Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Global Health Journal 6 (2022) 38–43

Contents lists available at ScienceDirect

Global Health Journal

journal homepage: https://www.keaipublishing.com/en/journals/global-health-journal/

REVIEW

Biology of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the humoral immunoresponse: a systematic review of evidence to support global policy-level actions and research

Shalini Nair*, Xinguang Chen

Department of Epidemiology, University of Florida, 2004 Mowry Road, Gainesville, Florida, 32610, USA

ARTICLE INFO

Article history:
Received 6 June 2021
Received in revised form 12 September 2021
Accepted 14 November 2021
Available online 19 November 2021

Keywords:
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
Coronavirus disease 2019 (COVID-19)
Immunoresponse
Antibody
Global health
Health policy
Decision-making
Serology testing

ABSTRACT

Background: Both population-level epidemiological data and individual-level biological data are needed to control the coronavirus disease 2019 (COVID-19) pandemic. Population-level data are widely available and efforts to combat COVID-19 have generated proliferate data on the biology and immunoresponse to the causative pathogen, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). However, there remains a paucity of systemized data on this subject.

Objective: In this review, we attempt to extract systemized data on the biology and immuno-response to SARS-CoV-2 from the most up-to-date peer-reviewed studies. We will focus on the biology of the virus and immunological variations that are key for determining long-term immunity, transmission potential, and prognosis.

Data Sources and Methods: Peer-reviewed articles were sourced from the PubMed database and by snowballing search of selected publications. Search terms included: "Novel Coronavirus" OR "COVID-19" OR "SARS-CoV-2" OR "2019-nCoV" AND "Immunity" OR "Immune Response" OR "Antibody Response" OR "Immunologic Response". Studies published from December 31, 2019 to December 31, 2020 were included. To ensure validity, papers in pre-print were excluded.

Results: Of 2 889 identified papers, 36 were included. Evidence from these studies suggests early seroconversion in patients infected with SARS-CoV-2. Antibody titers appear to markedly increase two weeks after infection, followed by a plateau. A more robust immune response is seen in patients with severe COVID-19 as opposed to mild or asymptomatic presentations. This trend persists with regard to the length of antibody maintenance. However, overall immunity appears to wane within two to three months post-infection.

Conclusion: Findings of this study indicate that immune responses to SARS-CoV-2 follow the general pattern of viral infection. Immunity generated through natural infection appears to be short, suggesting a need for long-term efforts to control the pandemic. Antibody testing will be essential to gauge the epidemic and inform decision-making on effective strategies for treatment and prevention. Further research is needed to illustrate immunoglobulin-specific roles and neutralizing antibody activity.

1. Introduction

In December 2019, clusters of pneumonia of unknown etiology were observed in Wuhan City, Hubei Province of China, and reported to the World Health Organization.[1] Initial sequencing discovered the pathogen to be a novel coronavirus, later named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—the causative agent for coronavirus disease 2019 (COVID-19). By March 7, 2020, a total of 100 000 COVID-19 cases worldwide had been reported.[1] Globally, as of 5:45 pm CEST, October 22, 2021, that number has reached upwards of 242 million, including 4 927 723 deaths, reported to WHO.[2]

SARS-CoV-2 retains genetic similarity to both severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), the two previous zoonotic coronavirus emergences.[3] Similar to most RNA viruses, this group has shared characteristics of high recombination rate and variability, thereby maximizing the potential for spread.[4] Additionally, like both SARS-CoV and pandemic influenza strains, age and presence of comorbidities have been identified as risk factors for severe clinical presentations.[3-4]

Varying immunological responses have been observed across patients with severe versus mild or asymptomatic presentations of illness and across varying periods of the disease after diagnosis.[5-11] A

* Corresponding author: shalsnair11@gmail.com.

