

Traveler's Infections: Understanding SARS-CoV-2 as a Potential Agent

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Abstract

Coronavirus disease 2019 (COVID-19) has become a major, global, public health challenge. Over 1,051,635 confirmed cases have been reported worldwide, and both local and international travelers are considered to represent populations at high risk of acquiring the infection. Many factors are involved in the spread of this viral agent, including travel to and from endemic areas, a history of contact with a traveler from an endemic country, the virus infection rate at the destination, individual health, and inadequate prevention and control measures. The virus is thought to be transmitted through respiratory droplets, generated by coughing or sneezing and spread through close contact with infected persons or contaminated surfaces. Diagnostic strategies include detection of antiviral antibodies, multiplex nucleic acid amplification, and microarray-based assays. Currently, no approved antiviral therapy or vaccine exists to treat or prevent the infection. Public health measures have been enforced, to slow spread of the virus, by governments. The World Health Organization (WHO) have recommended screening be performed at airports, for all travelers, before traveling to endemic countries and the restriction of travel to countries more than one thousand cases of infection. In response to the global outbreak, this review examines COVID-19 as a potential traveler's infection.

Keywords: COVID-19, incidence rate ratio, social restriction, time series analysis

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped, single-stranded, positive-sense, ribonucleic acid (RNA) virus that causes coronavirus disease 2019 (COVID-19), a zoonotic infectious disease that has been declared a global, public health emergency of international concern (PHEIC).^{1,2} The infection was reported to originate from Wuhan, Hubei Province, China, in 2019, and has been linked to Wuhan's Huanan Seafood Wholesale Market. Bats are reportedly the major natural reservoir of the virus, and a 5-year study indicated the coexistence of highly diverse SARS-CoVs in bat populations found in caves in Yunnan Province, China.³ A recombination event may have facilitated the 'spillover' from the virus's original host to a new host, humans. The viral agent may have been disseminated, from bats to an unknown intermediate host, followed by the infection of human beings.^{4,5} The viral infection has since spread to virtually all parts of the globe, due to travel and the global migration of infected and exposed individuals.⁶ On March 11, 2020, the World Health Organization (WHO) declared COVID-

19 to be a pandemic, due to its spread to almost all six WHO regions.⁷ A reported 1,051,635 (and counting) confirmed cases have been identified, worldwide, and both local and international travelers represent populations at high risk of acquiring the infection.^{7,8} Coronaviruses usually cause mild respiratory infections; however, the symptoms of SARS-CoV-2 infections can range from mild, including fever, cough, and difficulty breathing, to severe, causing pneumonia and multi-organ failure. Elderly individuals and individuals with pre-existing medical conditions are at high risk of progressing speedily and swiftly into acute respiratory distress syndrome, septic shock, and coagulation dysfunction, which can result in death.¹ This review examines SARS-CoV-2 infections and COVID-19 as a potential traveler's disease.

The Structure of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

SARS-CoV-2 also known as 2019-nCoV,2 is an enveloped, single-stranded, positive-sense RNA virus, with a 3'-poly-A tail and a 5'-cap structure. The name corona-

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virus derives from the crown-like characteristic appearance under electron microscopy (corona is the Latin term for crown), due to the presence of spike glycoproteins on the envelope (9) (Figure 1).

SARS-CoV-2 is a strain of SARS-related coronaviruses, from the taxonomic perspective. SARS-CoV-2 belongs to the family *Coronaviridae*, in the genus *Betacoronavirus*.¹¹ The genetic material found in SARS-CoV-2 is approximately 30 kb in length, which makes it the largest known genome that has been identified in an RNA virus. The SARS-CoV-2 virus is one of seven *Coronaviridae* capable of infecting human beings, in addition to NL63, HKU1, 229E, OC43, MERS-CoV, and SARS-CoV.^{12,13} The genome of a typical coronavirus contains a minimum of six open-reading frames (ORFs). Approximately 70% of the viral genome encodes the polyprotein pp1ab, which is further cleaved into 16 non-structural proteins, which play roles in genome replication and transcription through the viral-encoded chymotrypsin-like protease (3CLpro), in synergy with one or two papain-like proteases.^{14,15} The other 30% of the genome encodes four structural proteins, including spike (S), envelope (E), membrane (M), and nucleocapsid (N), and additional helper proteins. The S protein plays a significant role, mediating membrane fusion and receptor binding, which, in turn, determines the host tropism of the virus.^{16,17}

