Journal of Health and Social Sciences 2020; 5,2:209-218
The Italian Journal for Interdisciplinary Health and Social Development

MINI REVIEW IN
PUBLIC HEALTH AND COVID-19

SARS and MERS as learning tools for addressing the 2019-nCoV epidemic: A mini-review

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Abstract

The novel Coronavirus (2019-nCoV), named SARS-COV-2, originating in the Wuhan district of China, has reached pandemic proportion with a death toll that is steadily rising. Coronaviruses are classified by their distinct genomic make-up and have been in the spotlight due to their ability to cause fatal epidemics across national borders. Issues such as sub-par personal hygiene, overcrowding, and mass panic exacerbated the spread of the Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) and Middle East Respiratory Syndrome coronavirus (MERS-CoV), serving as crucial lessons for understanding the 2019-nCoV. Heightened sanitation measures with regards to waste disposal in healthcare clinics and in areas of mass transit are also of great importance. The 2019-nCoV is a concern for many different countries and governments of all levels due to its negative effects on public morale, national economies, and health standards and outcomes. There is an immense capacity to use past approaches to SARS and MERS epidemics to influence the design of strategies to control the 2019-nCoV epidemic. The 2019-nCoV has infected more individuals than previous coronaviruses SARS and MERS. In this minireview, we evaluated the SARS and MERS epidemics to provide context to the strategies against 2019-nCoV. We further identified drawbacks in the global approach to combating SARS and MERS to inform policies to curb 2019-nCoV.

KEY WORDS: 2019-nCoV; Coronavirus, Covid-19; epidemic; governments; MERS CoV, policies; SARS CoV.

Riassunto

Il nuovo Coronavirus (2019-nCo), denominato SARS-COV-2, che ha avuto origine nel distretto di Wuhan in Cina, ha raggiunto una proporzione pandemica, con una conta di morti in stabile crescita. I coronavirus sono classificati in base al losto distinto profilo genetico e sono stati messi in evidenza per la loro capacità di causare epidemie fatali tra i confini delle nazioni. Problematiche quali igiene personale al di sotto della mdia, affollamento, e panico di massa hanno esacerbato la diffusione del coronavirus SARS-CoV e del coronavirus MERS-CoV, servendo da lezioni cruciali per comprendere il nuovo coronavirus. Le rafforzate misure sanitarie con riguardo all'eliminazione dei rifiuti nelle strutture sanitarie ed in aree di transito di massa sono di grande importanza. Il nuovo coronavirus desta preoccupazione in differenti Paesi e governi di tutti i livelli a causa dei suoi effetti negativi sul morale pubblico, sulle economie nazionali e gli effetti sulla salute. Esiste una immensa capacità di adottare approcci passati rispetto alle epidemie di SARS e di MERS per influenzare la progettazione di strategie di controllo dell'epidemia causata dal nuovo coronavirus che ha infettato più persone rispetto ai precedent coronavirus della SARS e della MERS. In questa minireview valutiamo le epidemie di SARS e di MERS per fornire un contesto alle strategie contro il 2019-nCoV. Inoltre, abbiamo identificato gli aspetti negative nella lotta contro la SARS e la MERS per informare le politiche contro il 2019-nCoV.

TAKE-HOME MESSAGE

Policy approaches to SARS and MERS epidemics should inform the design of policy aimed to contain and address the novel Coronavirus (2019-nCoV). The 2019-nCoV has a greater geographic spread and an increased incidence rate compared to previous coronavirus epidemics, necessitating urgent policy interventions set in a backdrop of economic and political unrest.

Competing interests - none declared.
Sources of Funding - The authors did not receive funding from any funding sources in the public, commercial, or not-for-profit sectors.

Cite this article as: Udit D, Palaniappan A. SARS and MERS as learning tools for addressing the 2019-nCoV epidemic: A mini-review. J Health Soc Sci. 2020;5(2):209-218

DOI 10.19204/2020/srsn5

Received: 02/03/2020 Accepted: 14/07/2020 Published Online: 15/07/2020

INTRODUCTION

As we approach the twentieth anniversary of the 2002 SARS outbreak, China has been confronted with another barrage of coronavirus infections of epidemic proportions. Coronaviruses are a family of viruses that are capable of causing mortality in mammals and birds through respiratory and intestinal infections [1]. It was first named in the 1960s based on the shape of the glycoproteins present on the virus envelope surface, and they are delineated by the length of their genomic make up: a single-stranded RNA of 26,000 to 32,000 bases long. There are four distinct genuses of the Coronaviruses: *Alphacoronavirus, Betacoronavirus, Gammacoronavirus,* and *Deltacoronavirus* [2]. Coronaviruses are typically transmitted to uninfected humans via contact with airborne droplets of fluid from infected humans [3].