https://doi.org/10.1016/j.glohj.2021.11.005

continuing question is the likelihood of severe adverse outcomes from infection in immunocompromised individuals, in combination with emerging evidence of poor immune response generated from COVID-19 vaccination in this population.[12] Recent studies suggest that natural infection in the immunocompromised may present a risk of prolonged viral replication, intra-host evolution of variants, and overall poor clinical outcomes.[12] Along with immunosuppression, impaired immunity in older age has also been a topic of investigation prior to the onset of the COVID-19 pandemic, and has formerly revealed reduced antibody proliferation in response to variety of vaccines.[13] As the causative agent continues to evolve and mutate in the absence of sufficient global vaccination coverage, understanding of immunoresponse to the pathogen remains a crucial foundational tool in the creation or application of preventive and treatment-side measures to manage the pandemic.

A pandemic like COVID-19 can spread to a large country in days[14-15] and to the whole world in a few months.[16-17] Controlling a pandemic becomes increasingly challenging as economies become more globalized.[15,18] Epidemiological data at the population level are often collected immediately after an outbreak is detected. Typical data include daily and cumulative incidences, incidence and prevalence rates, hospitalization and death counts, and case fatality and mortality rates. In addition to aggregate epidemiological data, knowledge on the pathogen and the human immune response is essential for anti-epidemic planning and decision-making in all countries across the globe. Such knowledge comprises the foundation on key issues such as method selection to monitor the epidemic, vaccine development to protect the vulnerable, and therapeutic innovation to treat the infected. Global efforts have generated a large number of studies on the biology of SARS-CoV-2 and human responses to the pathogen. In this review, we attempted to summarize the findings that are key to policies and decision-making for COVID-19 prevention, control, and treatment.

2. Methods

Articles were identified through an electronic search of the database PubMed. The key words used for electronic search were: “Novel Coronavirus” OR “COVID-19” OR “SARS-CoV-2” OR “2019-nCoV” AND “Immunity” OR “Immune Response” OR “Antibody Response” OR “Immunologic Response”. Only peer-reviewed articles published in English during the study period from December 31, 2019 to December 31, 2020 were included. Articles that were not peer-reviewed, published in other languages, or not within the study period were excluded. With information from the articles obtained through the electronic search, a snowballing method was used to identify papers manually from all other databases, such as Google Scholar and Web of Science. Fig. 1 illustrates the methodological process of the literature search.

The primary literature search was conducted in October 2020 and subsequently repeated in February 2021 to ensure inclusion of the most up-to-date articles prior to the submission of this manuscript.

The identified articles were first screened to exclude duplicates and non-peer reviewed manuscripts (i.e., pre-print). Of the remaining articles, those indicated by title as irrelevant to the virology and immunoresponse of SARS-CoV-2 were excluded. Abstracts of remaining articles were reviewed and those deemed non-relevant to the search were excluded based on the following criteria: inadequate sample size (< 25), relevance (non-empirical and/or non-relevant topic area), or quantity of isotopes evaluated (< 2). Articles evaluating only a singular immune isotope or isotope assay were excluded due to their limited ability to draw comparisons or conclusions related to implications of the immune response or usefulness of assay testing.

Articles that were finally confirmed to be eligible via full-text review were included in the qualitative synthesis. Neither of the authors was blind to the journals, authors, or institutional affiliations of the included articles.

3. Results

Of the total 2 889 papers derived, 36 that met the inclusion criteria were included. The results were grouped by topic area as follows: genetic characteristics,[19-20] pathogenesis[5-11,19,21,] infection process,[19,21] seroconversion time,[6,8,10-11,22-30] clinical presentation,[6-7,9-11,31-35] lasting immunity,[5,7,34,36-42] and diagnostic relevance of antibody-based assays.[7,9,11,24-26,38,43-47] Between these groups, a total of 14 articles[5-11,19,21,24-26,34,38] spanned two or more topic areas and the remaining 22 were unique to a given subtopic.

