Understanding COVID-19: An Analogy to SARS and MERS

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Abstract: Background: To provide a comprehensive outlook of three deadly corona viruses global epidemics, their similarities and differences which will help provide critical assessment of modifiable risk factors and preventive measures for containing their spread in future as well as utilize the lessons learned from earlier two corona virus epidemics to help control the spread and end the recent epidemic of SARS-CoV-2. Material And Methods: Utilizing comprehensive review from PubMed database and WHO bulletins, we obtained genomics information, clinical signs & symptoms, treatment, diagnosis, transmission, methods of prevention, and risk factors for SARS, MERS and COVID-19. A comparison between viruses was made. Result: Tracing back of the origin of these corona virus epidemics puts China at the epicentre for two of the three outbreaks. Although SARS showed high fatality, COVID-19 has rapidly spread among symptomatic & asymptomatic cases. Inadequate risk assessment, possible data fudging and under reporting of virus considering urgency of situation within China has been a key reason for the spread of the new virus outside mainland to distant countries. None of the virus epidemics have resulted in development of a permanent cure with sporadic outbreaks remains distinct possibility. Conclusion: We conclude that with all available high-end technology and an experience of two prior epidemic of similar viral origin, we still look ill prepared to face challenges posed by epidemics especially the ongoing virus pandemic. Countries should work together in sharing and dispersing of information to limit spread and finally terminate the infection using technologies to best. [Natl J Integr Res Med, 2020; 11(3):77-87]

Key Words: Corona virus, epidemiology, epidemic, outbreak, MERS, SARS, COVID-19

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Introduction: In today's world, cases of un-identified diseases keep emerging, with at least 1 a year, and this trend of disease discovery is continuing for the last 2 decades. Outbreak of corona virus epidemics across the globe in form of SARS in 2003 and MERS in 2012 has caused great public health threats. On December 31st, 2019, the city of Wuhan, China registered 27 cases of pneumonia with unknown aetiology[1].

Some of these cases reported to have sore throat, dry cough and fever while others displayed severe symptoms of pneumonia, pulmonary oedema, septic shock, organ failure and Acute Respiratory Distress Syndrome (ARDS)[2]. On January 7th, 2020, results from the throat swab samples from these cases identified the triggering agent as a member of corona virus family & was labelled as SARS-CoV-2. Previous epidemic of respiratory disease caused by another beta-corona virus was registered in Saudi Arabia (2012), which presented with symptoms of acute respiratory illness similar to SARS. Upon sequencing the isolates extracted from the patients, highlighted some distinctive features thus named MERS-CoV[3]. However, the first of all corona virus epidemics occurred in 2003, when a novel virus spread globally at an alarming rate. This outbreak of unexplained pneumonia in Guangdong province of China[4] amplified during hospital care in China and then repeated itself outside the province among hospital staff in region of China, Vietnam, Hong Kong and Toronto. WHO alerted the world about this novel viral infection and gave the new disease its name SARS[5]. The rapid control by the public health sectors became the reason of containment of these corona viruses. The aim of our review is to provide an overview about the three corona virus diseases which caused cataclysmic epidemics globally, highlighting essentials in containment protocol and assessment of risk factors. Learning from the past epidemics of corona viruses might help the public health officials and doctors in battling the current COVID-19 progression.

Material & Methods: The information of corona virus regarding genomics, the spread of these epidemics, clinical signs & symptoms, transmission methods and prevention of SARS, MERS & COVID-19 was obtained from comprehensive review of literature from PubMed and other search engines. WHO website was used for global data on the COVID-19 epidemic and creation of graphs. Moreover, news articles that are verified were also used for retrieving information on cases and fatalities of COVID-19.

Results: Understanding The Epidemic: Severe Acute Respiratory Syndrome (SARS) was the first

major zoonotic infectious epidemic caused by corona virus family that spread globally. Patients with pneumonia like symptoms of high fever, dyspnoea and respiratory illness[6] were admitted in a hospitals of Guangdong province in southern China of which some developed severe breathing problems [7].The Chinese Ministry of Health reported the outbreak to WHO on 11th Feb 2003, it was on 12th March 2003 that WHO declared 'SARS' outbreak as an epidemic. Soon it became clear that the infection was spreading globally when cases with similar sign and symptoms started reporting from hospitals of Singapore, Vietnam & Toronto.

