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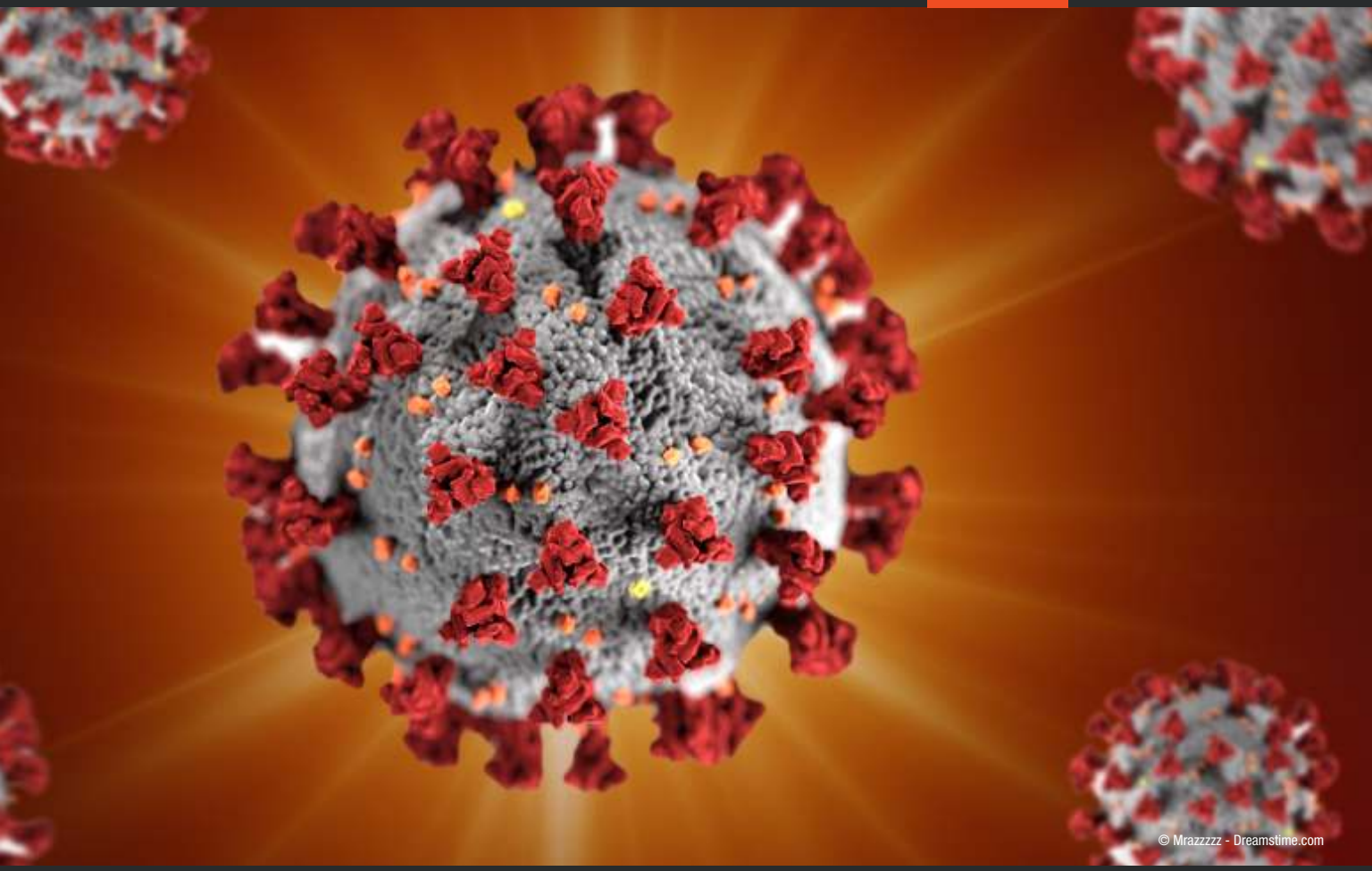

