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Review

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Abstract: This review explores and positions the value of serology testing to support current immunization policies and the broader policy response to the coronavirus disease 2019 (COVID-19) crisis in Europe. We applied an exploratory approach to analysing existing evidence, international recommendations, and national policies using desk research from secondary sources, document analysis, and expert information. Regional and country-level resources from five focus countries were included: France, Germany, Italy, Spain, and the United Kingdom. Seven experts in the fields of COVID-19 immunization, serology testing, seroepidemiology, and vaccine safety and effectiveness studies contributed to the review and convened in two online panel sessions. The paper includes an overview of (1) the impact of the pandemic to date, (2) testing strategies, (3) COVID-19 vaccination policies, (4) lessons on using serology testing to support immunization, (5) current policies and recommendations on the use of a serology testing strategy, and (6) implementation barriers and challenges. Finally, this paper also provides a set of knowledge-based recommendations to advance the effective and timely inclusion of serology testing and resolve impeding knowledge gaps. The recommendations herein are intended to support timely decision-making, raise awareness, guide advocacy initiatives, and inspire future studies.

Keywords: COVID-19; SARS-CoV-2; serologic tests; pandemic; health emergency; diagnostic testing; Europe; call to action; health policy; immunization

1. Objective and Methodology

The purpose of this paper is to explore and position the value of serology testing to support current coronavirus disease 2019 (COVID-19) immunization policies and the broader policy response in Europe and to deliver a call to action to advance the adequate and timely inclusion of this strategy in the region. The paper aims to summarize the available evidence, present relevant knowledge gaps, and propose a set of recommendations to inform and stimulate debate and further research.

The paper combines a desk review of secondary sources, document analysis, and expert information with a multistage process of discussion, validation, and feedback by a group of seven European experts. These contributors were selected based on academic merit across various disciplines, including microbiology, virology, pharmacology, epidemiology, vaccinology, infectious diseases, and public health. An in-depth understanding of serology testing, seroepidemiology, vaccine effectiveness studies, and/or COVID-19 immunization policies was deemed essential.

To organize the desk review, a framework to collect and analyse data was developed based on six primary topics: (1) impact of the pandemic, (2) testing strategies, (3) COVID-19 vaccination policies, (4) lessons on the use of serology testing to support immunization, (5) current policies and recommendations on the use of a serology testing strategy, and (6) implementation barriers and challenges.

Regional and country-level resources were included from five focus countries: France, Germany, Italy, Spain, and the United Kingdom (UK). Resources were retrieved and prioritized based on the following criteria:

- Scientific perspectives on Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) testing strategies, including challenges and opportunities,
- The health and socioeconomic impact of the pandemic,
- Guidelines and recommendations on the use of serology testing from key international organizations and focus countries,
- Current international guidelines and recommendations for COVID-19 immunization in the region, and
- The national COVID-19 immunization plan and/or strategy of the focus countries.

The information gathered was discussed, reviewed, and validated by all experts during two online panel sessions facilitated by Policy Wisdom, LLC. A set of recommendations was developed during the discussion process. Following the discussions, the authors compiled a working document. Experts had the opportunity to review the working document and provide written feedback. The paper was updated until consensus was reached. All panellists approved the final document.

2. The Impact of the Pandemic

On 1 December 2019, Wuhan's Municipal Health Commission reported a cluster of pneumonia-like cases in the Hubei Province of China, later attributed to a novel coronavirus named SARS-CoV-2. As new infections spread rapidly around the globe, the World Health Organization (WHO) declared the novel coronavirus outbreak a pandemic on 11 March 2020 [1].

As of 28 January 2021, 99,727,853 cases of COVID-19 were reported, leading to 2,137,670 deaths worldwide [2]. Unfortunately, the European region profiles as the worst-hit region with 32,218,360 cases and 701,991 deaths, being the continent with the highest death rate of the world at 91.73 per million population [3]. Based on the number of reported cases and mortality, the five worst-affected countries in Europe are the UK (97,939 deaths), Italy (85,461 deaths), France (73,049 deaths), Russia (69,918 deaths), and Spain (56,208 deaths). During the first half of January 2021, new infections increased in several European countries [4]. Governments across the region responded with a new wave of stringent policy measures, such as mandatory stay-at-home orders and traveling restrictions, especially affecting the UK, Ireland, Germany, Denmark, Norway, Spain, Portugal, and Italy [5].

Morbidity and mortality rates from SARS-CoV-2 infection have been particularly high among the vulnerable and high-risk populations [6–8]. The highest-risk populations are: (1) the elderly, particularly in long-term care facilities; (2) people living with comorbidities, including communicable and noncommunicable diseases such as diabetes, cancer, immunodeficiency disorders such as human immunodeficiency virus (HIV), cardiovascular disease, chronic respiratory disease, and obesity; (3) vulnerable communities, which include those in outbreak-prone settings; and (4) healthcare workers. The pandemic has also worsened conditions for people who need regular access to health facilities, such as people

living with chronic illnesses and other health conditions [9]. Socio-economic disparities may carry additional risks to lower-income and marginalized communities [9–12]. Among the most vulnerable populations are migrants (including seasonal workers), inmates in correctional institutions, and the homeless [11,12]. Finally, there has been an increase in mental health conditions, most notably anxiety and depression, as well as an increase in suicide risk [13,14], with healthcare workers being among the most affected [12,13,15].

