



Review

Coronavirus and co-infections: A Saudi Arabian perspective

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ABSTRACT

Mortality due to infectious diseases continues to rise globally, despite advances in antimicrobial therapy and supportive care. This is evident with the occurrence of coronavirus disease 2019 (COVID-19) pandemic, instigated by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Saudi Arabia, an eminent country within the Arab region, has had significant impact during global pandemics, concomitant with the fact that millions of Muslims travel to Saudi Arabia for pilgrimages every year. Herein, we discuss the significance of SARS-CoV-1, SARS-CoV-2, as well as the Middle East respiratory syndrome coronavirus (MERS-CoV) in Saudi Arabia with particular reference to global transmission and/or emergence of new variants due to genetic mixing of different strains. Furthermore, we also discuss the role of Saudi Arabia with reference to novel emerging infectious diseases and re-emerging infections, such as Ebola, zika, and monkeypox, as well as in the context on coinfections. Future strategies to limit the spread of viral infections and the pivotal role of Saudi Arabia, are deliberated upon.

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Contents

1. Introduction	1
2. Saudi Arabia: An international hub	2
3. Coronaviruses	2
4. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)	2
5. Severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1) versus Middle East respiratory syndrome-CoV (MERS-CoV)	3
6. Co-infections with COVID-19	3
7. Other infections of importance	4
8. Concluding remarks and future perspectives	4
Declaration of Competing Interest	5
Appendix A. Supplementary material	5
References	5

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1. Introduction

Deaths due to infectious diseases, in particular due to viral infectious diseases, continue to rise globally, despite the advancement of antimicrobial therapy and supportive care (Zumla et al., 2016, Xiao et al., 2020). This can be illustrated by the recent pandemic which began in 2019, whereby the emergence of an

infectious disease was ascertained in the city of Wuhan, China. The World Health Organization (WHO) designated this infection as: coronavirus disease 2019 (COVID-19) and the causative agent was identified: severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (DaSilva et al., 2022; Wu et al., 2020). The infection was recognized to be of global concern, and by the 11th of March 2020, the WHO affirmed that this is a pandemic (World Health Organisation, 2020). As of 31st August 2022, SARS-CoV-2 has ensued in over 601 million people being infected coupled with more than 6 million deaths, globally (Johns Hopkins University and medicine, 2022).

Saudi Arabia, an important country in the Arab region, has had a significant role to play during global pandemics. This is due to the fact the millions of Muslims travel to Saudi Arabia for annual pilgrimages: Umrah and Hajj, regarded as one of the major mass gatherings globally, making the region susceptible to the spread of infectious disease (Hoang et al., 2020). Umrah is an Islamic custom implemented by Muslims, in the city of Makkah, whereas the annual pilgrimage to holy sites in the city of Makkah is known as the Hajj (Al-Tawfiq et al., 2022; Ahmed and Memish, 2020). Furthermore, the Hajj is accomplished approximately by more than 2 million Muslims each year. Overcrowding, confined settings, inevitable close contacts may all be contributory factors in the spread of infectious disease. However, significant efforts are undertaken by the government of Saudi Arabia to ensure the wellness, health, as well as safety and security of pilgrims. In this regard, the ministry of health has narrated extensively on preparing for the pandemic as well as adherence to (WHO) strategies on infection prevention and control. Herein, we discuss the impact to Saudi Arabia owing to the advent of SARS-CoV-2 in 2019, the severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1) in 2002 and of the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, which drew much public consideration. Furthermore, we also elaborate upon co-infections with COVID-19 and discuss other infectious diseases of importance, such as influenza, zika, ebola and monkeypox.

2. Saudi Arabia: An international hub

Saudi Arabia can be described as an international hub; attributed to mass migration during the annual Hajj and Umrah pilgrimages which are unparalleled mass gatherings in scale, with approximately 2.5 million travellers visiting the nation in 2019; from over 180 countries (Ahmad et al., 2006, Ahmed and Memish, 2020, Ebrahim et al., 2020, Azmi et al., 2021). In the latter period of 2019, a respiratory infectious disease termed coronavirus disease 2019 (COVID-19) by the WHO, was recognized in the metropolis of Wuhan, China, with the causative pathogen designated as: severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), later on resulting in a pandemic (Mungroo et al., 2021). Following this devastating COVID-19 pandemic, the Saudi ministry of health have remained extremely vigilant in order to curtail the infection since its' inception, with only 10,000 residents from the kingdom being permitted for the Hajj pilgrimage in 2020. In 2021, 60,000 fully vaccinated Saudi residents and citizens were able to participate in the annual pilgrimage (Ahmed and Memish, 2020, Parveen, 2020, Mahdi et al., 2022). For the Hajj in 2022, approximately 1 million pilgrims were able to participate, again with important precautionary measures in place. To this end, the pivotal role of Saudi Arabia in monitoring and understand infectious disease epidemics within the region, is apparent. The role of effectively planning, implementing, and directing mass gatherings such as the Hajj pilgrimage, concomitantly with extensive preventative measures in place, as well as the use of digital

