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SARS, MERS AND COVID-19 ASSOCIATED ACUTE RESPIRATORY SYNDROME - A REVIEW

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ABSTRACT

This review highlights the relation between SARS-CoV, MERS-CoV and n-CoV-19. A review has been done in order to understand and analyse the association between the 3 diseases by retrieving a minimum of 20 articles within the timeframe of 2000 to 2020 from various data search engines including pubmed, Google scholar, MESH, core, bioRXiv, Semantic scholar and so on. All the data were retrieved from the literature studies done by esteemed authors. All the 3 disases, SARS-CoV, MERS-CoV and n-CoV-19 are zoonotic diseases. Research's have been performed to locate the similarities between SARS CoV, MERS CoV and n- CoV. They are part of the family Coronaviridae and are enveloped viruses with RNA genome. They are mainly related with respiratory diseases and can be highly fatal if left untreated. Disorders of the coagulation pathway and formation of intra alveolar or systemic fibrin clots were also seen in all 3 of the coronavirus infections. Previous studies indicate that MERS CoV affected the type II

pneumocytes whereas SARS and SARS 2 affected type I pneumocytes. Comparative studies on MERS CoV, SARS CoV and n-CoV may provide information for treating the present outbreak and to prevent future outbreaks. Due to their close structural and genetic correlation, each viral agent has to be analyzed and studied completely in order to find a prophylaxis and cure. This review highlights on the same and gives an overview on the strain variations and relation within the clades of the corona viruses.

Keywords: n-CoV-19; SARS-CoV; MERS-CoV; Prophylaxis; Receptors; Structure

INTRODUCTION

Corona viruses are part of the subfamily Coronavirinae in the family Coronaviridae and order Nidovirales. They are enveloped RNA viruses with a positive sense RNA genome which can cause respiratory diseases ranging from mild to fatal **[1]**. The novel coronavirus epidemic (COVID 19) which was said to have started in Wuhan China has emerged as an international distress by spreading over many parts of the world with a mortality rate of about 3.4% **[2]**. Based on the genetic makeup of the virus, the International Committee on Taxonomy of Viruses has renamed the virus as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) **[3]**. Evidence suggests the association of COVID 19 patients with cytokines storm syndrome. The leading cause of mortality is said to be the respiratory failure associated with acute respiratory distress syndrome **[4]**. COVID-19 virus is closely linked with a bat coronavirus. It has been theorized that the path of transmission of virus could have been from bats to pangolins, a type of scaly anteater, to humans. Mode of transmission is primarily through respiratory droplets, close contact and aerosols. Contact transmission is generally found in diseases such as MRSA and VRE **[5, 6]**. It was also found out that the virus can retain on surfaces and can be transmitted through touch. Angiotensin converting enzyme 2 receptor (ACE 2) is necessary for n-CoV binding and infection **[7]**. This receptor is mainly expressed in the airways, the lung and intestines. Researches indicate that adults and older individuals tend to show higher expression of ACE 2 receptors leading to higher incidences in this age group **[8]**.

The approximate incubation period was estimated to be 2 to 14 days with a median of 5.5 days. The period between time of expression of symptom to death was approximated to be 6 to 45days with a median of 25 days **[9]**. This timeline is

generally dependent on the age of the patient with the elderly being more susceptible to the disease. The initial symptoms observed are tiredness, cough and fever with a gradual onset of diarrhoea, dyspnoea, lymphopenia, haemoptysis, headache and sputum production **[10]**. Prophylactic vaccines are being researched by the use of several platforms such as mRNA, DNA, adenoviral vector and recombinant protein. Also clinical trials need to be performed along with preclinical studies of SAR-CoV-2 vaccine on candidates. Due to the absence of pharmaceutical intervention, the best strategy to minimise the spread of the virus is through social distancing **[11]**. It reduces the probability of susceptible and infectious people coming in contact through early assessment of cases and reduction of contact. The clinical manifestations were mostly similar in SARS, MERS and CoV-19, however with minor variations in its immuno-pathogenesis. This review thus highlights on the relations and cross reactions amidst the three dreadful corona viruses.