The epidemic declined after 3 months, with a cumulative number of 8,098 SARS probable cases and 774 deaths worldwide across 29 countries[5] with China and Hong Kong accounting for 87% of all cases and 84% of all deaths. Case fatality ratio was estimated to be as low as < 1 in persons below 25 years to 50% in those >65 years: an overall estimate of 9.6% to 11%[8].

In 2012, Middle East Respiratory Syndrome CoV (MERS-CoV) emerged in Saudi Arabia[3]. Several patients with symptoms similar to SARS like fever, sore throat, headache & shortness of breath[9,10] were hospitalized in Zarqa, Jordan on April 2012 from which, two died[5]. With first cases reported in Jeddah, it quickly spread overseas to Asia, Africa, Europe, and America[7,8].

Inadequate infection control practices lead to its spread across Arabian Peninsula raising the total figure of cases, to 2102 in Saudi Arabia with 780 related deaths, hiking the case fatality rate to: 37.1%-42%[11].Sporadic outbreak of human to human transmission occurred thereafter with the largest outbreak occurring outside Middle East in South Korea (2015), when 186 MERS cases with substantial morbidity and mortality [12]. Severity of infection was largely confined to average age of (~50 years) with elderly having greater probability of mortality from this disease: fatality of 90% in those above 80 years compared to ~10% with age of under 20 years [13].

On December 18th, 2019, China reported cases of pneumonia and acute respiratory distress[14].

These patients presented with range of symptoms similar to SARS and MERS like fever, coughing, fatigue, running nose, headache and breathlessness, a suggestive of lower respiratory tract involvement and a chest CT scan classical of a pneumonia[15-17]. One of these hospitalized patients died within next 10 days[18]. Presumed to be of nosocomial origin the infection was later identified as COVID-19 by January 2nd, 2020.

Exponential rise in number of confirmed case (571 to 1975) and deaths (17 to 56) were reported in 25 cities of China within 3 days[14]. By January 30th, 2020, 7734 cases were confirmed in China and 90 other cases reported from other Asian and European countries, with case fatality rate of 2.2% (170/7824)[19]. WHO on April 15th, 2020 declared COVID-19 as pandemic and confirmed globally death to be 1,23,010 and about 19,14,916 total positive cases (figure 1A and 1B). On 19th March 2020, for the first time since the beginning of epidemic no new domestic case was reported in China [20].

Evidences suggest increased propensity of virus to infect persons of old age (infections in India was more in middle age>40years)[21] with or without co-morbidities and/ or chronic diseases like diabetes, hypertension and cardiovascular disease. SARS-CoV-2 infected patients requiring ventilatory support have high mortality index[22] and a CFR of nearly 2% [23].

Virus Analogy Of Epidemics: SARS virus isolates from human was found to have similarity with virus isolated from racoons and civets, concluding the hypothesis that virus may have jumped from mammals to man[24]. Moreover, the animal isolates retain a 29-nucleotide sequence which was not found in most human isolates, expecting a mutation.

Two independent genome sequences were obtained from humans and observed that 99% of the sequences were conserved thus ruling out mutation during human transmission[25,26]. Endemic in dromedary camels of Arabian Peninsula, the MERS respiratory syndrome is still a threat to reintroduction in human populations.

Though camels are proposed to be the link for the transmission of MERS-CoV, studies suggest its origin from bats (HKU4 and HKU5) as so is SARS-CoV[3,7,27,28]. Present epidemic of COVID-19 corona virus also has its origin undetermined, but the virus has been suggested to be originated from wet animal market in Wuhan province in China. With no consistent evidence of corona reservoir other than mammals and aviaries [29].