technology, should be utilized to prevent infectious disease outbreaks globally.

3. Coronaviruses

The coronaviruses hail from a vast assemblage of ribonucleic acid (RNA) viruses which are enveloped, single-stranded positive-sense, and instigate respiratory, neuronal, gastrointestinal and hepatic diseases (Macchi et al., 2020; Zumla et al., 2016). Until recently, severe acute respiratory syndrome-CoV (SARS-CoV), HCoV-NL63, HCoV-OC43, Middle East respiratory syndrome-CoV (MERS-CoV), HCoV-HKU1 and HCoV-229E, were the coronaviruses that were recognized to cause diseases in humans (Bchetnia et al., 2020; Zumla et al., 2016). Infection caused by SARS-CoV and MERS-CoV lead to 10% and 40% death rates in humans respectively, which is amongst the greatest among these group of viruses (Gretebeck and Subbarao, 2015). The most recently encountered coronavirus, SARS-CoV-2, is the seventh affiliate of the coronavirus family, that is known to instigate infection.

4. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

Symptoms seen in individuals suffering from SARS-CoV-2 comprised of fever, fatigue and cough (Mungroo et al., 2020). The less frequent symptoms included, diarrhoea, haemoptysis, sputum production, dyspnoea, lymphopenia, vomiting, lack of appetite, headache and abdominal pain (Mungroo et al., 2020; Wu and McGoogan, 2020). Other reported symptoms of COVID-19, are the loss of smell (anosmia) and loss of taste (Perrigo, 2020). Nevertheless, numerous individuals infected with SARS-CoV-2 were presented as asymptomatic cases (Mungroo et al., 2020). COVID-19 cases are categorized into mild, severe, and critical types. Mild cases in individuals typically presented with mild pneumonia, whereas severe cases in individuals depicted dyspnoea, blood oxygen saturation, as well as elevated rates of respiration. Critical individuals typically underwent acute heart injury, septic shock, respiratory failure, and multiple organ failure (Wu et al., 2020; He, Deng and Li, 2020). The median incubation period for SARS-CoV-2 from the initial symptoms to dyspnoea, followed hospital admission and severe acute respiratory syndrome were 5, 7, and 8 days (Wang et al., 2020).

So far, since the 8th of June 2023, there have been 841,469 confirmed cases of COVID-19, reported to WHO that have been described in Saudi Arabia with approximately 9,646 deaths, by the WHO (WHO, 2022a). Among the first countries globally, Saudi Arabia employed precautionary and unprecedented procedures to prevent SARS-CoV-2 introduction into the country as well as mitigating its impact upon arrival. In fact, such precautions were employed on even before the first reported case on (March 2, 2020). Rather, a month prior to the first observed case of COVID-19, a proactive measure to limit spread of the infection was to cease all the direct flights linking Saudi Arabia and China (Algaissi et al., 2020). Furthermore, in late February 27th, all international Umrah pilgrims and tourist flights were suspended and the entrance points to Makkah and Madinah were monitored, with the curtailment of inbound travel from SARS-CoV-2 affected countries, incorporating Gulf Cooperation Council (GCC) citizens who may have journeyed to these areas. Saudi Arabia reported its first confirmed COVID-19 case on March 2nd, 2020 (Nurunnabi, 2021). Very shortly, in order to reduce the devastation of COVID-19 and prevent the spread of the infection, Umrah was adjourned entirely by March 4th, and the two holy mosques in Makkah and Madinah were cleaned and disinfected on a daily basis by March 5th (Ebrahim and Memish, 2020). Moreover, these measures were

accompanied by other important precautions, such as the shifting of schools and universities to online learning, as well as travel restrictions/bans to affected countries, and mandatory quarantine measures for travelers who had already arrived from such places. Of note, these measures were put in place while the number of recorded and confirmed cases in the region were below 300 (Algaissi et al., 2020).

