Review

Living with Coronavirus! Can the Immunoglobulin Report (Immunity Certificate) Help?

Tarique Hussain Ashraf, MBBS, MS Surgery*

In December 2019 from Wuhan, China, a respiratory disease emerged and soon spread to different parts of the world. It was declared a public health emergency of international concern (PHEIC) and a pandemic on 30 January 2020 by the World Health Organization (WHO).

The available test usually measures the binding antibodies and not neutralizing antibodies (NAB); therefore, we could not be sure whether these antibodies will protect against re-infection or not. However, in many viral diseases, total antibody responses usually correlate with NAB and we may consider it to be the same.

Considering the huge economic impact the pandemic has and a successful vaccine seems distant in the near future, the world needs to learn to live with corona, as the impact of joblessness, economic recession, and hunger will kill more than the virus itself.

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Coronaviruses were identified in chickens in the 1930s, and in humans it was first documented in the 1960s[1]. Up to date, 7 different types of coronaviruses in humans are known; 4 of them, namely HKU1, NL63, 229E, and OC43 are responsible for approximately 30% of seasonal flu attacks and are known as SHCV[2]. The other 3 are SARS COV, SARS COV2 and MERS; they cause severe disease in humans. Coronavirinae subfamily contains four genera Alpha-, Beta, gamma and delta coronaviruses. All novel CoVs, SARS, MERS and SARS COV 2 are Betacoronaviruses[3]. Coronaviruses are enveloped single-stranded RNA viruses with the largest known genome among RNA viruses[4]. Coronaviruses have a spherical shape with club-like projections on the virus surface referred to as "spikes". The four structural components of the virus membranes are the spike (S), envelope (E), membrane (M) and nucleocapsid (N) protein[4].

In the last 20 years, 3 novel coronaviruses SARS, MERS and SARS-COV2 have caused calamity. SARS and MERS were localized pandemics while SARS-COV2 was declared a pandemic. All the 3 are zoonotic diseases, all severely affect the lungs and the human to human transmission is via respiratory droplets and close contacts[5-7].

The characteristic features in a severely sick patient in all novel coronavirus infections were acute lung injury and acute respiratory distress syndrome (ARDS), elevated inflammatory markers in the serum, monocyte/macrophage activation, coagulation activation and high proinflammatory cytokines[8].

The aim of this review is to highlight the severity of coronavirus illness and its economic impact.

METHOD

A systematic literature search of PubMed and Embase (Elsevier) databases was performed on 8 August 2020 and updated on 9 August 2020 using the keywords "coronavirus, SARS, MERS, CoV-19, 2019-nCorona, and COVID-19" The search was also performed using the same keywords on Google Scholar, web of science to include the most recently published articles.

Studies about the prevalence of COVID-19, MERS, SARS, symptoms, preventions, economic impact, and immunity-related studies were included in this review.

All studies and news related to our objective published/ unpublished were included in the study.

A systematic review analysis was performed. Information was gathered and tabulated and comparative analysis was done between three pandemics (SARS, MERS and COVID-19).

RESULT

Three hundred one studies and unpublished data were reviewed. After removing the duplicate information, a total of 245 studies

Table 1: Comparison of MERS, SARS and COVID-19

	SARS	MERS	COVID-19
YEAR	2002	2012	2019
ORIGIN	Foshan, China	Saudi Arabia	Wuhan, China
Reservoir/ Intermediate host	Bat/palm civet	Bat/camel	Bat/pangolin
Numbers	8096	2494	>90 million
Last case	2004	Sporadic	Continues
Clinical features	Fever, cough, myalgia, sepsis, ARDS	Fever, cough, myalgia, diarrhea, ARDS	Fever, cough, myalgia, loss of taste, dyspnea, pneumonia, heart failure
Cause of death	ARDS, multisystem failure	ARDS, Multisystem failure	ARDS, heart failure
Receptors	ACE2	hDPP44	ACE2
Diagnosis			Rt PCR
Treatment	Lopinavir/ ritonavir/ ribavirin or IFN-α1 plus corticosteroids	Ribavirin and interferon alpha-2b	Dexamethasone or/and remdisivir or/and convalescent plasma therapy
Mortality	9.6	35-45	2.4
Vaccine	None	None	Clinical trial
R0	3	1	2.8-3.9

* Assistant Professor
Department of Surgery
College of Medicine King Khalid University
Kingdom of Saudi Arabia
E-mail: muhammadabidkhan@gmail.com

and unpublished material were included in this study. Out of 245, 184 (75%) were related to COVID-19 (symptoms, preventions prevalence, immunity, economic impact), the rest were regarding SARS and MERS and their comparisons with COVID-19.

