The Strengths, Weaknesses, Opportunities and Threats (SWOT) Analysis of the Severe Acute Respiratory Syndrome Coronavirus 2 of COVID-19

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Abstract

Introduction: SARS-CoV-2 is the etiologic agent of Coronavirus Disease 2019 (COVID-19), a highly contagious, emergent, acute, viral pneumonia that emanated sporadically in Wuhan, China, in December 2019. COVID-19 became a pandemic in February 2020, leading to 4,942,687 confirmed cases and over 321,987 deaths and grounding several economies around the world as of May 2020. Although global researchers, epidemiologists, virologists, and medical professionals rose steadily to contain the disease, in-depth knowledge of the virus and concerted efforts to combat it are still evolving. This research sought to elucidate the biological Strengths, Weaknesses, Opportunities, and Threats to SARS-CoV-2, with a view to understanding and devising holistic strategies to combat, mitigate, and overcome the scourge of COVID-19.

Methods: This narrative review utilized PubMed, Google, the Directory of Open Access Journals, ProMed, and other databases to search for and finally select 98 publications on coronaviruses, 2019-nCoV, and COVID-19 disease, using text word searches to generate the specific search terms. Relevant publications were reviewed and compared; findings were synthesized using a narrative method and presented qualitatively.

Results: Some identified *Strengths of SARS-CoV-2* include: the virus has the ability to effectively cross the species barrier and establish productive infection in humans; SARS-CoV-2 is a new strain of coronavirus; three virulence factors (Nsp1, Nsp3c and ORF7a) interfere with the host's innate immunity and immune escape; ORF8 and ORF10 proteins are uniquely associated with SARS-CoV-2; the genetic fitness of the spike protein facilitates attachment and fusion; a polybasic cleavage site exists in the genome; SARS-CoV-2 has a short serial interval of 4.0 days; the virus has the ability to resurge and enter into regular circulation after the initial pandemic wave.

The *Weaknesses* include: angiotensin-converting enzyme 2 (ACE2) is the sole receptor for SARS-CoV-2; host protease processing during viral entry is a significant barrier for several lineage β-coronaviruses; SARS-CoV-2 critically requires porphyrin to inhibit human heme metabolism. The *Opportunities harnessed by SARS-CoV-2* include: host cellular receptors for SARS-CoV-2 infection are expressed by several important organs in the human body; ease of travel, globalization, and aviation are potential avenues for global spread; underlying illnesses, older age, male gender, smoking, and immunosuppression increase vulnerability; knowledge is still evolving on the underlying pathogenic mechanisms of SARS-CoV-2; there is potential for silent transmission via blood and blood products; there is no approved COVID-19 vaccine; the virus is associated with a confounding pattern of signs and symptoms, as well a disproportionate "cytokine storm" or damaging evolution of effective defenses. The *Threats to SARS-CoV-2* include: prohibition of mass gatherings; prompt hospitalization, isolation, and quarantining of infected individuals; repurposing proven antimalarial/antiviral/anti-inflammatory drugs; deployment of rapid laboratory equipment and procedures for prompt detection; potential antiviral activities of coagulation factors Xa and IIa (thrombin) and convalescent plasma; elucidation of the genome sequences; and global COVID-19 research funding.

Conclusion: SARS-CoV-2 capitalizes on its biological strengths, conserves its weaknesses, and exploits the host opportunities to decimate human populations. For interventions to overcome the virus and end the COVID-19 pandemic, research scientists, academia, funders, industry, healthcare professionals, and the citizenry should scale up all promising research by strategically focusing on decreasing the Strengths and Opportunities, while capitalizing on the Weaknesses of and Threats to the virus.

Introduction

In December 2019, a cluster of human pneumonia of unknown etiology that emanated post-infection from a Wuhan seafood market was found in patients with respiratory distress in Wuhan, China, and was first described by Dr. Li Wenliang, an ophthamologist who eventually contracted 2019-nCoV from his glaucoma patient and died of COVID-19 at the Wuhan Central Hospital.[1, 2] This resulted in an outbreak, and the pathogen was subsequently identified as a human coronavirus that was provisionally named the "2019 novel coronavirus" (2019-nCoV) by the World Health Organization (WHO) on January 7, 2020. The WHO's Emergency Committee declared the 2019-nCoV outbreak to be a public health emergency of international concern (PHEIC) on January 30, 2020.[3] Following the criteria of International Committee on Taxonomy of Viruses (ICTV) for naming newly discovered viruses, the etiology of the pneumonia was renamed as "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2) on February 11, 2020, while the associated disease was named by the WHO as coronavirus disease 2019 (COVID-19).[4] COVID-19 is an acutely fatal respiratory illness caused by SARS-CoV-2, a strain of severe acute respiratory syndrome–related coronavirus, characterized predominantly by high fever, harsh dry cough, difficulty breathing, and fatigue. Other less commonly reported symptoms include body aches, joint pains, skin tingling, loss of smell, metallic taste, diarrhea, septic shock, coma, and death within three weeks of infection. SARS-CoV-2 has been moderately successful in penetrating the human species because of its virulence and low fatality rate (2–3%) compared to the Middle East respiratory syndrome coronavirus (MERS-CoV), which had a 35% case fatality.[5] The majority of initial cases of COVID-19 were epidemiologically linked to exposure to Wuhan's Huanan seafood market, where wild animals are traded.[6] Subsequent phylogenetic data implicated a zoonotic origin, and the ongoing rapid spread suggests person-to-person transmission in human populations. As of May 19, 2020 (17:27 GMT+1), statistics from 213 countries and territories and 2 international conveyances indicated that there were 4,942,687 confirmed cases of COVID-19 around the world. Out of the currently active 2,684,199 infected patients, 2,639,039 (98%) were in mild condition, while 45,160 (2%) were in critical condition. Of the 2,258,488 closed cases, 1,936,501 (86%) have recovered and been discharged while 321,987 (14%) have died.[7]

Nomenclature and taxonomy of SARS-CoV-2

For an outbreak of a new viral disease, there are three names to be decided: the disease (by the WHO), the virus (by expert virologists), and the species (by the ICTV). Based on phylogeny, taxonomy, and established practice, the coronavirus study group of the ICTV recognizes this virus as forming a sister clade to the pro-

totype human and bat severe acute respiratory syndrome coronaviruses (SARS-CoVs) of the species *severe acute respiratory syndrome-related coronavirus* and designates it "SARS-CoV-2".[8] In the realm *Riboviria*, the emergent SARS-CoV-2, like all other coronaviruses, is an RNA virus belonging to the order *Nidovirales*, suborder *Cornidovirineae*, family *Coronaviridae*, and subfamily *Coronavirinae*. This subfamily includes four genera, namely *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus,* and *Deltacoronavirus*. Both SARS-CoV-2 and SARS-CoV are in the genus *Betacoronavirus*.[6] The genome of SARS-CoV-2 is more than 85% similar to the genome of the SARS-like virus ZC45 (bat-SL-CoVZC45), and together, these viruses form a unique *Orthocoronavirinae* subfamily with another SARS-like virus, ZXC21, in the subgenus *Sarbecovirus* (lineage B) that shows typical *Betacoronavirus* gene structure.[8, 9] Among the original SARS-CoV coronaviruses currently known to infect humans, the new SARS-CoV-2 (identified in 2020) is the seventh strain after HCoV-OC43 and HCoV-229E (both detected in 1960s), SARS-CoV (identified in 2003), HCoV-NL63 (identified in 2004), HCoV-HKU1(identified in 2005), and MERS-CoV (identified in 2012).[10, 11] Based on individual specific isolate, SARS-CoV-2 may be named, for example, SARS-CoV-2/human/Wuhan/X1/2019.

In morphology, SARS-CoV-2, like SARS-CoV and MERS-CoV, derived its name from the crown-like ("corona" means crown in Latin) appearance that the glycoprotein spikes form on the surface of the virus particle. SARS-CoV-2 is an enveloped virus with RNA genome whose virion is morphologically round or elliptic and often pleomorphic with a diameter of approximately 50–200 nm. The linear, positive-sense, single-stranded RNA genome (belonging to Class IV of the David Baltimore classification system and a property that may explain its fast replication) has 10 open reading frames and contains 29,891 nucleotides, encoding 9860 amino acids (**Figure 1**). NSP1 to NSP11 are encoded in ORF1a, and NSP12 to NSP16 are encoded in ORF1b. ORF1a and ORF1b generate multiple nonstructural proteins (such as 3-chymotrypsin-like protease, papain-like protease, helicase, and RNA-dependent RNA polymerase) upon protease cleavage.[12, 13] The replicase proteins are involved in transcription and replication of viral RNAs. ORF2-10 encodes four viral structural proteins, comprising the spike glycoprotein (S), envelope (E), membrane (M), and nucleocapsid (N) and accessory proteins. The nucleocapsid encapsidates the RNA genome while the spike, envelope, and membrane proteins are uniquely involved in the formation of the viral coat/envelope.

