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Abstract: This paper provides a comprehensive summary of evidence to explore and position the role of serology testing in the context of coronavirus disease 19 (COVID-19) immunization and policy response in the Asia-Pacific (APAC) region. The document builds on a review of academic literature and existing policies followed by a process of discussion, validation, and feedback by a group of six experts. Six countries and territories—Australia, Hong Kong, India, Indonesia, Thailand, and Taiwan—were sampled to highlight the differing contexts and scenarios in the region. The review includes an overview of (1) the impact of the COVID-19 pandemic, including the emergence of Variants of Concern (VOCs), especially Omicron, (2) the introduction of immunization, (3) the available testing options and potential use of serology testing, (4) the landscape of guidelines and recommendations for their use, and (5) the barriers and challenges to implementing serology testing as a tool to support COVID-19 immunization. Based on the findings, the co-authors propose a set of recommendations to resolve knowledge gaps, to include the use of serology testing as part of the policy response, and to ensure adequate means of implementation. This paper's target audience includes members of the academic community, medical societies, health providers and practitioners, and decision-makers.

Keywords: COVID-19; SARS-CoV-2; pandemic; serology tests; antibody tests; diagnostic tests; health policy; immunization; vaccination; Asia-Pacific

1. Objective and Methodology

The aim of this paper is to contribute to the discussion on the use and value of serology testing in the short, medium, and long term to support the coronavirus disease 19 (COVID-19) pandemic response in the Asia-Pacific (APAC) region, by providing (1) a comprehensive summary of evidence regarding the potential use of serology testing to support COVID-19 policy responses, particularly regarding immunization, and (2) recommendations to address barriers to inclusion and guide uptake. The evidence and recommendations herein intend to provide a path forward to support critical and timely decision-making, assisting the academic community, decision-makers, and other key stakeholders involved in planning COVID-19 vaccination programs and strategies. In addition, this paper can be used when building the necessary partnerships to collaboratively address barriers.

This document builds on a review of academic literature, evidence, and existing policies followed by a process of validation and feedback by a group of six experts from across APAC. The experts were selected based on their in-depth understanding of serology testing, immunization policies, health emergency preparedness and responses, and the current COVID-19 pandemic. Experience in seroprevalence and seroepidemiology studies, as well as post-marketing vaccine effectiveness studies, were considered assets. Their expertise covered various fields of knowledge, including clinical microbiology, infectious disease, molecular epidemiology, epidemiology, biomedical sciences, pharmacology, vaccinology, immunology, and public health.

Evidence and policies from the region and six countries and territories of interest—Australia, Hong Kong, India, Indonesia, Thailand, and Taiwan—were collected and analyzed. The countries and territories of interest were selected to highlight different contexts and scenarios, based on [1,2]:

- Government and regulatory processes, including democratically elected governments (Australia, India, Indonesia, Taiwan, and Thailand) and Specialized Autonomous Regions (such as Hong Kong);
- Geographic location, including South Pacific, Western Pacific, Southern Asia, and South East Asia;
- Socioeconomic status, including high-income (Australia, Hong Kong, and Taiwan), upper-middle-income (Thailand), and lower-middle-income (India and Indonesia).

The APAC region covers a large geographic area comprising numerous countries and territories with varying sociopolitical and economic environments. By including a diverse range of cases, the paper reflects a holistic view of serology testing across its complex landscape, ensuring that findings and recommendations are relevant to the entire region.

This review was inspired by two similar projects conducted in Europe [3] and Latin America [4], and adopted similar frameworks for the discussion and validation of evidence and for data collection. Materials were reviewed and included for analysis based on the following criteria:

- Evidence on the health and socioeconomic impact of the pandemic in the region and focus countries and territories;
- Evidence on the impact of Variants of Concern (VOCs), especially regarding serology testing;
- Scientific perspectives on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) testing strategies, including challenges and opportunities;
- Evidence on the use of serology testing to support immunization policies across vaccine-preventable diseases;
- Current position, guidelines, and recommendations on the use of serology testing from key international organizations and focus countries and territories;
- National COVID-19 immunization plans and strategies of focus countries and territories.

Evidence on the characteristics and use of serology tests, the impact of VOCs, and knowledge on the antibody response to COVID-19 were retrieved from academic publications in peer-reviewed journals where possible. Evidence on the socioeconomic impact of the pandemic and the guidelines and recommendations for the use of serology testing were

retrieved from reports, websites, and official statements made by leading international organizations in the fields of health and development. These included, among others, the World Health Organization (WHO), Asia Pacific Society of Infection Control, European Centre for Disease Prevention and Control (ECDC), Food and Drug Administration (FDA), Centers for Disease Control (CDC), Gavi The Vaccine Alliance, International Federation of Red Cross and Red Crescent Societies, United Nations, Organization for Economic Co-Operation and Development, Asia Society Policy Institute, World Bank, International Monetary Fund, and Asian Development Bank. National COVID-19 vaccination policies and policies for the use of serology testing in focus countries were retrieved from government portals where possible and publications or statements made by local medical societies.

A working document was prepared, summarizing the findings. The experts discussed and validated the evidence presented in the document during an online panel session and multiple rounds of offline review. All participating experts approved the final paper.

2. Introduction and Background

On 31 December 2019, the WHO's Country Office in the People's Republic of China notified the corresponding regional International Health Regulations focal point of a cluster of pneumonia-like cases in Wuhan, Hubei Province of China, attributed to a novel coronavirus that was later named SARS-CoV-2 [5]. Within a couple of weeks, cases of COVID-19 (the disease caused by SARS-CoV-2) were confirmed in several APAC countries and territories, including Thailand [6,7], Taiwan [8], Hong Kong [9], Australia [10], India [11], and Singapore [12]. With new infections spreading rapidly in all regions, on 11 March 2020, the WHO categorized the COVID-19 outbreak as a global pandemic [5].

As of 8 June 2022, the COVID-19 pandemic has led to over 6.3 million deaths worldwide [13]. Of which, 13% are in the World Health Organization South East Asia Regional Office (WHO SEARO) and 4% are in World Health Organization Western Pacific Regional Office (WHO WPRO) [14]. The COVID-19 pandemic has also impacted all spheres of human life, with wide-ranging social, economic, and political consequences. A slowing of regular business activity across the primary, secondary, and tertiary sectors has been experienced worldwide and, in the APAC region, it is expected to cause the sharpest global economic contraction in history [15,16]. In parallel, public debt has surged due to an increase in government spending and borrowing and a decrease in revenue collection [17]. The fiscal deficit in APAC countries is estimated to have increased, on average, by more than 3% of GDP in 2020 as compared with previous years (2015–2019) [18]. The social consequences of the pandemic are also a topic of concern, revealing the devastating effects of pre-existing inequalities. The pandemic has aggravated the difficulties many families face accessing affordable and healthy diets [19–21]. With many jobs lost, especially in the services and manufacturing sectors [19,22], the COVID-19 crisis is expected to reverse the 20-year trend of poverty reduction in developing eastern APAC countries.

Regarding the impact of the pandemic on health care systems, one of the most apparent consequences in APAC is the disruption in providing regular health services. Delays in regular screening and immunization programs have been observed, as well as difficulties accessing health services by those who need ongoing care, such as the elderly and people living with chronic medical conditions [17,23]. Health care systems have also struggled to provide care to COVID-19 patients. Many countries in the region have experienced shortages of essential medicines and medical equipment, health workforce, hospital beds, and intensive care units [17]. This has been accompanied by concerns regarding the effects of long-COVID-19 and post-COVID-19 health complications [24] on the longer-term health of individuals [23], and the resulting possibility of an imminent health care system economic deficit [17].

3. The Impact of Variants of Concern Globally and in the APAC

Since the onset of the pandemic, and as of 8 June 2022, five variants of SARS-CoV-2 have been classified as VOCs by the WHO—Alpha, Beta, Gamma, Delta, and Omicron—

of which only the latter is currently in circulation [25]. According to the WHO, Delta outcompeted other variants and became the dominant lineage in early October 2021 [26]. Only one month later, on 26 November, the WHO designated Omicron as the fifth VOC [27]. Omicron is a highly divergent variant with many mutations, including 26–32 mutations in the spike protein, which could be associated with humoral immune escape and higher transmissibility. Since February 2022, Omicron has been the dominant variant globally [28].

