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## SARS-COV-2 Pandemic in Syria: Symptoms and Treatments

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### ABSTRACT

SARS-CoV-2 has caused global pandemic that resulted in a dramatic loss of human life worldwide. The first human case was reported in December 2019 in China, and while the first case in Syria was confirmed on March 2020. By July 1st, 2021, 25551 cases were reported in Syria with 1879 deaths. The most common symptoms of covid-19 are fever, dry cough, and shortness of breath. Some patients may endure from musculoskeletal, gastrointestinal and dermatologic symptoms. Many drugs (including antibiotics, corticosteroids, antiviral and Immunomodulatory drugs) have been evaluated and recommended to be used in COVID-19 treatment, resulting in clinical recovery.

**Keywords:** SARS-CoV-2, Syria, pandemic, remdesivir, corticosteroids, antiviral

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## INTRODUCTION

The world faced several epidemics and pandemics that affected millions of lives. Despite the advanced level in medicine and science humans reach, new pathogens pose threats to their lives, global economic security and healthcare systems <sup>1,2</sup>.

Coronaviruses (CoVs) represent a large family of enveloped, positive single-stranded RNA viruses. They infect a wide variety of animals, including humans, causing respiratory, enteric, hepatic and neurological diseases. CoVs are divided into four subfamilies: alpha-, beta-, gamma- and delta-coronavirus <sup>3</sup>. Alpha- and beta-coronaviruses arise from mammals, principally bats, causing more severe and fatal diseases to humans, whereas gamma- and delta- coronaviruses mainly arise from birds and pigs and cause asymptomatic or mild disease to humans <sup>1,4</sup>.

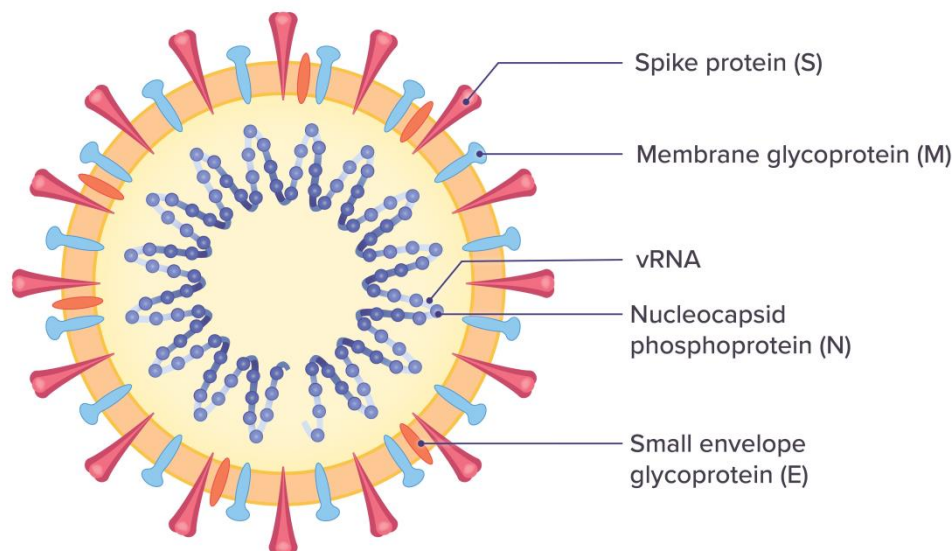
To date, seven human coronaviruses are known, including: HCoV-229E, HCoV-OC43, HCoV-HKU1, HCoV-NL63, MERS-COV, SARS-CoV and the most lately discovered, SARS-COV-2, which is called COVID-19 <sup>5</sup>. Coronaviruses have infected humans twice in the last two decades that led to major epidemics <sup>3,6</sup>.

Over 2002-2003, Severe Acute Respiratory Syndrome (SARS) spread to more than 30 countries affecting over 8,000 patients across five continents and killing 774 of them <sup>6,7,8</sup>. Since 2012, Middle East Respiratory Syndrome (MERS) spread to 27 countries affecting 2494 patients and killing 858 of them <sup>6,9,10</sup>.

### **Sars-COV-2 structure**

CoVs have the largest genomes (26–32 kb) among all RNA viruses' families <sup>11</sup>. SARS-CoV-2 belongs to the beta-coronavirus group and shares ~75–80% of its viral genome with SARS-CoV. It is spherical virion with a core shell and a surface that is similar to a solar corona based on its surface protein projections, which give the version its name (Latin: corona = crown) <sup>1,4,12</sup>.

