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SARS-CoV-2 population-based seroprevalence studies in Europe: A scoping review

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SARS-CoV-2 population-based seroprevalence studies in Europe: A scoping review

Abstract (239 words)

Objectives: We aimed to review SARS-CoV-2 seroprevalence studies conducted in Europe to understand how they may be used to inform ongoing control strategies for COVID-19.

Design: Scoping review of peer-reviewed publications and manuscripts on pre-print servers from January 2020 to 15 September 2020.

Primary measure: Seroprevalence estimate (and lower and upper confidence interval). For studies conducted across a country or territory, we used the seroprevalence estimate and the upper and lower confidence intervals and compared them to the total number of reported infections to calculate the ratio of reported to expected infections.

Results: We identified 23 population-based seroprevalence studies conducted in Europe. Among 12 general population studies, seroprevalence ranged from 0·42% among residual clinical samples in Greece to 13·6% in an area of high transmission in Gangelt, Germany. Of the 8 studies in blood donors, seroprevalence ranged from 0·91% in North-western Germany to 23·3% in a high transmission area in Lombardy region, Italy. In three studies which recruited individuals through employment, seroprevalence ranged from 0·5% among factory workers in Frankfurt, Germany to 10·2% among university employees in Milan, Italy. In comparison to nationally reported cases, the extent of infection, as derived from these seroprevalence estimates, is many folds higher and largely heterogenous.

Conclusion: Exposure to the virus in Europe has not reached a level of infection that would prevent further circulation of the virus. Effective vaccine candidates are urgently required to deliver the level of immunity in the population.

Article summary

Strengths and limitations of this study

Population-based SARS-CoV-2 seroprevalence studies have now been conducted in Europe.

We conducted a systematic search of Pubmed for peer-reviewed publications and MedRxiv/BioRxiv for manuscripts on pre-print servers from January 2020 to 15 September 2020.

For studies conducted across a country or territory, we used the seroprevalence estimate and the upper and lower confidence intervals and compared them to the number of reported infections to calculate the ratio of reported to expected infections.

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Competing interest statements

The authors declare no competing interests.

Introduction

With the emergence of a novel pathogen, such as SARS-CoV-2 – the virus that causes COVID-19 – initial surveillance focuses primarily on those who are hospitalized with severe disease and those who report symptoms. As a result, early estimates of the extent of infection in the population and disease severity often struggle to account for mild or asymptomatic infections that do not require medical care. This is further exacerbated when availability of molecular tests for diagnosis of acute infection or capacity for testing are limited. This was the case in the initial stages of the first epidemic peak of COVID-19 across Europe. Therefore, there is an urgent need for seroprevalence studies to enable refined estimates of the extent of infection, particularly when used in population-based serologic surveys.[1,2]

Understanding the extent of infection is important in the current context of the COVID-19 pandemic. Many countries in Europe were severely impacted by the initial epidemic peak in March – June 2020. Health care facilities were overwhelmed by the number of patients requiring hospitalisation and/or admission to ICU; as was public health capacity to 1) identify, isolate, test, and care for all COVID-19 cases and 2) trace and quarantine contacts of known COVID-19 cases. As a result, many countries in Europe were forced to implement blunt public health and social measures to break chains of transmission, such as nationwide stay at home orders, and the closing of borders, workplaces and schools.[3]

During this time in Europe, a number of population-based seroprevalence studies have been conducted. As countries have now lifted many of the initial broad-reaching measures, these studies are important not only to understand the extent of infection in the population, but also to refine estimates of disease severity and to enable better understanding of population protection against epidemic peaks. Nonetheless, population-based seroprevalence studies are not without caveats. Notably, the selection of participants, and the biases inherent in the selection, as well as the performance of the assays used to measure antibodies may affect the interpretation of the seroprevalence results.[4] We provide here a scoping review of the population-based seroprevalence studies from Europe available as of 15 September 2020 and a synthesis on how these results may be used to inform ongoing control strategies for COVID-19.

Methods

In addition to routine monitoring of population-based seroprevalence studies, we conducted a systematic search of Pubmed for peer-reviewed publications and MedRxiv/BioRxiv for manuscripts on pre-print servers from January 2020 to 15 September 2020. The search keywords included the terms COVID-19, SARS-CoV-2 and seroprevalence. The complete search strategy can be found in the Supplementary Material.

Inclusion criteria

We included publications that met all of the following criteria: 1) seroprevalence study conducted in Europe; 2) study population derived from the general population (rather than a health-care based population, or a population subject to a specific outbreak investigation); 3) sufficient detail on the type of assay used and the performance (specificity and sensitivity) of the assay for detecting anti-SARS-CoV-2 antibodies reported in the publication, included as a referenced publication, or publicly available by the manufacturer in the case of a commercially available assay; 4) date of sample collection for serologic testing included; 5) estimate of seroprevalence in the population reported as percentage of the study population with anti-SARS-CoV-2 IgG antibodies.

Article screening

All identified abstracts were screened in duplicate by two reviewers to assess eligibility criteria for inclusion in analysis. A third reviewer resolved discrepancies. The following data was extracted from each study:

Details of the study: authors, year of publication, country, type of publication (publication in peer-reviewed journal or manuscript on pre-print server)

Methodology: objectives of the study, methods including study population, sample size and methods of recruitment, assay used, sensitivity and specificity of the assay and how these were determined (reported by manufacturer for commercial assays or determined as part of the study), as well as the population used to determine sensitivity and specificity of the assay.

Outcome: study seroprevalence point estimate (and confidence interval, when reported)

While this may lead to an overestimate as to the performance of the assay, for commercially available assays, the most recent reported specificity and sensitivity data as reported by the manufacturer was reported.

Assessment of bias

The Joanna Briggs Institute checklist for studies reporting prevalence data was used to identify potential biases. Additionally, the qualitative categories defined by Bobrovitz N et al[5] were used to determine the magnitude of the biases into one of four categories: (i) High: Limited certainty in prevalence: the true prevalence may be substantially different from the estimated prevalence; (ii) Moderate: Moderate certainty in the prevalence: the true prevalence is likely to be close to the estimate, but there is a possibility that it is substantially different; (iii) Low: High certainty in the prevalence estimate: true prevalence is likely close to the estimate; and (iv) Unclear: There was insufficient information to assess risk of bias.

Further COVID-19 epidemiological information

We extracted epidemic curves and cases counts from the European Centre for Disease Prevention and Control on 19 September 2020 (https://www.ecdc.europa.eu/en/publications-data/download-todays-data-geographic-distribution-covid-19-cases-worldwide) for countries/territories in which seroprevalence studies included in our analysis were representative of the country/territory. Blood sample collection dates were overlapped on the epidemic curve to assist with the interpretation of the seroprevalence results.

Comparison of case ascertainment

For the general population studies that were implemented nationwide or across a territory, we used the seroprevalence estimate and the upper and lower confidence intervals and compared them to the number of reported infections 15 days before the end of the blood sample collection period for the seroprevalence study. This allowed us to estimate the number of infections expected based on the seroprevalence estimate and to calculate the ratio of reported to expected infections.

Results

Routine monitoring of literature on SARS-CoV-2 seroprevalence, in addition to a systematic search for publications on Pubmed and the MedRxiv/BioRxiv pre-print servers identified 315 publications. Of these, 23 met the inclusion criteria and were included in this review (Figure 1). Ten were published in peer-reviewed journals and 13 were manuscripts available on pre-print servers.

Twelve studies used randomly selected samples from the general population, with studies largely conducted through household surveys. A further eight studies were conducted in populations of blood donors, and three additional studies were conducted among individuals who were recruited through employment.

We did not pool the estimates due to heterogeneity of the populations and in dates of sample collection with respect to SARS-CoV-2 transmission dynamics. Instead, we provide a summary of the seroprevalence estimates based on study population (Figure 2).

Population-based seroprevalence studies

Among the 12 studies conducted in the general population,[6-17] seroprevalence ranged from 0·42% among residual clinical samples in Greece[7] to 13·6% in an area of high transmission in Gangelt, Germany.[14] All studies were conducted between March – June 2020, with the studies conducted May–June reflecting the post epidemic peak period in the respective study settings. The largest study was a nationwide cross-sectional study conducted in Spain in which 51958 household members were recruited after the first epidemic peak in the country and found seroprevalence using an immunoassay of 4·6% (95% CI 4·3–5·0).[8]

Three studies[7,9,10] performed serial sampling of participants. In Geneva, Switzerland, participants from an existing longitudinal cohort study were sampled across 5 consecutive weeks. While the same individuals were not sampled each week, seroprevalence increased: from 4·8% (95% CI 2·4–8·0, n=341) in the first week to 10·9% (7·9–14·4, n=577) in the third week, before stabilizing at 10·8% (8·2–13·9, n=775) in the fifth week.[9]

Similarly, in Belgium, residual clinical samples from hospitals and diagnostic labs were sampled across five collection periods from the end of March to the start of July. It was estimated that 2·9% (95% CI 2·3-3·6) of the Belgian population had detectable antibodies at the end of March, which doubled to 6·0% (95% CI 5·1-7·1) three weeks later but decreased to 4·5% (95% CI 3·70-5·40) in the fifth collection period (29 June - 3 July 2020).[10] In Greece, residual clinical samples were tested following a geographically stratified sampling plan based on regional units. Seroprevalence increased from 0·24% (95% CI 0·03-0·45) in March to 0·42% (95% CI 0·23-0·61) in April.[7]

Six of the 12 studies stratified seroprevalence estimates by age. In the nationwide seroprevalence study conducted in Spain, seroprevalence was found to increase with age and the lowest seroprevalence was found in those aged 0–19 years 3·8% (95% CI 3·2-4·6).[8] In Geneva, Switzerland, seroprevalence was 0·8% in 5-9 years,

compared to 9·6% in the 10-19 years and 9·9% in 20-49 years.[9] In Belgium and Greece, age-specific seroprevalence from residual clinical samples from hospitals and diagnostic labs was found to increase with age.[7,10] In Gangelt, Germany, infection rates were found to be lower in the 5-14 years, compared to any other age group.[14] In Neustadt-am-Rennsteig, Germany, seroprevalence in children and adolescents was found to be 1·7%, compared to 9·1% in adults.[15]

Seroprevalence studies in blood donors

Of the 8 studies in blood donor populations,[18-25] seroprevalence ranged from 0·91% in North-western Germany to 23·3% in the area of Lodi province (Lombardy, Italy) where high transmission of COVID-19 was detected from the end of February 2020.