Transmission Routes and Diagnosis of COVID-19

Epidemiological studies in Wuhan were the first outbreak was reported, associated the virus with a sea food market where live animals were sold, with many patients having worked in, or visited the market.^{4,5} Subsequently, secondary cases began to appear approximately ten days later.¹⁸ Although the new patients had no direct contact with the seafood market, contact tracing showed that they had contacts with inhabitants near the market.¹⁹ Advanced genetic and virologic studies have found that bats represent natural reservoirs of this viral agent.^{4,20} Studies have demonstrated that most bat CoVs have similar genomes as those found in beta-CoVs and alpha-CoVs.^{19,21}

The virus can be identified through different laboratory methods, including the rapid testing of Immunoglobulin G (IgG) and Immunoglobulin M (IgM) levels, electron microscopy, cell-culturing, and nucleic acid detection reverse transcriptase-polymerase chain reaction (RT-PCR), which is currently the gold standard for SARS-CoV-2 testing and is performed on a nasopharyngeal sample. When an individual is confirmed to be infected, contact tracing is performed, during which a detailed history of all persons in contact with a confirmed patient is examined, using precise laboratory testing.^{1,22} SARS-CoV-2 infections can also be determined by a myr-

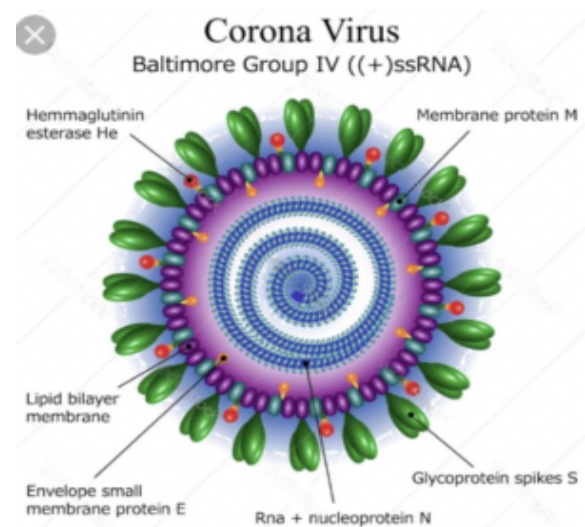


Figure 1. SARS-CoV-2 Morphology with the Minimal Set of Structural Proteins⁹⁻¹⁰

riad of clinical features, predictors, a chest computed tomography (CT) scans showing pneumonia characteristics and others.^{23,24} As of March 19, 2020, no antibody-based techniques have been developed, although serious ongoing studies are attempting to develop these techniques.²²

Clinical Features of SARS-CoV-2 Infection

The viral agent gains entry into the respiratory tract and infects the cells of the respiratory system,^{25,26} causing acute respiratory disease, with a high prevalence among travelers.²⁷ The incubation period for the viral infection is approximately 2–14 days, with an average incubation period of 5 days.¹⁹ The infection is usually asymptomatic among those with a travel history to endemic countries, but can also present with symptoms similar to those observed during flu infections, including fever, dry cough, and difficulty breathing.^{14,28} When these symptoms are present, the difficulty breathing and associated chest pain and pressure persists, resulting in walking difficulties, confusion, and a bluish tint to the lips and face. These symptoms indicate a critical situation that requires immediate medical attention.^{14,29} Zhang, *et al.*,²² reported the presence of the virus in fecal and blood samples, suggesting the possibility of multiple transmission routes. The identification of the viral receptor, angiotensin-converting enzyme 2 (ACE2), which is often present in large quantities on enterocytes in the small intestines and epithelial cells in the lung alveoli, is likely to assist researchers in understanding infection routes and the pathogenesis of the viral agent.³⁰

