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Serological evidence of human infection with SARS-CoV-2: a systematic review and meta-analysis

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Summary

Background A rapidly increasing number of serological surveys for antibodies to SARS-CoV-2 have been reported worldwide. We aimed to synthesise, combine, and assess this large corpus of data.

Methods In this systematic review and meta-analysis, we searched PubMed, Embase, Web of Science, and five preprint servers for articles published in English between Dec 1, 2019, and Dec 22, 2020. Studies evaluating SARS-CoV-2 seroprevalence in humans after the first identified case in the area were included. Studies that only reported serological responses among patients with COVID-19, those using known infection status samples, or any animal experiments were all excluded. All data used for analysis were extracted from included papers. Study quality was assessed using a standardised scale. We estimated age-specific, sex-specific, and race-specific seroprevalence by WHO regions and subpopulations with different levels of exposures, and the ratio of serology-identified infections to virologically confirmed cases. This study is registered with PROSPERO, CRD42020198253.

Findings 16 506 studies were identified in the initial search, 2523 were assessed for eligibility after removal of duplicates and inappropriate titles and abstracts, and 404 serological studies (representing tests in 5 168 360 individuals) were included in the meta-analysis. In the 82 studies of higher quality, close contacts (18·0%, 95% CI 15·7–20·3) and high-risk health-care workers (17·1%, 9·9–24·4) had higher seroprevalence than did low-risk health-care workers (4·2%, 1·5–6·9) and the general population (8·0%, 6·8–9·2). The heterogeneity between included studies was high, with an overall I^2 of 99·9% (p<0·0001). Seroprevalence varied greatly across WHO regions, with the lowest seroprevalence of general populations in the Western Pacific region (1·7%, 95% CI 0·0–5·0). The pooled infection-to-case ratio was similar between the region of the Americas (6·9, 95% CI 2·7–17·3) and the European region (8·4, 6·5–10·7), but higher in India (56·5, 28·5–112·0), the only country in the South-East Asia region with data.

Interpretation Antibody-mediated herd immunity is far from being reached in most settings. Estimates of the ratio of serologically detected infections per virologically confirmed cases across WHO regions can help provide insights into the true proportion of the population infected from routine confirmation data.

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For the Chinese translation of the abstract see Online for appendix 1

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Introduction

The COVID-19 pandemic, caused by SARS-CoV-2, was first reported in Wuhan, China, in December, 2019, and quickly spread globally.[1] As of Feb 9, 2021, more than 100 million COVID-19 cases, including 2 316 389 deaths, had been reported in 223 countries or regions.[2] The true number of SARS-CoV-2 infections is undoubtedly much higher than the officially reported number of cases due to various factors, including the occurrence of asymptomatic infections, variable seeking of health care for clinically mild cases, varied testing strategies in different countries, false-negative virological tests, and incomplete case reporting. Therefore, the reported COVID-19 cases based on clinical identification with virological confirmation only represent a small proportion, with a large number of asymptomatic and mild infections in the general population that might only be identified by sero-epidemiological studies.[3]

Serological studies are a useful tool to estimate the proportion of the population previously infected, to quantify the magnitude of transmission of pathogens, estimate the infection fatality rate,[4] assess the effect of interventions,[5] and when correlates of protection are available, estimate the degree of population immunity.[6,7] Insights from serological surveillance can be valuable for policy makers and health officials when planning public health decision making.

Several serological investigations across the world have been published during the 12 months of the COVID-19 pandemic, with highly variable estimates of seroprevalence that could largely be due to differences in attack rates, but which also feature heterogeneous

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Research in context

Evidence before this study

Serological evidence for SARS-CoV-2 infection is essential to understand the proportion of the population previously infected. Many serological investigations across the world have been done and the data analysed. We searched PubMed, Embase, Web of Science, and five preprint servers for articles published between Dec 1, 2019, and Dec 22, 2020, with the following primary search terms: "SARS-CoV-2", "COVID-19", "seroprevalence", "antibodies", and "seroepidemiological". Inclusion criteria were articles published in English that evaluated SARS-CoV-2 seroprevalence in humans after the first identified case in the area, and which reported the assays used. Several narrative reviews only summarised serological data at the early stage of the COVID-19 pandemic without using standard meta-analysis techniques. Another two meta-analyses separately estimated the seroprevalence of general populations and health-care workers, rather than providing a comprehensive assessment of seroprevalence in subpopulations with different levels of exposures. None of these reviews have made pooled estimates of the infection-to-case ratio (serologically detected infections per virologically confirmed cases).

Added value of this study

This systematic review and meta-analysis includes serological data for more than 5 168 360 study participants from 404 serosurveys and provides a comprehensive assessment of the seroprevalence of SARS-CoV-2 human infections. On the basis of study design, laboratory method, and outcome correction, we systematically assessed the overall quality of the existing seroprevalence studies of SARS-CoV-2 and found that it was generally low. A higher prevalence of SARS-CoV-2-specific antibodies was observed in close contacts (18·0%) and high-risk health-care workers (17·1%) than in low-risk health-care workers (4·2%) and the general population (8·0%). Seroprevalence varied hugely across WHO regions, with the highest seroprevalence of general populations in the South-East Asia region (19·6%) and the lowest in the Western Pacific region (1·7%). We also found that young people (<20 years) and older people (≥65 years) were less likely to be seropositive than were individuals aged 20–64 years, and no significant difference was found between men and women. The pooled infection-to-case ratio was similar between the region of the Americas and the European region, but higher in the South-East Asia region.

Implications of all the available evidence

Overall, existing serological evidence shows a higher infection risk among close contacts and health-care workers who do not have access to personal protective equipment. The relatively low prevalence of SARS-CoV-2-specific antibodies among general populations suggests that most populations examined have not been infected, and herd immunity is far from being achieved in most settings. The general low quality of most of the existing seroprevalence studies indicates the effect of differences in study design, laboratory methods, and outcome adjustment on the interpretability of serological studies of human infections with SARS-CoV-2. Therefore, international collaborations to standardise serological survey and laboratory methods are urgently required.