One study in Scotland performed serial sampling on blood samples collected through blood donation centres. All blood samples were negative in mid-March, but rose from end of March. Seroprevalence results were stratified by location across the country, and seroprevalence was found to be heterogenous by location. In Milan, serial sampling of blood donation samples found the seroprevalence to increase from 2·0% at the end of February to 5·0% by mid-March to early April.

While blood donor populations inherently do not include children, several adult blood donor populations were stratified by age. Among 20640 blood donors across Denmark, the youngest (17–29 years: 2·5%) and oldest (60-69 years: 2·5%) blood donors were found to have higher seroprevalence. In South East Italy, it was the 26-35 years old (2·0%) and the 56-65 years old (2·0%) age groups which had the highest seroprevalence.

Seroprevalence studies in employees / individuals recruited through non-health-care related employment

Three studies recruited individuals through employment. University employees without any symptoms in Milan were found to have a seroprevalence of 10·2%; factory workers in two counties in Croatia were found to have seroprevalence of 1·3%, while healthy volunteer industrial site operator in the metropolitan area of Frankfurt am Main were found to have a seroprevalence of 0·5%.

Comparison of case underascertainment

We were able to use the serology-derived estimates of extent of infection in the four general population studies that were implemented nationwide or across a territory to compare to the total number of reported infections reported 15 days prior to the end of the blood sample collection period by the country/territory. Across the four studies, the ratio of reported to expected number ranged from 10% to 63% (Table 2).

Discussion

In this scoping review of 23 published seroprevalence studies from Europe, we find heterogenous results, ranging from 0·42% among geographically-representative residual clinical samples across Greece to 23·3% in blood donors in an area of high transmission in Lombardy, Italy. The studies in which serial sampling was conducted noted that an increasing fraction of the population has been exposed to the virus. There was no consistency in age stratification so inferences as to differences in seroprevalence by age are difficult to make at this stage.

In comparison to total reported cases of infection, we observed that there was large heterogeneity among countries in the seroprevalence-derived estimates of extent of infection. This likely reflects testing strategies for molecular testing during the first epidemic peak in Europe and the laboratory capacity for diagnosing COVID-19, which in many places was restricted to those with severe disease or those requiring hospitalization. Understanding testing strategies is an important consideration for analyzing and comparing surveillance data, particularly in the COVID-19.

The heterogeneity that we observed in seroprevalence estimates across studies may be explained by several factors. Firstly, the heterogeneity of transmission within Europe and within countries. Across Spain, for example, seroprevalence ranged from 1·2% to 14·4%, likely reflecting the heterogeneity in transmission across the country.[8] Secondly, the study population and the biases inherent in how the study population has been selected in each study. Eight studies used blood donor populations, which, by definition, select adults without any recent symptoms consistent with COVID-19. As such, the seroprevalence in blood donors is likely to underestimate seroprevalence of the general population, particularly in early seroprevalence studies, as is the case in this review.[4] In addition, this population tends to be healthier than the general population.[3] The studies among blood donors found seroprevalence to be largely lower than the seroprevalence in studies that used household surveys targeting the general population, with the exception of the blood donors in Lombardy. The 23·3% seroprevalence, measured around the peak of transmission in the Lombardy region, likely reflects the intensity of transmission at that time.

When considering the lag time between infection and measurable antibodies, and the study population, the post peak seroprevalence in the general population may be in fact substantially higher. That is, those infected at or around the period of most intense transmission (within the 2-3 weeks prior to sample collection) would most likely have had a negative serologic test result but would have gone on to seroconvert shortly afterwards.

Further heterogeneity may derive from the serologic assays and the various performance of the assays. All assays show high sensitivity, however, in the context of low seroprevalence, as is the case for SARS-COV-2, specificity of less than 100% has a greater impact on the positive predictive value of the assay. A number of studies report the validation of the assay used as part of the study, as well as the populations used for this validation. Others report the validation performed as part of other studies, while others simply report the validation data from the

manufacturer. A number of studies used the Euroimmun ELISA assay, yet the performance of the assay varies in validation studies, likely due to differences in clinical and analytical validity.

A further consideration when interpreting the results of the review is the type of the assay used. Only three of the 23 studies used neutralization assays, while the rest used a rapid immunoassay, an ELISA or CLIA assay. While the latter detect immunoglobulins specific to SARS-CoV-2, often much quicker and less laboriously than the former, they do not implicitly indicate the strength of an individual's immune response. Neutralization assays, in contrast, reflect more closely the functional role of anti-SARS-CoV-2 antibodies in the immune response and therefore give a better indication as to protection from further infection. Additional validation studies are required to understand the correlation between antibody titres detected by a rapid immunoassay, ELISA or CLIA and the neutralizing antibody response. This is important - for other coronavirus, individuals who are IgG positive are able to be reinfected,[29,30] and there are now reports of SARS-CoV-2 reinfection.[31] There are several possible explanations for this, including the implications related to the detection of antibodies versus the detection of neutralizing antibodies.

In addition, no longitudinal cohort studies were able to be included in this review. As such, all studies present antibody responses in individuals at one point in time. For the studies that used serial sampling, these were different individuals who were sampled, selected from the same source population each time. We are therefore unable to comment on the duration or persistence of antibodies, nor how this may correlate to ongoing protection. Longitudinal studies that follow the same individuals over time are needed to understand how long antibody, ideally neutralizing antibodies, may persist.[32,33]

Finally, in addition to the humoral response, the body also mounts a cellular response against infection. Specifically, T-cells recognize and eliminate other cells infected with a virus. By looking only at antibody detection, studies to determine the extent of infection in the population, the study presupposes that everyone who is infected seroconverts, at least to levels that the assay can detect.[4] The proportion of those who mount a cellular response, but not a detectable antibody response, is currently unclear.[34,35] Further research that combines assessment of the humoral and cellular responses is needed to quantify the magnitude of those who may in fact have some protection from infection despite a negative antibody result.

Nonetheless, despite this heterogeneity and caveats implicit in the various studies, the picture across Europe after the first epidemic peak of SARS-CoV-2 is clear: exposure to the virus has been insufficient to deliver the level of infection in the population that would be required to prevent further circulation of the virus. The threshold beyond which such herd immunity may be achieved is estimated to be 50-67%.[36,37] Above this threshold, it is thought that the virus may no longer be able to circulate in the population.

These findings have important policy implications for countries in Europe:

While a few experts have recommended that countries seek primarily to achieve herd immunity by allowing the virus to circulate in societies unimpeded, the vast majority of scientists and experts have not recommended this strategy.[38] This position is based on a number of considerations:

Firstly, such a strategy has and will continue to overwhelm health-care systems. The devastating effect on the health-care systems was observed early in the pandemic in countries which were slow to respond to the identification of initial cases. Overwhelmed health-care systems not only disrupt the delivery of care to COVID-19 patients, but also the delivery of non-COVID-19 health services. Elective surgeries are delayed, vaccine campaigns are halted and access to health-care may be difficult.

Further, we now understand that transmission of SARS-CoV-2 is largely concentrated in crowded, close-contact and confined settings. Targeting these high-risk settings for control measures will create large reduction in transmission rates, more so than the blunt public health and social measures, and with the advantage of avoiding the adverse economic and societal impacts. Further, contact tracing and epidemiological studies indicate that a small proportion of all people infected likely account for a much larger proportion of onwards transmission,[39-42] although age-specific rates of contacts also likely influence transmission and immunity patterns.[43]

Overall, the results of the initial seroepidemiologic studies in Europe indicate the population immunity is below the likely threshold for herd immunity and that measures to 1) identify, isolate, test and care for all COVID-19 cases and 2) trace and quarantine contacts of known COVID-19 cases will need to be maintained far beyond the emergence of COVID-19 and the initial epidemic peak.[44,45] As a result, we urgently need the development of effective vaccine candidates to deliver the required level of herd immunity in the population.

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Author contributions

AF, RG, TD and XA designed the review.

RG, TD, XA conducted the literature search and extracted the data from eligible studies.

TD, XA and PP performed statistical analyses.

RG, TD and XA drafted the first versions of the manuscript.

HN, AW-S, PP and AF critically revised the first version of the manuscript.

All authors reviewed and approved the final version of the manuscript.

