**THE REVIEW OF THE AETIOLOGY, PATHOGENESIS, HISTOPATHOLOGICAL FEATURES, CURRENT POTENTIAL THERAPIES OF COVID-19**

**AND THE FUTURE OF COVID-19 ON PUBLIC HEALTH**

**COURSE CODE: ANA 404**

**MELLAH FAITH SEEMBER**

**MATRIC NUMBER: 17/MHS03/032**

**LECTURER: MR EDEM E. EDEM**

APRIL, 2020.

**AETIOLOGY OF COVID -19**

CoVs are positive-stranded RNA viruses with a crown-like appearance under an electron microscope (*coronam* is the Latin term for crown) due to the presence of spike glycoproteins on the envelope. The subfamily *Orthocoronavirinae* of the *Coronaviridae* family (order *Nidovirales*) classifies into four genera of CoVs: Alphacoronavirus (alphaCoV), Betacoronavirus (betaCoV), Deltacoronavirus (deltaCoV), and Gammacoronavirus (gammaCoV). Furthermore, the betaCoV genus divides into five sub-genera or lineages (Chan *et al.,* 2013, To *et al.,* 2013, Tse *et al.,* 2013, Jin *et al.,* 2013, Yuen *et al.,* 2013).  Genomic characterization has shown that probably bats and rodents are the gene sources of alphaCoVs and betaCoVs. On the contrary, avian species seem to represent the gene sources of deltaCoVs and gammaCoVs. Members of this large family of viruses can cause respiratory, enteric, hepatic, and neurological diseases in different animal species, including camels, cattle, cats, and bats. To date, seven human CoVs (HCoVs) — capable of infecting humans — have been identified. Some of HCoVs were identified in the mid-1960s, while others were only detected in the new millennium. In general, estimates suggest that 2% of the populations are healthy carriers of a CoV and that these viruses are responsible for about 5% to 10% of acute respiratory infections (Chen *et al.,* 2020, Liu *et al.,* 2020, Guo *et al.,* 2020). Common human CoVs: HCoV-OC43, and HCoV-HKU1 (betaCoVs of the A lineage); HCoV-229E, HCoV-NL63 (alphaCoVs) -CoV, SARS-CoV-2, and MERS-CoV (betaCoVs of the B and C lineage, respectively). They can cause common colds respiratory, extra-respiratory manifestations and self-limiting upper respiratory infections in immune competent individuals. In immune compromised subjects and the elderly, lower respiratory tract infections can occur.

Thus, SARS-CoV-2 belongs to the betaCoVs category. It has round or elliptic and often pleomorphic form, and a diameter of approximately 60–140 nm. Like other CoVs, it is sensitive to ultraviolet rays and heat. Furthermore, these viruses can be effectively inactivated by lipid solvents including ether (75%), ethanol, chlorine-containing disinfectant, peroxyacetic acid and chloroform except for chlorhexidine. In genetic terms, the genome of the new HCoV, isolated from a cluster-patient with atypical pneumonia after visiting Wuhan, had 89% nucleotide identity with bat SARS-like-CoVZXC21 and 82% with that of human SARS-CoV(Chan *et al.,* 2020, Kok *et al.,* 2020, Zhu *et al.,* 2020, Chu *et al.,* 2020, To *et al.,* 2020, Yuan *et al.,* 2020, Yuen *et al.,* 2020). For this reason, the new virus was called SARS-CoV-2. Its single-stranded RNA genome contains 29891 nucleotides, encoding for 9860 amino acids. Although its origins are not entirely understood, these genomic analyses suggest that SARS-CoV-2 probably evolved from a strain found in bats. The potential amplifying mammalian host, intermediate between bats and humans, is, however, not known. Since the mutation in the original strain could have directly triggered virulence towards humans, it is not certain that this intermediary exists.

**PATHOGENESIS OF COVID-19**

The severe symptoms of COVID-19 are associated with an increasing numbers and rate of fatalities especially in the epidemic region of China. On January 22, 2020, the China National Health Commission reported the details of the first 17 deaths and on January 25, 2020 the death cases increased to 56 deaths (Wang *et al.,* 2020, Tang *et al.,* 2020). The percentage of death among the reported 2684 cases of COVID-19 was approximately 2.84% as of Jan 25, 2020 and the median age of the deaths was 75 (range 48–89) years (Wang *et al.,* 2020, Tang *et al.,* 2020).

