Signa Vitae

RAPID REPORT

Analysis of the performances of the Covid-19 therapeutic approaches in the United Arab Emirates

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Abstract

Objectives: To evaluate the performances of the therapeutic approaches adopted in the United Arab Emirates to fight Covid-19 infection.
Methods: Statistical analysis of the number of cases and fatalities for the United Arab Emirates. The fatality rates are compared to those of reference countries adopting different approaches.
Results: The United Arab Emirates outperformed the reference countries with a much smaller number of fatalities. While this number is not only driven by therapies, the different therapeutic approaches are the most important driver.
Conclusions: Combination therapies are most effective than single drug therapies. The use of antivirals especially in the early stages reduces the number of fatalities.

Keywords

Covid-19; Antivirals; Combination therapies

1. Introduction

The response to the Covid-19 pandemic has been very different across the world, and as a result, also the impact of Covid-19 in terms of fatalities has been very different. There have been significant differences in terms of restrictions limiting the spread of the virus, as well as of treatment of the infected patients. Regarding treatment, in some countries, no antivirals are administered to asymptomatic or mild cases, and practically nothing more than corticosteroids are given to severe and critical cases, in addition to oxygen or ventilation. There are other countries where antivirals are given to asymptomatic patients in the risk categories in outpatient settings, as well as to mild, severe, and critical cases within hospital settings. The goal of this work is to highlight the different therapeutic approaches followed in the Arab States of the Gulf countries vs. those adopted in western countries. The antiviral drugs that are used in the Arab States of the Gulf countries are mostly discouraged in the western countries. This work aims to show differences in the number of cases, number of fatalities, and therapies and trying to correlate them.

2. Method

Information of the number of cases and fatalities, plus the number of tests and number of vaccines administered, has been obtained from ourworldindata.org. The CSV file downloaded from ourworldindata.org at the time of writing and containing all data used in the images and the statements about the number of cases, tests, fatalities, vaccines, are provided in the supplementary. Time series are shown when deemed necessary. Information on the therapies is obtained from publicly available links to health organizations.

3. Results

The latest percentages of infected are variables, but usually a few percent of the total population.

In the countries considered in Fig. 1.a (cumulative confirmed cases per 1,000,000 people), these percentages are variable from less than 0.1 to more than 6%. The vast majority of the cases are mild or asymptomatic. Even the World Health Organization admits that 80% of the total cases are mild or asymptomatic. Hence, those infected and undetected may be many more of those recorded, depending on the specific country.

The cumulative fatalities are also variable significantly, in the cases of Fig. 1.b (cumulative fatalities per 1,000,000 people), from practically 0.00% to 0.17%.

The cumulative case fatality rate (ratio between confirmed deaths and confirmed cases) of Fig. 1.c is variable from less than 0.1% to above 3.5%.

Including the undetected mild or asymptomatic, the true cumulative fatality rate is less.

The therapeutic approach to Covid-19, which is one relevant, if not the most relevant, part of the response of a country, has been also very different in different countries. The therapeutic approach is partially an explanation of the observed different cumulative fatality rates. The cumulative fatality rate is also affected by other drivers such as geographical, demographic, social, economic, cultural, and policing.