SARS-CoV-2 possesses four essential proteins: spike (S) , membrane (M) , envelope (E) and nucleocapsid (N) (Figure 1). S protein plays a crucial role in the viral attachment to the cell membrane receptor, membrane fusion, and eventually viral entry into the host cell. M and E proteins are responsible for the coronavirus envelope formation, while N protein, which combines with the genome RNA to form the helical nucleocapsid, is responsible for transcription increment and virus assembly <sup>1,10,11,13</sup>.



**Figure 1: SARS-CoV-2 structure <sup>1</sup>**

### **Timeline to SARS-CoV-2 (COVID-19) pandemic**

It is postulated that the outbreak for SARS-CoV-2 started in Wuhan around December 12<sup>th</sup>, 2019, with multiple patients having similar clinical symptoms (cough, fever, dyspnoea and atypical pneumonia). Then, on December 29<sup>th</sup>, four cases of “pneumonia of unknown aetiology” were reported by local Chinese hospitals, and all of them were thought to have a connection to a local seafood market that sold live non-aquatic wild animals <sup>1</sup>.

The Chinese authorities alerted the World Health Organization (WHO) of these cases on December 31<sup>st</sup>. Then, the Chinese Centre for Disease Control and Prevention (China CDC) upgraded the emergency response to Level 2 on January 6<sup>th</sup>, 2020. After that, the first case outside of China was reported in Thailand on January 13<sup>th</sup>. On January 15<sup>th</sup>, China CDC elevated the emergency response to Level 1. Over time, SARS-CoV-2 spread to all continents, which forced WHO to announce the pandemic state on March 11<sup>th</sup> <sup>1, 13</sup>.

By June 29<sup>th</sup>, more than 180 million cases have been reported and almost 4 million death <sup>14</sup>.

### **SARS-CoV-2 (COVID-19) pandemic in Syria**

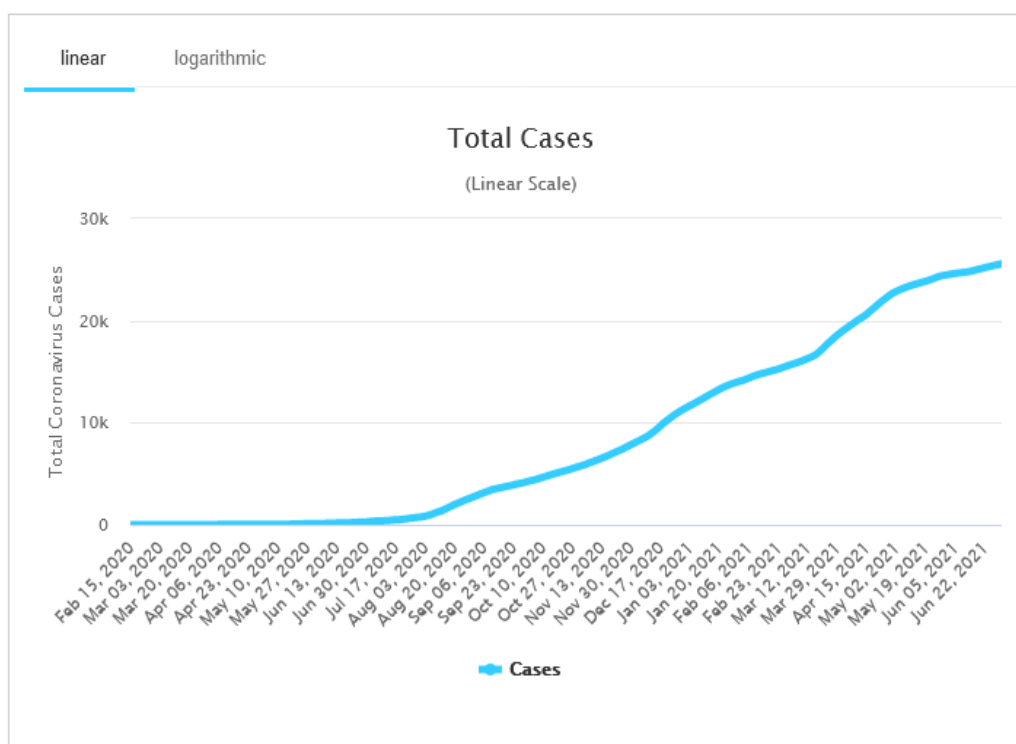
Several cases of COVID-19 were reported earlier in Lebanon, Jordan and Iran. However, the spread of the virus was late in Syria. The first COVID-19 case in Syria was confirmed on March 22<sup>nd</sup>, 2020, and a week later, the first death was reported. The disease has spread rapidly. The case numbers increased to 328 with 10 deaths by July 03<sup>rd</sup>, 2020, according to the Syrian Ministry of Health <sup>15</sup>.