Patients infected with COVID-19 showed higher leukocyte numbers, abnormal respiratory findings, and increased levels of plasma pro-inflammatory cytokines. One of the COVID-19 case reports showed a patient at 5 days of fever presented with a cough, coarse breathing sounds of both lungs, and a body temperature of 39.0 °C. The patient's sputum showed positive real-time polymerase chain reaction results that confirmed COVID-19 infection (Lei *et al.,* 2020, Li *et al.,* 2020). The laboratory studies showed leucopenia with leukocyte counts of 2.91 × 10^9 cells/L of which 70.0% were neutrophils. Additionally, a value of 16.16 mg/L of blood C-reactive protein was noted which is above the normal range (0–10 mg/L). High erythrocyte sedimentation rate and D-dimer were also observed (Lei *et al.,* 2020, Li *et al.,* 2020). The main pathogenesis of COVID-19 infection as a respiratory system targeting virus was severe pneumonia, RNAaemia, combined with the incidence of ground-glass opacities, and acute cardiac injury (Huang *et al.,* 2020, Wang *et al.,* 2020, Li *et al.,* 2020, Ren *et al.,* 2020, Zhao *et al.,* 2020). Significantly high blood levels of cytokines and chemokines were noted in patients with COVID-19 infection that included IL1-β, IL1RA, IL7, IL8, IL9, IL10, basic FGF2, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1α, MIP1β, PDGFB, TNFα, and VEGFA. Some of the severe cases that were admitted to the intensive care unit showed high levels of pro-inflammatory cytokines including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1α, and TNFα that are reasoned to promote disease severity (Huang *et al.,* 2020,Wang *et al.,* 2020, Li *et al.,* 2020, Ren *et al.,* 2020,Zhao *et al.,* 2020).

**HISTOPATHOLOGICAL FEATURES COVID-19**

The early histopathological features in COVID-19 in two patients who underwent surgical resections for lung adenocarcinoma but were later discovered to have had COVID-19 at the time of the operation (Tian *et al.,* 2020, Hu *et al.,* 2020,Niu *et al.,* 2020). The findings were non-specific and included oedema, pneumocyte hyperplasia, focal inflammation and multinucleated giant cell formation while no hyaline membranes were seen. Given that these patients were asymptomatic with respect to COVID-19 at the time of the operation, these are likely to reflect only early changes of acute lung injury in the infection (Tian *et al.,* 2020, Hu *et al.,* 2020, Niu *et al.,* 2020). In another case, a 50-year-old man died from severe COVID-19 infection and more marked histopathological findings were noted. (Xu *et al.,* 2020, Shi *et al.,* 2020, Wang *et al.,* 2020). Samples were taken by postmortem biopsy, and a description of the gross postmortem findings is not given, although multiple ground glass opacities were noted on chest X-ray. The microscopic findings included diffuse alveolar damage with exudates. (Xu *et al.,* 2020, Shi *et al.,* 2020, Wang *et al.,* 2020). The inflammation was predominantly lymphocytic, and multinucleated giant cells were seen alongside large atypical pneumocytes, although no definitive viral inclusions were noted. Micro vesicular steatosis with mild inflammation was noted in the liver, although it was unclear whether this was related to the virus or iatrogenic. The features are very similar to those seen in SARS and MERS-corona virus infections (Ding *et al.,* 2020, Wang *et al.,* 2020, Shen *et al.,* 2020, Al Hosani *et al.,* 2020, Keating *et al.,* 2020).