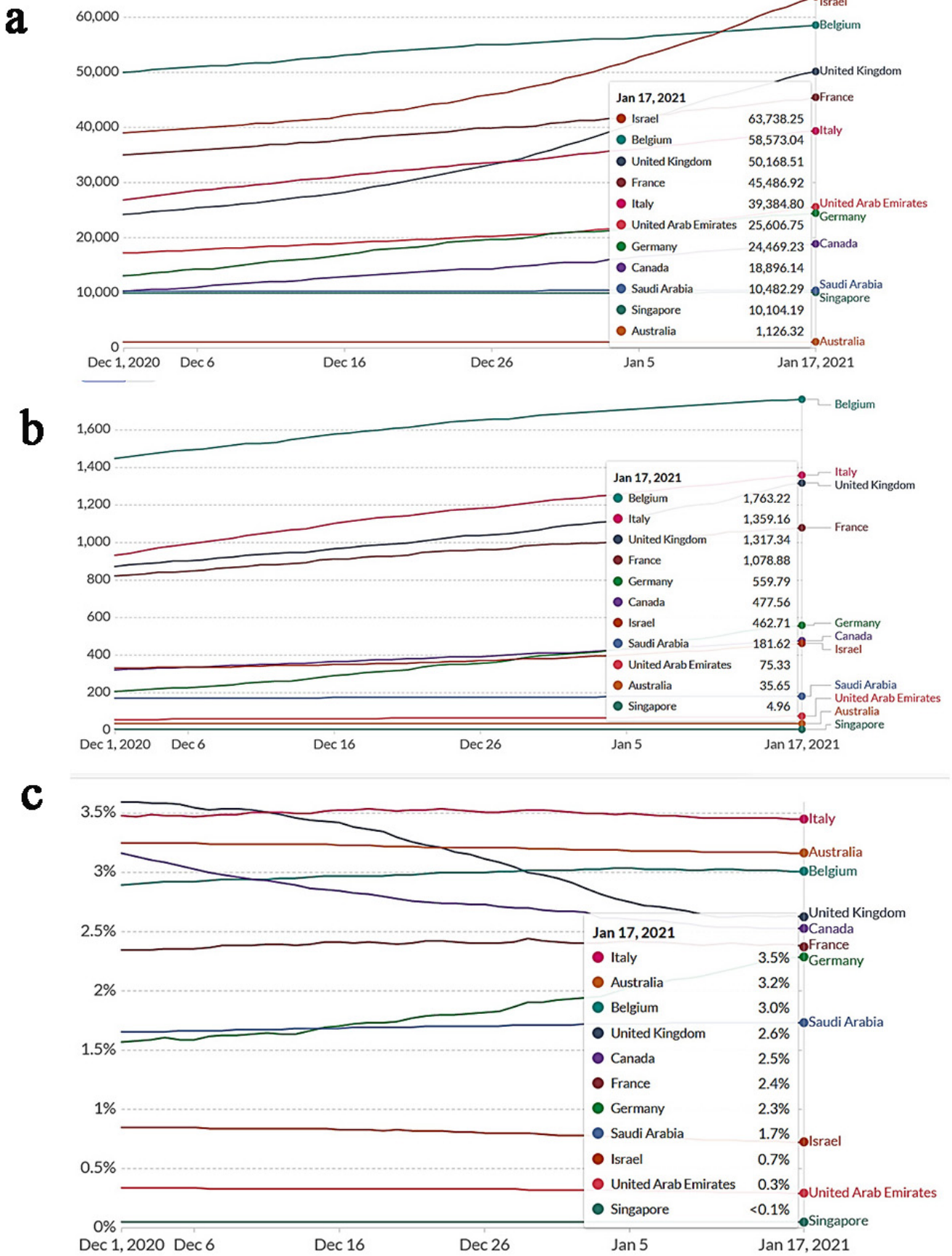Differences in therapies are relevant in early and mid-stages