Just as COVID-19 caused havoc worldwide, an increase in cases were observed in Saudi Arabia epidemiologically with distinct phases in the initial infections (March-May 2020), increased spread (June-July 2020), rapid waning of infections (July-September 2020), stability (September 2020-April 2021), another surge (April-September 2021), and successful regulation of the infection (October 2021 and onward). In this regard, efforts from the Ministry of Health, Saudi Arabia, and actions undertaken taken by members of the public, should be acknowledged, as the percentage of the affected population was low, based on the statistics. (Salam et al., 2021).

During the Hajj 2020 pilgrimage, extensive precautionary measures were put into place with no international pilgrims taking part, rather 1000 individuals between the ages of 20–65 years of age were permitted, as well as social distancing measure put into place, and the use of digital devices to monitor symptoms and requirements (Ebrahim et al., 2021, Al-Tawfiq et al., 2022). Remarkably, there were no confirmed cases of COVID-19 were identified during or after Hajj 2020 (Jokhdar et al., 2021). In 2021, the number of pilgrims was approximately 60 000 (18–60 years of age) and pilgrims were mandated to have two doses of approved COVID-19 vaccine, coupled with a negative SARS-CoV-2 PCR 72 h before arrival, as well as quarantining for 72 h plus another PCR test within 48 h of arrival, as well as complying with digital measures. Due to these extensive measures, no COVID-19 cases were detected during the 2021 Hajj pilgrimage.

At present, several precautionary measures have been put in place for the recent July 2022 Hajj pilgrimage, whereby 1 million pilgrims are thought to have attended. These comprise: pilgrim age should be below 65 years, be fully vaccinated with approved COVID-19 vaccine and to possess a negative PCR test. The numbers of any cases will need to be confirmed and analysed in future work.

5. Severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1) versus Middle East respiratory syndrome-CoV (MERS-CoV)

In November 2002, the first case of pneumonia caused by SARS-CoV was reported (Guan et al., 2004). The disease quickly spread across the world, and the WHO declared: “a worldwide health threat”. Following the advent of this infectious disease in mainland China, greater than 300 cases were reported; mostly amongst healthcare workers, which lead to the spread of the infection to other places comprising Vietnam, Hong Kong, Canada, and many others, largely as a result of global travel (Guan et al., 2004; Mungroo et al., 2021). In the beginning, it was feared that there may be global spread, causing serious economic downturn. Nonetheless, rapid action was implemented by the authorities in dealing with the epidemic, for instance isolation of suspected cases, contact tracing, as well as quarantine measures, were able to contain the infection (Anderson et al., 2004). The SARS pandemic concluded in July 2003, but 8096 individuals were infected and 774 mortalities were witnessed across 27 countries (Xiao et al., 2020). In addition, some more incidences of SARS were reported at the end of 2003 (December–January 2004) caused by zoonotic transmission (Wang et al., 2005). However, since then, no more human cases concomitant with SARS were observed (De Wit et al., 2016).

Of note, a case of acute pneumonia and renal fever was observed in an individual in 2012, in Saudi Arabia, a decade after

the incidence of SARS-CoV. The death of the individual was due to another new form of the coronavirus, now recognized as MERS-CoV (Middle East respiratory syndrome coronavirus), this was retrieved from the sputum of the patient (Memish et al., 2013). Furthermore, following the detection of this new coronavirus infection in the middle eastern region, other stored serum and respiratory samples from individuals were re-examined, and MERS-CoV diagnosis was established in two other cases. Subsequently, a few more case reports were described in the UK and spread to other parts of the globe due to travel. Of note, the majority of the imported MERS cases were observed due to nosocomial transmission. The first MERS patient in South Korea was noted in may 2012, who had travelled from the Middle East. Based on data from the WHO, since April 2012 till July 2022, 2591 laboratory-confirmed cases of MERS were reported worldwide, with 894 associated mortalities, and a case-fatality ratio of 34.5% (WHO, 2022b). Symptoms for MERS comprise cough, fever, and breath shortness. Pneumonia has also been commonly reported, albeit it is not always observed. In addition, gastrointestinal symptoms, including diarrhea, have also been noted. Of note, there were some laboratory-confirmed cases of MERS-CoV infection that were reported as asymptomatic, indicative that some patients did not exhibiting clinical signs, but still tested positive for the infection. Interestingly, most of these asymptomatic cases were identified due to the aggressive contact tracing following a laboratory-confirmed case (Reeves et al., 2015). The infection was mostly spread through human-to-human transmission in healthcare settings. Some reports also suggest that dromedary camels may have a role as possible reservoirs for MERS-CoV transmitting the MERS infection to humans. Nonetheless, the precise role of dromedaries in transmitting this virus are not fully understood (Reeves et al., 2015).