A novel coronavirus, 2019-nCoV, named SARS-COV-2, has been linked to the December 2019 outbreak of pneumonia in mainland China [4]. The virus started in the Huanan Seafood Wholesale market in Wuhan, China, and previously well-known viral vectors such as SARS-CoV, MERS-CoV, and other viruses known to cause respiratory complications were ruled out [5]. RNA studies utilizing relative synonymous codon usage (RSCU) have indicated that snakes are the most probable wildlife reservoir for the novel coronavirus [6]. Furthermore, a spike glycoprotein undergoing homologous recombination could be enabling the virus to transmit from snakes to humans [7]. The 2019-nCoV has had widespread impacts on the spheres of economics, social wellbeing, and public health in ways that are reminiscent of previous coronavirus outbreaks from the 21st century. Past epidemics of coronaviruses stress the importance of a close relationship between clinicians and public health frameworks on local, national, and international levels.

The aim of this paper is to review the biological and social factors contributing to the SARS and MERS epidemics and to compare these outbreaks and actions taken against them to the ongoing SARS-COV-2 pandemic to evaluate policies that may be effective in mitigating the spread of the novel coronavirus.

DISCUSSION

Severe Acute Respiratory Syndrome (SARS-CoV)

Several cases of a pneumonia-like disease were observed in the Guangdong Province of China in November 2002, followed soon after by an outbreak in Hong Kong in March 2003 [7]. Soon after, respiratory illnesses characterized by similar symptoms were reported in other parts of China, other Asian countries such as Taiwan, Vietnam, and Singapore, and in North America. This respiratory illness was soon characterized under the clinical name 'Severe Acute Respiratory Syndrome', or 'SARS'. By May 2003, over 6200 cases were identified in 30 countries, leading to 435 confirmed deaths [8]. In China, the origin of the disease, SARS claimed 349 lives nationwide and infected more than 5,300 people according to a 2003 Ministry of Health report [8]. In a study of 138 patients, 100% of patients experienced fevers and 50% of patients experienced coughing and headaches [9]. Furthermore, 69.6% of patients had lymphopenia and 44.8% of patients experienced thrombocytopenia. 32 patients were admitted to an intensive care unit, and 5 patients died. Lactate dehydrogenase levels were elevated in 71.0% of patients while creatine kinase levels were elevated in 32.1% of patients [9]. Those determined to be most at risk were older patients, those with high peak lactate dehydrogenase levels, and those with a high neutrophil count. SARS was deemed to produce significant morbidity and mortality [9].

SARS (Severe Acute Respiratory Syndrome) is caused by SARS-CoV, which is a polyadenylated RNA-virus. The virus has a genomic organization indicative of a coronavirus as it displays gene order: [5'-*replicase (rep)*, *spike* (S), *envelope* (E), *membrane* (M), *nucleocapsid* (N)-3'] [10]. The *rep* gene accounts for about two-thirds of the virus' genome, and this gene encodes ORF1a and ORF1b, whi-

ch are polyproteins that are cotranslationally proteolytically processed [10]. SARS translates *rep* gene products from genomic RNA whereas other viral proteins are encoded by mRNAs producing a 3'-coterminal nested set that has genomic 5' leader sequence [10].

After SARS' international outbreak, the World Health Organization led a collaborative effort to determine factors behind the spread of the virus. SARS-CoV was isolated in Vero cells, and antibodies from patients diagnosed with SARS displayed antibodies for SARS-CoV, suggesting the coronavirus was responsible for propagating the disease [10]. SARS-CoV was determined to be transmitted between humans through interpersonal contact, and individuals working in the healthcare field were found to be at the highest risk of contraction [7].

SARS-CoV was traced back to a restaurant in Guangzhou, China that served palm civets. A waitress as well as a person eating nearby the palm civet cages were diagnosed with SARS, and SARS-CoV was found in each of the six civets present at the restaurant [11]. A phylogenetic analysis of the viral sequences linked the virus to palm civets as well [11]. Bats were determined to be the original reservoir of SARS-CoV, and the greater diversity of SARS-CoV strains present in bats further suggests that mutations in the viral RNA of the SARS-CoV that initially infected bats enabled it to infect civets and thereafter humans [12].

