



Iran as the Center of challenges in the Middle East for the Outbreak of COVID-19 Delta Variant

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Abstract

Context: During the past three decades, the Middle East has experienced three major viral epidemics. Coronavirus disease 2019 (COVID-19) is a pulmonary disease which has been first reported in China in the early third decade of the 21st century and quickly infected people in Asia, the Middle East, and the entire world. This pandemic is life-threatening and has caused widespread financial losses; however, the exact extent of the damage is still unclear.

Evidence Acquisition: This review study aimed to present the latest on the COVID-19 symptoms, pathogenicity, host immune responses, etiology and epidemiology, transmission routes in the Middle Eastern countries, especially Iran, and the role this country plays in the spread of the disease. The search was conducted using Google scholar, PubMed, Scopus, and ISI Web of Science to identify relevant studies published from 2019 to 2021.

Results: Many countries do not have sufficient equipment to prevent, identify, and treat the disease and still have major challenges in controlling this deadly virus. In Iran, a Middle Eastern country, people faced widespread disease and deaths due to the lack of facilities caused by heavy economic and political sanctions. These challenges affect not only Iran but also many neighboring countries. Over time, mutations in the SARS-CoV-2 virus led to the emergence of various variants of the virus, such as Alpha (B.1.1.7), Beta (B.1.351), Gamma (B.1.1.28.1), and Delta (B.1.617.2).

Conclusion: Different variants of SARS-CoV-2 virus pose a substantial menace to public health due to their high transmissibility and ability to escape the immune system. Recently, concerns have increased about the risk of hospitalization and the high spread rate of the COVID-19 delta variant.

Keywords: COVID-19, Delta variant, Middle East, Pandemic, Political sanctions, Pulmonary disease

1. Context

Until recently, coronaviruses, including HCoV-229E, HCoV-NL63, HCoV-HKU1, and HCoV-OC43 have been introduced as mild virulent human viruses worldwide. The most popular coronaviruses in the last two decades include the Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV) with high mortality rates (1). The MERS-CoV virus was identified in a sputum sample of a man with pneumonia in the Middle East (Saudi Arabia) in 2012 (2). In 2019, a severe respiratory disease that could infect lung cells by the new COVID-19 virus was reported from Wuhan city of China and was subsequently declared a pandemic by the World Health Organization (WHO). More than half a million people worldwide became infected and thousands died within months of the outbreak (3-5). On January 30, 2020, the WHO introduced the COVID-19 outbreak

as a public health emergency and an international concern that posed a serious risk to countries with vulnerable health systems. It was announced that COVID-19 might be prevented by the early detection, isolation, rapid treatment, and implementation of a potent COVID-19 tracing system for the early detection of potential virus carriers (6, 7). Despite warnings given by WHO, the COVID-19 virus was not controlled well around the world and turned into a formidable pandemic (6). WHO website provided the daily reports on the number of COVID-19 cases in different areas of the world with the highest number of infected cases. Regarding the fact that the Middle Eastern countries have less equipped health systems, compared to developed countries, they play an important role in disease transmission (8). Recently, concerns have increased with the outbreak of the delta variant of COVID-19. Delta variant of COVID-19 was first reported in India and became more dominant than the alpha (Kent) variant which was first detected in the

UK. This delta variant has become a cause of concern due to the higher risk of hospitalization and the rate of spread (delta variant is roughly 60% more transmissible than the alpha variant) (9-10). Therefore, the number of infected cases increased rapidly in Iran, Pakistan, Kazakhstan, Bangladesh, Iraq, South Korea, Japan, Thailand, Malaysia, Myanmar, and Vietnam. However, it should be noted that Japan has been the most immunized country among the mentioned countries, with only 17.9% of the people being fully vaccinated (9). Meanwhile, due to Iran's strategic location in the Middle East, and the fact that more than 90% of the people have not been still vaccinated, this country can pose a serious threat for the transmission of delta variants of COVID-19. This review article has summarized the general symptoms of COVID-19, the etiology and epidemiology of the disease, the transmission routes, the pathogenesis and host immune responses, and the status of the COVID-19 outbreak in the Middle East, and possible problems of delta variant in Iran.

2. Symptoms

Based on the clinical findings, known symptoms of COVID-19 infection range from simple respiratory problems to septic shock (10). The symptoms of COVID-19 develop approximately 5.2 days after infection and lasts 41 days at a minimum and up to the end of one's life at maximum, with an average of 14 days (11). According to the results of hospitalized patients, most cases of COVID-19 (about 80%) presented without symptoms or with mild symptoms, while some other cases presented with severe symptoms (12, 13). The emergence of symptoms and their severity depends on the age and immune system of patients, and the most common symptoms of COVID-19 include fever, myalgia, cough, shortness of breath, and fatigue. It can also be associated with the appearance of sputum, hypoxemia, headache, haemoptysis, and lymphopenia (12, 14, 15). In addition, the results of another study have shown that patients infected with COVID-19 also develop other symptoms, such as nausea, vomiting, chest pain, and confusion (16). Other than clinical signs of pneumonia detected by chest CT scans, there are a number of abnormal features, such as acute respiratory distress syndrome, secondary infections, pneumothorax, RNAemia, the incidence of grand-glass opacities, and acute cardiac injury that can lead to the patient's death (12, 17). In some cases, opacities affect both lungs (bilateral multiple lobular and subsegmental areas of consolidation in comparison to viral pneumonia), lead to increased inflammation, and result in the worsened condition of patients due to the development of pulmonary opacities (12, 18). Moreover, COVID-19 has some unique clinical features that affect the lower airways. However, upper respiratory tract symptoms include sneezing,

rhinorrhoea, and sore throat (19). As confirmed by previous epidemics, patients with underlying comorbidities are expected to experience a more severe clinical course (20). It should be noted that patients infected with COVID-19 exhibit gastrointestinal symptoms, such as diarrhea. Therefore, health care workers need to test patients' faeces and urine specimens to interrupt transmission routes of the disease (19). While the appearance of all symptoms helps diagnose the disease, in some cases the patient may be a carrier without symptoms (21). The findings of a study conducted on 24 asymptomatic individuals who were in contact with patients showed that all of them were positive for COVID-19, based on molecular testing. After hospitalization, five patients showed symptoms, including cough, fever, and fatigue, 12 cases had typical CT images with ground glass opacities, and five cases had stripe shadow in lung, based on their CT images. However, seven cases had no symptoms and normal CT images. Therefore, monitoring and evaluation of people who have been in close contact with patients are very important for the disruption of the transmission pathway (22). Olfactory sensation disorder is an interesting symptom of COVID-19, which is said to occur in two-thirds of all patients and seems to be a temporary symptom. Odor disorder appears to be distinct from rhinitis or upper respiratory tract olfactory disorders caused by COVID-19 since most patients experience a relatively sudden onset of olfactory symptoms and almost a complete olfactory loss (almost anosmia, rarely Hypoxemia). In addition, there are usually fewer side effects, such as nasal breathing, nasal obstruction, clinical joint rhinitis or excessive diarrhea in patients with COVID-19. The pathomechanism of COVID-19 in causing olfactory nerve damage (usually maintaining a sense of taste) is still unclear (23). All of these symptoms are probably observed in delta variant of COVID-19. Currently, patients who contract COVID-19 in the UK experience the disease as something similar to a severe cold. Loss of taste and smell and shortness of breath were no longer prominent symptoms which can be related to the delta variant of COVID-19, vaccination status, and the age of infection which complicate control efforts. It has been shown that symptoms of delta variant appeared to be milder than COVID-19 symptoms, and therefore the patient might be wrongly diagnosed with hay fever or cold and not be isolated as a result (24). It has been reported that all key transmission parameters in delta variant of COVID-19 including the generation time (the interval between infection of the primary and secondary cases), the incubation period (the period of time from infection to illness onset), and the serial interval (the interval between the onset of symptoms in primary and secondary cases) occurred in shorter periods of time than previous variants (25) (Figure 1).