The comprehensive policy response to the pandemic has included pharmaceutical and nonpharmaceutical interventions. In an effort to "flatten the curve" of infection rates, governments have enforced restrictions with varying levels of stringency [5]. Containment and closure policies, such as cancellations of public events, restrictions on gatherings, school closures, and mandatory stay-at-home orders, aimed to reduce infections through social distancing. Given the disruptive effects of these measures on the economy, governments implemented financial policies to provide relief to affected sectors and vulnerable households. Simultaneously, health policies were also implemented to strengthen the capacity of health systems to deal with the pandemic [16].

Juxtaposed with efforts to reduce infection rates was a fear of impending economic crisis and recession [17]. It was estimated that a country might lose up to 2% of its gross domestic product per month during a total lockdown [18]. The turmoil created by social distancing measures permeated the primary, secondary, and tertiary economic sectors, as well as created broader socioeconomic externalities [19–21]. Some of the consequences include, among others, the disruption of supply chains, decline in global and regional stock markets and critical liquidity levels, and shortages of protective equipment and numbers of intensive care unit beds and ventilators [19]. Furthermore, school closures affected 69.3% of total enrolled learners at the highest points of the pandemic [22,23] and disproportionally impacted vulnerable households with concerns regarding food security, school dropout rates, and access to technology [19]. Increasing levels of domestic violence and poverty, notably child multidimensional poverty, were also recorded as a consequence of social distancing measures [19,20]. Finally, increased unemployment rates, amounting to five million jobs lost by the end of the second quarter of 2020, are expected to widen existing inequalities [21], affecting the hospitality, tourism, cultural, and aviation sectors in particular [19,24].

3. Testing Strategies to Mitigate Impact

Testing strategies can help to diagnose infection as well as provide essential surveillance data for policy planning purposes. Currently, there are three types of testing options for SARS-CoV-2: molecular tests, antigen tests, and serological tests for antibody detection (see Table 1). While the first two are used to assess acute infection, serological tests provide evidence of prior infection.

The real-time reverse-transcription polymerase chain reaction (RT-PCR) is the recommended assay and diagnostic tool to confirm SARS-CoV-2 infection [25]. Although many molecular tests for SARS-CoV-2 demonstrate high sensitivity and specificity (low risk of false-negative and false-positive results) [26], a negative result from this test does not discard the presence of recent infection and the possibility that the individual is incubating the disease [26–29]. Furthermore, in some contexts, the application of this test may be limited by the rigorous infrastructure and biosafety requirements for laboratory testing, as well as increased turnaround times and possible false-negative results on alternatives, such as when sample pooling [26].

Antigen-detecting tests have lower sensitivity than molecular tests but allow rapid detection of the most infectious patients, potentially expediting the detection of SARS-CoV-2 active infection [30]. Similar to molecular tests, antigen-detecting rapid diagnostic tests (Ag-RDTs) are likely to perform best in samples collected at or around the time of development of symptoms. The sensitivity of Ag-RDTs appears to be highly variable across brands, ranging from 0 to 94% [29,31], whereas the specificity of various Ag-RDT brands is reportedly high ($\geq$97 to 100%) [30,32]. Ag-RDTs are not recommended in settings or popu-

lations with a low expected prevalence of the disease and when confirmatory molecular testing is not readily available. Confirming Ag-RDT positive results with molecular tests in populations with a low prevalence of COVID-19 is recommended [27].

Table 1. Summary of testing strategies for Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2).

Testing Options for SARS-CoV-2	Sensitivity and Specificity	Recommended Use	Comparative Advantages	Comparative Disadvantages
Molecular tests	High sensitivity and specificity.	Use for diagnostic purposes—considered the gold standard.	Can accurately detect active infection.	A negative result does not discard the presence of a recent infection or that the individual is incubating the disease. Rigorous laboratory requirements.
Antigen tests	Variable sensitivity across brands and high specificity.	Use for diagnostics when molecular tests are not readily available.	Can expedite and simplify the detection of most infectious patients.	They are not recommended in low prevalence settings or when confirmatory molecular testing is not available.
Serological tests	High sensitivity from three weeks after symptoms onset and high specificity.	Surveillance and research purposes.	Can detect past infection and provide qualitative and quantitative data of the antibody response.	Test performance is conditional to the time of testing.

Elaborated based on overviewed literature [25–37].

