

A Comparative Study among SARS, MERS and Covid-19

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How to cite this article:

Yajnaseni Jena, Dipanweeta Rourtray, Swetaleena Ashe, Lora Mishra, A Comparative Study among SARS, MERS and Covid-19. Community and Public Health Nursing. 2021;6(3):81-87.

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Abstract

Epidemics have been inevitable part of human race since ages. Beta coronavirus family is known to have caused 3 highly infectious diseases namely SARS, MERS and COVID-19, spreading over maximum part of world. This review paper aims to compare all the 3 pandemic under sub-headings i) origin ii) viral pathogenicity iii) receptors used by the virus to infect the cells iv) symptoms v) public health measures taken. Research papers published in Google scholar and PubMed were used to gather information. It was summarized that SARS-CoV, MERS-CoV, SARS-CoV-2 have zoonotic sources and MERS spreading through dromedary camels. The case fatalities of MERS are noticed to be highest due to its high virulence. The infection rate of SARS-CoV-2 is highest all three. Both SARS-CoV and SARS-CoV-2 use the same antigen receptor called ACE-2 and MERS-CoV using DPP-4 as receptor protein. All the 3 are respiratory syndromes but may have other clinical symptoms owing to the presence of receptors. Strict public health interventions have to be helpful to control SARS and MERS. Various countries have reacted differently to the COVID-19 emergency and it has shaped the way virus affects the country. The gathered data can be useful in further research and also help in assessment of the diseases better.

Keywords: SARS; Coronavir US; COVID-19; MERS; Public Health.

Introduction

Epidemics have been inevitable part of human race since ages. In past centuries, the world has witnessed many pandemics like bubonic plague, influenza etc. Coronavirus have been a notorious group of viruses. Beta coronavirus family is known to have caused 3 highly infectious diseases spreading over maximum part of world hence to be coined pandemic. Viruses namely, SARS-CoV, which originated in Hubei province of China in 2002 and MERS-CoV, which originated in Saudi Arabia in 2012 and most recently SARS-CoV -2 originating in Wuhan city of China in 2019.

Aim

This review paper is an attempt to investigate and elaborate all three coronavirus epidemics in this century.

Methods

The review paper is divided into 5 sub headings and is

written under topics.

- Origin
- Viral pathogenicity
- Receptors used by the virus to infect the cells
- Symptoms
- Public health measures taken

Inclusion Criteria:

Research papers published in Pubmed and Google scholar are used in the review paper. Cross sectional studies, observational studies and univariate and multivariate analyses, longitudinal studies and review studies are used to track data for the comparison in the review paper.

Exclusion Criteria:

Single case reports are avoided in the study. The review paper is written under proper ethical guidance.

Origin:

SARS-CoV its emergence was noted in 2003 in China. Its origin is believed to be zoonotic and human to human transmission is noted. According to Yuan J et al¹, small carnivores, including civet cats and raccoon dogs are carrier of Scovs and hence thought to act as intermediate sources of the epidemic. The study suggested that there is potential recombinant origin of Rp3 and Rs672 viruses, whose major parent has a relatively closer phylogenetic relationship with human-ScoV which suggested the direct ancestry of Human – Scovs. In another study done by Ben Hu et al in 2017², reported that all bat SARS-CoVs described so far are quite distinct from SARS-CoV in S gene and accessory genes such as ORF3 and ORF8 and concluded that they are not likely the direct ancestor of SARS-CoV. Hence throwing light towards the recombinant origin.

MERS-CoV its first case was reported in 2012, affecting Qatar, Saudi Arabia and Egypt. According to Corman VM et al (2014)³, MERS-CoV antibodies in dromedary camels have been circulating as early as 1992, hence is in their more than 20 years. Their study suggested that lower seroprevalences in young dromedary camels point that they are more likely to carry infectious virus. Hence young, immunologically naïve animals support virus amplification in dromedary camel populations. In another study conducted by Yang Y et al, in 2014¹⁴, found out that MERS-CoV have originated from bat corona viruses, genetically related to HKU4. Dipeptidyl peptidase4 (DPP4), the receptor of MERS-CoV also serves as receptor for HKU-4 but not of HKU-5. It was noticed that there are functional differences where MERS-CoV prefers human DPP4 over Bat DPP4 whereas HKU-4 shows opposite. (HKU-4 and HKU-5 being the bat coronaviruses).