Table 1. Characteristics of included studies (N=23)

First author	Type of publication	Location of study	Study population	Sample size	Dates of sample collection	Seroprevalence estimate % [confidence interval]	Serologic assay used	Reported specificity and sensitivity of serologic assay	Assessment of bias[a]
General populations									
Petersen MS.[6]	Peer-reviewed publication	Faroe Islands	Random sample of population registry	1075	27 April – 1 May 2020	0·6 [0·2–1·2]	Wantai SARS-CoV-2 Ab ELISA kit (Beijing Wantai Biologic Pharmacy Enterprise)	Sensitivity: 94·4%, specificity: 100%	Low
Bogogiannidou Z.[7]	Peer-reviewed publication	Greece	Serial sampling of representative residual clinical samples	4511	March – April April 2020	0·42 [0·23–0·61]	ABBOTT SARS-CoV-2 IgG assay (Abbott Laboratories)	Sensitivity: 84·0%, specificity: 99·7%	Low
Pollan M.[8]	Peer-reviewed publication	Spain	Randomly selected households across Spain	61075	27 April – 11 May 2020	4·6 [4·3–5·0]	Orient Gene IgM/IgG (Zhejiang Orient Gene Biotech); Abbott Architect IgG (Abbott Laboratories)	Specificity 100%, sensitivity 82·1% (Orient Gene) Specificity 100%, sensitivity 89·7% (Abbott)	Low
Stringhini S.[9]	Peer-reviewed publication	Geneva, Switzerland	Serial sampling of population-representative cohort	2766	6 April – 9 May 2020 (5 consecutive weeks of sampling)	10·8 [8·2–13·9]	ELISA IgG (Euroimmun)	Manufacturer reported: Specificity: 94.4%, sensitivity: 99.6%	Low
Herzog S.[10]	Pre-print manuscript	Belgium	Serial sampling of residual clinical samples from hospitals and diagnostic labs	7820	30 March – 4 July 2020 (5 different sampling periods)	4·5 [3.7–5·4]	ELISA IgG (Euroimmun)	Manufacturer reported: Specificity: 94.4%, sensitivity: 99.6%	Moderate
Snoeck CJ.[11]	Pre-print manuscript	Luxembourg	Representative web-based sample of	1862	15 April – 5 May 2020	1·97 [1·25–2·69]	ELISA IgG and IgA (Euroimmun)	Specificity 89·2%; sensitivity 85·7% at day 15 after	High

			general population					symptom onset in PCR confirmed patients	
Wells P.[12]	Pre-print manuscript	South-East England	Ongoing community-based cohort	431	27 April – 02 June	12 [9·1–15·2]	In-house N/S ELISA (King's College London)	Specificity: 100 % Sensitivity: 84·7%, 87.0% at 14 days post onset and 96·4% after 20 days	High
Aziz NA.[13]	Pre-print manuscript	Bonn, Germany	Ongoing community-based cohort	4771	24 April – 30 June	0·97 [0·72–1·30]	ELISA IgG (Euroimmun); plaque reduction neutralisation test	Manufacturer reported: Specificity: 94.4%, sensitivity: 99.6%	Low
Streeck H.[14]	Pre-print manuscript	Gangelt, Germany	Randomly selected household members in Gangelt, Germany	919	31 March – 6 April 2020	13·6	ELISA IgG (Euroimmun)	Manufacturer reported: Specificity: 94.4%, sensitivity: 99.6%	Moderate
Weis S.[15]	Pre-print manuscript	Neustadt-am-Rennsteig, Germany	Household members	620	12 – 22 May 2020	8·4	ELISA IgG (Euroimmun); IgG CLIA kit (DiaSorin, Saluggia, Italy; Maglumi; IgG CMIA kit (Abbott) and Elecsys Anti-SARS-CoV-2 kit (Roche).	Manufacturer reported: Specificity: 94.4%, sensitivity: 99.6% (EuroImmun), specificity 99·3%; sensitivity 97·6% (Liaison CLIA), specificity 100%; sensitivity 91·2% (Maglumi), specificity 99·6%; sensitivity 100% (Abbott), specificity 99·8%; sensitivity 100% (Roche)	Low

Roxhed N.[16]	Pre-print manuscript	Stockholm urban area, Sweden	Randomly selected households	443	May 2020	10·84 [7·94–13·73]	In-house multiplexed serology assay	Sensitivity: 100% Specificity: 98% combining the scores from at least two of the included SPK protein	Moderate
Fenwick C.[17]	Pre-print manuscript	Vaud canton, Switzerland	Randomly selected residents	311	4 May – 27 June 2020	6·4	In-house S protein trimer	Specificity 98·5%; sensitivity 90% after 16 days after onset of symptoms	Moderate
Blood donor populations									
Erikstrup C.[18]	Peer-reviewed publication	Denmark	Blood donation centres	20640	6 April – 3 May 2020	1·9 [0·8–2·3]	Lateral flow immunoassay (Livzon Diagnostics)	Specificity 99.5%; sensitivity 82.6%	Moderate
Fischer B.[19]	Peer-reviewed publication	Three federal states in North-western Germany	Blood donation centres	3186	9 March - 3 June 2020	0·91 [0·58–1·24]	ELISA IgG (Euroimmun)	Manufacturer reported: Specificity: 94.4%, sensitivity: 99.6%	Moderate
Percivalle E.[20]	Peer-reviewed publication	High transmission area, Lombardy region, Italy	Blood donation centres	390	18 March – 6 April 2020	23·33	In-house microneutralization assay	Specificity 100%; sensitivity 95%	Moderate
Fiore JR.[21]	Peer-reviewed publication	Low incidence area, South East Italy	Blood donation centres	904	1 – 31 May 2020	0·99	Chemiluminescent analytical assay (New Industries Biomedical Engineering Co)	Specificity 97·3%; sensitivity 91·2%	Moderate
Slot E.[22]	Pre-print manuscript	Netherlands	Blood donation centers	7361	1 – 15 April 2020	4·2 [3·1–5·4]	ELISA (Beijing Wantai Biological Pharmacy Enterprise); ELISA IgG (Euroimmun)	Specificity 99·1%, sensitivity 100%	Moderate
Thompson CP.[23]	Pre-print manuscript	Scotland	Blood donation centres	1000	21 – 23 March 2020	1·2	In-house pseudotyped SARS-CoV-2	Specificity 100%; sensitivity 94·1%	Moderate

							microneutralisation assay		
Fontanet A.[24]	Pre-print manuscript	High transmission area, north of Paris, France	Blood donation centres	200	23 – 27 March 2020	3·0 [1·1–6·4]	In-house ELISA assay (Institut Pasteur); in-house flow cytometry assay (Institut Pasteur); in-house immunoprecipitation-based assay (Institut Pasteur)	Data reported from other validation study:[46] Specificity 100%; sensitivity 99·4%	High
Valenti L.[25]	Pre-print manuscript	Milan, Italy	Convenience sample from blood donation centres	789	24 February – 8 April 2020	5·07	IgG/IgM rapid lateral flow immunoassay (Prima Lab)	Specificity 98·3%; sensitivity 100%	Moderate
Individuals recruited through non-health-care related employment									
Milani GP.[26]	Peer-reviewed publication	Milan, Italy	University staff	194	30 – 31 March 2020	10·2	ELISA (Beijing Wantai Biological Pharmacy Enterprise); ELISA IgG (Euroimmun)	Data reported from separate validation study:[47,48] Specificity: 99·1%, sensitivity 100% Manufacturer reported: Specificity: 94.4%, sensitivity: 99.6% (Euroimmun)	High
Jerkovic I.[27]	Peer-reviewed publication	Split-Dalmatia and Šibenik-Knin County, Croatia	Factory workers	1494	23 – 28 April 2020	1·27 [0·77–1·98]	IgG/IgM rapid test (AMP Diagnostics)	Manufacturer reported: Specificity 96·4%; sensitivity 91·8%	Moderate
Kraehling V.[28]	Pre-print manuscript	Frankfurt am Main metropolitan area	Healthy voluntary employees of a large industrial site operator	1000	6 – 14 April 2020	0·5	In-house ELISA	Specificity 99·2%; sensitivity 100%	High

[a] As determined through the use of the Joanna Briggs Institute Critical appraisal checklist for studies reporting prevalence data, and the qualitative categories defined by Bobrovitz N et al.[5] High: Limited certainty in prevalence: the true prevalence may be substantially different from the estimated prevalence. Moderate: Moderate certainty in the prevalence: the true prevalence is likely to be close to the estimate, but there is a possibility that it is substantially different. Low: High certainty in the prevalence estimate: true prevalence is likely close to the estimate. Unclear: There was insufficient information to assess risk of bias.

Table 2. Comparison of reported and seroprevalence-derived expected number of infections

Country	Seroprevalence estimate (%) [lower CI - upper CI]	Number of infections reported 15 days prior to end of blood sample collection	Seroprevalence-derived expected number of infections	Seroprevalence-derived expected number of infections (lower confidence interval)	Seroprevalence-derived expected number of infections (upper confidence interval)	Ratio of reported infections to seroprevalence-derived number of infections
Spain	4·6 [4·3-5·0]	210623	2159105	2018294	2346853	0.10
Luxembourg	1·97 [1·25-2·69]	3550	12097	7685	16508	0.29
Faroe Islands	0·6 [0·2-1·2]	184	292	97	584	0.63
Belgium	4·5 [3·7-5·4]	60854	515498	423854	618598	0.12

Figure 1. Inclusion of studies in review

Figure 2. Study seroprevalence (point estimate and confidence interval, when reported)[a]

[a] For studies that used serial sampling, the most recent seroprevalence estimate was selected.

