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A REVIEW ON CORONA VIRUS DISEASE

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ABSTRACT
At this times, several life-threatening viruses have emerged and coronavirus are one of these. Corona virus (CoV) is responsible for acute respiratory syndrome in human. Coronaviruses are characterized by crown-like spike that project from their surface, an unusually large RNA genome, replication strategy. We also discuss the coronavirinae are subdivided into four groups i.e. α, β, γ, δ coronaviruses. In the past 14 years, the onset of severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) have HCoVs into spotlight of the research community due to their high pathogenicity in humans. They have infected with human and animal hosts, causing illness and respiratory tract infection in humans. In this article, we provide a introduction to coronaviruses discussing their structure of virus, replication, prevention and treatment.

KEYWORDS: Coronavirus, SERS-CoV, MERS-CoV, Virion, Transcription, Translation.

INTRODUCTION

Corona viruses are important pathogens for humans and vertebrae. Corona viruses are species in the genera of virus belonging to one of two subfamilies Coronavirinae. Corona viruses can cause multiple system infections in various animals and mainly respiratory tract, gastro-intestinal, central nervous system infections in humans, livestock, avian, bat, mouse and many other wild animals such as Severe Acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS).[1-3] Since 2002 outbreaks of the Severe acute respiratory syndrome (SARS) and in 2012 Middle East respiratory syndrome (MERS), the possibility of corona virus transmission from animals to human has been proved.[4,5] Human corona virus represent a major group of corona virus associated with various multiple respiratory disease of varying severity including common cold, cough, pneumonia and bronchitis.[6] There are six known HCoVs have been identified, namely HCoV-229E, HCoV-NL63 (α-coronavirus), HCoV-OC43, HCoV-HKU1(β-coronavirus), severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) are globally circulated in the human population.[7] In severe cases, especially in elderly, children and immunocompromised patients these four HCoVs can cause life-threatening pneumonia and bronchiolitis.[6,8] In 2002-2003, SARS-CoV first emerged in Guangdong, China as an atypical pneumonia marked by headache, fever and respiratory symptoms such as cough and pneumonia, which may later develop into life-threatening respiratory failure and acute respiratory distress syndrome.[9]

Different types of Corona Virus

1. ALPHA CO-V
Human examples: HCoV-220E, HCoV-NL63.
Pig, dog and cat CoVs.

2. BETA CO-V
HCoV-OC43, HCoV-HKU1, HCoV-SARS
MHV, rat, pig and cow CoVs
MERS-CoV

3. GAMMA CO-V
Chicken and turkey CoVs

4. DELTA CO-V
Bird CoVs

History of Coronavirus

In 1960, Corona virus was first identified as a cause of the common cold. In Canada one study carried out in 2001, more than 500 patients presented with flu-like symptoms. Virological analyses showed that 3.6% of these cases were positive for the HCoV-NL63 strain by polymerase chain reaction (PCR). Corona virus was considered a relatively simple, nonfatal virus upto 2002.

However in 2002-2003 in Guangdong province in China, which resulted in spread to many other countries, including Vietnam, Hong Kong Singapore, Thailand, Taiwan and the United States of America, caused severe acute respiratory syndrome (SARS) and high mortality rates in 1000 patients. After this outbreak, microbiologists and infectious disease experts focused on the understanding the pathogenesis of the disease and discovered that this infection was caused by a new form of corona virus. A total of 8096 individuals were infected with corona virus, resulting in 774 deaths, thus in 2004, the Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO) declared a state of emergency. Coronavirus is not a stable virus demonstrated by the evolution of this virus and can adapt to become more virulent, even lethal to human. In 2012 in Saudi Arabia resulted in many deaths and spread first to other countries in the Middle East and then worldwide.[10]

Genomic Organization

Corona viruses contain positive-sense RNA genome of 30 kb. The genome contains a cap structure 5′ end along with tail 3′ end, allowing it to act as mRNA for translation of the replicase polyproteins. The 5′ end of the genome contains untranslated region (UTR) and a leader sequence that contain multiple stem loop structures required for RNA replication and transcription. In 3′ untranslated region (UTR) also contains RNA structures required for replication and synthesis of viral RNA. The 5′-leader-UTR-replicase-S(Spike)-E (Envelope)-M (Membrane)-N (Nucleocapsid)-3′UTR-poly (A) tail is the organization of the coronavirus genome with accessory genes interspersed within the structural genes at the 3′ end of the genome. Some proteins have been shown to have important roles in pathogenesis. The accessory proteins are almost exclusively non-essential for replication in tissue culture.[11]

