Coronavirus Pandemic: An Update on the Transmission, Diagnosis, Clinical Features and Managment

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Opinion Article

ABSTRACT

The novel coronavirus, designated as "Severe Acute Respiratory Syndrome Coronavirus 2" (SARS-CoV-2), is a new coronavirus that has evolved as a global pandemic recently, and it has created a widespread interest in coronaviruses causing human infections. This article compares the pathogenesis, distribution, clinical characteristics, and treatment of the three highly pathogenic coronaviruses that caused epidemics, namely, "Severe Acute Respiratory Syndrome Coronavirus"

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(SARS), "Middle East Respiratory Syndrome" (MERS), and SARS-CoV-2. This narrative review is prepared using the data compiled from literature search using relevant MeSH terms. The clinical manifestation of SARS-CoV-2 infection (COVID-19) is mild with relatively low fatality rate than the other two coronaviruses; however, its overall capability to cause explosive spread of the disease and reach a pandemic level is greater. Unlike SARS and MERS, COVID-19 has no accepted treatment protocols at present. Extensive studies and analyses on COVID-19 are necessary before making strong recommendations for or against any particular treatment, although some recent medications have shown great potential. COVID-19 still needs further investigation, where all of the lessons gained from previous outbreaks of SARS and MERS and the experience from the countries that managed COVID-19 seem to be the best approaches to counteract this new global hazard at present until effective preventive vaccines are available in sufficient quantity for mass vaccination programs worldwide.

1. INTRODUCTION

Until a couple of decades ago, limited numbers of coronaviruses are considered to be relatively harmless human pathogens causing only trivial infections similar to common cold and cough.[1] However, with the start of the 21st century, outbreaks emerging periodically with a broad geographic spectrum caused by two highly pathogenic coronaviruses, namely, SARS-CoV and MERS-CoV, with the former causing severe acute respiratory syndrome or SARS outbreak in 2002 and the latter causing Middle East respiratory syndrome or MERS in 2012 have been reported.[2,3] This outbreak is followed by the novel coronavirus SARS-CoV-2, which appears toward the end of 2019 in Wuhan, China. SARS-CoV-2 has become the third major coronavirus affecting the human population. This viral pneumonia, which shares similar etiopathology, is the most frequent infectious disease that accounts for major clinical and socioeconomic impact worldwide, raising great public health concerns globally.

In late 2002, a number of beta-coronavirus-infected patients from Guangdong Province, China, were first identified with severe respiratory disease. It was accompanied with cases reported from neighboring countries such as Vietnam and even distant countries such as Canada. [4] The disease spread to communities and hospital facilities, and it was identified later as SARS in March 2003. This worldwide outbreak was contained by July 2003. [5]

MERS was the second coronavirus that caused infection, leading to a major global public health concern. MERS first emerged in 2012 in the Kingdom of Saudi Arabia (KSA), when a male patient died from acute severe pneumonia and renal impairment. [6] Subsequently, it caused an outbreak in 2014, where a total of 27 countries were affected, spanning across Europe, Asia, Middle East, and North America. In May 2015, another wave of MERS epidemic emerged when a South Korean man returned from the Middle East. [7]

The third major corona infection, SARS-CoV-2, was first identified in Wuhan, China, from where it crossed international borders to infect individuals in neighboring countries and then globally. Coronavirus Disease-2019 (COVID-19) is the term currently used to refer to the clinical disorders linked to SARS-CoV-2 infection as recommended by the World Health Organization (WHO). The virus was declared as a Public Health Emergency of International Concern by the WHO on 30 January 2020. COVID-19 is broadly described as a respiratory condition with a severity spectrum extending from insignificant signs to critically severe pneumonia cases and acute respiratory distress syndrome. Fatigue is complained by most of the patients. In addition, muscle or chest pain, headache, diarrhea, chills, abnormal smell or taste sensation, nausea, and confusion are observed in many patients. [8,9,10]

"SARS-CoV," "MERS-CoV," and "SARS-CoV-2" share some similarities. These viruses belong to the same beta-coronavirus type, and they are positive-sense single-stranded enveloped RNA viruses, zoonotic coronaviruses, and transmitted interspecies (animal to human) and intraspecies (between humans, between animals).[11] In addition, COVID-19 seems to be associated with less severe infections compared with the other viruses; however, COVID-19 is quickly and widely transmitted in the population, whereas SARS and MERS are primarily associated with a nosocomial spread. [12]

The present review article aims to highlight the similarities and variabilities with regard to pathology, epidemiology, clinical manifestation, and treatment among COVID-19, SARS, and MERS. Moreover, this review aims to improve the understanding of the infections caused by these viruses and the antiviral treatment options for these coronavirus epidemics, particularly the current COVID-19 epidemic.