Retrieval of data:

A review of scientific literature was done in preparation of the manuscript. The relevant articles were collected from databases such as pubmed, google scholar, MESH etc. The time frame of the articles were between the year 2000 to 2020. Around 25 articles were collected, analysed and reviewed. The articles were collected on the basis of containing keywords such as Sars CoV, MERS CoV, n-CoV-19, receptors, structure, prophylaxis etc. All topics irrelevant to the subject are excluded. The results of this review are based on previous studies done by other esteemed authors.

An overview on SARS- CoV - Its prevalence, transmission and mortality rates:

SARS CoV (Severe acute respiratory syndrome coronavirus) is a lethal form of pneumonia. This virus caused a major outbreak in March 2003, Hong Kong which eventually spread to neighbouring areas such as Toronto and Canada **[12]**. The disease is generally transmitted through droplets, fomites or faeco oral route. The symptoms of this disease are fever, dry cough, headache, muscle aches and dyspnoea. The incubation time was estimated to be from 2 to 11 days **[13]**. This also depends on the age of the patient. While the fatality rate in the general population is noted to be 11 to 14%, people more than 60 years old exhibit a fatality rate of 43.3% **[14]**. People with non specific symptoms had the risk of developing severe secondary complications. The world health organisation said that the disease affected

around 8,437 people with an approximate of 813 deaths **[15]**. Around 20% of the affected population was health care workers. Increased risk of cross contamination is of major concern. It can generally survive in respiratory samples for about 5 days at room temperature until 3 weeks at 4°C **[16]**. SARS CoV virus demonstrates dimerization and the S1 substrate-specificity pocket which is seen in other coronaviruses. An unique feature of this virus is its pH dependent activation switch which leads to collaborative movement of the side chains of Glu-166, Phe-140, Leu-141, and Tyr-118, and the N terminus of the partner protomer in the dimer **[17]**.

SARS consists of approximately 29,700 nucleotides and is larger than an average picornavirus. The enzyme replicate decodes for 2 poly proteins, pp1a and pp1ab, which take care of the viral replication and transcriptions in corona viruses **[18]**. The replication of the virus is mediated by non structural proteins which are encoded in 2 ORFs (Open reading frame), ORF1a and ORF1b. ORF is generally a stretch of codons beginning with a start codon and ending with a stop codon. One of important requisites for the structural integrity and protease activity of the virus is it's zinc binding ability **[19]**. The mortality rate for SARS CoV is around 10%. An in-depth understanding of the SARS-CoV PLpro domain is a prerequisite for understanding the virus for the development of antiviral drugs and prophylaxis.

MERS CoV and its immuno-biology:

MERS CoV or Middle Eastern Respiratory syndrome coronavirus belongs to the betacoronavirus family. MERS CoV was first identified in 2012 and emerged as an outbreak in mid March 2014 in Jeddah, Saudi Arabia **[20]**. It is spread by close contact and respiratory droplets or aerosols. It is a zoonotic disease whose reservoir host seems to be dromedary camels. The camels themselves may have mild or in apparent self limiting forms of the disease **[21]**. Secondary infection may spread in health care areas which resulted in huge outbreaks. The incubation period for the virus is around 2 to 15 days with a median of 6 days. The symptoms seen are generally fever, chills, generalized myalgia, cough, shortness of breath, nausea, vomiting, and diarrhea. It has a fatality rate of around 36%. Most of the patients reported multiple comorbid conditions along with MERS infection **[22]**. Even though there is no specific therapy or vaccine, Ribavirin, interferon alpha with corticosteroids and ribavirin with lopinavir

and ritonavir, and convalescent plasma may improve the condition of the patient **[23]**.