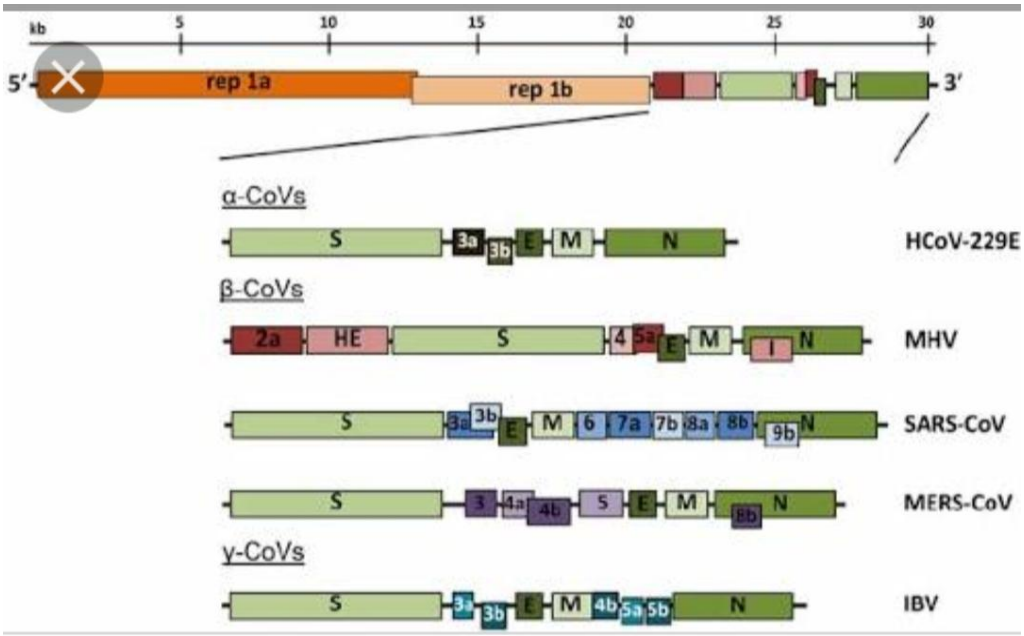
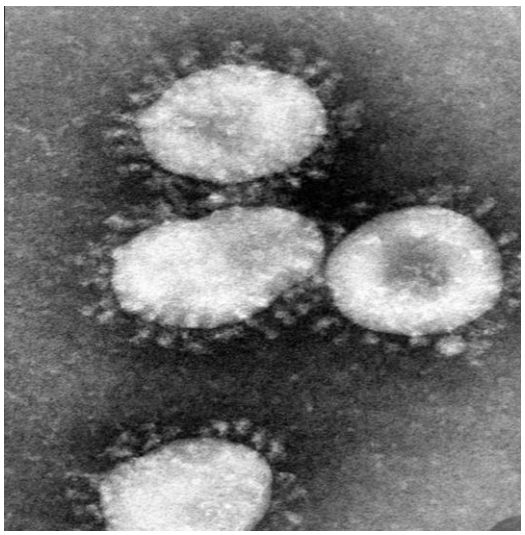


Figure 1: Genomic Organization.

The Structure of Virion

Coronavirus virions are round and sometimes pleiomorphic virions of approximately 80 to 120 nm in diameter. The club-shape spike projections emanating from the surface of the virion is the most prominent features of coronaviruses. Nucleocapsid is in the envelope of the virion. It contain positive-strand RNA, with largest RNA genome approximately 30 kb.[14] There are four main structural proteins in coronavirus particles. These are the spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins, all of which are encoded within the 3′ end of the viral genome.



Family: Coronaviridae.

Gender: Coronavirus.

Genome: Linear single stranded RNA +.

