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ORIGINAL ARTICLE

Optimal Selection of COVID-19 Serological Testing Kits

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Abstract:

Immunization is the ultimate objective to ensure safe return, for schools and jobs to be open. Fortunately, the government of Saudi Arabia had announced that Clinical trials for SARS-CoV-2 will start in August 2020. There is need to evaluate immune response among vaccinated individuals and recovered patients. The market is full of different commercial tests promoted for the health care providers. An accurate selection of tests is crucial specially that are approved by international authorities the FDA-CDC. By August 2020, forty-seven serology tests were authorized by the FDA-CDC under the -EAU emergency. The accuracy and reliability of the serological tests is reflected by the sensitivity and specificity of the test. However, serological testing has an inherent problem of false positive and false negative that are associated with tests. Therefore, the sensitivity and specificity values are not enough indicators for the interpretation of the results specially in variation of the prevalence rate. The positive predictive value (PPV) was calculated from sensitivity and specificity of 47 tests at different prevalence rates to show its effect on the interpretation of results at different populations. In conclusion, it is time to use serological testing for the public to return to normal life. Selecting the proper serological kit depends heavily on the specificity, more than the sensitivity, of the test and the prevalence of the disease among the group tested. In lower prevalence population use two kits to increase the PPV and reliability of the results.

Keywords: Middle East Respiratory Syndrome Coronavirus; Saudi Arabia; Quality Control.

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of a respiratory illness called coronavirus disease 2019 (COVID-19)[1]. The disease is highly contagious and, as a result, is still spreading globally. In March 2020, it was classified by the World Health Organization (WHO) as a pandemic (Figure 1). Up till now, 284,226 confirmed cases were reported in Saudi Arabia (No. 13 among the world) with 3,055 confirmed deaths (No. 30 among the world). Different countries had suffered with varying intensity. Some countries have been hit hardest such as Italy, Spain, and some parts of China[2]. Globally, governments did their best to control the disease. For example, Saudi Arabia had taken practical measures to control the spread of the disease. By July 2020, the number of reported cases went down to 5000 cases instead of more than 8000 reported cases in Sep 22, 2020 (Figure 2)[3]. Explicitly, the disease control became personal responsibility of Saudi citizens and residents.

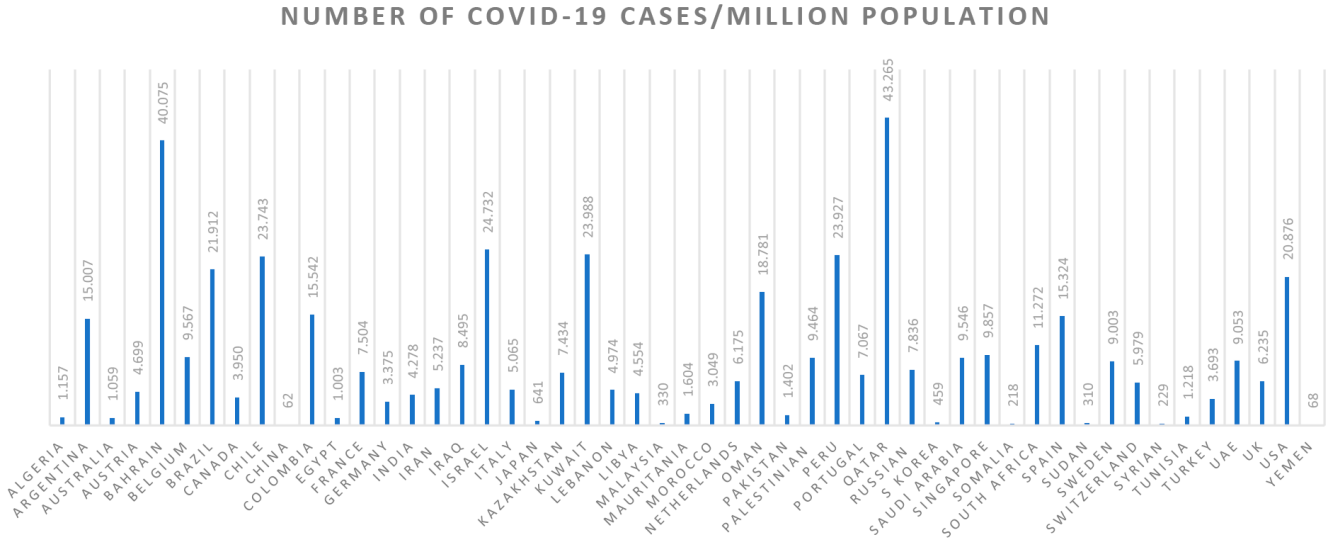

Figure 1. Number of cases per million in selected countries [5].

