



BMJ Open Systematic review of seroprevalence of SARS-CoV-2 antibodies and appraisal of evidence, prior to the widespread introduction of vaccine programmes in the WHO European Region, January–December 2020

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ABSTRACT

Objectives Systematic review of SARS-CoV-2 seroprevalence studies undertaken in the WHO European Region to measure pre-existing and cumulative seropositivity prior to the roll out of vaccination programmes.

Design A systematic review of the literature.

Data sources We searched MEDLINE, EMBASE and the preprint servers MedRxiv and BioRxiv in the WHO ‘COVID-19 Global literature on coronavirus disease’ database using a predefined search strategy. Articles were supplemented with unpublished WHO-supported Unity-aligned seroprevalence studies and other studies reported directly to WHO Regional Office for Europe and European Centre for Disease Prevention and Control.

Eligibility criteria Studies published before the widespread implementation of COVID-19 vaccination programmes in January 2021 among the general population and blood donors, at national and regional levels.

Data extraction and synthesis At least two independent researchers extracted the eligible studies; a third researcher resolved any disagreements. Study risk of bias was assessed using a quality scoring system based on sample size, sampling and testing methodologies.

Results In total, 111 studies from 26 countries published or conducted between 1 January 2020 and 31 December 2020 across the WHO European Region were included. A significant heterogeneity in implementation was noted across the studies, with a paucity of studies from the east of the Region. Sixty-four (58%) studies were assessed to be of medium to high risk of bias. Overall, SARS-CoV-2 seropositivity prior to widespread community circulation was very low. National seroprevalence estimates after circulation started ranged from 0% to 51.3% (median 2.2% (IQR 0.7–5.2%); n=124), while subnational estimates ranged from 0% to 52% (median 5.8% (IQR 2.3%–12%); n=101), with the highest estimates in areas following widespread local transmission.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This study provides a comprehensive systematic review of SARS-CoV-2 seroprevalence literature of all languages and unpublished data.
- ⇒ Thorough literature search of major electronic databases and reporting as per Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.
- ⇒ Due to heterogeneity between studies including sampling frame, population and stage of epidemic at time of serosurvey results are described narratively.
- ⇒ Seroprevalence may be underestimated as antibody waning was not taken into account.

Conclusions The low levels of SARS-CoV-2 antibody in most populations prior to the start of vaccine programmes underlines the critical importance of targeted vaccination of priority groups at risk of severe disease, while maintaining reduced levels of transmission to minimise population morbidity and mortality.

INTRODUCTION

The novel virus, SARS-CoV-2, was first identified in Wuhan, China in December 2019 and spread rapidly around the world. At that time, the transmissibility, population susceptibility, clinical spectrum and infection severity of this novel virus were all unknown. By 1 January 2021, approximately 83 million confirmed cases were reported globally, while in the WHO European Region, there were 4.9 million cases.¹ However, notified cases and deaths are an underestimate of the true number of infections for reasons including clinical presentation with a large proportion of asymptomatic or mildly symptomatic cases,

testing and reporting strategies and healthcare seeking behaviour.² Asymptomatic infection has been reported in many studies with the proportion ranging from 6% to 41%^{3–5} so a significant proportion of SARS-CoV-2 infections will be missed through case-based surveillance systems.⁶

Seroprevalence studies, which measure SARS-CoV-2 antibodies, can provide an important complement to routine surveillance, particularly as part of the assessment of novel emerging respiratory pathogens. Seroprevalence surveys are essential to assess the true extent of prevalence of pre-existing cross-reactive antibodies in the population; to measure population age-specific and geographical cumulative seroincidence as the novel virus spreads and to contribute to estimating infection severity. As the majority of SARS-CoV-2-infected individuals have a detectable humoral immune response on average 10–14 days after symptom onset and most individuals seroconvert within 3–4 weeks of infection,⁷ and anti-SARS-CoV-2 antibodies are predictive of immune protection,^{8,9} seroprevalence studies can provide an indication of population levels of humoral immunity and inform public health policies.

Since the start of the COVID-19 pandemic, there has been a rapid accumulation of seroepidemiological studies describing the seroprevalence of SARS-CoV-2. This review aims to provide a comprehensive review of studies conducted in the WHO European Region between 1 January 2020 and 31 December 2020 in the general population, with the aim to synthesise evidence on the extent of transmission across the region and population immunity to this newly emerging infection before the start of the COVID-19 vaccination programmes. As SARS-CoV-2 continues to circulate, understanding the age-specific population seropositivity remains critical for policymakers and public health officials to make informed decisions on optimal public health interventions.¹⁰

METHODS

Search strategy

We searched MEDLINE, WHO COVID, EMBASE and the preprint servers medRxiv and bioRxiv within the WHO 'COVID-19 Global literature on coronavirus disease' database on 21 October 2020 and 12 January 2021. The searches spanned the period 1 January 2020–31 December 2020 and was not restricted by language. We supplemented these articles with WHO-supported Unity seroprevalence studies and unpublished studies reported to WHO Regional Office for Europe and European Centre for Disease Prevention and Control (ECDC). The selection process followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.¹¹ The full search strategy, search terms as well as inclusion and exclusion criteria are described in online supplemental material 1.