The emergence of virus mutations has resulted in concerns regarding the possible effects on transmissibility, severity of disease, immunity, vaccines' effectiveness, and the effectiveness of diagnostic methods. As shown in Table 1, regarding previously circulating VOCs (Alpha, Beta, Gamma, and Delta) [25], numerous studies have found an increase in transmissibility [29–36], risk of hospitalization [37–43], and risk of reinfection associated with these VOCs [34,38–40,42,44–48]. However, the vaccines' impact has varied depending on the metrics used to gauge effectiveness, such as protection against infection, symptomatic disease, and severe disease. Importantly, studies have confirmed that vaccines retained effectiveness in reducing severe illness following infection by Alpha [49–52] and Beta [53–56]. In the case of Alpha, although outbreak prompt settings and retrospective studies analyzing periods of high case incidence have found evidence of retained protection against infection offered by vaccines [49,50,57], an *in vitro* microneutralization assays study and a study using pseudoviruses found a lower neutralization efficiency for the E484K strain among vaccinated and convalescent samples [58,59]. Notably, some studies found a reduction in vaccines' effectiveness against symptomatic disease among vaccinated individuals infected by the Beta variant [53–56] and a reduction in the resistance of naturally acquired or vaccine-induced antibodies in Gamma [60].

As for the Delta variant, evidence indicates an increase in transmissibility, characterized by the presence of a viral load 2.5-fold higher in this variant compared with Beta [61,62], higher risk of reinfection and pre-symptomatic transmission, and a secondary attack rate of 1.4% [61,63]. Moreover, evidence also confirms an increase in hospitalization among Delta cases [36]. According to evidence from outbreak prompt settings and retrospective studies, protection against infection offered by vaccines is retained against Delta [57,64,65]. Nonetheless, studies have also shown a potential reduction in vaccines' effectiveness against symptomatic disease [66] and an 18% absolute reduction in vaccine effectiveness against symptomatic disease with Delta compared with Alpha after a single dose. However, this difference considerably decreases after two vaccine doses (5–7% absolute reduction) [36,67,68].

Since Omicron was designated as a VOC, several descendant lineages have been identified, such as BA.1, BA.2, BA.3, BA.4, and BA.5. The WHO is regularly monitoring descendant lineages under the Omicron umbrella. The prevalence of BA.2 among Omicron cases sequenced globally has been steadily increasing [69]. According to the WHO, since April 2022, BA.2 has become the dominant variant in all six WHO regions [70]. Given the elevated level of transmission worldwide, it is likely that more variants will continue to emerge, including recombinants. In coronaviruses, recombination is an expected mutational event. Among recombinants currently monitored by the WHO, the XE Pango lineage (a recombinant of BA.1 and BA.2) is one of the most concerning; early estimates suggest a 10% transmission advantage compared with BA.2 [70].

In a general sense, Omicron shows a growth advantage over Alpha, Beta and Delta [35,71]. Of Omicron's descendant lineages, BA.2 appears more transmissible compared with BA.1 [72]. Evidence suggests a higher growth rate (median of 75.3% per week) [69] and secondary attack rate among contacts with BA.2 compared with BA.1 [73,74]. According to the WHO, the factors driving the growth advantage of Omicron over other variants are complex. Although Omicron's properties of immune escape have been associated with the rapid increase in the global incidence of COVID-19 cases between December 2021 and January 2022, the increase observed from March 2022 may relate to a delayed increase in case incidence in WHO WPRO and a rebound in the number of new cases reported in the WHO Europe region. This trend is a result of several factors, including the predominance of BA.1

and then BA.2 (with a transmission advantage over other Omicron lineages), the relaxation of public health and social measures, and the waning of humoral immunity following vaccination and/or prior infection [75]. Moreover, preliminary evidence from studies on antibody response and household transmission seem to suggest that the growth advantage of BA.2 over BA.1 might be associated with increased transmissibility rather than immune evasion [74,76].

Unlike previous waves, the recent wave driven by the Omicron variant shows a decoupling between the number of cases, hospitalizations, and deaths [22,75]. Omicron has consistently been associated with lower severity compared with Delta across different settings [69,77–83]. Despite the reduction in severity, the risk of hospitalization and death associated with an Omicron infection varies across countries. In some cases, no difference was found in the risk of hospitalization between individuals infected with BA.1 compared with BA.2 [69,84]. Other studies found a consistent decrease in the number of hospitalizations and deaths associated with an increase in BA.2 infections [85,86]. However, evidence from Denmark and Nepal also documented a rise in hospitalizations as BA.2 became the dominant lineage [84,87]. Notably, one study conducted in the United States of America found that although hospitalization rates among children aged 0–4 years were about five times higher during periods of Omicron predominance compared with Delta predominance (14.5 vs. 2.9 per 100,000), the length of hospital stay was shorter and the proportion of children requiring intensive care was lower during Omicron predominance [88]. These recorded differences might be associated with several factors, such as the coexistence of BA.1 and BA.2 and the substantial increases in Omicron cases observed in certain countries [75].

The Omicron variant has been found to evade immunity from natural infection and vaccines [89,90]. The Omicron variant represents a distinct new serotype, a potential reason why previous infection by Alpha, Beta, and Delta might grant only reduced protection against infection from the Omicron variant [91], especially among unvaccinated individuals [92,93]. Evidence on neutralization data found a 20-fold reduction in neutralization associated with the Omicron variant [94] and lower neutralizing antibody titers to BA.1 and BA.2 when compared with wild-type SARS-CoV-2 [76,95]. Studies indicate similar humoral responses among BA.1 and BA.2 [76,95,96]. This evidence complements the epidemiological observation of higher rates of reinfection reported for Omicron compared with other virus variants [70]. On the positive side, some evidence indicates that previous infection with one of the Omicron Pango lineages could potentially confer protection against infection with other Omicron Pango lineages [97], and that reinfection with BA.2 following BA.1 might associate to mild disease [98].

The impact of Omicron on vaccines' effectiveness is well documented and summarized by the WHO. According to a recent report [70], numerous studies have confirmed that the primary series COVID-19 vaccines offers reduced protection (including all outcomes such as severe disease, symptomatic disease, and infection) against Omicron when compared with other VOCs. Notably, estimates of vaccines' effectiveness against symptomatic disease and infection tended to be lower than against severe disease and decreased more substantially over time, whether following primary series and booster dose. Nonetheless, vaccines' effectiveness against severe disease remains high for Omicron and booster vaccination improves protection for all vaccine products. Most of the studies overviewed by the WHO found increased protection ($\geq 70\%$ vaccine effectiveness) against severe disease between 14 days and 6 months post-mRNA booster dose.

Table 1. Impact of Variants of Concern (VOCs) on transmissibility, severity of disease, immunity, and diagnostic tests.

VOC		Country Where First Detected	Earliest Documented Sample	Evidence of Increased Transmissibility	Evidence of Potential Increased Risk of Hospitalization	Evidence of Impact on Immunity ¹	Evidence of Impacts on Diagnostics ²
Previously circulating VOCs	Alpha	United Kingdom	September 2020	YES	YES	YES [Re-Inf] YES [Vac-Eff]	YES ³
	Beta	South Africa	May 2020	YES	YES	YES [Re-Inf] YES [Vac-Eff]	NO
	Gamma	Brazil	November 2020	YES	YES	YES [Re-Inf] YES [Vac-Eff]	NO
Currently circulating VOC	Delta	India	October 2020	YES	YES	YES [Re-Inf] YES [Vac-Eff]	NO
	Omicron	Multiple countries	November 2021	YES	n.d. ⁴	YES [Re-Inf] YES [Vac-Eff]	YES ⁵

¹ Referring to a potential increased risk of reinfection (Re-Inf) or reduction in vaccines' effectiveness (Vac-Eff). Vac-Eff includes impacts on chances of infection, symptomatic disease, and developing severe disease. ² According to impact on molecular tests and antigen tests. ³ Evidence of impact on the performance of molecular tests targeting only the S gene for the B.1.1.7 + E484K lineage; no impact on the overall result from multiple target molecular tests. No impact on antigen tests observed. ⁴ Not determined. Omicron has consistently been associated with lower severity when compared with Delta, evidence on the risk of hospitalization varies across countries. ⁵ Evidence of S-gene target failure on certain real-time reverse-transcription polymerase chain reaction (rRT-PCR) assays applicable to BA.1 and BA.1.1, and N-gene target failure applicable to BA.2. Source: elaborated based on reviewed reports and literature [22,25–105].