F I G U R E 1. Cumulative cases per million (a), cumulative fatalities per million (b) and the ratio of cumulative fatalities to cumulative cases (c) for selected countries. Images from ourworldindata.org. CC BY.
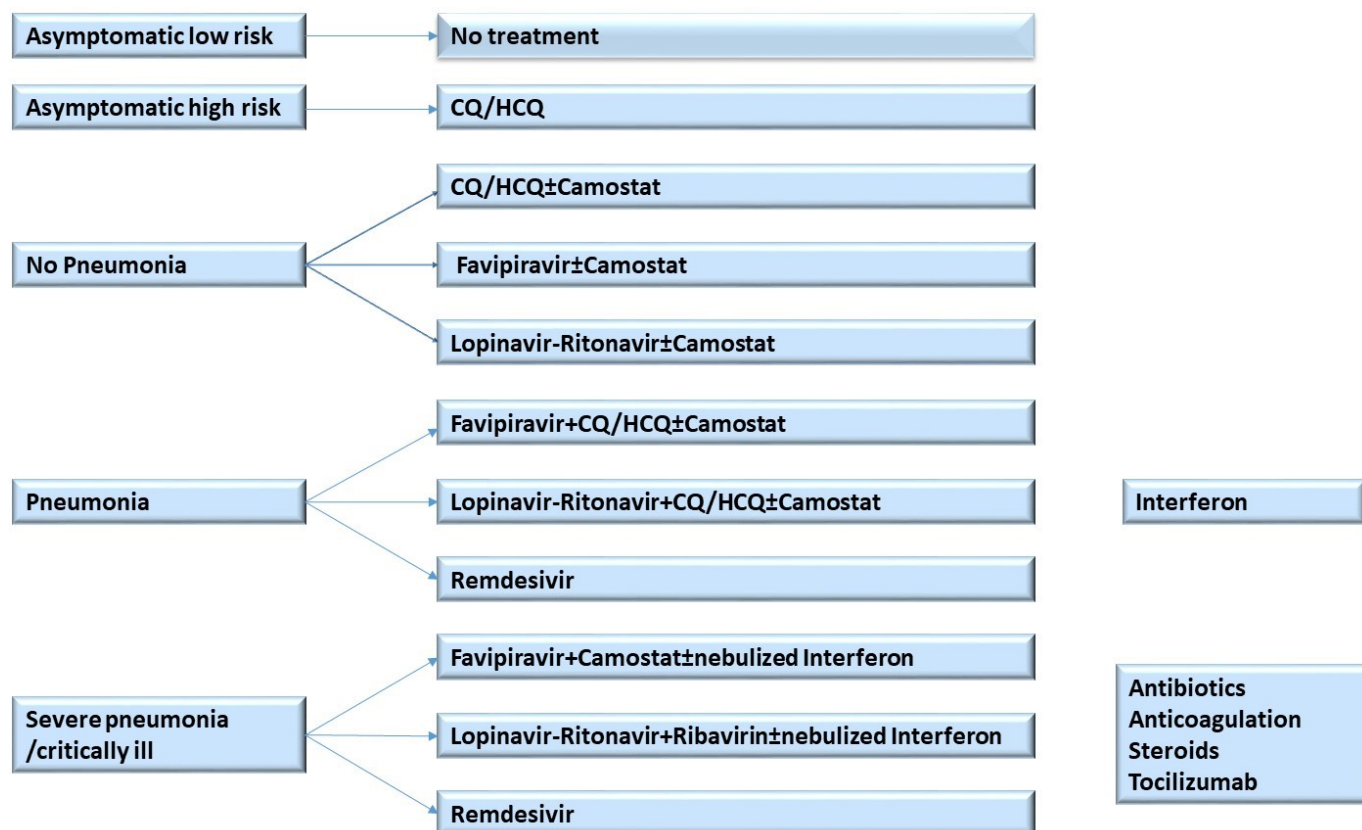
F I G U R E 2. Scheme of the therapeiutic options available in the UAE [4].

and medium to severe and critical cases.

While fatalities follow late-stages, it must be mentioned as the occurrence of late-stage infection is often the result of improper treatment during early stages, as the viral load build-up is determinant for Covid-19 infection fatalities [1–3].

3.1 COVID-19 guideline in the United Arab Emirates

The presence of pneumonia is frequent in medium to severe cases. Acute Respiratory Distress Syndrome (ARDS), the respiratory failure characterized by rapid widespread inflammation in the lungs often causing Covid-19 infection fatalities, is often present in critical cases. The way to address ARDS is first and foremost through earlier use of antivirals, i.e. targeting the primary cause of the pathology when it is easier. Without reaching very high viral loads, usually, patients do not have ARDS. Thus, early stages therapeutic interventions are determinant, more than late stages therapeutic interventions.

In addition to antivirals, other drugs that are targeting the immune system response, either in the direction of powering this response as well as calming the immune system, are also considered. Antibodies are also considered. Adjunctive therapies are also used to prevent or treat infection or complications.

Being the problem quite complex, different drugs may work better depending on the stage and the specific characteristics of the patient. Combination therapies may deliver better results.