SARS has an incubation period of about 2-16 days after which a fever typically sets in [7]. Patients diagnosed with SARS were quarantined for 1.5-2 weeks, which produced economic losses in many countries where the disease was widespread [7]. Diagnosis of the disease was also associated with high false-negative diagnoses, and as a result, some sites had underestimated viral loads. Furthermore, undiagnosed cases of SARS led to fewer distinct strains of SARS-CoV being identified than are likely in existence. Furthermore, reinfection rates were high due to the multiple strains of the virus developing [7]. Patients were treated with antiviral drugs that block receptor and S protein function to prevent the virus from propagating [7].

China's response to the SARS outbreak was characterized as insufficient by the World Health Organization [13]. Local governments lacked experience in handling epidemics of communicable diseases, and as a result, the government did not place a high priority on controlling the SARS epidemic. Eventually, as the number of infections continued to rise, the Chinese central government began to discuss the use of resources to combat the outbreak. Public trust of the government began to erode due to initial inaction; however, eventually, the Chinese government established a SARS Control Headquarters to coordinate containment efforts. The central government sent experts to facilitate inspections and guide local leaders in preventative techniques, became more transparent with the World Health Organization, and began to hold local leaders responsible for health outcomes [13].

Beyond China, economic models predicted that the reduction of productivity and limitations placed on trade could devastate the global economy [14]. However, the negative economic impacts the SARS epidemic posed were greatly overestimated, which revealed that models being used were inaccurate and did not correctly account for non-health sectors, which is where most costs are incurred [14].

In the United States, the federal government added SARS to its list of quarantinable communicable diseases [15]. This enabled the Centers of Disease Control and Prevention (CDC) to detain those infected with SARS. The CDC worked at points of entry in the U.S., especially airports, to inform passengers of traveling risks associated with SARS and evaluate potentially infected individuals entering the U.S. The SARS outbreak served as catalyst for the CDC to become better prepared in instances of communicable disease outbreak. Directly in response to the SARS outbreak, the CDC established a multistate teleconference program to improve the organization's legal preparation in the event of future epidemics necessitating the use of

its quarantine powers [15]. The incidence of SARS was 8,422 cases with a case fatality ratio (CFR) of 11% [17]. No cases of SARS-CoV have been reported worldwide since 2004.

Middle East Respiratory Syndrome (MERS-CoV)

Middle East Respiratory Syndrome (MERS) was first diagnosed in Saudi Arabia in 2012. It is a zoonotic virus, and the reservoir of infection is Arabian dromedaries. Dromedaries are one humped camels that are bred by humans in the Middle East, and they are believed to have been infected with the virus by South African vesper bats [17]. Human to human transmission occurs from close and unprotected contact or through care of infected individuals. This disease has spread globally, with reported cases in 27 countries since 2012 [17]. However, 80% of all human infections were observed in Saudi Arabia [17]. Human cases reported in regions outside the Middle East are typically due to contact with an infected individual who left the Middle East. MERS reveals that there are occupational hazards when dealing with coronaviruses because those who work with Arabian camels are expected to face an elevated risk for MERS contraction. An occupational hazard is present in the medical community as well, which is tasked with treating infected patients who are potential sources of MERS-CoV.

The average incubation period of the MERS-CoV is 10-14 days [18]. The clinical presentation of MERS ranges from asymptomatic to multi-organ failure. Symptoms include fever, chills, rigors, myalgia, malaise, cough, and shortness of breath [17]. Chief complaints tend to be gastrointestinal, including symptoms such as diarrhea, vomiting, and abdominal pain. The crude fatality rate average is 35% among primary cases and 20% among secondary cases [17]. Pediatric patients present with a milder version of MERS, which also tends to be asymptomatic. Additionally, pediatric MERS is associated with a lower mortality and morbidity than MERS in adults [17]. Studies suggest that approximately 12.5-25% of all MERS cases are asymptomatic, which makes the disease difficult to diagnose and screen [19].

MERS-CoV is an enveloped single-stranded RNA virus of the family Coronaviridae and subfamily Coronavirinae. The MERS-CoV genome encodes 4 structural proteins (S, E, M, N), and the S protein is of clinical interest due to its receptor specificity and its role as a targeted biomarker in the humoral immune response [17]. The S protein is composed of S1 and S2 subunits. The S1 subunit hosts a Receptor Binding Domain for cellular receptor binding, and the S2 subunit hosts HR1 and HR2 regions for virus fusion and entry into cells [20]. A key function of the Receptor Binding Domain in the S1 subunit is the ability to release neutralizing antibodies that are protected from MERS-CoV [21].