The ECDC, WHO, and FDA have expressed concerns regarding the potential loss of test performance as new variants emerge, although most molecular assays available worldwide use multiple targets [99–101]. The WHO recommends a diagnostic approach using different tests in parallel, or a test targeting different viral genes [100]. An impact on molecular test performance was observed from variant Alpha, affecting molecular tests targeting the S gene. No effect on the overall result from molecular tests targeting multiple genes was observed [102]. Regarding Omicron, concerns exist regarding the performance of single-target molecular tests to detect infection. Omicron Pango lineages BA.1 and BA.1.1 have a 69–70 deletion in the spike protein, leading to S-gene target failure on certain molecular assays [28]. N-gene target failure has also been reported for individuals with confirmed infection with BA.1 and BA.2 [103]. Nonetheless, an assessment of the performance of molecular tests including multiple gene targets found that Omicron had limited impact on test accuracy [101,104]. Evidence of antigen tests' sensitivity to Omicron compared with Delta and wild-type SARS-CoV-2 is also similar [105].

4. SARS-CoV-2 Immunization in the APAC Region

Since the beginning of the pandemic, efforts to minimize the human, financial, and social costs and commence the recovery process have mainly relied on the rollout of effective COVID-19 vaccines. With multiple COVID-19 vaccines being introduced across the globe to a widely diverse population, people have become increasingly concerned about the risks associated with vaccines. Efforts to surveil, identify and report adverse events following immunization (AEFIs) are particularly important for preserving and restoring confidence in vaccination programs and combating vaccine hesitancy [106,107]. In this context, AEFI post-mortem investigations have been instrumental in establishing the causality relationship between vaccine administration and fatal adverse events, as well as identifying the cause of death in such cases [106–108]. Concerns due to the persistence of high viral loads in exhumed corpses after a long post-mortem interval in spite of appropriate burial practices [109] highlight the importance of implementing shared guidelines for the safety of handling of COVID-19-positive and potentially infectious corpses during autopsy practices [106,109,110].

As shown in Table 2, immunization rollout in the APAC region began in January 2021. As of 7 June 2021, among the countries and territories of interest, Australia, Hong Kong, Taiwan, and Thailand lead immunization efforts, having covered over 75% of their populations with a complete initial vaccination protocol [111], and 53.35, 54.63, 66.07, and

40.45 per 100 people, respectively, with booster doses [112]. On the other end, India and Indonesia have only managed to cover 64% and 61% of their populations, respectively, with a complete initial protocol [111], and applied booster doses to fewer than 15 individuals per 100 inhabitants [112].

Table 2. COVID-19 immunization rollout in focus countries and territories: Australia, Hong Kong, India, Indonesia, Thailand, and Taiwan.

Focus Countries and Territories	Introduction of Vaccination	Percentage of People with a Complete Initial Protocol [111]	Booster Doses (per 100 People) [111]	Priority-Use Groups According to National COVID-19 Immunization Plans [112] ¹			
				Highest Priority-Use ²	High Priority-Use ³	Medium Priority-Use ⁴	Lowest Priority-Use ⁵
Australia	February 2021 [113]	84%	53.35	Phase 1	Phase 1 and 2	Phase 2	Phase 3
Hong Kong	February 2021 [114]	84%	54.63 ⁶	n/a	n/a	n/a	n/a
India	January 2021 [115]	64%	2.56	Phase 1 & 2	Phase 2	Phase 3	Phase 3
Indonesia	January 2021 [114]	61%	13.55 ⁶	n/a	n/a	n/a	n/a
Taiwan	March 2021 [116]	80%	66.07	n/a	n/a	n/a	n/a
Thailand	February 2021 [114]	75%	40.45	Phase 1	Phase 2	Phase 2 & 3	Phase 3

¹ Priority-use groups according to the WHO SAGE Roadmap for Prioritizing COVID-19 Vaccines, update 21 January 2022, [117] refers to the subgroups (or subpopulations) identified for the allocation and prioritization of COVID-19 vaccines. Priority-use groups are included according to immunization phases. These are catalogued as highest, high, medium, and lowest priority-use. ² Highest priority-use: older adults, health workers, and immunocompromised persons. ³ High priority-use: adults with comorbidities, pregnant persons, teachers, and other essential workers, and disadvantaged sociodemographic subpopulations at higher risk of severe COVID-19. ⁴ Medium priority-use: remaining adults, children, and adolescents with comorbidities. ⁵ Lowest priority-use: healthy children and adolescents. ⁶ Latest available evidence 3 June 2022. n/a, not available. Immunization in these contexts will likely be defined according to availability of doses. Source: elaborated based on reviewed resources [111–116]. All data are accurate as of 7 June 2022, unless stated otherwise.

Inequitable access to vaccines is a subject of concern worldwide, particularly because it may increase the risk of new and even more threatening variants emerging [22]. Although some APAC countries such as China and India have extensive manufacturing capabilities and serve as regional vaccine production hubs, in many cases, access across the region has been limited by delays in national regulatory agencies approving vaccine candidates, insufficient manufacturing capacity, governments' struggle to secure deals with pharmaceutical companies to purchase doses in advance, and vaccine hesitancy [118].

Three mechanisms have played a critical role in improving access to COVID-19 vaccines in the region: the COVID-19 Vaccines Global Access (COVAX), the Asia Pacific Vaccine Access Facility (APVAX), and the Quadrilateral Security Dialogue (Quad) Indo-Pacific Vaccines Partnership. The COVAX platform was launched in April 2020 by a coalition led by Gavi the Vaccine Alliance, to reduce the unequal distribution of doses globally [119,120]. COVAX provides a procurement mechanism that purchases vaccines on behalf of governments, securing favorable deals. During the second quarter of 2021, COVAX was heavily criticized due to considerable supply shortages caused by the Delta variant's emergence in India [121]. Shortages were particularly felt by many countries in the region whose access to vaccine doses largely depended on COVAX, donations, and bilateral deals [115,122]. Launched in December 2020 by the Asian Development Bank, APVAX provides a comprehensive financing mechanism to low- and middle-income APAC counties, offering a USD 9 billion complementary financing program [123–125]. COVAX and APVAX are mechanisms that facilitate the procurement of doses; however, the Quad aims to impact access by financing and supporting the Indian production of vaccine doses [122,126,127]. The Quad has pledged to produce at least one billion doses by the end of 2022 for the Indo-Pacific region [122,127].

The emergence of the Omicron variant has brought concerns regarding the dangers of vaccine inequity to the forefront. Although vaccines are not as effective in preventing infection from Omicron, data consistently show that those who are unvaccinated remain at higher risk of severe disease following infection than those who have been vaccinated [75]. Countries and territories that have higher vaccination rates will likely be more resilient to Omicron. In this context, the WHO recommends accelerating efforts to increase COVID-19

vaccination coverage among at-risk populations, particularly those who remain unvaccinated and those whose vaccination remains incomplete. The priority for booster doses is to maintain and optimize vaccine effectiveness against severe disease, especially in population groups that are more vulnerable to serious illness [128].

The latest update to the WHO Roadmap for Prioritizing COVID-19 Vaccines considers increased vaccine availability, vaccine coverage rates, and the evolving epidemiological situation including COVID-19 VOCs. The framework centers around scenarios in which vaccination coverage exceeds 50% of the population. The Roadmap identifies four priority-use groups and recommends prioritizing completed primary series vaccinations and an additional dose or booster dose depending on low, moderate, or high primary series coverage rates for each group. The optimal interval between completing a primary series and administering a booster dose should be determined according to the epidemiological setting, vaccine product, targeted age groups, background seroprevalence, and circulation of specific VOCs [117]. Notably, the new WHO Roadmap reflects a shift in the goal of COVID-19 immunization policies, from preventing infections to preventing severe disease outcomes. Although under current circumstances, recommendations made by previous guidelines to prioritize by epidemiological situation [129] are not viable, in any scenario where new vaccines are effective at reducing or suppressing virus transmission, prioritizing populations using data on disease prevalence, determined by the number of reported infections and seroprevalence, might be possible [113,130,131].