Figure 1A: Cumulative Covid-19 Confirmed Cases

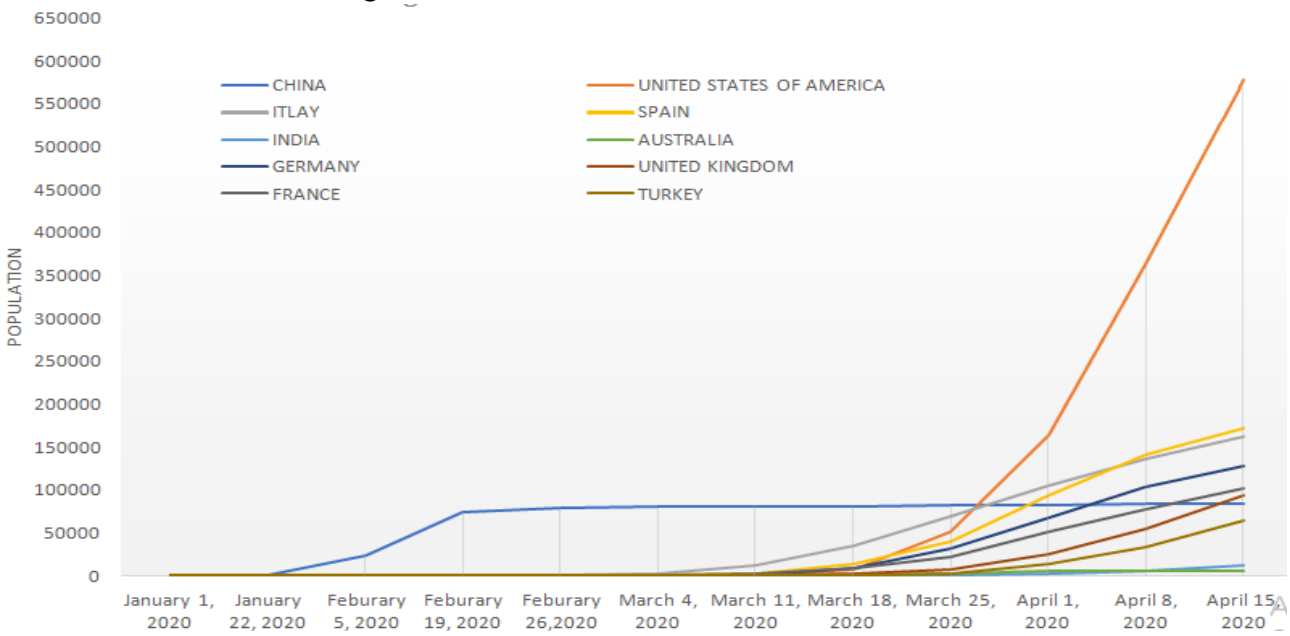

Figure 1A: Shows cumulative confirmed cases of COVID-19 across different countries. The rise in confirmed cases in China was slow over the period of first 2 months and is continuing at the same rate till date. In contrast, an exponential rise was observed in several European countries since their 1st detected case. From March 25th to April 15th the rise in USA far exceeded than those in Europe suggesting rapid spread of infection across the population. In India, with the first migratory confirmed case in February the rise has been relatively slower than the neighbouring countries. [Data was taken from World Health Organization. Corona virus disease 2019 (-COVID (19: situation report, 86.]