Figure 3. Blood sample collection periods of studies with respect to reported national epidemic curves of reported cases for those studies conducted nation-/territory-wide (n=7)

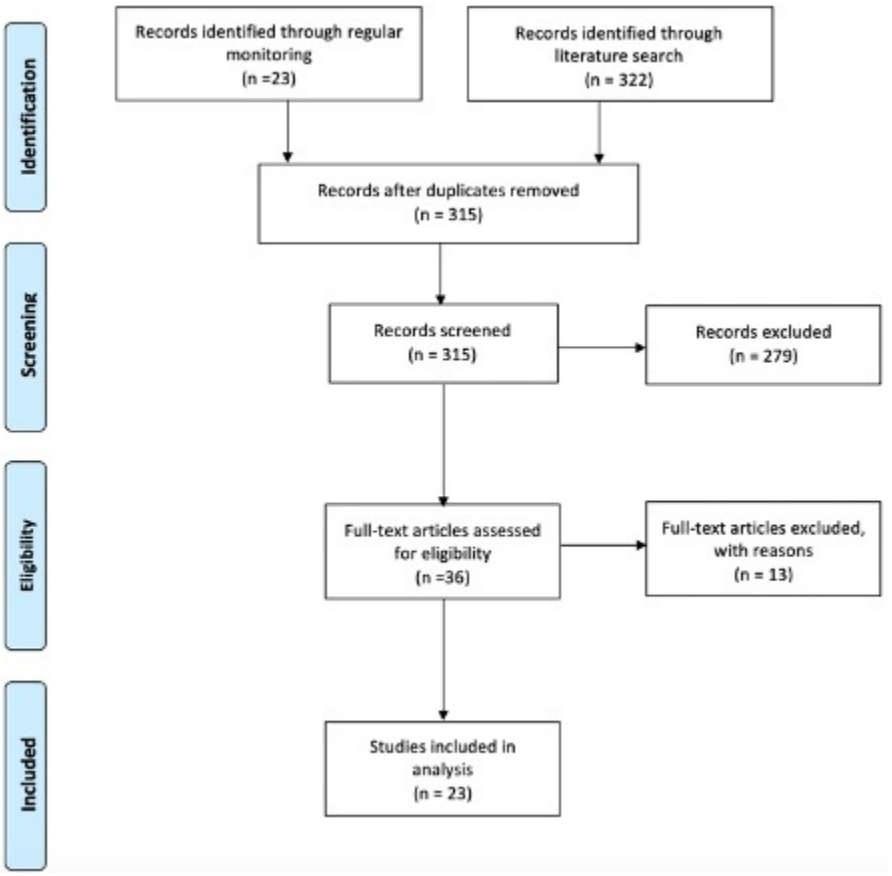

Figure 1. Inclusion of studies in review

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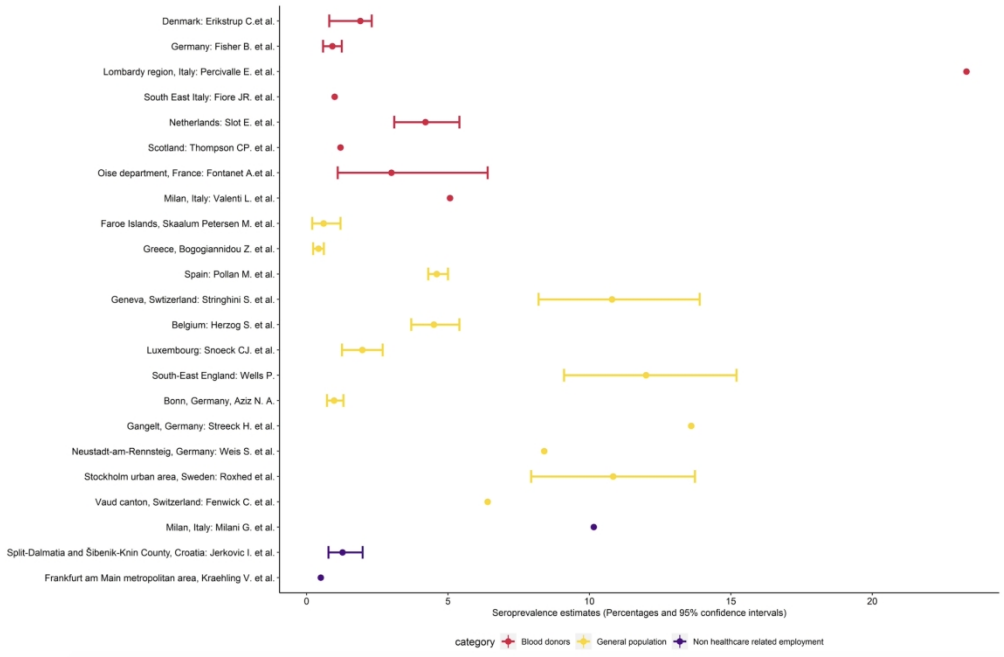

Figure 2. Study seroprevalence (point estimate and confidence interval, when reported)

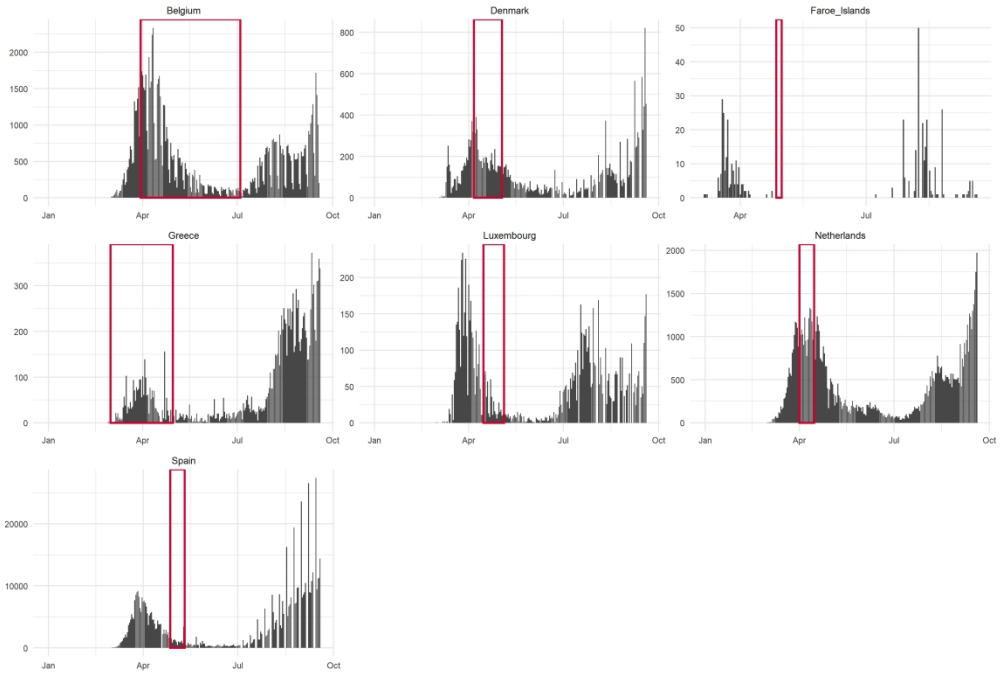

Figure 3. Blood sample collection periods of studies with respect to reported national epidemic curves of reported cases for those studies conducted nation-/territory-wide (n=7)

328x223mm (300 x 300 DPI)

SARS-CoV-2 population-based seroprevalence studies in Europe: A scoping review

Supplementary Material

Search strategy:
MedRxiv/BioRxiv
Full text or abstract or title "((COVID-19) OR (sars-cov-2)) AND ((seroprevalence)" (match whole all) and posted between "01 Jan, 2020 and 15 Sep, 2020"

NCBI PubMed
((((COVID-19[Text Word]) OR (sars-cov-2[Text Word])) AND (seroprevalence[Text Word]) AND (("2020/01/01"[Date - Publication] : "2020/09/15"[Date - Publication])))

Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	3
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	3
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	-
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	4
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	4
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	Supplementary material
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	Figure 1
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	4
Critical appraisal of individual	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe	4

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
sources of evidence§		the methods used and how this information was used in any data synthesis (if appropriate).	
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	4
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	Figure 1
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	Supplementary material, Table 1
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	Table 1
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	Table 1
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	6-8
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	8
Limitations	20	Discuss the limitations of the scoping review process.	9
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	10
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	2

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.

BMJ Open

SARS-CoV-2 population-based seroprevalence studies in Europe: A scoping review

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Keywords:	Epidemiology < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, EPIDEMIOLOGY

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SARS-CoV-2 population-based seroprevalence studies in Europe: A scoping review

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SARS-CoV-2 population-based seroprevalence studies in Europe: A scoping review

Abstract (239 words)

Objectives: We aimed to review SARS-CoV-2 seroprevalence studies conducted in Europe to understand how they may be used to inform ongoing control strategies for COVID-19.

Design: Scoping review of peer-reviewed publications and manuscripts on pre-print servers from January 2020 to 15 September 2020.

Primary measure: Seroprevalence estimate (and lower and upper confidence interval). For studies conducted across a country or territory, we used the seroprevalence estimate and the upper and lower confidence intervals and compared them to the total number of reported infections to calculate the ratio of reported to expected infections.

Results: We identified 23 population-based seroprevalence studies conducted in Europe. Among 12 general population studies, seroprevalence ranged from 0·42% among residual clinical samples in Greece to 13·6% in an area of high transmission in Gangelt, Germany. Of the 8 studies in blood donors, seroprevalence ranged from 0·91% in North-western Germany to 23·3% in a high transmission area in Lombardy region, Italy. In three studies which recruited individuals through employment, seroprevalence ranged from 0·5% among factory workers in Frankfurt, Germany to 10·2% among university employees in Milan, Italy. In comparison to nationally reported cases, the extent of infection, as derived from these seroprevalence estimates, is many folds higher and largely heterogenous.