2. METHODOLOGY

Using the data compiled from WHO's latest situation report, Centers for Disease Control and Prevention (CDC, USA) website, and literature reviews and research articles published in PubMed, Medline, ProQuest, and Google Scholar using the search MeSH terms "coronavirus," "SARS-CoV," "MERS-CoV," "SARS-CoV-2," "novel coronavirus," and "COVID-19," we collected information concerning epidemiology, clinical manifestations, pathophysiology, diagnosis, management, and related factors for MERS, SARS, and COVID-19.

2.1 Epidemiology

The worldwide SARS-CoV-2 spread spanned nearly over 220 countries/territories with the highest incidence in Europe, Indian subcontinent, and the Americas, with 183,934,913 confirmed cases and 3,985,022 deaths from late December 2019 until 6 July 2021, as reported by the WHO.[13] This result was significant as compared with that of SARS (spread to 32 countries with reports of 916 deaths from 8422 patients) and MERS-CoV (confirmed in more than 27 countries, resulting in 868 fatalities out of 2496 confirmed cases from April to Dec 2012; Table 1). COVID-19 is still in its diffusion stage with more than 500,000 people getting infected globally daily.[13] The COVID-19 situation in Saudi Arabia, at the time of this study (July 6th 2021) is standing with 494,032 confirmed cases with 7,891 deaths since the report of the first case of infection since March 2nd 2020.[13]

The patterns of SARS-CoV-2, SARS-CoV, and MERS-CoV infections seemed to have seasonal variations. A study on MERS reported that the outbreak primarily emerged during ̠summer, with the highest global seasonal occurrence in the month of June. However, the COVID-19 and SARS infection outbreaks started or took place in the winter season.[15] The gender-based analysis of this novel coronavirus disease demonstrated no gender disparity in the number of patients to date; however, a male predominance in the vulnerability to this illness and in the fatality rate was observed.[16] The median age ranged from 50 to 65 years, with less than half of the patients possessing underlying comorbidities, including diabetes mellitus, hypertension, and different types of cardiovascular diseases.[10] The overall mortality rate was 2% at the start of the epidemic, which increased to 3.4% and in KSA, the overall mortality rate was stabilized below 1%.[17] A recent study in KSA has reported a case fatality rate (CFR) of 16% in hospitalized COVID-19 patients, which is lesser as compared with that of USA (21%), Italy (27%), and UK (33%).[18] However, MERS outbreak had a higher fatality rate (35%) among all diagnosed patients, and it often necessitated mechanical ventilation because of the severity of the illness (in 50%–89% of the cases).[7] According to a study outlining MERS cases, the mean age of all cases was 50 years (SD=±18), where over half of the cases reported having comorbidities, and 7.6% reported direct contact with a camel. In addition, these cases from the Saudi Arabian population showed male predominance. [19] SARS-CoV had an overall CFR of 11%. Women were predominant of those diagnosed with SARS, but they had a lower CFR than men (13.2% vs 22.3%). About half of the cases were younger than 40 years. Nearly 25% of the confirmed cases were healthcare workers with the lowest CFR (2%). [20]

Old age and underlying comorbidities, particularly respiratory ones, were identified as the predominant risk factors for the progression of these diseases.

