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.

Travel Medicine and Infectious Disease 37 (2020) 101785

Contents lists available at ScienceDirect

Travel Medicine and Infectious Disease

journal homepage: www.elsevier.com/locate/tmaid

Serologic testing of coronaviruses from MERS-CoV to SARS-CoV-2: Learning from the past and anticipating the future

The recent emergence of the Coronavirus Disease 19 (COVID-19) had caused a global pandemic with significant impact on healthcare system. Similar to acute infection with the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), infection with SARS-CoV-2, causative agent of COVID-19, is associated with asymptomatic infection [1]. Testing for MERS-CoV and SARS-CoV-2 is currently dependent on molecular testing (rt-PCR). There were multiple generation of molecular tests that were developed over the proceeding few months in an effort to improve the sensitivity and specificity. However, there is a global shortage of molecular tests for SARS-CoV-2 with expanding scope of testing in many countries to identify cases for the isolation and application of quarantine measures. For serologic diagnosis of MERS-CoV and SARS-CoV-2 infections, the identifications of antibodies require both acute and convalescent serum sampling. This is particularly important as we witness an increased number of asymptomatic or pre-symptomatic COVID-19 infections. It is understandable that such serologic tests are not performed routinely to diagnose respiratory viral infections. However, it is not known if asymptomatic individuals are able to mount an antibody response. Serologic testing enables us to understand the extent of the tip of the iceberg (death rate) as we detect more asymptomatic individuals.

Serologic testing enables policy makers to make informed scientific decisions regarding the resumption of usual life and lifting social distancing and lockdown of cities especially if we have the 50–60% seroprevalence which is taken as a signal of herd immunity.

Serologic tests will enable the healthcare community to understand the extent of the infection as well as be an important tool to identify those who are already immune such as healthcare workers (HCWs). Identification of immune HCWs would allow those to go back to work. In addition, serology would be particularly important to assess the effectiveness of any vaccines.

The development of serologic tests requires better understanding of the SARS-CoV-2 structure, and the immunologic response to the virus. The most appealing site for such antibodies is the Spike (S) protein of the SARS-CoV-2. However, there are multiple parts of the S-protein and it is not clear which part of this protein offers the best site for antibody development [2]. It is also important to make sure that these antibody tests are unique and do not cross react with widely distributed common cold coronaviruses or MERS-CoV in areas of its endemicity. One study of such patients showed cross-reactivity with the SARS-CoV S and S1 proteins, and to a lower extent with MERS-CoV S protein, but not with the MERS-CoV S1 protein [3]. An excellent serologic test would be 100% sensitive and 100% specific especially for measuring SARS-CoV-2 S and RDB IgA, IgG, and IgM antibodies.

Having a helpful serology requires that we know that such antibodies are specific, confirm a long-lasting immunity and know how these antibodies protect against infection to avoid a false sense of security in relation to infection. An additional area of concern is the need to have a diagnostic stewardship as these tests will not be helpful in the diagnosis of acute COVID-19 infection. An early study of SARS-CoV-2 patients showed the presence of IgM antibodies at day 0 (the day of first sampling) and day 5 in 50% (8/16) and in 81% (13/16), respectively. In addition, IgG antibodies were detected in 81% (13/16) and 100% (16/16) of patients over the sampling time, respectively [4]. Additionally, the presence of IgM was detected in other studied patients [5]. The seroconversion was said to occur in 2 weeks in one study [3]. The S1 IgG and IgA ELISAs had lower specificity with variable sensitivity and that IgA ELISA had higher sensitivity [3].

In a study of contacts of a patient with mild symptoms, evaluation of IgM and IgG antibodies against SARS-CoV-2 was analyzed by immunofluorescence assays (IFA) based on Vero E6 cells. In the index patient IgG and IgM were undetectable on day 4 after onset of symptoms, however, IgG titers were 80 and 1280 and those of IgM were 80 and 320 on days 9 and 20, respectively [6]. None of the 19 healthcare contacts were positive [6]. In another study, the detection of antibodies was possible on days 3–42 for IgM and on days 5–47 for IgG [7].

There are few studies addressing serology to different SARS-CoV-2 antigens. One study of three patients, antibodies were detected against S1 subunit and RBD, and only two patients had detectable antibodies to the N-terminal (S1A) domain [3]. Serologic testing may facilitate the diagnosis of SARS-CoV-2 infection in families. One study showed a family cluster of COVID-19 among 5 of 6 members by serology vs. 2 members based on PCR testing [8].

Looking back at the lessons we learned from the MERS-CoV serology, we could deduce few similarities and differences with SARS-CoV-2. In family contacts of MERS-CoV cases, serologic analysis showed that of 280 contacts, 19 (6.7%) had positive recombinant enzyme-linked immunosorbent assay (rELISA) S1, 6 (2.1%) had positive recombinant immunofluorescence assay (rRIFA) full S, and only 4 (1.4%) had positive plaque-reduction neutralization testing (PRN) [8]. However, a follow up samples 2–6 months later showed serologic positivity among 44 samples of 5 (11.4%), 2 (4.5%), and 1 (2.3%) using rELISA, rRIFA, and PRN, respectively [9]. This study showed the following: subclinical transmission in the families, a minority of contacts had positive serology and a fraction had persistent antibodies months after infection. Currently, we do not have studies of SARS-CoV-2 serology extending overtime to document the persistence of these antibodies.

An area where serology would be beneficial is surveillance and this is

https://doi.org/10.1016/j.tmaid.2020.101785
Received 21 April 2020; Received in revised form 17 May 2020; Accepted 8 June 2020
Available online 10 June 2020

an awaited step to understand the epidemiology of SARS-CoV-2 infection. However, for MERS-CoV there was a nation-wide serosurviellance study in Saudi Arabia. That study examined the serologic response in 10,009 individuals and showed that anti-MERS-CoV antibodies were confirmed in 15 (0·15%; 95% CI 0·09–0·24) [10]. There is a large variation in the diagnostic capabilities of different serologic assays in different laboratories and it was recommended that laboratories use a testing algorithm including >2 tests to ensure correct diagnosis of MERS-CoV [11]. In addition, MERS-CoV S1 protein-based ELISA was used for surveillance studies and was found to have a low sensitivity in detecting infection in PCR-confirmed patients with mild clinical symptoms [12]. Although, patients with mild MERS-CoV infection as detected by PCR tests had seroconversion, not all of them had detectable levels of virus-neutralizing antibodies [12]. This may indicates that the presence of anti-MERS-CoV antibodies might not indicate immunity.

Thus, currently the evidence for the use of serologic testing of SARS-CoV-2 is not optimal. These tests are subject to variability in sensitivity and specificity, differences in the timing of the appearance of antibodies, and whether these antibodies confirm protection is not known. This is particularly important when making decisions about HCWs who might be at risk of contracting SARS-CoV-2.

CRediT authorship contribution statement

Jaffar A. Al-Tawfiq: Conceptualization, Data curation, Formal analysis, Methodology, Writing - original draft, Writing - review & editing. **Ziad A. Memish:** Methodology, Writing - review & editing.

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