SARS-CoV-2 COVID-19 caused by the virus SARS-CoV2 out broke in Wuhan, China in late December. As studied by Guo YR et al, in 2020⁵, SARS-CoV-2 belongs to beta-coronavirus, with highly identical genome to bat coronavirus. The epidemic is likely to originate from Huanan seafood market. SARS-CoV2 shares 80% similarity with SARS-CoV and 96% with bat coronavirus BAT-CoV RaTG13.⁶ Tang X et al⁷ carried a population genetic analysis of 103 SARS-CoV-2 genomes and classified into 2 categories according to evolution. L type and S type. L type is derived from S type and is evolutionarily more aggressive and contagious.

Viral Pathogenicity

SARS-CoV According to study conducted by Sins A et

al²¹, that SARS-CoV generally affected cells in the lower respiratory system through the apical surface exceeded 10^6 PFU/ml and viral titers in the basolateral compartments were low with peak titers below 10^5 PFU/ml. The study even suggested that ciliated cell-types had cytoplasmic vesicles filled with viral particles and were seen within the between the microcilia/villi shafts pointing towards the enormous capability for release of large quantities of SARS-CoV into the lumen of the conducting airway during viral replication. As per the studies²² on PH dependence of SARS-CoV using

retroviral and lentiviral vectors that have been pseudo typed with the SARS-CoV protein, it was found that the spike protein mediated entry into the target cells. Neither M nor E protein alone was able to support viral entry in the absence of spike protein hence recommending other functions to these viral glycoproteins. The study also found out that S glycoprotein is fusion competent and able to function in viral entry through a PH dependent mechanism. The pathological changes are stated by the study conducted by Nichollas J et al²³, in which post mortem tissue samples from 6 patients who died from SARS and open lung biopsy was obtained. It was found that alveolar pneumocytes also showed cytomegaly with granular amphophilic cytoplasm. Changes in morphology of cells were notified including bronchial epithelial denudation, loss of cilia and squamous metaplasia. In one patient atrophy of white pulp of spleen was noticed. Hence SARS is a systemic disease affecting several organs but the effect of the disease is more pronounced in respiratory system.

MERS-CoV A lot of similarities is found in MERS pathogenicity to the SARS-CoV pathogenicity.²⁵ Both the diseases are prevalent in the lower respiratory tract and patients showing hypoxia is common to both.²⁵ The case fatality in MERS-CoV is higher than the SARS-CoV and it is thought that MERS-CoV has higher virulence than SARS-CoV but cannot be proved because many MERS infections went unnoticed initially.²⁵ The lesions found in chest radiography of MERS patients is quite different from those found in SARS patients which have intra-alveolar organization with bronchiolitis obliterans organising pneumonia (BOOP) like pattern.²⁶ The MERS-CoV genomes shares more than 99% sequence identity pointing towards lower variance among genomes and less mutation rate.²⁷ It was found that during infection by MERS-CoV, the S protein is cleaved into a receptor-binding subunit S1 and a membrane fusion subunit S2²⁸⁻³¹ after which S1 subunit binds to DPP4 mediating a viral attachment. It has also been noted the MERS-CoV can get itself attached to the DPP4 of other animals like humans, camels, ferrets and bats.³²

SARS-CoV-2 In a study³⁴ consisting of 31 patients having mild/moderate COVID-19 symptoms and 25 patients with severe symptoms, it was found that WBC count had decreased significantly in patients showing mild symptoms. The total lymphocyte count was decreased in severe patients but not in mild patients suggesting lymphopenia in severe cases. The neutrophil to lymphocyte ratio had increased profoundly in severe patients than in mild patients suggesting a link between neutrophil to lymphocyte ratio to the severity of the disease including CD4+(cluster of differentiation 4) T helper and CD8+ cytotoxic cells. Total T cell number had decreased significantly in both mild and severe patients hence no major difference was noted in mild and severe patients. In the study it was also found that concentration of IL-6 (Interleukin-6) was significantly increased in severe patients but not in mild patients indicating towards the cytokine storm which worsens the condition of patient. In the study³⁵ conducted by Zhao J et al, had taken 173 patients whose serial plasma samples were collected during hospitalization. It was found that the seroconversion rate for Ab (total antibodies), IgM and

IgG was 93.1%, 82.7% and 64.7% respectively. The median conversion time for Ab, IgM and IgG were found to be day-11, day-12 and day-14 separately. The antibodies were detected <40% during 1 week of onset but rapidly increased to 100 % (Ab), 94.3 % (IgM), 79.8 % (IgG) since day-15 after onset. COVID-19 patients were also detected with RNAemia, acute cardiac injury .36