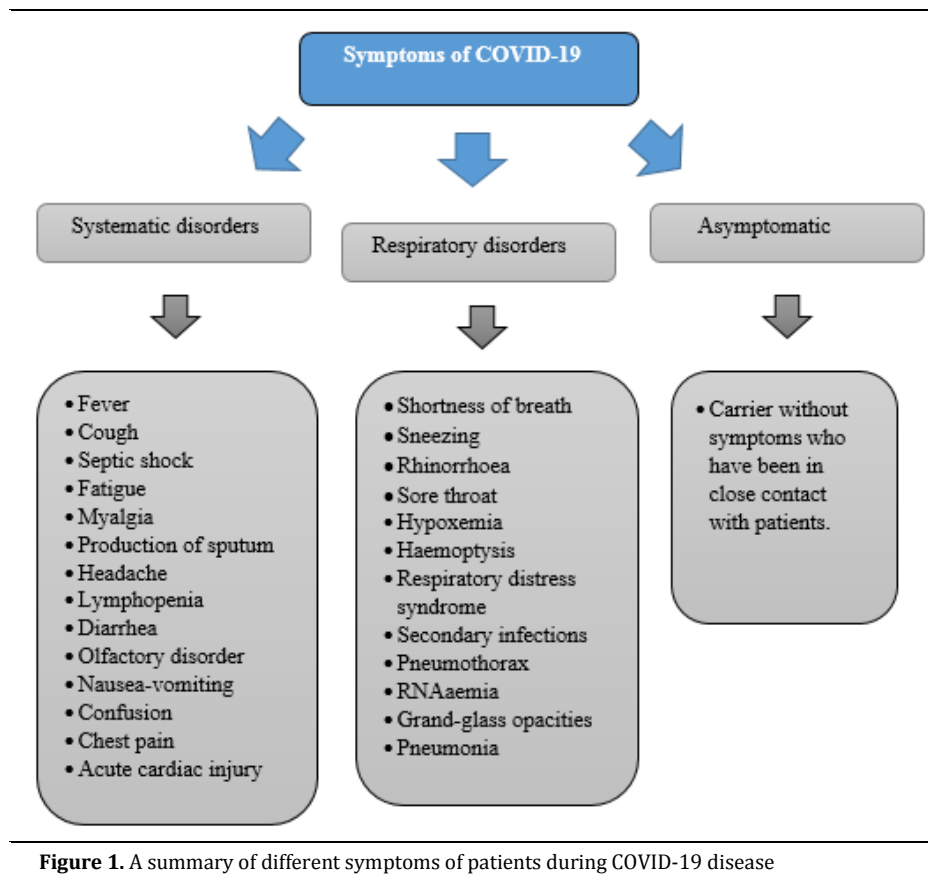


Figure 1. A summary of different symptoms of patients during COVID-19 disease

3. Etiology and Epidemiology

Coronavirus, as a potential cause of colds and respiratory diseases, has been identified for less than a century (26). Coronavirus is a virus from the family of positive-sense single-stranded RNA viruses belonging to the beta-coronavirus genus (27). The diameter of the virus is nearly 60 to 140 nanometers with spikes on the surface of the virus structure which can be polymorphic, oval, or spherical in shape. Cell lines can grow up to four days in ex-vivo conditions on Vero E6/Huh-7. The genomic RNA size of the virus is 29903 bp, and (Membrane)-N, 5-leader-UTR-replicase S, (Spike)-E, (Envelope)-M, (Nucleocapsid)-3' UTR poly (A) tail with unknown open reading frames from the genome (28). Based on genome sequencing results, COVID-19 is very similar to bat-SARS, such as bat-SARS-like (SL)-ZC45 and bat-SL-ZXC2 (29). Genome analysis of COVID-19 revealed about 80% similarity to the SARS-CoV genome; however, less similarity was observed with the MERS-CoV (30). The National Administration of Traditional Chinese Medicine reported that COVID-19 was highly sensitive to chlorine disinfectant, 75% ethanol, and 56 °C for 30 min, and even peracetic acid can inactivate the virus (31). According to the findings of a previous study, coronaviruses can be eliminated by exposure to other disinfectants, such as 0.5% hydrogen peroxide or 0.1% sodium hypochlorite within 1 min; however, some biocidal agents, such as 0.05-0.2% Benzalkonium

chloride or chlorhexidine digluconate (0.02%) are not as effective on virus inactivation (32). Human coronaviruses are sensitive to quaternary ammonium compounds, cetylpyridinium chloride, and ultraviolet (UV) light (33). The SARS-CoV-2 has the receptor called angiotensin-converting enzyme 2 (ACE2) that is a surface molecule and highly expressed in lung AT2 cells, esophageal epithelial cells, as well as ileum and colon enterocytes (34, 35). Studies conducted on patients with viral pneumonia have shown that exposure to high-risk animals increases the likelihood of infections that are transmitted from animals to humans. It was also reported that the novel COVID-19 originated from wild bats and its genome was very similar to that of the SARS-CoV, despite some genetic differences (36-38). Although research demonstrated that COVID-19 pneumonia originated from the Huanan seafood market in Wuhan city of China in December 2019, there were cases of laboratory-confirmed COVID-19 infected patients who were not exposed to the market (37, 39, 40). This indicates the fact that COVID-19 can be transmitted from human to human, and the intermediate host for the spread of the virus is still unknown (41, 42). The Spring Festival is the most famous traditional Chinese festival, where COVID-19 (like the SARS epidemic) spread during the festival, with around 3 billion people traveling around the country. The festival was held between January 10 and February 18, 2020, and led to a rapid increase in COVID-19 cases. Wuhan city of China has been the

center of the Spring Festival transportation network and became a main epidemic center during Spring Festival. The large-scale travel volume provided favorable conditions for the transmission of this highly contagious disease and created severe problems in the prevention and control of epidemics (43). In addition, it should be noted that demand for sheep, pigs, poultry, dogs, and cows is high in the Chinese Spring Festival; therefore, it has been suggested that dogs, sheep, pigs, and cows may serve as betacoronavirus reservoirs in this festival. However, some scientists believe that pigs are the intermediate host of the COVID-19 and that the virus has been transmitted from pigs to humans (26, 44). Following the localization of the epidemic in Wuhan city of China, COVID-19 disease was transferred to other cities and provinces, and eventually, it was observed in the Asian, African, European, Pacific, and American countries (3, 45). At this time, it is difficult to determine the death rate of COVID-19 precisely since the actual number of infected people is still unknown. However, according to the obtained reports, about 2.84% of patients died by novel COVID-19, and at least 10% of cases showed severe clinical symptoms (15, 46). Over time, mutations in the SARS-CoV-2 virus have led to the emergence of various variants of the virus, including Alpha (B.1.1.7), Beta (B.1.351), Gamma (B.1.1.28.1), and Delta (B.1.617.2) variants. These variants posed a substantial public health menace due to their high transmissibility and ability to escape the immune system (47). The occurrence of mutations containing L452R and P681R in the SARS-CoV-2 spike protein's receptor binding domain of the delta variant (amino acid change inside 438–506 position) was found to be correlated with high transmissibility as well as fast spread of severe cases of this variant in India. Furthermore, these mutations raised concerns about the impact of this variant and its ability to evade vaccines (48). According to the results of genetic studies, the delta variant is rapidly outcompeting alpha, and is a predominant lineage in the UK at present. Moreover, the latest statistics indicated that the delta variant is now accounting for 72.93% of all the new cases. Mutation in L452R can be contributed to increased interaction with the ACE2 receptor of the spike protein of delta variant and most likely enhanced the infection rate. In addition, other mutations (i.e., E484K/E484Q) enhanced the binding affinity through changing the electrostatic interactions, and newer hydrogen bindings occurred simultaneously (49). The very high rate of COVID-19 delta variant transmission is a major problem among individuals, compared to previous variants. The COVID-19 infections continued to increase intensely after the double mutated delta variant was detected in India. Therefore, the new daily cases pushed the healthcare system of India to the brink of collapse, and hospitals faced a shortage of beds and a lack of oxygen supply for critical patients. The delta variant of COVID-19 are transmitted from