Figure 1B: Cumulative COVID-19 Mortality Case

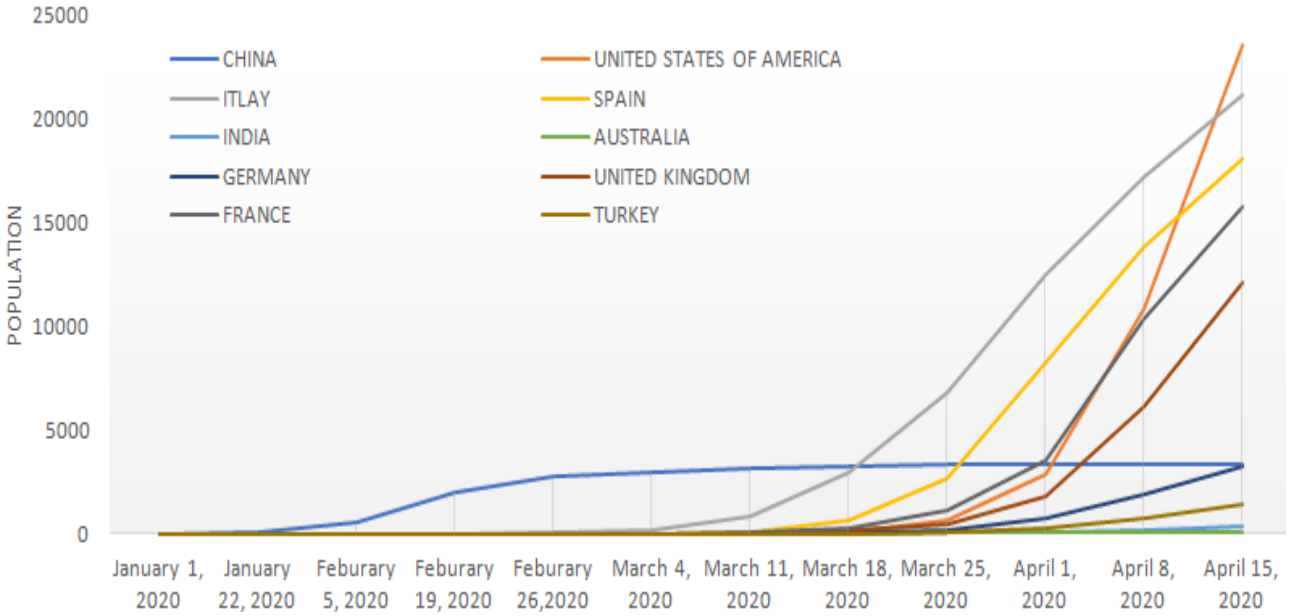

Figure 1B: Shows the rate of mortality in cumulative index across the globe. Mortality due to SARS-CoV-2 started to rise a little later to 1st detected case in almost all the countries. The rate of mortality paralleled the rise in confirmed cases in china. However, in European countries like Italy and Spain, the mortality was much higher in proportion to the number of confirmed cases from the country. Compared to European countries, USA observed a steep rise in mortality within the similar duration. [Data was taken from World Health Organization. Corona virus disease 2019 ((19-COVID : situation report, 86.]

Researches suggests that bats are natural reservoirs of SARS-CoV-2 and perhaps pangolin to be the intermediate host for SARS-CoV-2 (figure2), but possibility also remains for another sub-intermediate host [30].