Serology tests are designed to detect the presence of three types of antibodies: immunoglobulin M (IgM), immunoglobulin G (IgG), and immunoglobulin A (IgA), indicating if a person was infected with SARS-CoV-2, irrespective of whether the individual had severe, mild, or no symptoms. Current guidelines recommend serology testing for surveillance and research purposes only [33]. Serological data has an important place in the ongoing response to the COVID-19 pandemic, assisting surveillance activities, estimating epidemiological variables, and assessing the effect of nonpharmaceutical interventions at the population level [34]. The sensitivity for these tests is higher from three weeks after symptom onset. Specificities reportedly range from 96.6 to 99.7% (for tests measuring IgM/IgG and IgM, respectively) [35].

There are several types of serological tests depending on the choice of antibodies and antigens. Most serological tests use two classes of antibodies, IgM and IgG [9]. While IgM tests may indicate current or recent infection, IgG tests may indicate past exposure or infection at a later stage. However, evidence suggests SARS-CoV-2 antibody production may differ from the typical scenario and vary considerably between individuals, with IgM and IgG tending to appear almost simultaneously [38,39]. Understanding the immune response to SARS-CoV-2 infection is an ongoing process. Serological tests also vary according to the viral antigens measured. Spike (S) protein, nucleocapsid (N) protein, and receptor binding domain are the viral antigens used to detect antibodies for SARS-CoV-2. Evidence suggests that serological tests that target S or N proteins may be better at predicting immune status [36].

Serological tests can be performed through laboratory-based assays as well as through rapid diagnostic tests. While the first generate more accurate results and provide qualitative and quantitative data, the second may be easier for patients to access but only provide qualitative results and would likely require additional confirmation [11]. Notably, the neutralization assay, a lab-based test, is the gold standard for determining antibody efficacy. This test can help (1) understand immunity and evaluate vaccine effectiveness, (2) determine the actual number of infections by enhancing the serological diagnosis of asymptomatic infections, and (3) identify eligible donors for convalescent plasma ther-

apy [37]. Nevertheless, this test has a higher cost and requires a biosafety level 3 laboratory (a laboratory with permission to culture SARS-CoV-2-infected cells) [36]. Preliminary information suggests that new SARS-CoV-2 variants, such as the one initially identified in the UK (B.1.1.7. variant), may affect the performance of some diagnostic tools; specifically, the loss of performance of polymerase chain reaction assays that target the spike (S) gene of the virus [40–43]. Although assays targeting the S gene are not widely used and only one is on the list of in-house assays listed by the WHO [44], relying on this gene for primary detection of SARS-CoV-2 infection using RT-PCR is not recommended [45]. Aware of the potential impact that virus mutation may have on the performance of diagnostic tests, on 21 December 2020, the WHO recommended a diagnostic approach using different assays in parallel or multiplex assays targeting different viral genes to allow the detection of emerging variants [41].

4. Introduction of COVID-19 Vaccines in Europe

Since the beginning of the pandemic, unprecedented efforts have been made to develop COVID-19 vaccines in record time. Available data from marketing authorization clinical trials confirm that vaccines create a good immunological response, which could prevent COVID-19, thereby reducing the burden of the disease, hospitalizations, and deaths. There are four categories of COVID-19 vaccines in clinical trials: messenger ribonucleic acid (mRNA), viral vector, protein subunit, and whole inactivated virus [46]. According to the WHO, as of 26 January 2021, there are 237 vaccines under development, of which 16 are in clinical phase III trials [47]. On 21 December 2020, the European Commission granted conditional marketing authorization to the BioNTech-Pfizer vaccine, an mRNA vaccine [48], and on the 27th, vaccination against COVID-19 started across the European Union (EU), covering people in priority groups first, such as the elderly and healthcare professionals [49]. According to cumulative vaccination doses, as of 1 February 2021, coverage levels are higher in the UK, Serbia, Malta, and Denmark [50].

In 2020, the European Commission took two important steps to foster countries' preparedness for vaccination rollout. Launched on 17 June 2020, the EU Strategy for COVID-19 Vaccines [51] aims to accelerate the development, authorization, manufacturing, and deployment of vaccines against COVID-19. As a second step, on 15 October, the commission urged member states to start preparing their immunization plans, taking into consideration capacity, access, and logistic challenges [52], as well as the need for vaccine effectiveness studies [53]. Regarding the latter, per EU law, the commission attributed shared responsibility to member states and pharmaceutical companies, urging public health authorities to be prepared to undertake studies on vaccine effectiveness and safety [53]. Studies of this nature are essential to gathering valuable information, such as long-term protection or the need for and timing of booster doses [54]. Accordingly, the European Centre for Disease Prevention and Control (ECDC) published two strategic papers to support COVID-19 vaccine deployment and vaccine prioritization strategies [55,56].