India to many neighboring countries (due to frequent travels to India from other countries) to the point that all South Asian countries are now infected with the virus (50). The findings revealed that the delta variant of COVID-19 was extremely transmissible within households and in indoor sports settings (51). At present, various lineages are circulating in India and worldwide, and the speedy spread of delta variant compared to other variants can probably be due to natural selection and genetic displacement of the SARS-CoV-2 genome.

4. Transmission routes

It should be noted that many people infected with COVID-19 in the Chinese animal market have been exposed to live animals; therefore, it appears that COVID-19 is of zoonotic origin. Many studies have been performed to identify COVID-19 intermediate reservoirs or carriers (i.e., intermediate host animals); however, the researchers have not reached a consensus in this regard (26, 52, 53). According to genomic analysis, most similarities have been observed between human COVID-19 and the bat coronavirus genomes; therefore, the bat is most probably the intermediate host (27, 54). It has been proposed that other live animals, such as bats, camels, cattle, and cats can also be infectious agents for the transmission of COVID-19 (10, 55, 56). Numerous studies have reported that COVID-19 infection spreads through human-to-human by droplet particles. Droplet-borne pathogens can spread through close contact of a patient with a healthy person. In general, these pathogens do not remain infectious for a long period and cannot travel a relatively long distance; however, it appears that COVID-19 can potentially travel longer in the air. Therefore, it is necessary to place the patients in a single room, keep a distance of three feet with the patient, and use a mask for combating these pathogens (14, 57, 58). A study investigated the transmission of COVID-19 from mother to child in the third trimester. The results revealed that all of the women were infected; however, no mother-to-child transmission event was observed. Regarding the fact that all pregnant mothers underwent cesarean section, it was not clear whether the transmission of the disease occurred during vaginal birth (59).

Regarding the difference between the delta variant of COVID-19 and previous variants, it should be noted that the delta variant is an "improved" version of the alpha variant and more transmissible due to sets of mutations, especially important mutations in its spike protein. One of the mutations in the virus has occurred at the furin cleavage site, which has enhanced the adaptability of the delta variant to the human airway, compared to the Wuhan virus (60). The delta variant is "fitter in human airway cells", which results in the raised amount of the virus in the infected patients.

Therefore, more viruses are thrown out into the air and passed to others. Regarding the fact that the delta variant is better at infecting human airway cells, populations would probably be infected after a shorter exposure time (60).

5. Pathogenesis and host immune responses

The pathogenesis of COVID-19 is not yet well understood; however, similar to SARS-CoV and MERS-CoV, it can provide much information about the mechanism of pathogenesis (61). Human-to-human transmission by close contact is the main pathway for the transmission of COVID-19 infection when the droplets of an infected person spread through a cough or sneeze (62). The same as SARS-CoV, COVID-19 binds to the ACE2 receptor on the cell surface through the spike (S) protein and then enters the cell (28, 62). The process of entry into cells occurs through a direct fusion of the membrane between the virus and cell membrane of the host. The fusion is caused by the occurrence of an important proteolytic event at the S20 position of the protein S of coronavirus (63, 64). In addition to membrane fusion, clathrin-dependent and independent endocytosis pathways have also been implicated for the entry of SARS-CoV into the cell (65, 66). When the virus enters the cell, it releases its genome into the cytoplasm, which translates it into two proteins (i.e., polyprotein and structural protein) and then replicates the viral genome (67). The newly synthesized glycoprotein envelope is inserted into the endoplasmic reticulum (RE) or Golgi membrane, and the nucleocapsid is formed by a combination of genomic RNA and nucleocapsid protein. In the next stage, the viral particles germinate in the endoplasmic reticulum-Golgi intermediate compartment (ERGIC). Eventually, vesicles that carry the virus combine with the plasma membrane to release the virus out of the cell (62). The delivery of viral antigens to the antigen-presenting cells induces the central antiviral immunity in the body when the virus enters the cells. Virus peptide antigens are presented with the major histocompatibility complex and identified by specific cytotoxic T lymphocytes (68). Antigen presentation results in the stimulation of humoral and cellular immunity by virus-specific B and T cells and produces a pattern of IgM and IgG antibodies against SARS-CoV virus similar to acute viral infections in which IgG plays a protective role (69). CD4⁺ and CD8⁺ T cells were over-activated in cellular immunity and were significantly reduced in the peripheral blood of patients with SARS-CoV-2. The CD4⁺ and CD8⁺ memory T cells produced against coronavirus can be present for up to four years (even up to 6 years in some individuals) in the recovered patient's body (even in the absence of antigen) and result in capable T cell proliferation, delayed-type hypersensitivity

response, and IFN- γ production (70, 71). Acute respiratory distress syndrome (ARDS) is a common immunopathological event occurring in SARS-CoV and MERS-CoV infections and is the most important cause of COVID-19 death (12, 72). Cytokine storm is one of the main mechanisms involved in ARDS, in which large amounts of pro-inflammatory cytokines, such as IFN- α , IFN- γ , IL-1 β , IL-6, IL-12, IL-18, IL-33, TNF- α , G-CSF, IP-10, MCP-1, MIP-1A, TGF β as well as chemokines, such as CCL2, CCL3, CCL5, CXCL8, CXCL9, and CXCL10 are produced and released by immune cells against coronavirus infection (12, 73, 74). The cytokine storm leads to a deadly and uncontrolled systemic inflammatory response in a patient, through which the immune system attacks the body, causes ARDS, respiratory failure, shock, multiple organ failure, and even death in severe cases (72, 75).

The rate of transmission is higher in the delta variant of COVID-19, and it can escape the immune system more easily. Moreover, this variant affects human airway cells more than other variants. Therefore, the rate of inflammatory responses will likely be higher in this variant as a result (47, 60). The high prevalence of the delta variant leads to a shortage of beds and an increase in the number of patients. As a result, the health system of countries, especially countries with poor health systems, cannot cope with this variant, and cytokine storms caused by this disease can be very dangerous for patients.

6. Iran as the center of important events in the Middle East

The Middle East is a special geographical region encompassing most of the West Asian and Egyptian countries, with a total of 17 countries with different ethnicities (76). The region is one of the most populous political and economic centers in the world. People in this region perform many unique and varied religious and cultural practices, including the annual Hajj, pilgrimage to Mashhad city of Iran, traveling to both rural and urban areas, and using camel for food, medicine, and business (76, 77). About 2.5 million Muslims from 180 countries travel to Saudi Arabia every year to perform the Umrah Hajj. In addition, Karbala's annual pilgrimage is another Shia Muslim ritual that lasts for 40 days, with more than 20 million people gathering in Karbala, Iraq. Many pilgrims become ill and hospitalized due to respiratory tract disease during these religious events (78-80). Moreover, risk factors for severe diseases are common among people in the Middle East (76). These unique features have created favorable conditions for the rapid spread of newly mutated viruses.