Figure 2: Shows The Origin Of SARS-CoV, MERS-CoV And SARS-CoV-2 Virus Epidemics

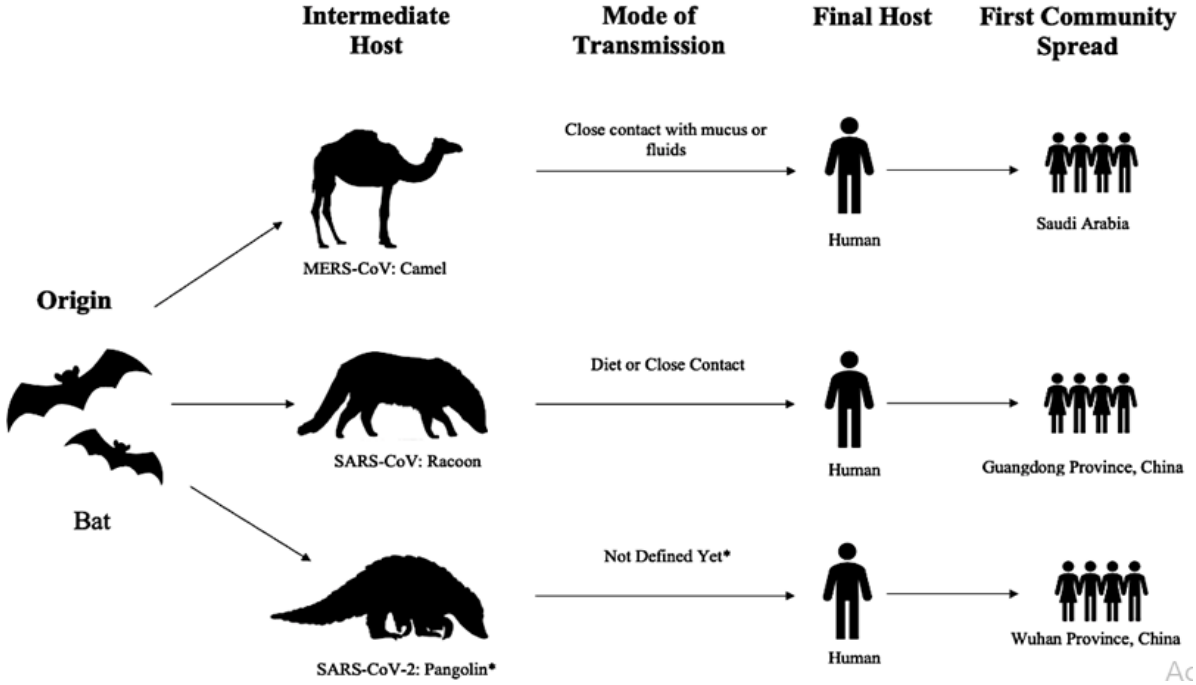

Figure 2: Shows the origin of SARS-CoV, MERS-CoV and SARS-CoV-2 virus epidemics and the probably intermediate host for its human transmission with their site of first community spread. [Diagram modified from Shereen MA, Khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: origin, transmission, and characteristics of human coronaviruses. Journal of Advanced Research. 2020 Mar 16.]

Genomics: Corona viruses are ssRNA molecule with a 5'cap and a 3'poly (A) tail and have been classified into three broad groups of procine, murine and avian viruses based on genetic sequencing. The distinctive feature of these viruses is the (S) spike protein which interacts with the host cell through its S1 domain. The entry is mediated by membrane fusion from the S2 domain of the protein. The genome of CoV's contains a 6–11 open reading frames (ORFs)[31].

Translation performed by the host cell machinery, overlaps these ORFs by a ribosomal frame-shifting mechanism in order to create pp1a and pp1ab polyproteins[32,33]. These polyproteins further encode for 16 non-structural proteins, which form replication-transcription complex in double-membrane vesicle[34]. Repetitive RTC replication and synthesis contributes to a sub-genomic RNAs[35].

These newly formed RNAs then codes for accessory and structural proteins: Spike (S) glycoprotein, Envelope (E) protein, Matrix (M) protein, and Nucleocapsid (N) protein)[36] (figure 3).

Phylogenetic analysis of SARS-CoV observed to have a close relation with group two members and might shares a common ancestor with them [37]. Sequential analysis of this virus reviled 29,740 bases which encoded for two proteases (PLPro and 3CLPro) and helicases responsible for duplex winding activities[26,35,34,38]. Both SARS-CoV and MERS-CoV belong to same phylogenetic clustering of Beta-CoV's with the difference being SARS-CoV belongs to 'B' lineage and MERS-CoV belongs to 'C' lineage[3]. However, MERS-CoV comprises a bigger spike (S) glycoprotein which enhances its ability for interaction[39-41].

The MERS genome encodes 5 unique accessory proteins that modulates the interferons[42] increasing its infectivity. The S1 domain of the protein fuses with the DPP4 cellular receptor of the host cell in order to gain entry. This use of DPP4 distinguishes it from SARS-CoV and SARS-CoV-2 which use ACE2 as their receptor[43,44] (figure 3).