There were some doubts about the accurateness of these figures, because of the limited testing capabilities and limited resources. Syrian Health Ministry in Damascus conducted almost one hundred tests daily. However as a consequence of testing kits shortage, the tests were available only to people with clear symptoms, or previous contact with confirmed cases or deaths <sup>15</sup>.

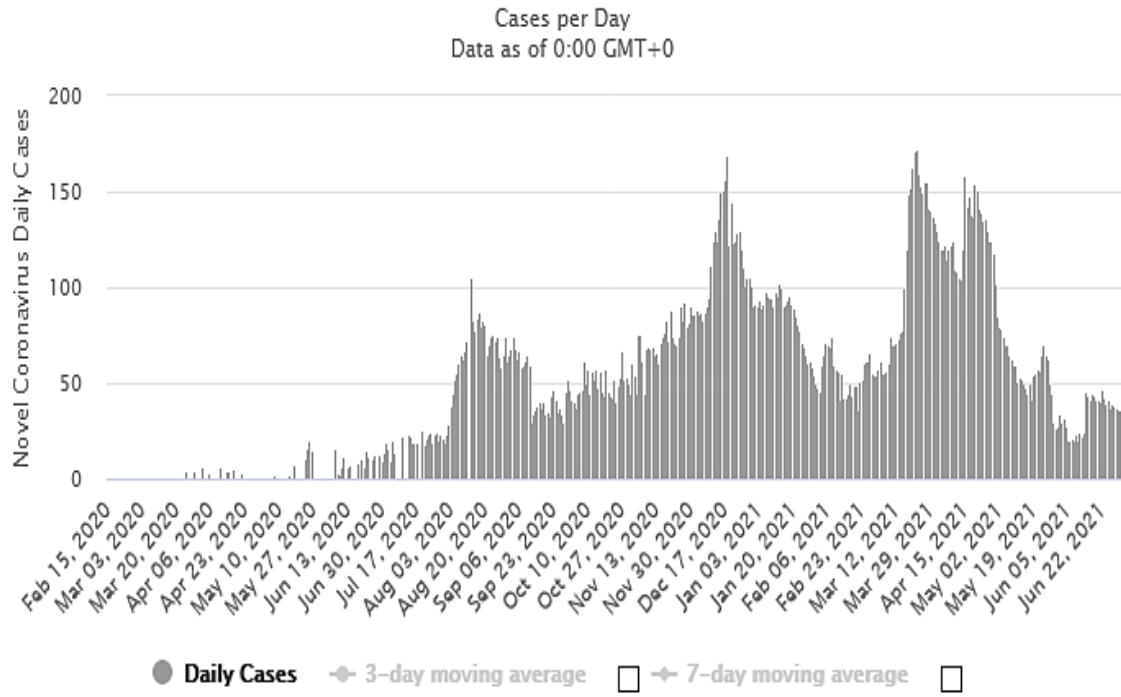
COVID-19 was expected to be a great challenge to the Syrian health system after several years of war. Hence, the WHO warned that Syria is at high risk of a major outbreak due to the lack of sufficient equipment and the loss of nearly 70% of health care workers<sup>15</sup>.

In order to stem the spread of COVID-19, strict measurements were imposed by the Syrian government, similar to those adopted by other countries. Thus, a partial lockdown was imposed from 6 pm to 6 am, with a complete closure of parks, markets, shops, and public transport. Classes at schools and universities were postponed for a while. Traveling between cities was banned, and all flights were suspended. In addition, full lockdown was posed on areas and neighbourhoods that contain confirmed or suspected infections or deaths. On May 26<sup>th</sup>, the government gradually loosed the curfew restrictions due to the deterioration in economy<sup>15,16</sup>.