Limited contact with camels and infected individuals is suggested to reduce chances of infection [22]. Additionally, heat has been proven to deactivate the MERS virus [17]. There is currently no approved vaccine for MERS-CoV, but the Modified vaccinia virus Ankara (MVA) vaccine in camels led to reduced levels of MERS-CoV and viral RNA transcripts [23]. The most common site of human to human transmission was healthcare settings. In fact, healthcare settings accounted for nearly a fourfold higher rate of transmission than any other setting, including the average home [17]. Furthermore, MERS has a mortality rate of 34.4%, which is the highest of any of the epidemic coronaviruses. MERS killed 858 individuals and infected 2,494 others from September 2012 to September 2019 [24]. Given this high mortality rate, it is important to educate individuals at risk and the global community of prevention techniques. A flaw in policy was evident during the MERS outbreak because in a study of a Saudi Arabian university affected by the outbreak, only 79% of participants could identify symptoms of MERS and only 67% of participants were aware of appropriate hygienic practices necessary to curtail transmission [25]. Since this study targeted a highly educated subsam-

ple of the Saudi population, there is likely an even higher knowledge deficit in the larger community. Another key takeaway from the MERS epidemic was the impact of overcrowding in healthcare settings. For instance, a study following a single patient with MERS in South Korea revealed how crowding in hospitals - especially in the emergency department - and insufficient control over visitation policies led to greater spread of the disease [26]. Therefore, for future outbreaks of similar diseases, strict policies concerning visitation restriction and patient capacity management should be stressed.

2019-nCoV (SARS-COV-2)

The latest strain of coronaviruses took root in Wuhan, China in December of 2019. Due to Chinese censorship, worldwide media exposure did not take effect until January 2020. The 2019-nCoV was named by the WHO as SARS-COV-2 and is a β CoV of group 2B with over 70% similarity in genetic sequence to the SARS-CoV [4, 5]. The disease caused by the SARS-CoV-2 virus was named 'COVID-19' by the World Health Organization in February 2020 [4]. COVID-19 stands for 'Coronavirus Disease 2019' [27]. Human to human transmission of the 2019-nCoV is substantiated on human ACE2 molecules through the S-protein [23]. As of July 14, 2020, there have been over 85,000 confirmed 2019-nCoV infections in mainland China alone, greatly surpassing the number of SARS infections in China from 2002-2003 [28]. Furthermore, the worldwide death toll of the disease stands at over 574,000 lives, and there have been almost 7.3 million global recoveries from the virus [28]. 215 distinct countries and territories have reported cases of 2019-nCoV, highlighting the wide geographical reach of this disease in a globalized world and the need to monitor disease transmission across borders and nationalities [29]. The three countries with the most confirmed cases are the United States with almost 3,375,000 cases, Brazil with almost 1,885,000 cases, and India with almost 907,000 cases [28].

Symptoms of COVID-19 include fever in over 90% of patients, malaise and dry cough in over 80% of patients, shortness of breath in over 20% of patients, and respiratory distress in over 15% of patients [5]. The time gap between appearance of initial symptoms and time of death has a median of 14.0 days and a range of 6 to 41 days [23]. Shorter time-frames are associated with patients older than 70 years [23].

The WHO has already published guidelines for healthcare networks and the general public in regards to the 2019-nCoV with some policies informed by how SARS and MERS were able to spread rapidly. For instance, the WHO recommends allowing patients with mild symptoms or symptomatic patients without a dire need for hospitalization to be cared for within their own homes [30]. This provides an avenue for the medical community to alleviate hospital overcrowding in regions where the 2019-nCoV has infected a significant portion of the population. Another prudent recommendation of the WHO is that healthcare professionals should wear personal protective equipment and minimize exposure both while collecting and transporting specimens of infected individuals [31].

On a larger scale, governments are urging their residents to wear masks to mitigate the spread of the 2019-nCoV. The Centers for Disease Control and Prevention advise that all individuals wear face coverings in public, especially in instances when social distancing and remaining six feet away from others is difficult [31]. Because COVID-19 is spread primarily through respiratory droplets that can be emitted by individuals, even those who are asymptomatic, when they speak, cough, or sneeze, the widespread use of masks helps mitigate the spread of the virus [32]. The public health benefit of using masks is exemplified in South Korea – a country that has a culture of mask-wearing due to its experiences with the SARS epidemic and has had a better COVID-19 pandemic outcome than many other countries [33, 34]. Many similarities can be seen among the SARS, MERS, and SARS-COV-2 outbreaks, but SARS-COV-2 has had a significantly greater worldwide ef-

Table 1. A comparison of the SARS, MERS, and SARS-COV-2 epidemics..