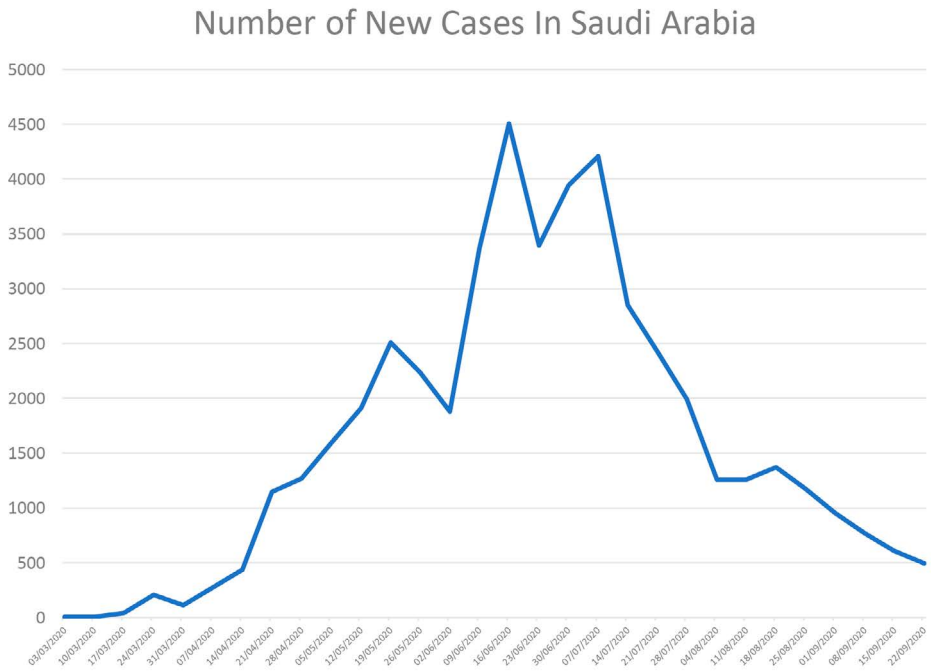

Figure 2. Number of cases reported in Saudi Arabia starting from March 3 to Sep 22, 2020[5].

COVID-19 can be controlled by accurate and rapid diagnostic tests. Molecular and serological tests are the two major categories of diagnostic tests for controlling the spread of COVID-19. Reverse transcriptase polymerase chain reaction (RT-PCR) is broadly utilized as the gold standard in diagnosing COVID-10. However, possible false negative results, precarious availability of test materials, and modifications in diagnostic accuracy over the disease course are its restrictions. Significant interest has been generated by serological tests as a subsequent or counterpart to RT-PCR in diagnosing acute infection, as few of them are easier and cheaper for integrating at the point of care. One of the core benefits of serological tests is that they can recognize individuals previously infected by SARS-CoV-2 as compared to RT-PCR. In particular, serological tests can be organized as surveillance tools for better comprehending the epidemiology of SARS-CoV-2 and possibly inform individual bias of future disease.