6. Co-infections with COVID-19

A coinfection refers to the simultaneous presence of multiple distinct infectious agents, such as viruses, bacteria, fungi, or parasites, within the host (Cox, 2001). Coinfections can have various effects on the affected person, including changes in the severity of the diseases, the potential for complications, and the need for different approaches to diagnosis, treatment, and prevention compared to single infections. Understanding and managing coinfections are crucial in healthcare as they pose unique challenges and require customized strategies to address their specific complexities. In a comprehensive analysis of 30 studies, encompassing 3,834 patients, it was demonstrated that 7% of COVID-19 patients admitted to the hospital had concurrent bacterial infections, with more occurrence observed among those in intensive care units. The most prevalent bacteria identified were *Mycoplasma pneumoniae*, *Pseudomonas aeruginosa*, and *Haemophilus influenzae* (Lansbury et al., 2020). Studies have revealed a significant variation in the occurrence of coinfection and superinfection among patients with SARS-CoV-2 (Omoush and Alzyoud, 2022). Specifically, the combination of bacterial and viral coinfection or superinfection appears to have severe consequences on the outcomes of COVID-19 patients, significantly raising the risks of mortality and critical illness (Omoush and Alzyoud, 2022). In general, bacterial coinfections have been observed to make viral respiratory infections more complex and are linked to severe infection outcomes. During previous influenza pandemics, secondary bacterial coinfection was recognized as a significant contributor to mortality (Alqahtani et al., 2022).

In a recent study involving 12 hospitalized patients with COVID-19 infection, the rate of bacterial coinfections was found to be 16.7% (Richardson et al., 2020). Similarly, a more recent

report from Spain, which included 989 hospitalized patients, observed a prevalence of 3.1% for bacterial coinfections (Garcia-Vidal et al., 2021). In a large cohort study conducted in the U.S., where swabs from 12,075 individuals who underwent SARS-CoV-2 testing were analysed for other pathogens, a high rate of positive bacterial coinfection (55.4%) was identified among the SARS-CoV-2 patients (Massey et al., 2020). Another retrospective study conducted in Asir Province, Saudi Arabia, aimed to investigate the impact of bacterial coinfections on ICU-admitted patients with COVID-19 (Alqahtani et al., 2022). The researchers analysed electronic medical records of hospitalized COVID-19 patients, revealing that patients infected with both SARS-CoV-2 and bacterial infections had a longer hospital stay, with an average of 35.2 days compared to 16.2 days for patients infected with only SARS-CoV-2. Moreover, the coinfection group had higher mortality rates (50%) compared to the group infected with SARS-CoV-2 alone (18.7%). The study also indicated that gram-negative bacteria were the most frequently isolated bacteria in COVID-19 patients with coinfections, highlighting that individuals with COVID-19 who experienced bacterial coinfections were at a higher risk of prolonged hospitalization and potentially increased mortality (Alqahtani et al., 2022).

In a separate study, four patients who visited the emergency department in August 2020 in Saudi Arabia, was described (Khalil et al., 2020). Patients presented with feverish symptoms who were subsequently diagnosed with concurrent infections of dengue fever and COVID-19. Notably, these patients had not travelled outside Jeddah city in the preceding six months (Khalil et al., 2020). Another recent study reported co-infection of COVID-19 and tuberculosis coinfection in Saudi Arabia (Shabrawishi et al., 2021). As indicated earlier, the most frequently documented symptoms of COVID-19 encompass cough, shortness of breath, fever, and fatigue, typically appearing following a brief incubation period. Less common symptoms encompass loss of smell and taste, sore throat, or gastrointestinal manifestations. Thus, from a diagnostic perspective, it is essential to evaluate for risk factors associated with tuberculosis infection, such as close contact with a tuberculosis patient or immigration status, as it can aid in determining the possibility of coexistence. Nonetheless, further studies are warranted to understand the impact of coinfections on COVID-19 in Saudi Arabia (Shabrawishi et al., 2021).