See Online for appendix 2

sampling strategies and assays used. Several systematic reviews and meta-analyses of SARS-CoV-2 seroprevalence were identified but had limited scope and did not investigate important differences between subpopulations, quantitatively assess study quality, or estimate the infection-to-case ratio.[8–12]

We did a systematic review and meta-analysis to summarise serological surveys for SARS-CoV-2 infections in humans; to comprehensively evaluate the study designs, laboratory methods, and outcome interpretations for each included serological study; and to estimate the risk of infections by populations with different presumed levels of exposure to SARS-CoV-2. We aim for these results to help inform decision makers and researchers as plans are made for the next phases of the global pandemic.

Methods

Search strategy and selection criteria

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[13] we did a systematic literature review from three peer-reviewed databases (PubMed, Embase, and Web of Science) and five preprint severs (medRxiv, bioRxiv, SSRN, Wellcome Open Research, and Europe PMC) with predefined search terms (appendix 2 pp 10–11). The search terms used for PubMed were as follows: "2019-nCoV" OR "coronavirus disease 2019" OR "COVID-19" OR "severe acute respiratory syndrome coronavirus 2" OR "SARS-CoV-2" AND (seroprevalen* OR seroincidenc* OR seroconversion OR seronegative OR seropositive* OR seroepidemiolog* OR serolog* OR serosurvey* OR antibod* OR infection* AND ("attack rate" OR "cumulative incidence"). Two independent researchers (Xinh C, ZC) screened titles and abstracts of papers published in English from Dec 1, 2019, to Dec 22, 2020, meeting the following criteria: (1) a report of seroprevalence in either the general population or some other well-defined population of non-COVID-19 clinical cases; (2) done after the first reported case in the area; and (3) reporting the specific assays used. We excluded studies that only reported serological responses among patients with COVID-19, those using samples with known infection status (eg, validation studies of assays), and animal experiments. We excluded abstracts of congress meetings or conference proceedings, study protocols, media news, commentaries, reviews, or case reports.

The full texts of included studies after initial screening were scrutinised to assess the overall eligibility based on the inclusion and exclusion criteria by two independent researchers (Xinh C, ZC). A third researcher (HY) was consulted when the two reviewers disagreed on study assessment. For eligible studies, data were extracted by researchers (Xinh C, ZC) on the number of participants who provided specimens and the number of these who were seropositive to calculate the seroprevalence. When data were inconsistent between reviewers, they were asked to discuss and revisit the article until reaching a consensus. If key information, such as the use of personal protective equipment (PPE) of health-care workers, was not reported in the paper, we contacted the corresponding author via email. For each included study, we described its characteristics, laboratory testing method, and primary outcome (appendix 2 pp 12–144).

To assess study quality, we developed a scoring system on the basis of a seroepidemiological protocol from the Consortium for the Standardization of Influenza Seroepidemiology,[14] a previously published scoring system for seroprevalence studies of zoonotic influenza viruses,[15] and a seroepidemiological protocol developed by WHO.[16] We comprehensively assessed study design (representativeness of study participants), laboratory assay (whether internal assay validations or a confirmatory assay was done), and outcome adjustment (correction for demographics or test performance, or both) and an overall score was determined for each included study (appendix 2 pp 145–46). From this score, two researchers (Xinh C, ZC) classified each study's quality into one of four grades: A, B, C, or D. When disagreements arose, a third investigator (HY) was consulted. Grade A, the highest quality category, spanned studies with scores ranging from 10 to 12, grade B from 7 to 9, grade C from 4 to 6, and grade D from 0 to 3. We only included grade A and grade B studies in the main analysis but provide additional results with all studies, irrespective of grade, in appendix 2 (pp 205–06).

Data analysis

Seroprevalence was defined as the prevalence of SARS-CoV-2-specific antibodies at or above a designated antibody titre to define a seropositive result in each original study. For serial cross-sectional studies, we calculated the sum of the total number of participants who provided specimens and total number of seropositive individuals during the whole study period, to avoid repeated inclusion of the same study. Similarly, only data from the first blood collection were analysed for studies with a longitudinal design to limit selection bias associated with retention in the study. For studies that used multiple serological assays, we used the seropositive results from the assay with the highest sensitivity and specificity (calculated by Youden's index). If a study used a confirmatory assay (eg, microneutralisation assay) to validate the positive or equivocal result from the initial screening, we used the results from the confirmatory assay. We also did a sensitivity analysis with results from the other assays (sensitivity analysis 1) and with individuals considered positive if they tested positive in at least one single assay (sensitivity analysis 2). For studies reporting multiple isotypes including IgG, we included only IgG in the main analyses because these isotypes remain elevated for a longer period post-infection than do IgM and IgA.[17] If seropositivity based only on IgG was not reported separately or seropositivity reported was based only on total antibodies, these results were also included. Although many studies did adjust for various factors, we decided to use the crude (unadjusted) estimates in our analyses to ease interpretation across different studies and did a sensitivity analysis with seroprevalence adjusted for test performance by using Bayesian measurement error models (sensitivity analysis 3).[18]

To reduce heterogeneity between individual seroprevalence estimates and to provide more policy-relevant summary statistics, we stratified eligible studies by WHO regions (ie, African region, region of the Americas, Eastern Mediterranean region, European region, South-East Asia region, and Western Pacific