Strengths, Weaknesses, Opportunities, and Threats (SWOT)

A SWOT analysis is usually represented as a grid, called a 2×2 contingency table. It is a business or strategic planning technique used to summarize the key
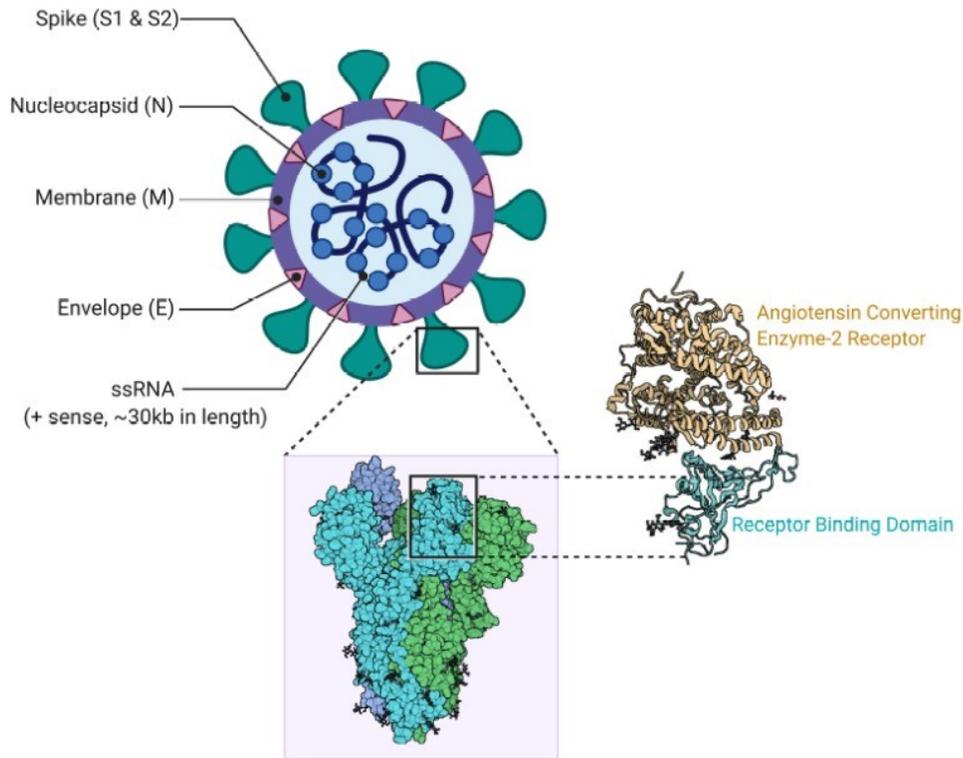
SARS-CoV 2 Structure

Figure 1. Morphology of SARS-CoV-2.[13] © 2021, StatPearls Publishing LLC; figure contributed by Rohan Bir Singh, MD. This is an open-access publication distributed under the terms of the Creative Commons Attribution License (CC BY 4.0). No changes were made to this figure.

components of the strategic environments. The technique is credited to Albert Humphrey at Stanford University between the 1960s and 70s, who led a research project that involved 5,000 interviews, was funded by fortune 500 companies, and took 9 years to develop.[14] SWOT is a widely used framework for organizing and using data and information gained from situation analysis. The technique enables a group or individual to move from everyday problems or traditional strategies to a fresh perspective. It generally is a framework for identifying and analyzing the internal and external factors that can have an impact on the viability of a project, product, government, place, organism, or person. The SWOT concept is an assessment technique originally developed for business and industry with a long track-record of effectiveness, equally useful in other areas, and applicable to a variety of levels of operation.[15] The benefits of SWOT include identification of areas of strengths and weaknesses, provision of comprehensive overview for contingency planning, and development of a "plan of action" to act on in a snapshot. SWOT analysis might be used to explore possibilities for new efforts or solutions to problems or

to make decisions about the best path for an initiative and is an excellent way to organize derived information from studies or surveys. SWOT is typically applied in a positive connotation but could be applied to the examination of SARS-CoV-2 and how it could be more pathogenic and more communicable. The multiplicitous effects of the COVID-19 pandemic are turning tables and fast-tracking global economies into recession with attendant attenuation of several human activities, such as education, religious activities, tourism, finance, governance, business, socialization, employment, technology, healthcare programmes, and sports. Therefore, urgent enduring interventions are required to stop the pandemic.

The objectives of this innovative review were to adapt the SWOT concept to: identifying the biological strengths of SARS-CoV-2, determining the weaknesses of SARS-CoV-2, identifying the opportunities harnessed by SARS-CoV-2, determining the threats to SARS-CoV-2, identifying gaps where scientists and researchers could key in for productive research, and encouraging scientists, researchers, patients, nations, industry, and academia to explore this paradigm shift
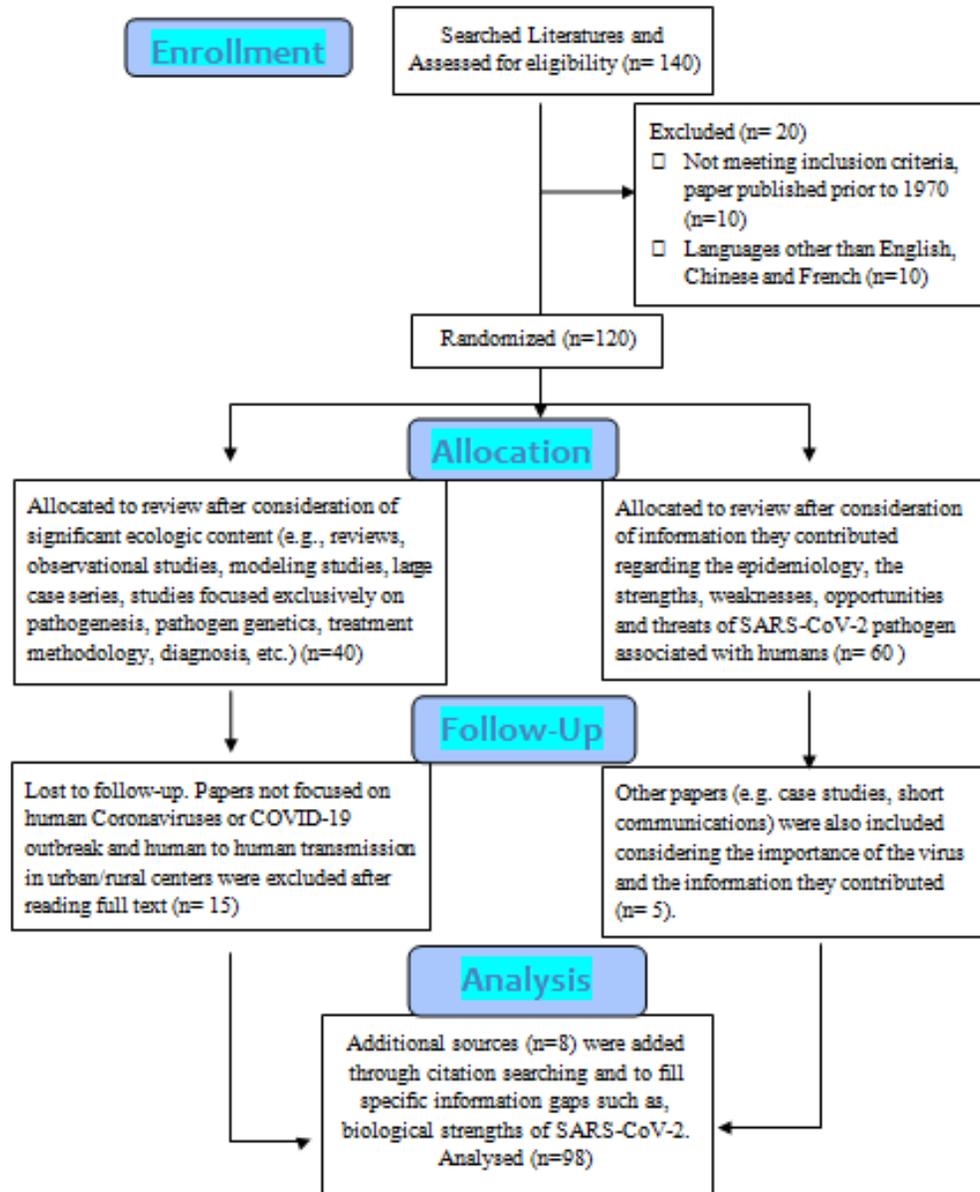
Figure 2. Flow diagram of literature searches for the SWOT Analysis of SARS-CoV-2.

for holistic knowledge in combating the recalcitrant emerging SARS-CoV-2.