Conclusion: Exposure to the virus in Europe has not reached a level of infection that would prevent further circulation of the virus. Effective vaccine candidates are urgently required to deliver the level of immunity in the population.

Article summary

Strengths and limitations of this study

Population-based SARS-CoV-2 seroprevalence studies have now been conducted in Europe.

We conducted a systematic search of Pubmed for peer-reviewed publications and MedRxiv/BioRxiv for manuscripts on pre-print servers from January 2020 to 15 September 2020.

For studies conducted across a country or territory, we used the seroprevalence estimate and the upper and lower confidence intervals and compared them to the number of reported infections to calculate the ratio of reported to expected infections.

Funding statement

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interest statements

The authors declare no competing interests.

Data availability statement

All data relevant to the study are included in the article; no additional data available.

Introduction

With the emergence of a novel pathogen, such as SARS-CoV-2 – the virus that causes COVID-19 – initial surveillance focuses primarily on those who are hospitalized with severe disease and those who report symptoms. As a result, early estimates of the extent of infection in the population often struggle to account for mild or asymptomatic infections that do not require medical care. This is further exacerbated when availability of molecular tests for diagnosis of acute infection or capacity for testing are limited. This may have been the case in the initial stages of the first epidemic peak of COVID-19 in many countries across Europe. Therefore, there is an urgent need for seroprevalence studies to enable refined estimates of the extent of infection, particularly when used in population-based serologic surveys.[1,2]

Understanding the extent of infection is important in the current context of the COVID-19 pandemic. Many countries in Europe were severely impacted by the initial epidemic peak in March – June 2020. Health care facilities were overwhelmed by the number of patients requiring hospitalisation and/or admission to ICU; as was public health capacity to 1) identify, isolate, test, and care for all COVID-19 cases and 2) trace and quarantine contacts of known COVID-19 cases. As a result, many countries in Europe were forced to implement blunt public health and social measures to break chains of transmission, such as nationwide stay at home orders, and the closing of borders, workplaces and schools.[3]

During this time in Europe, a number of population-based seroprevalence studies have been conducted. As countries have now lifted many of the initial broad-reaching measures, these studies are important not only to understand the extent of infection in the population, but also to refine estimates of disease severity and to enable better understanding of population protection against epidemic peaks. Nonetheless, population-based seroprevalence studies are not without caveats. Notably, the selection of participants, and the biases inherent in the selection, as well as the performance of the assays used to measure antibodies may affect the interpretation of the seroprevalence results.[4] We provide here a scoping review of the population-based seroprevalence studies from Europe available as of 15 September 2020 and a synthesis on how these results may be used to inform ongoing control strategies for COVID-19.

Methods

In addition to routine monitoring of population-based seroprevalence studies, we conducted a systematic search of Pubmed for peer-reviewed publications and MedRxiv/BioRxiv for manuscripts on pre-print servers from January 2020 to 15 September 2020. The search keywords included the terms COVID-19, SARS-CoV-2 and seroprevalence. The complete search strategy can be found in the Supplementary Material.

Inclusion criteria

We included publications that met all of the following criteria: 1) seroprevalence study conducted in Europe; 2) study population derived from the general population (rather than a health-care based population, or a population subject to a specific outbreak investigation); 3) sufficient detail on the type of assay used and the performance (specificity and sensitivity) of the assay for detecting anti-SARS-CoV-2 antibodies reported in the publication, included as a referenced publication, or publicly available by the manufacturer in the case of a commercially available assay; 4) date of sample collection for serologic testing included; 5) estimate of seroprevalence in the population reported as percentage of the study population with anti-SARS-CoV-2 IgG antibodies.

Article screening

All identified abstracts were screened in duplicate by two reviewers to assess eligibility criteria for inclusion in analysis. A third reviewer resolved discrepancies. The following data was extracted from each study:

Details of the study: authors, year of publication, country, type of publication (publication in peer-reviewed journal or manuscript on pre-print server)

Methodology: objectives of the study, methods including study population, sample size and methods of recruitment, assay used, sensitivity and specificity of the assay and how these were determined (reported by manufacturer for commercial assays or determined as part of the study), as well as the population used to determine sensitivity and specificity of the assay.

Outcome: study seroprevalence point estimate (and confidence interval, when reported)

While this may lead to an overestimate as to the performance of the assay, for commercially available assays, the most recent reported specificity and sensitivity data as reported by the manufacturer was reported.

Assessment of bias

The Joanna Briggs Institute checklist for studies reporting prevalence data was used to identify potential biases. Additionally, the qualitative categories defined by Bobrovitz N et al[5] were used to determine the magnitude of the biases into one of four categories: (i) High: Limited certainty in prevalence: the true prevalence may be substantially different from the estimated prevalence; (ii) Moderate: Moderate certainty in the prevalence: the true prevalence is likely to be close to the estimate, but there is a possibility that it is substantially different; (iii) Low: High certainty in the prevalence estimate: true prevalence is likely close to the estimate; and (iv) Unclear: There was insufficient information to assess risk of bias.

Further COVID-19 epidemiological information

We extracted epidemic curves and cases counts from the European Centre for Disease Prevention and Control (ECDC) on 19 September 2020 (https://www.ecdc.europa.eu/en/publications-data/download-todays-data-geographic-distribution-covid-19-cases-worldwide) for countries/territories in which seroprevalence studies included in our analysis were representative of the country/territory. Blood sample collection dates were overlapped on the epidemic curve to assist with the interpretation of the seroprevalence results.

Comparison of case ascertainment

For the general population studies that were implemented nationwide or across a territory, we used the seroprevalence estimate and the upper and lower confidence intervals and compared them to the number of reported infections 15 days before the end of the blood sample collection period for the seroprevalence study, based on current understanding of anti-SARS-CoV-2 antibody kinetics and the ability to detect these antibodies in the second week of infection.[6] This allowed us to estimate the number of infections expected based on the seroprevalence estimate and to calculate the ratio of reported to expected infections.

Patient and public involvement

Our study involved the secondary analysis of data and, as such, there was no direct patient involvement.

Results

Routine monitoring of literature on SARS-CoV-2 seroprevalence, in addition to a systematic search for publications on Pubmed and the MedRxiv/BioRxiv pre-print servers identified 315 publications. Of these, 23 met the inclusion criteria and were included in this review (Figure 1). Ten were published in peer-reviewed journals and 13 were manuscripts available on pre-print servers (Table 1).

Twelve studies[7-18] used randomly selected samples from the general population, with studies largely conducted through household surveys. A further eight studies[19-26] were conducted in populations of blood donors, and three additional studies[27-29] were conducted among individuals who were recruited through employment (Table 1).

We did not pool the estimates due to heterogeneity of the populations and in dates of sample collection with respect to SARS-CoV-2 transmission dynamics. Instead, we provide a summary of the seroprevalence estimates based on study population (Figure 2). In addition, seven seroprevalence studies were representative of a country/territory for which epidemic curves and cases counts were available from ECDC.[7-9,11,12,19,23] Figure 3 demonstrates that four studies[8,11,19,23] involved blood sample collection that included a period of time prior to the first epidemic peak, while three were conducted following the first epidemic peak, as determined by the epidemic curve.[7,9,12]

We extracted epidemic curves and cases counts from the European Centre for Disease Prevention and Control on 19 September 2020 (https://www.ecdc.europa.eu/en/publications-data/download-todays-data-geographic-distribution-covid-19-cases-worldwide) for countries/territories in which seroprevalence studies included in our analysis were representative of the country/territory. Blood sample collection dates were overlapped on the epidemic curve to assist with the interpretation of the seroprevalence results.

Population-based seroprevalence studies

Among the 12 studies conducted in the general population,[7-18] seroprevalence ranged from 0·42% among residual clinical samples in Greece[7] to 13·6% in an area of high transmission in Gangelt, Germany.[15] All studies were conducted between March – June 2020, with the studies conducted May–June reflecting the post epidemic peak period in the respective study settings. The largest study was a nationwide cross-sectional study conducted in Spain in which 51958 household members were recruited after the first epidemic peak in the country and found seroprevalence using an immunoassay of 4·6% (95% CI 4·3–5·0).[9]

Three studies[8,10,11] performed serial sampling of participants. In Geneva, Switzerland, participants from an existing longitudinal cohort study were sampled across 5 consecutive weeks. While the same individuals were not sampled each week, seroprevalence increased: from 4·8% (95% CI 2·4–8·0, n=341) in the first week to 10·9% (7·9–14·4, n=577) in the third week, before stabilizing at 10·8% (8·2–13·9, n=775) in the fifth week.[10]

Similarly, in Belgium, residual clinical samples from hospitals and diagnostic labs were sampled across five collection periods from the end of March to the start of July. It was estimated that 2·9% (95% CI 2·3-3·6) of the Belgian population had detectable antibodies at the end of March, which doubled to 6·0% (95% CI 5·1-7·1) three weeks later but decreased to 4·5% (95% CI 3·70-5·40) in the fifth collection period (29 June - 3 July 2020).[10] In Greece, residual clinical samples were tested following a geographically stratified sampling plan based on regional units. Seroprevalence increased from 0·24% (95% CI 0·03-0·45) in March to 0·42% (95% CI 0·23-0·61) in April.[8]

Seven of the 12 studies stratified seroprevalence estimates by age[7-11,15,16]. In the nationwide seroprevalence study conducted in Spain, seroprevalence was found to increase with age and the lowest seroprevalence was found in those aged 0–19 years 3·8% (95% CI 3·2-4·6).[9] In Geneva, Switzerland, seroprevalence was 0·8% in 5-9 years, compared to 9·6% in the 10-19 years and 9·9% in 20-49 years.[10] In Belgium and Greece, age-specific seroprevalence from residual clinical samples from hospitals and diagnostic labs was found to increase with age.[8,11] In Gangelt, Germany, infection rates were found to be lower in the 5-14 years, compared to any other age group.[15] In Neustadt-am-Rennsteig, Germany, seroprevalence in children and adolescents was found to be 1·7%, compared to 9·1% in adults.[16] In the Faroe Islands,[7] although estimates are reported by age, only 6 participants were found to be seropositive so inferences as to age-specific seroprevalence are more difficult.