DATA EXTRACTION

We combined the references from all databases, removed duplicates and imported the remaining articles into

Rayyan software¹² for screening of titles and abstracts according to the inclusion and exclusion criteria (online supplemental table S1). After the initial screening of title and abstracts, two independent researchers assessed full-text publications for eligibility. Data from preprint articles were extracted and later replaced with data from published articles, where necessary. At least two independent researchers extracted the eligible studies; a third researcher resolved any disagreements on assessment of eligibility or extraction. We extracted the following data: first author, publication date, country, region, period of study, population type, population age, sampling method, sample size, laboratory methods used, confirmatory testing, test performance, crude and adjusted point seroprevalence estimates, antibody type and analysis methodology.^{13–128} Comparison was made with weekly laboratory-confirmed case and death reports.

Study quality assessment

We used a modified Joana Briggs quality assessment scoring system to assess the overall risk of bias of each study.¹²⁹ The criteria included: (a) the sampling frame (to assess representativeness of the general population); (b) stratification (age, sex or population); (c) recruitment method (random, convenience), (d) adequacy of sample size, (e) serological methods and validation; (f) and statistical analyses (adjustment of results to account for the sensitivity and specificity of the test). A cumulative quality score classified the overall risk of bias of each study into high risk of bias (1–3), medium risk of bias (4–6) or low risk of bias (>6). Two independent researchers conducted the quality assessment; a third researcher resolved any disagreements. See online supplemental table S2 for more details on the quality criteria. For the purposes of quality assessment, the threshold for acceptable test performance was $\geq 95\%$ sensitivity and $>97\%$ specificity for laboratory assays and $\geq 90\%$ sensitivity and $>97\%$ specificity for point-of-care tests.¹³⁰

DATA ANALYSIS

We used descriptive statistics to summarise estimates by subgroup (median and IQR). We generated forest plots to display the data and explore variations according to specific characteristics, including time, geographical location and population group. Correlation between cumulative incidence and cumulative deaths and seroprevalence estimates from studies of the general population was explored using Spearman's rank correlation. We compared seroprevalence estimates from studies of the general population and the cumulative incidence and deaths at the start of each study. Analyses were performed in Microsoft Excel (V.2016) and R V.4.0.4.

Patient and public involvement

No patient involved.

RESULTS

Literature search

The literature search resulted in 4063 studies. After deduplication, application of inclusion and exclusion criteria