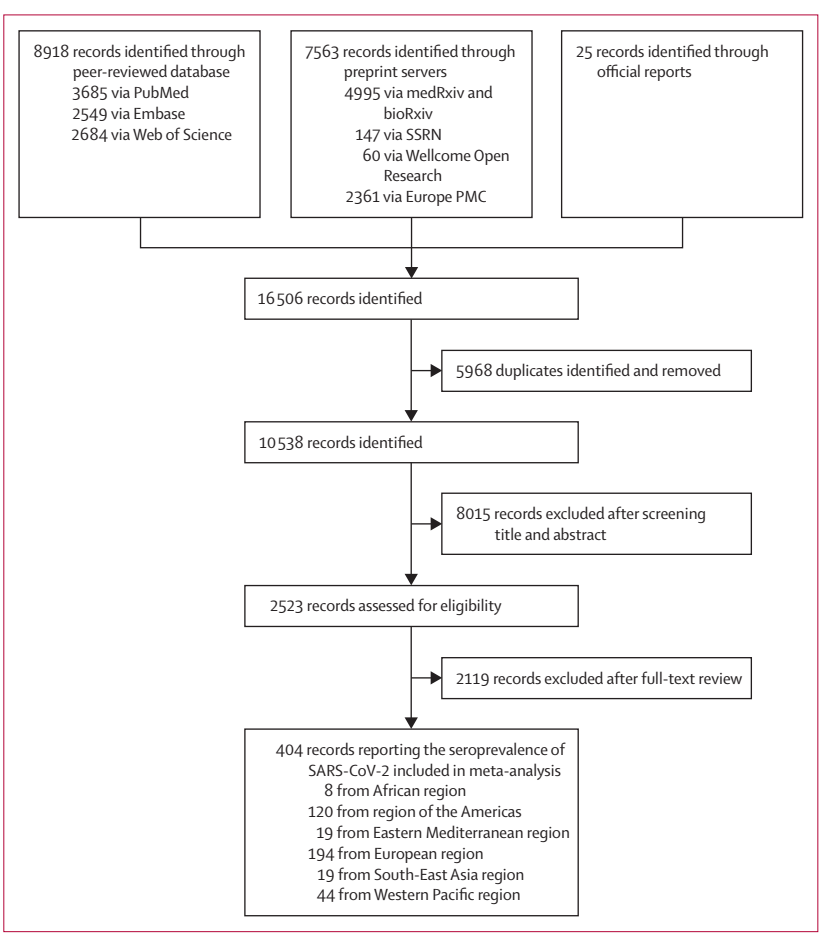


Figure 1: **Study selection**
Flowchart of the selection of serological studies of SARS-CoV-2 infection from Dec 1, 2019, to Dec 22, 2020.

region).[19] To estimate seroprevalence by different types of exposure, within each WHO region, we categorised all study participants into five groups: (1) close contacts, (2) high-risk health-care workers, (3) low-risk health-care workers, (4) general populations, and (5) poorly defined populations (appendix 2 pp 147–48). The poorly defined population classification represents populations with undefined or unknown exposure to patients with laboratory-confirmed or suspected COVID-19 (eg, blood donors, residual blood samples from laboratories, patients with other diseases), as well as study populations that cannot be categorised into the first four study populations due to limited exposure information (eg, health-care workers without reporting use of PPE or COVID-19-related exposures). On the basis of a random-effect meta-analysis model, we used the inverse variance method to estimate pooled seroprevalence by WHO regions and different subpopulations, combined with the use of the Clopper-Pearson method to calculate 95% CIs.[20,21]

For seroprevalence estimates from the general population, we further explored potential determinants affecting the seroprevalence, such as sex, age, race, and the reported cumulative incidence of virologically confirmed SARS-CoV-2 infections (referred to throughout as COVID-19 cases or confirmed COVID-19) for the location. Age-specific, sex-specific, and race-specific seroprevalence and corresponding relative risk (RR) by WHO regions were estimated. Due to evidence that the median time to IgG seroconversion is about 2 weeks,[22,23] we calculated cumulative incidence of confirmed COVID-19 by dividing the number of cases reported in the same target population as the serosurvey 2 weeks before the serosurvey mid-point at the location, by the estimated population size. Spearman's rank correlation was established between the cumulative incidence and the seroprevalence among studies involving the general population and, following this, the corresponding correlation coefficient was calculated. Furthermore, we meta-analysed the number of serologically detected infections (the number of individuals with positive SARS-CoV-2 serology) per confirmed case (the number of reported cases in the target population of the serological study), which we refer to as the infection-to-case ratio, with available epidemiological data included in the articles and other sources.[24] Unless reported in the article, we used population size estimates from WorldPop[25] or a local statistics bureau.[26] Studies were included in the meta-analyses of the ratio of serologically detected infections per confirmed cases if they reported seroprevalence in the representative general population (non-convenience sample) with population data and confirmed case data available for the same population. We estimated the pooled infection-to-case ratio with a random-effect meta-analysis model using inverse variance weighting.

Variability between studies was determined by the heterogeneity tests with Higgins' I^2 statistic. We explored the reasons for variations among eligible studies and examined whether prevalence of SARS-CoV-2-specific antibodies varied by study location, study quality, level of exposure, and test performance by multivariable meta-regression models. For all statistical tests, a two tailed p value of less than 0·05 was considered statistically significant. All statistical analyses were done with R (version 3.6.3), with the meta package to do the meta-analysis. This study is registered with PROSPERO, CRD42020198253.