COVID-19: Part 1—Separating science fact from science fiction

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Abstract

With the rapid pandemic incited by SARS-CoV-2, which causes the disease COVID-19, widespread governmental and societal changes have affected much of our society. Airborne transmission of respiratory diseases has been shown to contribute to community spread of COVID-19 and respiratory diseases overall are common, causing up to 6 million deaths annually.[1] While the current pandemic is caused by a virus that is similar to previous viral causes of epidemics/pandemics, it appears to be unique in its characteristics regarding the clinical presentation of the infection. SARS-CoV-2 is a coronavirus, and understanding the virology associated with this particular virus is critical to evaluating the biologic rationale for future interventions. This continuing education course will review the current status of understanding regarding the SARS-CoV-2 virus, its activity with host cells, and potential biologic targets for future interventions.

Educational objectives

Upon completion of this course, the dental professional should be able to:

- Discuss the current understanding of the structure and function of the SARS-CoV-2 virus.
- List related viruses and the diseases they caused.
- Understand the differences in infectivity and viral activity between SARS-CoV-1 and SARS-CoV-2.
- Develop an understanding of the potential therapeutic targets for SARS-CoV-2.

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Introduction

A novel β-coronavirus (SARS-CoV-2) causing severe and potentially fatal pneumonia (COVID-19) purportedly originated in a seafood market in the city of Wuhan, Hubei province, China, and has demonstrated pandemic spread throughout the globe.[2–4] The typical clinical symptoms of patients who became symptomatic after SARS-CoV-2 infection included loss of smell/taste, nausea/vomiting, fever, dry cough, mylagias, and fatigue. In cases of pneumonia, these symptoms are often accompanied with abnormal chest computerized tomography (CT).[5–7] Less common symptoms included sputum production, headache, hemoptysis, and diarrhea.[5–7]A zoonotic origin for SARS-CoV-2 is presumed to be a native virus in the bat *Rhinolophus affinis*, as the human virus demonstrates 96.2% of whole-genome identity to BatCoV RaTG13, and this novel virus demonstrates over 99% genetic similarity to β-corona virus (b-CoV) samples found in pangolins (scaly anteaters).[8,9] It is suspected, based upon the current evaluations of the viral fingerprint, that the virus was initially present in bats and that pangolins were a secondary vector prior to transmission to humans.[8,9] While these data strongly suggest a zoonotic source, the ultimate species-level source of the virus is currently unknown. The understood person-to-person transmission routes of SARS-CoV-2 include direct transmission, such as cough, sneeze, saliva, and other droplet inhalation transmission, and contact transmission, such as contact with oral, nasal, and eye mucous membranes.[10–13]

What we know and what we do not know

A novel β-corona virus emerged in China in late 2019 and, as of this publication, has caused over 17 million diagnosed cases of its associated disease, COVID-19, worldwide.[2–4] Trends indicate that one in four people may be asymptomatic and/or exhibit very mild symptoms and that these individuals may be fueling the spread of disease.[14] While limited testing of individuals makes characterizing overall infection rates and mortality rates difficult, the mortality rate of COVID-19 has been estimated to be 3.7%, compared with a mortality rate of less than 1% from influenza.[15] Given the rapidly evolving global pandemic, the differences in health-care delivery in different countries and communities, and the emerging scientific evidence regarding specifics of the virus, its transmission and the resultant disease are of interest to dental health-care providers.

COVID-19 characteristics

The novel pneumonia was named coronavirus disease 19 (COVID-19) by the World Health Organization (WHO) and is associated with the SARS-CoV-2 virus.[16] In addition, some patients might suffer from headache, dizziness, abdominal pain, diarrhea, nausea, and vomiting.[5–7] Onset of disease may lead to progressive respiratory failure due to alveolar damage and even death.[5–7] Current management of COVID-19 is supportive, with supplemental oxygen and anti-inflammatory and anti-viral medications, and respiratory failure from acute respiratory distress syndrome (ARDS) is the leading cause of mortality.[17] The most severe presentation occurs in a subset of infected individuals and appears to be mediated by a hyperinflammatory cytokine storm.[18]