Methods

Databases used in this study included: Medline, PubMed, DOAJ, BIOSIS Previews, medRxiv, JAMA network, JohnsHopkinsCSSE, the WHO and CDC websites, the COVID-19 Resource center, and the Google search engine. Text word searches (including "wildcards" to capture term variations, e.g., SWOT analysis, COVID-19, 2019-nCoV, SARS-CoV-2, SARS, Pathophysiology, diagnosis, zoonotic disease, biological strengths of SARS-CoV-2, weaknesses of SARS-CoV-2, opportunities harnessed by 2019-nCoV, SARS pneumonia outbreak in China, threats to 2019-nCoV, viral pneumonia, and multiorgan failure due to viral pneumonia) were conducted using keywords pertaining to 2019-nCoV, COVID-19 and pangolins, coronaviruses, bushmeat trade, bat-associated zoonoses, and the urban environment. Groups of key words were combined using boolean operators. Medline was searched using Medical Subject Headings (natural reservoir, horseshoe bats, zoonoses, COVID-19, Coronaviruses, 2019-nCoV pneumonia outbreaks) in various combinations. The literature search was conducted between January and April 2020. A total of 140 articles were identified/selected for consideration (**Figure 2**). To ensure that the review was focused on the most up-to-date researches, all papers published prior to 1970 and in languages other than English, Chinese and French were excluded (*n*=20). Remaining papers (*n*=120) were organized for inclusion and reviewed according to the amount of information that they contributed regarding the ecology, transmission, strengths, weaknesses, opportunities, and threats of SARS-CoV-2 pathogen associated with humans. Articles with significant ecologic content were retained (*n*=100) and other articles were also included considering the importance of the virus and information obtained (*n*=5). Finally, articles not focused on human Coronaviruses or SARS-CoV-2 outbreak and transmission around the world from human to human or from bats in urban centers were excluded (*n*=15). Additional sources (*n*=8) were added through citation searching and to fill specific information gaps. A total of 98 papers were reviewed in detail, data from these papers were extracted and synthesized based on the methodology for narrative synthesis as described.[16] The goal of narrative synthesis is to identify common themes across research regarding a particular subject that then can be used to identify commonalities and critical differences among included articles.

Results and Discussion

Strengths of the Severe Acute Respiratory Syndrome Coronavirus 2

Strengths are the characteristics of SARS-CoV-2 that confer the pathogen advantages over the host and other diseases. They comprise the positive tangible and intangible attributes internal to SARS-CoV-2. Essentially, the biological strengths and attributes (**Table 1**) that facilitate the pathogenicity, establishment, and spread of the SARS-CoV-2 include the following.

Ability to effectively cross the species barrier and establish productive infection in humans: The species barriers separating humans from nonhuman animal species represent a major challenge for effective exposure to, infection by, and subsequent spread of zoonotic pathogens among humans.[17] These species barriers can be divided into three largely complementary sets. First, the interspecies barrier, which determines the nature and level of human exposure to zoonotic pathogens. Second, the intrahuman barrier, which determines the ability of zoonotic pathogens to productively infect a human host and effectively cope with the immune response. Third, the interhuman barrier, which determines the ability of zoonotic pathogens to efficiently transmit among humans, causing outbreaks, epidemics, or pandemics. Only the zoonotic pathogens that cross the three barriers have the potential to sustainably establish themselves in the human population.[18] Coronaviruses primarily cause enzootic infections in birds and mammals but, in the last few decades, have proven to be capable of infecting humans as well. The outbreaks of SARS in 2003 and, more recently, MERS have demonstrated the lethality of coronaviruses when they cross the species barrier and infect humans. The emergent novel SARS-CoV-2 has successfully crossed to humans from animal species, causing the pandemic of COVID-19. Identifying the factors that allow SARS-CoV-2 to cross each of these three sets of barriers is essential to mitigate burdens of COVID-19. In addition, intensive domestic animal breeding facilitates viral mixing and increased targets for spillover from wild viruses.[19] In the current epidemic, pet dogs and cats, ferrets, and tigers in zoos have been identified, so far, as animals infected with SARS-CoV-2, thereby increasing the host range and potential reservoirs. These findings emphasize probable human to animal and animal to human transmissions. Contrary to SARS-CoV-2, one of the factors that led to the scientific success in the eradication of smallpox was the inability of the pox virus to cross the species barrier, thereby limiting it to productive infection only in a susceptible single host (i.e., humans).[20, 21]

SARS-CoV-2 is a new strain of coronavirus: SARS-CoV-2 is a new strain of coronavirus not previously identified in humans. As a new virus, nobody has

Table 1. Contingency Table (2 by 2) of SWOT Analysis of SARS-CoV-2.

|	Helpful to SARS-CoV-2 in achieving pathogenic objective (decrease)	Harmful SARS-CoV-2 in achieving pathogenic objective (increase)
Internal factors (attributes of SARS-CoV-2)	**Strengths** (i) Ability to effectively cross the species barrier and establish productive infection in humans. (ii) SARS-CoV-2 is a new strain of coronavirus. (iii) Natural reservoir of SARS-CoV-2 is unconfirmed. (iv) Three virulence factors (Nsp1, Nsp3c and ORF7a). (v) Interferes with host's innate immunity and escape. (vi) ORF8 and ORF10 proteins are uniquely associated with SARS-CoV-2. (vii) SARS-CoV-2 is highly infectious at very low levels and has a short incubation period. (viii) Genetic fitness of the spike protein facilitates attachment and fusion. (ix) Existence of polybasic cleavage site in the genome. (x) SARS-CoV-2 elicits myocardial injury and multiorgan failure. (xi) SARS-CoV-2 primarily targets the anatomical vulnerability of the lungs. (xii) Permissiveness of the oral cavity for infection and possibility of virus transmission via saliva. (xiii) SARS-CoV-2 has a short serial interval of 4 days. (xiv) SARS-CoV-2 is very stable on most surfaces. (xv) Ability to resurge and enter into regular circulation after the initial pandemic wave. (xvi) SARS-CoV-2 evolves *in vivo* after infection, promoting virulence, infectivity, etc.	**Weaknesses** (i) Angiotensin-converting enzyme 2 (ACE2) is the sole receptor for SARS-CoV-2. (ii) Host protease processing during viral entry is a significant barrier for several lineage B viruses. (iii) Low basic reproduction number (R_0) of 3.8. (iv) SARS-CoV-2 critically requires porphyrin to inhibit human heme metabolism.
External factors	**Opportunities** (i) Host cellular receptors for SARS-CoV-2 infection are expressed by several important organs in human body. (ii) Ease of travel, globalization, and aviation as potentials for global spread. (iii) Underlying illnesses, age, gender, smoking, and immune suppression are risk factors. (iv) Rumors and misinformation about origin. (v) Knowledge is yet evolving on the underlying pathogenic mechanisms of SARS-CoV-2. (vi) Potential silent transmission via blood and blood products. (vii) No approved COVID-19 vaccine. (viii) Low sensitivity of upper respiratory specimens for detection of SARS-CoV-2. (ix) Confounding pattern of signs and symptoms. (x) Disproportionate "cytokine storm" or damaging evolution of effective defenses. (xi) Potential transmission via fecal-oral route. (xii) Collection, consumption, and trade of wild game.	**Threats** (i) Prohibition of mass gatherings, prompt hospitalization, isolation, and quarantine of infected individual. (ii) Prohibition of all wildlife trade to effectively prevent viral prevalence. (iii) Repurposing proven antimalarial/antiviral/anti-inflammatory drugs. (iv) Deployment of rapid laboratory equipment and procedures for prompt detection (ELISA, Western Blot, PCR). (v) Active contact tracing and monitoring. (vi) Appropriate burial practices according to international best practices. (vii) Sterilization or disinfection of equipment and safe disposal of waste. (viii) Potential antiviral activities of coagulation factor Xa, IIa (thrombin), and convalescent plasma. (ix) Availability of the genome sequences. (x) Global COVID-19 research funding.

Transmission Cycle of SARS CoV 2
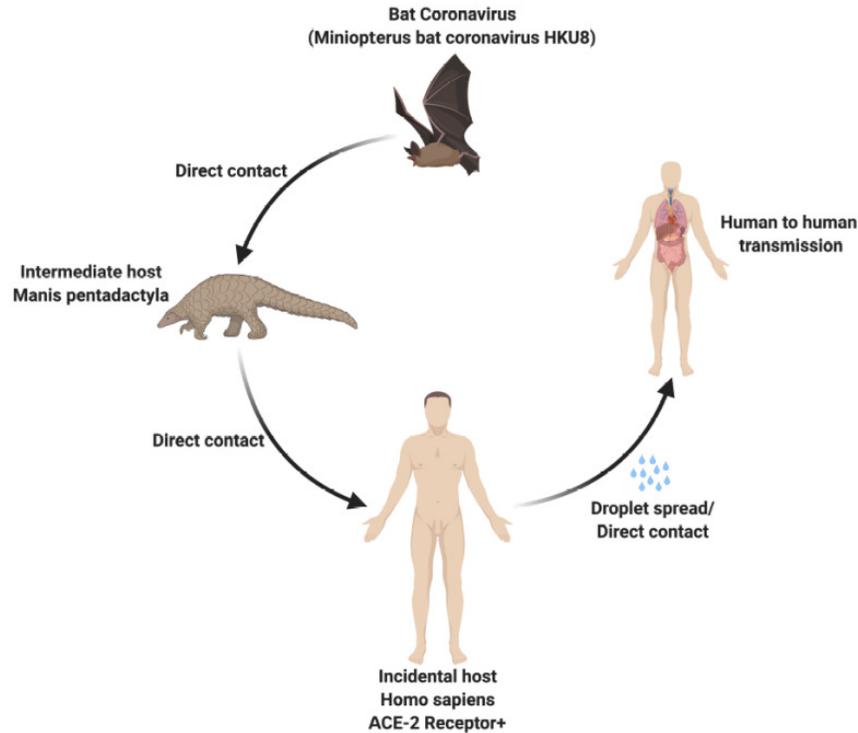
Figure 3. Transmission cycle of SARS-CoV-2.[13] © 2021, StatPearls Publishing LLC; figure contributed by Rohan Bir Singh, MD. This is an open-access publication distributed under the terms of the Creative Commons Attribution License (CC BY 4.0). No changes were made to this figure.