MERS CoV targets the DPP4 receptor (dipeptidyl peptidase 4) or CD26. This interaction is mediated by the receptor binding protein on the viral spike. It utilises the viral S protein for entry into the host cell **[24]**. DDP4 does not have any structural similarities with the ACE2 receptor. It is expressed in the surface of many cells including the cells in the human airways. It also exhibits exopeptidase activity **[25]**. The RBD of the virus contains a core subdomain which is similar to the spike protein of SARS CoV **[26]**. The S glycoproteins can be further cleaved by proteases present in the host to N-terminal S1 subunit and a membrane-bound C-terminal S2 region. Papain like proteases (PLpro) are multifunctional enzymes encoded by coronaviruses. It is used in processing of the viral replicase polyprotein and has deubiquitinating properties **[27]**.

Clinical relevance between the strains:

Researches have been performed to locate the similarities between SARS CoV, MERS CoV and n- CoV. All 3 belong to the betacoronavirus genera which are generally zoonotic **[28]**. It has been found that n- CoV has approximately 30 kb single stranded positive sense RNA genome with a structure indicative of other coronaviruses such as SARS and MERS. There is also no observable difference in the incubation time of all the 3 **[29]**. Compared to SARS and MERS, the spread of COVID 19 is more rapid. SARS-CoV and MERS-CoV patients with serious forms of the disease tend to show diffuse alveolar damage with hyaline membrane formation, inflammation in the alveolar walls and desquamation of pneumocytes. n- CoV generally affects the upper respiratory tract **[30]**. All the 3 diseases show high homology at the nucleotide level and exhibit similar Pathogenesis. The N protein of n- CoV also shares approximately 90% amino acid identity with SARS- CoV. Finding the relation between the 3 diseases can aid in future pharmaceutical pursuits **[31]**. Lopinavir is an agent effective in inhibiting the corona virus invitro and in animal studies. It was effective in SARS and MERS and is said to be a potential treatment for n CoV 19 **[32]**.

In a study done on cynomolgus macaques, it was found that MERS CoV affected the type II pneumocytes whereas SARS and SARS 2 affected type I pneumocytes . Damage to type I pneumocytes can result in pulmonary oedema and hyaline tissue formation which may be the reason why there is hyaline membrane formation in SARS and COVID

19 and not in MERS **[33]**. All coronaviruses have similar structure which has 14 ORFs which encode 27 proteins. The 3' terminal encodes for the important proteins which include, spike protein (S), envelope protein (E), membrane protein (M), and nucleocapsid (N). It also codes for 8 accessory proteins **[34, 35]**. The spike protein is essential for the protein entry into the target cell by attaching to the receptor **[36]**.

Evidence based studies on the SARS virus incidence:

The structure of nCoV 19 is similar to the structure of SARS CoV and thus, could indicate the slower rate of mutation of the virus and thus, better chance of finding a prophylaxis based on the vaccine studies made on SARS and MERS **[37]**. Disorders of the coagulation pathway and formation of intra alveolar or systemic fibrin clots are seen in all 3 of the coronavirus infections **[38]**. Male-to- female ratio of nCoV infection is 0.99:1 in Wuhan, 1.04:1 in Hubei and 1.06:1 in China **[39]**. Also researchers indicate that males and females are equally susceptible to the disease **[40]**. But, a contradicting study in Wuhan states that males are more prone to infection than women, attributing the lesser sensitivity in women to the protection by the X chromosome **[41]**. Corticosteroids therapy with ribavirin while helping in resolution of fever, lung opacities and pulmonary and systemic inflammation are claimed to be toxic and while useful for MERS and SARS, it may not be so effective in treating the SARS 2 **[42]**. IFN-β is claimed to be effective in reducing viral replication in a time dependent manner in SARS, MERS and n- CoV. Chloroquine phosphate is effective against coronaviruses, but is contraindicated in people with heart conditions **[43]**.