3.1. Genetic characteristics

SARS-CoV-2 retains two distinct characteristics from previously documented coronaviruses including severe acute respiratory syndrome (SARS-CoV) and Middle East respiratory syndrome (MERS-CoV). First, entry of SARS-CoV-2 into the host cell is mediated by its distinctive S glycoprotein (spike protein) which binds to receptors primarily located in the epithelial tissue of the nose, mouth, and lungs.[19] Like its predecessors, SARS-CoV-2 exhibits a receptor binding domain (RBD) that has high affinity for the angiotensin-converting enzyme 2 (ACE2) receptor in humans.[20] Despite this affinity, analyses predict that the interaction between the ACE2 receptor and the binding domain is still not ideal. This evidence suggests the unique RBD sequence of SARS-CoV-2 arose via natural selection in pursuit of optimal binding.[20]

Second, SARS-CoV-2 demonstrates acquisition of a polybasic cleavage site and O-linked glycans at the junction of S1 and S2 subunits of the spike protein. These additions are unique to SARS-CoV-2 and previously unseen in other lineage B betacoronaviruses such as SARS-CoV.[20] In MERS-CoV, efficient cleavage of the spike protein allows for transmission of the virus from bats to humans.[20] The function of these mutations in SARS-CoV-2 is currently unclear, however potential ramifications have been suggested related to increased viral transmissibility and pathogenesis within animal models.[20]

3.2. Pathogenesis

SARS-CoV-2 could be the most transmissible of the three documented coronaviruses, with an estimated R_0 of approximately 2.2 (95% *CI*, 1.4 to 3.9).[19] Additionally, like past epidemic coronaviruses and pandemic influenza strains, age and presence of comorbidities have been identified as risk factors for severe clinical presentations of COVID-19 after infection.[19,21] Unique to SARS-CoV-2 is the presence of significant viral shedding prior to the onset of symptoms, which has differential impacts compared to its predecessors in regard to transmission.[21]

Given its novelty, understanding of the pathogenesis of SARS-CoV-2 is limited. However, related knowledge has been accumulated rapidly, including findings on immunological responses that reflect pathogenesis across patients with severe versus mild or asymptomatic presentations of illness and across varying periods after illness onset.[5-11] Based on previous work, Cevik and colleagues[21] summarized the pathogenesis of SARS-CoV-2. According to this study, pathogenesis consists of 10 steps: binding of SARS-CoV-2 to the ACE2 receptor and viral entry, viral genome release, genome translation, proteolysis, replication of viral RNA, transcription and replication of the viral genome, translation of viral proteins, viral assembly, virus maturation, and finally, virus release.

3.3. Infection process

After entry into the host cell, SARS-CoV-2 activates the T-cell response. This results in recovery for most asymptomatic or mild cases.[21] However, a dysregulated immune response has been observed in patients who develop severe forms of illness.[21] Outcomes have been shown to also be influenced by such factors as age, sex, obesity, cardiovascular diseases, and other pre-existing conditions.[21]