prior immunity to SARS-CoV-2 infection. This theoretically means that the entire human population is potentially susceptible to SARS-CoV-2 infection. Immunological memories to infections are important in immune responses. Therefore, recruitment of memory T-cells is lacking in SARS-CoV-2 exposure-naive individuals. Although development of antibodies (seroconversion) was found after 7 days in 50% of patients (14 days in all), it was not followed by a rapid decline in viral load.[22] This empowers the virus to deride the host prior to the emergence of any protective antibody. Yet, despite the high homology of bat Coronavirus RaTG13 and SARS-CoV-2 in spike sequences, a recent report found that four among the five most important amino acids (L465, L495, Y502, D510, and H514) that bind to ACE2 in Bat-CoV RaTG13 differ from SARS-CoV-2.[23] Furthermore, there is no related research literature to date about whether Bat-CoV RaTG13 can infect humans, making the SARS-COV-2 a unique virus.

Natural reservoir of SARS-CoV-2 is unconfirmed: The natural reservoir of a pathogen is the natural host that harbors the pathogen and in which it replicates without any clinical manifestation of the disease. The

exact origin, locations, and natural habitat (known as the "natural reservoir") of SARS-CoV-2 remain unconfirmed. Recently, it was reported that the sequence similarity between SARS-CoV-2 and the coronavirus isolated from *Rhinolophus affinis* was 96.2%, suggesting that bats may be the source of the virus (**Figure 3**). Further data indicated that the intermediate host between bats and humans was a pangolin (*Manis pentadactyla*, a scaly anteater), an endangered and commonly trafficked mammal, in which genetic recombination or reassortment of the bat and pangolin coronaviruses could have occurred.[24, 25] This was corroborated on February 7, 2020, as it was announced that nucleic acid sequences from a pangolin sample shared 99% similarity with the pandemic human SARS-CoV-2 strain.[26]

Three virulence factors (Nsp1, Nsp3c and ORF7a) interfere with the host's innate immunity and assist SARS-CoV-2 immune escape: In coronaviruses, Nsp1 interacts with the host 40S ribosomal subunit that induces specifically host mRNA degradation and also inhibits type-I interferon production.[27] Nsp3c has the ability to bind with the host's ADP-ribose to help the coronavirus resist host innate immunity.[28]

Research shows that bone marrow matrix antigen 2 (BST-2) can inhibit the release of newly assembled coronavirus from host cells while SARS-CoV ORF7a directly binds to BST-2 and inhibits its activity by blocking the glycosylation of BST-2.[29] Consequently, the trajectory of this evidence suggests that Nsp1, Nsp3c and ORF7a may be potential targets for anti-viral drug discovery.

ORF8 and ORF10 proteins are uniquely associated with SARS-CoV-2: The ORF3b, ORF8, and ORF10 proteins have no homology proteins in SARS-CoVs. They may play a bigger role in the infectivity and pathogenicity of SARS-CoV-2.[30]

SARS-CoV-2 is highly infectious at very low doses and has a short incubation period: COVID-19 spreads through close contact, by direct inhalation of droplet nuclei (containing SARS-CoV-2 virions) that are released when the infected coughs, speaks, yawns, sneezes, or breathes (although the virus may become airborne). Susceptible individuals may also pick up the virus from contaminated surfaces and then inadvertently inoculate the mucosal membranes of the eyes, nostrils, mouth, and possibly other orifices (ear, anus, urethra) of the body. About 10,100 pfu of the virus is sufficient for infection, and the time interval from infection with the virus to the onset of symptoms is 1–14 days, but more often within 3–5 days.[31]

Genetic fitness of the spike protein facilitates attachment and fusion: The critical SARS-CoV-2 spike glycoprotein S is responsible for virus binding and entry. Whether through natural or genetic engineering, the spike protein has been well modified to latch on to human ACE2 enzymes for attachment. Research shows that the receptor binding domain of the spike glycoprotein of pangolin-coronavirus was found to be virtually identical to the SARS-CoV-2 strain, with one amino acid difference as a result of mutation.[32] The S precursor protein of SARS-CoV-2 can be proteolytically cleaved into S1 (685 aa) and S2 (588 aa) subunits. The S1 protein of 2019-nCoV shares about 70% identity with that of human SARS-CoVs while the S2 protein is well conserved among SARS-CoV-2 strains.[33] The highest number of variations of amino acids in the receptor binding domain is located in the external subdomain, which is responsible for the effective direct interaction between the virus and host receptor.[26]

Existence of polybasic cleavage site in the genome: The incorporation of a polybasic cleavage site (RRAR) that enhances pathogenicity makes the SARS-CoV-2 unique among known 'lineage B' beta coronaviruses.[34] SARS-CoV-2 spike glycoprotein harbors a furin cleavage site at the boundary between the S1/S2 subunits, which is processed during biosynthesis. The presence of a furin cleavage site sets SARS-CoV-2's spike apart from SARS-CoV and SARS-related coronaviruses that possess a monobasic S1/S2 cleavage site. This site allows effective cleavage by furin and other proteases and has a role in determining viral infectivity and host range.[35] In addition, a leading proline inserted at this site in SARS-CoV-2 (PRRA) is predicted to result in the addition of O-linked glycans to S673, T678, and S686, which flank the cleavage site and are unique to SARS-CoV-2, thereby impacting the transmissibility and pathogenesis, such as is obtained in the HA spike of avian influenza viruses.[36, 37] The function of the predicted O-linked glycans could create a "mucin-like domain" that shields epitopes or key residues on the spike protein of SARS-CoV-2 such as in HIV, thereby utilizing glycan shields in immune evasion.[38]

SARS-CoV-2 elicits myocardial injury and multiorgan failure: Initial symptom of COVID-19 in some patients include cardiovascular presentation such as heart palpitations, tightness in the chest without respiratory symptoms. Increased cardiac troponin (>28 pg/mL), higher blood pressure (145 mm Hg) and increased creatinine kinase were often recorded as indications of heart injury.[39] Scientists have found that chest computer tomography (CT) scan had high sensitivity for diagnosis of COVID-19. PCR testing sensitivity may be as low as 60-70%.[39] Patients may have pneumonia and CT abnormalities but be initially PCR negative while peripheral focal or multifocal ground-glass opacities affecting both lungs may be observed in up to 75% of patients during the early course of the disease.[39, 40] As ACE2, a type I membrane protein is hijacked by SARS-CoV-2, the primary physiological role in the maturation of angiotensin (Ang), a peptide hormone that controls vasoconstriction and blood pressure is attenuated.[41] Consequently, decreased expression of ACE2 is associated with cardiovascular diseases. SARS-CoV-2 infection and enrichment of ACE2 expression in cholangiocytes (hepatobiliary system) was proposed to potentially lead to direct damage of intrahepatic bile ducts and in COVID-19 patients, mild to moderate liver injury were often reported with elevated aminotransferases, hypoproteinemia and prothrombin time prolongation, in up to 60% of patients.[41, 42]

SARS-CoV-2 primarily targets the anatomical vulnerability of the lungs: The original SARS virus displays less affinity for ACE2 compared to SARS-CoV-2 which has a higher tropism for the highly expressed human ACE2 in the mucous membrane of the alveolar epithelial cells of the lungs (Type II pneumocytes). The spongy nature of the lungs and cell-to-cell fusion of the pneumocytes upon infection, leads to the pathological cellular syncytial formation, fibrosis, symptomatic asphyxiation, hypoxemia, alveolar edema, or pulmonary congestion owing to fluid accumulation and drowning feeling experienced by severe patients.[43, 44]

SARS-CoV-2 has a short serial interval of 4.0 days: Serial interval indicates how long it takes one infected

person at a particular stage of the disease to infect another person to the point of the same stage of the disease. To epidemiologists, the serial interval is the second most important number. The serial interval suggests how rapidly the disease can spread, which in turn determines whether public health officials can identify and quarantine all known contacts of an infected individual. Although the (R_0) of SARSCoV-2 is known, the median serial interval of 4.0 days appears to be short.[45] meaning that the virus has the potential to spread faster, as being witnessed in the current pandemic. The incubation-period distribution of SARS-CoV-2 is 5.0 days.[31, 46] This is higher than the serial-interval, meaning that the infected have started transmitting the virus at pre-symptomatic stage, which consequently makes contact tracing and quarantining difficult.

