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Review Article

Coronavirus SARS-CoV-2 is the Newly Emerged Zoonotic Virus Causing Pandemic Death and Economic Loss

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Abstract

Coronaviruses are a large family of enveloped viruses with positive-sense single strand RNA (ssRNA) and a helical symmetry nucleocapsid. This family cause illnesses ranging from mild, to lethal and death. In general, infection with coronaviruses begin with high fever followed by headache and body aches. some patients develop mild respiratory symptoms, dry cough, and diarrhea. Coronavirus infection could develop pneumonia that could be deadly specially for elderly with preexistent conditions, patients with compromise immune system, and others with underline illness symptoms.

On December 2019, World Health Organization (WHO) reported patients with pneumonia cases of unknown cause detected in Wuhan City, Hubei Province of China. In the early of January 2020, coronavirus disease COVID-19 was identified by Chinese authorities. Although, mild cases with COVID-19 illness have likely gone undetected, the virus infection spread fast globally and became pandemic with high number of cases in United States of America, China, Spain and Italy. The death rate from the virus SARS-CoV-2 transmission that cause COVID-19 illness varied from country to country and in the range of 1 to 5%. This pandemic outbreak affected over 150 countries with urgent needs to bring the transmission of SAR-CoV-2 in widespread communities under control by large scale quarantine, travel restriction, and social-distancing measure. This massive worldwide quarantine caused growing impact on the global economy, putting significant pressure on banking's and world financial systems. This COVID-19 pandemic is rapidly changing our lives and forcing us to view many social behaviors in our lives with a new light.

Keywords: *Coronaviridae; Beta-Coronavirus; Coronavirus; SARS-CoV; MERS-CoV; SARS-Cov-2; COVID-19; Mechanism of Infection; Spike (S) Glycoprotein; ACE-2; ELISA; RT-PCR; Blood Plasma Transfer; Antivirals; Monoclonal Antibody*

Introduction

Coronavirus was isolated and identified as new virus in the year 1961. Electron microscopy examination to this newly isolated virus showed a club- shaped surface which give the appearance of a solar corona (Figure 1). Because of this solar corona shape the family name for this newly identified virus was named Coronaviridae. Coronavirus morphology is an enveloped virus contain positive-sense single-stranded RNA (ssRNA) and has a helical shape with spike (s) glycoproteins (Figure 2) that promote the virus entry into host cells.

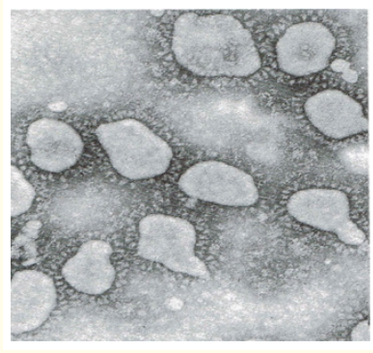

Figure 1: *Electron micrograph of coronaviruses.*

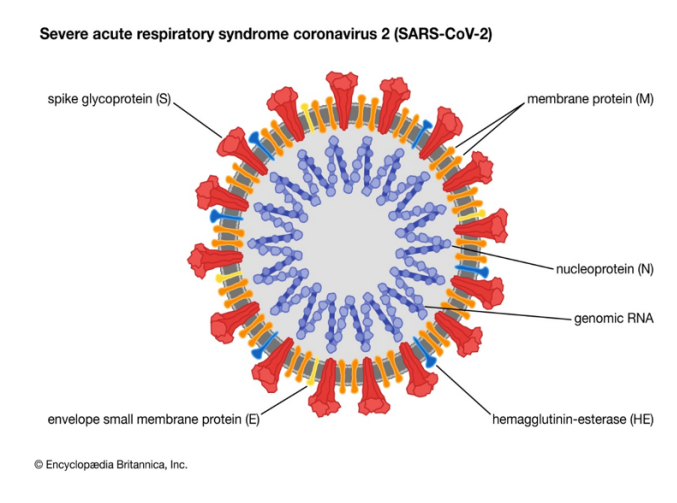

Figure 2: *SARS-CoV-2 has four structural proteins, known as the S (spike) glycoprotein responsible for allowing the virus to attach to the host cell membrane, E (envelope), M (membrane), and N (nucleocapsid) proteins, the N protein holds the RNA genome.*