**THE CURRENT POTENTIAL THERAPIES OF COVID-19**

The person-to-person transmission of COVID-19 infection led to the isolation of patients that were administered a variety of treatments. At present, there are no specific antiviral drugs or vaccine against COVID-19 infection for potential therapy of humans. The only option available is using broad-spectrum antiviral drugs like Nucleoside analogues and also HIV-protease inhibitors that could attenuate virus infection until the specific antiviral becomes available (Lu *et al.,* 2020). The treatments that have so far been attempted showed that 75 patients were administrated existing antiviral drugs. The course of treatment included twice a day oral administration of 75 mg oseltamivir, 500 mg lopinavir, 500 mg ritonavir and the intravenous administration of 0·25 g ganciclovir for 3–14 days (Chen *et al.,* 2020, Zhou *et al.,* 2020, Dong *et al.,* 2020, Qu *et al.,* 2020, Gong *et al.,* 2020, Han *et al.,* 2020). Another report showed that the broad-spectrum antiviral remdesivir and chloroquine are highly effective in the control of 2019-nCoV infection in vitro. These antiviral compounds have been used in human patients with a safety track record. Thus, these therapeutic agents can be considered to treat COVID-19 infection (Wang *et al.,* 2020,Cao *et al.,* 2020,Zhang *et al.,* 2020,Yang *et al.,* 2020, Liu *et al.,* 2020, Xu *et al.,* 2020,). Furthermore, there are a number of other compounds that are in development. These include the clinical candidate EIDD-2801 compound that has shown high therapeutic potential against seasonal and pandemic influenza virus infections and this represents another potential drug to be considered for the treatment of COVID-19 infection (Toots *et al.,* 2019, Yoon *et al.,* 2019, Cox *et al.,* 2019, Hart *et al.,* 2019, Sticher *et al.,* 2019, Makhsous *et al.,* 2019). Along those lines, until more specific therapeutics become available, it is reasonable to consider more broad-spectrum antivirals that provide drug treatment options for COVID-19 infection include Lopinavir/Ritonavir, Neuraminidase inhibitors, peptide (EK1), and RNA synthesis inhibitors. It is clear however, that more research is urgently needed to identify novel chemotherapeutic drugs for treating COVID-19 infections. In order to develop pre-and post-exposure prophylaxis against COVID-19, there is an urgent need to establish an animal model to replicate the severe disease currently observed in humans. Several groups of scientists are currently working hard to develop a nonhuman primate model to study COVID-19 infection to establish fast track novel therapeutics and for the testing of potential vaccines in addition to providing a better understanding of virus-host interactions (Rothan *et al.,* 2020, Byrareddy *et al.,* 2020).

**THE FUTURE OF COVID-19 ON PUBLIC HEALTH**

Extensive measures to reduce person-to-person transmission of COVID-19 are required to control the current outbreak. Special attention and efforts to protect or reduce transmission should be applied in susceptible populations including children, health care providers, and elderly people. A guideline was published for the medical staff, healthcare providers, and, public health individuals and researchers who are interested in the 2019-nCoV (Toots *et al.,* 2019, Yoon *et al.,* 2019, Cox *et al.,* 2019, Hart *et al.,* 2019, Sticher *et al.,* 2019, Makhsous *et al.,* 2019). The early death cases of COVID-19 outbreak occurred primarily in elderly people, possibly due to a weak immune system that permits faster progression of viral infection ((Wang *et al.,* 2020,Tang *et al.,* 2020, Li *et al.,* 2020, Guan *et al.,* 2020, Wu *et al.,* 2020, Wang *et al.,* 2020, Zhou *et al.,* 2020, Tong *et al.,* 2020).The public services and facilities should provide decontaminating reagents for cleaning hands on a routine basis. Physical contact with wet and contaminated objects should be considered in dealing with the virus, especially agents such as faecal and urine samples that can potentially serve as an alternative route of transmission ((Assiri *et al.,* 2013,Al-Tawfiq *et al.,* 2013, Al-Rabeeah *et al.,* 2013, Al-Rabiah *et al.,* 2013, Al-Hajjar *et al.,* 2013, Al-Barrak *et al.,* 2013, Lee *et al.,* 2013, Hui *et al.,* 2013, Wu *et al.,* 2013. Chan *et al.,* 2013, Cameron *et al.,* 2013, Joynt *et al.,* 2013). China and other countries including the US have implemented major prevention and control measures including travel screenings to control further spread of the virus (Carlos *et al.,* 2020, Dela Cruz *et al.,* 2020, Pasnick *et al.,* 2020). Epidemiological changes in COVID-19 infection should be monitored taking into account potential routes of transmission and subclinical infections, in addition to the adaptation, evolution, and virus spread among humans and possible intermediate animals and reservoirs. There remain a considerable number of questions that need to be addressed. These include, but are not limited to, details about who and how many have been tested, what proportion of these turned positive and whether this rate remains constant or variable. Very few pediatric cases have so far been reported; is this due to lack of testing or a true lack of infection/susceptibility? Of the ones that have so far been tested, how many have developed severe disease and how many were tested positive but showed no clinical sign of disease? There are some basic questions that would provide a framework for which more specific and detailed public health measures can be implemented.