According to [4], the proposed therapeutic regimens for adults in the United Arab Emirates (Abu Dhabi) are those summarized in Fig. 2. The details are given below, specific to the stage:

Asymptomatic Covid-19 cases usually receive no treatment, but if high risk, they are treated with Chloroquine (CQ) Phosphate 500 mg PO (by mouth) BID (twice a day) X 2 doses, then 250 mg PO BID or Hydroxychloroquine (HCQ) 400 mg PO BID X 2 doses then 200 mg PO BID. All these alternatives are a total of 5 days [4].

Covid-19 cases without pneumonia for 5 days receive HCQ 400mg PO BID then 200 mg PO BID, or CQ Phosphate 500 mg PO BID X 2 doses, then 250 mg PO BID, or Favipiravir 1600 mg PO BID X 2 doses, then 600 mg PO BID, or Lopinavir-Ritonavir (200/50 mg) 2 tablets PO BID. All these alternatives are a total of 5 days. The addition of Camostat 200 mg PO TID (three times a day) X 5 days is optional [4].

Covid-19 cases with pneumonia for 7 days receive Favipiravir 1600 mg PO BID X 2 doses then 600 mg PO BID (total 7 days) + HCQ 40 0mg PO BID X 2 doses then 200 mg PO BID (total 5 to 7 days) ± Camostat 200 mg PO TID for 5 to 7 days, same as before with CQ Phosphate 500 mg PO BID X 2 doses then 250 mg PO BID (total 5 to 7 days) replacing HCQ, or Lopinavir-Ritonavir (200/ 50 mg) 2 tablets PO BID (total 7 days) + HCQ 400 mg PO BID X 2 doses, then 200 mg PO BID (total 5 to 7 days) ± Camostat 200 mg PO TID (5 to 7 days), same as before with CQ Phosphate 500 mg PO BID X 2 doses, then 250 mg PO BID) (5 to 7 days) replacing HCQ, or Remdesivir 200 mg IV (Intravenous) on day 1, followed by 100 mg IV daily. Interferon therapy is an option in cases of moderate disease [4].

Covid-19 cases with severe pneumonia/critically ill patients for 10 days receive Favipiravir 1600 mg PO BID X

a

b
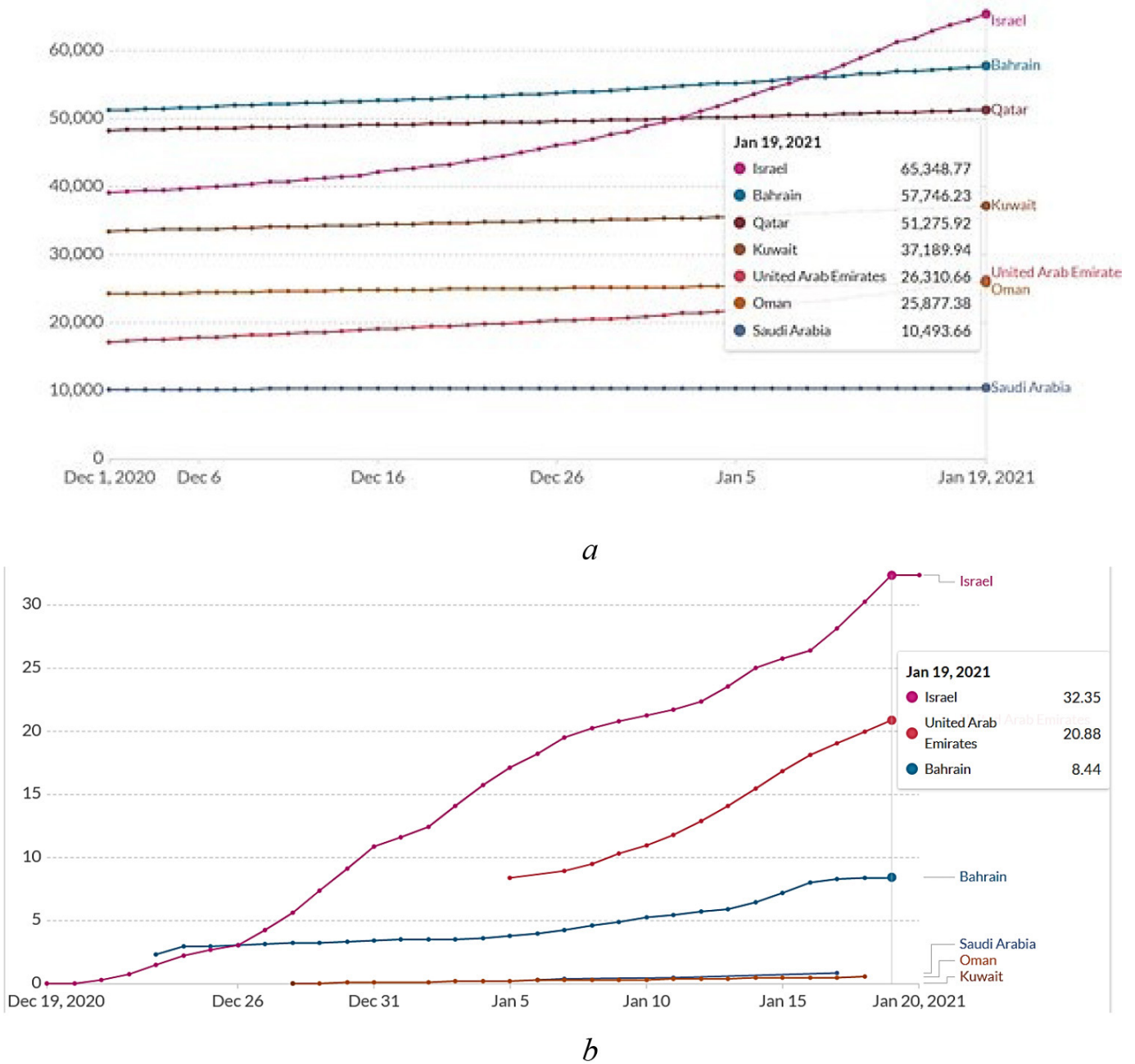
F I G U R E 3. Cumulative cases per million people (a) and vaccine doses administered per 100 people (b). Images from ourworldindata.org. CC BY.