The efforts of the Saudi government were successful in creating an effective health care system facing the pandemic especially when looking at the number of deaths during the period from March 3 to July 12, 2020. The low death rate is also due to the effective testing programs initiated by the Ministry of Health (MOH) for the patients, people who get in contact with the patients, and suspected cases[4]. In addition to the personal responsibilities of the public, the government of Saudi Arabia had taken huge measures of providing free laboratory testing for those who are visiting healthcare centers, those who want to check themselves by calling the MOH line, and taking an appointment to the closest testing center to their residence. Since the start of the pandemic, early detection of the disease by Nucleic Acid Amplification Test (NAAT) testing was made available for patients in hospitals and medical centers, and health care facilities. Also, it was made available for the public (citizens and residents) in specific residents' centers for free in Saudi Arabia. Lab results were sent to the person's mobile number as either positive or negative. The serological testing will take place soon. By Sep 22, 2020 there were about 2,217,002 tests performed that corresponds to 63.6 tests per one thousand (Figure 3)[3].

There is a dire need to include serology to the testing algorithms in order to evaluate the degree of virus circulation in the community, and the possibility to protect patients against a re-infection. The pre-requisite performance of a serological assay will rely on

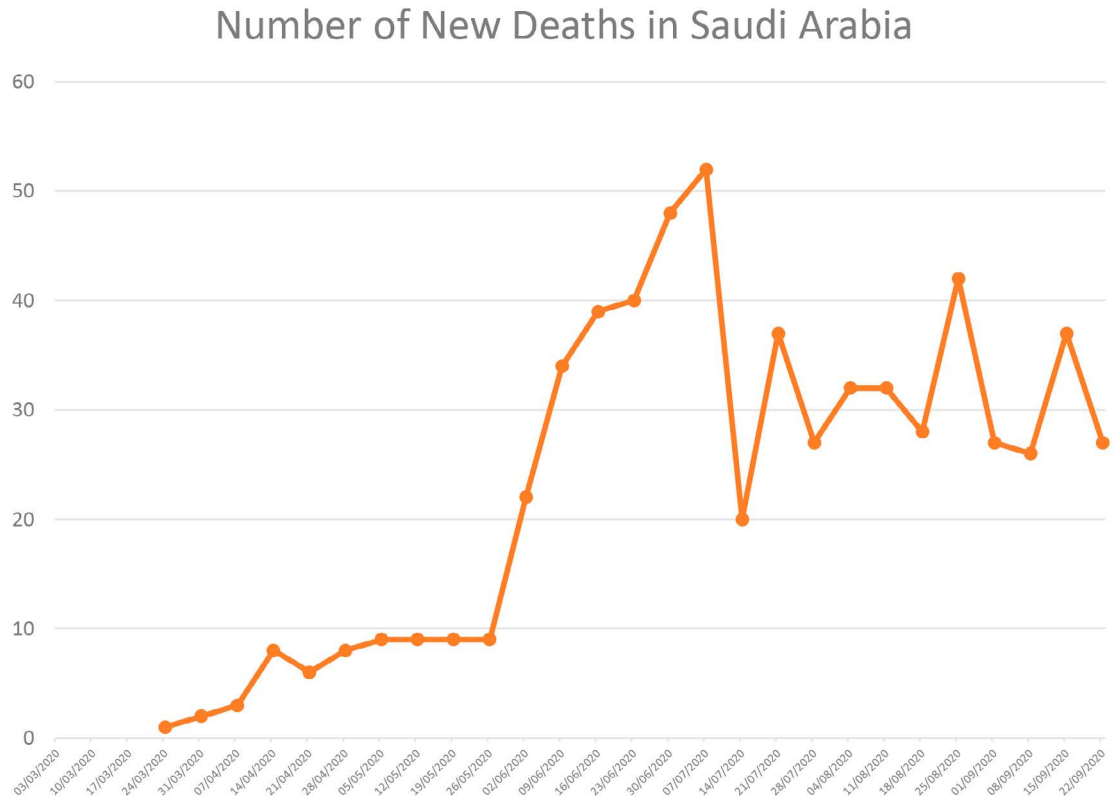

Figure 3. Number of new deaths reported in Saudi Arabia starting from March 3 to Sep 22, 2020[5].

the particular testing objective, which might be either diagnostic support or population screening[5]. Elevation in the antibodies directed against the S1 subunit of the SARS-CoV-2 and correlation of virus neutralization was strongly observed with the receptor binding domain throughout the S1 subunit. The potential of diagnosing protective antibody responses will; therefore, elevate when using either RBD or S1 antigens in the assay[6]. The specificity of serological tools might be disrupted due to the occurrence of antibodies against other circulating diseases in the population and; therefore, testing for cross-reactivity is important.