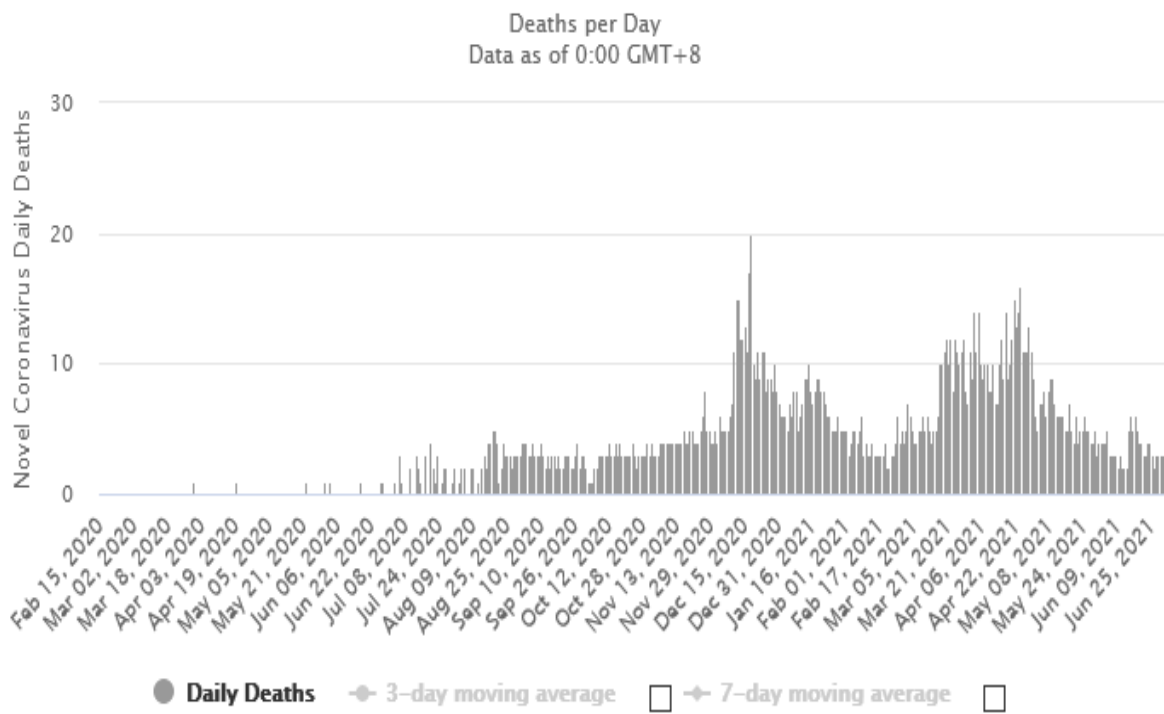
The number of reported cases rose to 25551 cases (21831 recovered and 1879 deaths) on July 1<sup>st</sup>, 2021. Figures 2, 3 and 4 show the increment of COVID-19 cases in Syria, daily new cases and new deaths, respectively, from the beginning of the outbreak until the end of June 2021. By July 1<sup>st</sup>, 21831 patients have recovered from COVID-19. The majority of them were under 69 years and did not have any other diseases (Figure 5)<sup>17</sup>.