Secondary hemophagocytic lymphohistiocytosis (sHLH) is an underrecognized, hyperinflammatory syndrome characterized by a fulminant and fatal hypercytokinemia and multiorgan failure.[19] In adults, sHLH is most commonly triggered by viral infections and occurs in 3.7%–4.3% of sepsis cases.[20] Cardinal features of sHLH include unremitting fever, cytopenia, and hyperferritinemia. Pulmonary involvement, including ARDS, occurs in approximately 50% of patients.[21] A cytokine profile resembling sHLH is seen in patients with ARDS associated with COVID-19, particularly in severe cases of the disease. This presentation is characterized by increased interleukin-2 (IL-2), IL-7, granulocyte colony-stimulating factor (GCSF), interferon-γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, and tumor necrosis factor-α (TNF- α).[5] Predictors of fatality from a recent retrospective, multicenter study of 150 confirmed COVID-19 cases in Wuhan, China, included elevated ferritin (p<0·001) and IL-6 (p<0·0001), suggesting that mortality might be due to virally driven hyperinflammation.[17]

Characteristics of SARS-CoV-2

Coronaviruses (*Coronaviridae*, of the order *Nidovirales*) are large, single, plus-stranded RNA viruses.[22,23] Currently, there are four known genera of coronaviruses: α-CoV, β-CoV, γ-CoV, and δ-CoV.[24,25] Coronaviruses have been identified as the causative agents of diseases in humans and other vertebrates. SARS-CoV-2 belongs to the β-CoV family, which—along with α-CoV viruses—are known to infect mammals and humans.[22,26,27] SARS-CoV-2 possesses an ultrastructure typical of other coronaviruses, namely a lipoprotein membrane envelope with multiple spike glycoproteins extending from the envelope.[28] The viral capsule has also been found to express other polyproteins, nucleoproteins, and membrane proteins, including specifically RNA polymerase, 3-chymotrypsin-like protease, papain-like protease, helicase, glycoprotein, and accessory proteins.[8,28,29] SARS-CoV-2 enters host cells after binding to the angiotensin-converting enzyme receptor (ACE2).[30-33] This is

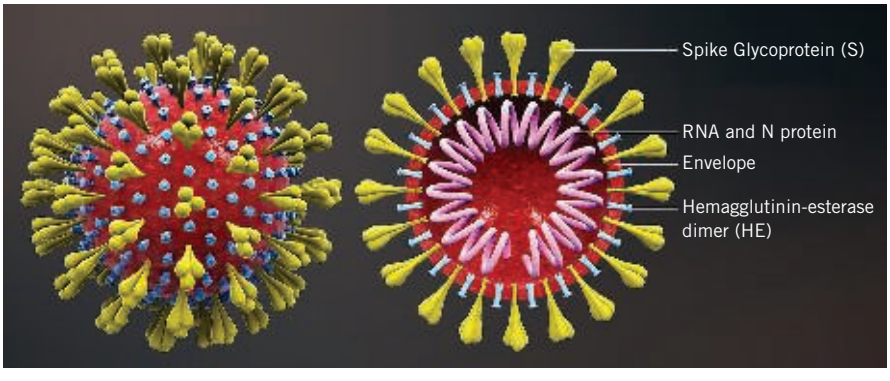

FIGURE 1: Diagram of the ultrastructure of the SARS-CoV-2 virus.[67] Photo courtesy of Wikimedia Commons.

accomplished via the S protein on the viral surface, which facilitates viral entry into such target cells (figure 1).[30–33]

It is also notable that SARS-CoV-2 is a single-stranded RNA virus.[22,23] It is well established that RNA viruses have higher rates of mutation than DNA viruses and bacteria.[34] On a per-site level, DNA viruses typically have mutation rates on the order of 10^{-8} to 10^{-6} substitutions per nucleotide site per cell infection (s/n/c). RNA viruses, however, have higher mutation rates that range between 10^{-6} and 10^{-4} s/n/c. Given this rapid mutation rate, novel RNA viruses with high rates of pathogenicity, such as SARS-CoV-2, are able to develop and propagate more frequently in the environment.[34]