The arrangement of priority-use groups according to the latest immunization strategy per country can be found in Table 2. Following WHO recommendations, all countries and territories of interest have considered older adults, health workers, and essential workers among the priority groups, whether they are covered during the first or second phase of the respective immunization plan. Surprisingly, only two of the focus countries and territories identified and prioritized populations by considering socio-demographic disadvantages to contracting and developing severe COVID-19—indigenous people in the case of Australia, and care recipients at social welfare organizations in the case of Taiwan [132]. Disadvantaged subgroups are more likely to experience a higher burden of infection and COVID-19 because of crowded work or living conditions over which they exert no control; in addition to a higher prevalence of poor health, which leads to an increased risk of severe COVID-19. In Hong Kong and Indonesia, immunocompromised people and adults and children living with comorbidities are not currently identified as priority-use population groups. Notably, none of the focus countries and territories identify pregnant persons as a priority-use population group [112].

5. Testing Options to Diagnose Infection and Mitigate COVID-19 Impacts

A comprehensive policy response to the pandemic includes pharmaceutical and non-pharmaceutical interventions. Among the first group, testing has been one of the key interventions to respond to the pandemic. Currently, there are three primary types of COVID-19 tests: (1) those that detect the genetic material of the virus (molecular tests), (2) those that detect specific viral antigens (antigen tests), and (3) those that measure the antibody response (serology tests). The first two types of tests are widely recommended to diagnose acute infection; however, serology tests can be used to perform retrospective diagnoses and provide essential information for individual and outbreak pandemic management.

The real-time reverse-transcription polymerase chain reaction (rRT-PCR), also known as a molecular test, is the recommended assay type to confirm acute SARS-CoV-2 infection. Nevertheless, a negative result of this test does not eliminate the possibility that an individual was recently infected and is incubating the disease [133–136]. rRT-PCR tests for SARS-CoV-2 demonstrate high sensitivity and specificity but require rigorous laboratory infrastructure and biosafety conditions, which implies a higher cost and longer results turnaround time [133].

Antigen detection tests, usually performed through rapid diagnostic kits (Ag-RDTs), can be used as an alternative to diagnose the most infectious patients [137]. Similarly to

molecular tests, Ag-RDTs are likely to perform best using samples collected at or around the development of symptoms. The specificity (98.5% to 99.5%) and sensitivity (56.5% to 83.5%) of Ag-RDTs is reportedly high; however, the positive predictive value (PPV) when there is no or low transmission of Ag-RDTs has been found to be low. In settings of low prevalence, there will likely be too many false positives [138]. Thus, current WHO guidelines recommend the use of rRT-PCR for first-line testing and for confirming Ag-RDT-positive results, including for Ag-RDTs self-testing kits, in settings with a SARS-CoV-2 prevalence below 5%. In all cases, Ag-RDTs should meet the minimum performance requirements of $\geq 80\%$ sensitivity and $\geq 97\%$ specificity compared with an rRT-PCR reference assay [137–139].

According to WHO guidelines, both molecular and antigen detection tests are appropriate for diagnosing SARS-CoV-2 [137,138]. Given that Ag-RDTs offer a faster and less expensive means of testing for SARS-CoV-2 than the reference method rRT-PCR test, the use of Ag-RDTs is prioritized for (1) primary case detection in symptomatic individuals suspected to be infected and asymptomatic individuals at high risk, (2) contact tracing, (3) outbreak investigations, and (4) monitoring trends of disease incidence in communities [138]. However, because no test is perfect, a negative result from either a molecular or antigen-detection test should always be interpreted within the clinical and epidemiological context [128,138].

Serology tests, also known as antibody tests, can detect the presence of antibodies starting at one to three weeks [140,141] and up to at least six months post-infection [142]. Serology tests can be used to determine if a person was infected with SARS-CoV-2, whether the individual experienced severe, mild, or no symptoms [143], or if the individual received immunization [144]. Although studies suggest that detecting antibodies against SARS-CoV-2 does not contribute significantly to early diagnoses of COVID-19, beyond a two-week threshold after symptom onset, using serology testing methods alongside viral detection assays may help diagnose recent infection [145–147], especially as the sensitivity of rRT-PCR wanes [148]. Serology tests can be performed through laboratory-based assays and rapid diagnostic tests (RDT). Laboratory-based assays can generate more accurate results and provide qualitative and quantitative data. In contrast to RDT, they have an increased turnaround time, higher cost, and require laboratory capacity.

Although this information can help to manage individual cases, at a larger scale, serological data can assist monitoring, surveillance, and research activities as part of a COVID-19 response. By estimating epidemiological variables, assisting contact-tracing activities, assessing the effect of non-pharmaceutical interventions [149], and helping to understand the antibody response triggered by both immunization and natural infection [144], serology tests play a vital role in evidence-based policymaking for disease control.

There are several types of serology tests depending on the choice of antibodies and antigens being measured. Serology tests can measure three antibody isotypes—immunoglobulin M (IgM), immunoglobulin A (IgA), and immunoglobulin G (IgG)—of which IgM and IgG are the main targets [150]. The sensitivity of these tests is higher starting at three weeks after symptom onset, and specificity is high, ranging from 96.6% to 99.7% [151]. A meta-analysis confirmed these findings, further detailing the specificity and sensitivity for IgG and IgM tests depending on the testing method. Specificity was found to reach higher levels (99%) for methods such as the enzyme-linked immunosorbent assay (ELISA) and lateral flow immunoassays (LFIAs). At 90–96%, sensitivity was higher for ELISAs and chemiluminescence enzyme immunoassays (CLIAs) than for LFIA and fluorescence immunoassays (FIA), which range between 80% and 89% [152]. SARS-CoV-2 antibody production is characterized by an almost-simultaneous rise in IgM and IgG antibodies [140,153,154], and a more rapid decline in the three antibody isotypes than the trajectory observed in other viral infections. Some studies suggest that simultaneously measuring multiple isotypes can help interpret the results of serosurveys and epidemiologic studies to estimate the time of infection, because earlier decay of IgA and IgM is observed compared with IgG [147].

The main viral antigens used to detect antibodies for SARS-CoV-2 in serology tests are the spike protein (S) and nucleocapsid protein (N). Evidence suggests that tests targeting antibodies against N, S, or their corresponding receptor binding domains (RBDs) can be used to indicate a prior infection [155]. Compared with the N protein, higher sensitivity, specificity, and earlier immune response to the S protein have been reported [152]. According to one study, the positive rate of N-based ELISAs (targeting antibody IgM and/or IgG) was 80.4%, and 82.2% for S-based ELISAs [156]. However, to evaluate potential protective immunity, the use of N-protein-based serology tests should be avoided [157].

Evidence suggests that the RBD of the S protein is the main target for neutralizing antibodies [158–162]. In immune-competent individuals, infection with SARS-CoV-2 triggers an adaptive antiviral humoral and cellular immune response. Although immunity is likely achieved by a combination of both, with B and T cells playing an important role [158,163,164], the humoral response may also be critical. This is especially significant because studies suggest that the RBD of the subunits S1 of the S protein may play a crucial role in mediating the binding of the virus to cells [159,160]. The neutralization antibody assay, a lab-based serology test that requires a biosafety level 3 laboratory (a laboratory with permission to culture SARS-CoV-2-infected cells), is considered the gold standard for determining potential protective immunity. This test could play a significant role in monitoring vaccines' effectiveness, conducting retrospective diagnoses of asymptomatic infections, and screening potential plasma donors for convalescent plasma therapy [144].

6. Potential Use of Serology Testing and Seroepidemiological Evidence to Support Immunization Policies and COVID-19 Measures

The use of serology tests to support immunization activities is well documented [165], having a role in the short, medium, and long term. According to evidence gathered studying various vaccine-preventable diseases, serology tests can be used as a tool to (1) monitor the effectiveness of the protective immunity triggered by vaccines during immunization rollout, (2) provide evidence to support the planning and implementation of immunization policies, and (3) evaluate the effectiveness of immunization programs [165–168].