2.2 Clinical Features and Diagnosis

In Table 2, the main clinical and biological features from typical SARS-CoV-2 patients were presented in comparison with the updated information on SARS and MERS. The COVID-19 patients had a mean age of 59 years, which was comparable to SARS and MERS; more than half of the COVID-19 cases had a chronic comorbidity but in a marginally less occurrence than MERS cases. Many asymptomatic patients were diagnosed with COVID-19 during screening of contacts. The typical presenting symptoms in most of the cases with mild to moderate COVID-19 infection were fever, dry cough, with or without sore throat and mild dyspnea; at least one symptom was being noted in most of the patients. Gastrointestinal symptoms, loss of smell and/or loss of taste were also being reported among COVID-19 patients. Patients

with severe disease may present with evidence of pneumonia (fever, shortness of breath, rapid breathing, rales in lungs, weakened breath sounds, dullness in the percussion, and oxygen saturation < 90% in room air).[21] Critically ill patients can rapidly develop acute respiratory distress syndrome (ARDS), or respiratory failure, multi-organ dysfunction syndromes, systemic manifestations (sepsis, septic shock), or multiple organ failure, with high risk for fatality.[9]

In KSA the median age was 36 years with nearly 10% being asymptomatic. Cough, fever, and sore throat were the most common symptoms reported in KSA. [22]

MERS might be suspected when a patient with a history of contact with probable or confirmed cases of the illness, or reported a history of travel or residence within the Arabian countries, presented with fever and cough, or hospitalization with possible lower respiratory tract involvement, although PCR-based techniques were still the preferred methods of confirmation of the diagnosis.[6,28]

SARS is diagnosed with a positive reverse transcription polymerase chain reaction (RT-PCR) test result from at least two specimens obtained from different locations or tested in different laboratories, from patients before or after death, or a seroconversion by enzyme-linked immunosorbent assays (ELISA).[29] The diagnosis of COVID-19 is achieved initially by assessing the clinical manifestations of the presenting patient, chest screening and excluding common bacterial and viral pneumonia, and then by obtaining specimens from the respiratory tract for culture and sequencing analysis or serological tests (anti-SARSr-CoV IgG and IgM antibody response testing ELISA kits with the antigen SARSr-CoVRp3 NP that shares more than 90% similarity to all SARSr-CoVs).[9,30]

Table 1. Comparison of epidemiological characteristics of MERS, SARS, and COVID-19

	SARS-CoV	MERS-CoV	COVID-19*[13]
Year of the outbreak	2002	2012	2019
Country origin	Guangdong, China	Saudi Arabia	Wuhan, China
Total confirmed cases	8422	2494	183,934,913
Total deaths	916 (10.87%)	858 (34.77%)	3,985,022 (2.16%)
Fatality rate	9.19%	34.4%	0.1-25%**
No. of affected countries/territories	32	27	220

*: Current statistics (July 6th 2021) [13]
**: Widely variable estimates of case fatality rate (CFR) by country due to ongoing pandemic [14]

Table 2. Biological and clinical characteristics of coronaviruses

Characteristics	COVID-19 [8,23]	SARS [24,25]	MERS [26,27]
Causative virus	SARS-CoV-2	SARS-CoV	MERS-CoV
Biological characteristics			
Incubation period	2–14 (5.2) days	2–10 (7) days	2–10 (5.5) days
Target receptors	Angiotensin-converting enzyme 2 (ACE2)	Angiotensin-converting enzyme 2 (ACE2)	Dipeptidyl peptidase-4 (DPP4)
Median age of patients	59 years	65 years	50 years
Male/female	Male predominance	Male predominance	Male predominance
Origin/suspected source	Seafood, Pangolins, Bats*	Bats, Civet cats	Bats, Camels
Speed of spread	High	Moderate	Low
Season	Winter	Winter	Summer
Clinical characteristics (% of cases)			
Fever	>80	Almost all	>80
Cough	>50	>55	55–85
Shortness of breath	20–30	≃40	25–70
Pharyngitis	≃30	15–25	≃10
Confusion	≃20	5–43	5
Diarrhea	15	23–70	20–26

*: Several animals implicated but source still inconclusive

Laboratory tests in COVID-19 patients were similar to those of patients infected with other coronaviruses. All three viruses were definitively diagnosed by utilizing cultures of the respiratory fluids and serum antibody analysis or RT-PCR analysis of respiratory fluids from suspected patients. Non-specific findings of COVID-19 included lymphopenia (most frequent observation), often in combination with thrombocytopenia and hypoalbuminemia. In some cases, elevated creatine kinase, aminotransferase, C-reactive protein, and lactic dehydrogenase levels were recorded.[31]