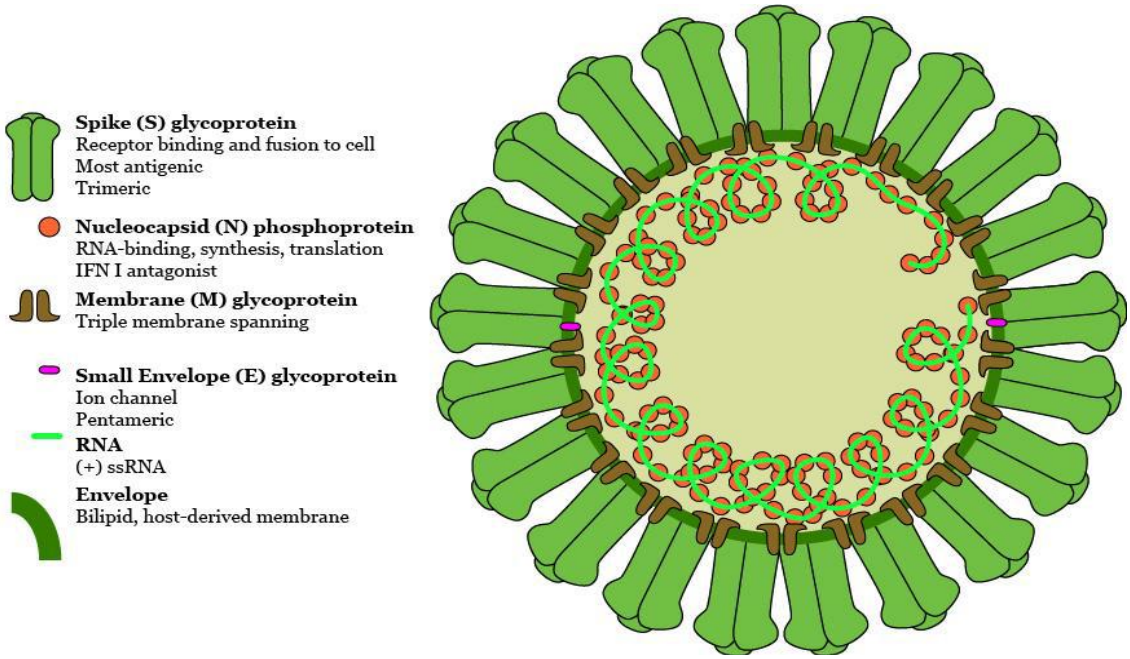


Figure 2: Structure of Coronavirus.

S Glycoproteins: Spike (S), in the electron microscope, the type I glycoprotein that forms the peplomers on the virion surface, giving the virus its corona- or crown-like morphology. These are located outside the virion and give the typical shape to the virion. S proteins bind to the virion membrane via the C-terminal transmembrane regions and they interact with M proteins.

M Glycoproteins: The most abundant structural protein in the virion is the membrane (M) protein. It is a small (25-30 kDa) protein with 3 transmembrane domains and thought to give the virion its shape. It has a small N-terminal glycosylated ectodomain and a much larger C-terminal endodomain that extends 6-8 nm into the viral particle.[15,16] Despite being co-translationally inserted in the ER membrane. The M protein plays a key role in regenerating virions in the cell. N protein forms a complex by binding to genomic RNA and M protein triggers the formation of interacting virions in this endoplasmic reticulum-Golgi apparatus intermediate compartment (ERGIC) with this complex.

E Glycoproteins: The E protein (8-12 kDa) is found in small quantities within the virion. E protein from coronaviruses have common architecture and are highly divergent. These are small proteins composed of approximately 76 to 109 amino acids. Coronavirus E proteins play a critical role in the assembly and morphogenesis of virions within the cell. The membrane topology of E protein is not completely resolved but most data suggest that it is a transmembrane protein. The E protein has a N-terminal ectodomain and a C-terminal endodomain and has ion channel activity. The E protein has other functions but also facilitates assembly and release of the virus. The ion channel activity in SARS-CoV E protein is not required for viral replication but is required for pathogenesis.[17,18]

N Glycoproteins: The N protein constitutes the only protein present in the nucleocapsid. It is composed of two separate domains, an N-terminal domain (NTD) and a C-terminal domain (CTD), both capable of binding RNA in vitro, but each domain uses different mechanism to bind RNA. It has been suggested that optimal RNA binding requires contributions from both domains.[19,20] N protein is also heavily phosphorylated and phosphorylation has been suggested to trigger a structural change enhancing the affinity for viral versus non-viral RNA. N protein binds the viral genome in a beads-on-a-string type conformation. The TRSs and genomic packaging signal; two specific RNA substrates have been identified for N protein. The genomic packaging signal has been found to bind specifically to the second, or C-terminal RNA binding domain.[21,22]