Permissiveness of the oral cavity for infection and ability of virus transmission via saliva: ACE2 receptors are present and highly enriched in epithelial cells of the tongue, suggesting potentiality of infectious susceptibility of the oral cavity.[47] Similarly, SARS-CoV-2 sequences were reportedly detected in saliva thereby indicating replication in the salivary glands.[30] This portends the potentials of saliva as a vehicle of transmission from asymptomatic cases via dental care, sexual contacts, sharing feeding utensils and spitting.

SARS-CoV-2 is very stable on most surfaces compared to other respiratory viruses: For a respiratory virus to perpetually transmit, it is required that the virus particles remain viable and stable in air and on surfaces long enough after expulsion from the host to be taken up by a fresh susceptible host. The median half-life estimate for SARS-CoV-2 is around 13 hours on steel and around 16 hours on polypropylene. Viable virus could be detected in aerosols up to 3 hours post aerosolization, up to 4 hours on copper, up to 24 hours on cardboard and up to 2-3 days on plastic and stainless steel indicating that SARS-CoV-2 shows relatively long viability on stainless steel and polypropylene compared to copper or cardboard.[48] These show that aerosol and fomite transmission of COVID-19 is plausible, as the virus can remain viable in aerosols for multiple hours and on surfaces up to days.

Ability to resurge and enter into regular circulation after the initial pandemic wave: Mathematical modeling was used to predict the transmissibility dynamics of SARS-CoV-2. Using a two-strain ordinary differential equation (ODE), susceptible-exposed-infectious-recovered (SEIR) compartmental model, and maximum likelihood parameter values, transmission of HCoV-OC43, HCoV-HKU1 and SARS-CoV-2 were simulated for sustained transmission. Model simulations demonstrated that:

1. SARS-CoV-2 can proliferate at any time of year.

2. If immunity to SARS-CoV-2 is not permanent, it will likely enter into regular circulation much like pandemic influenza, possibly in annual, biennial, or sporadic patterns over the next five years.

3. Short-term immunity (40 weeks, similar to HCoV-OC43 and HCoV-HKU1) favors the establishment of annual SARS-CoV-2 outbreaks, while longer-term immunity (two years) favors biennial outbreaks.

4. If immunity to SARS-CoV-2 is permanent, the virus could disappear for five or more years after causing a major outbreak. If SARS-CoV-2 induces cross immunity (70%) against HCoV-OC43 and HCoV-HKU1, the incidence of all betacoronaviruses could decline and even virtually disappear.

5. Low levels of cross immunity from the other betacoronaviruses against SARS-CoV-2 could make SARS-CoV-2 appear to die out [49], only to resurge after a few years (possibly in 2025).

Therefore, longitudinal serological studies are urgently needed to determine the duration of immunity to SARS-CoV-2.[49] In addition, even if the outbreak appears to die out after this first pandemic wave, SARS-CoV-2 surveillance should be maintained.

SARS-CoV-2 evolves in vivo after infection, promoting virulence, infectivity, and transmissibility: By metatranscriptome sequencing of the genomes of SARS-CoV-2 samples in the current pandemic, the intra-host variants per individual patients ranged from 0 to 5 with a median number of 4, suggesting a high evolution rate of the virus.[50] As with other RNA viruses, SARS-CoV-2 undergoes a strong immunologic pressure in humans, and may thus accumulate mutations that could result in changes in viral virulence, infectivity, drug resistance and transmissibility to outmaneuver the immune system.[51, 52] The mutation rate of SARS-CoV-2 is yet unclear, but it is suggested to be at the same order of magnitude (0.80-2.38×10-3 nucleotide substitution per site per year) in SARS-CoV.[53] Observation of shared intra-host variants among different individuals implied the possibility of adaptive evolution of the virus in patients, which could potentially affect the antigenicity, virulence, and infectivity of the virus.[52] Similarly, mutations in the RNA-dependent-RNA-polymerase (RdRp) gene (nsp12) were reported in isolates from patients in North America, England and Italy. This suggests that the virus is evolving, with potential effects on antiviral drugs targeting the RdRp.[54] Roman *et al.* reported independent virus replication by consistent detection of sequence-distinct virus populations from the throat and lung samples of the same patient, thereby substantiating the evolution of quasi-species. [22] Thus, the SARS-CoV-2 genome in patients could be highly diverse, as also observed in other RNA viruses such as HIV with circulating recombinant forms. The high diversity could potentially

increase the fitness of the viral population, making the elimination difficult.

Conjunctival and conjunctival discharges (or tears) are potential sources of exposure and contamination: COVID-19 may be confusing, as it mimics conjunctivitis associated with Adenovirus infection. Recent findings indicated that SARS-CoV-2 infection might present ocular signs such as photophobia, irritation, conjunctival infection, and watery discharge, which are potential sources of contamination and infection in about 1-2% of COVID-19 cases.[55, 56] Therefore, extreme caution is recommended in ocular discharge transmission and contraction of COVID-19.

Weaknesses of the Severe Acute Respiratory Syndrome Coronavirus 2

Weaknesses are the characteristics that places the virus at a disadvantage, relative to the host and the environment. The virus weaknesses detract it from its ability to attain the core goal, and influence its infectivity, replication, and establishment. Essentially, the attributes of SARS-CoV-2 that present as "Achilles' heel" and targets for elimination (**Table 1**) are as follows.

Angiotensin-converting enzyme 2 (ACE2) is the sole receptor for Spike protein of the emergent SARS–CoV-2: So far, three membrane exopeptidases—Dipeptidyl peptidase-4 (DPP4), ACE2, and Aminopeptidase N (APN)—have been identified as entry receptors for human-infecting coronaviruses.[57] Among these cellular receptors, the angiotesin-converting enzyme 2 (ACE2) is the most potent and specific for SARS-CoV-2 [58], although research is ongoing about the use of basigin (CD147) as a novel route by SARS-CoV-2 to also assist in host cell entry. ACE2 entry is lineage B clade 1 specific. Studies have shown that protease treatment only enhanced entry of clade 1 RBDs on cells expressing human ACE2, but not human DPP4 or APN.[59] The requirement for this indispensable receptors renders the virus vulnerable to molecules or neutralising antibodies that would block acess to the ACE2 protein or that will coat the S1 domain of the viral ligand, thereby preventing attachment.[60]

Host protease processing during viral entry is a significant barrier for several lineage B viruses: For betacoronaviruses, a single region of the spike protein called the receptor-binding domain (RBD) mediates the interaction with the host-cell receptor. After binding the receptor, a nearby host protease cleaves the spike that releases the spike fusion peptide, thereby facilitating virus entry.[60, 61] The RBD of lineage B betacoronaviruses is a single, continuous domain that contains all of the structural information necessary to interact with the host receptor. Consequently, synthetic antiviral drugs that will bind a fusion protein and prevent its elaboration, such as a protease inhibitor, to prevent

cleavage by the protease and elicit abortive infection, such as in oseltamivir (influenza antiviral drug) will be of great value.

Low basic reproduction number (R$_0$) of 3.8: The SARS-CoV-2 is a highly contagious virus (although much less than measles) and one of the currently known most infectious human viruses to which there is no vaccine. However, it has a low reproduction rate compared to MERS-CoV and Ebola virus. The current estimates of the basic reproduction number (the number of people that 1 infected person can infect during its infectious period, R$_0$) are between 1.4 and 3.77 persons.[62] This means that each infection from the virus is expected to result in 1.4 to 3.8 new infections in an unexposed population, when no preventive measures are taken.

SARS-CoV-2 critically requires Porphyrin to inhibit human heme metabolism: Research literature shows that SARS-CoV-2 is dependent on porphyrins, thereby suggesting that it may have originated from an ancient virus. As the virus' ORF8 and surface glycoprotein binds to the porphyrin, the orf1ab, ORF10, and ORF3a proteins coordinately attacks the heme on the 1-beta chain of hemoglobin to dissociate the iron at the same time, to form and capture the porphyrin. The attacks reduce hemoglobin levels that carry oxygen and carbon dioxide. Consequently, the pneumocytes have extremely intense poisoning and inflammation due to the inability to exchange carbon dioxide and oxygen, leading to ground-glass-opacification of the lungs, inhibition of human heme metabolism and eventual disease.[63] Stemming from this requirement, to effectively relieve the symptoms of respiratory distress, chloroquine has been found to prevent orf1ab, ORF3a, and ORF10 in attacking the heme, thereby preventing availability of the porphyrin and as well inhibit the ORF8 and surface glycoproteins from binding to porphyrins.[63] In addition, presence of high level of glycated hemoglobin or deoxyhemoglobin (a combination of hemoglobin and blood glucose) in older people and diabetics is another reason for the high infection rate in those groups of patients.

