Original Article

The Role of Preventive Measures or a Previously Immunized Population: A Pilot Study on Coronavirus Disease-19 in Syria

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Abstract

Background: A recent ongoing pandemic of coronavirus disease named coronavirus disease 2019 (COVID-19) has spread in Syria from March 2020 with a pattern of a slow case increase. So far, the government has put the country under lock-down orders as a preventive measure. However, there is a considerable belief in the medical community of our country supposes that the virus has previously passed through the country depending on the high numbers of diagnosed severe respiratory infections early in 2020. Thus, this study was designed to determine the number of people with detectable antibodies to SARS-CoV-2 from two samples of healthy adults with and without a previous history of severe respiratory infection in the last 6 months of the study.

Materials and Methods: To this end, samples were collected from 123 and 198 subjects with a previous severe respiratory infection and healthy controls, respectively. Then, immunoglobulin M (IgM) and IgG anti-SARS-CoV-2 antibodies were tested as well.

Results: None of the samples from both groups tested IgG positive in the assay while four tested IgM samples were positive. Accordingly, these positive samples were re-analyzed and remained IgM positive in the second test although the reverse transcriptase-polymerase chain reaction for the SARS-CoV-2 virus was negative.

Conclusion: Based on our findings, there is no evidence concerning the previous COVID-19 infection in Syria thus it is suggested that all isolation and lock-down orders should be respected as an effective preventive tool in this regard.

Keywords: COVID-19, Preventive, SARS-CoV-2, Herd immunity, Syria

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Introduction

According to Adhikari et al (1), coronavirus disease 2019 (COVID-19) is a newly described syndrome labeled with a severe acute respiratory disease caused by coronavirus 2 (SARS-CoV-2). The virus was recognized as the cause of the Wuhan pneumonia outbreak in December 2019 in China (2). In addition, it has rapidly spread causing a pandemic within three months from the first case detection in China reaching outbreaks in widely spaced countries in South America and Europe (3). However, the case has not been the same in many other regions where the number of cases is still relatively low (4).

An ongoing pandemic of COVID-19 has spread to Syria since March 2020, when the first confirmed case has been announced in Damascus on 22 March. Then, a few numbers of cases were registered to reach the number of 58 confirmed cases on May 19, 2020, showing a pattern of a slow case increase reflecting the situation of slow community transmission (5). The clinical presentation of this disease resembles the other viral respiratory infections and its severity ranges from mild, moderate, to severe (6). However, many patients may be asymptomatic or minimally symptomatic (1).

Further, the disease can represent with mild symptoms such as fever, dry cough, anosmia, and muscle pain, progressing to pneumonia with severe lung involvement, which can lead to death (7). However, the majority of cases can evolve without symptoms, representing a challenge to prevent the dissemination of the infection since these asymptomatic people might be the source of transmission (8).

The symptoms of COVID-19 infection are largely overlapping with other bacterial and viral respiratory infections, especially flu. In such cases, the diagnosis

depends on the detection of the RNA nucleic acid of the SARS-CoV-2 virus using reverse transcriptase-polymerase chain reaction (RT-PCR) which is considered as the gold standard for COVID-19 disease confirmation (8, 9). However, multiple studies have shown a high rate of false-negative tests because of many factors such as inadequate sample collection, viral load, and time between exposure to the virus and the onset of the symptoms (10). In this context, serological tests are necessary for detecting *immunoglobulin* M (IgM) or IgG antibodies (11). Nonetheless, it is difficult to identify the actual number of asymptomatic patients and those with mild illness and spontaneous recovery, and one can accept the probability of developing herd immunity (12).

Several hypotheses were supposed to interpret the relatively low number of cases and slow transmission in Syria. One of these theories is preventive measures that have been taken by the Ministry of Health early in March 2020. However, there is a general trend in the medical community in the country suggesting that coronavirus has passed through Syria in the last six months and the population has got immunity to the SARS-CoV-2 virus.

The immunity to a pathogen through an infection typically takes place over two weeks, and it is a multi-step process (13). Initially, the body responds to a viral infection with a kind of non-specific innate response, where the neutrophils, macrophages, and dendritic cells start to reduce the viral virulence in order to prevent it from causing symptoms (14). This innate response is followed by an adaptive response with the formation of antibodies that specifically bind to the virus. These antibodies are called immunoglobulins (13, 14). At this stage, the body also makes T-cells that eliminate other infected cells with the virus. As a result, this response may clear the virus from the body and may prevent re-infection by this virus or progression to severe infections (13). This response is measured by the presence of antibodies in the blood (14).

Given the above-mentioned explanations, the current study aimed to evaluate the concept of previous exposure to the SARS-CoV-2 virus in Syria. More precisely, the study determined the number of people with detectable antibodies to SARS-CoV-2 from two samples of healthy adults with and without a previous history of a severe respiratory infection in the last six months of the study. To the best of our knowledge, so far, this has been the first study in Syria addressing the SARS-CoV-2 seroprevalence in asymptomatic populations.

Materials and Methods
Study Design
A cross-sectional study was conducted, consisting of the serological detection of IgM and IgG antibodies in healthy adults with and without a previous history of a severe respiratory infection.