Several virus mutations have been reported in countries around the globe, raising concerns about increased transmissibility and severity of the disease and decreased effectiveness of diagnostic tests and vaccines [43]. On 14 December 2020, the UK reported the identification of a new virus variant referred to as SARS-CoV-2 VOC 202012/01 [41], also known as B.1.1.7 + E484K. By the end of the month, cases of this new variant were reported in Australia, Denmark, France, Germany, Italy, Ireland, the Netherlands, Spain, Switzerland, and Sweden [40,57]. Preliminary findings suggest that this variant may lead to worse health outcomes and increased transmissibility by up to 70% [43,58]. As of 24 May 2021, five variants are of current concern in the European Union and European Economic Area (EU/EEA) and UK (see Table 2). The variants of concern (VOC) in this region include B.1.1.7 and B.1.1.7 + E484K, first identified in the UK, 501Y.V2, first identified in South Africa, P1, first identified in Brazil, and B.1.617.2, first identified in India. Evidence indicates increased transmissibility in all five VOC and increased severity of disease in four of them. Furthermore, VOC 501Y.V2 and B.1.617.2 also have record reduced vaccine efficacy

or efficiency [58]. Concerned by the new virus mutations, the ECDC and WHO advised authorities to closely monitor recovered and vaccinated individuals to identify possible vaccination failure [40,43]. These studies are ongoing.

Table 2. SARS-CoV-2 virus mutations of concern in the European Union and European Economic Area and the United Kingdom.

Virus Mutation Lineage + Additional Mutations	Country Where First Community Transmission was Detected	Year and Month First Detected	Evidence for Increased Transmissibility	Evidence for Increased Severity	Evidence for Impact on Immunity [1]
B.1.1.7	United Kingdom	September 2020	Yes	Yes	Unclear
B.1.1.7 + E484K	United Kingdom	December 2020	Yes	Yes	Neutralization
B.1.351	South Africa	September 2020	Yes	Yes	Escape
P.1	Brazil	December 2020	Yes	Yes	Neutralization
B.1.617.2	India	December 2020	Yes	-	Escape

[1] Evidence on immunity is annotated to indicate whether impact has been identified on neutralizing antibodies (neutralization) or in terms of vaccine efficacy or efficiency (escape). Elaborated based on the European Centre for Disease Prevention and Control Variants of Concern update report as of 24 May 2021 [58].

COVID-19 immunization policies must maximize early impact, particularly since wider coverage could help reduce variant emergence [59]. Most COVID-19 vaccines use a two-dose approach to reach functional virus neutralization [60,61]. While some countries have chosen to delay second dose administration to enable more people to receive the first dose [62], an alternative approach could be to administer a single dose to individuals who have recovered from infection. Recent evidence suggests that previous infection could be analogous to immune priming, similar to that achieved by administering the first vaccine dose. Thus, in such cases, a second dose might not be needed [59,63]. Another potential approach is to include serology testing before or concurrently with the first vaccination dose and prioritize the use of booster doses for individuals with no previous infection, possibly accelerating vaccine rollout [59]. Countries such as Spain [64] and France [65] are currently considering this recommendation.

5. Brief Overview of Past Experiences Implementing Seroepidemiological Data to Support Immunization Policies

Seroepidemiological data have been used in the past to support immunization policies and strategies across a variety of vaccine-preventable diseases, providing critical information to support the planning and monitoring of immunization policies, as well as to conduct postmarketing surveillance studies on the efficacy and duration of protection generated by vaccines [34,66–69]. Seroepidemiological data was used to estimate disease burden and estimate theoretical herd immunity thresholds, especially for subclinical, underrecognized, or undernotified diseases. The information gathered regarding population immunity profiles was particularly important in guiding decision-making regarding the need for supplemental immunization activities and changes to immunization schedules. Furthermore, numerous studies have recorded the use of seroprevalence data to identify age groups requiring campaigns to eliminate transmission [66,67].

Seroepidemiological data has also been used for monitoring activities to evaluate the effectiveness of immunization policies. In this context, serology testing helped to investigate possible causes of infection resurgence, such as reduced effectiveness of vaccines following immunization schedules or vaccine formulation changes. Studies have used serological testing to gain insight on waning antibody levels after vaccination as a means of monitoring progress toward elimination targets. Studies on pre- and postvaccination campaigns have also used serology testing to evaluate the extent and age distribution of hotspots [66,67].

Finally, studies on vaccine effectiveness have used serology testing to determine the duration of immunity created by primary series, the efficacy of a vaccine on a specific population, and evaluate different dose strategies [67,69]. Moreover, seroprevalence studies,

often triggered by disease resurgence, have influenced decisions on the need for and timing of booster doses, catch-up strategies, and supplemental immunization activities [67].

Although serology testing has provided sound and essential data to guide critical decision-making at different stages of immunization activities, specific conditions are necessary to enable the adequate use of this strategy; thus, lessons cannot be extrapolated directly to the current scenario. While some concerns arise from the lack of understanding of the immune response to SARS-CoV-2 infection and vaccines, others highlight the absence of sound and valid evidence for the adequate use of SARS-CoV-2 serology testing. Moreover, as evidence on the possible benefits of using serology testing to support immunization policies is gathered from the experience with other vaccine-preventable diseases, in scenarios where vaccine campaigns targeted specific population groups, further concerns arise regarding extrapolating this experience to the current scenario. Given the need to vaccinate the whole population, implementing large-scale serosurveys might be challenging due to limited resources and demanding logistical requirements.