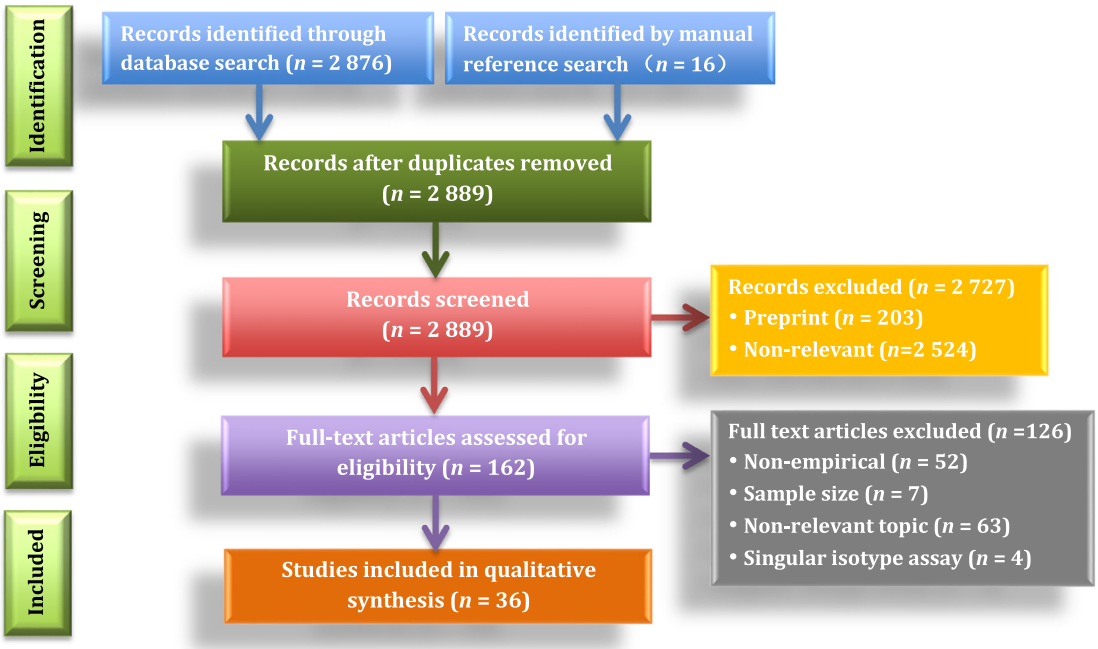

Fig. 1. PRISMA flow diagram detailing the database search by records identified, screened, and full text records evaluate in the review.

Data from these studies indicate that manifestations of COVID-19 range from entirely asymptomatic to acute respiratory failure, with an average time from infection to symptom onset of approximately 5 days.[19] The primary mechanism for person-to-person transmission is via respiratory droplets.[21] Peak of viral load within the respiratory tract is observed within the first week after infection, followed by a progressive decline.[21] The very high viral load during the early stage of the infection with no significant clinical symptoms greatly increases the likelihood for an infected person to pass the virus to a vulnerable subject who has not been infected yet.

3.4. Seroconversion time

IgA, IgM, and IgG are the three routinely identified markers of humoral responses to an infection. Seroconversion time presents a key parameter to detect infection using antibody assays. Results comparing serum neutralizing antibodies have shown IgA may contribute more to the early neutralizing response than IgG,[22] in addition to being a more stable marker than IgM.[23]

With regard to SARS-CoV-2, a total of 6 studies reported median time to seroconversion for IgA, IgM, IgG, or total Ab.[6,10-11,24-26] The earliest observed median time to seroconversion was for IgA and IgM at 5 days post-onset. IgG had a uniformly later median seroconversion at 12–14 days, aside from one outlier at 4 days. Significantly fewer studies reported on total Ab assays, but these showed a median seroconversion of 11–15 days.

Results in Fig. 2 suggest that, overall, both total Ab and isotype-specific levels tend to markedly increase between one- and two-weeks post-onset of symptoms.[10-11,27] However, early evidence has indicated that increases in antibody levels may not correlate with viral clearance in some patients.[8,11,28-29] Patients may either continue to produce detectable levels of virus while convalescing, or alternatively achieve viral clearance before entry into the convalescent stage.[8,11] New evidence suggests that this prolonged viral shedding may be more common in recovered patients with low antibody titers.[30]

3.5. Immunoresponse as related to clinical presentation

Magnitude of antibody response has been suggested as a possible indicator of clinical severity. In patients with severe disease, relative levels of Ab, IgA, and IgG antibodies were significantly higher than those seen in non-severe cases.[7,9,11,31-33] These higher antibody levels have been identified as being correlated with male sex, older age, and hospitalization.[34] The timing of response may be partially determined by factors such as age or pre-existing conditions.[35] This elevated effect was most commonly observed 2 weeks after symptom onset. [6,11]