A 5th structural protein, the hemagglutinin-esterase (HE), is present in a subset of β-coronaviruses. The protein acts as a hemagglutinin, contains acetyl-esterase activity and binds sialic acids on surface glycoproteins. These activities are thought to enhance S protein-mediated cell entry and virus spread through the mucosa. HE enhances murine hepatitis virus (MHV) neurovirulence.[23]

Life Cycle of Coronavirus

- Attachment and Entry

The initial attachment of the virion to the host cell is initiated by interactions between the S protein and its receptor. The site of receptor binding domains (RBD) within the S1 region of the coronavirus depending on the virus, with some having the RBD at the C-terminus of S1 while others have the RBD at N-terminus of S1. The S-receptor interaction is governs the tissue tropism of the virus and the primary determinant for coronavirus to infect a host species. Peptidase as their cellular receptor utilize by many coronavirus. It is unclear why peptidase ar used, as entry occurs even in the absence of enzymatic domain of these proteins. SARS-CoV and HCoV-NL63 use angiotensin-converting enzyme 2 (ACE2) as their receptor, many α-coronaviruses utilize aminopeptidase N (APN) as their receptor, MHV enters through CEACAM1, and recently identified MERS-CoV binds to dipeptidyl-peptidase 4 (DPP4) to gain entry into human cells.

Following receptor binding, the virus must next gain access to the host cell cytosol. This is generally accomplished by acid-dependent proteolytic cleavage of S protein by cathepsin, TMPRRS2 or another protease, followed by fusion of the viral and cellular membranes. S protein cleavage occurs at two sites within S2 portion of the protein, first cleavage important for separating the RBD and fusion domains of the S protein and the second for exposing the fusion peptide i.e. cleavage at S2′

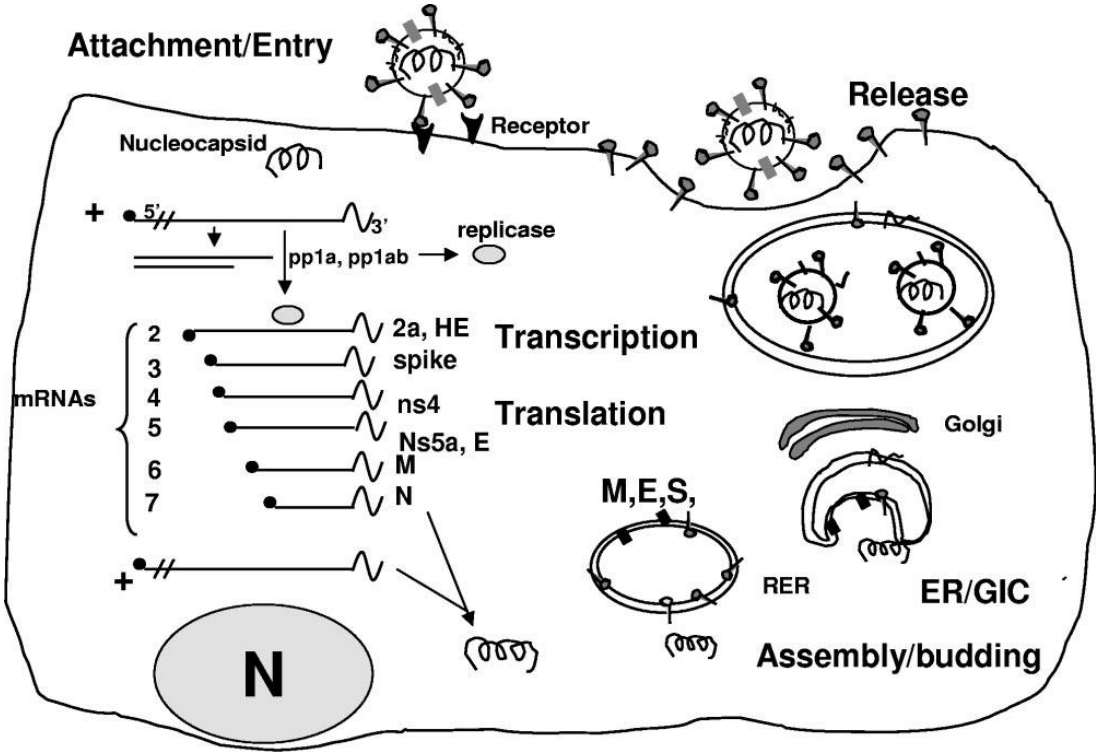


Figure 3: Life Cycle of Coronavirus.