2 doses, then 600 mg PO BID + Camostat 200 mg PO TID ± nebulized Interferon Alpha or Interferon Beta (for 5 days), or Lopinavir-Ritonavir (200/50 mg) 2 tablets PO BID + Ribavirin 400 m PO BID for 7 days + nebulized Interferon, or Remdesivir 200 mg IV on day 1, followed by 100 mg IV daily. Antibiotics may also be used if bacterial co-infection is suspected, plus anticoagulation and steroids when deemed necessary. Tocilizumab may be also considered in the case of the cytokine storm. Convalescent plasma is an additional experimental therapy [4].

4. Discussion

The latest share of the population infected (confirmed cases), an indicator of the extension of the infection, is 6.1% for Belgium and Bahrein, 5.6% for the UK, 5.3% for Qatar, 4.2% for Italy, 3.1% for the UAE, and 0.1% for Australia. With about the same shares of the population infected, the case fatality rates are very different. The latest case fatality rate in the UAE is 0.3%, and neighboring countries such as Qatar and Bahrain have 0.2% and 0.4% respectively. The case fatality rate of the UK is 2.8%, Belgium 3%, Australia 3.2%, and Italy 3.5%. While not only therapies contribute to this huge difference, however, therapies also contribute to making this difference.

The use of antivirals during the initial stages of the infection (asymptomatic at risk, and mild cases) is likely the main reason behind the reduced number of fatalities of countries such as the UAE, Bahrein, and Qatar. It is certainly during the first phase of Covid-19, that viral-induced effects are prominent, and the

antiviral therapies may prevent the build-up of the viral load.

Nebulized interferon is optional in late cases, pneumonia for 7 days, or severe pneumonia/critically ill patients for 10 days [4]. For severe pneumonia/critically ill patients for 10 days, Tocilizumab may be considered in case of cytokine storm [4]. The antivirals are still administered in these late cases [4].

The UAE protocol is based on the available therapeutic options and specific experience. Other antivirals such as umifenovir, oseltamivir, or azithromycin, which are not mentioned in [4], may certainly be valuable.