Decision-making should encompass the existing knowledge on antibody specifications, functions, and kinetics when choosing an adequate assay for a particular objective[7]. The lack of knowledge on antibody kinetics is always a challenge for validation and design of serological assays throughout the break. In both hospitalized patients and patients with mild disease, recent studies have shown that seroconversion rates captured 100% after 10-14 days in COVID-19 patients, and that antibody levels might be associated with clinical severity[8]. This is linked with insights in COVID-19, in which antibody responses differ relying on disease severity, with asymptomatic and mild infections, which result in weaker immune responses. Thereby, sufficient samples from individuals with asymptomatic and mild disease should be encompassed in validation studies for significant interpretation of serological assays and extrapolation of findings to population screening[9].

Testing

At the beginning of the pandemic, the emphasis was on detection of the disease. China was the first to develop an RT-PCR test for the SARS-CoV-2[9]. COVID-19 pandemic has created extraordinary demand, in both volume and urgency, for immediate testing. Saudi Arabia had acquired tests authorized by well-respected authorities in the world such as the CDC, the WHO, and the European commission federation authorities. The use of accurate tests is very essential for individual patients and public at large in case of public health emergency. Lab results with high false positive and false negative probabilities will contribute to the spread of COVID-19. As a result, test validation is essential to avoid spread of the disease due to false negative results.

However, the chronic problem with laboratory testing is always debatable between physicians and lab consultants when they encounter a patient who is ill and need hospitalization, but the lab result is negative or healthy individuals whom their lab results are positive. This article explains the reason for false positive and false negative results and the quality control measures that are usually taken to clear the ambiguity in lab results. An important factor that affects the NAAT is the site of specimen collection. Oro- or naso-pharyngeal swabs and sputum samples were the most appropriate samples used for NAAT testing. Virus can be detected in other body fluids in a lower percentile of patients. Virus can be detected in feces samples in 78% of patients, in the blood samples of 67% of patients, and in 56% of urine samples of patients[10,11]. However, serum is required for serological testing.

There is no release of recommendations or guidelines for the use of serological testing to determine protective immunity and infectiousness amongst patients infected with SAR-CoV-2[12]. Therefore, there is a need for more information about serological testing. Such data will shed more light on the immune response to SARS-CoV-2 and will be essential to foresee the effectiveness of vaccination. There is no agreement on the type and level of antibodies that are produced by infected individuals. Some data showed the usual immunological pattern or scenarios that IgM appears first and then followed by IgG, while other data showed the appearance of both IgM and IgG together. Moreover, the appearance of IgA is a critical factor because it is a part of the innate immunity and is more protective for viruses like SARS-CoV-2, which gets into the body through the mucus membranes of the nasopharynges. Despite the data uploaded from countries around the world, there is still need for additional data to help in determining the prevalence of SARS-CoV-2.

The detection of IgM antibodies indicates an active or recent infection while the detection of IgG often indicate a past infection. In cases where both IgM and IgG are present, both indicates that the patients are still contagious. Viral infections induced IgG antibodies provide long lasting immunity and last longer than IgM antibodies. It was not clearly established for SARS-CoV-2 yet due to the shortage of serological testing. The kits available were developed to detect IgG only, both IgG and IgM, or total antibodies. Additionally, there are serological kits that can detect IgA too. IgA is usually found at lower concentration in serum because it is known as a secretary Ab (sIgA) and found mainly in mucus secretions, including tears, saliva, and respiratory epithelium. Its presence may be the most important defense against the COVID-19.

Availability of serologic kits is important to monitor the public immune response to the COVID-19

pandemic. The performance of the assays is monitored by the MOH. The serological tests available in the market can be found as IgG, IgM, IgA or combined IgG and IgM. The S1 and N-proteins are the common targets. A local study showed a significantly strong correlation between IgG response against S1 and N. This study had suggested that both assays could be used for the evaluation of the immune status of the general population[13]. It is believed that the seropositivity means immunity against SARS-CoV-2 and they are not susceptible to the disease and can return to work safely without the fear that they will spread the disease or get re-infected.