Fusion generally occurs within acidified endosomes. MHV like coronaviruses can fuse at the plasma membrane. Cleavage at S2′ exposes a fusion peptide within the membrane, which is followed by joining of two heptad repeats in S2 forming an antiparallel six-helix bundle. Allows for the mixing of viral and cellular membranes by the formation of bundle.

- Replicase Protein Expression

After attachment and entry, coronavirus lifecycle is the translation of the replicase gene from the virion genomic RNA. The replicase gene encodes two large ORFS, rep 1a and rep1b, which express two co-terminal polyprotein, pp1a and pp1ab. In order to express both polyproteins, the virus utilizes a slippery sequence (5′-UUUAAAC-3′) and an RNA pseudoknot that cause ribosomal frameshifting from the rep 1a reading frame into the rep1b ORF. The pseudoknot blocks the ribosome from continuing elongation, causing it to pause on the slippery sequence, changing the reading frame by moving back one nucleotide -1 frameshift, before the ribosome is able to melt the pseudoknot structure and extend translation into rep 1b, resulting in the translation of pp1ab. *In vitro* studies predict the incidence of ribosomal frameshifting to be as high as 25%, but this has not been determined in virus infection. Pp1a and pp1ab polyproteins contain the nsps 1-11 and 1-16 respectively.

In pp1ab, nsp11 from pp1a becomes nsp12 following extension of pp1a into pp1b. γ-coronaviruses do not contain a comparable nsp1. Polyproteins are subsequently cleaved into the replicase polyproteins. They are the papain-like protease, encoded within nsp3 and a serine type protease, the main protease, or Mpro, encoded by nsp5. Most coronaviruses encode two PLpros within nsp3, except the γ-coronaviruses, SARS-

CoV and MERS-CoV, which only express one PLpro. The Mpro is responsible for the remaining 11 cleavage events while the PLpros cleave the nsp1/2, nsp2/3, and nsp3/4 boundaries. Many of nsps assemble into the replicase-transcriptase complex (RTC) to create an environment suitable for RNA synthesis, and are responsible for RNA replication and transcription of the sub-genomic RNAs. In addition to the replication functions other activities, such as other largely unknown functions (nsp3-ADP-ribose-1"-phosphatase; nsp 15-endoribonuclease) identified, and blocking innate immune responses (nsp1;nsp16-2′-O-methyl transferase; nsp3-deubiquitinase) have been identified for some of the nsps.

- Replication and Transcription

Viral RNA synthesis follows the translation and assembly of the viral replicase complexes. Genomic and sub-genomic RNAs both are produces by viral RNA synthesis. Sub-genomic RNAs serve as mRNA for the structural and accessory genes which resides downstream of the replicase polyproteins. Both genomic and sub-genomic RNAs are produced through negative strand intermediates. These negative-strand intermediates are only about 1% as abundant as their positive-sense counterparts and contain both poly-uridylate and anti-leader sequences.

For the replication of the viral RNAs many cis-acting sequences are important. Seven stem-loop structures that may extend into the replicase 1a gene within the 5′ UTR of the genome. A bulged stem-loop, a pseudoknot, and a hyper variable region contains in the 3′ UTR. Interestingly, the stem-loop and the pseudoknot at the 3′ end overlap and thus cannot form simultaneously. Therefore, these different structures are proposed to regulate alternate stages of RNA synthesis, although exactly which stages are regulated and their precise mechanism of action are still unknown. The most novel aspects of coronavirus replication is how the leader and body TRS segments fuse during production of sub-genomic RNAs. This was originally thought to occur during positive-strand synthesis, but now it is largely believed to occur during the discontinuous extension of negative-strand RNA. Many pieces of evidence currently support this model, including the presence of anti-leader sequence at the 3′ end of the negative-strand sub-genomic RNAs.

Coronaviruses are also known for their ability to recombine using both homologous and non-homologous recombination. The ability of these viruses to recombine is tied to the strand switching ability of the RdRp. Recombination plays a prominent role in viral evolution and is basis for the targeted RNA recombination.