6. Current Guidelines and Recommendations on the Use of Serology Testing in the Context of Immunization Campaigns

The three leading and most influential health international organisations in the region—the WHO, ECDC, and European Commission—have supported the use of serology testing to provide vital information for policymaking purposes. The WHO recommends using serology testing for surveillance and research [33]. Accordingly, the use of serology in epidemiology and public health research could help to determine (1) the size of an outbreak retrospectively, (2) the degree of spread of infection in a population under study, (3) an estimate of mild and asymptomatic infection, (4) the proportion of fatal infection among those infected, and (5) the proportion of the population who may be protected against infection in the future [33,70]. The WHO provides a global platform to support the use of serology testing for public health research. This platform aims to enable countries to rapidly gather robust data on key epidemiological indicators by sharing scientific protocols, training materials, and information, as well as to evaluate and validate available serological assays [70].

Throughout 2020, the European Commission recognized the value of large-scale population serosurveys to provide essential information supporting the effective and tailored management of the response. Like the WHO, the commission recognized the role of serology testing to help estimate the speed of immunity development during community outbreaks, particularly the value of this evidence to inform vaccination [71] and de-escalation strategies [72]. While the commission defined the use of RT-PCR testing as the gold standard for COVID-19 diagnostics in the region [25], it encouraged the use of serological testing for surveillance and planning purposes [73].

Aligned with the European Commission, the ECDC proposed using population-based seroprevalence studies to guide de-escalation strategies across the region. Serology testing in this context would provide additional information regarding age-specific population immunity against SARS-CoV-2 (for the case of community transmission, the centre suggested using RT-PCR) [74]. Urged by the need to generate comparable evidence, and at the request of the commission, the ECDC also established a virtual coordination mechanism for seroepidemiology studies [71,75]. Furthermore, the centre also launched two technical reports to support decision-making on vaccination and prioritisation strategies against COVID-19 in the region [51,56]. Aided by mathematical modelling, the centre recommended using data from investigations of COVID-19 outbreaks, including, among others, seroepidemiology studies, to identify population groups that are highly exposed to SARS-CoV-2 infection and target vaccination to them. Moreover, the centre recommended clinical serology studies to investigate correlates of protection (a correlate of protection is an immunological measurement or marker that reliably predicts protection against disease or infection following vaccination or natural infection), seroepidemiology studies for determination of seropositivity in a population and specific settings, and cohort studies using

serology to investigate the duration of immunity. Finally, postmarketing vaccine efficacy studies were also deemed critical in the rollout of vaccines [56].

Within national COVID-19 immunization plans, several European countries had recommended serology testing to support immunization policies. Spain, Italy, and Germany are currently using seroprevalence surveys to monitor and estimate the prevalence of SARS-CoV-2 infection over time through antibody testing. The scope of these activities varies between countries. In Germany, the focus is on the general population and selected population groups, such as healthcare workers, and existing cohort studies [76]. In Italy, seroprevalence surveys aim to estimate of size and extent of the infection spread in the population and determine its frequency in relation to certain factors such as gender, age, region, and economic activity [77]. Notably, Spain has been focusing on providing estimates on the prevalence of IgG antibodies against SARS-CoV-2 [78]. Following international guidelines, the UK, France, and Spain are considering serological data as part of the epidemiological evidence for prioritisation exercise to determine vaccination target groups [79–81]. Furthermore, Italy is using serological surveys to evaluate the immune response induced by the vaccine, gather evidence on the specificity of this response, measure the duration of immunological memory, and identify the correlates of protection [82] (see Table 3).

Table 3. The landscape of national recommendations on the use of serology testing within immunization policies.

The Landscape of National Recommendations	
Country	**Purpose of Use of Serology Testing within Immunization Policies**
United Kingdom	• Prioritization of target groups.
France	• Prioritization of target groups.
Spain	• Provide estimates on the prevalence of antibodies across population groups. • Prioritization of target groups.
Italy	• Provide estimates on the prevalence of antibodies across population groups. • Evaluate immune response induced by the vaccines.
Germany	• Provide estimates on the prevalence of antibodies across population groups.

Elaborated based on reviewed documents [76–82].

7. Challenges and Barriers Related to the Use of Serology Testing to Support Immunization Policies

Besides the diversity of recommendations on using serology testing, some critical challenges and barriers must be considered moving forward. The first group of barriers centre around existing knowledge gaps for the adequate use of serology testing, with particular concerns regarding test calibration, choice of assay and antibody type, and correlates of protection. The second group of challenges relates to implementing vaccine effectiveness studies, serosurveys, and seroepidemiology studies, including funding and logistic challenges.