Figure 3: Schematic Representation Of The Coronaviruses

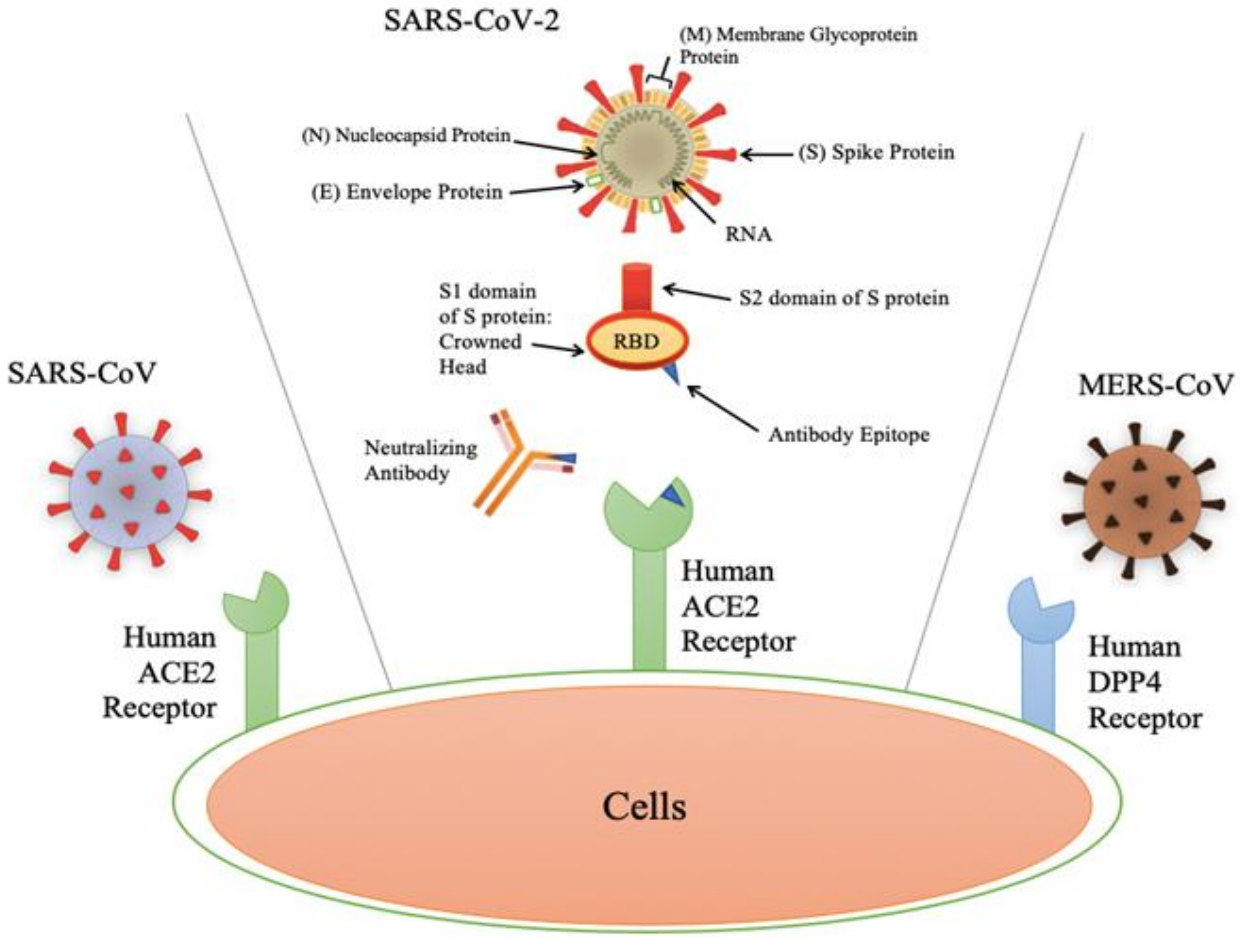

Figure 3: Schematic representation of the corona viruses. Comprising (S) spike glycoprotein, (E) envelope protein, (M) matrix protein and (N) nucleocapsid protein. Showing the mode of entry of SARS, MERS and SARS-CoV-2 corona virus based on their respective spike protein and corresponding human cell receptors. [Diagram modified from Jonathan Corum and Carl Zimmer "How coronavirus hijack your cells", The New York Times, updated on 13th March 2020, https://www.nytimes.com/interactive/2020/03/11/science/how-coronavirus-hijacks-your-cells.html.

In contrast, to SARS-CoV which submitted to rigorous mutation in order to adapt with human ACE2 protein, the genetic variations in MERS-CoV, showed no evidence that it has mutated to enhance binding with DPP4[45]. SARS-CoV-2, genome has size between that of SARS-CoV (27.9 kb) and MERS-CoV (30.1 kb)[46]. It is a Beta-corona virus with an envelope, non-segmented, positive sense RNA[47]. Presence of an exclusive amino acid sequence in the surface glycoprotein makes it different from the three groups[48]. The genomic sequence of SARS-CoV-2 was found to be 96.2% identical with Bat-CoV and 79.5% identical with SARS-CoV[49]. The (S) protein of SARS-CoV-2 attaches to the ACE2 receptor (similar to SARS-CoV) on the surface of human cell found abundantly in respiratory tract and could be responsible for cross-species and human to human transmission[50].

However, SARS-CoV has 14 binding residues interacting with human ACE2 receptors but only 8 were conserved in SARS-CoV-2[51]. At protein level, differences in the spike protein of the RBD has been observed between SARS-CoV and SARS-CoV-2[52]. Isolates of SARS-CoV-2 from patients of different provinces in china, highlighted mutations in the genotype[53]. The mutations in the spike protein (NSP2 and NSP3) of SARS-CoV-2 were found to enhance the infections capabilities of the virus[54].