For the **COVID 19 Dashboard by the Center for Systems Science and Engineering at Johns Hopkins University** see https://coronavirus.jhu.edu/map.html

For the **WHO COVID-19 Dashboard** see https://covid19.who.int/

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

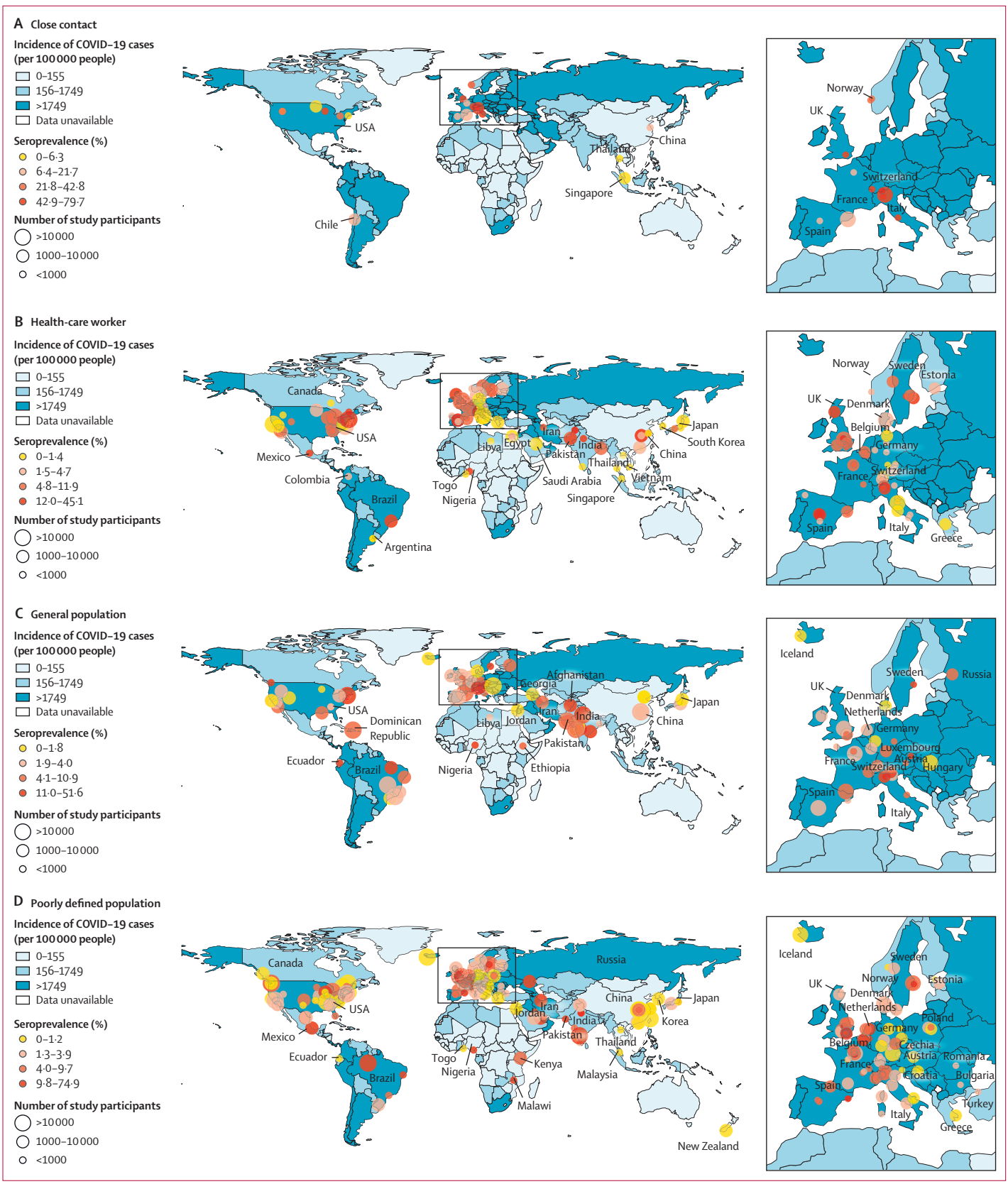
We identified a total of 16 506 studies after systematically searching multiple data sources, with 8918 identified from peer-reviewed databases, 7563 from preprint severs, and 25 reports from governments or health authorities. After excluding 5968 duplicates and a further 8015 following screening of titles and abstracts, 2523 studies reporting serological evidence of SARS-CoV-2 infections were assessed for eligibility. 2119 studies were considered ineligible for inclusion, resulting in a total of 404 studies involving 5 168 360 participants included in the meta-analysis after full-text scrutiny (figure 1). Most studies were done in the European region (n=194), the region of the Americas (n=120), and the Western Pacific region (n=44; figure 1, figure 2; appendix 2 p 218). Among 388 studies reporting the exact starting sampling date, 18 (5%) were done after more than 75% of the total cases (in that country, state, or province) had been reported as of Dec 22, 2020, most of which (17 of 18, 94%) were done in China (appendix 2 pp 208–17).

The overall quality of studies was low based on our grading system, with only 20% (82 of 404) classified as grade A or grade B studies included in the main analysis (appendix 2 pp 182–84). Most studies were categorised as grade C or grade D, including all but two studies of high-risk health-care workers and close contacts. Of the 84 general population-based studies, ten were classified as grade A and 28 were classified as grade B (appendix 2 p 207).

About two thirds of studies (259 of 404, 64%) described serological results from convenience samples, while 45 studies (11%) used multistage or stratified random sampling to select study participants. Most studies measured IgG antibodies using chemiluminescence

***Figure 2*: Geographical distribution of SARS-CoV-2 serosurveys by study populations from Dec 1, 2019, to Dec 22, 2020**

The colours on the maps indicate the cumulative incidence of reported cases, with darker colours representing higher values. Cumulative incidence data are reproduced from the WHO COVID-19 Dashboard.