**REFERENCES**

1. Chan J.F., To K.K., Tse H., Jin D.Y., Yuen K.Y., (2013). Interspecies transmission and emergence of novel viruses: lessons from bats and birds. *Trends Microbiol. 2*1(10), 544-55.
2. Chen Y., Liu Q., Guo D., (2020). Emerging corona viruses: Genome structure, replication, and pathogenesis. *J. Med. Virol. 92*(4), 418-423.
3. Chan J.F., Kok K.H., Zhu Z., Chu H., To K.K., Yuan S., Yuen K.Y., (2020). Genomic characterization of the 2019 novel human-pathogenic corona virus isolated from a patient with atypical pneumonia after visiting Wuhan*. Emerg Microbes Infect. 9*(1):221-236.
4. Wang W., Tang J., Wei F., (2019). Updated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan, China. *J. Med. Virol., 92* (4) pp. 441-447.
5. Lei J., Li J., Li X., Qi X., (2019**).** CT imaging of the 2019 novel coronavirus (2019-nCoV) pneumonia. *Radiology,* pp. 200-236.
6. Huang C., Wang Y., Li X., Ren L., Zhao J., Hu Y., (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet, 395* (10223), pp. 497-506.
7. Xu Z., Shi L., Wang Y., (2020). Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *The Lancet respiratory medicine.*
8. Tian, Hu, Niu, (2020). Pulmonary pathology of early phase 2019 novel coronavirus (COVID-19) pneumonia in two patients with lung cancer. *J Thorac Oncol* (20), pp 30132-30135.[OpenUrl](https://jcp.bmj.com/content/early/2020/04/01/%7Bopenurl%7D?query=rft.jtitle%253DJ%2BThorac%2BOncol%26rft_id%253Dinfo%253Apmid%252Fhttp%253A%252F%252Fwww.n%26rft.genre%253Darticle%26rft_val_fmt%253Dinfo%253Aofi%252Ffmt%253Akev%253Amtx%253Ajournal%26ctx_ver%253DZ39.88-2004%26url_ver%253DZ39.88-2004%26url_ctx_fmt%253Dinfo%253Aofi%252Ffmt%253Akev%253Amtx%253Actx)
9. Ding Y., Wang H., Shen H., (2003)*.* The clinical pathology of severe acute respiratory syndrome (SARS): a report from China. *J Pathol 200,* pp 282–289.
10. Chen N., Zhou M., Dong X., Qu J., Gong F., Han Y., (2020**).Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *J.*** *Lancet, 395*, pp. 507-513.
11. Wang M., Cao R., Zhang L.,Yang Z., Liu J., Xu M., (2020**).Remdesivir and Chloroquine Effectively Inhibit the Recently Emerged Novel Coronavirus (2019-nCoV) in Vitro. *J.*** *Cell research.*
12. Toots M., Yoon J., Cox R., Hart M., Sticher Z., Makhsous N., (2019).**Characterization of orally efficacious influenza drug with high resistance barrier in ferrets and human airway epithelia.** *Sci. Transl. Med*, p. 11.
13. Wang W., Tang J., (2020**). Updated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan, China.** *J. Med. Virol.,* *92* (4)*,* pp. 441-447.
14. Li Q., Guan X., Wu P., Wang X., Zhou L., Tong Y., (2020). **Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia.** *N. Engl. J. Med.*
15. Assiri A., Al-Tawfiq J., Al-Rabeeah A., Al-Rabiah F., Al-Hajjar, Al-Barrak A., (2013).**Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study.** *Lancet Infect. Dis., 13*, pp. 752-761.
16. Lee N., Hui D., Wu A., Chan P., Cameron P., Joynt G., (2003).**A major outbreak of severe acute respiratory syndrome in Hong Kong***. Engl. J. Med., 348*, pp. 1986-1994.
17. W.G. Carlos, C.S. Dela Cruz, B. Cao, S. Pasnick, S. Jamil, (2020). **Novel Wuhan (2019-nCoV) coronavirus*.*** *Am. J. Respir. Crit. Care Med., 201* (4), pp. 7-8.