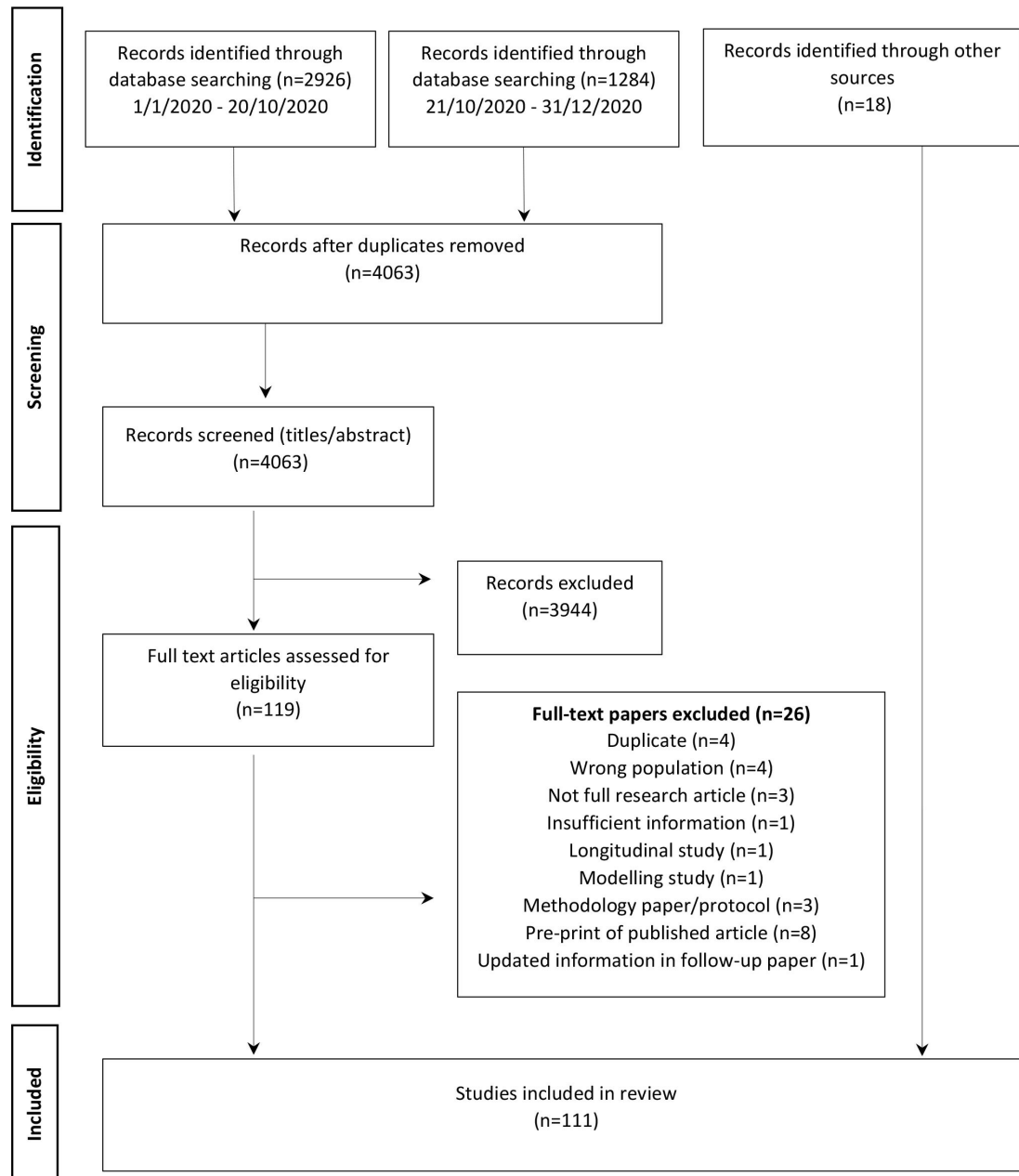


Figure 1 PRISMA flow chart of SARS-CoV-2 seroprevalence study selection. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

and supplementation with articles from other sources, a total of 111 studies were included in this review. Of these, 77 were published articles, 19 were preprints, 9 were institutional report and 6 were studies were identified through reporting of unpublished results to WHO or ECDC. See [figure 1](#) PRISMA flow diagram study selection.

Study characteristics

The 111 studies included 224 seroprevalence estimates from 26 of the 53 countries in the WHO European Region ([figure 2](#)). The majority of studies (n=82; 74%) were conducted in 19 European Union/European Economic Area (EU/EEA) countries, while 29 studies (26%) conducted in 7 non-EU/EEA countries (Bosnia and Herzegovina, Georgia, Kyrgyzstan, Republic of Moldova,

Russian Federation, Switzerland and the UK) ([figure 2](#); [table 1](#)). Fifty-six (50%) studies were aligned with the WHO Unity population-based seroepidemiological investigation criteria related to study design, data collection and analysis.¹³¹ The majority of studies (n=69, 62%) used non-random or convenience sampling of the population. Forty-one (37%) studies used random sampling, while one study did not report sampling methodology. Characteristics and details of included studies are shown in [table 1](#) and online supplemental table S1, respectively.

In total, 72 (65%) of the studies provided representative estimates from the general population, of which sample frames included 45 (41%) studies of household or community samples, 13 (12%) residual sera, 13 (12%)