All three viruses cause pneumonia, where a radiological presentation of the lungs is an important diagnostic tool for preliminary and broad identification of the severity of the disease. During early disease stages, chest x-rays have less sensitivity, not enough to detect these changes. However, computed tomography (CT) has better sensitivity for the detection of early or mild disease. Typical CT manifestations include ground-glass opacities (GGO), consolidation, and interlobular septal thickening. [32] CT imaging manifestations in COVID-19 patients can differ regarding disease stages and patients. In fact, in early stages, GGO with single or multiple lesions can be found in addition to the sub-pleural areas or bronchi.[33] On the other hand, severe patients might present bilateral multifocal consolidation, partially fused into massive consolidation with small pleural effusions and even manifesting with 'white lung'.[34]

The radiological findings of the novel coronavirus have some similarities to the other two zoonotic coronaviruses; however, a higher rate of bilateral findings was found in patients with COVID-19. Xie X et al, suggested that 3% of the patients with suspected COVID-19 in Hubei Province had a CT screening that was confirmative of SARS-CoV-2 diagnosis but had a negative RT-PCR test result. These patients were treated in isolation, and the results turned positive for COVID-19 on repeated swab testing between 2 and 8 days later. [35]

2.3 Transmission

COVID-19 transmission was found to occur from person to person primarily through respiratory droplets when an infected patient coughs, sneezes, or speaks. The viral particles contaminate the objects and surfaces, which are transmitted by touch. In addition, the virus may be transmitted airborne; however, the transmission occurs primarily through droplets, contact, and fomites. Some reports have suggested the possibility of fecal–oral transmission, thereby indicating multiple routes of transmission. A person can be infected by breathing in the virus if that person is within a close distance (1–2 m) of an infected person or by touching a contaminated object or surface and then touching his face before washing the hands. The first cases of COVID-19 supposedly came from the seafood market in Hunan in China, with secondary cases occurring at hospitals among health care workers who came in contact with the infected patients.[10] MERS and SARS are also transmitted from close human-to-human contact through respiratory secretions from coughing and sneezing, whereas primary cases of MERS have been traced back to contact with infected camels, which was identified as the original reservoir host for MERS.[36] Other less common methods of transmission for SARS include fomites or fecal transmission and handling of animals such as bats.[2]
The spread of the novel coronavirus (COVID-19) is the fastest compared with the previous outbreak of coronaviruses, followed by SARS.

Even before the viral infection was formally declared a global pandemic, the Government of Saudi Arabia implemented preventative measures prior to any reported national deaths associated with COVID-19. The government imposed strict curfew, reinforced by financial penalties for anyone disregarding rules and constantly educated its citizens through mass media. Furthermore, Tawakkalna, a mobile application, was developed by the Ministry of Health and the Ministry of the Interior, to allow people to meet their needs and plan their journeys during the curfew period. [37]

2.4 Treatment

To date, the treatment of the novel coronavirus primarily involves isolation and supportive care to manage the symptoms or signs of clinical deterioration and providing respiratory assistance with oxygen therapy and ventilator support along with prophylactic antibiotics to prevent secondary infection. Anti-thrombotic such as heparin or low molecular-weight heparin may be given to patients with high thrombosis risk. [38] At present, no effective antiviral agent is available. Initial reports showed that oseltamivir was given to a large number of patients (150 mg/day) in combination with antibiotics such as azithromycin without any appreciable benefits. Corticosteroids

(dexamethasone 6 mg or methylprednisolone 40–120 mg/day equivalent) were given to patients requiring ventilator support to reduce lung inflammation caused by high levels of cytokines produced in response to the viral infection.[10] The monoclonal antibody targeting IL-6, tocilizumab (4–8 mg/kg as a single dose; repeated after 12 h as necessary), has also been found to be beneficial in the management of patients that have cytokine release syndrome.[39,40] Researchers have previously described the prophylactic use of chloroquine and its therapeutic benefits during the SARS-CoV outbreak. In vitro activity of hydroxychloroquine against COVID-19 showed apparent clinical efficacy. [41,42] The use of hydroxychloroquine (400–800 mg per day for 5 days) in the management of COVID-19 cases remains debatable and requires additional clinical evidence. Early intravenous infusion of human immunoglobulin may be recommended as a rescue treatment for critically ill patients based on their clinical condition. [43]