Opportunities for the Severe Acute Respiratory Syndrome Coronavirus 2

Opportunities are the chances to make greater gains in the environment, that is, external attractive factors that represent the reason for SARS-CoV-2 to exist, infect and spread. Opportunities arise when the virus can take benefit of conditions in its environment to infect and execute strategies that enables it to become established and spread. The various host and environmental factors (**Table 1**) harnessed for infection by SARS-CoV-2 are as follows.

Several important organs in the human body express host cellular receptors for SARS-CoV-2 infection: SARS-CoV-2 selectively targets the ACE2 proteins that are constitutively expressed by several important organs in human body. Most importantly, different levels of ACE2 receptor expression exist in the colon, gall bladder, heart, kidney, epididymis, breast, ovary, lungs, prostate, esophagus, tongue, liver, pancreas, and cerebellum. These present opportunities for the virus to replicate in the target sites subsequent upon systemic dissemination of SARS-CoV-2 which may circulate through the blood and then attack ACE2 receptors in the endothelia cells of blood capillaries in the brain, breaching the blood-brain barrier and invading neurons. Therefore, all these organs with ACE2 expression are subject to infection with attendant pathological effects such as disseminated intravascular coagulation (DIC), olfactory and gustatory perception impairments and probable long-time neurological dysfunction even after recovery.[64]

Ease of travel, globalization, and aviation as potentials for global spread: Frequent air travel or road transport are major risk factors to the global spread of infectious diseases. It is feasible to visit as many as three countries in a few hours and spread infectious pathogens. In contrast to airlines, public trains, buses, etc., are rarely fitted with high efficiency particulate air filters (HEPA). It is not only humans that travel: the International Air Transport Association estimates that around 80,000 caught wild animals are air freighted each year; many being placed in holding facilities close to populated areas whilst in transit.[65] The potential routes of transmission of infectious agents on board are mainly by inhalation of droplets nuclei, direct contact with organic residues, indirect contact with respiratory secretions and other biological fluid-contaminated surfaces. Adventure touring or ecotourism, international importation by air and cruise-ship travels have been documented in the spread of diseases to humans. In the current SARS-CoV-2 pandemic, many of the cases outside of China were linked to travels. A particularly large outbreak occurred among the passengers and crew of the *Diamond Princess* cruise ship, where more than 700 COVID-19 infections were reported during the Spring Festival transportation peak in China.[66] Index cases in many African countries were imported from overseas travelers prior person-to-person transmission and community spread. A cluster of COVID-19 outbreaks were also detected in Hawkeys Bay, New Zealand, that was epidemiologically linked to a Ruby Pincess cruise ship that sailed on to Australia with more than 439 cases and 7 deaths. Once the virus is introduced to a passenger or crew member on board, the ship becomes a perfect incubator.

Underlying illnesses, age, gender, smoking, immune suppression, and blood grouping: Hypertension, diabetes mellitus, cardiovascular disease and lung cancer are proven conditions that present opportunities to severe COVID-19 disease. Elderly patients with hypertension, coronary heart disease or diabetes have higher risk of infection (58% hypertension, 25% heart disease, 44% arrhythmia). Early estimates showed that about 80% of those who died were over the age of 60, and 75% of them had pre-existing health conditions such as cardiovascular diseases and diabetes.[67] SARS-CoV-2 infects host cells through ACE2 receptor. When the spike protein binds to ACE2, it reduces ACE2 expression, thereby inducing cellular shedding of the receptor, induction of TNF-a production and viral entry into host cells. Reduction of ACE2 results in pathophysiology in the lungs, blood pressure, renal function impairment and aldosterone-dependent blood sugar dysregulation which may result in COVID-19-related pneumonia, acute myocardial injury, and chronic damage to the cardiovascular system. Therefore as the virus replicates and decreases ACE2 levels, low ACE2 aggravates heart dysfunction, hypertension, diabetes mellitus, prostate and lung cancers. Therefore, the trade-off is to either increase ACE2 synthesis or allow it at the level of the pathogen. However, ACE2 levels can be increased by the use of RAS inhibitors as antihypertension therapy with ACE inhibitors or angiotensin-receptor blockers but the disease become severe in such compromised individuals.[67] Furthermore, the ACE2 enzyme is expressed in type II alveolar cells, and some data suggest that Asian males have a large number of ACE2-expressing cells in the lungs, which may partially explain the male predominance of COVID-19. However, other factors such as a higher prevalence of smoking among men in China may explain the difference in the sex distribution of the disease. Furthermore, research found that individuals with blood group A were more susceptible to SARS-CoV-2 infection than blood group O. Therefore, emphasis should be considered for protecting people with prior illnesses, older age, smokers, blood group A, poor hygiene and eating habits.

Rumors and misinformation about origin of SARS–CoV-2: Conspiracy theories on social media and sensationalist reporting, suggesting that COVID-19 does not have a natural origin are challenging efforts of outbreak response. Scientists have made concerned statements over the spread of yet unsupported claims that the new coronavirus, SARS-CoV-2 was created and leaked from a laboratory in Wuhan, China. Spread of misinformation and conspiracy theories have generated panic and mistrust among the general public, diverted attention away from the outbreak response, and impeded the activities of health-care workers. Researchers from multiple countries have published and analyzed genomes of SARS-CoV-2, and they overwhelmingly concluded that this Coronavirus originated in wildlife. On March 17, 2020, scientists reported that the novel SARS-CoV-2 virus originated *naturally*, and is not a laboratory construct or a purposefully manipulated virus.[35, 68]

Knowledge is yet evolving on the underlying pathogenic mechanisms of SARS-CoV-2: As an emerging pathogen scientists are still in the course of understanding the underlying pathogenic mechanisms of SARS-CoV-2.[69] In-depth knowledge will reveal more targets for better therapy of COVID-19.

Potential silent transmission via blood and blood products: SARS-CoV-2 was initially isolated in samples of bronchoalveolar lavage fluid and viral RNA has thereafter been detected in nasopharyngeal and throat swabs as well as in serum, blood, rectal swabs, saliva, urine, and stool.[70, 71] SARS-CoV-2 is a respiratory pathogen with inherent ability to disseminate via plasma or serum. This will impact negatively on substances of human origin (SoHo). While it seems that the risk of SARS-CoV-2 transmission through SoHO is very low, uncertainties about viraemia during the incubation period, during an asymptomatic course of infection, or after symptom resolution continue to be of concern in relation to the safety of SoHO. Therefore, a theoretical risk of transmission of Coronaviruses through the transfusion of labile blood products is emphasized as a small percentage of blood samples had positive PCR test results, suggesting that infection sometimes may be systemic.[72] Therefore matters arising from these involve the inclusion of screening for SARS-CoV-2 in potential blood donors or virus inactivation and removal in blood products or plasma derivatives before transfusion or in organ donor and transplantation.

No vaccine has yet been approved to treat human COVID-19: Several options can be envisaged to control or prevent emerging infections of SARS-CoV-2, including vaccines, monoclonal antibodies, oligonucleotide-based therapies, peptides, interferon therapies and small-molecule drugs. The magnitude of the current pandemic of COVID-19 and the likelihood of future human exposures, underscores the necessity for pre- and post-exposure therapeutics.[73] Historically, vaccination is the best option in controlling viral diseases when epidemics refuse to self-attenuate. Therefore, the absence of proven vaccines constitutes an opportunity for the virus to deride the host. In developing a vaccine against the disease, inactivated or attenuated virus particle-based preparation is advisable. This can be achieved by large-scale, regulated laboratory culture of SARS-CoV-2 in a BSL-4 facility and then inactivated by either UV light, formaldehyde or β-propiolactone. Alternatively, the process to attenuate by several passages and carefully screen the serially propagated viruses for competent immunogenicity and reduced pathogenesis (induced minimal lung injury, diminished limited neutrophil influx, and increased anti-inflammatory cytokine expressions) compared with the wild-type virus would also prove viable.[74] However, new interventions are likely to require months to develop but it is hoped that as soon as other FDA approved drug (in addition to Remdesivir)

or vaccine is found, the rage of the virus would be curtailed.