Seroprevalence studies in blood donors

Of the 8 studies in blood donor populations,[19-26] seroprevalence ranged from 0·91% in North-western Germany to 23·3% in the area of Lodi province (Lombardy, Italy) where high transmission of COVID-19 was detected from the end of February 2020.

One study in Scotland performed serial sampling on blood samples collected through blood donation centres. All blood samples were negative in mid-March, but rose from end of March. Seroprevalence results were stratified by location across the country, and seroprevalence was found to be heterogenous by location. In Milan, serial sampling of blood donation samples found the seroprevalence to increase from 2·0% at the end of February to 5·0% by mid-March to early April.

While blood donor populations inherently do not include children, several adult blood donor populations were stratified by age. Among 20640 blood donors across Denmark, the youngest (17–29 years: 2·5%) and oldest (60-69 years: 2·5%) blood donors were found to have higher seroprevalence. In South East Italy, it was the 26-35 years old (2·0%) and the 56-65 years old (2·0%) age groups which had the highest seroprevalence.

Seroprevalence studies in employees / individuals recruited through non-health-care related employment

Three studies[27-29] recruited individuals through employment. University employees without any symptoms in Milan were found to have a seroprevalence of 10·2%; factory workers in two counties in Croatia were found to have seroprevalence of 1·3%, while healthy volunteer industrial site operator in the metropolitan area of Frankfurt am Main were found to have a seroprevalence of 0·5%.

Comparison of case underascertainment

We were able to use the serology-derived estimates of extent of infection in the four general population studies[7,9,11,12] that were implemented nationwide or across a territory to compare to the total number of reported infections reported 15 days prior to the end of the blood sample collection period by the country/territory. Across the four studies, the ratio of reported to expected number ranged from 10% to 63% (Table 2).

Discussion

In this scoping review of 23 published seroprevalence studies from Europe, we find heterogenous results, ranging from 0·42% among geographically-representative residual clinical samples across Greece to 23·3% in blood donors in an area of high transmission in Lombardy, Italy. The studies in which serial sampling was conducted noted that an increasing fraction of the population has been exposed to the virus. There was no consistency in age stratification so inferences as to differences in seroprevalence by age are difficult to make at this stage.

In comparison to total reported cases of infection, we observed that there was large heterogeneity among countries in the seroprevalence-derived estimates of extent of infection. This likely reflects testing strategies for molecular testing during the first epidemic peak in Europe and the laboratory capacity for diagnosing COVID-19, which in many places was restricted to those with severe disease or those requiring hospitalization. Understanding testing strategies is an important consideration for analyzing and comparing surveillance data, particularly in the COVID-19.

The heterogeneity that we observed in seroprevalence estimates across studies may be explained by several factors. Firstly, the heterogeneity of transmission within Europe and within countries. Across Spain, for example, seroprevalence ranged from 1·2% to 14·4%, likely reflecting the heterogeneity in transmission intensity across the country.[9] Secondly, the study population and the biases inherent in the study design how the study population has been selected in each study prevent us from being able to pool seroprevalence estimates.[30] Eight studies used blood donor populations, which, by definition, select adults without any recent symptoms consistent with COVID-19. As such, the seroprevalence in blood donors is likely to underestimate seroprevalence of the general population, particularly in early seroprevalence studies, as is the case in this review.[5] In addition, this population tends to be healthier than the general population.[4] The studies among blood donors found seroprevalence to be largely comparable to studies that used household surveys targeting the general population, as shown in Table 1, with the exception of the blood donors in Lombardy. The 23·3% seroprevalence, measured around the peak of transmission in the Lombardy region, likely reflects the intensity of transmission at that time.

When considering the lag time between infection and measurable antibodies, and the study population, the post peak seroprevalence in the general population may be in fact substantially higher. That is, those infected at or around the period of most intense transmission (within the 2-3 weeks prior to sample collection) would most likely have had a negative serologic test result but would have gone on to seroconvert shortly afterwards.

Further heterogeneity may derive from the type of serologic assays and the various performance of the assays.[30] All assays report high sensitivity as shown in Table 1, however, a context of low seroprevalence, as is the case for SARS-COV-2, means low positive predictive value for antibody testing. A number of studies report the validation of the assay used as part of the study, as well as the populations used for this validation. Others report

the validation performed as part of other studies, while others simply report the validation data from the manufacturer. A number of studies used the Euroimmun ELISA assay,[10-12,14-16,20,23,27] yet the performance of the assay varies in validation studies, likely due to differences in clinical and analytical validity.

A further consideration when interpreting the results of the review is the type of the assay used. Only three of the 23 studies used neutralization assays,[14,21,24] while the rest used a rapid immunoassay, an ELISA or CLIA assay. While the latter detect immunoglobulins specific to SARS-CoV-2, often much quicker and less laboriously than the former, they do not implicitly indicate the strength of an individual's immune response. Neutralization assays, in contrast, reflect more closely the functional role of anti-SARS-CoV-2 antibodies in the immune response and therefore give a better indication as to protection from further infection. Additional validation studies are required to understand the correlation between antibody titres detected by a rapid immunoassay, ELISA or CLIA and the neutralizing antibody response. This is important - for other coronavirus, individuals who are IgG positive are able to be reinfected,[31,32] and there are now reports of SARS-CoV-2 reinfection.[33] There are several possible explanations for this, including the implications related to the detection of antibodies versus the detection of neutralizing antibodies.

In addition, no longitudinal cohort studies were able to be included in this review. As such, all studies present antibody responses in individuals at one point in time. For the studies that used serial sampling, these were different individuals who were sampled, selected from the same source population each time. We are therefore unable to comment on the duration or persistence of antibodies, nor how this may correlate to ongoing protection. Longitudinal studies that follow the same individuals over time are needed to understand how long antibody, ideally neutralizing antibodies, may persist.[34,35]

Finally, in addition to the humoral response, the body also mounts a cellular response against infection. Specifically, T-cells recognize and eliminate other cells infected with a virus. By looking only at antibody detection, studies to determine the extent of infection in the population, the study presupposes that everyone who is infected seroconverts, at least to levels that the assay can detect.[4] The proportion of those who mount a cellular response, but not a detectable antibody response, is currently unclear.[36,37] Further research that combines assessment of the humoral and cellular responses is needed to understand the correlates of protection and to quantify the magnitude of those who may in fact have some protection from infection despite a negative antibody result.

Our findings are limited by the quality of the individual studies. Our assessments showed that many were subject to biases. It likely means that the true prevalence may be different from that estimated in the study. For this reason, we did not pool seroprevalence estimates across the region.

Nonetheless, despite this heterogeneity and limitations implicit in the various studies, the picture across Europe after the first epidemic peak of SARS-CoV-2 is clear: exposure to the virus has been insufficient to deliver the

level of infection in the population that would be required to prevent further circulation of the virus. The threshold beyond which such herd immunity may be achieved is estimated to be 50-67%.[38,39] Above this threshold, it is thought that the virus may no longer be able to circulate in the population.

These findings have important policy implications for countries in Europe:
While a few experts have recommended that countries seek primarily to achieve herd immunity by allowing the virus to circulate in societies unimpeded, the vast majority of scientists and experts have not recommended this strategy.[40] This position is based on a number of considerations:

Firstly, such a strategy has and will continue to overwhelm health-care systems. The devastating effect on the health-care systems was observed early in the pandemic in countries which were slow to respond to the identification of initial cases. Overwhelmed health-care systems not only disrupt the delivery of care to COVID-19 patients, but also the delivery of non-COVID-19 health services.[41] Elective surgeries are delayed, vaccine campaigns are halted and access to health-care may be difficult.

Further, we now understand that transmission of SARS-CoV-2 is largely concentrated in close-contact settings through large droplets, aerosols and contaminated surfaces.[42] Targeting these high-risk settings for control measures will create large reduction in transmission rates, more so than the blunt public health and social measures, and with the advantage of avoiding the adverse economic and societal impacts. Further, contact tracing and epidemiological studies indicate that a small proportion of all people infected likely account for a much larger proportion of onwards transmission,[43-46] although age-specific rates of contacts also likely influence transmission and immunity patterns.[47]

Overall, the results of the initial seroepidemiologic studies in Europe indicate the population immunity is below the likely threshold for herd immunity and that measures to 1) identify, isolate, test and care for all COVID-19 cases and 2) trace and quarantine contacts of known COVID-19 cases will need to be maintained far beyond the emergence of COVID-19 and the initial epidemic peak.[48,49] In parallel, efficient rollout of effective vaccines is needed to deliver the required level of herd immunity in the population.

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Author contributions

AF, RG, TD and XA designed the review.

RG, TD, XA conducted the literature search and extracted the data from eligible studies.

TD, XA and PP performed statistical analyses.

RG, TD and XA drafted the first versions of the manuscript.

HN, AW-S, PP and AF critically revised the first version of the manuscript.

All authors reviewed and approved the final version of the manuscript.