Serology testing can be used to conduct long-term prospective follow-ups of vaccine trials, as well to evaluate vaccine-induced immunity in specific population groups that are not possible to include within traditional clinical efficacy studies in phase III randomized controlled trials. Serology testing can contribute to understanding how the antibody response to vaccines relates to protective immunity, and determine the duration of immunity after primary series, along with the need for and timing of booster doses [165,167,168]. With the emergence of Omicron, serology testing in vulnerable cohorts could help researchers and physicians understand the timing of boosters and the need to advise vulnerable patients regarding precautionary measures. There is mounting evidence on the benefits of stratifying individual risk based on antibody levels, especially for immunocompromised individuals [169]. Risk groups that could benefit from such efforts include the elderly [90,170], cancer patients [169,171], hemodialysis patients [172], transplant patients [173,174], and patients on tumor necrosis factor inhibitors, such as inflammatory bowel disease [175], psoriatic arthritis [176], and inflammatory rheumatic diseases [177]. The availability of correlates of protection is a requirement for this use.

Serology testing can also inform policy on relevant epidemiological variables, such as the prevalence of infection. In diseases where many cases are subclinical, unrecognized, or under-reported, serology testing has been used to estimate disease burdens across populations, contributing to the analysis and interpretation of clinical surveillance data. Reliable estimates on disease prevalence can help to assess the risk of outbreaks, identify high-risk population subgroups, and estimate theoretical herd immunity thresholds. This evidence can be further used for decision-making regarding the need for supplemental or targeted immunization activities, changes in the immunization schedules, and the identification of priority groups [165,166].

Likewise, estimates gathered through serology testing might play an important role in predicting the spread of COVID-19. The accuracy of susceptible exposed infectious removed (SEIR), the most widely used model to forecast epidemic diseases, such as COVID-19, primarily depends on valid estimates of asymptomatic or mildly symptomatic cases [178–180], which are difficult to calculate without population-wide testing [181,182]. A substantial proportion of COVID-19 cases are mild or asymptomatic; therefore, serology testing is a valuable tool to provide accurate estimates, enabling informed decision-making to optimize public policy measures.

Seroepidemiological data have also been used to monitor the effectiveness of immunization policies, namely to [165,166]:

- Monitor progress towards elimination and identify population gaps in immunity;
- Investigate the potential cause of disease resurgence (often associated with changes in diagnostic or reporting patterns, waning immunity, or reduced vaccine effectiveness following changes in vaccine formulations or schedules);
- Determine whether target immunity prevalence has been reached;
- Estimate vaccine coverage in the absence of virus circulation.

Although evidence on the potential use of serology testing described under the first two types of activities—monitor the antibody response following vaccination and provide evidence to support public policy measures, including immunization—can easily be extrapolated to the current COVID-19 immunization scenario, the use to evaluate the effectiveness of immunization programs is less promising. The clinical and epidemiological relevance of waning antibody levels after vaccination needs to be better understood [165], particularly with the presence of new virus variants and the introduction of new vaccines. Moreover, using serology testing to evaluate the effectiveness of immunization policies largely depends on the absence of natural transmission, a condition which is unlikely to be met under current circumstances. Although vaccines have high efficacy in preventing disease, severe outcomes of infection, and mortality [183], effectiveness in preventing virus transmission is still contested. Some evidence suggests that systemically vaccinated patients, although asymptomatic, may still become infected and transmit the virus [184]; however, others suggest that vaccines might make infected people less contagious or less infectious due to a reduced viral load [51,185–188]. Confirmation on whether observed reductions in viral load are sufficient to make someone less infectious is ongoing [185], and subject to change as new virus mutations emerge.

What Do We Know So Far Regarding the Antibody Response in the Context of the COVID-19 Pandemic, and How Can This Information Impact Serology Testing and Immunization Policies?

To provide evidence that can support the clinical management of patients and inform the policy response to the pandemic, academics from different fields of expertise have collectively contributed to better understanding the antibody response to COVID-19 infection and vaccination. Although these efforts are ongoing and require corroboration by more extensive longitudinal studies, much of the generated evidence can be used to explore potential policy options regarding the use of serology testing within the current health crisis. A summary of key findings and their policy implication is provided in Table 3.

Table 3. Summary of evidence on COVID-19 and immunization antibody response.

Evidence According to Studies	Is There a Need for Further Studies?	Potential Derived Areas of Use and Policies
Previous infection triggers an antibody response similar to immune priming [189–196].	YES <ul style="list-style-type: none"> • Longer-term follow-up; • Larger cohorts; • Clarify T cell memory and its role in immunity; • Determine window for vaccination timing. 	<ul style="list-style-type: none"> • Apply a single vaccine dose to individuals that can document previous infection either/or by a diagnosis certificate or a positive serology test.

Table 3. Cont.

Evidence According to Studies	Is There a Need for Further Studies?	Potential Derived Areas of Use and Policies
Previous infection might lead to a reduced risk of reinfection in the following six to seven months [192,197–199].	YES <ul style="list-style-type: none"> Determine the correlates of protection; Larger studies across different populations. 	<ul style="list-style-type: none"> Consider vaccine prioritization by identifying individuals with no pre-existing immunity certified by negative serology tests; Use serology testing to help determine the time of booster doses once correlates of protection are available.
Prioritization by antibody status might reduce incidence at a faster rate and can lead to more rapid elimination of infection and return to normalcy [200].	YES <ul style="list-style-type: none"> Long-term follow-up of immunity; Determine length and quality of protective immunity; Effect of virus mutations on immunity. 	<ul style="list-style-type: none"> Consider vaccine prioritization by identifying individuals with no pre-existing immunity certified by negative serology test.
Individuals who have SARS-CoV-2 antibodies are less likely to experience reinfection [191,197–199,201–208]. Lower (or absent) SARS-CoV-2 IgG titers and lower levels of neutralizing antibodies may correlate to a higher risk of reinfection [209].	YES <ul style="list-style-type: none"> Discrepancies of the antibody response across populations; Determine correlates of protection; Impact of emerging variants on immunity; Need to standardize processes and conduct studies that are larger, longitudinal, and more representative. 	<ul style="list-style-type: none"> Use serology testing to help determine the need for and timing of booster doses for the public and particular populations (i.e., immunocompromised individuals [210]) once correlates of protection are available. Use serology testing to help monitor and evaluate vaccine immunogenicity, and potential protective immunity across populations once correlates of protection are available. Help understand the effect of virus mutation on antibody response both from vaccination and infection.
Vaccinated individuals are less contagious than unvaccinated individuals [172,177,191,204–207,210–216].	YES <ul style="list-style-type: none"> Determine the correlate of protection from severe infection or infection in vulnerable populations; Larger studies across different populations, especially vulnerable and older populations; 	<ul style="list-style-type: none"> Promotion of vaccination and policies to fight misinformation and vaccine hesitancy.
Antibody tests can help identify asymptomatic cases [217].	YES <ul style="list-style-type: none"> Role of mucosal immunity in clearing SARS-CoV-2 infection. 	<ul style="list-style-type: none"> Help estimate the “real number” of infected individuals in a community (prevalence) for policy-planning purposes.

Source: elaborated based on the reviewed literature [172,177,189–217].

Although cases of reinfection have been documented [218,219], several studies that followed individuals who recovered from COVID-19 reported a significantly reduced risk of reinfection lasting up to six or seven months after the initial infection [192,197–199]. Studies on antibody levels report an association between antibody presence and the reduced likelihood of reinfection compared with individuals who do not have such antibodies [191,199,201–208] of up to 84% [197,198]. This has further been validated by a higher risk of reinfection in individuals with lower or absent SARS-CoV-2 IgG titers and lower levels of neutralizing antibodies [209]. Although more studies are needed to understand discrepancies in the antibody response across populations, to determine sound correlates of protection and the impact of emerging variants on immunity, current evidence indicates the key role of antibody levels in protective immunity.

Therefore, governments may consider using serology testing to prioritize individuals based on seroprevalence data or antibody status. Prioritizing immunization groups by antibody status has been found to reduce disease incidence more quickly, potentially leading to a more rapid return to normalcy [200]. Once correlates of protection are available, decision-makers may also consider using serology testing to help determine the timing of booster doses, evaluate vaccines’ immunogenicity, and monitor the effect of virus mutations on antibody response. Such endeavors can provide critical evidence for policies that may apply to the general public and particular populations (i.e., immunocompromised individuals) [210]. However, this approach also raises concerns about vaccine non-responders, as seen in other vaccines (i.e., hepatitis B vaccines). Evidence indicates that despite introducing additional immunization regimens, some individuals remain vulnerable to infection and are deemed non-responders [220]. The non-responder issue should be studied in more

detail and addressed in vaccination programs when serology testing is considered part of the strategy.