7.1. Challenges Related to the Adequate Use of Serology Testing

There are two primary sources of concern regarding the adequate use of serology testing, namely challenges related to testing accuracy and the limited evidence on correlates of protection. Regarding the former, considerable variations have been observed in the results of SARS-CoV-2 seroprevalence studies, raising concerns regarding serology testing accuracy. Four challenges are critical for the performance of serology testing: (1) the choice

of antibody, (2) the adequate selection of target antigen, (3) issues with test calibration, including the effect of demographic factors and timing, and (4) test validity.

It has been reported that studies using serology testing may misestimate the true seroprevalence of SARS-CoV-2 for several reasons. While seroprevalence can be overestimated in a low prevalence setting due to false positives, testing may also underestimate prevalence due to false negatives. Test accuracy demands using an assay sensitive enough to detect antibody responses reliably, even in mild and asymptomatic cases. The choice of antibody also influences test performance. While most tests rely on IgG and IgM antibodies, IgA also has an important role and seems immunologically relevant, particularly in asymptomatic cases. Test calibration, including the effect of timing and demographic factors (such as age, sex, and ethnicity) on antibody responses, is critical to capture past infection. Though IgG antibodies last longer than IgM, preliminary reports show a decline in IgG levels, suggesting that testing too late may also miss cases. Furthermore, concerns on test performance also arise from the fact that serology tests have been validated predominantly in people who experienced severe symptoms. This scenario implies that unless assay performance is also evaluated in mild and convalescent cases, the threshold for a positive result may be too high, resulting in missed community cases [83].

Another source of concern regards the use and choice of viral antigens to determine and study COVID-19 immunity. The entry of SARS-CoV-2 into host cells is mediated by the binding of the S protein of the viral particle to a host receptor in the cell through a receptor binging domain (S-RBD) [84,85]. Evidence suggests that antibodies against S-RBD may provide a higher sensitivity and specificity for diagnosis than those against nucleocapsid responses [85]. Coherently, although the immune response to SARS-CoV-2 is variable, the S protein has been found to be highly immunogenic [86,87], and the S-RBD to this protein is possibly considered the main target to elicit potent neutralizing antibodies [84,85,87–89], further confirmed by the presence of S-RBD in most infected individuals [84]. While overall agreement exists on the use of IgG antibodies against S-RBD as a means to inform on acquired SARS-CoV-2 immunity [90–92], many serology detection kits that are commercially available detect binding antibodies against N protein. Recent evidence suggests that not only is there a heterogeneous IgG response to the two viral antigens, S and N protein, but that binding antibodies against N protein may not correlate with having S-RBD binding antibodies or possessing neutralizing capacity [93]. Considering this new evidence, although serological tests that detect binding antibodies against N protein may still be used to detect prior exposure to the virus, they do not overly provide evidence to measure potential COVID-19 immunity [93].

Concerns regarding the adequate use of serology testing also arise from the limited evidence on the correlation of antibody results to protection against disease or (re)infection. A correlate of protection is an immunological measurement that reliably predicts protection against disease or infection following vaccination or natural infection [94,95]. The roles of humoral and cellular immune responses on protective immunity against SARS-CoV-2 are not fully understood in humans, with most available studies performed in animal models. Furthermore, determining the correlates of protection may be challenged by differences in the antibody response in particular population groups, such as immunocompromised individuals. Studies to provide information about the duration and significance of antibody response in this population are ongoing, but preliminary evidence suggests that immunocompromised patients may experience a delayed antibody response to SARS-CoV-2 [96,97]. Further studies are needed to assess long-term antibody response and its potential correlation with COVID-19 re-infections in these populations. Particular attention must be paid to the potential sub-optimal performance of COVID-19 vaccines.

It is difficult to predict when a population will reach herd immunity when the risk of infection after natural and vaccine-induced immunity is unknown. While studies to understand the protection granted by vaccines are ongoing, during the past year, several initiatives have been undertaken to understand how antibody response to infection correlates to protection against re-infection. Evidence from these studies suggests that

previous infection may grant an 80 to 84% reduction of risk of re-infection [98,99] that can last up to six or seven months after primary infection [98–101]. Furthermore, re-infection was associated with lower SARS-CoV-2 IgG titres and absent or lower levels of neutralizing antibody activity [102]. Unlike some hypotheses, pre-existing immunity to other seasonal coronaviruses was found to provide only limited protection against SARS-CoV-2 infection [103]. Additional evidence also suggests that protection against re-infection may vary between populations according to age. While a study undertaken on young males found an 82% reduced incidence rate of re-infection [102], another study observed only a 47.1% reduction among people aged 65 years and above [99]. Although some evidence has led to suggestions of delaying immunization of individuals with a known history of COVID-19 to maximize the chance to reach herd immunity at the earliest possible time [104], further studies are still needed to safely justify this path.