As indicated by previous surveys, three major viral epidemics have occurred in the last three

decades, all originating from regions in Asia and the Middle East and spreading to other countries in the world (81-83). In the first decade of the 21st century, the world was witnessing the devastating outbreak of SARS in China. The emergence of MERS syndromes in the second decade of this century led to the outbreak of a severe respiratory epidemic in the Middle East, Europe, Africa, Asia, and North America (84, 85). Beginning in the third decade of the 21st century in China, COVID-19 infected people all around the world within a few months (86). In this condition, Iran has played a very important role among the Middle East countries due to the largest number of COVID-19 infected cases and mortality rate. Several countries in the vicinity of Iran (i.e., Bahrain, Iraq, Kuwait, Oman, Afghanistan, Saudi Arabia, Qatar, and Pakistan) and even more remote countries (e.g., Estonia, Georgia, New Zealand, and Belarus) reported the COVID-19 cases transmitted from Iran (Figure2) (8, 87, 88).

An important point to note here is the poor economic condition of Iran due to crippling sanctions that have been imposed on this country for decades and have reached the highest level shortly before the COVID-19 epidemic. In 2019, the United States increased the sanctions and economically pressured Iran. These sanctions even included heavy penalties imposed on non-American companies for trading with Iran which has affected the overall potential of the health sector and resulted in the rapid growth of the disease and lack of facilities to combat COVID-19. Accordingly, with the sudden increase in COVID-19 cases, the issue of outbreak and control has come to the forefront, and a National Committee was formed to fight COVID-19 using skilled personnel, facilities, and knowledge available in the country (89).

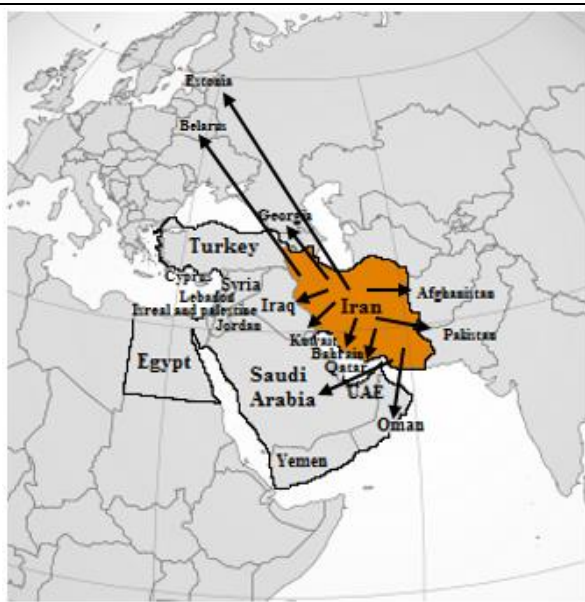


Figure 2. Distribution of confirmed cases of COVID-19 from Iran to other coun

Iran used national media to disseminate protective recommendations of WHO which requested people to wash hands frequently, keep a distance of at least one meter, avoid hand-to-face contact, wear a mask, and refer to medical centers upon the appearance of the disease symptoms, such as fever, cough, and shortness of breath. Other measures taken in this regard included a) obstruction of crowded areas of pilgrimage, tourism, markets, kindergartens, schools, and universities, b) reduction of office work hours, c) cancelation of Friday prayers and sports competitions, d) disinfection of public places, e) identification of COVID-19 suspects on New Year's holiday trips, and f) formation of groups in health centers for the diagnose of the disease (89). People have been faced with a shortage of preventive, pharmaceutical, and laboratory equipment during the forced sanctions, and shortly there was an increase in mortality which was considered a danger to the neighboring countries (8, 88, 90). Many countries (even those not close to Iran) have reported the prevalence of COVID-19 originating from Iran, and there is a possibility that these cases include the delta variant as well. In a study, lineages were identified as the delta variant for the first time in Pakistan, and the infected patients were associated with international travel with one patient traveling back from Saudi Arabia and the other from the Middle East.

Delta variant in infected patients with travel history to Saudi Arabia exhibited high similarities to viral isolates from Bangladesh, England, and India. A close correlation with Indian isolates was observed in another patient with a history of Middle East travel. There were reported cases infected with B.1.617.2 (Delta) variant which had traveled back from Bahrain to Pakistan. One significant mutation E484Q was found in this variant which made it more resistant to monoclonal antibodies and contained bamlanivimab and convalescent plasma (91, 92). The first detected and reported cases of patients with COVID-19 included two Omani nationals in Oman who had returned from a trip to Iran. This data proposes the introduction of the delta variant through the importation of patients from different Middle East countries (93). Although vaccination is taking place in the Middle Eastern countries, the delta variant has still the ability to escape the immune system due to the slow vaccination rate in these countries. It was reported that a single dose of the Pfizer-BioNTech or AstraZeneca vaccines was 50% and 33% effective against Alpha and delta variant of COVID-19 (three weeks after the first dose), respectively. However, the effectiveness of Pfizer-BioNTech and AstraZeneca vaccines against the delta variant has been reported to increase up to 88% and 60% two weeks after the second dose, respectively (60). Furthermore, it was presented that mRNA-based vaccines were effective and induced a substantial antibody response against the

known delta variant of COVID-19, while the neutralizing levels were significantly lower, compared with the original virus variant (48). On the other hand, the ease of restrictions (about two years after the onset of the disease) following the start of vaccination and the reduced number of patients led to the spread of the mutated form of delta variant in Iran. The pure scientific basis of delayed COVID-19 restriction ease allowed more population groups to receive two doses of the vaccine.

After the second dose of the vaccine, it takes about 7 days for the immune system to be boosted up against the virus (60). To this date, less than 10 percent of Iran's population are vaccinated, and sanctions impacted the vaccination process profoundly. Although the country has become self-sufficient in the production of medical equipment such as masks, gloves, and disinfectants, the medical staff are exhausted, and there is a lack of empty hospital beds for the patients with delta variant that is rapidly spreading throughout the country and creating the fifth wave of the disease. Many of the drugs required for the treatment of COVID-19 are either scarce or very expensive in Iran due to the imposed sanctions. Therefore, the strategic position of Iran in the expansion of COVID-19 in the Middle East, and the circulation of the delta variant among Iranians should be an early warning to national health authorities to take timely decisions in this regard. This also highlights the urgent need for tracing the virus and preventing its spread, which requires the cooperation of various global organizations.

7. Conclusion

The COVID-19 pandemic has led to a daily increase in the number of patients and mortality in different countries. Identification of asymptomatic people who are in close contact with patients can help break the chain of transmission. However, prevention of the disease, identification of asymptomatic individuals, and timely treatment of COVID-19 cases require adequate facilities. However, despite having the highest rate of incidence and mortality in the Middle East, Iran cannot potentially cope with the COVID-19 due to the shortage of facilities, drugs, and vaccines caused by economic sanctions. This issue puts all of Iran's neighbors in the Middle East and associated countries at great risk.

Iran is also one of the countries in which the delta variant of COVID-19 is increasing daily due to its vicinity with India. This is a major risk since the delta variant of COVID-19 is highly contagious among the unvaccinated population, and about 90% of Iranians are not yet vaccinated. Therefore, the emergence of the fifth wave of the COVID-19 with this new variant is not far from expectation.

Therefore, great attention should be paid to the prevalence of different variants, and non-pharmacological interventions should be maintained,

even after continuous COVID-19 vaccination. Transmission of the delta variant of COVID-19 is faster and more intense than previous variants. At present, proper education of people about non-drug interventions can be effective against the spread of this pandemic, and the ignorance of people about symptoms of delta variant will make things much worse. Therefore, WHO recommendations should be maintained until the pandemic is fully controlled in different areas. Otherwise, the rise in the hospital admission rates increases the pressure on the poorly equipped health care system.