DISCUSSION

COVID-19 is a respiratory disease that emerged from the seafood market of Wuhan, China in December 2109. It soon spread to different parts of the world and was declared a public health emergency of international concern on 30 January 2020. It was declared a pandemic on 11 March 2020 by the WHO[9]. The new virus was named "COVID-19" which means "coronavirus disease 2019" and it was also called SARS-CoV-2 because of its similarity with SARS[10,11]. To date, it has affected approximately 188 countries with more than 21 million cases reported worldwide and 77,462 deaths, (COVID-19 dashboard). This number may be misleading as the number of tests varies from nation to nation; some are doing much lesser tests compared to others; therefore, the real number of cases maybe 10-20 times higher as to what is being reported[12]. Usually, only symptomatic cases are being tested, while the majority was asymptomatic; therefore, these numbers might be the tip of the iceberg.

The disease is more severe in old age and in those with comorbidities: diabetes, hypertension, chronic liver disease, kidney disease, cancer, immunodeficiency and morbid obesity [13].

The disease severity also varied from nation to nation with very high mortality seen in Europe and America compared to Asian countries. Those nations having universal BCG vaccination, such as India and Pakistan are reporting lesser deaths compared to those who do not have universal vaccination (USA, Italy), as well as also those who started BCG late, such as Iran (from 1984)[14]. The CDC reports an overall case-fatality rate of 2.3%, a higher rate of 14.8% in patients over 80 years and 49% among critically ill requiring mechanical ventilation[15].

The coronavirus is a highly contagious disease with R0 (average number of people being infected by a patient) is 3.28[15]. The droplets usually fall on the ground or surface and an individual can be infected while touching the surface and then touching his/her face by the contaminated hand[16]. The virus may live on surfaces for 4 hours on copper, 1 day on cardboard, and up to 3 days on plastic and steel[17]. The virus particles may be suspended in the air for some time, usually in closed spaces and thus, it may spread as an airborne disease in closed spaces. It has also been found in stool samples; therefore, the feco-oral route may be a possible route of transmission[18].

The symptoms varied widely from asymptomatic up to 45% to mildly symptomatic to fatal pneumonia-like picture[19]. The usual incubation period is 5-6 days but ranges from 1-14 days[20]. The most common symptom is fever, dry cough, malaise, weakness, loss of smell and shortness of breath[21]. Anosmia was the presenting symptom in up to 30% of cases[22]. Eighty-one percent of infections are mild, 14% are severe which includes pneumonia, and 5% are critical, which could result in respiratory failure, septic shock, multi-organ failure and death[23].

The diagnosis depends on testing for virus particles (antigens) in the body or by antibody presence in the body. The standard method to diagnose the case is real-time reverse transcriptase Polymerase Chain Reaction (PCR) test from a nasopharyngeal swab. In this test, the RNA of the virus is converted into DNA then amplified by PCR[24]. Isothermal nucleic acid amplification tests amplify RNA directly without a need for RNA to DNA conversion; therefore, it may be a cheap and easy alternative[25].

Antibody testing may be good for community surveillance, to assess the immunity of the community and to diagnose recovered patients[26-28].