Future research perspectives:

Some drugs which were effective for MERS CoV and SARS CoV may not be effective for nCoV 19 because of the viral mutations and unique characteristics of the emerging virus. Also, due to social distancing, research has reduced to a degree which can impact on the time taken to analyse the data and find a prophylaxis. Even Though broad spectrum antibiotics have been prescribed in COVID infections, there is very less data for the association of coronary diseases with bacterial or fungal coinfection like infection by Acinetobacter baumannii **[44–47]**. Bacterial infestation can occur in cases where the immunity is reduced to an extent due to the viral COVID infection **[44, 48, 49]**. It is also claimed that mouthwash can aid in prevention of COVID and cross infection in medical professionals **[50, 51]**. While the pharmaceutical industry has improved a lot

from the past years, drugs to combat viral infections seem scarce due to the special properties of the viral particles **[52]**. Due to the eradication of the previous 2 epidemics without much drug intervention, there is a lack of knowledge on the pharmaceutical part of the viral diseases. However researches are being performed and expanded so as to find an antiviral drug to inhibit the virus **[53]**. As the spread of CoV 19 is of a much larger scale than SARS and MERS, it affects a larger population but has less virulence when compared with the former 2. Comparative studies on MERS CoV, SARS CoV and n-CoV may provide information for treating the present outbreak and preventing any future outbreaks **[54]**. Also, it can aid in finding specific drugs and create new areas of research in the pharmaceutical industry. It can give a better understanding of the working, transmission of the virus and how it causes diseases within the body and provide ways to counteract the process.

Table 1: The self illustrated table shows the correlation and comparison between MERS CoV (Middle Eastern Respiratory syndrome coronavirus), SARS CoV (Severe acute respiratory syndrome coronavirus) and n CoV-19 (Novel coronavirus or SARS CoV-2) based on their genera, year of outbreak, animal host, mode of transmission, incubation time, symptoms, receptor in the human body, mortality rate and prophylaxis

	SARS CoV	MERS CoV	n CoV 19
GENERA	Betacoronavirus	Betacoronavirus	Betacoronavirus
YEAR OF OUTBREAK	2002	Identified in 2012, outbreak in 2014	2019
ANIMAL RESERVOIR	Bats	Bats, dromedary camel	Bats, pangolins
MODE OF TRANSMISSION	Aerosol, close contact	Aerosol, close contact, faeco oral route	Aerosol, touching contaminated surfaces, close contact
INCUBATION TIME	2 to 11 days	2 to 15 days with a median of 6 days	2 to 14 days with a median of 5.5 days
SYMPTOMS	Fever, dry cough, headache, muscle aches and dyspnoea	Fever, chills, generalized myalgia, cough, shortness of breath, nausea, vomiting, and diarrhea	Tiredness, cough and fever with a gradual onset of diarrhoea, dyspnoea, lymphopenia, haemoptysis, headache and sputum production
RECEPTOR	Angiotensin Converting enzyme 2 (ACE2)	Dipeptidyl peptidase 4 (DPP4)	Angiotensin Converting enzyme 2 (ACE2)
FATALITY RATE	11% - 14%	36%	3.4%
PROPHYLAXIS	No specific treatment. Ribavirin with or without corticosteroids can be used	No specific treatment. Ribavirin, interferon alpha with corticosteroids and ribavirin with lopinavir and ritonavir, and convalescent plasma can be used.	Social distancing. No specific prophylaxis found. Antiviral drugs can be used. Dexamethasone seen to show good results in patients.

CONCLUSION

MERS-CoV, SARS-CoV and n-CoV are the 3 major epidemics from the start of the 21st century. Due to their close structural and genetic correlation, each viral agent has to be analyzed and studied completely in order to

find a prophylaxis and cure. Their physical, chemical and biological properties have to be compared and correlated so as to figure out their genetic making and thus aid in preventing further viral breakouts of such severity in the future. Even though existing antiviral drugs are effective to a certain extent, newer and better drugs have to be brought to the market in order to combat the crisis.

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Author Contributions:

S. Vidyashri, contributed to the data acquisition and drafting of manuscript. Dr. A. S. Smiline Girija, contributed to the design, editing and critical revision of the manuscript. Dr. Jayalakshmi Somasundaram, contributed to the supervision and proof reading of the manuscript.

Conflict Of Interest:

The authors declare no conflict of interest.

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