Information about virus pathophysiology, if needed, can be found in [5, 6].

Antiviral drugs inhibit viral entry, viral membrane fusion, and endocytosis, or the activity of the 3-chymotrypsin-like protease and the RNA-dependent RNA polymerase [7, 8].

Favipiravir is an oral antiviral RNA polymerase inhibitor [9–12], of formula $C_5H_4FN_3O_2$.

Camostat mesylate is an oral antiviral serine protease inhibitor [13, 14].

Lopinavir-Ritonavir, of formula $C_{37}H_{48}N_6O_5S_2$, is an antiretroviral medication for the treatment and prevention of HIV/AIDS repurposed for Covid-19 [15–17].

Ribavirin, of formula $C_8H_{12}N_4O_5$, is an antiviral previously considered for RSV infection, hepatitis C and some viral hemorrhagic fevers, then repurposed for Covid-19 [18–20].

Remdesivir, of formula $C_{27}H_{35}N_6O_8P$, is a broad-spectrum antiviral repurposed for Covid-19 [21–23].

Immune-based-therapy is centered on human blood-derived products and immunomodulatory therapies [24–31].

Interferons are a family of cytokines with indirect antiviral properties [32–34]. They are signaling proteins made and released by host cells in response to viral infection. interferons are cytokines, molecules used for communication between cells to trigger protective defenses.

Corticosteroids, as well as interleukin inhibitors, interferons, kinase inhibitors, are more used as anti-inflammatory treatments, rather than antivirals.

Immune-based therapies (interferon) are used in [4] most as therapies supporting antiviral therapies, rather than standalone options, for anti-inflammatory effects.

Other adjunctive therapies are possible to prevent and/or treat the infection or its complications, and we mention antithrombotic therapy [35, 36], Vitamin C [37, 38], Vitamin D [39, 40], and Zinc [41, 42] as additional lines of actions.

One of the antiviral agents of [4] is CQ/HCQ, which has been at the center of great controversy. Statistically, from the analysis of the works published so far, 230 total, of which 165 peer-reviewed [43], almost 100% of the works support early treatment use. Controversial results are limited to the late cases, with however 74% of the studies still reporting positive effects. The use in early stages, generally supported in the literature [44–52], is also adopted with success in [4].

The protocols of neighboring countries (such as Bahrein and Qatar) also use CQ/HCQ with similarly positive results.

The work [53] that determined the ban of CQ/HCQ in the western countries, was a late study on extremely ill patients that were administered very high HCQ dosage, 1.6 g in the first 24 hours, 9.6 g total over 10 days, with no mention of weight or obesity status of patients to adjust for toxicity. Almost all excess mortality was from ventilated patients who received these extremely high doses for too many days. Asymptomatic Covid-19 cases or Covid-19 cases without pneumonia for 5 days, receive half these dosages over half the total time in [4]. Severe pneumonia/critically ill patients do not receive CQ/HCQ in [4].

While safety vs. efficacy of antivirals has to be considered carefully, without any doubt antivirals are determinant in the fight against Covid-19 infection.

Finally, the UAE is in second place in the world for administered vaccine doses after Israel. The curve of new cases is not decelerating, but accelerating phased on the administration of vaccines, Fig. 3.a,b. While this occurrence may be only temporary, and correlation is not causation, if antivirals are "imperfect", vaccines also have issues.

While vaccine doses are not the same for vaccinated people, as two shots are usually needed, a significant amount of the population of Israel and the UAE starts to be vaccinated, but the number of cases does not stop growing.

While the WHO [54] states that remdesivir, hydroxychloroquine, lopinavir/ritonavir, and interferon "had little or no effect on overall mortality, initiation of ventilation and duration of hospital stay in hospitalized patients" and "only corticosteroids have been proven effective against severe and critical Covid-19" cases, many countries such as the UAE (and Qatar or Bahrein) are using these "imperfect" antivirals while measuring reduced case fatality rates vs. countries that rigidly follow the WHO guidelines.