Multiple studies have found that COVID-19 infection triggers an antibody response similar to immune priming [189–196], an antibody response comparable to that achieved by the administration of the first dose from a two-dose vaccine. In such cases, a second dose might not be needed [195,196]. Further research is necessary to confirm the effectiveness of this strategy, particularly since Omicron emerged. Given the advantage that maximizing immunization coverage may have on reducing variant emergence [196], the limited supply of vaccines doses, and the costs of vaccines, governments could consider administering a single dose to individuals who have recovered from infection. This could be documented by a past diagnosis certificate and/or a positive serology test result. Studies are needed to ensure the feasibility and cost-effectiveness of this approach to reducing the burden of COVID-19 in the medium and long term.

Studies have also reported that vaccinated individuals are less contagious compared with their unvaccinated counterparts [101,177,191,204–207,210–216]. Although more extensive studies across different populations, especially those including vulnerable and older populations, are required to determine the correlates of protection against severe infection, such evidence can be used to provide arguments for policies that promote vaccination and fight misinformation and vaccine hesitancy. Finally, serology testing can be used to identify asymptomatic cases, helping estimate the actual prevalence of infection in a community [217]. This information is critical for the planning of immunization policy and non-pharmaceutical measures to combat the COVID-19 pandemic.

7. The Landscape of Global, Regional, and National Guidelines and Recommendations on the Use of Serology Testing

The WHO, the world's leading health organization, and its regional offices, have provided relevant recommendations on the use of serology testing in the context of the COVID-19 pandemic. From the beginning of the pandemic, the WHO has recognized the use of serology testing as a tool to support surveillance and research purposes [143,221], primarily to [222,223]:

- Measure the prevalence of antibodies against COVID-19 in the general population to quantify the accumulated immunity;
- Understand the full spectrum of COVID-19 infection across different population groups;
- Estimate the proportion of pre-symptomatic, asymptomatic, and subclinical infections in the population;
- Establish the risk factors for contracting the infection by comparing the exposures of infected and uninfected people;
- Accurately calculate the fatality rate;
- Help to understand the kinetics of antibodies against COVID-19;
- Determine the duration of immunity following natural infection and vaccination.

To support these activities, the WHO has developed a global collaboration platform, known as Solidarity II, to promote the implementation of SARS-CoV-2 serosurveys [221]. Solidarity II provides a collaborative environment for public health agencies and academic institutions worldwide to work together to answer some of the most urgent questions about the COVID-19 pandemic. This initiative reflects the WHO's belief that understanding how frequently infection occurs among different populations is critical information [121].

In parallel, the WHO's initiative in collaboration with technical partners, known as the Unity Studies, aims to standardize seroepidemiology studies to promote international research comparability and address knowledge gaps [224–226]. In partnership with SeroTracker, a knowledge hub that tracks and synthesizes findings from SARS-CoV-2 serosurveillance efforts worldwide, the WHO is synthesizing “real-time” seroprevalence data to bridge evidence and decision-making [227,228]. According to the SeroTracker, seroprevalence studies have been conducted in many APAC countries, such as India, Malaysia, Indonesia, Australia, New Zealand, Japan, and China [229,230].

On the other hand, the WHO has recommended against using serology testing to diagnose acute infection [231] and issue immunity passports [134,232]. Taking a similar stand, the WHO SEARO and WHO WPRO have also advised against using serology testing for diagnoses. However, regional offices have recognized the use of serology testing to detect past infections [233,234]. For example, the WHO WPRO highlights the value of serology testing to detect past exposure, supporting contact tracing activities [234].

Having a similar position, the Asia Pacific Society of Infection Control (APSIC) and Australia's Public Health Laboratory Network (APHLN) have endorsed the WHO's recommendations on serology testing for surveillance and research purposes [224,235–237]. Although APSIC also recognized the role of IgM and IgG antibody testing to facilitate early diagnosis at the beginning of the pandemic, as presented by the WHO–China Joint Mission on COVID-19 Report [235,236], APHLN now recommends against the use of serology testing to diagnose acute infection, although specimens can be collected and stored for later testing. According to APHLN, serology tests may support diagnosis only in cases where rRT-PCR results are inconclusive or when the window of opportunity has passed. Other uses include conducting seroepidemiology studies to define the degree of population infection, survey frontline health care workers, identify candidates for plasma donation, investigate outbreaks, and estimate the timing of infection to help determine the infectious period when not evident from symptoms or exposure history [237]. Sharing a comparable position, the FDA, CDC, and Gavi recommend using serology tests to help identify donor candidates for blood convalescent plasma therapy [238,239] and estimate the cumulative incidence of infection in a community by identifying people who may have had prior infection [238,240,241]. Gavi emphasizes using serology tests to predict future virus transmission by determining the proportion of the population still at risk, identifying high-risk environments, and supporting the planning of vaccination efforts [189].

In addition to the public health value, the CDC recognizes the key role of serology testing in research (contributing to the understanding of COVID-19 immunity) and clinical purposes (providing patient care). Regarding the former, the CDC highlights the use of neutralization assays as surrogates of protection in epidemiological and clinical studies. The clinical utility of serology testing involves the diagnosis of COVID-19 or complications derived from COVID-19. According to this recommendation, a positive serology test seven days following the onset of acute illness can be used to determine infection when a person had a previous negative seroconversion and had not received a positive viral test. In such cases, this test might indicate infection between the dates of the negative and positive seroconversion. A positive serology test can also help support a diagnosis when patients present complications of COVID-19 [241].

Moreover, according to the CDC, the clinical, occupational health, and public health uses of serology testing also include the application of serosurveys to help differentiate past infection from vaccination, using tests that measure antibodies against different protein targets. In cases of people never vaccinated, testing positive for antibodies against N, S, or RBD indicates prior infection. In vaccinated people, testing positive for antibodies against S protein and negative for antibodies against N protein can indicate the antibody response to vaccination and rule out previous infection. Testing positive for antibodies other than the vaccine-induced antibody, such as the N protein, can indicate resolving or past infection that occurred before or after vaccination [241]. Notably, serology and efficacy studies have found non-mRNA vaccines to produce lower immune responses [242]. Thus, the use of serology testing to differentiate the antibody response triggered by natural infection and vaccination is restricted to countries and cases where mRNA vaccines have been administered. For example, this use might not be applicable in Asian countries such as Indonesia and Thailand where inactivated vaccines are heavily used.

Importantly, the FDA, CDC, Gavi, and WHO WPRO do not recommend using serology tests to assess the robustness and durability of immunity to SARS-CoV-2 following COVID-19 vaccination, nor the need for vaccination in unvaccinated individuals [234,240–244].

Regarding immunization, the WHO has provided recommendations on the use of serology testing in the context of the emergence of the Omicron variant. According to the WHO, the public health strategy for optimizing vaccine use, including deciding on the optimal interval between completion of a primary series and administration of a booster dose, depends on the vaccine product, the targeted age groups, and the burden of disease and local epidemiology. The use of evidence to inform decision-making should contemplate transmission patterns, seroprevalence from infection-induced immunity in target populations, the circulation of specific VOCs, and incidence rate of infection in specific settings [117].

However, uncertainty remains on the relative protection granted by infection-induced versus vaccine-induced immunity. Initial evidence suggests that some COVID-19 vaccines provide higher levels of protective immunity than infection and that infection/vaccination-induced hybrid immunity may provide a superior neutralization capacity against VOCs, including Omicron, compared with a full vaccination protocol or previous natural infection without vaccination [245]. Thus, determining the need and the optimal timing of a primary vaccination series and booster dose may vary according to whether the individual has experienced prior infection(s), breakthrough infection after initiation of the primary series, or no previous infection. At the population level, this means that the number of doses, dose interval, and need for booster doses may differ in high seroprevalence settings. Although the WHO recognizes the significant role of seroprevalence to inform strategies and as part of comprehensive surveillance activity, basing national vaccination policies on seroprevalence rates or individual pre-vaccination screening is not currently recommended. The WHO is concerned by the limited capacity for serological testing and capacity to manage increasingly complex vaccination roll-outs in many settings, a reason why implementing serology testing as part of immunization policies may not be pragmatic or cost-effective. The WHO will update its recommendations on how infection-induced immunity should be considered in national vaccination policies as new evidence emerges [117].