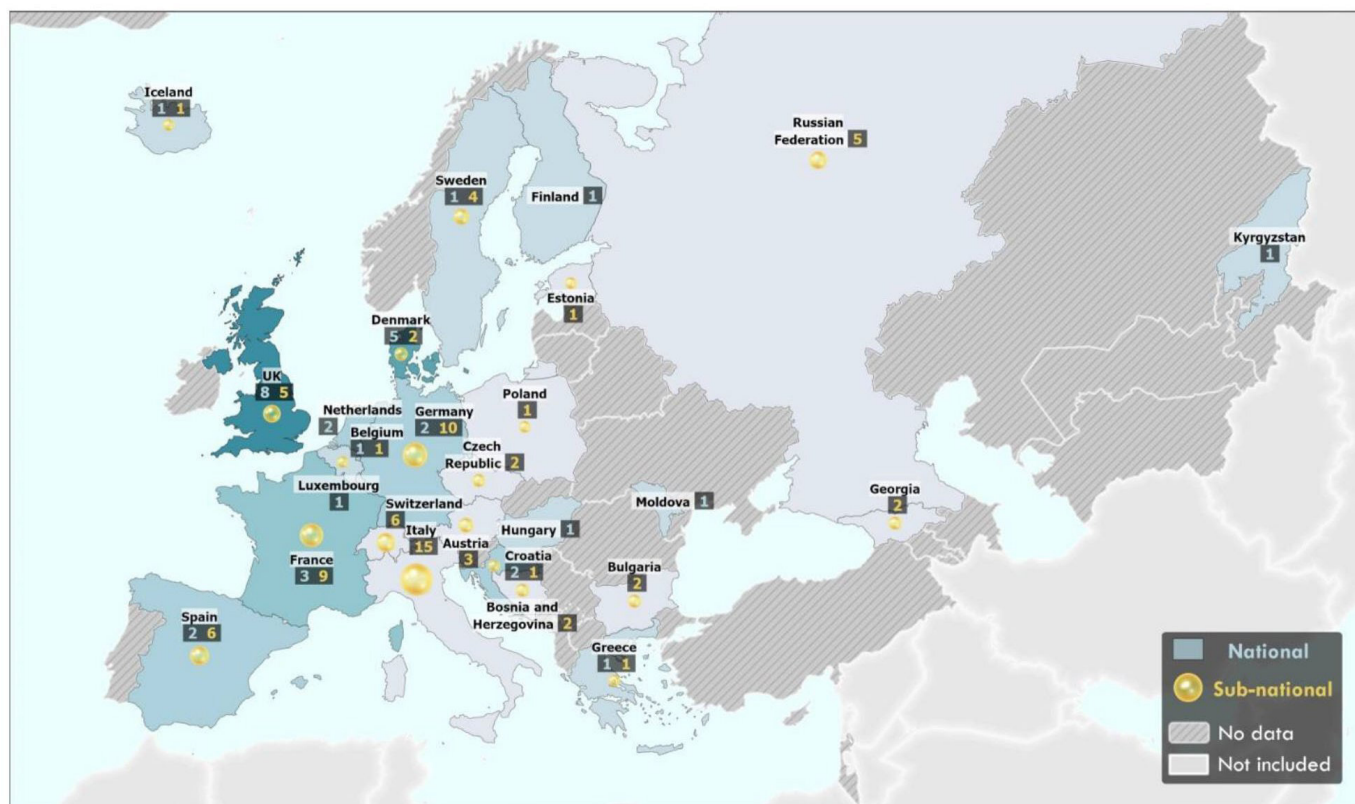


Figure 2 Geographical distribution of SARS-CoV-2 seroprevalence studies published in the WHO European Region between 1 January 2020 and 31 December 2020. Countries with national-level seroprevalence studies are reported in blue (shade of blue reflects the number of studies conducted in the country/territory). Subnational-level seroprevalence studies are reported as a yellow circle (size of circle reflects number of subnational studies conducted in the country/territory). A number of studies are listed in boxes under name. Countries with not studies are coloured in grey. The designations employed and the presentation of this material do not imply the expression of any opinion whatsoever on the part of the secretariat of the WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers and boundaries. Dotted and dashed lines on maps represent approximate locations for which there may not yet be full agreement.

patients seeking healthcare for non-COVID-19-related issues, 7 (6%) pregnant or parturient women. Sixteen (14%) studies sampled blood donors as a proxy for the general population while 23 (21%) sampled other or multiple populations. Studies were conducted at differing geographical levels within a country, including at the national level (n=33; 30%), regional level (n=27; 24%) and city or local level (n=50; 44%). One study reported both national and regional estimates.

Over half of the studies used one serological assay (71; 67%) while 34 (31%) used at least two different assays. In 82 studies (74%), commercial assays from various sources were used, 20 (18%) studies used an in-house assay only and 6 studies (5%) used both a commercial and in-house developed assay. The test method was not reported in two studies. An ELISA was the method most commonly employed (n=55, 50%), followed by chemiluminescent immunoassay or chemiluminescence microparticle immunoassay (n=42, 38%) and lateral flow immunoassays (LFAs) (n=25, 23%). Seventeen studies (15%) used LFAs exclusively. Ten studies (9%) employed in-house micro-neutralisation assays to assess the neutralising ability of SARS-CoV-2 antibodies.

Of 90 studies that used a commercial assay, 33 studies (37%) reported the use of tests with acceptable sensitivity and specificity. Of those that independently validated assay performance (n=41, 46%), 14 (34%) reported acceptable sensitivity and specificity, while 27 (66%) did not meet these thresholds. Of the 20 studies that used an in-house assay, 9 (45%) reported an acceptable test performance, 4 (20%) performed below these thresholds and 7 (35%) did not report on test performance. The majority of studies (n=83, 75%) did not report adjustment for test sensitivity or specificity in their analysis.

Based on our quality scoring system (online supplemental table S2), 81 studies (73%) were of high or medium quality reflecting a low or medium risk of bias, respectively (medium quality: n=40, 36%; high quality n=41, 37%) (online supplemental table S3). A total of 24 studies (22%) were determined to be at high risk of bias, largely due to non-random sampling frame, weak representativeness of the general population or lack of adjustment for sampling bias or test performance.

Table 1 Study characteristics

Characteristics	No of studies	%
Total	111	100
Study characteristics		
Country		
WHO European Region (EU/EEA*)	82	74
WHO European Region (outside of EU/EEA)	29	26
WHO UNITY alignment		
Unity-aligned	56	50
Not unity-aligned	55	50
Publication type		
Peer-reviewed article	77	69
Preprint	19	17
Institutional report	9	8
Not yet published	6	5
Geographical level		
National	33	30
Regional	27	24
City/local	50	44
Multiple	1	1
Sampling strategy		
Convenience	69	62
Random	41	37
Not reported	1	1
Population type		
Household/community	45	41
Residual sera	13	12
Blood donors	16	14
Patients seeking healthcare (non-COVID-19)	13	12
Pregnant or parturient women	7	6
Other/multiple	23	21
Quality assessment		
Low risk of bias	41	37
Medium risk of bias	40	36
High risk of bias	24	22
N/A	6	5
Sample size		
<1000	45	41
≥1000	66	59
Laboratory characteristics		
Serological method		
ELISA	55	50
CMIA/CLIA	42	38
LFA	25	23
MN	10	9

Continued

Table 1 Continued

Characteristics	No of studies	%
Other	8	7
Not reported	2	1
Type of assay		
Commercial	90	81
In-house	26	23
Not reported	2	1

*EU/EEA: European Union/European Economic Area
 CLIA, chemiluminescent immunoassay; CMIA, chemiluminescence microparticle immunoassay; LFA, lateral flow immunoassay; MN, microneutralisation assay; N/A, not available.