While the role of serum IgA has not been fully explored, previous research has suggested a possible mediation of pro-inflammatory responses, which has the potential to instill further damage in cases of severe COVID-19.[10] The observation of reduced inflammatory response and low circulating cytokine and chemokine levels in asymptomatic individuals with low overall Ab titers is supportive of this hypothesis.[7] Similar to the pathogenesis of SARS-CoV, these findings suggest that high antibody titers may possibly confer antibody-dependent disease enhancement effects (ADE).[11] Based on what is known about commonly seen organ impacts of COVID-19, there is potential that severe disease is at least partially mediated by IgA.[10]

3.6. Lasting Immunity

One critical issue in question is whether IgM and IgG are indicative of neutralizing antibody response. In patients with acute COVID-19 infection, neutralizing responses have been shown as directly correlated with antibody titers—a promising indication of some degree of protective immunity following infection with SARS-CoV-2.[34, 36-39] However, the length of this immunity remains in contention. Long et al. [7] reported that within an 8-week period post-discharge, 40.0% of asymptomatic individuals had converted to seronegative, in comparison with only 12.9% in the symptomatic group.

The reported findings are consistent with previous studies demonstrating a more robust humoral response in severe versus mild or

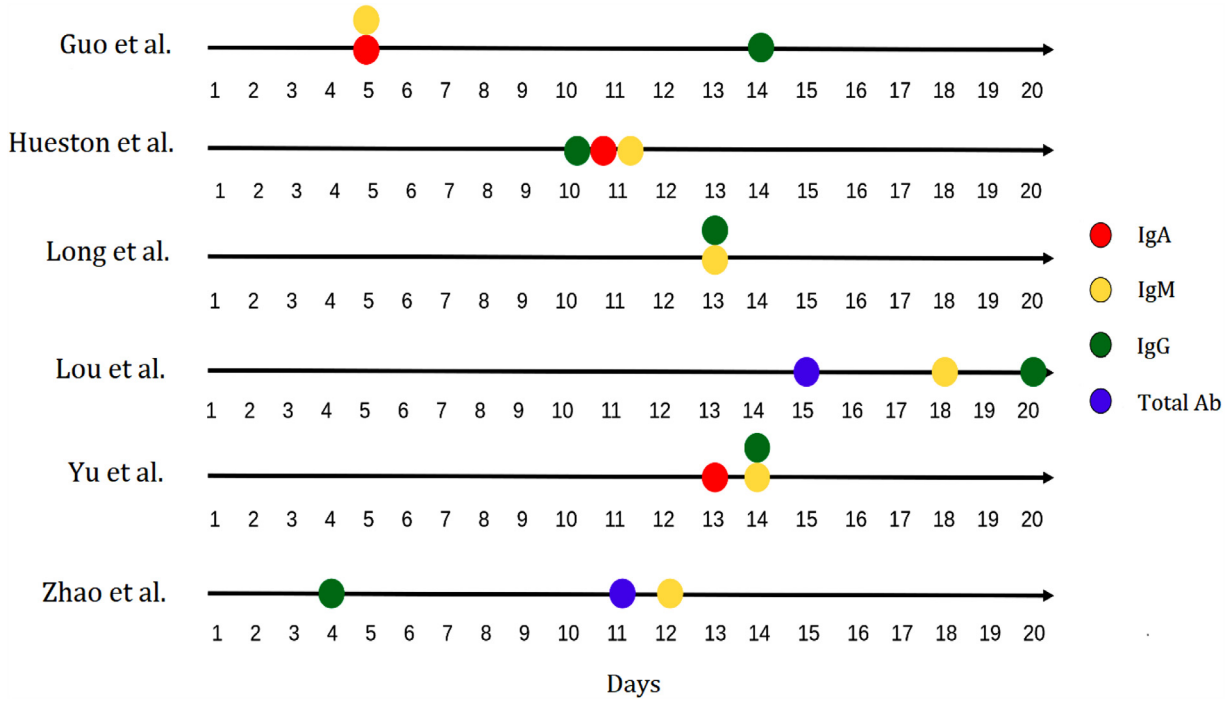

Fig. 2. Reported median times to seroconversion for individual isotypes and joint antibody measures after infection with SARS-CoV-2.

