Learning from SARS and MERS: COVID-19 reinfection where we stand?

Jaffar A. Al-Tawfiq [1,2,3*], Ali A. Rabaan[4], Awad Al-Omari[5,6], Abbas Al Mutair[5,7], Manaf Al-Qahtani[8], Raghavendra Tirupathi[9,10]

[1]Specialty Internal Medicine and Quality Department, Johns Hopkins Aramco Healthcare, Dhahran, Saudi Arabia, [2] Division of Infectious Diseases, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN, USA, [3] Division of Infectious Diseases, Department of Medicine Johns Hopkins University School of Medicine, Baltimore, MD, USA; [4]Molecular Diagnostic Laboratory, Johns Hopkins Aramco Healthcare, Dhahran, Saudi Arabia,; [5]Research Center, Dr. Sulaiman Al Habib Medical Group, Riyadh, Saudi Arabia; [6]College of Medicine, Alfaisal University, Riyadh, Saudi Arabia; [7]Wollongong University, Australia; [8]Bahrain National Taskforce to Combat COVID-19, Bahrain Defense Force Hospital, Bahrain; [9]Penn State University School of Medicine, Hershey, PA, USA; [10]Wellspan Chambersburg and Waynesboro (Pa.) Hospitals, Chambersburg, PA, USA

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In the last 20 years, we had witnessed the emergence of the Severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV-1), initially reported from Guangdong province, China in 2002, the Middle East respiratory syndrome (MERS) coronavirus (MERS-CoV) from Jeddah, Saudi Arabia, in 2012 and SARS-CoV-2 in December 2019 in Wuhan, Hubei province in China. SARS-CoV-2 had caused an ongoing global pandemic of COVID-19 (COronaVIrus Disease-2019). These viruses are genetically related to the circulating seasonal human coronaviruses: alphacoronaviruses, NL63 and 229E, and betacoronaviruses, HKU1 and OC43. These viruses, mainly NL63 or 229E, show a seroprevalence of 75% and 65 % of children by 2.5–3.5 years of age [1]. In addition, these seasonal coronaviruses are the etiology of respiratory infection in 22-25 % of adults with acute respiratory illness [2,3]. The occurrence of reinfection with OC43 is at least partially attributed to genetic substitution in the potential cleavage site sequence of the spike protein [4].

Since the emergence of COVID-19, it has been debated and discussed whether it is possible or frequent to have reinfection. It is a real possibility and it would be a major threat to the current measures to control the COVID-19 pandemic. In a recent commentary, three questions were posed regarding reinfection with SARS-CoV-2. These questions are: how common is reinfection? how severe are reinfections? and what does reinfection mean for vaccines? [5]. A positive SARS-CoV-2 PCR after resolution of symptoms and a negative PCR may not indicate reinfection [6]. A true positive SARS-CoV-2 by PCR may indicates: persistence of non-viable RNA after the first episode, reinfection, or a relapse [7–9]. The mean time to negative SARS-CoV-2 RT-PCR was 24 days after symptom onset and 10% were positive at 33 days after symptom onset [10].

In a small study of 12 patients who had recurrent infection with common coronaviruses, the median time to reinfection was 37 weeks (4-48 weeks) and 9 of those patients had reinfection with OC43 and reinfection was milder [11]. In another study, 8.5% of 470 patients had reinfection with new or the same coronavirus was 566 and 676 days, respectively [12].

SARS pandemic was controlled easily and did not extend in time. Thus, it might had not been possible to examine weather reinfection is a real possibility or not. Despite, the extended occurrence of MERS-CoV cases since 2012, there is no clinical data on MERS reinfection. In a rabbit model, reinfection was associated with enhanced pulmonary inflammation, without an increase in viral RNA titers [13].

In a rhesus macaque model of SARS-CoV-2 infection, a rechallenge with an identical SARS-CoV-2 strain in the early recovery phase was not associated with viral dissemination, clinical manifestations, or histopathological changes [14]. However, the study did not look at a different strain and did not examine the possibility of reinfection months after initial challenge as the reinfection was done at day 28 of the first infection [14].

There are few studies showing that positive SARS-CoV-2 continues 20–22 days from onset of symptoms and few patients may have positive results up to 44 days [15–17]. A pregnant woman had positive SARS-CoV-2 PCR up to 104 days after the initial infection [18]. In one case series, asymptomatic patients had repeat positive RT-PCR 5- and 13-days post negative testing [7].

In one study, there were three patients who were proposed to have been reinfected [19]. The interval between the two infections was between 22 and 41 days and two patients had positive

culture at the second episode and an identified B1 (European) lineage, according to the Pangolin classification [19,20]. Another patient was classified to have reinfection three months apart. Full-length genome sequencing showed initial infection was due to a lineage B.1.1 and relapsing infection by a lineage A SARS-CoV-2 [21].