Seroprevalence estimates

Seroprevalence estimates (n=88) from national studies ranged from 0% (95% CI 0.0% to 0.7%) in Finland in May²³ to 51.3% in Georgia in December²⁵ (median 2.2% (IQR 0.7%–5.2%); n=124) (figure 3A), while seroprevalence estimates from studies spanning regions, cities or towns (n=101) ranged from 0% (95% CI 0.0% to 0.5%) in Czech Republic in August 2020²⁵ to 52% in a Médecins Sans Frontières centre in Paris, France during an outbreak with widespread community transmission in June 2020¹¹¹ (median 5.8% (IQR 2.3%–12%); n=101) (figure 3B).

A total of 45 studies provided seroprevalence estimates (n=105) from community or household samples and 39 studies (87%) were found to be of high or medium quality. Seroprevalence estimates ranged from 0% (95% CI 0% to 0.7%) in Finland in May and to 51.3% in December 2020 in Georgia²⁵ (median 2.6% (IQR 0.5%–10%) n=105) (online supplemental figure S1).

Thirteen studies screened residual clinical samples^{26–39} between February and November 2020, of which 9 (70%) were of high or medium quality. Seroprevalence estimates (n=34) in this population varied across countries ranging from 0% (95% CI 0% to 0.23%) in Greece in March to 18.7% (95% CI 16.7% to 23.3%) in Sweden in June (median 4.5% (IQR 3.5%–5.9%); n=34) (online supplemental figure S2A).

Eighteen studies (17%) used blood donors as a proxy for the general population between February and December 2020, of which 16 were of high or medium quality. Seroprevalence estimates (n=42) in blood donors varied across countries, ranging from 0.4% in Germany between March and June⁷³ to 30% in Tensta (Stockholm) following a period of high incidence in June⁷⁸ (median 5.8% (IQR 2.1%–5.7%) n=42) (online supplemental figure S2B).

Eight studies investigated the seroprevalence of SARS-CoV-2 in pregnant or parturient women, reporting estimates ranging from 2.6% (95% CI 1.7% to 4%) and 14.3% between March and June 2020 (median 6.9% (IQR 5.1%–12%); n=8)^{99–105} (online supplemental figure S2C). One study provided combined estimates of blood donors

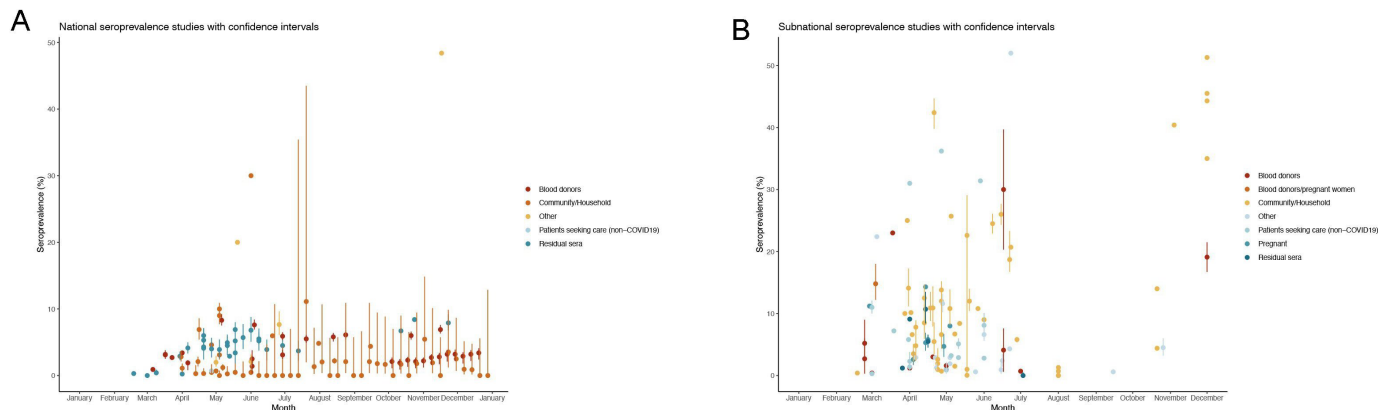


Figure 3 National (A) and subnational (B) seroprevalence estimates of SARS-CoV-2 antibodies over time in the WHO European Region (1 January 2020–31 December 2021).

and pregnant women of 14.8% in Sweden between March and December.¹²⁷

Fourteen studies provided 16 estimates from individuals seeking healthcare for non-COVID-19-related reasons and seven (50%) of these were medium or high quality. Estimates ranged from 0.3% in Zurich, Switzerland in March¹²⁶ to 36.2% in London in April⁹⁷ (median 4.1% (IQR 2.1%–8.8%); n=16) from March to August 2020. The highest seroprevalence estimates (>10%) in this group were observed in three patient groups investigated following local widespread community transmission, oncology patients (31%) in Bergamo, Italy in April 2020,⁸⁹ oncology patients (31.4%) in Madrid between May and June 2020⁹⁵ and haemodialysis patients (36.2%) in London in April and May 2020⁹⁷ and patients (38.5%) in Barcelona, Spain in April¹²⁵ (online supplemental figure S2D).