Eventually, the implementation of preventive measures, such as efficient screening, maintenance of strict quarantine protocols for international flights, and faster vaccination can help restrict new variants of COVID-19 in the community. In this critical situation, the United States and the international community must reduce sanctions imposed on Iran to prevent the spread of the disease that endangers the lives of thousands. The European Union must also abide by its commitments to support the Iranian people in a difficult situation. It should be noted that not only the Iranian people but also people all over the world, even in countries that have imposed sanctions against Iran, were negatively affected by the sanctions since viruses do not differentiate between their hosts. Accordingly, the international community and the United States should decide to stop sanctions that endanger the lives of thousands of people worldwide.

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Footnotes

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References

1. Organization WH. Laboratory testing for coronavirus disease 2019 (COVID-19) in suspected human cases: interim guidance. 2020. *WHO*. 2020.
2. Yavarian J, Rezaei F, Shadab A, Soroush M, Gooya MM, Azad TM, et al. Cluster of Middle East respiratory syndrome coronavirus infections in Iran, 2014. *Emerg Infect Dis*. 2015;21(2):362-4. doi: [10.3201/eid2102.141405](https://doi.org/10.3201/eid2102.141405). [PubMed: [25626079](https://pubmed.ncbi.nlm.nih.gov/25626079/)].
3. WHO. Novel Coronarities (2019-Nov) situation report - 55. 2020.
4. Dousari AS, Moghadam MT, Satarzadeh N. COVID-19 (Coronavirus disease 2019): a new coronavirus disease. *Infect Drug Resist*. 2020;13:2819-28. doi: [10.2147/IDR.S259279](https://doi.org/10.2147/IDR.S259279). [PubMed: [32848431](https://pubmed.ncbi.nlm.nih.gov/32848431/)].
5. Moghadam M, Babakhani S, Rajabi S, Baravati F, Raeisi M,