There are thee outbreaks occurred from two strains of this coronavirus. These strains are SARS-CoV and MERS-CoV. The name SARS stand for Severe Acute Respiratory Syndromes and the MERS stand for Middle Eastern Respiratory syndromes.

SARS-CoV was first reported in China in February 2003 and spread so quickly globally infected over 8,000 persons before it was contained, causing over 774 death (10%) as estimated by World Health Organization (WHO) and cost between 30 to 50 billion to global economy for the year 2003 [1]. The origin of human SARS-CoV strain is believe to be from the bat virus reservoir beta-coronavirus [2]. This beta-coronavirus is a sub-genus of Sarbecovirus, that is mainly infect bats, but also infect other species like humans, camels, and rabbits [3].

Molecular divergence investigation between the newly emerged SARS-COV-2 strain and other related coronaviruses resulted in only 4% variability in genomic nucleotides, specially between SARS-COV-2 strain and human SARS-COV strain [4], Also, research investigation suggested that the variation functional site is in the virus receptor-biding domain (RBD) known by the name spike (S) glycoprotein is likely caused by mutation via natural selection or recombination. In addition, genetic analysis of the genome for this recently immerged SARS-COV-2 strain indicated that this virus evolved into two variants (types) designated by symbols L and S. These two types are will defined by two different SNPs (Sullivan Nicolaides Pathology) showing early complete linkage across the viral strain sequences [5]. The type (L) is more aggressive and spread quickly. It appears that human intervention place more selective pressure on this aggressive type (L) causing this COVID-19 pandemic outbreak.

COVID-19 symptoms

COVID-19 is the name of the disease caused by this recent emerged virus SARS-CoV-2 strain. This name was decided based on agreement between World Health Organization (WHO) for animal health and Food and Agriculture Organization (FAO). This name was chosen because it didn't refer to a specific geographic location, a specific animal, or a specific group of people, easy to pronounce and related to the disease. This name stands for CO (Corona), VI (virus), D (disease), and 19 (year 2019)". This COVID-19 name was release by World Health Organization (WHO) in February 11, 2020 [6].

Patients with COVID-19 may have mild symptomatic (illness) or asymptomatic (no symptoms), but some especially elderly with pre-existent conditions, Patients with compromise immune system, or with other underline illness symptoms become severely ill and die. Symptoms of this disease include fevers, dry cough, and shortness of breath. Patients with severe disease may develop lymphopenia and pneumonia [7]. The incubation time of the virus to show symptoms is not exactly known but it is estimated in the range of 2 to 14 days and the mortality increases with age.

COVID -19 transmission

The early COVID-19 case was linked to a live animal market in Wuhan-China suggesting that this virus was initially transmitted from animals to humans (Zoonosis). The disease spread from person to person contact through infected secretions via the contact with large respiratory droplets. In addition, the transmission could also occur via the contact with dry surface contaminated with respiratory droplets [8]. It appears that COVID-19 more transmissible than the other coronavirus outbreaks (SARS, and MERS).

Mechanism of infection

Coronavirus particles contain four main structural proteins. These are the Spike (S). glycoproteins promote the virus entry into host cells and are the main target for developing antibodies [9]. Furin (F) protein is a proteolytic enzyme that cleave Spike (S) glycoprotein into two subunits. These are S1 subunit responsible for receptor binding, and S2 subunit responsible to mediate membrane fusion [10], envelope (E) glycoprotein is a small integral membrane protein involved in virus lifecycle such as virus assembly, budding, and pathogenesis [11] and nucleocapsid (N) protein that forms complexes with virus RNA, and responsible to interact with the viral membrane protein during virus assembly, In addition, N protein plays a critical role in enhancing the efficiency of virus transcription and assembly [12].