A Close contact
Incidence of COVID-19 cases (per 100 000 people)
0–155
156–1749
>1749
Data unavailable
Seroprevalence (%)
0–6·3
6·4–21·7
21·8–42·8
42·9–79·7
Number of study participants
>10 000
1000–10 000
<1000
USA
Chile
China
Thailand
Singapore
Norway
UK
Switzerland
France
Italy
Spain
B Health-care worker
Incidence of COVID-19 cases (per 100 000 people)
0–155
156–1749
>1749
Data unavailable
Seroprevalence (%)
0–1·4
1·5–4·7
4·8–11·9
12·0–45·1
Number of study participants
>10 000
1000–10 000
<1000
Canada
USA
Mexico
Colombia
Brazil
Argentina
Togo
Nigeria
Libya
Egypt
Iran
Pakistan
India
Thailand
Saudi Arabia
Japan
South Korea
China
Vietnam
Singapore
Norway
Sweden
Estonia
UK
Denmark
Belgium
Germany
France
Switzerland
Spain
Italy
Greece
C General population
Incidence of COVID-19 cases (per 100 000 people)
0–155
156–1749
>1749
Data unavailable
Seroprevalence (%)
0–1·8
1·9–4·0
4·1–10·9
11·0–51·6
Number of study participants
>10 000
1000–10 000
<1000
USA
Dominican Republic
Ecuador
Brazil
Nigeria
Libya
Jordan
Iran
Afghanistan
Georgia
Pakistan
India
Ethiopia
China
Japan
Iceland
Sweden
Russia
UK
Denmark
Netherlands
Germany
Luxembourg
France
Austria
Switzerland
Hungary
Spain
Italy
D Poorly defined population
Incidence of COVID-19 cases (per 100 000 people)
0–155
156–1749
>1749
Data unavailable
Seroprevalence (%)
0–1·2
1·3–3·9
4·0–9·7
9·8–74·9
Number of study participants
>10 000
1000–10 000
<1000
Canada
USA
Mexico
Ecuador
Brazil
Togo
Nigeria
Kenya
Malawi
Malaysia
Thailand
Pakistan
India
Iran
Jordan
Russia
China
Japan
Korea
New Zealand
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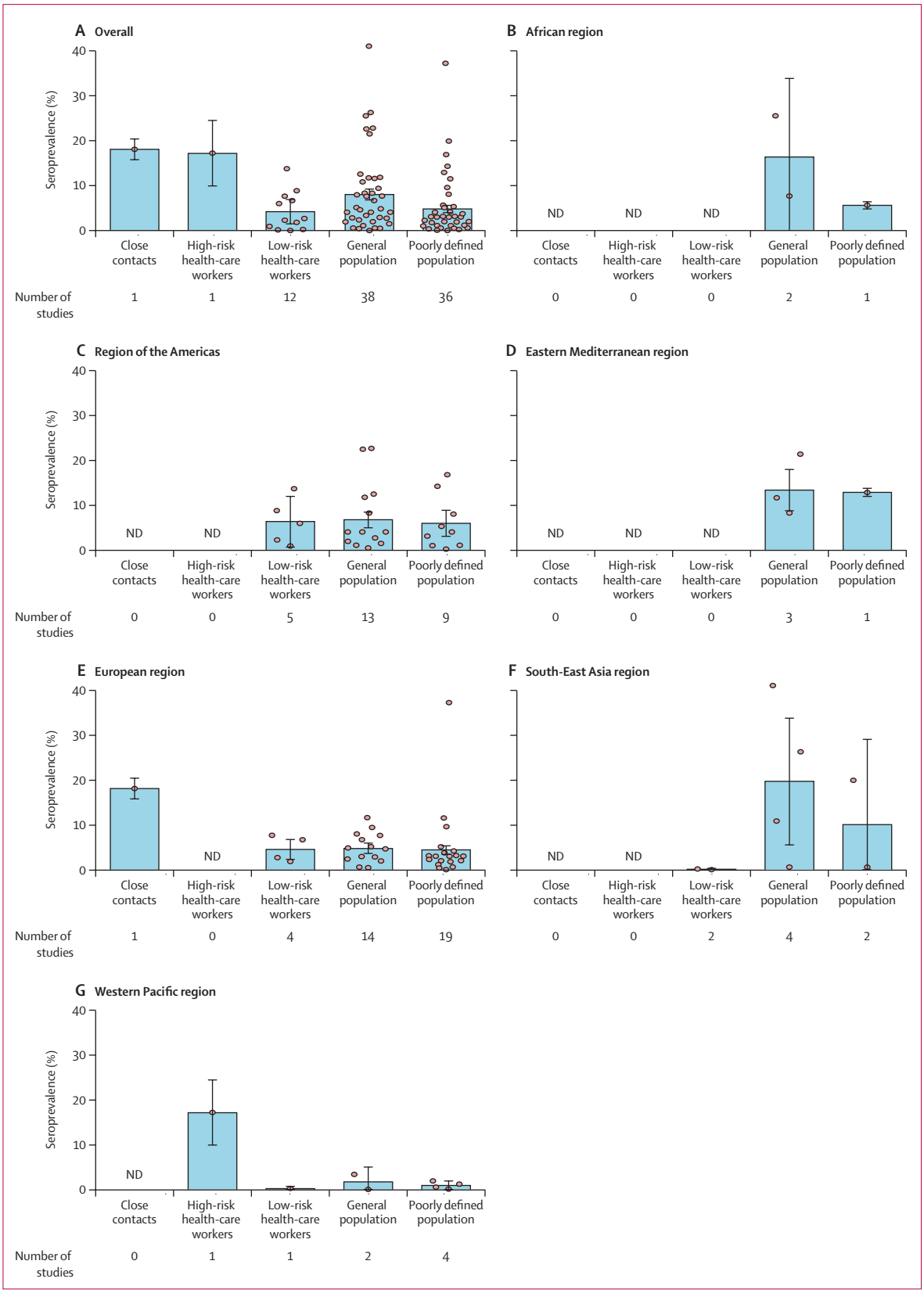

***Figure 3*: Estimated seroprevalence by WHO regions and study populations**
The bar represents the pooled estimates and the error bars represent the 95% CI. Each dot represents the result of one single study. ND=no data.