- Dousari A, et al. Does Stress and Anxiety Contribute to COVID-19?. *Iran J Psychiatry Behav Sci.* 2021;**15**(1):1-2. doi: [10.5812/ijpbs.106041](https://doi.org/10.5812/ijpbs.106041).
6. Organization WH. Coronavirus disease 2019 (COVID-19) Situation Report 12, 30th January 2020. 2020.
 7. Moghadam MT, Taati B, Paydar Ardakani SM, Suzuki K. Ramadan fasting during the COVID-19 pandemic; observance of health, nutrition and exercise criteria for improving the immune system. *Front Nutr.* 2021;**7**:1-10. doi: [10.3389/fnut.2020.570235](https://doi.org/10.3389/fnut.2020.570235). [PubMed: [33521030](https://pubmed.ncbi.nlm.nih.gov/33521030/)].
 8. Zhuang Z, Zhao S, Lin Q, Cao P, Lou Y, Yang L, et al. Preliminary estimation of the novel coronavirus disease (COVID-19) cases in Iran: a modelling analysis based on overseas cases and air travel data. *Int J Infect Dis.* 2020;**95**(2020):319-320. doi: [10.1016/j.ijid.2020.04.073](https://doi.org/10.1016/j.ijid.2020.04.073). [PubMed: [32360940](https://pubmed.ncbi.nlm.nih.gov/32360940/)].
 9. Dyer O. Covid-19: Indonesia becomes Asia's new pandemic epicentre as delta variant spreads. *BMJ.* 2021;**374**(1815):1-1. doi: [10.1136/bmj.n1815](https://doi.org/10.1136/bmj.n1815). [PubMed: [34272255](https://pubmed.ncbi.nlm.nih.gov/34272255/)].
 10. Sahin AR, Erdogan A, Agaoglu PM, Dineri Y, Cakirci AY, Senel ME, et al. 2019 Novel Coronavirus (COVID-19) Outbreak: A Review of the Current Literature. *Eurasian J Med Oncol.* 2020;**4**(1):1-7.
 11. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N Engl J Med.* 2020;**382**(13):1-10. doi: [10.1056/NEJMoa2001316](https://doi.org/10.1056/NEJMoa2001316).
 12. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020;**395**(10223):497-506. doi: [10.1016/S0140-6736\(20\)30183-5](https://doi.org/10.1016/S0140-6736(20)30183-5).
 13. Chan JF-W, Yuan S, Kok K-H, To KK-W, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet.* 2020;**395**(10223):514-23. doi: [10.1016/S0140-6736\(20\)30154-9](https://doi.org/10.1016/S0140-6736(20)30154-9).
 14. Carlos WG, Dela Cruz CS, Cao B, Pasnick S, Jamil S. Novel wuhan (2019-nCoV) coronavirus. *Am J Respir Crit Care Med.* 2020;**201**(4):p7-p8. doi: [10.1164/rccm.2014P7](https://doi.org/10.1164/rccm.2014P7). [PubMed: [32004066](https://pubmed.ncbi.nlm.nih.gov/32004066/)].
 15. Wang W, Tang J, Wei F. Updated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan, China. *J Med Virol.* 2020;**92**(4):441-7. doi: [10.1002/jmv.25689](https://doi.org/10.1002/jmv.25689). [PubMed: [31994742](https://pubmed.ncbi.nlm.nih.gov/31994742/)].
 16. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet.* 2020;**395**(10223):507-13. doi: [10.1016/S0140-6736\(20\)30211-7](https://doi.org/10.1016/S0140-6736(20)30211-7). [PubMed: [32007143](https://pubmed.ncbi.nlm.nih.gov/32007143/)].
 17. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, Villamizar-Peña R, Holguin-Rivera Y, Escalera-Antezana JP, et al. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. *Travel Med Infect Dis.* 2020;**34**:1-14. doi: [10.1016/j.tmaid.2020.101623](https://doi.org/10.1016/j.tmaid.2020.101623) [PubMed: [32179124](https://pubmed.ncbi.nlm.nih.gov/32179124/)].
 18. Lei J, Li J, Li X, Qi X. CT imaging of the 2019 novel coronavirus (2019-nCoV) pneumonia. *Radiology.* 2020;**295**(1):1-1. doi: [10.1148/radiol.2020200236](https://doi.org/10.1148/radiol.2020200236). [PubMed: [32003646](https://pubmed.ncbi.nlm.nih.gov/32003646/)].
 19. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *J Autoimmun.* 2020;**109**:1-5. doi: [10.1016/j.jaut.2020.102433](https://doi.org/10.1016/j.jaut.2020.102433). [PubMed: [32113704](https://pubmed.ncbi.nlm.nih.gov/32113704/)].
 20. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. *Lancet.* 2020;**395**(10223):470-3. doi: [10.1016/S0140-6736\(20\)30185-9](https://doi.org/10.1016/S0140-6736(20)30185-9). [PubMed: [31986257](https://pubmed.ncbi.nlm.nih.gov/31986257/)].
 21. Hellewell J, Abbott S, Gimma A, Bosse NI, Jarvis CI, Russell TW, et al. Feasibility of controlling COVID-19 outbreaks by isolation of cases and contacts. *Lancet Glob Health.* 2020;**8**(4):488-96. doi: [10.1016/S2214-109X\(20\)30074-7](https://doi.org/10.1016/S2214-109X(20)30074-7). [PubMed: [32119825](https://pubmed.ncbi.nlm.nih.gov/32119825/)].
 22. Hu Z, Song C, Xu C, Jin G, Chen Y, Xu X, et al. Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. *Sci China Life Sci.* 2020;**63**(5):706-711. doi: [10.1007/s11427-020-1661-4](https://doi.org/10.1007/s11427-020-1661-4). [PubMed: [32146694](https://pubmed.ncbi.nlm.nih.gov/32146694/)].
 23. Lüers J-C, Klusmann JP, Guntinas-Lichius O. Die Covid-19-Pandemie und das HNO-Fachgebiet: Worauf kommt es aktuell an? *Laryngo-Rhino-Otol.* 2020;**99**(5):1-5. doi: [10.1055/a-1095-2344](https://doi.org/10.1055/a-1095-2344).
 24. Burki TK. Lifting of COVID-19 restrictions in the UK and the Delta variant. *Lancet Respir Med.* 2021;**9**(8):e85. doi: [10.1016/S2213-2600\(21\)00328-3](https://doi.org/10.1016/S2213-2600(21)00328-3). [PubMed: [34265238](https://pubmed.ncbi.nlm.nih.gov/34265238/)].
 25. Zhang M, Xiao J, Deng A, Zhang Y, Zhuang Y, Hu T, et al. Transmission Dynamics of an Outbreak of the COVID-19 Delta Variant B. 1.617. 2—Guangdong Province, China, May–June 2021. *China CDC Wkly.* 2021;**3**(27):584-6. doi: [10.46234/ccdcw2021.148](https://doi.org/10.46234/ccdcw2021.148). [PubMed: [34594941](https://pubmed.ncbi.nlm.nih.gov/34594941/)].
 26. Zhou D, Zhang P, Bao C, Zhang Y, Zhu N. Emerging Understanding of Etiology and Epidemiology of the Novel Coronavirus (COVID-19) Infection in Wuhan, China. *Preprints.* 2020:1-12. doi: [10.20944/preprints202002.0283.v1](https://doi.org/10.20944/preprints202002.0283.v1).
 27. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet.* 2020;**395**(10224):565-74. doi: [10.1016/S0140-6736\(20\)30251-8](https://doi.org/10.1016/S0140-6736(20)30251-8). [PubMed: [32007145](https://pubmed.ncbi.nlm.nih.gov/32007145/)].
 28. Wu F, Zhao S, Yu B, Chen Y-M, Wang W, Song Z-G, et al. A new coronavirus associated with human respiratory disease in China. *Nature.* 2020;**580**(7803):e7. doi: [10.1038/s41586-020-2202-3](https://doi.org/10.1038/s41586-020-2202-3). [PubMed: [32296181](https://pubmed.ncbi.nlm.nih.gov/32296181/)].
 29. Chen Y, Liu Q, Guo D. Emerging coronaviruses: genome structure, replication, and pathogenesis. *J Med Virol.* 2020;**92**(4):418-23. doi: [10.1002/jmv.25681](https://doi.org/10.1002/jmv.25681). Epub 2020 Feb 7. [PubMed: [31967327](https://pubmed.ncbi.nlm.nih.gov/31967327/)].
 30. Ceraolo C, Giorgi FM. Genomic variance of the 2019-nCoV coronavirus. *J Med Virol.* 2020;**92**(5):522-28. doi: [10.1002/jmv.25700](https://doi.org/10.1002/jmv.25700). [PubMed: [32027036](https://pubmed.ncbi.nlm.nih.gov/32027036/)].
 31. National Health Commission of the people's Republic of China, Medicine NAOtC. Handbook of Prevention and Treatment of the Pneumonia Caused by the Novel Coronavirus (2019-nCoV) (Trial version 5).
 32. Lai C-C, Shih T-P, Ko W-C, Tang H-J, Hsueh P-R. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): the epidemic and the challenges. *Int J Antimicrob Agents.* 2020;**55**(3):1-9. doi: [10.1016/j.ijantimicag.2020.105924](https://doi.org/10.1016/j.ijantimicag.2020.105924). [PubMed: [32081636](https://pubmed.ncbi.nlm.nih.gov/32081636/)].
 33. Organization WH. Water, sanitation, hygiene and waste management for COVID-19: technical brief, 03 March 2020. *WHO.* 2020.
 34. Hoffmann M, Kleine-Weber H, Krüger N, Mueller MA, Drosten C, Pöhlmann S, et al. The novel coronavirus 2019 (2019-nCoV) uses the SARS-coronavirus receptor ACE2 and the cellular protease TMPRSS2 for entry into target cells. *BioRxiv.* 2020
 35. Zhang H, Kang Z, Gong H, Xu D, Wang J, Li Z, et al. The digestive system is a potential route of 2019-nCoV infection: a bioinformatics analysis based on single-cell transcriptomes. *BioRxiv.* 2020;**0**:1-9. doi: [10.1101/2020.01.30.927806](https://doi.org/10.1101/2020.01.30.927806).
 36. Yin Y, Wunderink RG. MERS, SARS and other coronaviruses as causes of pneumonia. *Respirology.* 2018;**23**(2):130-7. doi: [10.1111/resp.13196](https://doi.org/10.1111/resp.13196). [PubMed: [29052924](https://pubmed.ncbi.nlm.nih.gov/29052924/)].
 37. World Health Organization, 2019-nCoV Situation Report. 2020.
 38. Gralinski LE, Menachery VD. Return of the Coronavirus: 2019-nCoV. *Viruses.* 2020;**12**(2):1-8. doi: [10.3390/v12020135](https://doi.org/10.3390/v12020135). [PubMed: [31991541](https://pubmed.ncbi.nlm.nih.gov/31991541/)].
 39. Imai N, Dorigatti I, Cori A, Donnelly C, Riley S, Ferguson NM, et al. Report 2: Estimating the potential total number of novel Coronavirus cases in Wuhan City, China. *Imperial College London.* 2020:1-6. doi: <https://doi.org/10.25561/77150>
 40. Guan W-j, Ni Z-y, Hu Y, Liang W-h, Ou C-q, He J-x, et al. Clinical characteristics of 2019 novel coronavirus infection in China. *medRxiv.* 2020. doi: [10.1101/2020.02.06.20020974](https://doi.org/10.1101/2020.02.06.20020974).
 41. Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Di Napoli R. Features, Evaluation and Treatment Coronavirus (COVID-19). *StatPearls [Internet]: StatPearls Publishing.* 2021. [PubMed: [32150360](https://pubmed.ncbi.nlm.nih.gov/32150360/)].
 42. Phan LT, Nguyen TV, Luong QC, Nguyen TV, Nguyen HT, Le HQ, et al. Importation and human-to-human transmission of a novel coronavirus in Vietnam. *N Engl J Med.* 2020;**382**(9):872-4. doi: [10.1056/NEJMc2001272](https://doi.org/10.1056/NEJMc2001272). [PubMed: [31991079](https://pubmed.ncbi.nlm.nih.gov/31991079/)].