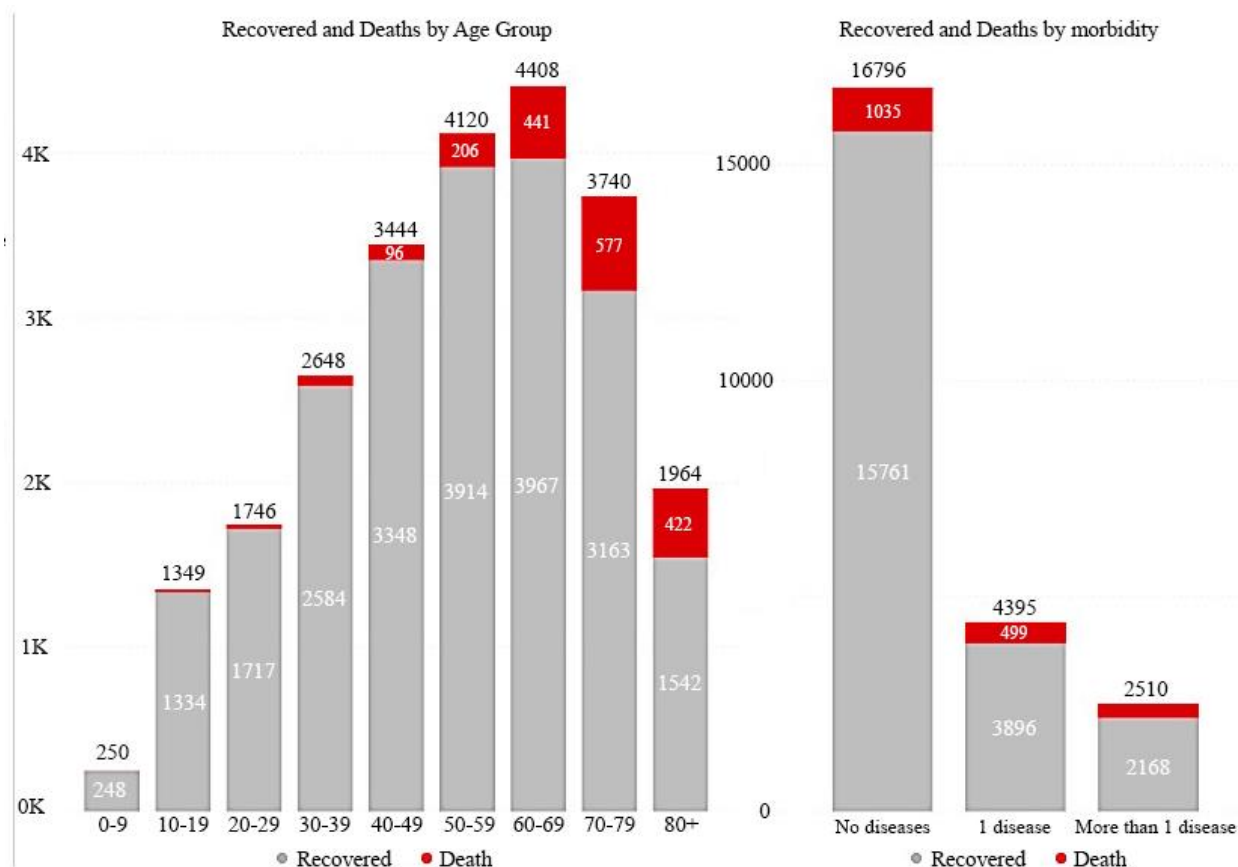
**Figure 2: Total cases of COVID-19 in Syria<sup>54</sup>**



**Figure 3: Daily cases of COVID-19 in Syria** <sup>54</sup>



**Figure 4: Daily deaths of COVID-19 in Syria** <sup>54</sup>



**Figure 5: Recovered cases of COVID-19 in Syria by age group and morbidity**<sup>17</sup>

As for the distribution of COVID-19 in the Syrian governorates (excluding Idleb), Damascus ranked first (5606 cases) followed by Aleppo (3938 cases) and Lattakia (3896 cases) as shown in Table 1<sup>17</sup>.

**Table 1: Total cases of COVID-19 in Syria according to governorates**<sup>17</sup>

Governorates	Total cases	Active	Recovered	Death	New cases	New recovered	New deaths	CFR
Damascus	5,606	386	4,618	602	15	1	0	10.74%
Aleppo	3,938	534	3,149	255	17	2	2	6.48%
Lattakia	3,896	295	3,376	225	4	2	0	5.78%
Homs	3,022	134	2,594	294	0	0	0	9.73%
Rural Damascus	2,581	100	2,445	36	0	0	0	1.39%
Tartous	1,856	42	1,612	202	0	1	1	10.88%
Dar'a	1,322	56	1,202	64	0	0	0	4.84%
As-Sweida	1,292	69	1,140	83	0	0	0	6.42%
Hama	1,178	167	971	40	0	0	0	3.40%
Quneitra	493	21	443	29	0	0	0	5.88%
Deir-ez-Zor	234	21	170	43	0	0	0	18.38%
Al-Hasakeh	109	11	94	4	0	0	0	3.67%
Ar-Raqqa	24	5	17	2	0	0	0	0.00%

### SARS-CoV-2 (Covid-19) symptoms and clinical features

The incubation period of COVID-19 is 5–6 days, but can last up to 14 days. During this period, which is called presymptomatic period, the infected individuals can transmit the virus to healthy ones<sup>18</sup>.

COVID-19 has different degrees of severity, from flu-like symptoms to death<sup>19</sup>. The clinical spectrum of this virus varies from asymptomatic or paucisymptomatic forms to serious forms accompanied with respiratory failure, which necessitates mechanical ventilation and support in an intensive care unit (ICU), and multiorgan and systemic manifestations in terms of sepsis, septic shock, and multiple organ dysfunction syndromes (MODS)<sup>20, 21</sup>.