As of August 2020, forty-seven antibody tests were approved by the US-FDA under emergency use authorizations (EUA). Additional antibody kits are expected to be approved in the future. Those kits will be used in hospitals and examination centers and their sensitivity and specificity were established by manufacturers to be watched for further validation due to the variations in the prevalence rate. PPV value established by the FDA was calculated at 5% prevalence rate. However, the prevalence of COVID-19 varies widely (1-15%) and may reach 30-50% in different areas or populations[10].

That assumption and the social demand for opening will add more pressure for immunologic screening and as a result seropositive individual may have false sense of protection while they may get infected and contribute to the spread of the disease, and may cause a second wave of SARS-CoV-2 infection.

This paper will concentrate on the serology tests that granted the permission by the US-FDA-EUA (by August 2020), but were not given full approval; and were used due to the need for screening[14]. Those tests are now available in the market, but there is a need for review of their results because they have limited information about their efficacy (sensitivity and specificity). The sensitivity and the specificity provided from the company's laboratory experiments showed very limited number of subjects. Afterward, the predictive value of positive results (PPV) and the negative predictive value (NPV) were calculated at 5% prevalence rate.

Effect of Prevalence Rate on Lab Result Interpretation

Observing the attack rate (from which we can calculate the prevalence), it is possible to identify a vast difference in the prevalence from country to country and from city to another and even within cities. Therefore, a lower COVID19 attack rate will result in a lower prevalence of less than 1% to 5%. Therefore, it will result in more people compliance with government recommendations. This low prevalence had led to concentrate on the population immune response. Since the prevalence of COVID-19 is not determined yet, the prevalence values of 1%, 5%, 10%, 15%, 20%, 30%, and 40% were used to calculate the PPV by using the following formula[15], respectively:

$$PVpositive(PPV) = \frac{Se * Prev}{(Se * Prev) + [(1 - Sp) * (1 - Prev)]}$$

The formula was used to calculate the PPV of 47 tests approved under the CDC-EAU and listed in the CDC web page (updated August 2020)[14]. One can refer to index A for more details about the the different kits' information. The results are shown in Table 1. From the calculated PPV (Table 1), it is obvious that PPV is affected by the specificity. The higher the specificity of the disease the higher the PPV. PPV of <70% is considered low, PPV >70% and lower than <90% is considered intermediate and PPV >90% is considered high. Also, the prevalence has a significant effect on PPV. The number of tests with high, intermediate, and low PPV are shown in Table 2.

At a prevalence of 1%, the PPV of 25 tests were low, 9 tests were intermediate, and the PPV of 12 tests were high. At a prevalence of 5%, the PPV of 9 tests were low, 15 tests were intermediate, and the PPV of 23 tests were high. From Table 2, it is obvious that serological kits' PPV is proportional to the prevalence rate. As the prevalence rate increases, the PPV increase, becomes more informative in areas than areas with low prevalence rate. At a prevalence rate of 1%, only 13 kits have high PPV, 9 kits have intermediate PPV, and 25 kits have low PPV. At 5% prevalence rate, as predicted by the CDC, approximately half of the kits (23/47) have high PPV, 10 kits have intermediate PPV, and 9 kits have low PPV at a prevalence of 10%. Additionally, 30% more kits have high PPV with less than 25% of the kits with intermediate PPV and no kits with low PPV. When the prevalence was equal or higher than 40%, all kits have high PPV values.

DISCUSSION

Serological tests have great advantages when used properly, but one must understand their performance limitations. The performance of the test is best represented by its sensitivity and specificity. The sensitivity will tell the test's ability to detect patients

Table 1. Positive Predictive Value (PPV) of antibody tests different prevalence rates of COVID-19 and accuracy (sensitivity and specificity) of antibody tests.