Mild to moderate diseases need just supportive treatment, such as antipyretics and/or antibiotics for prophylaxis against secondary pneumonia[29]. Those who develop dyspnea should get admitted into a hospital, as they may need oxygen and ventilators. Initially, chloroquine was claimed to be the game-changer; however, it soon lost its sheen especially when some deaths were reported due to its effect on QTC interval especially when used along with azithromycin[30]. No drug has been approved by the FDA for the treatment of COVID-19[31]. More than 300 drugs are under clinical trials and some of them are being used in different parts of the world for seriously sick patients[32]. Drugs are mainly antiviral, such as remdesivir, umifenovir , favipiravir, and immunomodulatory, such as dexamethasone, tocilizumab and interleukin-6 receptor antagonist[33,34]. Dexamethasone treatment has been recommended by the National Institutes of Health for patients with COVID-19 who are on ventilators[35]. The one therapy which has generated interest is the transfusion of convalescent plasma from a cured COVID-19 patient[36].

ACE2 is expressed in almost all organs of the body; it is abundant on surfactant producing type 2 alveolar cells of lungs and on ciliated and goblet cells of the airways and that is the reason lungs are the most affected organs[37,38]. High ACE2 expression is also observed on the intestinal epithelium, cardiac cells and vascular endothelium[38]. ACE 2 not only acts as a receptor for the virus but plays a role in controlling the infection n inflammation via ACE2/angiotensin-[1–7]/MAS system[39]. The virulence of the disease and mortality is due to the inflammatory reaction unchecked rather than continued viral replication. Approximately 20% of hospitalized patients develop significant cardiovascular morbidity and thromboembolic events[40]. Lymphopenia, cytopenia, highly elevated C-reactive protein, proinflammatory cytokines (IL-6, IL-10 and TNF-α, etc), serum ferritin, and D-Dimers are an indicator of high mortality and usually require hospitalization and intensive care support. Neurologic manifestations, such as seizure, stroke, encephalitis, and Guillain–Barré syndrome have been reported sporidacly[41].

Twenty-two treated patients of COVID-19 returned to the hospital with pulmonary fibrosis[42]. A decrease of 20% to 30% of the lung capacity in some patients who recovered from the disease has been reported[43]. Three lung transplants have been performed for fulminant pulmonary failure in post-COVID-19 patients[44]. In a study of recovered COVID-19 patients, there was evidence of heart abnormalities in 78 patients and 60 of them had signs of inflammation in the heart muscle[45]. Deranged liver function tests need further studies[46]. There have been reports of children developing picture similar to Kawasaki disease[47-49].

Wearing a facemask (surgical/homemade) plays an important role in preventing the spread[50,51]. These viruses could be killed by lipids; therefore, frequent handwashing with soap for 20 seconds or hand sanitizer with a minimum of 70% alcohol is recommended[52]. Cleaning of possibly contaminated surfaces,

such as doorknobs, steel surfaces, handles with bleach should be done to prevent infection[53]. Social distancing has to be practiced between 2 persons[54].

Protective antibodies appear after infection, but as per various reports, these antibodies disappear as early as 2-3 months after infection. These antibodies can be easily checked from the blood sample test[27]. In a small study within eight weeks of infection, antibodies were not detected in 40% of the asymptomatic patients, and 12.8% of symptomatic patients[55]. The IgG level is also important from a prognosis point of view[56]. The test available usually measures the binding antibodies and not neutralizing antibodies (NAb); therefore, it is unsure whether these antibodies will protect against re-infection[57,58]. However, usually, total antibody responses correlate with NAb and we may consider it to be the same[59].

Specific antibodies to SARS were seen in negligible quantity after 2-3 years, but memory T cells persisted 11 years after recovery; memory T cells can alter the response to repeat infection[60,61]. In a study on T-cell response to structural (NP) in non-structural protein (NSP7, NSP13) in COVID-19 convalescent patient, it was found all the patients have CD4 and CD8 T lymphocytes against NP antigen[62]. They also found memory T cell reactive to SARS COV-Np in all patients recovered from SARS even after 17 years of infection and it also showed cross-reactivity to NP of COVID-19. They also found SARS Cov2 antibodies in many patients with no history of COVID-19/SARS and with no history of any contact with any COVID-19 patient. The study also found T cells recognizing particular protein regions that are not similar to those found in the "common cold". However, they are very similar to various animal coronaviruses suggesting humans were exposed to many zoonotic diseases in the past which were not severe and they may provide some immunity against COVID-19. According to the study, the T cells formed as a result of other coronaviruses, such as SARS or other SHCVs[62].