Participants
In general, 321 subjects were recruited in this study, including 123 subjects with a previous history of severe respiratory infection, with positive clinical history supported by chest X-ray findings, and positive *creatine phosphokinase* with decreased white blood cell counts; and 198 healthy controls with a mean age of 33±9 years. All healthy adults over 18 years old could participate in the survey unless they had any illness or known exposure to the SARS-CoV-2 virus. In addition, all participants provided written informed consent for their participation and undergoing serological tests for SARS-CoV-2.

Antibody Testing
Random serum or capillary blood samples were collected from 320 healthy adults (the study group). The rapid test was used for detecting the IgM and IgG anti-SARS-CoV-2 antibodies and it was run according to the manufacturer's instructions (COVID-19 IgG/IgM Rapid Test Cassette (Serum/whole blood/plasma), Lot: N01G09T, HANGZHOU REALY TECH Company, LTD. Hangzhou, P, R, China). Briefly, 10 µL of the serum or one drop of the whole blood (approximately 20 µL) was added to the test slide, then two drops of the buffer (provided in the kit) was added as well. The results were read after 15 minutes. The tests were considered valid only when the control line changed its color. Further, the test was considered positive when a line was detected for IgM and/or IgG. Eventually, any shade of color in the test line region(s) IgG and/or IgM was considered as positive.

Results
All descriptive and analytic data of both groups are provided in Table 1.

IgM and IgG Reactivates
None of the 320 samples from healthy subjects tested IgG positive in the assay although 4 tested IgM were positive (Table 1). These four IgM positive samples including 1 in the first group (subjects with a previous severe respiratory infection) and 3 in the control (healthy subjects) group

Table 1. Descriptive and Analytic Data of Study Groups

	Previous Respiratory Infection Group	Healthy Controls Group	*P* value
Sample size	123	198	
Age (Mean ± SD)	32.46 ± 8.5	34.48 ± 9.2	0.147
Gender	Female/Male 40/83 (32.5%, 67.5%)	Female/Male 53/145 (26.7%, 73.3%)	0.07
IgM	Positive/Negative 1/119 (<1% positive)	Positive/Negative 3/195 (1.5% positive)	0.582
IgG	All negative	All negative	-

Note. SD: standard deviation; IgM: *immunoglobulin M*; IgG: *immunoglobulin G*.

were re-analyzed and remained IgM positive in the second test while RT-PCR for the SARS-CoV-2 virus was negative for these four cases.

Statistical Analysis

A nonparametric test of independence (Fisher's exact test) was used to study the association between the previous history of respiratory infection and the positive IgM test and the results showed no association in this regard (Fisher's test value $(1, 321) = 0.303$, $P = 0.582$). On the other hand, no expected association was observed between the same variables and IgG results because there were no positive IgG values.

Discussion

The main question of this study was to find out whether COVID-19 passed in Syria earlier in January and February since there were many reported cases of severe respiratory infections while no diagnostic tests were performed for SARS-CoV-2. The results demonstrated no positive IgG values for all subjects with and without respiratory infections. Moreover, four cases had positive IgM values without having the disease. Therefore, there is no previous immunization for the virus in this population and the other hypotheses should be tested as well.

Although the question of why the virus has overwhelmed some places and left others relatively untouched is still unanswered, any information in this field can be extremely helpful in determining the proper approach regarding protecting our community (15). Two months after the detection of the first case in Syria, the number of SARS-CoV-2 confirmed cases reached 58 individuals on 19th May, reflecting that the epidemic curve is not on the rise. This raises several points for discussion to explain the reasons for whether it is the role of preventive measures or the past supposed exposure or there are other unknown factors in this regard.

Before confirming any cases and coinciding with the increase in SARS-CoV-2 confirmed cases in neighboring countries, the government has made many preventive measures in Syria. It instructed the public to stay at homes and closed all colleges, schools, and markets. Besides, the government imposed a partial curfew from 6 PM to 6 AM. These early measures could play an important role in the reduction of viral spread. On the other hand, there was a concept that there have been previous exposure to the SARS-CoV-2 virus in Syria with the formation of immunity between the public. Nonetheless, this concept had to be tested otherwise, it might be a misleading concept.

Antibody testing could identify those who had the disease at some points but did not receive the confirmation of infection and those with asymptomatic or mild infections (16). The findings of this study provided us with useful information about the supposed previous exposure. Our findings implied that there is no evidence concerning the previous COVID-19 infection in Syria because all blood samples were negative for IgG. This demonstrated that there was no previous infection with the SARS-CoV-2 virus or there was mild exposure to the virus causing no immunization. On the other hand, IgM antibodies were positive in four cases and they were asymptomatic and negative RT-PCR for the SARS-CoV-2 virus, this could be explained as the cross-reaction with another coronavirus, but not SARS-CoV-2 virus (17).

Conclusion

In general, SARS-CoV-2 is the most unusual virus since it has a relatively long incubation period, a high mortality rate, and a large number of asymptomatic carriers (18). Traditional epidemiological surveillances depend on sick people who are reported with identifiable symptoms (19). Since no approved vaccination or treatment has so far been found against COVID-19 and considering our preliminary pilot data of negative IgG, the researchers ascertain the role of protective measures and recommend the continuation of all current preventive measures which aim to restrict the social interactions of the public.

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