Test	Published		Calculated PPV at Prevalence						
	Sensitivity	Sppecificity	1%	5%	10%	15%	20%	30%	40%
1.	93.6	94	13.5	44.9	73.2	73.2	0.79	86.9	91.2
2.	96.7	95	16.3	50.4	77.3	77.3	0.83	89.2	92.8
3.	96.7	95	16.3	50.4	77.3	77.3	0.83	89.2	92.8
4.	96.7	95	16.3	50.4	77.3	77.3	0.83	89.2	92.8
5.	93.8	96	19.2	55.2	80.5	80.5	0.85	91	94
6.	100	96.4	21.9	59.4	83.1	83.1	0.87	92.3	94.9
7.	96.7	97.5	28.1	67.1	87.2	87.2	0.91	94.3	96.3
8.	100	97	28.1	67.1	87.2	87.2	0.91	94.3	96.3
9.	100	97.5	28.8	67.8	87.6	87.6	0.91	94.5	96.4
10.	57.8	98.9	33.7	72.6	89.9	89.9	0.93	95.6	97.1
11.	98.1	98.6	41.4	78.7	92.5	92.5	0.95	96.8	97.9
12.	88	98.8	42.6	79.4	92.8	92.8	0.95	96.9	98
13.	0.97	0.99	43.9	80.3	93.2	93.2	0.95	97.1	98.1
14.	1	0.99	44.7	80.8	93.4	93.4	0.95	97.2	98.2
15.	1	0.99	44.7	80.8	93.4	93.4	0.95	97.2	98.2
16.	100	98.8	45.7	81.4	93.6	93.6	0.95	97.3	98.2
17.	100	98.8	45.7	81.4	93.6	93.6	0.95	97.3	98.2
18.	70.9	99.3	49.5	83.6	94.5	94.5	0.96	97.7	98.5
19.	97.8	99	49.7	83.7	94.5	94.5	0.96	97.7	98.5
20.	99	99	50	83.9	94.6	94.6	0.96	97.7	98.5
21.	100	99	50.3	84	94.6	94.6	0.96	97.7	98.5
22.	97.6	99.3	58.5	88	96.1	96.1	0.97	98.4	98.9
23.	98.2	99.4	62.3	89.6	96.7	96.7	0.98	98.6	99.1
24.	99	99.4	62.5	89.7	96.7	96.7	0.98	98.6	99.1
25.	92.2	99.6	67.9	91.7	97.4	97.4	0.98	98.9	99.3
26.	92.2	99.6	70	92.4	97.6	97.6	0.98	99	99.4
27.	89.3	99.6	70.9	92.7	97.7	97.7	0.98	99	99.4
28.	100	99.6	71.6	92.9	97.8	97.8	0.98	99.1	99.4
29.	0.97	1	73.3	93.5	98	98	0.99	99.1	99.4
30.	95.7	99.7	76.3	94.4	98.3	98.3	0.99	99.3	99.5
31.	100	99.8	83.5	96.3	98.9	98.9	0.99	99.5	99.7
32.	100	99.8	83.5	96.3	98.9	98.9	0.99	99.5	99.7
33.	100	99.8	83.5	96.3	98.9	98.9	0.99	99.5	99.7
34.	100	99.8	83.5	96.3	98.9	98.9	0.99	99.5	99.7
35.	100	99.9	91	98.1	99.4	99.4	1.00	99.8	99.9
36.	100	100	100	100	100	100	1.00	100	100
37.	90	100	100	100	100	100	1.00	100	100
38.	100	100	100	100	100	100	1.00	100	100
39.	93.3	100	100	100	100	100	1.00	100	100
40.	100	100	100	100	100	100	1.00	100	100
41.	96.7	100	100	100	100	100	1.00	100	100
42.	100	100	100	100	100	100	1.00	100	100
43.	92.5	100	100	100	100	100	1.00	100	100
44.	90	100	100	100	100	100	1.00	100	100
45.	100	100	100	100	100	100	1.00	100	100
46.	83.3	100	100	100	100	100	1.00	100	100
47.	87.5	100	100	100	100	100	1.00	100	100

Low PPV Moderate PPV High PPV

Table 2. Number of kits with high, intermediate and low PPV at different prevalence values.