Mode Of Transmission: SARS transmission from human to human occurred during direct exposure to infected respiratory droplets expelled during coughing or sneezing, physical contact and fomites[52]. The exposure area was defined to be 0.91 m (3 feet) in a closed

environment[55]. Infectivity by R Naught had a median of 0.49 [IOR 0.19–1.08], with 25% of R naught distribution having R0 > 1 even with perfect isolation[56]. Most countries reported a mean incubation period 2-7 days.

Interhuman transmission by MERS was also considered to be from droplets, aerosols or fomite. Its ability to survive in environment for up to 24 hours also raised possibility of surface transmission[57]. The MERS-CoV was estimated to have an R Naught < 0.7, significantly lower than an R_0 of 1, which marks of an epidemic potential[58]. However, asymptomatic carriers also played a role in spread MERS-CoV.

Recent epidemic of SARS-CoV-2 appears to be transmitted primarily through large respiratory droplets but its presence in blood & faecal makes it a potential mode of transmission[59]. Since the virus is heavy, the transmission by air borne is less likely [60] as the respiratory droplets are more than 5 micrometre which drops down this virus by gravity on the surfaces in immediate environment[55]. It can be concluded that transmission of this virus is primarily via direct contact [56] or through droplet nuclei of >5 microm[56] spread by coughing and sneezing by infected individuals[61]. Transmission through asymptomatic carrier appears to be possible, which if confirmed will have important implications for screening and isolation. The R Naught for SARS-CoV-2, is assessed between 2 and 3, suggesting a pandemic potential which is than SARS[60,62].

Diagnosis & Treatment: In all three epidemics standard diagnostic test of RT-PCR was done for confirmation and antimicrobial treatment instituted irrespective of the presence or absence of bacterial infection for pneumonia & sepsis. Till date no specific vaccine has been developed for all the three viral epidemics.

Suspected cases of SARS were laboratory confirmed by a positive RT-PCR from two or more clinical specimens and suspecting seroconversion by enzyme linked immunosorbent assay, indirect fluorescent antibody test or neutralization assay[63,64]. Serological testing of antibodies for IgG was also developed for rapid testing for screening population. A combination therapy by Loinavir and ritonavir was found effective with fewer adverse clinical outcomes[65]. MERS diagnosis was also based on the symptoms and was confirmed by laboratory RT-PCR as in SARS[66].

Clinical trial found the combination of Lopinavir-ritonavir to be highly effective with interferon (beta-1b) being used in severe MERS cases[66]. A broad-spectrum antiviral nucleotide prodrugs 'Remdesvir' showed potent efficacy for treatment of SARS as well as MERS in preclinical studies[67]. With respect to diagnosis of SARS-Cov-2 a suspected case is defined by its clinical presenting characteristics of either or both upper & lower respiratory tract infection with or without chest x-ray and CT scan showing pneumonia with no other aetiology. A positive RT-PCR from the nasal secretions is being used to confirm the diagnosis[68]. Initial reports showed use of oseltamivir in 93% of patients in combination with antibiotics[10].

Patients reporting with severe illness were given corticosteroids to reduce lung inflammation as part of procedure for cases that were community acquired and diagnosed at the designated hospital[10]. With experience of the combination of lopinavir and ritonavir on MERS & SARS, randomized controlled trial were initiated to assess the efficacy and safety of these drugs in patients hospitalized with COVID-19 infection[23]. Debates on the commercial use of anti-malarial drugs for this pandemic are still on as no confirmatory evidence has proven its efficacy, although it has been recommended for the prophylaxis for immediate health care providers in hospital setting[75]. Till the writing of this paper, April 15, 2020 no antiviral-agent has been proven to be effective against COVID-19.

Discussion: Overview of the three global epidemics finds them very closely related not only with signs and symptoms but also mode of transmission and the similarity of virus genetic isolates. The global epidemics were of zoonotic viral origin and have crossed the species barrier at some point of entry to spread globally.