The infection of host cell begins with the virus SARS-CoV-2 spike (S) glycoprotein bind to cellular receptor ACE-2, after binding the virus spike (S) glycoprotein facilitate the fusion of viral envelope with the host cell membrane through the endosomal pathway [13]. The virus releases RNA into the host cell, RNA goes through translation and transcription process to produce virus protein particles and virus RNAs. Viral proteins and viral RNAs are subsequently assembled into virion (SAR-CoV-2 virus) in the host endoplasmic reticulum (ER), and Golgi apparatus (G), then transported via vesicles and released out of the cell (Figure 3) to infect neighboring healthy cells in the host (patient), and virus replications cycles continue in host cells, or released through the patient mouth, nose, and eyes contaminate the air with infected secretion that infect healthy person via person to person contact or via the contact with dry surface contaminated with respiratory droplets.

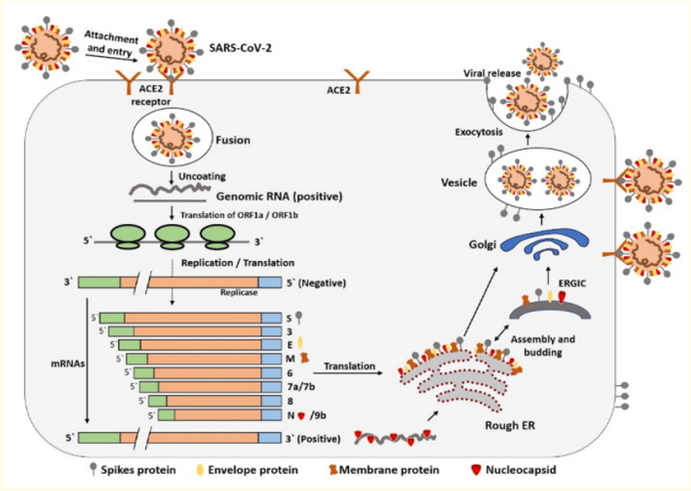

Figure 3: *Virus spike (S) glycoprotein interact with host cell receptor ACE-2, virus inters the host cell, virus RNA and proteins are synthesized in the host cytoplasm, new virions assembled in endoplasmic reticulum (rough ER) and Golgi apparatus, finally, mature viruses (virions) are released through vesicles by host cell secretory system.*

Diagnostics

Diagnostics tests for virus's infection in general can be classified into two major methods, direct detection, and indirect detection [14]. Direct detection methods include; nucleic acid amplification tests [15] and immune assay tests [16]. Indirect detection includes cell culture [17]. The two common rapid virus diagnostic methods are nucleic acid amplification tests, and immune assay methods.

Nucleic acid amplification test: Coronavirus RNA of SARS- CoV-2 is transcribed into cDNA by reserve transcriptase enzyme, followed by PCR assay method. Reagents for this RT-PCR assay method are: enzyme reverse transcriptase, primers, DNA polymerase, and nucleotides. Replicated cDNA can be detected by specific detection methods or instruments (Figure 4). In summary, this test method has two steps, the first step virus RNA is reverse transcribed into complementary single strand DNA (cDNA), and the second step, a specific segment of cDNA is amplified into double strand cDNA using DNA polymerase, specific primers, and nucleotide [18]. Real time RT-PCR detection (Figure 5) is currently favored for the detection of coronavirus because it is simple quantitative assay, with high sensitivity and permits virus detection soon after infection or even before the onset of the disease [19].