	SARS	**MERS**	**SARS-COV-2**
Initial Origin	Guangdong Province, China (2002)	Saudi Arabia (2012)	Wuhan, China (2019)
Confirmed Deaths	435	858	571,840 as of July 14, 2020
Zoonotic Source	Palm Civets	Arabian Dromedaries	Bats
Incubation Period	2 - 16 days	10 - 14 days	4 – 5 days
Chief Complaints	Fever, coughing, headaches	Fevers, coughing, shortness of breath	Fevers, coughing, shortness of breath
Treatment	No Standard Treatment	No Standard Treatment	Clinical Trials in Progress
Vaccine	No Vaccine	No Vaccine	Clinical Trials in Progress

fect than the other two coronaviruses. Table 1 presents a summary of the biology and worldwide effects of these three coronaviruses.

COVID 19: Recommendations for policy-makers

Based on the experience of combatting SARS and MERS outbreaks of past years, current policy aimed at ending the 2019-nCoV outbreak should center around early detection of infection. Maximal screening of elevated body temperatures should be employed in areas of interest and Schelling points. These locations should have heightened sanitation policies such as requiring security personnel to change their gloves frequently and questioning individuals who are flying from known infection hotspots and are displaying common visible symptoms of the disease. Airlines transporting quarantined passengers with possible 2019-nCoV infections should hire personnel specializing in hazardous material handling to ensure subsequent flights are safe for passengers and airline employees. Additionally, healthcare professionals should be screened both at the start and end of their shifts to ensure they are not infected with 2019-nCoV and to ensure they are physically capable and not worked to exhaustion [35]. A major factor contributing to rapid spread of 2019-nCoV is the overcrowding of patients within clinics and healthcare facilities. Local governments should invest resources in installing pop-up healthcare facilities in high-infection areas to increase the area within which potential patients are held to prevent disease transmission. Waste produced within healthcare facilities that treat patients with 2019-nCoV should be disposed of immediately and efficiently. Similarly, the posthumous formalities should be done with a goal of minimizing exposure to non-infected individuals in isolated areas. Governments from the local to the national levels should continue to urge citizens to wear masks in public and should consider passing legislation that institutes a fine on individuals who endanger others by neglecting to cover their faces in public. Efforts should also be taken to survey stray animals in Wuhan and other hotspots for potential infection, while simultaneously ensuring that those with poor respiratory systems are not in close contact with the animals.

Furthermore, major public health organizations such as the CDC and the WHO should continue to disseminate accurate information and comprehensive guidelines surrounding the COVID pandemic. Periods involving quick-spreading disease outbreaks are often accompanied by a bevy of misinformation and sensationalism, which can result in individuals being gripped by feelings of fear and hopelessness rather than concrete plans for disease prevention. Public health groups should continue to provide updates about the spread of the virus and progress towards finding a viable vaccine while simultaneously reminding the general public to engage in normal hygienic behaviors, such as washing and sanitizing hands before touching one's eyes, ears, or mouth, sneezing into elbows, avoiding the sharing of drinks or utensils, and wearing facemasks in public.

International cooperation is also of paramount

importance in ensuring the mitigation of this pandemic. All countries must work together to follow WHO guidelines and equitably share resources. Countries with plentiful resources cannot afford to ignore countries that are in need of resources due to the degree to which the world is globalized. It is becoming increasingly difficult to restrict travel, and unless 2019-nCoV is effectively eradicated in all countries, the entire world will remain at risk until a vaccine is developed. Governments should continue to combat the economic slowdown associated with COVID-19 with direct subsidies, especially to small businesses and low-income citizens, rather than reopening larger gathering spaces and international travel without restrictions.

CONCLUSION

Addressing the 2019-nCoV outbreak will require a multifaceted approach that is informed by the successes and failures of approaches to the SARS and MERS epidemics. The initial estimate of CFR of SARS-CoV-2 was 2%, which is distinctly lower than that of SARS and MERS [36]. However, a precise estimate of CFR is presently impossible because the pandemic is still ongoing [37]. Moreover, the geographical reach of 2019-nCoV vastly overshadows that of the previous coronavirus epidemics. Globalization amplifies the effects of diseases arising in regions that can seem insular, ultimately allowing them to have a worldwide footprint. It has been shown that accounting for occupational hazards will help reduce the possibilities of new infections arising in humans from both zoonotic and healthcare settings. Additionally, policy constructed to combat SARS and MERS contained weaknesses pertaining to the logistics of patient care. Policy developed to fight the 2019-nCoV outbreak should address overcrowding in clinics and hospitals, lax visitation rules, and general hygienic education. It is imperative that the experiences of fighting SARS and MERS are used to curb 2019-nCoV because 2019-nCoV has already spread across a larger geographical region and infected more individuals than its coronavirus predecessors.

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