A study in the stored blood collected between 2015 and 2018 found antibodies reactive to COVID-19, generating the hypothesis that earlier infections with the common cold coronaviruses might help protect against COVID-19[63]. Russia has announced its vaccine with a lot of skepticism amongst Western countries[64]. Approximately 20 active human clinical trials are going on around the world and the leading one seems to be the UK vaccine led by Oxford University, which has shown good results with excellent T cell and antibody response in the initial trials[65].

A domestic cat in Belgium was infected by the owner and she was symptomatic[66]. Tigers and lions in New York Zoo as well as Minks in the Netherlands have tested positive[67,68]. In a study, cats and ferrets were found to be "highly susceptible", while dogs appeared to be less susceptible; pigs, ducks, and chickens were found to be not susceptible to COVID-19[69].

Will the antibodies be effective? If yes, for how long will it provide protection? Can we rely upon memory cells? Will the antibodies in mothers protect the newborn? Will the vaccine be successful? If yes, will it need to be repeated with boosters? Will those who have recovered be considered for the vaccine when the immunoglobulins fall? Will the virus persist in the body and reappear as the immunity fades, such as herpes? Will animals be a source of infection for humans?

As compared to December 2019, 81% of nations have reported a decrease in industrial production of an average of 6% in March 2020 and decrease of 20% compared to April 2020 and December 2019. Industrial production across the globe deteriorated further in April 2020 compared to March 2020 because almost everywhere there was a lockdown. The average decrease was 15% within one month. While almost all the industries faced the same impact, motor vehicles were one of the biggest "losers"[70].

The five countries doing the worst in the trade volume of goods were South Africa, India, Mexico, France and Italy[71]. The UK economy could shrink by a record of 35% by June 2020[76]. An additional 2.9 million Americans filed for unemployment in the week ending 9 May 2020, increasing the total number of jobless claims over two months to more than 36 million[76]. Meanwhile, India's lockdown resulted in 122 million job losses in April alone[71]. On 15 April 2020, the IMF gave a warning to Asian countries that it would see no growth this year, for the first time in 60 years. China had a steep decrease in exports and data released on 16 March 2020 showed China's factory production plunged at the sharpest pace in three decades in the first two months of 2020 and the country's economic growth is expected to fall by 2.5% in 2020. The International Air Transport Association (IATA) predicted the Covid-19 outbreak could cost airlines $113 billion in lost revenue[70,71].

CONCLUSION

The world needs to learn to live with coronavirus considering the impact it has on all aspects of human life. Those who have the antibodies against COVID-19 should be considered immune to reinfection and they should be provided with immunity certificate by health authorities that should be valid across borders. Their certificates should be renewed periodically by checking the immunoglobulins every 3 months.

1. **The IgG test should be done for all high-risk groups, such as medical and paramedical staff and those having IgG antibodies should work in front as corona fighters.**
2. **Even asymptomatic individuals should go for the IgG test. In some countries about 85% are asymptomatic and those should be considered immune from the disease.**
3. **The antibody titer should be repeated every 3 months in high-risk groups and those working in crowded places like airports and stores.**
4. **Those with an immunity certificate should travel from one place to another without the need for quarantine or isolation or any other preventive measures, such as masks.**
5. **Those having an immunity certificate should be allowed to resume all sorts of activities whether in crowded or non-crowded places.**
6. **Vaccine available should be used for high-risk individuals, medics, and paramedical staff first and those having good antibodies level need not to be vaccinated.**
7. **As there is a risk of fading of antibodies, the IgG antibodies should be checked regularly and booster doses should be considered.**
8. **Those lacking antibodies or unexposed should follow preventive measures like social distancing.**
9. **Tourist places should be opened and those having immunity cards should be allowed to visit as normal.**
10. **Religious activities are an important part of the economy and should be resumed with those having an immunity certificate.**
11. **Immunity certificates should be a must for those professions requiring close contacts like barbers, mortuary staff, teachers, baby care staff, healthcare workers.**

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