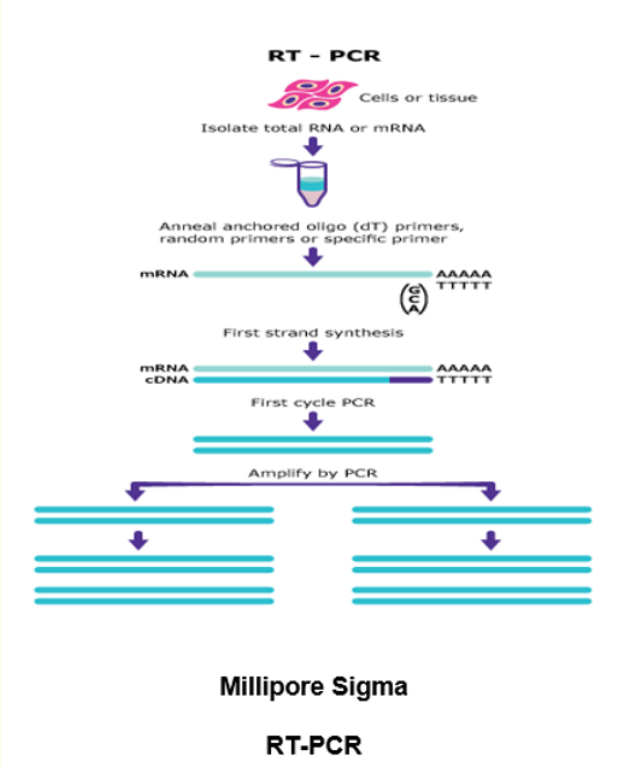

Figure 4: *The enzyme reverse transcriptase and RNA virus and the standard PCR reagents are used in this reaction. The reaction mixture (reverse transcriptase, and RNA virus) is heated to 370C, which enables the production of virus cDNA from the virus RNA. In PCR virus cDNA anneals to one of the primers leading to first-strand synthesis. Standard PCR proceeds and virus double strands DNA (dsDNA) is produced for virus cDNA detection.*

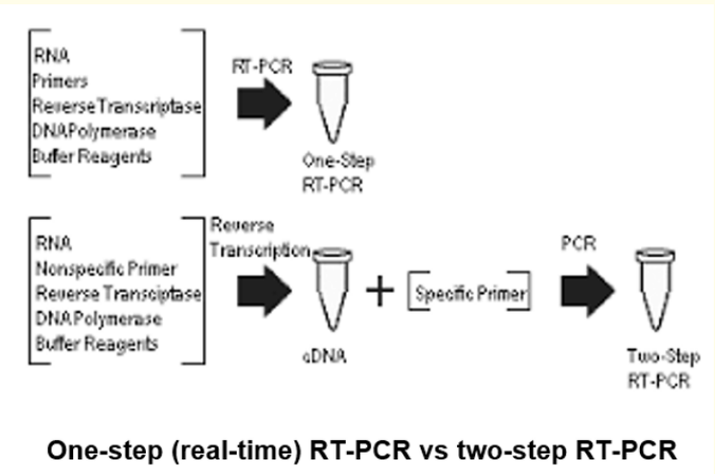

Figure 5: *Real-time RT-PCR (top) is a common virology one step diagnostic method is widely used to quantify RNA transcript levels in virus. The bottom is two steps RT and PCR.*

Immune assay test: This test detects antibodies produced in response to the SARS coronavirus infection. These antibodies IgM and IgG appears during the course of infection and can be undetectable in the early stage of infection, after resolution of the illness these antibodies are detectable in-patient serum [20]. Enzyme Linked Immunosorbent Assay (ELISA) is used for the detection antibodies in the patient serum or detect antigen (virus) in the patient nasal swap. In summary, the detection of sample (x) antibody (Ab_X) or antigen (Ag_X) is by using correspondent reagent (r) antigen (Ag_r) or antibody (Ab_r) respectively in question firmly fixed on solid phase, such as plastic surface. Antibody (Ab_X) or antigen (Ag_X) presence in the test sample will react with correspondent immobilized (Ag_r) or (Ab_r) respectively forming (Ab_X-Ag_r) or (Ag_X-Ab_r) complex. Followed by enzyme labelled antibody is added which will combine with either test antigen (Ag_X) or Fc portion of test antibody (Ab_X). At the end enzyme substrate is added to give the endpoint color (Figure 6). The intensity of the color is proportional to the amount of antibody or antigen present in the test sample [21]. ELISA test methods are sensitive and requires microliter quantities of test reagents (Figure 7).