Pneumonia appears to be the most frequent serious symptom. It is characterized mainly by fever, dry cough, dyspnea, and bilateral infiltrates on chest imaging. The less common symptoms usually include sore throat, rhinorrhoea, shortness of breath, headache, fatigue, myalgia and arthralgia and fatigue<sup>18, 20, 22, 23, 24, 25</sup>. Apart from respiratory and musculoskeletal symptoms some patients may have gastrointestinal ones such as abdominal pain, nausea, vomiting and loose stools<sup>18, 20, 22, 23, 24, 26, 27, 28, 29</sup>.

On the other hand, some COVID-19 patients may endure some dermal lesions. A recent Italian study revealed that more than 20% of COVID-19 patients had cutaneous manifestation as erythematous rash, urticaria and chickenpox-like vesicles basically in the trunk with little or no itching<sup>30</sup>. In another study, the most observed symptoms were chilblains/pernio-like lesion, erythematous maculopapular rashes, and viral exanthema<sup>31</sup>.

Generally, the cutaneous manifestations of COVID-19 were classified into five main clinical patterns: aculopapules (47%), pseudo-chilblain (19%), urticarial lesions (19%), other vesicular eruptions (9%), and livedo or necrosis (6%)<sup>32, 33, 34</sup>.

According to Casas *et al.* (2020), vesicular eruptions appeared early in the evolution of the disease (15% before other symptoms), whereas pseudo-chilblain pattern frequently appeared late in the course of the COVID-19 disease (59% after other symptoms)<sup>32</sup>.

Moreover, some COVID-19 patients may have complications, such as acute respiratory distress syndrome (ARDS), acute respiratory failure, sepsis, disseminated intravascular coagulation, acute liver and kidney injury and pulmonary embolism. In rare cases, one can observe rhabdomyolysis, multisystem inflammatory syndrome, aspergillosis, pancreatitis, autoimmune haemolytic anaemia or neurological complications<sup>18</sup>.

The previous complications, such as the excessive production of proinflammatory cytokines (such as interleukin (IL)-1, (IL-6), and tumor necrosis alpha (TNF- $\alpha$ )) all lead to ARDS aggravation and widespread tissue damage causing multiple organ failure and death<sup>35, 36, 37</sup>.

Such complications are mostly linked to the cytokine storm

### **Pharmacologic treatments for Covid-19**

Agents previously used to treat SARS-CoV and MERS-CoV represent potential candidates to treat COVID-19<sup>38</sup>. The following classes of drugs are being evaluated or developed for the management of COVID-19: antivirals, antibodies, anti-inflammatory agents, targeted immunomodulatory therapies, anticoagulants, and antifibrotics.

### ***Antibiotics***

Although it is not always recommended in viral pneumonia, the optimum antibiotic regimen helps to prevent secondary bacterial infections and sepsis. Macrolides like azithromycin are highly efficient in preventing pulmonary infections in viral pneumonias patients, in addition to their important anti-inflammatory effect on the airways<sup>18, 39, 40</sup>.

### ***Corticosteroids***

Steroids can be used for 3–5 days in patients having gradual deterioration of oxygen saturation, enhanced pro-inflammatory response activation and rapid aggravation of features on chest imaging. Methylprednisolone was the first steroid that used to treat COVID-19 (0.5–1 mg/kg/day for moderate cases and 1–2 mg/kg/ day for severe cases). Higher doses were not recommended because of the steroid mediated immunosuppression, which delay the viral clearance<sup>18, 41, 42, 43</sup>.

Lately, dexamethasone is started to be used for reducing mortality in severe and critical cases<sup>18, 44</sup>.

### ***Antiviral drugs***

Remdesivir (CIPREMI/COVIFOR): Remdesivir is a broad-spectrum antiviral drug. It blocks the action of viral RNA- dependent RNA polymerase, which is essential for the virus replication<sup>45, 46, 47</sup>. It was used to treat the first COVID-19 patient in the USA, who showed speedy improvement after only one day of treatment<sup>18, 38, 48</sup>.