Prevalence Rate	1%	5%	10%	15%	20%	30%	40%
Number of kits with High PPV	13	23	37	37	41	43	47
Number of kits with Intermediate PPV	9	10	10	10	6	4	0
Number of kits with Low PPV	25	9	0	0	0	0	0

who have the antibody against SARS-CoV-2, while the specificity will tell the test's ability to identify who do not have the antibody against SARS-CoV-2.

Test sensitivity is calculated by determining the number of seropositive COVID-19 patients divided by the total number of NAAT positives multiplied by 100. For example, if there are 100 patients with NAAT positives, the sensitivity of the test will be 95%. Then, 95 patients will be seropositive (True Positive) while 5 patients will be seronegative (False Negative). On the other hand, the specificity of a test can be determined when it does not detect antibodies in stored frozen serum of patients who had respiratory infection, such as other coronaviruses, before the occurrence of SARS-CoV-2 is known. For example, if 100 stored serum COVID-19 negative were examined using a test with a specificity of 99%, then 99 samples will be negative (True Negative) while only one sample will be positive (False Positive). The number of samples used in testing is essential for the confidence interval. The higher the number of samples used in validation, the lower the confidence interval will be, which results in more confidence in the test.

The time stratified analyses recommend that existing serological tests for COVID-19 have restricted utility in the diagnosis of acute COVID-19. For instance, on aggregate, 44% to 85% will be falsely recognized as not having infection for COVID-19 throughout one week of symptom occurrence. In addition, important false negative rates were found at this time period, while sensitivity estimates were higher in the third week or later. For instance, ELISA IgG will misinterpret 18% as not having been infected and LFIA IgG will misinterpret 30% in patients with COVID-19. Overall, the poor performance of current serological tests raises questions regarding the utility of utilizing such methods for medical decision-making, specifically undertaking effort and time needed for doing these tests and the challenging capabilities experienced by clinics.

Another factor that explains the test is the PPV and NPV of the test. The PPV and NPV are calculated from the sensitivity and specificity and prevalence rate. The prevalence rate is the "percentage of individuals in the population who have antibodies to SARS-CoV-2". To interpret test result, the PPV and NPV help in identifying how probable the person with positive result is truly have antibodies against the SARS-CoV-2 and how probable the person with negative result does not have antibodies against the SARS-CoV-2. For antibody testing to be used as screening tool, it should have high PPV. The positive results will be taken as positive with confidence.

Up to date prevalence of the SARS-CoV-2 antibody positive is unknown and is subjected to change. Moreover, prevalence may vary widely between countries, areas within different countries, cities and districts, and even among groups like medical staff, due to different rates of infection. Low prevalence is usually reported from areas with asymptomatic population, the use of a single antibody testing will not provide enough information whether the tested individual had been infected and produced antibody against SARS-CoV-2. An additional test targeting another viral protein, or another epitope should be used to increase the accuracy of the test. The most common SARS-CoV-2 viral proteins used for testing are the spike protein and core protein.

Additionally, it is very important to use IgM, IgG and IgA kits for the immunologic status of the population. The IgM was expected to be high in patients who were recently exposed to the disease. IgG; on the other hand, is expected to appear in patients or individuals who were exposed to the disease more than once. Additionally, high IgG titer is a positive indicator that the patient is immune and has a long-lasting immunity, which is the ultimate objective for prevention.

CONCLUSION

In conclusion, serological testing is essential for the public to return to normal life. Selecting the proper serological kit depends heavily on its sensitivity and specificity as well as the prevalence of the disease **among** the group to be tested. The higher the prevalence value the more reliable are the results. Also, using two tests in lower prevalence population will increase the PPV which is reflected in increased accuracy of the test.

Future studies should assess serological tests for COVID-19 for overcoming the major restrictions of the

current evidence base. This can be willingly achieved by following the fundamentals of the design for diagnostic accuracy studies. The reference standard should comprise of RT-PCR performed on approximately two consecutive specimens in order to mitigate the possibility of misclassification, and when appropriate, encompass viral cultures. Sensitivity and specificity should be stratified by severity of illness, the number of days elapsed since symptom occurrence, and setting.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests regarding the publication of this paper.

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