Receptors Used By the Viruses to Infect Cells:

SARS-CoV-ACE2 a metalloproteinase angiotensin converting enzyme 2 is identified to be the receptor protein. In a study conducted by Wenhui Li⁸ and team in 2003, found that potential amount of ACE2 messenger RNA in bronchus and lung parenchyma as well as in the heart, kidney and gastrointestinal tracts. Lungs and kidney act as primary sites of expression of murine ACE2. According to conclusion drawn by Wenhui Li, SARS viruses are detected in faeces henceforth indicating towards the expression of ACE2 in small and large intestines. According to the study conducted by I Hamming et al⁹ in 2004, on tissue distribution of ACE2 protein, the functional receptor for SARS- coronavirus, found that ACE2 expression is found in nasal and oral mucosa in the basal layer of non- keratinizing squamous epithelium. The study also pointed towards the oral faecal transmission due to presence of functional receptor of SARS-CoV (ACE2) in the small intestine provided the virus is present in the stool of the patients. It is to be noticed that despite presence of ACE2 in the endothelia of maximum organs and SARS-CoV in blood plasma infected individuals, very few organs become virus positive. This implicates towards the need of a co-receptor for cellular entry of SARS-CoV just like in case of HIV. Physiological role of ACE2 in most tissues has not been elucidated, although it is thought to act as an essential regulator of cardiac function and blood pressure control by acting as counterpart of ACE1.⁹

MERS-CoV-CD-26 or also called as DPP-4 (Dipeptidyl peptidase) is identified as the receptor of MERS-CoV. CD-26 is identified as the third functional coronavirus receptor after amino peptidase N and ACE2¹¹. CD-26 is found as a homodimer on the cell surface and is classified as a type II transmembrane protein. As studied by Bosch BJ et al¹¹ in 2013, DPP4 is multifunctional and plays a major role in glucose metabolism by its degradation of incretins. Incretins are metabolic hormones regulating the level of glucose by decreasing it. Its other physiological roles as identified in T cell activation, chemo taxis modulation, cell adhesion and apoptosis. It is expressed in epithelial cells of lungs, kidney, and small intestine, liver and prostate and activated leukocytes and occurs in circulation in soluble form.

SARS-CoV-2 According to the study conducted by Hoffmann M et al in 2020¹², SARS-CoV-2 uses the SARS-CoV receptor ACE2 for entry and serine protease TMPRSS 2 for 2 protein priming. Transmembrane protease, serine 2 has a type II transmembrane domain which belongs to class A domain.

Symptoms

SARS-CoV- SARS mainly affected the respiratory system. Higher fatality rates were observed among older patients

and people with co-morbidities due to less active immune system¹⁰. SARS-CoV infection also causes massive necrosis of spleen and lymph nodes. According to a study conducted by WANG JT et al¹³, most occurrent symptoms at initial stages were fever, cough, myalgia, dyspnea, diarrhoea and rigor. The incubation period averages to 10 days and maximum virus excretion from the respiratory tract occurs on about 10th day illness and then declines.³⁸ In the study it was found that abnormalities on chest radiography suggested pneumonia which was found in 56 of the 76 patient¹³. Lesions were found in one lobe in 33 patients, in two lobes in 15 patients, in three lobes in 4 patients, in four lobes in 2 patients and five lobes in 2 patients.¹³ Adding to these common symptoms, other were lymphopenia (69.6%), thrombocytopenia (44.8%) and elevated lactate dehydrogenase (71.0%) and elevated creatine kinase (32.1%).¹⁴ Inspiratory crackles could be heard at the base of lungs.¹⁵ According to a study¹⁰, of the infected people 20% to 30% required mechanical ventilation and nearly 10% died.

MERS-CoV-MERS shares many clinical features with SARS as it also primarily involves respiratory system. Of the many symptoms included severe atypical pneumonia, yet key differences are evident like patients with MERS have prominent gastrointestinal symptoms and often acute kidney failure.¹⁰

In severe cases multi organ failure may even lead to death. In a descriptive study conducted by Assiri A et al¹⁵ in 47 cases it was found that 98% had fever, 87% patients had fever with chills or rigor, 83% patients reported to have cough and 32% of patients had myalgia. Gastrointestinal symptoms were also frequent; including diarrhoea (26%), vomiting (21%) and abdominal pain (17%). All patients had chest findings having unilateral or bilateral abnormalities in chest radiography. Biochemically the same study suggested, raised concentration of lactate dehydrogenase (49%) and aspartate aminotransferase (15%) and thrombocytopenia (36%) and lymphopenia (34%). In another study conducted by Zumla A et al¹⁶, it was found that patients infected with MERS have neutrophil and macrophage infiltration and alveolar oedema in infected lung tissue. Infectious B-cell and T-cell responses with prolonged cytokine expression have been detected with severe disease whereas a more rapid shut off of innate immune response and a potent anti-SARS-CoV antibody response was reported in recovered patients.