asymptomatic COVID-19 cases.[40] Further quantifying this relationship, Ibarrando et al.[5] estimated IgG to have an approximate half-life of 36 days. As compared to length of detection of IgG levels for MERS-CoV and SARS-CoV, findings of this study suggest a shorter period of conferred immunity (approximately 3 months) to SARS-CoV-2.[5,40-41] Studies have also shown that antigen binding strength and robustness of the immune response can be affected by age of infected patients.[42]

3.7. Diagnostic relevance

It has been accepted as standard practice that antibody assays should not be used alone to assess infection with SARS-CoV-2.[9] This is based on the assumption that the innate immunity mechanism by which individuals achieve viral clearance may be independent of an antibody response. Collective evidence asserts that the use of antibody assays in complement to traditional RNA testing has the potential to supplement shortfalls.[11,24,26,43-46] Individuals with undetectable levels of viral RNA who were thereby ruled negative via nucleic acid tests (NAT), were identified using Ab testing or a combination of the two with significantly higher accuracy than NAT alone in the early stages of infection.[11,47] Long et al.[7] further validated the ability of Ab testing to detect true positives originally missed by traditional RT-PCR.

In an evaluation of IgM specifically, the detection rate of qPCR remained most effective within 5.5 days of symptom onset, whereas enzyme-linked immunosorbent assay (ELISA) shifted ahead at later timepoints.[24] Considering the established role of IgM as the primary indicator of acute infection, this is not a surprising result. PCR positive rates beyond 3 days post-onset were found to decline dramatically to under 80%.[24] However, this decrease in detection was alleviated through the application of IgM ELISA to PCR negative cases.[24] This time-dependent efficacy remained consistent in findings on IgG assays as a proxy for neutralizing effects and is reasonable if under the assumption that viral load decreases inversely to antibody titer.[38] Overall, findings demonstrate high sensitivity and specificity of IgA, IgM, and IgG assays as complementary tools to diagnose COVID-19.[25]

4. Discussion

In this study, we reviewed and extracted information from a list of 36 of the most up to date peer-reviewed articles addressing the biology, immune response, and use of antibody assays for diagnosing SARS-CoV-2. Findings of this study provide data unique to the understanding of the virus and human immunoresponse to the pathogen. Such findings are of fundamental importance for policy formation and decision-making to control the COVID-19 pandemic and to prevent future emerging epidemics.

Overall, immunological response to SARS-CoV-2—the pathogenic agent of COVID-19, is similar to that from infection by other pathogenic coronaviruses. While diagnostic and immunity approaches may be informed by levels of IgM and IgG, a better standard for understanding the pathogenesis of SARS-CoV-2 may rely on additional investigation into the role of IgA and the pathophysiology of the inflammatory response. This issue must be considered in decision making for prevention and control.

The growing body of evidence supports the premise that increased antibody titers have the potential to be a prognostic indicator for severe infections with SARS-CoV-2. Additionally, the presence of a more robust immune response for patients with more severe infection appears to confer a slightly extended period of antibody maintenance. Whether or not this causally relates to the circulation of neutralizing antibodies, and therefore immunity from reinfection, is an area requiring further investigation.

Beyond the scope of this review, the cellular immune response may also play a crucial role in determining the clinical course of COVID-19. The induction of SARS-CoV-2 specific T cells may have implications on the pathogenesis of the virus, as well as be a key indicator of long-term protection. Current evidence suggests that depletion or early dysregulation of the T cell response is correlated with disease severity and viral load during acute infection.[48-49] Notably, the T cell response has been cited as a potential mechanism for protection against severe infection in children.[48] Additionally, presence of T cells targeted towards the SARS-CoV-2 spike protein have been shown to be correlated with serum IgG

and IgA titers and found in patients who have recovered from COVID-19 infection.[49] Similar to the humoral response, the extent to which the cellular response provides durable protection against the virus remains unknown to this point. Additional research into the mechanisms by which T cells regulate clinical course and impact long-term immunity is recommended.