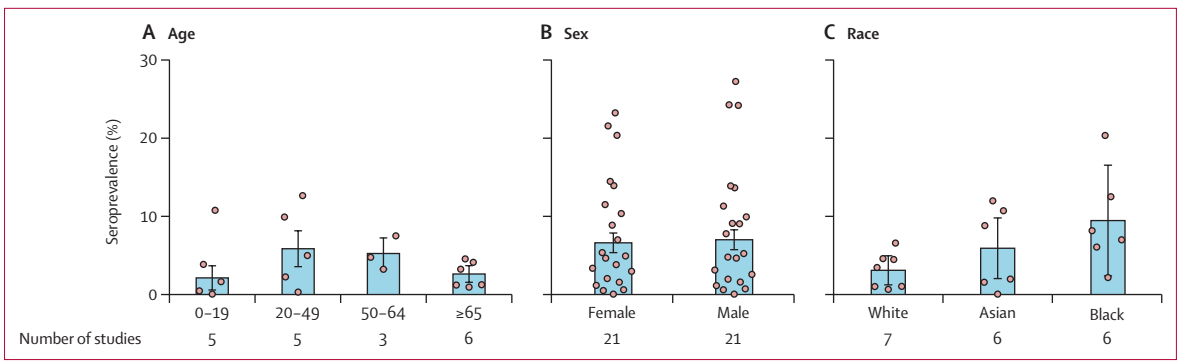

Figure 4: **Estimated seroprevalence by age groups, sex, and race**

immunoassays (182 of 404, 45%), followed by ELISA, (162 of 404, 40%), and lateral flow immunoassays (97 of 404, 24%), with 20% (82 of 404) of studies using more than one serological assay. Additionally, 42 studies used a neutralisation assay to detect neutralising antibodies. Among 323 studies that reported the target protein for serological assays, 219 (68%) studies used tests targeting the S protein, and 191 (59%) used tests targeting the N protein. More than half of the studies (243 of 404, 60%) reported age-specific or sex-specific seroprevalence or corrected their findings for age or sex or both. 60 studies (15%) adjusted for sensitivity and specificity of the serological assays.

Among 82 grade A and grade B studies, seroprevalence varied across WHO regions and study populations (figure 3). Generally, close contacts (18·0%, 95% CI 15·7–20·3) and high-risk health-care workers (17·1%, 9·9–24·4) had a higher seroprevalence than did low-risk health-care workers (4·2%, 1·5–6·9) and general populations (8·0%, 6·8–9·2; figure 3A, appendix 2 pp 185–87). The seroprevalence of the populations in studies that did not specify exposure was 4·8% (95% CI 4·0–5·6; figure 3A, appendix 2 pp 185–87). Pooled estimates of seroprevalence in the general population was highest from four studies done in the South-East Asia region (19·6%, 95% CI 5·5–33·6, all in India), followed by two studies done in the African region (16·3%, 0·0–33·7), Eastern Mediterranean region (three studies, 13·4%, 8·8–18·0), region of the Americas (13 studies, 6·8%, 5·0–8·5), and European region (14 studies, 4·7%, 3·6–5·9), with the lowest seroprevalence in studies done in the Western Pacific region (two studies, 1·7%, 0·0–5·0; figure 3B–G, appendix 2 pp 185–87). Sensitivity analyses using different definitions of positivity and accounting for serological test performance showed no qualitative differences from the primary results (appendix 2 pp 188–92).

Within grade A and grade B studies of the general population, seroprevalence of those younger than 20 years was 2·1% (95% CI 0·5–3·6), 5·8% (3·5–8·1) for those aged 20–49, 5·2% (3·2–7·2) for those aged 50–64, and 2·6% (1·5–3·6) for those aged 65 years and older (figure 4A). After further merging the middle two age groups (20–49 years and 50–64 years), the RR of seropositivity in the young (<20 years) was approximately 20% lower than that of working age adults (20–64 years; RR 0·77, 95% CI 0·72–0·84; appendix 2 pp 195–96). The risk of seropositivity in older people (≥65 years) was also lower than for working age adults (RR 0·76, 0·59–0·96; appendix 2 pp 195–96).

The pooled seroprevalence for men (7·0%, 5·7–8·2) and women (6·6%, 5·3–7·8) was similar, with 52% (11 of 21) of sex-specific seroprevalence point estimates being higher in men than in women (figure 4B). Similarly, pooling sex-specific relative risks across studies to adjust for the differences in risk across settings revealed no significant increase in risk of seropositivity in men (RR 1·02, 95% CI 0·95–1·09), with similar estimates across WHO regions (appendix 2 pp 195–96). Furthermore, across the seven studies that compared different races, Black (RR 2·70, 95% CI 2·30–3·18) and Asian (RR 1·91, 1·82–2·03) individuals showed a significantly higher risk of infection than did White individuals (figure 4C, appendix 2 pp 195–96).

The relationship between reported COVID-19 incidence (confirmed cases reported from public sources) and the number of infections identified through serological surveys can be useful for understanding the evolution of the pandemic without serological surveillance in each and every locale. For studies of the general population, the cumulative reported incidence of COVID-19 correlated with seroprevalence across locations (Spearman's rank correlation coefficient, 0·59; appendix 2 pp 223–24). For studies including individuals from general populations, the ratio of serologically detected infections to virologically confirmed cases varied across locations, with a pooled ratio of 11·1 (95% CI 8·3–14·9), suggesting that for each virologically confirmed SARS-CoV-2 infection, at least ten infections remained undetected by surveillance systems. This ratio was similar in the region of the Americas (6·9, 2·7–17·3) and the European region (8·4, 6·5–10·7), but higher in the South-East Asia region (56·5, 28·5–112·0); although