43. Chen Z, Zhang W, Lu Y, Guo C, Guo Z, Liao C, et al. From SARS-CoV to Wuhan 2019-nCoV outbreak: similarity of early epidemic and prediction of future trends. *Cell Host Microbe* . 2020. doi:10.1101/2020.01.24.919241.
44. Pulliam JR, Epstein JH, Dushoff J, Rahman SA, Bunning M, Jamaluddin AA, et al. Agricultural intensification, priming for persistence and the emergence of Nipah virus: a lethal bat-borne zoonosis. *J R Soc Interface* . 2012;9(66):89-101. doi: 10.1098/rsif.2011.0223 . [PubMed: 21632614].
45. Millán-Oñate J, Rodríguez-Morales AJ, Camacho-Moreno G, Mendoza-Ramírez H, Rodríguez-Sabogal IA, Álvarez-Moreno C, et al. A new emerging zoonotic virus of concern: the 2019 novel Coronavirus (COVID-19). *Infectio* . 2020;24(3):187-92. doi: 10.22354/in.v24i3.848.
46. Organization WH. Novel coronavirus (2019-nCoV)-situation report-10-30 January 2020. 2020.
47. Yadav PD, Sapkal GN, Ella R, Sahay RR, Nyayanit DA, Patil DY, et al. Neutralization of Beta and Delta variant with sera of COVID-19 recovered cases and vaccinees of inactivated COVID-19 vaccine BBV152/Covaxin. *J Travel Med* . 2020;28(7):1-9. doi: 10.1093/jtm/taab104. [PubMed: 34230972].
48. Lustig Y, Zuckerman N, Nemet I, Atari N, Kliker L, Regev-Yochay G, et al. Neutralising capacity against Delta (B.1.617.2) and other variants of concern following Comirnaty (BNT162b2, BioNTech/Pfizer) vaccination in health care workers, Israel. *Euro Surveill* . 2021;26(26):2100557. doi: 10.2807/1560-7917.ES.2021.26.26.2100557. [PubMed: 34212838].
49. Kirola L. Genetic emergence of B.1.617.2 in COVID-19. *New Microbes New Infect* . 2021;43:1-4. doi: 10.1016/j.nmni.2021.100929.
50. Moona AA, Daria S, Asaduzzaman M, Islam MR. Bangladesh reported delta variant of coronavirus among its citizen: Actionable items to tackle the potential massive third wave. *Infect Prev Pract* . 2021;3(3):100159. doi: 10.1016/j.infpip.2021.100159. [PubMed: 34316588].
51. Dougherty K, Mannell M, Naqvi O, Matson D, Stone J. SARS-CoV-2 B.1.617.2 (Delta) variant COVID-19 outbreak associated with a gymnastics facility—Oklahoma, April–May 2021. *Weekly* . 2021;70(28):1004-1007. doi: 10.15585/mmwr.mm7028e2.
52. Ji W, Wang W, Zhao X, Zai J, Li X. Homologous recombination within the spike glycoprotein of the newly identified coronavirus may boost cross-species transmission from snake to human. *J Med Virol* . 2020;92(4):433-440. doi: 10.1002/jmv.25682.
53. Zhang T, Wu Q, Zhang Z. Probable Pangolin Origin of SARS-CoV-2 Associated with the COVID-19 Outbreak. *Curr Biol* . 2020;30(7):1346-1351. doi: 10.1016/j.cub.2020.03.022. [PubMed: 32197085].
54. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from wuhan: an analysis based on decade-long structural studies of SARS coronavirus. *J Virol* . 2020;94(7). doi: 10.1128/JVI.00127-20 . [PubMed: 31996437].
55. Coronavirinae in ViralZone. Available online: <https://viralzone.expasy.org/785> (accessed on 05 February 2019).
56. Subissi L, Posthuma CC, Collet A, Zevenhoven-Dobbe JC, Gorbalenya AE, Decroly E, et al. One severe acute respiratory syndrome coronavirus protein complex integrates processive RNA polymerase and exonuclease activities. *Proc Natl Acad Sci U S A* . 2014;111(37):E3900-E9. doi: 10.1073/pnas.1323705111. [PubMed: 25197083].
57. Chen X, Shang Y, Yao S, Liu R, Liu H. Perioperative care provider's considerations in managing patients with the COVID-19 infections. *Transl Perioper Pain Med* . 2020;7(2):216-24. doi: 10.31480/2330-4871/116.
58. Wu P, Hao X, Lau EH, Wong JY, Leung KS, Wu JT, et al. Real-time tentative assessment of the epidemiological characteristics of novel coronavirus infections in Wuhan, China, as at 22 January 2020. *Euro Surveill* . 2020;25(3):1-6. doi: 10.2807/1560-7917.ES.2020.25.3.2000044. [PubMed: 31992388].
59. Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *Lancet* . 2020;395(10226):809-15. doi: 10.1016/S0140-6736(20)30360-3.
60. Mahase E. Delta variant: What is happening with transmission, hospital admissions, and restrictions?. *BMJ* . 2021. doi: 10.1136/bmj.n1513. [PubMed: 34130949].
61. Li X, Geng M, Peng Y, Meng L, Lu S. Molecular immune pathogenesis and diagnosis of COVID-19. *J Pharm Anal* . 2020;10(2):102-108. doi: 10.1016/j.jpha.2020.03.001. [PubMed: 32282863].
62. de Wit E, van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. *Nat Rev Microbiol* . 2016;14(8):523-34. doi: 10.1038/nrmicro.2016.81 . [PubMed: 27344959].
63. Simmons G, Reeves JD, Rennekamp AJ, Amberg SM, Piefer AJ, Bates P. Characterization of severe acute respiratory syndrome-associated coronavirus (SARS-CoV) spike glycoprotein-mediated viral entry. *Proc Natl Acad Sci U S A* . 2004;101(12):4240-5. doi: 10.1073/pnas.0306446101. [PubMed: 15010527].
64. Belouzard S, Chu VC, Whittaker GR. Activation of the SARS coronavirus spike protein via sequential proteolytic cleavage at two distinct sites. *Proc Natl Acad Sci U S A* . 2009;106(14):5871-6. doi: 10.1073/pnas.0809524106. [PubMed: 19321428].
65. Wang H, Yang P, Liu K, Guo F, Zhang Y, Zhang G, et al. SARS coronavirus entry into host cells through a novel clathrin-and caveolae-independent endocytic pathway. *Cell Res* . 2008;18(2):290-301. doi: 10.1038/cr.2008.15. [PubMed: 18227861].
66. Kuba K, Imai Y, Ohto-Nakanishi T, Penninger JM. Trilysin of ACE2: A peptidase in the renin-angiotensin system, a SARS receptor, and a partner for amino acid transporters. *Pharmacol Ther* . 2010;128(1):119-28. doi: 10.1016/j.pharmthera.2010.06.003. [PubMed: 20599443].
67. Perlman S, Netland J. Coronaviruses post-SARS: update on replication and pathogenesis. *Nat Rev Microbiol* . 2009;7(6):439-50. doi: 10.1038/nrmicro2147 . [PubMed: 19430490].
68. Liu J, Wu P, Gao F, Qi J, Kawana-Tachikawa A, Xie J, et al. Novel immunodominant peptide presentation strategy: a featured HLA-A* 2402-restricted cytotoxic T-lymphocyte epitope stabilized by intrachain hydrogen bonds from severe acute respiratory syndrome coronavirus nucleocapsid protein. *J Virol* . 2010;84(22):11849-57. doi: 10.1128/JVI.01464-10. [PubMed: 20844028].
69. Li G, Chen X, Xu A. Profile of specific antibodies to the SARS-associated coronavirus. *N Engl J Med* . 2003;349(5):508-9. doi: 10.1056/NEJM200307313490520. [PubMed: 12890855].
70. Fan Y-Y, Huang Z-T, Li L, Wu M-H, Yu T, Koup RA, et al. Characterization of SARS-CoV-specific memory T cells from recovered individuals 4 years after infection. *Arch Virol* . 2009;154(7):1093-9. doi: 10.1007/s00705-009-0409-6 . [PubMed: 19526193].
71. Tang F, Quan Y, Xin Z-T, Wrämmert J, Ma M-J, Lv H, et al. Lack of peripheral memory B cell responses in recovered patients with severe acute respiratory syndrome: a six-year follow-up study. *J Immunol* . 2011;186(12):7264-8. doi: 10.4049/jimmunol.0903490. [PubMed: 21576510].
72. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* . 2020;8(4):420-422. doi: 10.1016/S2213-2600(20)30076-X. [PubMed: 32085846].
73. Williams AE, Chambers RC. The mercurial nature of neutrophils: still an enigma in ARDS?. *Am J Physiol Lung Cell Mol Physiol* . 2014;306(3):L217-L30. doi: 10.1152/ajplung.00311.2013. [PubMed: 24318116].
74. Cameron MJ, Bermejo-Martin JF, Danesh A, Muller MP, Kelvin DJ. Human immunopathogenesis of severe acute respiratory syndrome (SARS). *Virus Res* . 2008;133(1):13-9. doi: 10.1016/j.virusres.2007.02.014 . [PubMed: 17374415].
75. Prompetchara E, Ketloy C, Palaga T. Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. Prompetchara E, Ketloy C, Palaga T. Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. *Asian Pac J Allergy Immunol* . 2020;38(1):1-9. doi: 10.12932/AP-200220-0772 . [PubMed: 32105090].