Forty-four (41%) studies reported seroprevalence estimates stratified by age. Seroprevalence estimates varied considerably across age groups and estimates tended to be lower in children (<18 years)^{36 38 49} and older age groups (>60 years).^{33 41 47 49 66 67 132} While a number of studies reported a high seroprevalence in older age groups (>55 years),^{26 32 33 41 70 75 94 122} some studies also reported a higher seroprevalence in younger age groups (<40 years).^{38 50 70 77} In studies that reported seroprevalence estimates by sex, similar seroprevalence results were observed between females and males with the exception of a study in Italy,⁹⁴ Russian Federation⁴³ and Kyrgyzstan³⁶ which each found a higher seroprevalence in females.

Seroprevalence estimates over time

A number of studies provided seroprevalence estimates prior to, or at the early stages of the epidemic in the country (online supplemental figure S3). Of these, overall study estimates were largely below 10%, however higher seroprevalence was noted in a number of population-specific, regional or local studies,^{13 28 29 32 33 89 108 110} with suggestion of earlier undetected transmission in some countries.^{36 104 116 127} A total of 16 studies reported seroprevalence estimates spanning multiple timepoints or stages of the epidemic.^{20 23 25 46 49 50 52 55 58 61 62 65 76 79–84 113 117 120 125 126}

In a serial cross-sectional study in France,⁵⁸ residual blood sampled before, during and after a national lockdown showed a seroprevalence of 0.41%, 4.14% and 4.93%, respectively. In Georgia, in a community sample, an increase in seroprevalence from 0%–1.3% in August 2020 to 35%–51.3% in the same regions in December 2020 was noted.²⁵ A seroprevalence study in blood donors conducted in Milan between February and April 2020 during a period of intense transmission found an increase in seroprevalence from 2.7% (95% CI 0.3% to 6.0%) to 5.2% (95% CI 2.4% to 9.0%), with an adjusted rate of increase in antibodies (IgG) of 2.7%±1.3% per week as social distancing measures were gradually implemented.⁷⁶ While in Finland, weekly testing of blood donors from April 2020 onwards showed a consistently low seroprevalence in the general population over time (0.28% (95% CI 0.05% to 1.55%) in early April 2020 to 0% (95% CI 0% to 12.87%) in late December 2020.⁶⁴

Correlation between seroprevalence and cumulative incidence

The relationship between seroprevalence and reported SARS-CoV-2 laboratory-confirmed cumulative case and deaths incidence was also explored. While seroprevalence from national studies correlated moderately with cumulative incidence (Spearman's rank correlation coefficient, 0.471) (figure 4A), a stronger correlation was observed between seroprevalence estimates and cumulative SARS-CoV-2 deaths (Spearman's rank correlation coefficient, 0.666) (figure 4B).

DISCUSSION

In this study, we report the results of 111 studies, including 224 seroprevalence estimates from 26 countries in the WHO European Region undertaken until December 2020, prior to the implementation of national COVID-19 vaccine campaigns. A large variation in study methodologies was noted across the studies, with an over-representation of studies from high-income countries in Western Europe.

Overall, population-wide seroprevalence estimates were low (below 10%) across the Region early in 2020

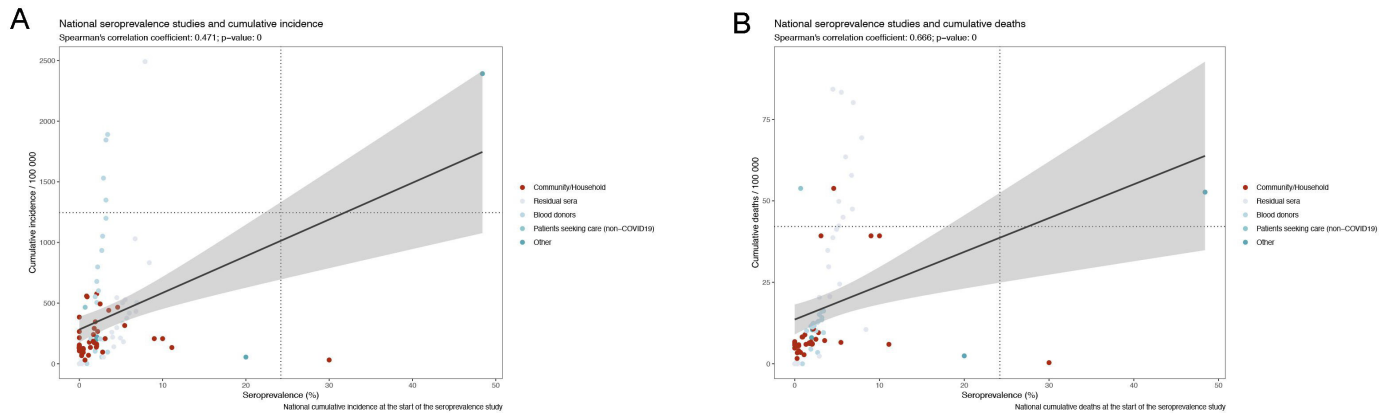


Figure 4 Correlation between seroprevalence point estimates from low to medium risk of bias studies and cumulative (A) incidence and (B) deaths in all populations, in the WHO European Region (1 January 2020–31 December 2020).