Confounding pattern of signs and symptoms with common diseases complicate diagnosis: Variability of clinical presentations complicate early detection and management of COVID-19 as it mimicks the presentation of other common respiratory diseases. Early signs of SARS-CoV-2 infection are nonspecific and mimicks other acute respiratory illnesses such as RSV, SARS-CoV, Influenza, MERS-CoV and even typhoid fever. In patients with COVID-19, blood tests typically show leukopenia and lymphopenia and most chest computed tomography scans show ground-glass opacities and consolidation with bilateral lung involvement. These characteristics are also shared by influenza A and other respiratory viruses.[67, 75] Mild and presymptomatic cases might easily remain undetected, especially during the influenza season when respiratory symptoms are common.[76] COVID-19 is characterized by sudden onset of fever (>390C), chills, fatigue, exhaustion, sore throat, headache, and joint/muscle aches. Late signs are asphyxiation, pneumonia, kidney failure, septic shock, and death.[8] The major difference between SARS-CoV-2 and her predecessors is that this virus symptomatically elicits dry cough and rarely produces rhinorrhea in those infected, which are common in MERS and SARS cases. Co-infection of SARS-CoV-2 and influenza A virus has been reported, thereby demonstrating additional challenges to detection, especially when patients test negative for SARS-CoV-2 but positive for another virus. Therefore, in addition to the non-specific symptoms, COVID-19 might be underdiagnosed because of false-negative results or co-infection with other respiratory viruses.[77]

Low sensitivity of upper respiratory specimens for detection of SARS-CoV-2: Diagnosis of COVID-19 is made mainly on the basis of nucleic acid detection from nasopharyngeal swabs. A previous report indicated 2 challenges in the diagnosis of COVID-19. First, the sensitivity of tests to detect SARS-CoV-2 from upper respiratory specimens might be insufficient and two, repeated rRT-PCR testing of nasopharyngeal swabs were usually negative for SARS-CoV-2. In that report, SARS-CoV-2 was finally identified by using metagenomic next-generation sequencing (mNGS) and rRT-PCR of a bronchoalveolar lavage fluid (BALF) sample. This was achieved with the persistence of the Clinician because of the patient's travel history. Therefore, suitable sputum or BALF specimens are necessary to maximize detection in cases of high clinical suspicion for identifying SARS-CoV-2 because the highest viral loads were found in sputum with moderate loads in nose-throat swabs.[72] Testing of specimens from multiple sites may improve the sensitivity and reduce false-negative test results.

Disproportionate or damaging evolution of effective defenses against the virus ("Cytokine storm"): The balance and timing of early immune responses to infection play a critical role in determining the outcome of infections. In some cases, a reaction takes place which as a whole is labeled a 'cytokine storm' that results in extensive tissue damage. The protagonist of this storm is interleukin 6 (IL-6), produced by activated leukocytes and acts on a large number of cells and tissues. The major role of IL-6 is pro-inflammatory, it increases during inflammatory diseases, infections, autoimmune disorders, cardiovascular diseases, and some types of cancer. It is also implicated in the pathogenesis of the cytokine release syndrome (CRS) that is an acute systemic inflammatory syndrome characterized by fever and multiple organ dysfunction. Pathological investigation on a COVID-19 patient using peripheral blood flow cytometric analysis shows hyperactivated CD4 and CD8 T cells with increased concentration of highly proinflammatory CCR6+ Th17 in CD4 T cells, while the CD8 T cells were found to harbour high concentrations of cytotoxic granules and were perforin/granulysin positive.[78] These imply that overactivation of T cells, manifested by increase of Th17 and high cytotoxicity of CD8 T cells, accounts for, in part, the severe immune injury in the patients.[78] In the case of septic shock in COVID-19, fatal infection of humans appears to be associated with an elevation or overproduction of anti-SARS-CoV-2 pro inflammatory cytokines, TNF-α, and alveolar macrophages, among others. If SARS-CoV-2 elicits damaging host responses particularly in the elderly, then therapeutic interventions that modify those responses may help the immune system to control viral replication and achieve survival.

Potential silent transmission via the fecal-oral route: Transmission of SARS-CoV-2 by respiratory and extrarespiratory routes may be responsible for the rapid spread of COVID-19 disease. Prior to respiratory symptoms, many patients reported diarrhea, nausea, vomiting and abdominal discomfort. Immunofluorescent studies show ACE2 receptors in glandular cells of gastric, duodenal, and rectal epithelia. ACE2 had been reported to be co-localized with TMPRSS2 in absorptive enterocytes and upper epithelial cells of esophagus. The first USA confirmed case had a 2 day history of nausea, vomiting and dry cough while SARS-CoV-2 sequences were detected from the stool.[71] Similarly, in a previous study, out of 73 patients, 39 tested positive in the stool (10-78 years of age) for 1-12 days while 17 patients remained positive in the stool even after negative respiratory samples. The live virus was detected in feces, implying that SARS-CoV-2 may be transmitted by the fecal-oral route and possibly urine.[41] Therefore, generation and inhalation of bio-aerosols during flatulence or flushing of the commodes should be avoided and it may be shown that individuals should not use the toilet immediately after use by another person.

Collection, consumption, and trade of wild game: The index cases of several viral diseases outbreaks have been more or less directly associated with hunting, trading, or consumption of bush meat such as monkeys, antelopes, and bats.[79] The SARS, which has shown its potential in China as a respiratory and gastrointestinal disease, was because of the illegal trade of wildlife, where an infected masked palm civet (*Paguma larvata*) was the culprit for the spread of SARS.[80] The index case of the initial Coronavirus disease 2019 (COVID-19) were epidemiologically linked to exposure to Wuhan's Huanan seafood market in China, where wild animals are traded and SARS-CoV-2 infections have been detected in dogs, cats, ferrets, and tiger.[81] As activities like hunting wild animals and consumption of game meat/ bush meat result in the spread of zoonotic diseases to humans, about 13,000 pounds of bushmeat were estimated to be imported into the UK annually. Therefore, the trade and consumption of 'bushmeat' should be highly regulated as these could serve as sources of outbreak in the respective destinations.

Lack of emergency preparedness, infection control practices and paucity of health infrastructures: Owing to misplacements of priorities, the dearth of funding, lack of test kits, medical equipment, and accessories (e.g. ventilator), COVID-19 patients were often cared for without the use of personal protective equipment (face masks, gowns, gloves, goggles, disposable suits, boots, etc). These risks expose health care providers to infections and hastens the spread and death in severe cases. Developing economies, especially African, should establish effective and functional public health facilities with the appropriate advanced infrastructure and virologists to cope with emergency situations and emergency preparedness. Disease surveillance, intelligence and monitoring in human and animal populations should be mandatory. Social mobilization and awareness campaigns should also be strengthened to dispel dangerous rumors that encourage spread of dangerous infectious diseases.

Overcrowded institutions, military establishment, warships, camps, and correctional facilities are potentially vulnerable: As a respiratory virus, the person-to-person transmission in crowded, overcrowded, and confined environments can be exponential. Educational institutions, correctional facilities (prisons) and military camps are formidable environments for COVID-19 ravage. COVID-19 infection was first detected on a Naval vessel at sea on March 24, 2020 aboard the US Nuclear Naval ship Aircraft carrier (Theodore Roosevelt) with reported outbreak among the crew of more than 4,000 on March 31, 2020 at Guam.[82] The outbreak was a dangerous phenomena altogether considering the inherent limitation of space in warships, usually full of weapons, with billion of dollars of equipment, where those positive cases

jumped exponentially, where fire hazards and nuclear reactors are present, where quarantine and social distancing is also impossible. Tight quarters in warships make the virus conducive to spread among large numbers of sailors in a confined space sharing sleeping quarters, restrooms, workspaces, and mess hall, with potential susceptibility to reinfection even after recovery. To avert unwarranted spread of COVID-19 in prison facilities of Nigeria, Indonesia and several other countries, some inmates were set free by the Government.

Threats to the Severe Acute Respiratory Syndrome Coronavirus 2

Threats are external elements in the environment that could cause trouble for SARS-CoV-2. That is, external factors, which make the virus vulnerable, beyond the pathogen's control, which could place the virus' mission or operations at risk. Essentially, the external conditions that are inimical to SARS-CoV-2's establishment, and which may be harnessed for elimination of the virus as presented in **Table 1**, include the following.

Prohibition of mass gatherings, prompt hospitalization, isolation, and quarantine: Quarantine is regarded as enforced isolation of areas or individuals who may be infected. It may involve closure of schools, markets, worship congregations, relaxation centres, conferences and sports competitions, as well as total shutdown of the system or lockdown of countries. In addition, social/physical distancing, use of face masks, respiratory etiquete and hand hygiene are milestones in reducing transmission of the virus. In the implementation of these threats, the ethical and social aspects should not be overlooked. Required isolation of patients to avoid transmission should not be seen as segregation and palliative measures must be put in place to avoid revolts.

Prohibition of all wildlife trade to effectively prevent viral prevalence: The pathogens of SARS-Coronavirus and SARS-CoV-2 are both derived from wild animals. Therefore, hunting, selling, and eating wild animals not only seriously damage the ecosystem, but also lead to the spread of epidemic diseases.