Although significant gaps in the use of serology testing in surveillance activities were identified, endeavours of this nature are likely to remain helpful for supporting immunization policies. Phase III clinical trials cannot provide sufficient evidence on how effective the upcoming COVID-19 vaccines are across populations, nor provide sufficient information on the duration of protection [105]. Likewise, questions regarding whether the vaccines prevent people from carrying and transmitting the virus are pending [105]. Studies designed to answer these questions are necessary, particularly as different formulations, types, and brands of vaccines become available to the public and given the presence of mutations of the SARS-CoV-2 virus. Serology testing can be a critical element to support efforts to understand and monitor vaccines' effectiveness. Some studies have been launched to examine whether different vaccines can safely be used for two-dose regimes in the future [106].

7.2. Challenges Related to the Adequate Implementation of Serosurveys and Seroepidemiology Studies

Several challenges surround the adequate implementation of serosurveys and seroepidemiology studies, namely: (1) the absence of sufficient evidence on correlates of protection to evaluate vaccine effectiveness and immunological level of populations; (2) issues regarding access, time, logistics, and financial constraints; and (3) concerns surrounding appropriate study design and implementation.

As previously mentioned, one of the main limitations of seroprevalence surveys in the context of the COVID-19 pandemic is that it is not yet wholly known if having SARS-CoV-2 antibodies can protect against re-infection. Notably, the immune response is difficult to measure and can vary significantly between individuals and over time. Although recent evidence suggests that previous infection might be associated with a substantially reduced risk of re-infection in the subsequent six to seven months, the conditions that lead to protection (such as whether protection is conferred through antibodies or T-cell immunity) and re-infection remain unclear [101]. While some individuals develop a very effective immune response, protecting them against repeat infection, other individuals create antibodies that protect them from the COVID-19 disease but remain infected and able to transmit the infection to others. Despite concerns on the heterogeneity in memory to SARS-CoV-2 and the use of antibody testing to predict immunity [107], the British Society of Immunology recommends using antibody tests as the best marker and the most feasible option for this purpose [105].

Sound evidence on correlates of protection is necessary for adequate serology testing to evaluate the immunological level of populations, providing crucial information for public health strategies [108]. Correlates of protection are also essential to monitor vaccine effectiveness. They can be used as a surrogate marker within vaccine effectiveness studies without having to observe clinical endpoints [109–111]. A surrogate marker in vaccine research is a laboratory measurement or physical sign that is used as a substitute for a clinically meaningful endpoint, often used because the clinical endpoint is difficult to study or wants to be avoided. The availability of correlates of protection can help run immunological trials, saving more than 60% of the time and over 80% of the expense compared to large-scale efficacy trials [108], facilitating the approval process of vaccine

candidates [112]. The use of serology testing to evaluate vaccine effectiveness is also conditional on evaluating the diagnostic performance of serological assays and their timelines related to vaccine types.

Moreover, it is worth noting that the use of serology testing for postmarketing vaccine efficacy studies requires continued incidence of disease so that comparisons can be made between the immunity generated by the vaccines and natural infection. This scenario contradicts the paramount goal of putting a stop to the pandemic at the earliest possible time. Given that waning antibody levels are a critical factor in interpreting serosurveys, the effects of immunization on triggering an antibody response may represent a subsequent challenge. Finally, during vaccine rollout, there may be an easing of personal protection measures by vaccinated people, creating a possible confounding factor for the correlation between protection and vaccination.

Additional concerns arise from access, time, technology, and financial constraints. As mentioned earlier, with multiple tests currently available in the market, access to quality tests and adequate selection of test properties is critical to ensure the implementation of serosurveys. Based on experience, many have also judged serosurveys to be high-cost, logistically challenging, time-consuming, and requiring sophisticated statistical analysis, entailing the engagement of qualified personnel [66,67]. Although serology tests are often less costly than other testing strategies, accessibility may, to some extent, depend on the type of test used. For example, the enzyme-linked immunosorbent assay (ELISAs) can be more accessible both financially and in terms of laboratory requirements than virus neutralization assays. Challenges to time and resources may also be reduced by selecting a smaller sample size and international collaboration, so comparable evidence is aggregated using cohorts distributed across countries. Establishing the necessary partnerships and leadership to run such an endeavour could be challenging, nonetheless, as it requires the standardized use of the tests to enhance comparability and integration of evidence, the availability of adequate qualified laboratories, and appropriate oversight.

Finally, the adequate implementation of serosurveys requires certain conditions that may not exist in all contexts: (1) collaboration between epidemiologists and laboratory scientists, (2) existence of adequate laboratory capacity and methods, including biosafety conditions, (3) suitable survey design and sufficient sample size, and (4) appropriate standard operating procedures to ensure training, quality control, and oversight of the survey implementation [66,113].

While international organizations have anticipated the need for prioritization strategies, given the limited initial supply of COVID-19 vaccines, and advised countries to consider seroprevalence data to identify target groups, countries' prioritization strategies are instead defined by age, comorbidities, and risk factors. Constrained financial resources and logistical limitations, including the capacity to carry out and oversee these studies, may impede the use of seroprevalence data to prioritize population groups to be vaccinated. Furthermore, increasingly debates at the political level also question the use of serological data to regulate travel requirements and social gatherings, among other things.