To summarize the landscape of recommendations, in contrast to other testing strategies, serology testing can be used to mitigate the impact of COVID-19 rather than to diagnose acute infection. General agreement exists on the value of serology testing for individual and outbreak management (including for retrospective diagnosis, estimating epidemiological variables, and identifying potential plasma donors), which can inform decision-making related to immunization policies. However, the use of serology tests to evaluate protective immunity as part of a vaccination strategy is still contested. In the absence of reliable correlates of protection, and challenges on the capacity of countries to deal with a surge in serology testing and increasingly complex immunization programs, recommending this particular use remains debatable.

Table 4 summarizes the current use of serology testing in the countries and territories of interest. Notably, serology testing is not included in any national immunization plan [225,246–251]. Australia, India, Indonesia, and Taiwan have taken a stand similar to that of international organizations, warning against using serology testing to diagnose acute infection [237,252–258]. Aligned with the FDA, CDC, Gavi, and WHO WPRO recommendations, India and Thailand recommend against using serology testing before and after vaccination [259,260]. Notably, India's Council of Medical Research recommends against using serology testing to determine the immunization status of individuals and to enroll participants in clinical trials [254,255].

In some countries and territories, serology testing is currently used to remove and reduce compulsory quarantine times. Such is the case in Hong Kong, where a negative result from a serology test (showing the absence of antibodies to SARS-CoV-2) can be used to avoid quarantine for people in close contact with a COVID-19 patient [261]. For incoming travelers, a positive result (showing the presence of antibodies to SARS-CoV-2) along with a vaccine certificate and a negative rRT-PCR can be used to reduce mandatory quarantine time to only seven days [262].

A general agreement exists regarding the use of serology tests to support individual and outbreak management. Australia, India, Indonesia, Thailand, and Taiwan recognize the benefit of serology testing to [237,256–258,263–268]:

- Retrospectively determine infection and detect asymptomatic in individuals;
- Provide accurate estimates on epidemiological variables;
- Help predict the extent of infection in the future;
- Detect hot spots;
- Conduct community surveillance activities;
- Identify plasma donors for convalescent plasma therapy;
- Perform outbreak investigation.

Notably, in India, authorities recognize the value of seroepidemiology evidence for policy decision-making. They recommend using seroprevalence data for immunization planning, particularly for prioritization, and to inform decisions on the return to normalcy at a local district level [263].

Table 4. The landscape of recommended use of serology testing in focus countries and territories.

Countries and Territories of Focus	Is Serology Testing Included in the COVID-19 Immunization Plan?	What Is the Recommended Use of Serology Testing?
Australia	NO [246]	<ul style="list-style-type: none"> • Not recommended for diagnostic purposes, with financial penalties in cases of no compliance [237,252,253]; • Recommended for individual and outbreak management to retrospectively determine infection and estimate its timing, conduct seroepidemiology studies, survey frontline health care workers, identify plasma donors, and conduct outbreak investigations [237].
Hong Kong	NO [225]	<ul style="list-style-type: none"> • Negative tests can be used to avoid quarantine for people who are in close contact with a COVID-19 patient [261]; • A positive result of a serology test (alongside a vaccine certificate and a negative nucleic acid test) can be used to reduce mandatory quarantine time to seven days for incoming travelers [262].
India	NO [247,248]	<ul style="list-style-type: none"> • Not recommended for diagnostic purposes or determine immune status to declare that individual as recovered [254,255]; • Not recommended to enroll human subjects in any clinical trials [254,255]; • The Indian Council of Medical Research and relevant medical societies recommend using seroprevalence data for immunization planning, as well to inform decisions to lift lockdowns and return to normalcy at district level [263].

Table 4. Cont.

Countries and Territories of Focus	Is Serology Testing Included in the COVID-19 Immunization Plan?	What Is the Recommended Use of Serology Testing?
Indonesia	NO [249]	<ul style="list-style-type: none"> • Not recommended for diagnostic purposes [257,258]; • The Indonesian Society of Allergy and Immunology does not recommend using serology tests before or after COVID-19 vaccination [260]; • Recommended as a screening tool for community surveillance [257,258]; • Recommended to identify plasma donors for convalescent plasma therapy [268].
Taiwan	NO [250]	<ul style="list-style-type: none"> • Not recommended, as the single proof, for diagnostic purposes [256]; • Not recognized as proof for flying purposes [269]; • Recommended to determine past infection, outbreak investigation, and surveillance of community infection [256].
Thailand	NO [251]	<ul style="list-style-type: none"> • The Thai Department of Medical Science advises against antibody testing after receiving a COVID-19 vaccine [259]; • Members of the academic community have recommended using serology testing for preliminary screening to reduce the number of patients who visit the hospital, help predict the extent of infection in the future, detect hot spots, identify plasma donors [264–266], and detect asymptomatic individuals through mass screenings [267].

Source: elaborated based on overviewed resources and policy documents [225,237,246–269].

8. Challenges and Limitations for the Use of Serology Testing to Support Immunization Policies

Several challenges to and limitations on the use of serology testing in the context of immunization policies have been identified in the literature. According to their nature, these challenges can be organized into three major groups: those related to the intrinsic limitations of serology testing; those related to the conditions necessary to collect, process, and interpret seroepidemiology data; and those related to the emergence of the Omicron variant.

8.1. Challenges Related to the Intrinsic Limitations of Serology Testing

The first cause for concern relates to the variations in test results. These variations can potentially lead to significant discrepancies in the results of SARS-CoV-2 seroprevalence studies. Test results might vary due to multiple conditions, including [270–272]:

- The choice of assay and antibody;
- The type of sample (blood or plasma) and collection methods and its consequence on test sensitivity and specificity;
- Issues with test calibration as result of missed community cases and several demographic factors such as age, sex, and ethnicity;
- Test accuracy, particularly in terms of challenges with false-positive or false-negative results.

Test cross-reactivity has also been a source of concern. Cross-reactivity is the direct competition between the molecule of interest and other molecules for antibody binding sites due to structural similarities. This has implications for any test or assay, including diagnostic tests in medicine, and can cause false positives. As serology tests for COVID-19 become available, academics and experts have questioned whether these tests can cross-react with other endemic coronaviruses [224]. Evidence suggests low cross-reactivity with other coronaviruses, influenza A, and influenza B [273–276]. Nonetheless, future studies would need to determine whether these results will persist through time and whether SARS-CoV-2 mutations will impact cross-reactivity [274,276,277].

Finally, although the use of serologic testing to evaluate the antibody response from natural infection is well accepted, the FDA, CDC, Gavi, and WHO WPRO have argued that serology tests are not entirely validated to assess immunity following vaccination [236,241,243]. The appropriateness of this use might also be challenged due to the lack of clarity over the properties that different serology tests might have, with only a few able to distinguish between the antibody response to natural infection and vaccination.

8.2. Challenges to the Collection and Interpretation of Seroepidemiology Data to Support Decision-Making

Using serology testing to support immunization policies will depend on resolving current knowledge gaps, particularly identifying sound correlates of protection applicable to different virus variants and vaccines. A correlate of protection is an immune marker that can be used to predict protection against disease or infection [278,279]. Although remarkable efforts are ongoing to determine the correlates of protection, in the context of COVID-19, it remains unclear what level of antibody titers might confer protection, whether triggered by infection or vaccination.

As mentioned above, studies have found a reduced risk of reinfection in individuals who have SARS-CoV-2 antibodies [199,201–203,208], and increased risk of reinfection in individuals with lower or absent SARS-CoV-2 IgG titers and neutralizing antibodies [209]. This provides ground for the argument that post-immunization antibody levels could potentially be used as correlates of protection. Notably, one study using data from 171 cases of SARS-CoV-2 infection and 1404 non-cases found a decrease and increase in the probability of infection relative to a higher and lower immune response, respectively. In the absence of a single threshold value indicative of protective immunity, this publication provides antibody estimates that correspond to 50% to 90% vaccines' efficacy [280].