76. Chan JF, Lau SK, To KK, Cheng VC, Woo PC, Yuen K-Y, et al. Middle East respiratory syndrome coronavirus: another zoonotic betacoronavirus causing SARS-like disease. *Clin Microbiol Rev*. 2015;**28**(2):465-522. doi: [10.1128/CMR.00102-14](https://doi.org/10.1128/CMR.00102-14). [PubMed: [25810418](https://pubmed.ncbi.nlm.nih.gov/25810418/)].
77. Pinto PG. Pilgrimage, commodities, and religious objectification: the making of transnational Shiism between Iran and Syria. *Comparative Studies of South Asia, Africa and the Middle East*. 2007;**27**(1):109-25. doi: [10.1215/1089201x-2006-047](https://doi.org/10.1215/1089201x-2006-047).
78. Gautret P, Benkouiten S, Al-Tawfiq JA, Memish ZA. Hajj-associated viral respiratory infections: a systematic review. *Travel Med Infect Dis*. 2016;**14**(2):92-109. doi: [10.1016/j.tmaid.2015.12.008](https://doi.org/10.1016/j.tmaid.2015.12.008). [PubMed: [26781223](https://pubmed.ncbi.nlm.nih.gov/26781223/)].
79. Yavarian J, Jandaghi NZS, Naseri M, Hemmati P, Dadras M, Gouya MM, et al. Influenza virus but not MERS coronavirus circulation in Iran, 2013–2016: Comparison between pilgrims and general population. *Travel Med Infect Dis*. 2018;**21**:51-5. doi: [10.1016/j.tmaid.2017.10.007](https://doi.org/10.1016/j.tmaid.2017.10.007). [PubMed: [29031546](https://pubmed.ncbi.nlm.nih.gov/29031546/)].
80. Al-Ghamdi SM, Akbar HO, Qari YA, Fathaldin OA, Al-Rashed RS. Pattern of admission to hospitals during muslim pilgrimage (Hajj). *Saudi Med J*. 2003;**24**(10):1073-6. [PubMed: [14578971](https://pubmed.ncbi.nlm.nih.gov/14578971/)].
81. Hilgenfeld R, Peiris M. From SARS to MERS: 10 years of research on highly pathogenic human coronaviruses. *Antiviral Res*. 2013;**100**(1):286-95. doi: [10.1016/j.antiviral.2013.08.015](https://doi.org/10.1016/j.antiviral.2013.08.015). [PubMed: [24012996](https://pubmed.ncbi.nlm.nih.gov/24012996/)].
82. Al-Tawfiq JA, Zumla A, Memish ZA. Travel implications of emerging coronaviruses: SARS and MERS-CoV. *Travel Med Infect Dis*. 2014;**12**(5):422-8. doi: [10.1016/j.tmaid.2014.06.007](https://doi.org/10.1016/j.tmaid.2014.06.007). [PubMed: [25047726](https://pubmed.ncbi.nlm.nih.gov/25047726/)].
83. Hilgenfeld R. From SARS to MERS: crystallographic studies on coronaviral proteases enable antiviral drug design. *FEBS J*. 2014;**281**(18):4085-96. doi: [10.1111/febs.12936](https://doi.org/10.1111/febs.12936). [PubMed: [25039866](https://pubmed.ncbi.nlm.nih.gov/25039866/)].
84. Stanhope MJ, Brown JR, Amrine-Madsen H. Evidence from the evolutionary analysis of nucleotide sequences for a recombinant history of SARS-CoV. *Infection, Infect Genet Evol*. 2004;**4**(1):15-9. doi: [10.1016/j.meegid.2003.10.001](https://doi.org/10.1016/j.meegid.2003.10.001). [PubMed: [15019585](https://pubmed.ncbi.nlm.nih.gov/15019585/)].
85. Zhang Z, Shen L, Gu X. Evolutionary dynamics of MERS-CoV: potential recombination, positive selection and transmission. *Scientific Reports*. 2016;**6**(1):1-10.
86. Guarner J. Three Emerging Coronaviruses in Two Decades: The Story of SARS, MERS, and Now COVID-19. *Am J Clin Pathol*. 2020. doi: [10.1093%2Fajcp%2Faqaa029](https://doi.org/10.1093%2Fajcp%2Faqaa029). [PubMed: [32053148](https://pubmed.ncbi.nlm.nih.gov/32053148/)].
87. Arab-Mazar Z, Sah R, Rabaan AA, Dhama K, Rodriguez-Morales AJ. Mapping the incidence of the COVID-19 hotspot in Iran—Implications for Travellers. *Travel Med Infect Dis*. 2020;**34**:101630. doi: [10.1016/j.tmaid.2020.101630](https://doi.org/10.1016/j.tmaid.2020.101630). [PubMed: [32184130](https://pubmed.ncbi.nlm.nih.gov/32184130/)].
88. WHO. Novel Coronaviruses (2019–Nov) situation report . 2020.
89. Abdi M. Coronavirus disease 2019 (COVID-19) outbreak in Iran; actions and problems. *Infect Control Hosp Epidemiol*. 2020;**41**(6):754-755. doi: [10.1017/ice.2020.86](https://doi.org/10.1017/ice.2020.86). [PubMed: [32192541](https://pubmed.ncbi.nlm.nih.gov/32192541/)].
90. Takian A, Raoofi A, Kazempour-Ardebili S. COVID-19 battle during the toughest sanctions against Iran. *The Lancet*. 2020;**395**(10229):1035-1036. doi: [10.1016/S0140-6736\(20\)30668-1](https://doi.org/10.1016/S0140-6736(20)30668-1). [PubMed: [32199073](https://pubmed.ncbi.nlm.nih.gov/32199073/)].
91. Umair M, Ikram A, Salman M, Badar N, Haider SA, Rehman Z, et al. Detection and whole-genome sequencing of SARS-CoV-2 B. 1.617. 2 and B. 1.351 variants of concern from Pakistan during the COVID-19 third wave. *medRxiv*. 2021. doi: [10.1101/2021.07.14.21259909](https://doi.org/10.1101/2021.07.14.21259909).
92. Gottlieb RL, Nirula A, Chen P, Boscia J, Heller B, Morris J, et al. Effect of bamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild to moderate COVID-19: a randomized clinical trial. *Jama*. 2021;**325**(7):632-644. doi: [10.1001/jama.2021.0202](https://doi.org/10.1001/jama.2021.0202).
93. Al-Mahruqi S, Al-Wahaibi A, Khan AL, Al-Jardani A, Asaf S, Alkindi H, et al. Molecular epidemiology of COVID-19 in Oman: A molecular and surveillance study for the early transmission of COVID-19 in the country. *Int J Infect Dis*. 2021;**104**:139-49. doi: [10.1016/j.ijid.2020.12.049](https://doi.org/10.1016/j.ijid.2020.12.049). [PubMed: [33359061](https://pubmed.ncbi.nlm.nih.gov/33359061/)].