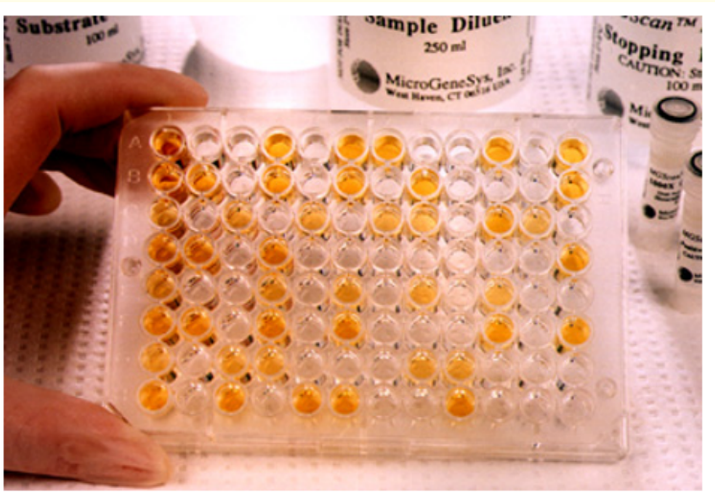

Figure 6: *A microtiter plate is used to perform the antibody/antigen test. The plate contains wells where the virus antigen (target molecules) or specific antibody are immobilized in wells, patient sample (nasal swap) for virus detection, or (blood) for antibody detection are inserted and allowed to interact. Colored wells indicate reactivity. The darker the color, the higher the reactivity.*

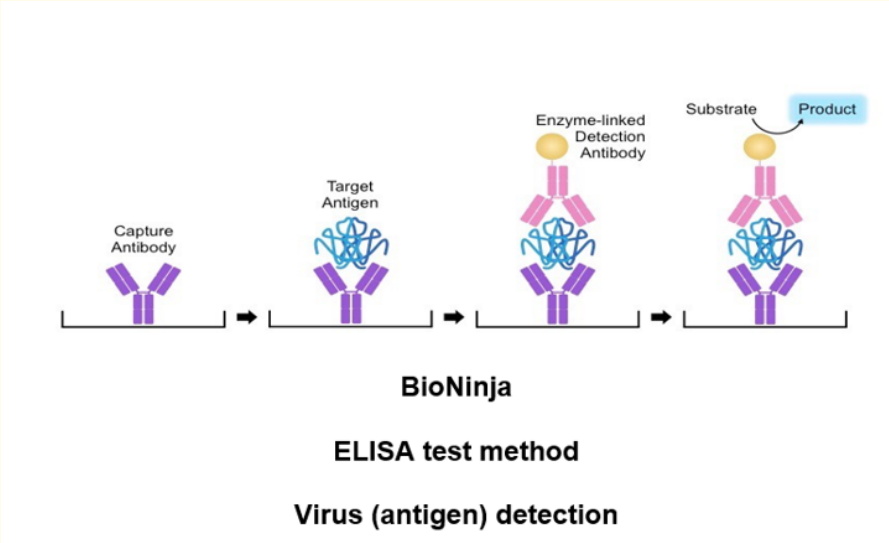

Figure 7: *Known monoclonal antibodies (capture antibodies) are affixed to wells in a plate, sample is added to the well and any antigen (virus) present will bind to capture antibody, plates then washed to remove unbound particles, the second monoclonal antibody (detection antibody) linked to enzyme are added to the well, the detection antibody will bind to captured antigen (virus) creating a sandwich (antibody-antigen-antibody), the enzyme substrate is added to the well and the enzyme -linked to detection antibody will trigger a color change to identify the presence of an antigen (virus).*

Worldwide pharmaceutical companies and researchers are currently working to produce antibodies and antigens of SARS-CoV-2 for diagnostic tests for COVID-19 Illness treatment. Spike (S) glycoprotein of the virus is the glycoprotein to which antibodies will raise in animals [22].