Remdesivir (200 mg intravenous loading dose followed by once daily 100 mg infusions for 5–10 days), an Ebola-antiviral drug, with its broad range of antiviral activity in vitro and in animal studies against numerous RNA viruses, including coronaviruses (SARS and MERS), showed potential as an anti-COVID-19 medication [40,44] and clinical improvement in non-randomized compassionate use cohorts. [45] On 22 October 2020, the USFDA released an update stating that remdesivir was approved for treating hospitalized COVID-19 patients (adult and pediatric) aged 12 years and above.[46] However, on 20 November 2020, the WHO released an advisory with a conditional recommendation, which opposed the usage of remdesivir irrespective of the severity in patients hospitalized with COVID-19.[47] The lopinavir/ritonavir therapy (400 mg lopinavir/ritonavir twice daily for 6–10 days) has been recommended by health authorities of several countries; however, recent studies from China and United Kingdom report no efficacy with lopinavir/ritonavir treatment versus the usual therapeutic care.[48,49] In an experimental study, favipiravir showed significantly higher treatment benefits for COVID-19 in contrast to lopinavir/ritonavir, and it is used 3600 mg/day in two divided doses on the first day followed by 1600 mg/day in two divided doses for 7–10 days.[50] Finally, type 1 interferons (interferon β-1b 8 million units every 48 h for three doses) with or without ribavirin (800 mg/day) could be considered as a treatment against COVID-19 but

mostly in the early phases of the disease.[51] Combinations of the above mentioned agents have been recommended by various health agencies in their treatment protocols. Triple regimen involving lopinavir/ritonavir, ribavirin, and interferon β-1b for 14 days was recommended in many countries such as Hong Kong and the KSA.[40] Baricitinib (a janus kinase inhibitor) at a dose of 4 mg per day for 14 days in combination with remdesivir was found to be superior to remdesivir alone in a randomized double-blind trial.[52]

After trials with various medications and based on the experiences from various countries and studies, the treatment protocol in KSA was continuously updated to the current protocol. The treatment protocol in KSA recommends use of favipravir or remdesivir along with systemic steroids
(dexamethasone/ hydrocortisone/prednisolone) in severe cases while critically ill patients are recommended remdesivir alone or in combination with baricitinib along with the systemic steroids. Patients experiencing rapid deterioration in respiratory function may be offered tocilizumab with systemic steroids. Thromboprophylaxis is recommended in all admitted patients after evaluation for bleeding risk. Patients with mild to moderate respiratory symptoms may be offered favipravir or inhaled budesonide according to the discretion of the treating physician. [53]

The main focus of the treatment for SARS-CoV-2 was the isolation of infected subjects, antivirals, and supportive treatments. Combination therapy of lopinavir/ritonavir was beneficial with fewer adverse clinical outcomes. [54] A clinical study in the KSA showed that lopinavir/ritonavir combined with interferon beta-1b was effective among MERS cases along with supportive care. [55]

2.5 Preventive vaccines

Vaccine research in MERS and SARS is still in its early stages of clinical evaluation, and a number of vaccines for COVID-19 have been fast tracked for approval in various countries. There is a concern that, as with natural coronavirus infection, vaccination may not induce long-lived immunity and hence re-infection or breakthrough infections may be possible.[56]

In USA, two mRNA-based vaccines have been authorized for use, BNT162b2 or tozinameran an mRNA-1273. BNT162b2 showed 95% efficacy

against symptomatic COVID-19, whereas mRNA-1273 vaccine showed 94.1% efficacy, and both vaccines showed acceptable safety profile in clinical trials.[57,58] The United Kingdom approved ChAdOx1 nCoV-19 or AZD1222 for emergency use. ChAdOx1 nCoV-19 vaccine efficacy ranged from 60% to 95%.[59] Other vaccines that were authorized for early emergency use included inactivated BBIBP-CorV vaccine in China and Adenovirus-based Sputnik V vaccine in Russia, which showed promising results in early studies. [60, 61]

BNT162b2 and ChAdOx1 nCoV-19 were given emergency approval for vaccination in KSA with 2nd dose recommended after 42 days of the first dose. As of 27 June 2021, a total of 18,495,398 vaccine doses have been administered to the Saudi population as reported by WHO.[13]