SARS-CoV-2-clinical symptoms of COVID-19 patients include fever, cough, fatigue and gastrointestinal infection was also found in some patients. More recently one study¹⁸ on 214 COVID-19 patients by MAO et al further found that about 88% among serious patients showed neurologic problems that consist of acute cerebrovascular diseases and impaired consciousness. Study conducted by Young BE¹⁹, virus was detectable in the stool sample (50%) and blood sample (8%) collected from patients of Singapore by PCR technology but virus was not found in urine sample. Lymphopenia (<1.1*10⁹/L) was present in 7 out of 16 patients and an elevated C-reactive proteins (>20mg/L) in 6 out of 16 patients.

Public Health Measures Against Epidemics

SARS-CoV Some public health measures were implemented pursuant to world health organization and others were implemented by the governments of respective countries. Infra-red scanners were used to detect fever which is a most common symptom of SARS-CoV among people at international borders or at gatherings.³⁸ Airline transmission was noted to be one of the main causes of rapid transmission of SARS in different parts of world.³⁸ In Canada (Toronto), nosocomial transmission was responsible for transmission at the beginning of the outbreak due to infection in healthcare workers prior to implementation of hospital wide infection control precautions.³⁸ Separate hospitals were not designated as SARS hospitals which further added to number of cases.³⁸ In China, 2 super spreaders were identified. The Guangzhou infection resulted in transmission in two hospitals with 3 generation of infections.³⁸ The 2nd super spreading incident travelled to Guangdong province.³⁸ The epidemics in Hong Kong, mainland China, Singapore, Taiwan and Toronto have been of particular concern because of the multiple generations of local transmission seen in those areas.³⁸ One of the key reasons that Hong Kong could combat SARS is the good quality data capture systems to permit detailed epidemiological analyses day by day, to inform both health policy formulation and the evaluation of intervention impact.³⁹ The Chinese government introduced draconian measures designed to strictly regulate movements and mixing or crowd gathering.³⁹ The Beijing government began purchasing emergency supplies both nationally and from abroad.⁴⁰ All hospitals were closed as early infection transmission was noticed among health workers due to lack of information and proper steps were not taken.⁴⁰ Separate hospitals for SARS patients were opened and a large number of healthcare faculties were trained to treat patient through video clips and printed materials about PPEs and infection control.⁴⁰ Negative pressure chambers were made available.⁴⁰ The close contacts of a patients were traced and were quarantined for at least 14 days.⁴⁰ All sites of public entertainment (theaters, bars libraries and indoor sports) facilities were closed.⁴⁰ Fever checks were instituted through thermal scanner at airports and major train stations.⁴⁰ For better information transmission to the public and to avoid all kinds of rumours based on SARS, the Beijing television ran daily 2 hours educational programs about SARS.⁴⁰ Proper dissemination of information was ensured so that to avoid panic among the citizens.⁴⁰

MERS the Middle East respiratory syndrome (MERS) outbreak in Korea in 2015 may be attributable to poor nosocomial infection control procedures implemented. In MERS, both community acquired and hospital acquired cases have been reported with little human to human transmission reported in the community.⁴¹ Most human cases of MERS have been linked to lapses in infection prevention and control in healthcare settings, with approximately 20% of all virus detections reported among healthcare workers (HCWs) and higher exposures in those with occupations that bring them into close contact with camels.⁴² Surprisingly, testing of adult pilgrims performing Hajj in 2012 to 2014 have not detected any MERS-CoV.⁴² Most pilgrims arrived had

arrived were from MERS free countries.⁴³ Infection prevention and control implications included the need for hand hygiene and personal protective equipments to minimize self-contamination and to protect against inoculation of mucosal surfaces and the respiratory tract and enhanced surface cleaning and disinfection in healthcare settings.⁴³ According to a study conducted by Alqahtani AS et al⁴⁵ investigating the awareness about MERS in the population of middle east countries, found out that over 79% of participants knew that MERS-CoV transmits through coughing and sneezing. Intensified public health measures, including contact tracing, quarantine and isolation of all contacts and suspected cases and infection prevention and control had brought the MERS in control in the Republic of Korea.⁴⁶