As it is emerging from the UAE and Israel, where mass vaccinations are ongoing, vaccines are not perfect. In the news, thousands of Israelis tested positive for Covid-19 despite receiving the vaccine [55, 56]. As of January 20, 2021, 189,000 people were tested for Covid-19 after being vaccinated. 12,400 or 6.6% returned a positive result. This is above the levels in the general population at about 5%. The majority was infected shortly after the first of the two shots of the specific vaccine (by Pfizer/BioNTech). However, 1,410 returned a positive result 2 weeks after the first injection, and 69 returned a positive result after both shots of the vaccine. How many people were tested after two shots are unknown.

As of January 20, 2021, 2.15 million people have been vaccinated in Israel over roughly one month. 300,000 of them have received a second dose. The population is 9 million. These vaccinations haven't produced so far any benefit in the curve of newly infected cases.

Further comments are presently impossible, because of the limited data available subjected to continuous update.

The vaccine Israel uses is the Pfizer/BioNTech vaccine. A small number of doses from Moderna have also been administered. Both the Moderna and the Pfizer/BioNTech vaccines require two shots, priming, and booster shots. The interval between shots is 28 days for Moderna and 21 days for the Pfizer vaccine. The three vaccines in the UAE are the Pfizer-BioNTech, the Sinopharm, and the Sputnik V. Sinopharm and Sputnik V are also two doses.

Regarding the very latest vaccination number, the statistic of ourworldindata now includes the number of fully and partially vaccinated.

As of January 30, 2021, in Israel, the cumulative Covid-19

vaccination doses administered per 100 people are 54.72. On December 20, 2020, they were 0.09. The positive rate (the share of Covid-19 tests that are positive) is 5.7% as of January 29, 2021. On December 20, 2020, it was 5.1%. The tendency was decreasing till December 23, 2020, when the tendency changed. A flat 5% positive rate was measured till December 31, 2020. Then, since January 1, 2021, the positive rate started to grow. As of January 30, 2021, in Israel, 19.98% of the population has received full vaccination, and 34.74% of the population received at least one vaccine dose.

As of January 31, 2021, in the UAE the cumulative Covid-19 vaccination doses administered per 100 people are 33.71. On January 5, 2021, they were 8.35. While no prior data is available, vaccinations started December 15, 2020. As of January 29, 2021, the positive rate is 1.2%. On December 20, 2020, it was 1.0%. As of January 31, 2021, in the UAE, 2.53% of the population has received full vaccination, and 31.18% of the population received at least one vaccine dose. Same as Israel, the tendency in the positive rate was a decreasing positive rate till December 27, 2020, when a slightly less than unity positive rate was measured till December 31, 2020. Then, since January 1, 2021, the positive rate started to grow.

The number of tests is much larger in the UAE, while the severity of the outbreak is much worse in Israel.

On January 15, 2021, the UAE was conducting 14.76 tests per 1,000 people, and Israel 12.76. Then, Israel decided to reduce the number of tests, while the UAE decided the opposite. On January 29, 2021, the UAE has performed 17.23 tests per 1,000 people, while Israel has reduced the number of tests to 7.75. The reduction in the number of tests started when the press raised concern about the growing number of cases.

Thus, while vaccinations may certainly help to resolve the Covid-19 emergency, unlikely they will completely address the issue. It is therefore of paramount importance to improve the therapies for those infected, learning from the best performing protocols under objective parameters.

5. Conclusions

The therapeutic approach followed in the UAE seems particularly successful, as the cumulative fatality rate, that however also depends on many other factors, is about 10 times smaller than the one in Italy, Belgium, Australia, or the United Kingdom. The use of antivirals in every phase of Covid-19 infection, but especially asymptomatic and mild to medium cases, is likely one driver of reduced fatalities. Different opportunities are available in the UAE, also based on combining different therapeutic agents. The best treatment of ARDS, often leading to fatalities, is to prevent this occurrence in the early stages. This depends on the way asymptomatic to mild cases are treated, before becoming critical. The use of antiviral agents is determinant to reduce the fatalities of Covid-19 infection. This is the lesson we learn from comparing cases, fatalities, and therapies of different countries.

AUTHOR CONTRIBUTIONS

Single author paper.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

DATA AVAILABILITY

The data used to support the findings of this study are available from the listed references.

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