The vaccines have not undergone long-term studies, a requisite to assess the long-term side effects and safety, which is very much a cause of concern. Currently reported common side effects following COVID 19 vaccinations were generally mild and included injection site reactions, headache, muscle pain, fatigue, arthralgia, fever and chills and allergic reactions including anaphylaxis. [57,58,59]

3. DISCUSSION

The infection moved from China to Europe and North Americas to Latin American countries, Africa, and the Indian Subcontinent and then back to Europe for a second round, and based on the trends of the global spread of the disease, the disease may do another round in several countries unless preventive measures are continued. The Americas, Europe, and United Kingdom are currently at the epicenter of the pandemic. The lack of adequate testing facilities and access to health care is a major concern in many countries. The current statistics may be only a fraction of the actual figures because of the poor testing facilities, fewer tests, documentation, and transparency in COVID-19 data in many countries. Thus, governments must be prepared to face the outbreak by strategic planning. Systematic lockdown with social distancing is currently the most effective way of slowing down disease transmission. Such measures will remain as the primary measure for disease control until sufficient quantity of effective vaccines can be produced to vaccinate a significant part of the population –worldwide. Adequate risk evaluation, considering the

seriousness of the current setting and prompt dissemination of outbreak-related information, can provide comprehensive understanding of the pandemic dynamics and help us slacken the spread of SARS-CoV-2 worldwide. [62]

The infection rates among healthcare professionals are high during the outbreaks of MERS and SARS, particularly those involved in high-risk procedures such as intubation and endotracheal suction.[63,64] This result is similar to that of COVID-19, which has affected the medical practice and functioning of hospitals during the current coronavirus outbreak. Furthermore, the novel coronavirus is transmitted to healthcare workers, although comparisons with MERS and SARS have not yet made.

Meticulous monitoring and supportive care can reduce the risk of mortality in COVID-19; however, such care cannot be offered to all patients when a large number of patients are infected with the virus. The use of steroids and tocilizumab may be beneficial in critically ill patients with lung involvement by modulating the cytokine-mediated inflammatory responses; however, tocilizumab is an expensive option for widespread use. In the current scenario of non-availability of a specific antiviral agent, potential medications (as suggested by in vitro studies or based on experience with other coronavirus infections) for COVID-19 with less serious side effects along with good supportive care can be considered. A logical approach in the management of symptomatic COVID-19 patients is the combination of safe agents. Currently reported results are based on observational studies or studies that are not conducted in randomized control settings. Several factors such as timing of initiation of antiviral therapy, concomitant use of other antiviral drugs, potential antiviral enhancing/suppressing effect of other concomitant medications, severity of illness, or severity of comorbid illness may influence the outcomes of antiviral therapy. These factors should be considered before accepting any positive or negative results being reported currently as a recommendation. Adopting treatment protocols from countries with significant number of cases but with significantly low mortality rate is another option, which may be considered until more concrete evidence emerges regarding antiviral therapy.

Mass vaccinations and building vaccine-acquired herd immunity are potential approaches for containing the infection; however, mass

production of vaccines to provide adequate supply of vaccines is a great challenge that the manufacturers are facing. However, questions still remain regarding the long-term side effects and duration of the protective efficacy of the preventive vaccines developed and approved in such a short time frame.

Studies have shown mutations of the novel coronavirus genome, and some mutations have become more aggressive and contagious; this mutation may be an outcome of natural evolution.[65] Similar mutations in the spike (S) protein are found during the initial phase of the SARS 2002–2003 epidemic, which eventually dominates the outbreak, concluding new adaptations to humans.[66] The spread of COVID-19 widely across the Middle East also raises concerns about MERS and COVID-19 co-infection in human or animals with possible emergence of new strains of coronavirus.

4. CONCLUSION

The experiences from previous outbreaks of SARS and MERS and from the countries affected initially with COVID-19 are the best lessons currently available as there is a lot to known about COVID-19. Although we have a number of potential antiviral medications for COVID-19, more extensive studies and analyses are needed before strong recommendations can be made for or against any particular treatment. Unlike MERS and SARS, novel coronavirus SARS-CoV-2 is highly contagious, and proper hygiene and protocols for limiting human-to-human transmission along with improved epidemiologic surveillance and monitoring are recommended to reduce viral transmission until vaccines are available for mass vaccination programs.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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