The implications for these findings to the growing pandemic are manifold. Understanding the ultrastructure of the virus also informs the types of disinfectants and antimicrobial agents that are potentially efficacious against such a virus. The SARS-CoV-2 viral affinity for ACE2 receptors has been thought to be one potential explanation for the increased viral loads seen in older individuals, due to an increased expression of the ACE2 receptor with age.[35] It is also notable to identify potential oral cellular targets for SARS-CoV-2 based upon their expression of ACE2. ACE2-positive cells are abundant throughout the respiratory tract and salivary gland duct epithelium.[36,37] Finally, current estimation of the reproduction number (R_0) of SARS-CoV-2 is thought to be between 1.5 and 6.49, with a median value of 2.78.[38] The R_0 is the number of cases, on average, an infectious patient will cause during their infectious period. The R_0 is often described as either "basic" (reproduction in a wholly susceptible population) or "effective" (dependent upon the population's current susceptibility).This R_0 is greater than that of SARS-CoV-1 (median R_0=1.3)[38] and H1N1 influenza (median R_0=1.46),[39] but less than that of measles (median R_0=16.1).[40] The effective R_0 is likely to change as exposure in the environment changes and based upon mitigation practices, including social distancing, face mask usage, and limiting travel, particularly to and from areas with high levels of community spread. For example, after quarantine protocols were implemented during the SARS (SARS-CoV-1) outbreak, the effective R_0 dropped below 1, an instance where the disease is unlikely to propagate within a population.

Potential modes of transmission for SARS-CoV-2 in the dental office

Evidence suggests that SARS-CoV-2 can be transmitted both directly from person to person by respiratory droplets/aerosols and via indirect fomite-mediated transmission.[5,6] Viral shedding by asymptomatic and presymptomatic individuals has been reported during a prodromal period of up to 14 days and for a total length of up to 24 days.[41] While the mean viral load of asymptomatic patients is currently unknown, live SARS-CoV-2 viruses have been isolated from saliva of infected individuals both with and without symptoms and, in some cases, at higher levels than on nasopharyngeal swabs.[42,43] The viral presence in saliva as well as in other bodily fluids and demonstration of transmission through exposed mucous membranes are from respiratory admissions, such as from otolaryngologic procedures and intubation/extubation of infected patients.[7,44] It is also notable that certain individuals may be more susceptible to infection given the viral binding to ACE2 receptors to access host cells and the variability in expression based upon age and genetic factors.[8,35] ACE2-positive cells are abundant throughout the respiratory tract and salivary gland duct epithelium[36,37] and during the SARS epidemic in the early 2000s caused by a related virus, SARS-CoV-1, epithelial cells of the salivary gland ducts were early targets for viral infection.[45]

The Centers for Disease Control and Prevention (CDC) has expressed concern about aerosol formation during speaking and other close interactions. Within the dental setting, close interpersonal contact between individuals and procedures performed during the delivery of dental care are both at-risk activities for aerosol formation.[46–49] During such interactions, both