before the onset of widespread community transmission and remained low across the Region throughout 2020, despite circulation of SARS-CoV-2 over this period. Higher estimates were observed at a regional or local level in populations that had experienced intense community transmission (up to 52%). Furthermore, a positive correlation between seroprevalence estimates and national cumulative incidence was observed, with a stronger correlation between seroprevalence and cumulative mortality.

The wide variation in seroprevalence estimates across the region are likely to reflect many factors including the differences in the population studied, local stage of the epidemic and the public health and social measures implemented in response to the epidemic at that time. The general low seroprevalence both at the start of the pandemic and at the end of 2020 is in line with a number of global systematic review conducted to date^{133–136} and together indicates that the majority of the proportion of the population in the WHO European Region were and remain susceptible to infection 1 year after the identification of SARS-CoV-2 and prior to the start of national vaccination campaigns. In a global systematic review, Chen *et al* estimated a seroprevalence of 4.2% (2.7%–5.8%) across the European Region until August 2020¹³⁵ while Rostami *et al* estimated a pooled prevalence of 3.17% (1.96%–4.38%), 4.41% (2.20%–6.61%), 5.27% (3.97%–6.57%) in Western, Southern and Northern Europe, respectively.¹³⁴ In the same period, Bobrovitz *et al* reported a pooled estimate of 1.6% (1.1%–5.2%) seroprevalence in studies conducted across Central Europe, Eastern Europe and Central Asia¹³⁷ and 12.2% (4.5%–25.4%) from population-wide studies conducted until December 2020.¹³³

A number of studies reported low seroprevalence in younger and older age groups, a finding observed in other systematic reviews.^{133 135 138} Such findings have important implications, as groups such as the elderly are at higher risk of severe outcome following infection—and lack of cross-protective immunity indicates that all age groups will anticipate seeing high infection attack

rates without implementation of measures such as vaccination of priority groups, together with strengthening of public health and social measures to reduce SARS-CoV-2 transmission.

When reviewed alongside case notification data, seroprevalence estimates can provide greater insight into the local evolution of the pandemic. In this review, a positive correlation between seroprevalence estimates and national cumulative incidence in a number of countries was observed, suggesting that seroprevalence is a reflection of the duration and intensity of community transmission. It should be noted, however, that during the initial peak of infections in Europe in the spring of 2020, testing in many countries was not yet optimal and case notification data at this time are unlikely to provide a robust proxy for incidence in many instances. In line with this, several studies found seroprevalence estimates to be higher than the corresponding cumulative incidence of SARS-CoV-2 infections, suggesting a substantial underascertainment of infection through notifications, due to a number of factors including the asymptomatic or mild nature of disease, healthcare seeking behaviour, lack of testing capacity and testing and reporting strategies. Indeed, we also found a stronger association between seroprevalence and cumulative case mortality than cumulative case incidence, providing further evidence to support the suggestion of case underascertainment, as laboratory-confirmed mortality surveillance for COVID-19 is likely to be more comprehensive.

The varying quality of studies in this review reflects the challenge of conducting seroepidemiological studies of high quality. Indeed, this review found that only 50% of all studies undertaken in the WHO European region in 2020 were aligned with the WHO Unity study initiative. Few of the national (n=5; 15%) or regional (n=2; 7%) studies were determined to be of high risk of bias, while 17 (34%) of studies conducted at a local level (cities or towns) were graded as such. This variation may be explained by the level of resources and epidemiological support available to studies conducted at the regional or national level.



The majority of studies identified in this review used convenience rather than random sampling, which may have reduced the true representativeness of the estimates derived, though such convenience sampling is likely to provide a good estimate of population exposure for widely circulating viral infections. Many studies also included individuals that were not fully representative of the population under study, which may have introduced bias. For example, this review included studies that explored seroprevalence in the general population by using various proxy populations such as blood donors and residual blood. Blood donors are known to differ from the general population in that they are often a young, healthy adult population selected on the basis of lack of recent infection¹³⁹ and seroprevalence may, therefore, be over or underestimated in this group. Residual sera, on the other hand, derives from individuals who have sought healthcare and may therefore have pre-existing comorbidities or be at higher risk of SARS-CoV-2 infection. However, we found that seroprevalence estimates for these distinct populations are in good agreement with the general population.