- Assembly and Release

The viral structural proteins S, E and M are translated and inserted into the endoplasmic reticulum (ER), following replication and subgenomic RNA synthesis. These proteins move along the secretory pathway into the endoplasmic reticulum-golgi intermediate compartment (ERGIC). Viral genomes encapsidated by N protein bud into membranes of the ERGIC containing viral structural proteins, forming mature virions. The M proteins directs most protein-protein interactions required for assembly of coronaviruses.

Virus like particles (VLPs) cannot formed by M protein expression alone, M protein is not sufficient for virion formation. When M protein is expressed along with E protein VLPs are formed, suggesting these two proteins function together to produce coronavirus envelopes. N protein enhances VLP formation, suggesting that fusion of encapsidated genomes into the ERGIC enhances viral envelopment. The S protein is not required for assembly and incorporated into virions at this step. The E protein is only present in small quantities in the virion, while the M protein is relatively abundant. The M protein interactions provide the impetus for envelope maturation. It is unknown how E protein assists M protein in assembly of the virion and several possibilities have been suggested. The E may have a separate role in promoting viral release by altering the host secretory pathway.

The M protein also binds to the nucleocapsid, and the completion of virion assembly by this reaction. These interactions have been mapped to the C-terminus of the endodomain of M with CTD3 of the N protein. A packaging signal for MHV has been identified in the nsp15 coding sequence, but mutation of this signal does not appear to affect virus production, and a mechanism for how this packaging signal works has not been determined. Following assembly, virions are transported to the cell surface in the vesicles and released by exocytosis. In several coronaviruses, S protein that does not get assembled into virions transits to the cell surface where it mediates cell-cell fusion between infected cells and adjacent, uninfected cells.[24]

Sign and Symptoms

Some people infected with MERS-CoV developed severe respiratory illness but some infected people had mild symptoms or no symptoms at all.

Symptoms include

- fever ($\geq 38^0$ C/100.4^0 F)
- cough
- runny nose
- fatigue
- fever a pharyngitis in rare cases
- shortness of breath
- exacerbated asthma attack

Others reported having gastrointestinal symptoms like diarrhea, nausea, vomiting and kidney failure.[12] Pneumonia is common finding but not always present. Severe illness can cause respiratory failure that requires mechanical ventilation and support in an intensive care unit. Symptoms vary from person to person, and a few

kinds of the virus will be fatal. Approximately 36% of reported patients with MERS-CoV have died.[13]

Risk Factors

Humans being exposed to MERS-CoV in affected areas through.

- Contact with other domestic species
- Direct contact with dromedary camels
- Handling or consumption of dromedary products (meat, milk) body fluids and excreta
- Contact with bats and other wildlife species
- Infected people have spread MERS-CoV to others in healthcare setting such as hospitals
- The coronavirus was transmitted through large droplets and via direct contact
- The virus can reach a concentration of about 100 million particles per ml of sputum and can survive on contaminated surfaces and objects at room temperature for upto six days.

Diagnosis

In 2019 coronavirus can be diagnosed to other viral infections: using a blood, saliva or tissue sample. In United States, only the CDC currently has the ability to diagnose a COVID-19 infection. A lab technician will either draw a sample of your blood with a needle or use a cotton swab to take a small sample of saliva or respiratory secretions from your nose or the back of your throat. The sample is then sent to a testing facility to confirm the presence of viral material or antibodies that respond to the virus. The PCR diagnosis method is used to identify and diagnose several infectious diseases, can be used to confirm MERS-CoV positive cases by collecting sputum or any other sample from the patient.[25] SARS virus RNA was detectable in plasma by PCR, with viremia most readily detectable between days 4 and 8 of infection. Isolation of human coronaviruses in cell culture has been difficult. However, the SARS virus was recovered from oropharyngeal specimens using Vero monkey kidney cells. Because of the difficulty of virus isolation, serodiagnosis using acute and convalescent sera is the practical means of confirming coronavirus infections. ELISA and Hemagglutination tests may be used.