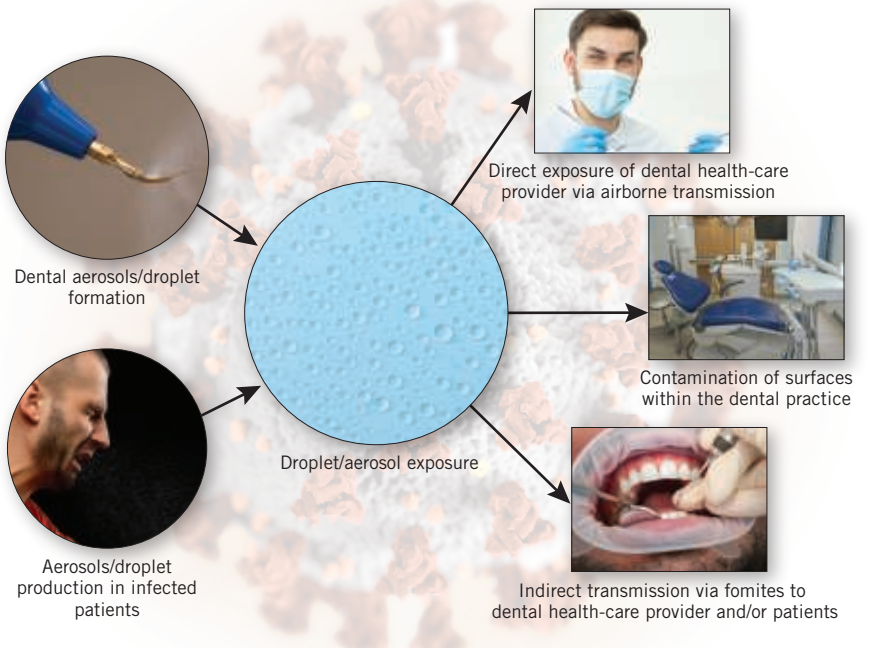

FIGURE 2: Potential transmission pathways for SARS-CoV-2 in the dental office (Adapted from Peng et al., 2020).[36] Images © Mrazzzzz, Vasyl Rogan, Aleksandr Malikov, Yuwarin Thititanamethikorn, Paul Vinten, Tetyana Afshar, Volodymyr Scherbak | Dreamstime.com.

concerns for transmission potential in the dental practice. Furthermore, at the start of the global pandemic, higher infection rates and symptom levels were noted in individuals who had close contact with bioaerosols dental practitioners and patients may be at risk due to droplets and/or aerosols containing microorganisms or through contact with bodily fluids from conjunctival, nasal, or oral mucosal tissues.[46–54] Furthermore,

SARS-CoV-2 may survive up to two to three days on particular hard, nonporous surfaces, which can lead to indirect exposure after touching contaminated surfaces.[55] The likelihood of such transmissions may be dependent upon the viral load of the infectious individual and is currently unclear.[56] Figure 2 summarizes potential routes of transmission in dental practice.

Similarities and differences between SARS-CoV-2 and other viruses

SARS-CoV-2 is likely most closely related to SARS-CoV-1, the β-coronavirus that caused the 2002–2003 outbreak of severe acute respiratory syndrome (SARS). SARS-CoV-1, like its successor that is now causing a global pandemic, emerged from China and infected more than 8,000 people. SARS-CoV-1 was eradicated by intensive contact tracing and case isolation measures. No cases have been detected since 2004.[57] SARS-CoV-2 has demonstrated some similar characteristics to SARS-CoV-1, including its stability in the environment. In an in vitro study, SARS-CoV-2 was detectable in aerosols for up to three hours, up to four hours on copper, up to 24 hours on cardboard, and up to three days on plastic and stainless steel.[49] Despite this similarity, SARS-CoV-2 has proven to be significantly more difficult to eradicate. Emerging evidence suggests that people infected with SARS-CoV-2 may be infectious and transmit the virus without recognizing, or prior to recognizing, its symptoms.[56] This asymptomatic and presymptomatic transmission may decrease the effectiveness of the disease control measures that proved integral to the control of SARS-CoV-1.[56] In contrast to SARS-CoV-1, most secondary cases of viral transmission of SARS-CoV-2 appear to be occurring in community settings rather than health-care settings.[56] However, health-care settings are also vulnerable to the introduction and spread of SARS-CoV-2, and the stability of the virus in aerosols and on surfaces likely contributes to transmission of the virus in health-care settings.[56]

Both of these viruses demonstrate binding affinity to the ACE2 receptor and utilize that pathway to enter host cells. However, the S protein from SARS-CoV-2 is less stable than that of SARS-CoV-1, and polyclonal anti-SARS S1 antibodies inhibit entry of SARS-CoV-1, but are not effective against SARS-CoV-2 pseudovirions.[58] Further studies using recovered SARS and COVID-19 patients' sera show limited cross-neutralization, suggesting that recovery from one infection might not protect against the other.[58] This may have implications for therapeutic targets and vaccine development for SARS-CoV-2 going forward.