Repurposing proven Antimalarial/Antiviral/ anti-inflammatory drugs: Small-molecule agents for treating other human diseases may modulate the virus–host interactions of SARS-CoV-2. A number of proven drugs against some diseases are being tested with the aim of using such to treat COVID-19. Some of these drugs include remdesivir first developed for Ebola virus treatment (is now approved by the FDA for COVID-19); interferon alfa-2b currently used for Hepatitis C with efficacy in animal models against MERS-CoV; combination of lopinavir and ritonavir (Kaletra) for HIV-AIDS; favipiravir for Influenza; sarilumab;

chloroquine and azithromycin are now being tested.[9] Chloroquine**,** an approved immune modulator has been shown to demonstrate inhibitory effects against SARS-CoV-2 (EC_{50}=1.13 μM in Vero E6 cells) and evaluation in an open-label clinical trials with COVID-19 patients was promising, although an observational study did not show a benefit.[83-85] With EC_{50} of 1.13 μmol/L and selectivity index (SI) greater than 88, chloroquine can effectively inhibit pH dependent endocytosis of SARS-CoV-2 in the cell level as chloroquine phosphate turns into chloroquine in the body and target the virus' Nsp3b or E-channel to play therapeutic effect.[84] Darunavir is an HIV-1 protease inhibitor that selectively inhibits the cleavage of HIV-encoded Gag-Pol polyprotein in virally infected cells, thereby preventing the formation of mature infectious virus particles. At a concentration of 300 μmol/L, darunavir can significantly inhibit virus replication while the docking results showed that the possible targets were Nsp3c, PLpro, E-channel or spike proteins.[86] Umefenovir (Arbidol hydrochloride) is a broad-spectrum anti-viral drug, mainly for the treatment of influenza A and B viruses, but effective against SARS-CoV and MERS-CoV. Arbidol blocks virus replication by inhibiting the fusion of the lipid membrane of the virus with the host cells and effectively inhibited Coronavirus up to 60 times at a concentration of 10–30 μmol/L, thereby preventing the virus's pathological effects on cells while the docking results with the possible drug targets of the SARS-CoV-2 showed interaction with Nsp7_Nsp8 complex, Nsp14, Nsp15, E-channel, or the spike.[86] Considering the challenges with vaccine development, it is pertinent to consider further research into exploiting a shift from the current paradigm of 'profitable Pharma model' in medicine to a worldwide integrative /alternative / holistic medical practitioners "in the field" for their experiences in treating otherwise difficult to treat infections, and a fair review for consideration of traditional, complementary and alternative drugs.

Deployment of rapid laboratory equipment and procedures for prompt detection (ELISA, Western Blot, PCR): A number of diagnostics and techniques are currently available for laboratory diagnosis of COVID-19. Acute infection is diagnosed by RT-PCR tests to detect viral antigens. These tests can be positive from day 3 to 14 days of infection. These technologies and personnel should be made available for use. Development and deployment of Rapid point of care diagnostics (such as Immunochromatographic EIA kits) will help in overcoming challenges of weak surveillance. This will also facilitate testing, and retesting for decisions on isolation, quarantine, treatment, and discharge as appropriate.

Active contact tracing and monitoring: Contact tracing involves finding everyone who had contact with infected individuals and watching / monitoring for signs of illness for 21 days, usually 14 days. Contacts in-

clude close, casual, and distant. If any of the contacts comes down with the ailment, they should be isolated, tested, and treated. The process is then repeated by tracing the contacts' contacts.[87] In respect of Ship, buses or air travels, as direct contact is the main route of transmission for COVID-19, only the passengers who were seated in direct proximity to the index passenger should be included in the trace-back, i.e. only passengers who were one seat away from the index case (± 1 seat in all directions) should be traced back. If the index case occupied an aisle seat, the three passengers seated directly across the aisle from the index case should also be traced back, as in cases of other virulent viruses.[88]

Appropriate burial practices according to international best practices: To avoid excessive manipulation of the body, embalming is not recommended. People who have died from COVID-19 can be buried or cremated only as a matter of cultural choice, available resources, and national and local requirements that may dictate the handling and disposition of the remains.[89] Health care workers, mortuary staff or families, and traditional burial attendants (e.g. family member or religious leader) preparing the deceased (e.g. washing, cleaning or dressing body, tidying hair, trimming nails or shaving) should wear appropriate PPE according to standard precautions (gloves, impermeable disposable gown [or disposable gown with impermeable apron], medical mask, eye protection including the use of face shield or goggles) for any activity that may involve splashing or leakage of bodily fluids.[89] Anyone who has assisted in preparing the body should thoroughly wash their hands with soap and water when finished. Family and friends should reduce their exposure as much as possible and may view the body after it has been prepared for burial, in accordance with customs at a minimum distance of 1 m. They should not touch or kiss the body and should wash hands thoroughly with soap and water after the viewing. Children, older people (>60 years old), and anyone with underlying illnesses (such as respiratory illness, heart disease, diabetes, or compromised immune systems) should not directly interact with the body. Burials should take place in a timely manner with limited number of participants, in accordance with local practices. Participants should observe physical distancing at all times, plus respiratory etiquette, and hand hygiene. Those tasked with placing the body in the grave, or the funeral pyre, should wear gloves and wash hands with soap and water after removal of the gloves once the burial is complete. Funeral ceremonies should be postponed, as much as possible, until the end of the epidemic. The belongings of the deceased person should be handled with gloves and cleaned with a detergent followed by disinfection with a solution of at least 70% ethanol or 0.1% (1000 ppm) hypochlorite.[89]

Sterilization or disinfection of equipment and safe disposal of waste: Like other Coronaviruses, SARS-CoV-2 is sensitive to ultraviolet rays and heat. It can be effectively inactivated by lipid solvents including ether, ethanol, chlorine-containing disinfectant, peroxyacetic acid and chloroform. Appropriate concentration of calcium or sodium hypochlorite (a lipid solvent, an inactivating agent which distrupts the viral envelope, the ligands, and in effect subsequent attachment and infectivity) is effective to decontaminate the premises and disinfect equipment and other materials exposed to biological contamination with SARS-CoV-2. Patient' excretions should be disposed of properly, and hands washed frequently using soap and water for 20 seconds, as well as hand sanitizers containing at least 60% ethanol or 70% isopropanol.[90] Used articles, beddings and linens should be machine washed with laundry detergent and warm water at 60–90°C (140–194°F), dry and disinfected.[89]

Potential antiviral activities of Coagulation Factor Xa, IIa (thrombin) and convalescent plasma: Coagulation Factor Xa and IIa (thrombin)were shown to cleave and activate the Spike S protein of Coronavirus into S1 and S2 domains, thereby facilitating cellular infectivity.[91] This finding was employed recently by Ai *et al.* who identified "Dabigatran" as a possible therapeutic for COVID-19.[39] Similarly, the possible benefit of dipyridamole (anticoagulant) for COVID-19 was also reported.[92] Convalescent plasma or immunoglobulins have been used as a last resort to improve the survival rate of patients with SARS, and recovered from Ebola virus disease was recommended by WHO as an empirical treatment during Ebola outbreaks while a protocol for the use of convalescent plasma in the treatment of MERS was established in 2015.[73] Following these previous successes, these treatment strategies can also be adapted in the current fight against COVID-19.

Availability of the genome sequences of SARS–CoV-2: The genome composition and divergence of the novel coronavirus was determined by sequencing in mid January in China as well as in Australia, Philipines and USA, while cryo-EM technique has revealed the atomic structure of the spike protein of SARS-COV-2.[93, 94] As of March 2020, 183 genome sequences of the SARS-COV-2 isolates around the world have been provided in the GenBank. These rapid achievements provide information that will specifically help in development of appropriate diagnostic tests, therapeutics, and vaccine design against the virus.[95]

Global COVID-19 research funding: The outbreak has prompted WHO and some other major global and national health organizations to announce the research on COVID-19 as a priority with dedicating huge funds for the related investigations. A meeting for the assessment of current knowledge on this viral disease and determining the research directions was held by WHO in

collaboration with GloPID-R (the Global Research Collaboration for Infectious Disease Preparedness) with the participation of scientists from various disciplines and funders from different parts of the world.[96] Individual countries are taking the initiatives in providing fundings for research as well as mitigating the impacts of lockdown and shutdown while philantropists around the world are donating money, equipment, reagents, test kits, personal protective equipment, and so on, to overcome this "millenium enemy against humanity."

Conclusion

As in any battle, knowing the enemy is a major step for defeating it. There are still many unknowns about the emergent SARS-CoV-2. Great efforts are being taken to elucidate the virus behavior, transmission, biological strenghts, opportunities for infection and other aspects. As a paradigm shift, the SWOT concept can be adopted to help us as scientists to formulate and apply strategies that augment our research and enable us to understand and combat emerging and/or recalcitrant infectious diseases. This research contributes answers to some of the questions that borders on exposing the "Achilles heel" of the virus for interventions in eradication of the COVID-19 pandemic.

The identified capacities and gaps presented in this study are an inexhaustive framework to combat the SARS-CoV-2 virus and COVID-19. Mankind is dealing with a major threat to human life on earth, and a transboundary human and animal disease that could easily be turned into a bioweapon. Committed research communities can and will tap from these findings, in addition to established foundational knowledge, to guide appropriate responses to the COVID-19 challenges.

It is pertinent to state that SARS-CoV-2 explores its biological strengths, conserves its weaknesses, and exploits host opportunities to decimate human population to the extent that within 5 months, over 310,082 lives have been lost to this virus around the world. To undermine and overcome the virus, research focus should be aimed at strategically crushing the strengths and opportunities that are helpful to SARS-CoV-2 in achieving the pathogenic objective, while increasing further the weaknesses of, and threats to the virus that are harmful to achieving the pathogenic objective.

Research scientists, the academia and the industry should scale up all promising research findings by holistically harmonising all the identified factors, putting them into perspective and build more on threats to the virus.

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