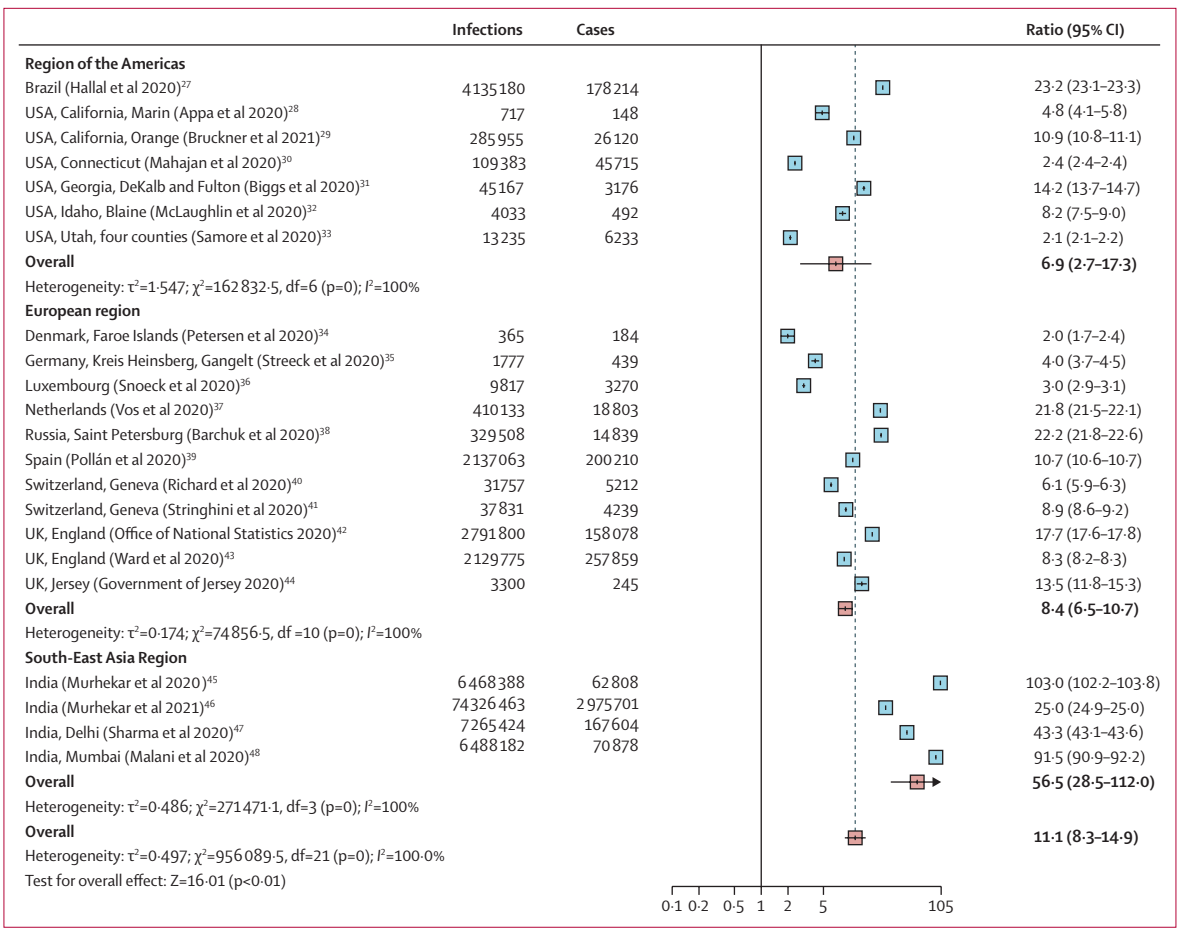

Figure 5: **Estimated ratio of serologically detected infections to confirmed cases of COVID-19**
The size of boxes represents the weight for each study. The whisker represents the 95% CI. Values higher than 1 suggest greater under-reporting of infections (due to both mild or asymptomatic infections, care-seeking behaviours, and testing practices).

this final estimate is only based on studies done in India (figure 5).

Discussion

With the increasing availability of serological assays for SARS-CoV-2, a large body of literature describing seroprevalence studies in different populations has emerged. In this study, we examine the quality and results of 404 reports of seroprevalence studies from around the globe, both published and in preprint form. In general, the quality of existing serological studies was low, involving less rigorous sampling strategies, poorly validated and non-standardised laboratory methods, and scarcity of statistical correction for demographics and test performance in analyses. As expected, we found that close contacts and high-risk health-care workers had a higher prevalence of SARS-CoV-2-specific antibodies than did low-risk health-care workers and the general population. Young individuals (<20 years) and older people (≥65 years) were less likely to be seropositive than those aged 20–64 years, and there was no significant difference in seroprevalence between men and women. Additionally, we found that the ratios of infections per confirmed case were similar in the European region and the region of the Americas on average, but higher in the South-East Asia region (in which all estimates were from India).

Representative serosurveys can provide useful snapshots of the infection history of a population. However, very few studies provided representative estimates for their target population. An optimal study design for estimating seroprevalence includes a detailed sampling framework, rigorous sampling methods (ie, multistage, stratified sampling), and adjustments for selection bias and assay performance.[14]

Various detection assays were used for determination of seropositivity.[49] We found large variations in test performance, targeted antigens and immunoglobulin isotypes, and threshold used. Additionally, more than half of the studies lacked independent validations of the sensitivity and specificity of the diagnostic kits before assessment of serosurvey samples to verify their initial results.[50–52] Furthermore, few independent validations were done in the target population of serosurvey, which

might lead to mis-specification of assay performance.[53] Notably, although WHO has established a generic population-based serological study protocol, standardised guidelines and procedures for laboratory testing are scarce, which might contribute towards such heterogeneity in performance and reporting of results. We call on national and international governance bodies to develop standardised antibody testing protocols and reporting practices and create biobanks of reference standards (eg, monoclonal antibodies), to reduce laboratory-to-laboratory variations, thus facilitating the comparability and interpretability among seroprevalence studies. Despite the WHO recommendations, the estimates described by many of the population-based serosurveys did not adjust for the demographic structure of the target population,[16] nor for the testing performance (sensitivity and specificity) of the assay, which made the comparison among studies difficult.