Remdesivir could be considered for patients with moderate illness (200 mg intravenous over 1–2 hours on the first day, then 100 mg intravenous daily for 5–10 days). However, the contraindications for remdesivir usage include children, pregnant or lactating females, and patients with severe hepatic or renal impairment. Therefore, it should be used to treat hospitalised COVID-19 patients with moderate-to-severe disease, and requiring supplemental oxygen therapy<sup>18, 38, 48</sup>.

Finally, it should be noted that treatment with remdesivir alone is not adequate because of the high mortality rates<sup>18</sup>.

Lopinavir/ritonavir (KALETRA): LPV inhibits the coronavirus protease activity in vitro and in animal studies and lowers mortality rates. At first, it was thought to be potential treatment option for COVID-19<sup>18</sup>. However, a recent trial revealed that no benefit was observed with LPV/RTV therapy as compared to routine management protocol<sup>18, 49</sup>.

Favipiravir (FABIFLU): Favipiravir shows activity against RNA viruses. It is an RNA polymerase inhibitor preventing the viral<sup>18, 38, 46</sup>.

Favipiravir was the first approved oral medication for COVID-19 treatment in India (1800 mg twice on the first day, then 800 mg twice a day up until day 14. It shows a considerable

improvement in mild to- moderate cases of COVID-19, which is related to rapid decrease in the viral load and the early symptomatic improvement <sup>18</sup>.

Although individual antiviral drugs are slightly effective in mild-to-moderate cases, future strategies should evaluate combination of antiviral agents, or antiviral drugs with other therapeutic protocols, to improve the critical COVID-19 cases <sup>18</sup>.

### ***Immunomodulatory drugs***

**Tocilizumab:** Tocilizumab is a humanised IgG1 monoclonal antibody, directed against the IL-6 receptor. It could be used to treat patients with moderate disease (with increase in inflammatory markers (IL-6) and oxygen demand) and mechanically ventilated patients who are not responding to therapy. The approved dosage is 8 mg/kg (maximum 800 mg at one time) given slowly in 100ml normal saline over one hour. If necessary, it can be repeated once after 12–24 hours. Active tuberculosis and neutropenia are contraindications for treating with tocilizumab. It is worth noting that tocilizumab may decrease the risk of invasive mechanical ventilation or death in COVID-19 patients with severe pneumonia <sup>18</sup>.

**Chloroquine and hydroxychloroquine:** Chloroquine is an antimalarial drug that has a broad-spectrum as antiviral activity. Chloroquine (500 mg every 12 hours) prevents the virus infection by increasing the endosomal pH required for virus fusion within the cell, and/or blocking SARS-CoV receptor glycosylation. Chloroquine reduce the exacerbation of COVID-19 pneumonia and accelerates viral and symptomatic clearance <sup>18, 42, 50, 51</sup>.

As for hydroxychloroquine (HCQS) (200 mg every 12 hours), it is a better chloroquine analogue with regard to safety and anti-SARS-CoV activity *in vitro* <sup>18</sup>. Both chloroquine and HCQS have immunomodulatory effects and can to suppress the cytokine storm by reducing the production of several pro-inflammatory cytokines, like IL-1, IL-6, interferon-  $\alpha$  and tumour necrosis factor <sup>18, 42, 52</sup>.

On June 15<sup>th</sup>, 2020, the Food and Drug Administration (FDA) cancelled the emergency use authorization for using HCQ and CQ to treat hospitalized COVID-19 patients, and stated that none of them was efficient in COVID-19 therapy <sup>52, 53</sup>.

In fact, Based on the serious cardiac and other potential side effects, the possible benefits of HCQ and CQ may not exceed the potential risks for the authorized use <sup>53</sup>.

## **CONCLUSION**

Novel types of coronaviruses have become a real threat to human health. SARS-CoV and MERS-CoV outbreaks were contained by the world health systems. However, new emerging coronavirus was identified in 2019 in Wuhan, China. The new Covid-19 is highly contagious and has resulted in a global pandemic. In 2020, many Covid-19 cases were reported in the Middle East countries. Actions were taken by governments to prevent the spread of the virus

such as full lockdowns and social distancing enforcement. By July 1st, 2021, 25551 cases were reported in Syria with 1879 deaths.

Several drugs were re-proposed to be used as treatment for Covid-19 including azithromycin, remdesivir, tocilizumab, chloroquine and hydroxychloroquine. Clinical evaluation of these drugs was carried out in many countries and some of them have exhibited promising results and led to reduction in mortality rate and decrease the time to recovery.

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