In a patient from Hong Kong, he was reported to have SARS-CoV-2 reinfection 4.5 months after the first infection [22]. He initially had symptomatic COVID-19 with cough, sore throat, fever and headache for three days and tested positive March 26, 2020. He recovered and upon travel-related screening, he tested positive as he returned to Hong Kong from Spain via the United Kingdom on August 15, 2020. He was asymptomatic and genetic analysis showed that the first infection was caused by SARS-CoV-2 strain closely related to strains from the United States or England, and the second infection was most closely related to strains from Switzerland and England with 24-nucleotide difference [22]. Sequence analysis is important in this case as it excluded the possibility of persistent or re-appearance of positive SARS-CoV-2 after initial negative test, a phenomenon that is described as intermittent SARS-CoV-2 test [23]. However, it is important to note that the two infections occurred 4.5 months apart and that the second infection was asymptomatic. In addition, the first infection was not associated with antibodies whereas the second infection elicited antibodies. An additional case of possible SARS-CoV-2 reinfection was suspected in a case from Peru [24].

Two healthcare workers were reported to have asymptomatic reinfections within 3.5 months of the first infection [25]. In these patients, the genomes revealed 9-10 unique variant differences between the virus isolates from the two episode [25]. Another reinfection was reported within 2 months in a healthcare worker [26]. One case of reinfection was thought to occur within 1

month [27]. In a case series and systematic review, a total of 1359 cases were presumed to have reactivation/reinfection [28]. This occurrence was observed in a mean days of 34.5 after initial COVID-19 infection and 5.6% had fever and 27.6% symptoms [28]. In 6 of 9 such cases, the virus was not cultured in the second infection [28]. However, these cases were more a persistent PCR positivity rather than a reinfection. In a recent case from Nevada, USA, a 25-year-old male re-tested positive for a second but distinct SARS-CoV-2 variant from the initial infection after two negative SARS-COV-2 tests [29]. The second infection occurred 48 days after the first infection and was more severe than the first infection [29]. In a patient from Ecuador, he had re-infection 10 weeks apart with two clades (B1.p9 GISAID and A.1.1 GISAID) [30].

An immunocompromised patient was thought to have two COVID-19 episodes fifty-nine days apart [31]. There were no negative samples in between the two episodes and the two strains differed at ten nucleotide positions [31]. This difference was thought to be enough to classify the second episode as a re-infection and she died 2 weeks in her second illness [31].

The duration of SARS-specific IgG was reported in 176 patients and showed that these antibodies were maintained for a mean of two years with significant reduction of titers the third year [32]. In another study of 623 SARS patients, neutralizing IgG antibodies peaked at 20-30 days and were sustained for >150 days [33]. A third study showed that SARS neutralizing antibodies appeared in the second week, peaked during week 4, and persisted in some patients for >200 days after onset of fever [34]. Additionally, one study showed that anti-nucleocapsid protein IgG antibody were positive at day 240 [35]. In a study of 56 SARS patients, neutralizing antibodies peaked at 4^{th} month after the onset of disease and were undetectable in 11.8% of

patients at month 24 [36]. In 18 SARS patients, IgG titer peaked on day 60, and remained high until day 180 and decreased gradually until day 720 [37]. Anti-SARS IgG antibodies remained positive in 17 patients at 12 months [38].

What about the response to MERS-CoV infection? There are limited studies of persistence of neutralizing antibodies after MERS-CoV infection. In one study of 7 patients, neutralizing antibodies were detectable in 86% for at least 34 months [39]. Thus, neutralizing antibodies against MERS persist for a longer duration than those reported for SARS-CoV-2.

SARS-CoV-2 antibodies decline within 8 weeks [40,41]. In addition, asymptomatic or mildly symptomatic patients may not develop antibodies. In one study, 40% of asymptomatic and 12.9% of symptomatic individuals became seronegative for IgG in the early convalescent phase [41]. Thus, it is presumed that individuals become vulnerable to reinfection over time. This has implications for building herd immunity and effectiveness of developed vaccines. However, it is important to note that antibody response is not the only immune response for protection and T-cell immune response is also important. Antibodies help in neutralizing viruses and killer T-cells help in destroying cell-infected with viruses. While neutralizing antibodies could prevent an infection from occurring, T-cells deal with established infection and facilitate a robust antibody cell response and maturation.

Thus, the data suggest that neutralizing antibodies in SARS and MERS patients last longer than those in COVID-19 patients. As expected, the developed immunity is partial and individuals could get reinfected. However, the reported cases are spare and these could not be generalized. Also, it is not known if the majority of the reinfection with SARS-CoV-2 would be of

the same, less, or more severe. These are important questions to be answered as we continue the battle against COVID-19 pandemic. The role that memory cells play is of paramount importance The recent COVID-19 vaccinations such as those of Pfizer-BioNTech, Moderna, and Oxford AstraZeneca and the race to achieve community immunity are important to end this pandemic. However, the emergence of new variants and reports of evading the immune response [42] are additional burdens on the global immunization efforts. The recently emerged variants such as B.1.1.7 variant emerged in the United Kingdom, South Africa and Brazil. For example, SARS-CoV-2 B.1.1.7 variant is thought to be more transmissible than other variants. However, there is a concern that these variants may not be covered by immune responses in relation to the currently available vaccines. Thus, reinfection with SARS-CoV-2 is possible, indicating that exposure to the virus may not translate to total immunity. Given the fact that > 111 million are infected with SARS-CoV-2, and the limited number of reported reinfections, it is not clear till now how significant of a problem this is likely to be. However, it is imperative that all individuals, whether previously diagnosed with COVID-19 or not should take identical precautions to avoid re-infection with SARS-CoV-2.

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