Most of the high-quality serological surveys identified were done in the region of the Americas and the European region, predominantly in general populations.[31,33,36,41,54–58] The number of high-quality studies of exposed populations were few, especially for health-care workers and close contacts, and studies to address this knowledge gap are needed.[59–62] For the other four WHO regions examined, there was a paucity of high-quality studies across all populations examined, suggesting that attention should be paid to optimise the design of future seroepidemiological studies to include good representativeness of samples, standardised laboratory methods, and reasonable adjustments. Higher-quality studies provide more accurate measures of disease burden and transmission to better inform public health efforts against COVID-19.

We found high seroprevalence among high-risk health-care workers, defined as those who provided routine medical care to patients with COVID-19, who did not have access to PPE. On the contrary, low-risk health-care workers, defined as those wearing adequate PPE or those who provided care for patients who did not have COVID-19, had significantly lower seroprevalence than their high-risk counterparts, indicating the necessity of proper use of PPE for front-line health-care workers.[63] We found a pooled seroprevalence of 8·0% in the general population, suggesting that globally, the number of people infected by the end of 2020 was unlikely to satisfy estimates of what it would take to achieve antibody-mediated herd immunity.[39,41,64] The seroprevalence in the general population also varied across WHO regions, with a higher prevalence of SARS-CoV-2-specific antibodies in the South-East Asia region (eg, India, range: 10·8–40·8%)[46–48] contrasting with a relatively lower seroprevalence in the Western Pacific region (eg, China, range: 0·8–3·3%),[65,66] indicating different levels of community transmission of SARS-CoV-2 in different locales, potentially due to differences in non-pharmaceutical interventions.[67] Additionally, the very limited number of high-quality studies in all but two of the WHO regions underlines our incomplete understanding of SARS-CoV-2 transmission in much of the world.[39,43,68–71] We also found notable differences in seroprevalence between age groups, with the seroprevalence increasing with age among participants younger than 65 years. We found that the young (<20 years) were less likely to be seropositive than were individuals aged 20–64 years, consistent with reports of lower numbers of virally confirmed cases in children compared with other age groups.[72] In some areas, this might have been due to the effects of lockdowns limiting exposures of school-aged populations, in contrast to adult-aged essential workers who had continued community exposure.[73,74] The prevalence of SARS-CoV-2-specific antibodies and the relative risk of being seropositive among older people (≥65 years) was also low, which could be explained by poorer serological responses after infection,[75] lower rates of infection as a result of biological differences or, perhaps more likely, due to behaviour changes leading to reduced frequency of infectious contacts.

The seroprevalence is a reflection of the duration and intensity of community transmission. By use of a regression analysis, we showed that higher cumulative incidence of reported cases is associated with higher seroprevalence. For locations where data on the number of confirmed cases were available, we found that the number of infections per confirmed case varied greatly, although estimates in Europe and the USA were similar on average. Such evidence indicates the existence of many undetected cases in the community and provides a range of scaling factors for translating the observed confirmed cases into unobserved infections in the community.[27]

Our study has several limitations. First, although we did meta-regression and subgroup analysis to explore heterogeneity of varied seroprevalence for different populations, there are still some factors that we have not taken into account, so that some heterogeneity cannot be well explained quantitatively. Second, misclassification bias can occur due to the limited information on exposures for the study populations, especially for the so-called poorly defined populations. For certain variables (eg, the use of PPE for health-care workers) for which data cannot be extracted from the original articles, we tried to contact the authors, but the response rate was low. Third, we pooled the estimates of studies at different stages of the pandemic, which makes interpretation of the pooled estimates more nuanced. However, we did summarise the relationship between starting timepoint and local epidemic to demonstrate temporal distributions for each included study. Fourth, current seroprevalence estimates are limited by the lack of knowledge of the time-varying sensitivities of the immunoassays used, which might have led to underestimation of seroprevalence, especially those of asymptomatic or mild cases. Additional longitudinal studies are needed to examine the long-term kinetics of antibody responses

to inform appropriate correction for immunoassay sensitivity. Finally, we have not included studies examining the use of T-cell responses for estimates of prevalence. Although there is evidence that SARS-CoV-2-specific T-cell responses might be detectable in those that lack antibody response, measuring T-cell responses at a population level is not feasible.[76]

In conclusion, the overall quality of the existing seroprevalence studies of SARS-CoV-2 is low and international efforts to standardise study design and assays are urgently required.[16] Pooled estimates of SARS-CoV-2 seroprevalence based on currently available data show a higher infection risk among close contacts and health-care workers who did not use PPE, while the relatively low prevalence of SARS-CoV-2-specific antibodies among general populations suggests that the majority of examined populations have not been infected. Therefore, antibody-mediated herd immunity is probably far from being reached in most settings, and continuous serological monitoring is necessary to inform public health decision making.

Contributors

HY designed and supervised the study. Xinh C and ZC did the literature search, set up the database, and did all statistical analyses. Xinh C, ZC, ASA, and DTL co-drafted the first version of the article. Xinh C, ZC, XD, WL, ZZ, Xing C, RS, TZ, and NZ helped with checking data and constructed the figures. Xinh C, ZC, and HY have verified the underlying data used in the analysis. DTL, ASA, JY, MA, CV, and HY commented on the data and its interpretation and critically revised the content. All authors contributed to review and revision, approved the final manuscript as submitted, and agree to be accountable for all aspects of the work. All authors had full access to all the data in the study and accept responsibility for the decision to submit for publication.

Declaration of interests

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Data sharing

All datasets generated and analysed are available in the Article and appendix 2. Some tables of appendix 2 in Excel format are available at Github, and are more informative than the PDF supplement provided with the Article.

For the **appendix 2 tables in Excel format** see https://github.com/zychenfd/Serological-evidence

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