Treatments

There is currently no treatment specifically approved for COVID-19 illness, and there is no cure for this infection, Instead, the treatment focuses on managing symptoms as the virus take its course which often involve fever, cough and shortness of breath. Some experimental treatments are tested by physicians to see how its effective in the case of symptoms of complications. These experimental therapies used for these complications are similar to treatments used for early outbreaks by SARS CoV, and MERS CoV and includes, antiviral or retroviral medications to inhibit virus RNA replication, steroids to reduce lung swelling, and blood plasma transfusion [23]. In the cases of pneumonia symptoms that inhibits breathing, treatment involves ventilation with oxygen using ventilators to blow air into the lungs through a mask or a tube inserted directly into the windpipe [24].

Prevention

COVID -19 pandemic is caused by newly emerged virus (SARS-CoV-2) that is still much to learn about, and there is no vaccine available for prevention. Only known preventions are restriction of traveling, quarantine, school/business closing, and mass social distancing. In addition, general measures is recommended for individual such as, avoid sick individuals, cover nose and mouth when sneeze, wash hands for 20 seconds after coughing or sneezing, wash hands with soap and water for 20 seconds before eating, or bathroom visits, don't touch the face, mouth, eyes, etc. disinfect frequently touched household objects, stay home if ill, and the suggestion of using a facemask [25].

Potential therapeutic strategies against COVID-19

Developing new drugs is a lengthy process and impractical specially when global face immediate challenges as in the case of this COVID-19 pandemic outbreak. Currently, there is emerging strategy exist to test medicines that have been already tested for safety in early clinical trials. Using such repurposed drugs individually may not yield a significant clinical benefit. These repurposed drugs strategy are to test carefully combined cocktail of medicines [26] for the possibility to show clinical benefits as previously shown in 1990s for HIV/AIDS cases. This drug repurposing strategy is currently activated for this urgent SARS-CoV-2/COVID-19 pandemic [27].

Remdesivir: It is an adenosine analogue developed decades ago, with mechanism to incorporates into nascent viral RNA chains causing the virus pre-mature termination [28]. Its clinical trials against Ebola virus was failed, but it is generally safe [29]. It was tested against MERS-CoV virus and showed to block the virus replication [30]. It's now in clinical trial against SARS-CoV-2.

Kaletra: Lopinavir/ritonavir (LPV/r) is a combination of two drugs that work against HIV [31]. Clinical trials are planned to see whether it works against the virus SARS-CoV-2 that causes COVID-19 illness.

Chloroquine: This antimalarial drug might work against the virus by blocking infection. A small clinical trial of this drug in France suggested it may work as a treatment for COVID-19 illness. However, the study wasn't randomized, and large clinical trials is in progress for a mixture of hydroxychloroquine, and the antibiotic azithromycin [32].

Favipiravir: Also known by the names T-705, Avigan or favilavir, it is antiviral drug active against many RNA viruses [33]. This drug is approved in some countries outside the United States to treat influenza. Some reports from China not published yet suggested that it may work as a treatment for COVID-19 illness.

In addition, Scientists are working on known conventional methods to target the virus or treat the complications of COVID-19 illness. These methods are:

Monoclonal antibodies: MAbs as a drug trigger the immune system to attack the virus. Chinese Company isolated antibodies from patients who survived SARS and testing this isolated antibody against SARS-CoV-2 for COVID-19 illness treatment [34].