The following steps might be necessary to achieve consensus on the correlates of protection [281–283]:

- Establishing a framework that enables comparable antibody measurements across countries, within states/provinces, within countries, in laboratories, and research institutes;
- Agreeing on a neutralization assay to serve as the gold standard reference point for all tests;
- Calculating, where possible, the protective threshold in phase III trials to identify an objective pre-determined point on the correlate of protection, ideally across different platforms;
- Convening stakeholders to reach a consensus through discussion and despite discrepancies between studies;
- Verifying that the correlate of protection applies to new variants using appropriately adapted assays.

The use of serology tests to support immunization policies is also subject to fully understanding the conditions that lead to protection and reinfection, including the roles of humoral and cellular immune responses. The absence of IgG antibodies in approximately 5–10% of COVID-19 cases is particularly concerning [208,284]. So too is the fact that not all individuals believed to have been infected had a positive result for antibodies [217] and the potential effect of the choice of antibody test on the observed persistence and decay of antibody levels [285].

Implementing serosurveys or testing requirements also has challenges related to time, technology, and financial constraints. Conducting larger serosurveys is financially demanding, logistically challenging, and time-consuming [286]. Likewise, the feasibility of widespread serology testing strategies will also depend on cost and how the population accesses and pays for testing [200]. Another source of concern particular to serosurveys is having appropriate study designs. Serosurveys require integrating clinical, laboratory, and epidemiology aspects to ensure an optimal sample size, the adequacy of laboratory methods, the use of standardized and validated procedures, and the design of adequate algorithms [166,271,272,286,287]. The credibility of results may also be affected by the age distribution of the population and under-reporting of deaths [229]. Finally, because study designs need to account for several factors, such as diversity in the types of vaccines, infection by different variants of COVID-19, and prior infection status (either diagnosed or undiagnosed), they become exceptionally complicated to execute.

8.3. Challenges Associated with the Emergence of the Omicron Variant

Given that Omicron is currently the dominant variant responsible for the most recent surge of infections globally [288,289], it has changed the immunization landscape significantly, shifting the goal from preventing infections to preventing severe outcomes. As presented earlier, evidence indicates that Omicron can evade immunity garnered through natural infection and vaccines [89,90]. Although vaccines are less effective against symptomatic disease and infection, effectiveness against severe disease remains high for Omicron, especially after booster doses [26]. Although serology tests are still effective in detecting antibodies to Omicron [290] and predicting the risk of hospitalization and severity of disease [281,291], studies suggest that Omicron breakthrough infections can happen even in individuals with high concentrations of antibodies [292]. Nonetheless, in such cases, it was also observed that infections are primarily mild or asymptomatic [290]. Moreover, because antibody thresholds may be quite different for new variants—especially ones with numerous mutations that may compromise vaccines' effectiveness across all outcomes—identifying new cut-off values is crucial for the use of serology testing as a tool to support immunization policies, including decision-making regarding the need and time of booster doses for different population groups [169].

9. Recommendations for the Use of SARS-CoV-2 Serology Testing in the Context of Immunization Initiatives and Policies for COVID-19 in the Region

Based on the possible use of serology testing as well as the barriers and challenges that limit the uptake of serology testing, a set of 18 recommendations organized in three themes are provided: (1) recommendations to develop evidence and clarify the role of serology testing; (2) recommendations for the inclusion of serology testing to impact immunization policies; and (3) recommendations to ensure adequate means of implementation. The first group of five recommendations identifies further research to develop evidence and address knowledge gaps. The second group of six recommendations acknowledges the areas and actions needed to include serology testing within the COVID-19 immunization policies and response. Finally, the third group of seven recommendations aims to ensure the necessary conditions for conducting research and implementing impactful serology testing policies.

9.1. Recommendations to Develop Evidence and Clarify the Role of Serology Testing

1. Research institutes and the academic community are encouraged to continue conducting and disseminating research and studies that evaluate the role of serology testing in assessing the longitudinal dynamics of vaccine-related seropositivity and immunogenicity and the value of previous infection. Serology tests may potentially be used as a surrogate for overall SARS-CoV-2 immunity, whether natural or vaccine-related;
2. Governments should promote longitudinal and multicenter studies to overcome knowledge gaps for the effective use of serology testing, including determining correlates of protection. As a result, recommendations should be made to clarify the

appropriate use of serology testing in clinical settings, surveillance activities, public health policies, and research, as applied to their context;

3. Initiatives of this nature are encouraged to consider using a standardized study design to ensure the comparability of data across countries. Existing international guidelines, platforms, and resources might be used to support this effort;
4. The academic community should consider the role of serology in studies investigating the medium- and long-term outcomes of recovered COVID-19 patients;
5. Countries and international organizations with the capacity to implement studies to generate knowledge on the role of serology have an opportunity to collaborate with countries that require support generating data that will further help inform policy.

9.2. Recommendations for the Inclusion of Serology Testing to Impact Immunization Policies

1. Governments should make decisions informed by experts when considering the role of serology testing to support the monitoring of infection and disease and using the best available evidence for policymaking purposes. Once correlates of protection are established, serology tests could help monitor population immunity over time and investigate cases of infection surges;
2. Governments in partnership with research institutes should conduct serosurveys paired with clinical outcomes of vaccinated and recovered individuals, both in specific risk population groups and the general public, to evaluate and monitor the dynamics of seropositivity and immunogenicity and consider the need/timing of prime vaccination and booster doses;
3. Serology may help identify asymptomatic spread in vaccinated individuals when a community has an endemic disease. This may obviate the need for booster doses, resulting in reduced wastage of vaccine doses which can then be targeted towards people who need it the most, enabling improved health system efficiency;
4. Governments could implement serology testing to indicate population antibody profiles and assess the risk of outbreaks, informing decision-making regarding the need for supplementary immunization activities and modification of immunization schedules;
5. Given vaccine shortages and the financial burden of immunization, governments should consider using serology testing to study and guide decisions about the appropriateness of applying a single dose only to individuals who can document previous infection. The use of serology testing or previous infection certificate to apply a single dose to an individual should only be considered when a one-dose strategy is a well-accepted practice by national health authorities;
6. Community engagement to raise awareness on the value, role, and appropriate use of serology testing among the general population can be considered as needed, especially regarding the application and interpretation of results.

9.3. Recommendations to Ensure Adequate Means of Implementation

1. International organizations and governments are encouraged to understand and consider the value and role of serology testing to ensure that purchases are appropriate for the needs of the particular country;
2. Emerging information on the evolving value of serology tests should be shared freely and globally. Such changes may relate to new generation tests, levels of sensitivity and specificity, and their role in predicting immunity;
3. International organizations and professional societies should provide guidance and support to national decision-makers on the use of serology data across the distinct stages of the pandemic and the post-immunization era;
4. If not already in place, governments should develop digital health registries for immunization and test (including serology) results that can be regularly updated and accessible by health care providers. The registries can be used to direct the provision of resources, and potentially by researchers to monitor trends and identify shifts in the clinical behavior of populations. Countries challenged by limited resources could

- initially consider implementing registries of immunization coverage and targeted seroepidemiology data;
5. Policymakers, payers, medical societies, and health care providers should form a cross-functional partnership to collaborate on the ongoing development of knowledge related to serology testing;
 6. Medical societies should develop and publish clinical guidelines specific to COVID-19 that incorporate serology testing and other diagnostic tests, vaccination, and acute treatment and acknowledge the impact on comorbidities;
 7. Collaboration efforts should bring together decision-making bodies and the academic community to help translate findings into policy recommendations.

10. Conclusions

Evidence and current national and international guidelines and recommendations highlight multiple areas of use of serology testing within and beyond the scope of COVID-19 immunization policies. According to past evidence across vaccine-preventable diseases, serology tests are a valuable tool to help understand the antibody response, monitor vaccines' effectiveness, monitor the effectiveness of vaccination programs, and provide vital information for evidence-based immunization policies. Studies highlight the potential benefits of using serology testing to evaluate the effectiveness of immunization policies. However, using serology testing for this purpose in the current scenario is unlikely, especially because evidence suggests that COVID-19 vaccines reduce but do not eliminate virus transmission. The potential use of serology testing in this context will require the development of necessary evidence to address significant knowledge gaps, such as the correlates of protection and better understanding the role of vaccines in preventing virus transmission. Moving forward, an agenda for the inclusion of serology testing within immunization policies requires the engagement of public and private stakeholders and the international and academic communities.

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