Treatment and Prevention

At present there are no specific antiviral therapies for coronavirus.[26] The main treatment strategy for corona virus infection is supportive therapy, administration of antipyretics and analgesics, maintenance of hydration, respiratory support by either mechanical ventilation or extracorporeal membrane oxygenation (ECMO) and treatment with antibiotics in the case of bacterial super infections. However such treatments may not be sufficient for MERS-CoV infections, which may be more severe. Ribavirin and interferon alpha have been shown to have synergistic effects and are more beneficial when started early. Mycophenolic acid has been shown to be efficacious and can be used as monotherapy. Several companies are attempting to develop MERS-CoV vaccines, none are available yet. There are various vaccine strategies for coronavirus.[10]

Vital work remains, however, to develop medication that concentrate on these processes and ready to inhibit infectious agent replication. Only limited options are available to prevent coronavirus infections. Vaccines have only been approved for IBV, TGEV and Canine CoV, but these vaccines are not always used because they are either not very effective, or in some cases have been reported to be involved in the selection of novel pathogenic CoVs via recombination of circulating strains. In the case of SARS-CoV, several potential vaccines have been developed but none are yet approved for use.

All travelers to avoid interaction with camels, attending camel farms, eating, unpasteurized milk or undercooked meat with stress on the importance of hand wash and hygiene. Foods are prepared under unsanitary conditions and properly washing fruits and vegetables before eating the food. As general precaution anyone visiting farms, market or other places where camels and other animals present should practice general hygiene measures including regular hand washing before and after touching animals and should avoid contact with sick animals. Wash hands with soap and water.

Cases have been reported on the following continents

Asia: China (PRC) (44 665), Macao (Special Administrative Region) (10), Hong Kong (Special Administrative Region) (49), Singapore (47), Thailand (33), Japan (25), Malaysia (18), United Arab Emirates (8), India (3), Cambodia (1), Nepal (1) and Shri Lanka (1).

Europe: Germany (16), France (11), United Kingdom (8), Italy (3), Spain (2), Russia (2), and Sweden (1).

Oceania: Australia (15).

America: the United States (13) and Canada (7).

CONCLUSION

Millions of people are at severe risk of acquiring several evolving viral infections through several factors. In this review, many different coronaviruses that cause a wide variety of human and veterinary diseased has occurred. Also include sign, symptoms, diagnosis of respiratory syndrome and treatment. SARS-CoV and MERS-CoV can be transmitted directly to humans from dromedary camels needs further investigation. The relative ease with which assays could be designed for this virus, in contrast to SARS-CoV in 2003, proves the huge collective value of descriptive studies of disease ecology and viral genome diversity. Modern techniques of identification of viruses by PCR and genetic coding techniques may be unable to provide an early and accurate isolation of the virus. The challenge now is to incorporate advance techniques in the investigative efforts done to understand

further the biology of Corona virus. Due to work and difficulty are developed vaccines that naturally cover yet have no effective medication that has resulted.