Potential therapeutic targets for SARS-CoV-2

Potential anticoronavirus therapies can be divided into two categories depending on the target: 1) human immune system or human cells, or 2) SARS-CoV-2 itself. Human targets for potential therapeutic interventions include interference with the ACE2 receptor binding that allows the virus to enter host cells, or blocking the signal pathways within host cells that are harnessed for viral replication.[59] Viral targets include the viral RNA genetic material to prevent viral synthesis, antagonizing critical viral enzymes used for replication, blocking viral binding to human cells, and/or inhibiting the viral structural proteins to prevent the virus's assembly process.[59]

Because the process of new drug development is time-consuming, drug repositioning may be the only timely solution in the case of this pandemic. As such, testing existing antiviral medications to evaluate their efficacy against SARS-CoV-2[60] and utilizing molecular databases to screen for those that may have a therapeutic effect on this virus[61,62] are more likely to provide a realistic solution rather than reliance on novel drug development, which could require up to 10 years.[63] Computer modeling may help identify potential therapeutic agents for future in vivo testing.[59] Chloroquine phosphate has shown both positive and negative anti-SARS-CoV-2 effects in recent studies, but this drug's mechanism of action is currently unknown, and there are serious known side effects that are particularly severe in individuals with underlying cardiac issues.[64] Currently several treatments—including chloroquine, umifenovir (Arbidol), remdesivir, dexamethasone, favipiravir, and convalescent sera—are undergoing clinical studies to test their efficacy and safety in the treatment of COVID-19 worldwide, and some promising results have been achieved thus far.[65] Other potential targets that are purported to be of particular interest include ACE2 inhibitors, but emerging evidence suggests that they may not be suitable to use as drugs for treating SARS-CoV-2 infection because the poor prognosis would be induced by the inhibition of ACE2 enzyme activities, as the ACE2 enzyme was considered to be a protective factor of lung injury. [66]

Summary

Since its first identification in Wuhan, China, in November–December 2019, the novel coronavirus (SARS-CoV-2) has been implicated in the COVID-19 global pandemic. Similar to a previous coronavirus (SARS-CoV-1), SARS-CoV-2 enters host cells through human cell receptor ACE2, but appears to demonstrate higher binding affinity and has been shown to potentially have a higher reproduction number, indicating a higher level of transmissibility. Given these emerging data and what is known about the transmission of other coronaviruses, airborne transmission via droplets and/or aerosols from infected individuals is the likely primary mode of person-to-person transmission. Because this situation is rapidly evolving, dental healthcare providers are urged to continue close monitoring of emerging science and advisory statements from governmental and other agencies regarding best practices.

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Notes

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QUESTIONS

1. COVID-19 is a disease causing severe pneumonia in patients infected by:
   A. Yersinia pestis
   B. SARS-CoV-1
   C. SARS-CoV-2
   D. BatCoV RaTG13

2. The virus responsible for COVID-19 was first identified in:
   A. Brescia, Italy
   B. Wuhan, China
   C. New York, NY
   D. Johannesburg, South Africa

3. The origin of the novel coronavirus is presumed to be:
   A. Zoonotic
   B. Novel human specialist virus
   C. Long-standing evolution of human specialist virus
   D. None of the above

4. Typical clinical symptoms of COVID-19 include:
   A. High fever
   B. Cough
   C. Abnormal chest CT
   D. All of the above

5. Trends indicate that __% of patients may be asymptomatic and/or exhibit very mild symptoms and that these individuals may be fueling the spread of disease.
   A. 10%
   B. 25%
   C. 40%
   D. 60%

6. The mortality rate of COVID-19 has been estimated to be __% , compared with a mortality rate of less than 1% from influenza.
   A. 0.5%
   B. 1.5%
   C. 3.7%
   D. 5.4%

7. Acute respiratory distress syndrome (ARDS) has been associated with an inflammatory component and resultant:
   A. Cytokine storm
   B. Autoimmune response
   C. Cyclic neutropenia
   D. Osteoclast activation

8. The reproduction number (R_0) describes the:
   A. Number of cases, on average, that will become infected annually
   B. Percentage of cases, on average, that will be infected but asymptomatic during the course of a disease outbreak
   C. Number of cases, on average, an infectious patient will cause during his/her infectious period
   D. Number of times a virus will replicate prior to one meaningful genetic mutation