SARS-CoV-2 the spread of SARS-CoV-2 has already taken over 100 countries. The global health systems worldwide are implementing strict public health interventions to control the pandemic.⁴⁷ A coordinated global response is must at this time. Italy and Spain have faced the hardest blow of COVID-19 among the European countries counting 34,167 deaths in Italy and 27,136 deaths in Spain as of 12th June 2020. Italy and Spain have a highly socially citizens, moderate weather and a few densely populated cities. The population of both countries has an affectionate social physically and large percentage of population comprises of elderly people. The government of both countries neglected the facts and did not impose any regulatory actions against pandemic. Spain also celebrated Women's day where a huge gathering took on to streets and the infection just spread over the masses. Lombardy and Veneto are worst hit cities of Italy. Italy had different policies put on different cities which had a clear impact on the clear impact on the virus spread. Spain had to impose one of the world's strictest lockdowns on March 14 till April 25 to handle the situation. The initial exponential curve of infected persons of Italy matched with that of China's curve⁴⁷. The change in curve's slope is the most important concern otherwise clinical and social problems will take on unmanageable dimensions resulting in catastrophe only⁴⁸. Lombardy implied non-pharmacological and pharmacological interventions, including antiretroviral medications⁴⁸. Trust of public on government official also plays a crucial roles imposing public measures as it ensures how obediently public follows them⁴⁹. Indian governments seeing the situation of COVID-19 announced to maintain social distancing (1 m distance) which was unaffordable by people of weaker section like daily wage workers.⁵⁰ The government announced complete lockdown in phases and curfews were issued in different parts of the country.⁵⁰ Few state governments ensured monetary help for the weaker section so that their condition would not be perished.⁵⁰ Focus was maintained on personal hygiene and sanitization.⁵⁰ Gatherings were strictly prohibited and police force was deployed to ensure to crowding takes place.⁵⁰ Separate infrastructures to treat COVID-19 patients were made to avoid nosocomial infection.⁵⁰ In India, the management of patients with coronavirus was divided into several stages including 1. Management of Mild Cases 2. Management of Moderate Cases 3. Management of Severe Cases. Mild cases are managed at Covid Care Centre, First Referral Units (FRUs), Community Health

Centre (CHC), sub-district and district hospitals.⁵² The government of USA did not completely shut down the affected areas even after cases getting reported.⁵¹ Lack of enough ventilators and medical staffs was also a concern in the country.⁵¹ Lack of enough testing kits to test for COVID-19 positive patients also concerned the officials.⁵¹

Results

SARS-CoV originated from zoonotic sources and phylogenetically resembles Bt-SCoV and sourcing towards recombinant in origin. MERS-CoV spread through dromedary camels and phylogenetically it also originates from bats. The recent SARS-CoV-2 has 96% genetic similarity with bat coronavirus BAT-CoV RaTG13. All the coronaviruses normally attack the lower respiratory system. The case fatalities of MERS being higher than SARS and its spread was limited due to its high virulence nature. The pathogenicity of SARS-CoV-2 is less than SARS-CoV and MERS-CoV but its infection rate is quite higher than both. Both SARS-CoV and SARS-CoV-2 use same receptor to infect the cell that is ACE-2 which is a metalloproteinase. MERS-CoV use DPP-4 as receptor protein. All the 3 syndromes have quite similar symptoms like fever, cough, myalgia, dyspnea, diarrhoea, rigor and abnormalities in chest radiographies.

Strict public health interventions in past has proved to be helpful to control SARS and MERS. Efficient and good quality data capture to analyse the epidemiology of the epidemic is a must in every country. Immediate lockdown and shutdown of public institutions and boycotting every gathering, is one of the measures that has been taken during SARS-CoV-2. Separate hospitals for the infected people should be built to avoid nosocomial infection. Hence the data collected was compiled and reviewed systematically by the authors.

Table 1: Severity Vs Clinical Features (According to study by Wang Y²⁰).

Severity	Features
Mild	Mild symptoms without radiographic features.
Moderate	Fever, Respiratory symptoms with radiographic features.
Severe	- Dyspnea, respiratory rate greater than 30 times/min. - Oxygen saturation less than 93% ambient air. - PaO₂/FiO₂ less than 300 mm hg (ratio of arterial oxygen partial pressure to fractional inspired oxygen). *Should meet one of the 3 criterias.
Critical	- Respiratory failure. - Septic shock. - Multiple organ failure. *Should meet one of the 3 criterias.

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