Statistical methods appropriate	Risk of bias 1: identification of contacts through symptoms	Risk of bias 2: % of contacts recruited / tested	Quality summary
Bi	1	1	1	0	1	1	1	No	95%	Medium
Zhang	1	1	1	0	1	1	1	No	U	Medium
Jing	1	1	1	0	1	1	1	No	100%	Medium
Li	1	1	0	0	1	U	1	No	100%	Medium
Cheng	1	1	0	0	1	0	1	No	31%	Low
Wang	1	1	0	0	1	0	1	No	66%	Low
Mizumoto	0	U	1	0	0	U	1	U	U	Low
Wu	1	1	0	0	1	U	1	No	100%	Medium
NCIRS	1	1	1	1	1	0	1	No	31%	Low

Table 2b: Quality Assessment of Population-Based Studies

Author	Clear objectives	Were the participants identified suitable for the objectives of the study?	Adequate sample size	Setting clearly described	Description of participants	Valid testing method	Statistical methods appropriate	Risk of bias: identification of population through symptoms	Risk of bias: % of population recruited / tested	Quality summary
Gudbjartson	1	1	1	1	1	1	1	No	U	Medium
Lavezzo	1	1	1	1	1	1	1	No	82.3% 0-10y; 89.7% 10-19y	High
Pienter	1	1	1	U	U	1	1	No	U	Uncertain
Streek	1	1	1	1	1	1	1	No	91.2% overall; for children the	Medium

									participation rate was 55/109 i.e. 50%	
Stringhini	1	1	1	1	1	1	1	No	31%	Medium
UK ONS	1	1	1	U	U	1	1	No	U	Uncertain
Stockholm	1	1	1	1	1	1	1	No	U – potentially 30%	Uncertain
ENE-COVID-19	1	1	1	1	1	0	1	No	62.3% participated, of whom 89.4% provided samples	Uncertain

Appendix / Supplementary Material

Appendix Table 1. Web links for included studies.

Bi et al. https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30287-5/fulltext

Zhang et al. https://science.sciencemag.org/content/sci/early/2020/04/28/science.abb8001.full.pdf

Wu et al. https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa557/5835845

Wang et al. https://www.journalofinfection.com/article/S0163-4453(20)30169-9/pdf

Jing et al. https://www.medrxiv.org/content/10.1101/2020.04.11.20056010v1

Li et al. https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa450/5821281

Cheng et al: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2765641

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Appendix Figure A1.