Table 1. Characteristics of included studies (N=23)

First author	Type of publication	Location of study	Study population	Sample size	Dates of sample collection	Seroprevalence estimate % [confidence interval]	Serologic assay used	Reported specificity and sensitivity of serologic assay	Assessment of bias[a]
General populations									
Petersen MS.[7]	Peer-reviewed publication	Faroe Islands	Random sample of population registry	1075	27 April – 1 May 2020	0·6 [0·2–1·2]	Wantai SARS-CoV-2 Ab ELISA kit (Beijing Wantai Biologic Pharmacy Enterprise)	Sensitivity: 94·4%, specificity: 100%	Low
Bogogiannidou Z.[8]	Peer-reviewed publication	Greece	Serial sampling of representative residual clinical samples	4511	March – April April 2020	0·42 [0·23–0·61]	ABBOTT SARS-CoV-2 IgG assay (Abbott Laboratories)	Sensitivity: 84·0%, specificity: 99·7%	Low
Pollan M.[9]	Peer-reviewed publication	Spain	Randomly selected households across Spain	61075	27 April – 11 May 2020	4·6 [4·3–5·0]	Orient Gene IgM/IgG (Zhejiang Orient Gene Biotech); Abbott Architect IgG (Abbott Laboratories)	Specificity 100%, sensitivity 82·1% (Orient Gene) Specificity 100%, sensitivity 89·7% (Abbott)	Low
Stringhini S.[10]	Peer-reviewed publication	Geneva, Switzerland	Serial sampling of population-representative cohort	2766	6 April – 9 May 2020 (5 consecutive weeks of sampling)	10·8 [8·2–13·9]	ELISA IgG (Euroimmun)	Manufacturer reported: Specificity: 94.4%, sensitivity: 99.6%	Low
Herzog S.[11]	Pre-print manuscript	Belgium	Serial sampling of residual clinical samples from hospitals and diagnostic labs	7820	30 March – 4 July 2020 (5 different sampling periods)	4·5 [3.7–5·4]	ELISA IgG (Euroimmun)	Manufacturer reported: Specificity: 94.4%, sensitivity: 99.6%	Moderate
Snoeck CJ.[12]	Pre-print manuscript	Luxembourg	Representative web-based sample of	1862	15 April – 5 May 2020	1·97 [1·25–2·69]	ELISA IgG and IgA (Euroimmun)	Specificity 89·2%; sensitivity 85·7% at day 15 after	High

			general population					symptom onset in PCR confirmed patients	
Wells P.[13]	Pre-print manuscript	South-East England	Ongoing community-based cohort	431	27 April – 02 June	12 [9·1–15·2]	In-house N/S ELISA (King's College London)	Specificity: 100 % Sensitivity: 84·7%, 87.0% at 14 days post onset and 96·4% after 20 days	High
Aziz NA.[14]	Pre-print manuscript	Bonn, Germany	Ongoing community-based cohort	4771	24 April – 30 June	0·97 [0·72–1·30]	ELISA IgG (Euroimmun); plaque reduction neutralisation test	Manufacturer reported: Specificity: 94.4%, sensitivity: 99.6%	Low
Streeck H.[15]	Pre-print manuscript	Gangelt, Germany	Randomly selected household members in Gangelt, Germany	919	31 March – 6 April 2020	13·6	ELISA IgG (Euroimmun)	Manufacturer reported: Specificity: 94.4%, sensitivity: 99.6%	Moderate
Weis S.[16]	Pre-print manuscript	Neustadt-am-Rennsteig, Germany	Household members	620	12 – 22 May 2020	8·4	ELISA IgG (Euroimmun); IgG CLIA kit (DiaSorin, Saluggia, Italy; Maglumi; IgG CMIA kit (Abbott) and Elecsys Anti-SARS-CoV-2 kit (Roche).	Manufacturer reported: Specificity: 94.4%, sensitivity: 99.6% (EuroImmun), specificity 99·3%; sensitivity 97·6% (Liaison CLIA), specificity 100%; sensitivity 91·2% (Maglumi), specificity 99·6%; sensitivity 100% (Abbott), specificity 99·8%; sensitivity 100% (Roche)	Low

Roxhed N.[17]	Pre-print manuscript	Stockholm urban area, Sweden	Randomly selected households	443	May 2020	10·84 [7·94–13·73]	In-house multiplexed serology assay	Sensitivity: 100% Specificity: 98% combining the scores from at least two of the included SPK protein	Moderate
Fenwick C.[18]	Pre-print manuscript	Vaud canton, Switzerland	Randomly selected residents	311	4 May – 27 June 2020	6·4	In-house S protein trimer	Specificity 98·5%; sensitivity 90% after 16 days after onset of symptoms	Moderate
Blood donor populations									
Erikstrup C.[19]	Peer-reviewed publication	Denmark	Blood donation centres	20640	6 April – 3 May 2020	1·9 [0·8–2·3]	Lateral flow immunoassay (Livzon Diagnostics)	Specificity 99.5%; sensitivity 82.6%	Moderate
Fischer B.[20]	Peer-reviewed publication	Three federal states in North-western Germany	Blood donation centres	3186	9 March - 3 June 2020	0·91 [0·58–1·24]	ELISA IgG (Euroimmun)	Manufacturer reported: Specificity: 94.4%, sensitivity: 99.6%	Moderate
Percivalle E.[21]	Peer-reviewed publication	High transmission area, Lombardy region, Italy	Blood donation centres	390	18 March – 6 April 2020	23·33	In-house microneutralization assay	Specificity 100%; sensitivity 95%	Moderate
Fiore JR.[22]	Peer-reviewed publication	Low incidence area, South East Italy	Blood donation centres	904	1 – 31 May 2020	0·99	Chemiluminescent analytical assay (New Industries Biomedical Engineering Co)	Specificity 97·3%; sensitivity 91·2%	Moderate
Slot E.[23]	Pre-print manuscript	Netherlands	Blood donation centers	7361	1 – 15 April 2020	4·2 [3·1–5·4]	ELISA (Beijing Wantai Biological Pharmacy Enterprise); ELISA IgG (Euroimmun)	Specificity 99·1%, sensitivity 100%	Moderate
Thompson CP.[24]	Pre-print manuscript	Scotland	Blood donation centres	1000	21 – 23 March 2020	1·2	In-house pseudotyped SARS-CoV-2	Specificity 100%; sensitivity 94·1%	Moderate

							microneutralisation assay		
Fontanet A.[25]	Pre-print manuscript	High transmission area, north of Paris, France	Blood donation centres	200	23 – 27 March 2020	3·0 [1·1–6·4]	In-house ELISA assay (Institut Pasteur); in-house flow cytometry assay (Institut Pasteur); in-house immunoprecipitation-based assay (Institut Pasteur)	Data reported from other validation study:[50] Specificity 100%; sensitivity 99·4%	High
Valenti L.[26]	Pre-print manuscript	Milan, Italy	Convenience sample from blood donation centres	789	24 February – 8 April 2020	5·07	IgG/IgM rapid lateral flow immunoassay (Prima Lab)	Specificity 98·3%; sensitivity 100%	Moderate
Individuals recruited through non-health-care related employment									
Milani GP.[27]	Peer-reviewed publication	Milan, Italy	University staff	194	30 – 31 March 2020	10·2	ELISA (Beijing Wantai Biological Pharmacy Enterprise); ELISA IgG (Euroimmun)	Data reported from separate validation study:[51,52] Specificity: 99·1%, sensitivity 100% Manufacturer reported: Specificity: 94.4%, sensitivity: 99.6% (Euroimmun)	High
Jerkovic I.[28]	Peer-reviewed publication	Split-Dalmatia and Šibenik-Knin County, Croatia	Factory workers	1494	23 – 28 April 2020	1·27 [0·77–1·98]	IgG/IgM rapid test (AMP Diagnostics)	Manufacturer reported: Specificity 96·4%; sensitivity 91·8%	Moderate
Kraehling V.[29]	Pre-print manuscript	Frankfurt am Main metropolitan area	Healthy voluntary employees of a large industrial site operator	1000	6 – 14 April 2020	0·5	In-house ELISA	Specificity 99·2%; sensitivity 100%	High

[a] As determined through the use of the Joanna Briggs Institute Critical appraisal checklist for studies reporting prevalence data, and the qualitative categories defined by Bobrovitz N et al.[5] High: Limited certainty in prevalence: the true prevalence may be substantially different from the estimated prevalence. Moderate: Moderate certainty in the prevalence: the true prevalence is likely to be close to the estimate, but there is a possibility that it is substantially different. Low: High certainty in the prevalence estimate: true prevalence is likely close to the estimate. Unclear: There was insufficient information to assess risk of bias.