9. The effective reproductive number differs from the basic reproductive number in that:
   A. Basic reproductive number refers to the rate of infection in a completely susceptible population.
   B. Basic reproductive number assumes social distancing and vaccination.
   C. Effective reproductive number considers the number of asymptomatic individuals in the population.
   D. All of the above

10. The overall likelihood of viral transmission is dependent upon a susceptible host. The susceptibility of the host is dependent upon:
    A. Overall health status
    B. Genetic influences
    C. Vaccination/infection history
    D. All of the above

11. The four known genera of coronaviruses include all of the following except:
    A. α-CoV
    B. β-CoV
    C. γ-CoV
    D. δ-CoV

12. Which of the following statements about the structure of SARS-CoV-2 is false?
    A. It contains a peptidoglycan wall.
    B. It is a single, plus-stranded RNA virus.
    C. It is enveloped by a lipoprotein membrane envelope.
    D. It has numerous spike glycoproteins that are embedded in the envelope.

13. Entry into host cells of coronaviruses is facilitated by the S protein. In the case of both SARS-CoV-1 and SARS-CoV-2, this entry is through binding to the:
    A. CD4 receptor
    B. Major histocompatibility complex (MHC)
    C. Angiotensin II receptor (ARB)
    D. Angiotensin-converting enzyme 2 receptor (ACE2)

14. RNA viruses have higher rates of mutation than bacteria or DNA viruses. The rates of substitutions per nucleotide site per cell infection (s/n/c) of RNA viruses are greater than DNA viruses by a factor of 100–1,000-fold.
    A. Both statements are true.
    B. The first statement is true; the second statement is false.
    C. The first statement is false; the second statement is true.
    D. Both statements are false.

15. The reproduction number of SARS-CoV-2 is thought to be between 1.5 and 6.49, with a median value of 2.78. This is greater than all of the following except:
    A. Measles
    B. H1N1 Influenza
    C. SARS-CoV-1
    D. All of the above are less than the R_0 of SARS-CoV-2

16. Viral shedding by asymptomatic individuals infected by SARS-CoV-2 has been reported during a prodromal period of up to:
    A. 5 days
    B. 7 days
    C. 14 days
    D. 24 days

17. SARS-CoV-2 and SARS-CoV-1 are similar in all of the following ways except:
    A. Both viruses are thought to be of zoonotic origin.
    B. Both viruses utilize the ACE2 receptor to enter host cells.
    C. Both viruses are able to be shed during an asymptomatic period in human hosts.
    D. Both viruses are detectable in aerosols for up to three hours.

18. Viral targets for potential therapeutic interventions for SARS-CoV-2 include all of the following except:
    A. Destruction of viral RNA genetic material to prevent viral synthesis
    B. Reverse transcriptase antagonism
    C. Blocking viral binding to human cells
    D. Inhibition of the viral structural proteins to prevent the virus's assembly process

19. Novel drug design can take up to 10 years. Rational drug evaluation and testing of existing FDA-approved medications to identify their efficacy against SARS-CoV-2 may provide more timely and appropriate therapeutic interventions.
    A. Both statements are true.
    B. The first statement is true; the second statement is false.
    C. The first statement is false; the second statement is true.
    D. Both statements are false.

20. Drugs currently undergoing clinical studies to evaluate efficacy and safety in COVID-19 treatment include:
    A. Chloroquine
    B. Arbidol
    C. Remdesivir
    D. All of the above

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ANSWER SHEET

COVID-19: Part 1—Separating science fact from science fiction

NAME: TITLE: SPECIALTY:

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Educational Objectives

1 Discuss the current understanding of the structure and function of the SARS-CoV-2 virus.

2. List related viruses and the diseases they caused.

3. Understand the differences in infectivity and viral activity between SARS-CoV-1 and SARS-CoV-2.

4. Develop an understanding of the potential therapeutic targets for SARS-CoV-2.

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5.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	15.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
6.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	16.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
7.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	17.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
8.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	18.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
9.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	19.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
10.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	20.	Ⓐ	Ⓑ	Ⓒ	Ⓓ

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