Weak immunoresponse and lack of effective treatment represents another challenge to planners and decision-makers. As of now, treatment options for COVID-19 remain as broad categories of antivirals, IL-6 inhibitors, and convalescent plasma, necessitating more evidence from clinical trials before establishment of a recommended regimen.[50] Strategically, development of effective anti-viral agents specific to SARS-CoV-2 will be essential, as existing mainstream treatments have shown limited efficacy.[50]

Based on the evidence synthesized in this study, serological testing is proposed to be an objective, powerful, and expedient tool for both supplementing traditional diagnostic tests, as well providing crucial insight into the eventual progression of the disease at an individual level.[46,51] Not only would this data deepen our understanding of the epidemiology of COVID-19, but also support evidence-based decision-making to mobilize resources and organize activities for testing, tracing, and patient treatment.[51-52]

Per the current recommendations, guidance from both the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) in the United States (U.S.) warn against the use of serologic testing alone to establish active infection.[53-54] Following CDC's guidance, implementation of a combined approach should be the strategy for surveillance and forecast for policies and regulations related to isolation and quarantine.

The approval of emergency use of multiple COVID-19 vaccines including those from Pfizer, Moderna, and Johnson & Johnson is a significant breakthrough in controlling this pandemic. However, in addition to growing concern regarding vaccine hesitancy and equity, data on length of antibody resilience from vaccination remains to be determined. Consistent with evidence from our study, the U.S. CDC estimates that immunity may last for approximately 90 days after onset of the first naturally acquired infection.[53] Recent data from vaccine trials suggests vaccine-conferred immunity of at least six months.[55] Continued study on the durability of the vaccine response along with increased concern of variant evasion suggests a potential future need for routine vaccination for COVID-19.[56] To manage the pandemic, we require serological testing as a strategic measure to bolster surveillance and to inform treatment and prevention. In our views, future studies may target the use of antibody testing as a foundational strategy for public health and anti-epidemic response.

5. Conclusion

This review provides a novel synthesis of biological-level data much needed for evidence-based policy and action to manage and control the ongoing pandemic. Conventional approaches focus on social distancing, masking, isolation, and treatment. Based on the evidence of this study, global policy should re-orient back to a focus also inclusive of diagnostic and prognostic tools as key components of the surveillance and mitigation strategy. Adoption of an antibody-supplemented surveillance strategy, particularly in countries or regions lacking sufficient vaccination access or coverage, offers an opportunity for more accurate forecasting of the current state of COVID-19 to inform resource needs and preventive action. With the rapid progress in biological research on COVID-19, new studies are anticipated to supplement our findings in this study. Ultimately, this research is crucial for effective control and prevention of COVID-19 as well as emerging pandemics in general.

There are limitations to this study. This study is limited to papers published between December 31, 2019 and December 31, 2020. New studies on the same subject continue to emerge and these are not included in this review. Limiting the search to papers published in English only may have missed relevant papers published in other languages. Given the evolving nature of research on COVID-19, it is possible that data from selected articles have been amended following the publication of this manuscript. Lastly, this review did not span evidence relating to the cellular immune response and the potentially important role of T cells in steering the clinical course of SARS-CoV-2 infection and treatment. Future studies should seek to better understand this function.

Despite the limitations, we confirm the accuracy of the information synthesized in this study and advocate for the importance of these findings in guiding global health policy related to COVID-19 and future emerging infectious diseases. We will continue our effort with this line of instrumental studies and synthesize new findings to support the global efforts to end the COVID-19 pandemic.

CRediT authorship statement

Shalini Nair: Conceptualization, Methodology, Formal analysis, Writing—Original draft. **Xinguang Chen:** Writing—Review & Editing, Supervision.

Consent for publication

All authors provide consent for the final accepted version of the manuscript to be considered for publication in *Global Health Journal*.

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Submission declaration

This paper has not been published and is not under review for publication consideration elsewhere.

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