Possible species for origin for all the three viruses was linked to bats but the spread in human was caused by an intermediate mammal host. Human infection to the virus from the possible intermediate host has still a mystery but its outbreaks of at least two of the epidemics have its roots in mainland China. Being a market for animal trade and their use in traditional medicines, human-animal interaction is likely

which raises the possibility of human infection of zoonotic diseases: SARS, MERS & present day COVID-19. This large interaction may also provide environment for mutation in the genomics as evidenced by the similarity of the isolates of these two viral epidemics to each other and to natural reservoirs. With nearly the same median incubation period the spread of SARS was relatively slow, but its case fatality rate was much higher than the present epidemic of SARS-Cov-2 and has higher infectivity evidenced by exponential increase in the cases across the globe (Table 1).

Table 1: Comparison Between SARS, MERS And Covid-19

Parameters	Epidemics		
	SARS	**MERS**	**COVID-19**
Pathogen	Sars-Cov	Mers-Cov	Sars-Cov-2
Possible Species Responsible For Spread In Human	Paguma Larvata, Nyctereutes Procyonoides	Dromedary Camels	Manis Javanica
Possible Species For Origin Of Virus	Rhinolophus Affinis	Rhinolophus Affinis	Rhinolophus Affinis
First Infected Human	Guangdong Province Of Southern China In 16 November 2002.	The Kingdom Of Saudi Arabia In April 2012.	Wuhan City, Hubei Province, China, 31 December 2019.
Public Health Emergency Of International Concern By WHO	March 12, 2003	Not Declared	January 30, 2020
Human To Human Transfer	Yes	Rare	Yes
Basic Reproductive Number (R0)	0.19 – 1.08	0.3 – 0.8	2.0 – 3.0
Case Fatality Rate (CFR):	9.6 – 11%	34.4%	1.5 - 2.5%
Mean Incubation Period	2 – 7 Days	5-7 Days	5– 6 Days
Community Spread Rate	10 - 60 %	4 – 13 %	30 – 40 %
Globally Infected Report By WHO	8,098 (Till July 2003)	2494 (Since September 2012- Till April 2020)	21,60,207 (Till 18 April 2020)
Global Mortality Report By Who	774 (Till July 2003)	858 (Since September 2012- Till April 2020)	1,46,088 (Till 18 April 2020)

Similarities of human to human transmission in SARS-CoV-2 epidemic can be drawn closely to SARS and MERS because of the rapid rate of infection. Its spread via respiratory droplets from coughing and sneezing by infected persons resembles any other respiratory pathogen. The spread of corona virus seems to limit to close contacts and a travel history to epicentres. Contrary to respiratory illness by SARS and MERS which were limited to the upper respiratory tract, the new SARS-CoV-2 gravitates down in lungs and is presenting with symptoms of lower tract infection (shortness of breath and dyspnoea) along with upper respiratory tract infection. Therefore, WHO advised avoidance of unprotected contact with animals and those with respiratory symptoms? Lessons learned from SARS and MERS outbreak can provide valuable information to handle the new outbreak which includes hand hygiene, isolation and use of masks to prevent droplet spread. Although the present case fatality of COVID-19 is far less than SARS and MERS till date, reason of high mortality may be unpreparedness of the hospitals, ventilators, and support system which were not upgraded even after the experience of similar epidemics in recent past. Although, control measures were put into effect, their timing relative to spread of the current virus suggests that the lessons learnt from previous epidemic of corona viruses were not made use of. Use of technology for disease surveillance though helped us report, monitor,

sort, track and analyse the data of disease across the globe. Therefore, the countries were able to rapidly share the information about the genetic sequence of new corona virus which helped us to reach the diagnosis of the novel virus. Evident with the difference in the rate of spread, CFR and doubling time globally it can be said that we have not still reached the peak of the present COVID-19 epidemic. On the contrary it raises possibility of finding some modifiable factor which can decrease its infectivity and severity. At the time of writing this paper no vaccine has been developed for present epidemic although several countries have started with clinical trials.

Conclusion: With the experience of two epidemics of similar aetiology, wealth of information and containment strategy developed by global agencies like WHO, we were still not able to contain the new emergent viral epidemic. We conclude that with all the available high-end technology and an experience of two prior epidemic of similar viral origin, we still look ill prepared to face challenges posed by epidemics especially the ongoing COVID-19 virus pandemic. Possibility with a high community spread rate of SARS-CoV-2 and emergence of asymptomatic cases its spread is likely to continue. Countries need to work in close coordination with sharing and dispensing of new information to limit the spread and finally terminate the infection for the survival of mankind.

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