Blood plasma transfers: FDA in United States of America announced that medical facilities are conducting experiment trials to treat COVID-19 patients by using blood plasma from people who have recovered from COVID-19. The theory is plasma from recovered patients contains antibodies will attack this particular coronavirus SARS-CoV-2 in COVID-19 patients [35].

Stem cells: Last year preliminary research data showed that stem cell treatment could potentially benefit people with acute respiratory distress syndrome (ARDS) [36]. This ARDS condition occurred in some people with severe COVID-19 illness. Currently, testing this stem cells concept in a small group of patients with COVID-19 illness showed some promising results.

The standard protocol for discovery of potential drugs after laboratory and animal testing, must pass through three human clinical trials before can be approved for widespread use to treat virus COVID-19 illness. Up-to-date, no timeline for when these clinical trials will complete for potential approval of potential therapy to be used more widely to treat COVID-19 illness.

Discussion

Early COVID-19 cases were linked to a live animal's market in Wuhan China. This virus transmitted from animal to humans, then transmitted from person to person through infected secretions of large respiratory droplets or could be via touching a surface contaminated with respiratory droplet then touching the face nose, mouth or eyes. It appears that this strain of virus is more transmissible than early

SARS outbreak that was occurred in the year 2002 and is probably spread similar to Spanish flu (influenza) outbreak that was occurred in the year 1917. Viruses are continually mutated and SAR-CoV-2 is probability a mutant from SAR-CoV in the 2002 outbreak. In addition, genetic analysis of SAR-COV-2 genome indicated that this virus RNA evolved in two variants (types) designated by L and S. The type L is more aggressive and spread quickly, and it appears that human intervention place more selective pressure on this aggressive type L causing this current pandemic outbreak.

Coronaviruses are enveloped viruses with outer layer membrane at the stage before infecting host cells (free virus). Enveloped virus also has a protein layer called capsid located between the envelope and virus genetic material (ssRNA). The envelope is typically derived from portion of host cell membranes with chemical structure of phospholipid and proteins, the extended cell membrane structural loop is viral spike (S) glycoprotein contains basic amino acids and sensitive to proteolytic enzyme furin. This proteolytic enzyme furin split spike (S) glycoprotein into two domains S1 and S2. Virus S1 glycoprotein is receptor binding domain that is responsible to attach to the host cell receptor ACE-2. Virus S2 glycoprotein is fusion domain that assist the attached virus to host cell receptor ACE-2 to inter the cell. The Chemical structure of host cell receptor ACE-2 (angiotensin-converting-enzyme-2) is transmembrane metallo-carboxypeptidase [37].

The life cycle of SARS-CoV-2 in host cells begin when respiratory droplet from COVID-19 symptomatic or asymptomatic patient inhaled through the nose or mouth of a healthy person, the virus spike (S) glycoproteins have a high chance to attach to host cells receptors ACE-2. After binding to the host cell receptor, the Spike (S) glycoprotein confirmation change by the enzyme furin to facilitates viral envelope fusion with host cell membrane through the endosomal pathway. Inside the host cell the virus releases ssRNA into the host cell. The released virus ssRNA goes through translation and transcription process to produce virus protein particles and virus RNAs. Viral proteins and viral RNA are subsequently assembled into virion (SAR-CoV-2) in the host endoplasmic reticulum (ER) and Golgi apparatus (G), then transported via vesicles and released out of the infect cell to infect neighboring healthy cells in the patient, and virus replication life cycles continue [38]. The replicated virus is also released through the patient mouth, nose, eyes and contaminate the air with infected secretion that infect healthy person via person to person contact or via the contact with dry surface contaminated with respiratory droplets.

The spike (S) glycoprotein protein is the focus by researchers for developing diagnostic tests, and antiviral drugs for COVID-19 treatment, and vaccination for COVID-19 illness prevention. In addition, the host cell receptor ACE-2 that is responsible for mediating SARS-CoV-2, can be utilized for developing anti-ACE-2 antibodies to disrupt the interaction between virus and ACE-2 receptor and virus spike (S) glycoprotein. Developing anti- ACE-2 drug is also effective approach for developing antiviral drugs [39].