8. Recommendations

8.1. Recommendation to Develop Evidence for the Adequate and Valid Use of Serology Testing

- European governments should promote and conduct multicentre studies to resolve the knowledge gaps for the effective use of serology testing, addressing concerns regarding the type of assay, type of antibody, test calibration, and test validity in different contexts. Sound recommendations should be made regarding the choice of alternatives to enhance the adequate use of serology testing within surveillance activities.
- European governments are encouraged to foster and undertake research to acquire further evidence on the correlation between antibody types (i.e., IgG, IgM, IgA) and protein specificity (S versus N) and the risk associated with infection, both preceding and after vaccination. This evidence would provide a sound understanding of the association of antibodies across different population groups and the risk of infection,

transmission, hospitalization, and mortality, data that can enable adequate knowledge-based policymaking.
- European governments should invest to aggregate, collect, and create evidence on the specificity of the immune response, duration of the immunological memory and to identify the correlates of protection to evaluate vaccine effectiveness.

8.2. Recommendation for the Inclusion of Serology Testing to Impact Immunization Policies

The following six recommendations must build on sound evidence ensuring the adequate and valid use of serology testing for surveillance as well as epidemiological and vaccine effectiveness studies/activities:

- European governments should conduct serosurveys on vaccinated individuals, both in specific risk population groups and the general public, to evaluate and monitor vaccine effectiveness across populations. Monitoring is particularly important as various vaccine types and brands become available to the public and virus mutations have been reported and are expected to continue.
- Serology testing should be included in efforts to understand the immune response induced by vaccines. Using serology testing to monitor vaccinated individuals can provide information regarding the duration of the protection generated by different vaccines, thus providing evidence to determine the need and timing of future and/or subsequent booster doses.
- European governments should consider using serology testing to support the monitoring of infection and disease. Seroprevalence studies can help understand how the infection spreads in the population, the proportion of the population with a certain degree of immunity, and to identify outbreaks. Thus, studies of this nature can help monitor population immunity over time, investigate cases of a resurgence of infection, and, in due time, monitor progress toward elimination.
- International organizations and professional societies should provide guidance and support to national decision-makers on using serology data across the different stages of immunization. Particular attention should be paid to ensure the correct and standardized use of serology testing and serosurvey protocols, ensuring the comparability of data across countries and enhancing collaboration.
- A steering committee should be established to coordinate efforts across European countries. Ensuring good leadership and coordination is essential to integrate and align efforts, enhancing comparability of evidence and, potentially, reducing financial, time, and resource constraints.
- Collaboration efforts should be directed toward bringing together decision-making bodies and the academic community to establish necessary partnerships at local, national, and international levels.
- Governments and international organisations should invest to ensure capacity and resources for the adequate implementation of serosurveys and seroepidemiology studies, paying particular attention to laboratory capacity, adequate study design, qualified personnel, and implementation oversight.

9. Conclusions

Pandemics require decisive actions. Serology testing serves as a valuable resource by generating evidence that can inform planning for future outbreaks or pandemics. Hence, the importance, and relevance, of serology testing applies to all phases of a pandemic. Prepandemic—to perfect tests for more efficient and accurate use and better management of financial resources. During a pandemic—to properly identify cases and trends of infection and support contention and immunization strategies. Postpandemic—to gather data and evidence that can guide the way and enhance preparedness for future eventualities.

European countries and others worldwide must make these evaluations and address gaps for the adequate use of serology testing at a difficult time, amid the crisis. Compiling sound evidence to validate the use of serology testing is a necessary first step. Collaboration

between countries is also essential to foster knowledge and proper assessment of current and future pandemics.

Although mounting evidence from a variety of vaccine-preventable diseases points at serology testing as a tool to provide sound and essential data to guide critical decision-making at different points of the immunization activities, we have identified some critical knowledge gaps that might concern decision-makers when considering this strategy, especially when time and resources are limited. Nevertheless, past evidence, regional recommendations, and current national policies highlight the value that serology testing can bring during the COVID-19 immunization rollout and the implementation of policies for a return to normalcy.

The recommendations in this paper can be used by international, national, and subnational health policy decision-makers—such as national immunization technical advisors, ministries of health, and other independent decision-making entities—involved in the planning and implementation of COVID-19 vaccination strategies in Europe. Elements of this document can also contribute to establishing necessary partnerships and alliances with the research community and key national research centres to enhance joint efforts between governments and academia to resolve knowledge gaps. Thus, the review and recommendations presented are intended to support decision-making, raise awareness, guide advocacy initiatives, and motivate future studies. Nevertheless, readers should bear in mind that, since the pandemic is ongoing, the contents of this document must be considered within the parameters and time frame of its production.

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