We also found that there was a high degree of heterogeneity across serological assays used. The majority of studies used commercial tests of varying sensitivity and specificity to detect SARS-CoV-2 targeted antibodies, although some of these assays have now been shown to have excellent performance.^{140 141} However, under half of studies performed independent validation of these kits with internal controls and serum panels and only 25% accounted for the sensitivity and specificity of the tests in their statistical analyses. As SARS-CoV-2 serological tests have been found to have variable test performance,^{140 141} independent validation at local level in combination with use of an WHO International Standard and Reference Panel for anti-SARS-CoV-2 antibody has been widely promoted as part of the Solidarity II initiative.^{142 143} Other options include the Joint Research Centre¹⁴⁴ reference materials for the quality control of SARS-CoV-2 antibody tests. Use of these materials will allow for the potential correction for sensitivity and specificity during the statistical analysis, would allow for more robust estimates and greater comparability among countries in the region.

Overall, the findings of this review highlight the need for international collaboration to standardise approaches and support countries in conducting robust comparable studies. WHO, in collaboration with technical partners, has developed the Unity studies,^{15 90} a global seroepidemiology standardisation initiative for COVID-19, which aims to increase quality evidence-based knowledge in country and regions for action through the availability of standardised seroepidemiology investigation protocols and antibody assays. A primary aim of this global initiative is the provision of direct support to countries to develop country specific protocols, with particular attention provided to low-income and middle-income countries (LMICs), and to support aggregation, comparison and analysis of robust Unity-aligned studies through

strong coordination between WHO Country offices, Regional offices and Headquarters. A large proportion of the studies identified in this systematic review were conducted in Western European countries, with a relative scarcity of seroprevalence studies from other countries by the end of 2020, an observation noted in other systematic reviews.^{133–135 138} This highlights the urgent need for enhanced capacity, the provision of additional support to LMICs and the sharing of information to address the gap in knowledge and tackle research inequity. To counteract the skewedness in the WHO European Region, the WHO Unity protocols have been widely promoted by WHO and ECDC and technical support has been provided to tailor the protocols to local contexts, together with laboratory and financial support to LMICs. In addition, WHO and ECDC jointly established a network of approximately 300 public health professionals to facilitate discussions in related to SARS-CoV-2 seroprevalence, promote timely sharing of results and knowledge and further build capacity in the WHO European Region.

This systematic review comprehensively describes the seroprevalence of SARS-CoV-2 in the first year of the pandemic, prior to the widespread implementation of national vaccine programmes. With the inclusion of as yet unpublished data from LMICs, this review contributes to research equity across Member States income levels and provides a more representative overview of the situation in the WHO European Region than would published studies alone. In addition, we evaluated the UNITY study alignment of studies to assess quality and comparability.

This review has some limitations. First, there was significant heterogeneity among the studies, including sampling frame, population and stage of epidemic at time of serosurvey, which makes comparability across studies difficult. Due to such heterogeneity, we opted to not provide one pooled estimate nor conduct a meta-analysis, as interpretation would be difficult and may not accurately reflect the picture in the WHO European Region. Second, while population-based serological surveys can provide a more accurate estimation of the overall rates of SARS-CoV-2 infection within a population, this approach does not consider antibody waning, which cannot be easily accounted for as antibody levels vary depending on disease severity¹⁴⁵ and longevity is expected to vary greatly across SARS-CoV-2-infected individuals.¹⁴⁶ In addition, while seroprevalence studies provide an estimate of population exposure, seropositivity is not the only predictor of susceptibility to infection. Finally, due to the rapid accumulation of data related to SARS-CoV-2 seroepidemiology and the advent of the 'preprint era', not all included studies have been published and may, therefore, be subject to change on peer review.

Conclusion

As SARS-CoV-2 continues to circulate, understanding the population seropositivity remains critical for policy-makers and public health officials to make informed decisions on optimal public health interventions, such as lifting or

tightening of restrictions and targeted vaccination.^{10 147} In this study, we found evidence that SARS-CoV-2 antibody seroprevalence across the WHO European Region was low prior to widespread circulation and remained low in the general population during 2020. This suggests that much of the population remained susceptible to infection prior to the implementation of national COVID-19 vaccine campaigns from early 2021 onwards. We also found variation in seroprevalence estimates between and within countries during 2020, with evidence of increased prevalence in areas following high levels of transmission and some association with incidence and mortality trends over time. It is clear that antibody-mediated ‘herd immunity’ through natural infection is not attainable in most countries and COVID-19 vaccines should continue to be distributed widely and equitably to protect priority groups and the wider population. Given the issue of antibody waning, all efforts must be also directed towards well-informed and evidence-based implementation and maintenance of non-pharmaceutical interventions at a local and national level to stem any future waves of the pandemic. Indeed, as vaccine programmes continue to be implemented, standardised seroprevalence studies will be instrumental to evaluate both natural and vaccine derived immunity overtime to guide public health actions and decision-making.

Seroprevalence studies have been of great value to COVID-19 pandemic response efforts, providing estimates of the true extent and dynamics of SARS-CoV-2 infection overtime and the lessons identified from COVID-19, in particular the need for standardised global serosurveillance systems, will inform future pandemic preparedness.

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