The principle of viral immunodiagnostics methods is based on virus glycoproteins structure by developing antibody against the virus antigenic glycoprotein as rapid detection methods [40]. These viral immunodiagnostics methods can be applied as a diagnostic test for the detection of SARS-CoV-2 in patient nose (nasal swap) based on the presence of spike (S) glycoprotein as an antigen on the virus surface This test use lectins or monoclonal antibodies as a probe for quantitative measuring (titer) of host antibodies (immunity) against the virus infection.

Viruses cannot reproduce on their own but propagate by subjugating in a host cell to produce copies of themselves. Understanding the virus mechanism of infection assist researchers in designing effective antiviral drugs, and vaccines. From understanding the virus life cycle and its mechanisms of infection, antiviral drugs can be developed based on the inhibition of virus attack to the host cell [41] and can be summarized as follow:

- Inhibit the attachment of the virus to the host cell.
- Inhibit enzymes responsible in releasing virus genetic material into the host cell.
- Inhibit the replication of viral components using the host cell machinery.

- Inhibit the assembly of viral components into complete viral particles (virion).
- Inhibit the released of assembled viral particle (virion) from infected cell to infect new host cell.

Currently researchers are applying these strategies of virus inhibition for developing effective antiviral drugs to treat COVID-19 patients. Developing antiviral against SARS-CoV-2 required multiple stages of evaluations that are time consuming and very costly. These experimental stages are *in vitro* (tissue culture), animal tastings for safety, and three human clinical trials for efficacy. The challenge is viruses use host cells to replicate themselves, and constantly mutate causing viral variations. and researchers must design antiviral drug that effect the virus without harming the host organism's cells.

In the case of new virus pandemic, the temporary solution in a short time is developing plasma antibody therapy by using pool of plasma as antivirus from recovered infected patients to treat new patients. The concept of this plasma antibody therapy is patients infected with the virus and recovered develop antibodies (IgM, and IgG) against virus infection in their bloods. Blood plasma extracted from recovered patients contains the antibody against the infected virus and can be used to treat newly patients. This concept does not need the long time for clinical trials and can be applied in a short time as a temporary treatment for COVID -19 patients until new antiviral drugs against SARS -CoV-2 are developed.

Finally, this SARS-CoV-2 coronavirus pandemic has dramatically disrupted every day social and economic pattern of societies around the world. Governments are trying to support business and workers who are losing income, and in the same time ramp up the production of urgent essential hospitals needs of ventilators, gloves, masks, and hospital beds. This COVID-19 pandemic shut down world economic activities, forced people to stay in their homes, killing hundred thousand of people, and plunging countries into possible deep recession rapidly.

Conclusion

There are three ways to stop the spreading of COVID-19 illness. These three ways are; First way, restriction of people free movement (social distancing) to prevent virus transmission, currently implemented worldwide, the second way is developing vaccine against the virus SARS-CoV-2 that cause COVID-19 illness, This second way still under development. The third way is to wait until enough people infected and survivors become immune, this third way is known by the name herd immunity. This third way is potentially effective but costly on human death tolls.

Finally, coronaviruses are deadly zoonosis viruses infected humans because some countries selling live exotic animals including snakes, and bats for meat consumption. To minimize future pandemic outbreaks with these deadly viruses selling live domestic animals, exotic animals and birds to be slaughtered by consumers for meat consumption must be forbidden. These scarified animals, and birds must be inspected first by veterinarians, slaughtered in certified slaughterhouses, processed under safety food protocols, and marketed to consumers as raw meat, pre-cooked or fully cooked meat in refrigerated sealed packages. Such regulations will minimize these deadly outbreaks in the future.

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