REFERENCES

1. Wang LF, Shi Z, Zhang S, Field H, Daszak P, Eaton BT. Review of bats and SARS. Emerging infectious diseases, 2006 Dec; 12(12): 1834.
2. Ge XY, Li JL, Yang XL, Chmura AA, Zhu G, Epstein JH, Mazet JK, Hu B, Zhang W, Peng C, Zhang YJ. Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor. Nature, 2013 Nov; 503(7477): 535-8.
3. Chen Y, Guo D. Molecular mechanisms of coronavirus RNA capping and methylation. Virologica Sinica, 2016 Feb 1; 31(1): 3-11.
4. Cui J, Li F, Shi ZL. Origin and evolution of pathogenic coronaviruses. Nature reviews Microbiology. 2019 Mar; 17(3): 181-92.
5. Cauchemez S, Van Kerkhove MD, Riley S, Donnelly CA, Fraser C, Ferguson NM. Transmission scenarios for Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and how to tell them apart. Euro surveillance: bulletin Europeen sur les maladies transmissibles= European communicable disease bulletin, 2013; 18(24).
6. Pene F, Merlat A, Vabret A, Rozenberg F, Buzyn A, Dreyfus F, Cariou A, Freymuth F, Lebon P. Coronavirus 229E-related pneumonia in immunocompromised patients. Clinical infectious diseases, 2003 Oct 1; 37(7): 929-32.
7. van der Hoek L. Human coronaviruses: what do they cause?. Antiviral therapy, 2007; 12(4 Pt B): 651.
8. Walsh EE, Shin JH, Falsey AR. Clinical impact of human coronaviruses 229E and OC43 infection in diverse adult populations. The Journal of infectious diseases, 2013 Nov 15; 208(10): 1634-42.
9. Graham RL, Donaldson EF, Baric RS. A decade after SARS: strategies for controlling emerging coronaviruses. Nature Reviews Microbiology, 2013 Dec; 11(12): 836-48.
10. Al-Osail AM, Al-Wazzah MJ. The history and epidemiology of Middle East respiratory syndrome corona virus. Multidisciplinary respiratory medicine, 2017 Dec 1; 12(1): 20.
11. Zhao L, Jha BK, Wu A, Elliott R, Ziebuhr J, Gorbalenya AE, Silverman RH, Weiss SR. Antagonism of the interferon-induced OAS-RNase L pathway by murine coronavirus ns2 protein is required for virus replication and liver pathology. Cell host & microbe, 2012 Jun 14; 11(6): 607-16.
12. https: //www.cdc.gov/features/novelcoronavirus/index.html (27/06/2018).
13. http: //www.who.int/news-room/fact-sheets/detail/middle-east-respiratory-syndrome-coronavirus-(mers-cov) (28/06/2018).
14. Law PT, Wong CH, Au TC, Chuck CP, Kong SK, Chan PK, To KF, Lo AW, Chan JY, Suen YK, Chan HE. The 3a protein of severe acute respiratory syndrome-associated coronavirus induces apoptosis in Vero E6 cells. Journal of general virology, 2005 Jul 1; 86(7): 1921-30.
15. Armstrong J, Niemann H, Smeekens S, Rottier P, Warren G. Sequence and topology of a model intracellular membrane protein, E1 glycoprotein, from a coronavirus. Nature, 1984 Apr 19; 308(5961): 751-2.
16. Nal B, Chan C, Kien F, Siu L, Tse J, Chu K, Kam J, Staropoli I, Crescenzo-Chaigne B, Escriou N, van der Werf S. Differential maturation and subcellular localization of severe acute respiratory syndrome coronavirus surface proteins S, M and E. Journal of general virology, 2005 May 1; 86(5): 1423-34.
17. Godet M, L'Haridon R, Vautherot JF, Laude H. TGEV corona virus ORF4 encodes a membrane protein that is incorporated into virions. Virology, 1992 Jun 1; 188(2): 666-75.
18. Nieto-Torres JL, DeDiego ML, Verdia-Baguena C, Jimenez-Guardeno JM, Regla-Nava JA, Fernandez-Delgado R, Castano-Rodriguez C, Alcaraz A, Torres J, Aguilella VM, Enjuanes L. Severe acute respiratory syndrome coronavirus envelope protein ion channel activity promotes virus fitness and pathogenesis. PLoS pathogens, 2014 May; 10(5).
19. Chang CK, Sue SC, Yu TH, Hsieh CM, Tsai CK, Chiang YC, Lee SJ, Hsiao HH, Wu WJ, Chang WL, Lin CH. Modular organization of SARS coronavirus nucleocapsid protein. Journal of biomedical science, 2006 Jan 1; 13(1): 59-72.
20. Hurst KR, Koetzner CA, Masters PS. Identification of in vivo-interacting domains of the murine coronavirus nucleocapsid protein. Journal of virology, 2009 Jul 15; 83(14): 7221-34.
21. Molenkamp R, Spaan WJ. Identification of a specific interaction between the coronavirus mouse hepatitis virus A59 nucleocapsid protein and packaging signal. Virology, 1997 Dec 8; 239(1): 78-86.
22. Kuo L, Masters PS. Functional analysis of the murine coronavirus genomic RNA packaging signal. Journal of virology, 2013 May 1; 87(9): 5182-92.
23. Klausegger A, Strobl B, Regl G, Kaser A, Luytjes W, Vlasak R. Identification of a coronavirus hemagglutinin-esterase with a substrate specificity different from those of influenza C virus and bovine coronavirus. Journal of virology, 1999 May 1; 73(5): 3737-43.
24. Fehr AR, Perlman S. Coronaviruses: an overview of their replication and pathogenesis. InCoronaviruses 2015 (pp. 1-23). Humana Press, New York, NY.
25. Al-Hazmi A. Challenges presented by MERS corona virus, and SARS corona virus to global health. Saudi journal of biological sciences, 2016 Jul 1; 23(4): 507-11.
26. Chen Y, Liu Q, Guo D. Emerging coronaviruses: genome structure, replication, and pathogenesis. Journal of medical virology, 2020 Jan 22.