Table 2. Comparison of reported and seroprevalence-derived expected number of infections

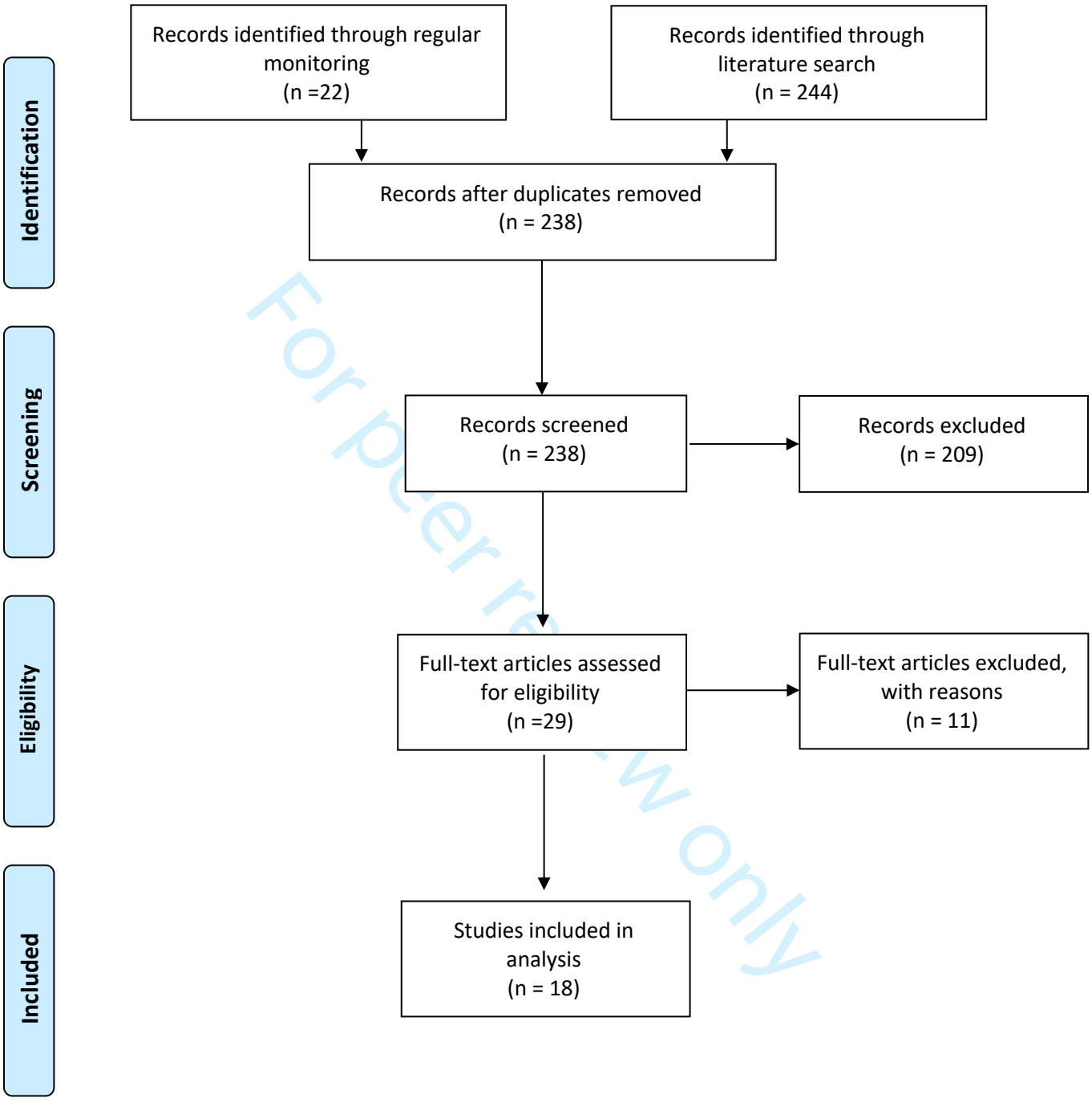
Country	Seroprevalence estimate (%) [lower CI - upper CI]	Number of infections reported 15 days prior to end of blood sample collection	Seroprevalence-derived expected number of infections	Seroprevalence-derived expected number of infections (lower confidence interval)	Seroprevalence-derived expected number of infections (upper confidence interval)	Ratio of reported infections to seroprevalence-derived number of infections
Spain[9]	4·6 [4·3-5·0]	210623	2159105	2018294	2346853	0.10
Luxembourg[12]	1·97 [1·25-2·69]	3550	12097	7685	16508	0.29
Faroe Islands[7]	0·6 [0·2-1·2]	184	292	97	584	0.63
Belgium[11]	4·5 [3·7-5·4]	60854	515498	423854	618598	0.12

Figure 1. Inclusion of studies in review

Figure 2. Study seroprevalence (point estimate and confidence interval, when reported)[a]

[a] For studies that used serial sampling, the most recent seroprevalence estimate was selected.

Figure 3. Blood sample collection periods of studies with respect to reported national epidemic curves of reported cases for those studies conducted nation-/territory-wide (n=7)



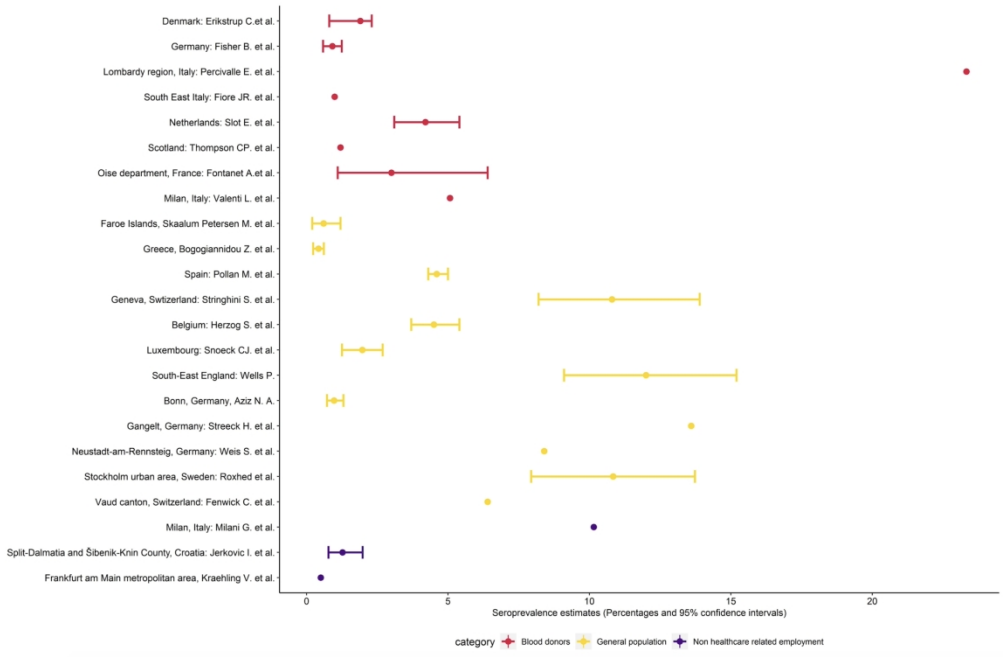


Figure 2. Study seroprevalence (point estimate and confidence interval, when reported)

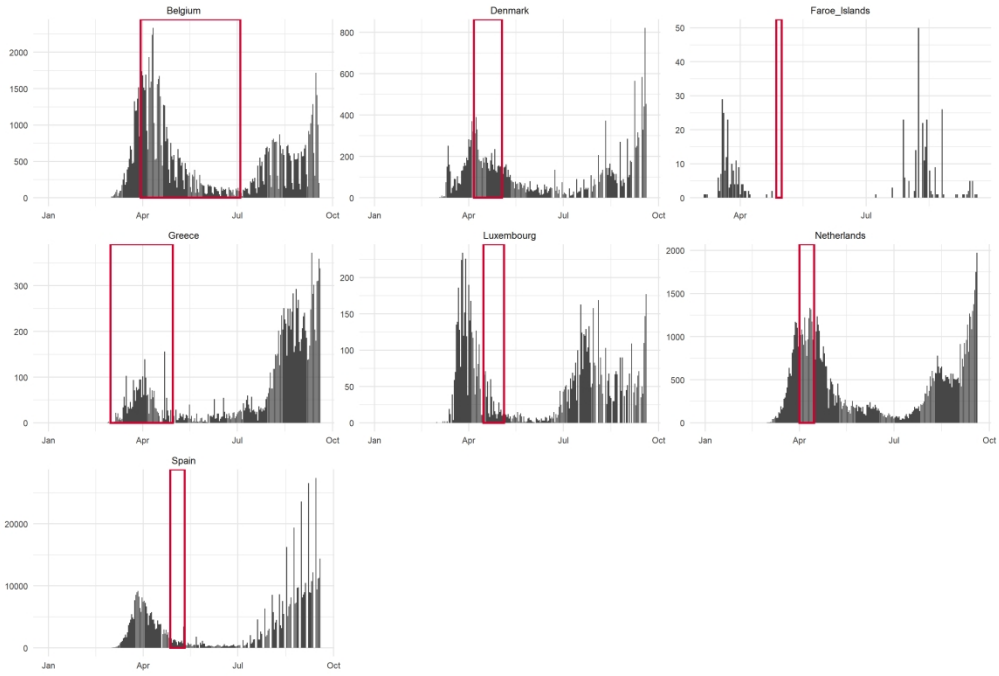


Figure 3. Blood sample collection periods of studies with respect to reported national epidemic curves of reported cases for those studies conducted nation-/territory-wide (n=7)

328x223mm (300 x 300 DPI)

SARS-CoV-2 population-based seroprevalence studies in Europe: A scoping review

Supplementary Material

Search strategy:
MedRxiv/BioRxiv
Full text or abstract or title "((COVID-19) OR (sars-cov-2)) AND ((seroprevalence)" (match whole all) and posted between "01 Jan, 2020 and 15 Sep, 2020"

NCBI PubMed
((((COVID-19[Text Word]) OR (sars-cov-2[Text Word])) AND (seroprevalence[Text Word]) AND (("2020/01/01"[Date - Publication] : "2020/09/15"[Date - Publication]))

Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	3
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	3
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	-
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	4
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	4
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	Supplementary material
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	Figure 1
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	4
Critical appraisal of individual	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe	4

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
sources of evidence§		the methods used and how this information was used in any data synthesis (if appropriate).	
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	4
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	Figure 1
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	Supplementary material, Table 1
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	Table 1
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	Table 1
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	6-8
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	8
Limitations	20	Discuss the limitations of the scoping review process.	9
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	10
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	2

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.