7. Other infections of importance

Respiratory tract infections were found to be the most common reason for hospital admissions during the Hajj pilgrimage, most commonly being attributed to the pathogens: *Klebsiella pneumoniae*, *Haemophilus influenzae*, and *Streptococcus pneumoniae* (Ahmed et al., 2006). Furthermore, viral respiratory tract infections, in particular due to influenza have commonly been observed during the Hajj. Thus, influenza vaccination is recommended by the Saudi ministry of health (Ahmed et al., 2022). In addition, Muslim men usually finish the Hajj pilgrimage by shaving hair on their heads, which may facilitate the transmission of hepatitis B and C, and even HIV, albeit there are strict regulations to testing barbers for HIV and hepatitis B (HBV) and C (HCV), and utilization of single-use and disposable blades is mandated (Ahmed et al., 2006).

Emerging infectious diseases also pose a risk in Saudi Arabia, such as Ebola and zika virus (Memish and Al-Tawfiq, 2014; Siddiqui et al., 2021; Tambo et al., 2020). However, for the Saudi Arabian ministry of health and other authorities, it is part of their standard practice to convene international public health consultations each year prior to the Hajj, in order to propose disease-specific recommendations. Furthermore, with the stationing of

public health staff at all entry ports in Saudi Arabia, who have been trained extensively to carefully observe all arriving travellers for potential signs and symptoms of infectious diseases, for those that may require quarantine, as well as the implementation of any required travel restrictions (Memish and Al-Tawfiq, 2014). Furthermore, thermal cameras are installed at all borders. In a recent study, screening for summary, flaviviruses among mosquitoes in 2016 accomplished during Hajj period, and at the height of the zika virus epidemic was accomplished and no known flaviviruses were revealed, but possibly a novel type of flavivirus was detected (Yesli et al., 2021). However, future studies are needed to investigate the novel mosquito virus identified.

Eight cases of monkeypox, a rare viral disease, endemic to Africa were detected in Saudi Arabia, as of 30th August 2022 (Monkeypox data finder, 2022). Most of these, were linked with travel to Europe (Barry et al., 2022). However, as there is effective presence of well-established surveillance, such as thermal cameras at the borders, and preventative measures in place, as a result of previous infectious-disease outbreaks, only few cases were seen in the region at the moment. Nonetheless, clinicians need to continue their vigilance, and suspect monkeypox for other febrile illnesses that may present with rash such as chickenpox (Barry et al., 2022).

8. Concluding remarks and future perspectives

Future work is urgently warranted and emphasis should be placed on comprehending the pathogenesis of viruses. Elucidating the precise mechanisms by which viruses may cause pathogenicity, further insight may be acquired on the various molecules that should be targeted by drugs and vaccines to effectively thwart cases. A recent paper recommends the use of multiple, parallel surveillance systems, investment in digitalization, and the exploration of participatory surveillance systems. Additionally, the study emphasizes the importance of multi-pathogen testing and representative sampling strategies for age groups, geographical distribution, disease severity, use of antivirals and/or monoclonal antibodies, and vaccination status, which is of value for Saudi Arabia, given its' importance in the middle east (Teirlinck et al., 2023). Saudi Arabia has a significant role to play as an international hub hosting millions of pilgrims annually. The majority of these pilgrims were elderly (Pre-COVID-19) and originate from all of the world, with countries that may have sub-optimal health care, thus the pilgrimage presents distinctive challenges to human health and in the global transmission of infectious diseases (Ebrahim et al., 2009; Ahmed et al., 2019). Furthermore, with the emergence of new 'variants of interest' or 'variants of concern' systems to implement systematic SARS-CoV-2 genomic surveillance are needed. This is of particular importance in the Saudi Arabian context, due to global transmission and/or emergence of new variants due to genetic mixing of different strains, with so many people traveling from many countries. Additional studies are also needed to determine effects of complete quarantine and travel restrictions in Saudi Arabia and the timings of these restrictions on travel and movement of individuals during these peaks and relationships between both. Nonetheless, the ministry of health in Saudi Arabia has introduced robust and extraordinary precautionary measures in order to combat the spread of infectious diseases following the global COVID-19 pandemic, through digital technology as well as social distancing, applying concepts of "safe bubbles", assigning health officers, managing quarantining, to name a few (Jokhdar et al., 2021). The pivotal role of Saudi Arabia in multifaceted planning, monitoring and understanding infectious diseases, such as COVID-19, is apparent and highlights that effectively implementing a mass gathering such as the Hajj pilgrimage is possible. This should serve as a guideline to prevent infectious disease outbreaks

in the future, as well as emulated where ever possible in the organization of global mass gatherings.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.sjbs.2023.103739>.

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