Aspects of COVID-19 Epidemiology as a Traveler's Infection

In December 31, 2019, the novel SARS-CoV-2 outbreak was first reported in Wuhan City, Hubei Province, China,³¹ as pneumonia outbreak without a known causal agent. The WHO announced that the etiology was a new coronavirus, which was temporarily referred to as 2019-nCoV, and was posited to be the causal agent for the infection on January 12, 2020.³² Similar to SARS, the COVID-19 outbreak is thought to have initiated at a local seafood market, the Huanan Seafood Wholesale Market, and 2/3 of the first 41 confirmed cases were linked to the market. Within a few weeks, the virus had spread to other countries, including those in Europe. Most SARS-CoV-2 cases reported during the first 6 days (January 23–28, 2020) were associated with direct contact with someone who traveled to or from Wuhan.³³ In Germany, a 33-year-old man (patient 1) became ill with cold and flu symptoms, on January 24, 2020, after attending a meeting in Munich with a Chinese business partner, on January 20, 2020.²¹ The business partner was visiting from Shanghai and she did not experience any signs or symptoms of illness. In Italy, a Bayesian phylogenetic reconstruction suggested that the virus found in Italy was imported by Chinese travelers, who were infected before they arrived in Italy.³⁴ Japan identified its first case of viral infection on January 16, 2020, associated with a Chinese traveler from Wuhan.³⁵ Australia's first case was identified on January 25, 2020, associated from a man who traveled to Wuhan.³⁶ On January 20, 2020, the USA identified its index case, a traveler who returned from Wuhan, China.³⁷ On January 24, 2020, France identified its first confirmed case of the novel coronavirus, which was also connected with a travel history to China.³⁸ A traveler from Wuhan and Qom imported the first case of the infection from China to Iran on January 19, 2020.³⁹ The index case for Pakistan was identified on February 26, 2020, when a young man with travel history to Karachi tested positive for the virus.⁴⁰ On March 10, 2020, Turkey reported its index case, in a Turkish male who traveled to Europe.⁴¹ The initial report of viral infection in South Africa was March 5, 2020, in a patient who had traveled to Italy with his wife.⁴² The WHO has reported that the median age of people testing positive for the virus was approximately 45 years and that over two-thirds of those infected were males.¹⁸ The mortality rate among confirmed positive cases was 4.5%, as of March 25, 2020, and appears to range from 0.2%–15%, depending on age group and other health-related factors.¹⁸ The fatality rates differ among countries and over time, based on differences in the rate of diagnosis and due to differences in access to adequate healthcare workers and facilities.

Prevention and Control of SARS-CoV-2 Infection

Preventive measures that have been implemented against the spread of the novel coronavirus include staying at home, practicing social distancing (avoiding crowded places), washing hands with soap and running water, regularly, for at least 20 seconds, good personal hygiene practices and the avoidance of picking or touching the nose, eyes, mouth, and other parts of the face with unwashed hands.⁴³⁻⁴⁵ Recommendations by the Centers for Disease Control and Prevention (CDC) included covering the nose and mouth with tissues when sneezing or coughing or using the inside of the elbow when tissue availability is scarce.⁴⁶ Social distancing, which refers to people remaining at least 6 feet apart from one another, was introduced to reduce contact between people carrying the virus and uninfected populations. Workplaces and schools were closed, travel restrictions were implemented, and mass gatherings of more than 50 individuals were canceled.⁴⁷ According to the WHO and CDC, surgical masks should only be used when an individual is symptomatic or is administering care to infected or suspected-infected persons, such as health workers.^{43,44}

Measures that benefit the community, such as the cancellation of mass gatherings, social distancing, the closing of schools, and the creation of plans that allow employees to work from home can help mitigate the dissemination of SARS-CoV-2 infections, and these types of preventive measures have been recommended by different CDC agencies, worldwide.^{46,47} Public health experts should provide travelers with information and guidelines regarding how they can mitigate their overall risks of viral infections and other respiratory complications, which can be disseminated through travel agencies, conveyance operators, travel health clinics, and at points of entry.⁴⁶

Possible Treatments and Vaccine Candidates for COVID-19 Infection

A variety of treatment methods and antiviral agents are being explored for the potential treatment of SARS-CoV-2 infections, and some are progressing to the clinical trial stage.⁴⁸ WHO has launched "Solidarity", which is a multi-country trial including 10 countries, in response to the COVID-19 pandemic, on March 2020.⁴⁴ The following drugs are being studied: chloroquine and hydroxychloroquine, ritonavir / lopinavir and remdesivir in synergy with beta interferon.^{45,49} Scientific reports exist showing that remdesivir can be used to treat the viral infection,⁵⁰ because it inhibits SARS-CoV-2 RNA transcription, *in vitro*.

Chloroquine, a drug that is currently used to treat malaria, is another potential drug that is currently being tested in China, with positive preliminary evidence.^{4,51} Chloroquine and hydroxychloroquine can effectively stop

the effects of the viral agent, in vitro, and hydroxychloroquine has been shown to be more potent than chloroquine, with a more tolerable safety profile.⁴⁷ Chloroquine and hydroxychloroquine have been listed as drugs with good preliminary outcomes for COVID-19 therapy, by the Italian Pharmaceutical Agency (IPA) in March 17, 2020.^{46,52}

Currently, no vaccines are available for SARS-CoV-2 infections; however, vaccine development is crucial for inducing herd immunity and the possible eradication of this disease.⁴³ Various ongoing studies are examining mRNA, epitope, and S protein-RBD structure-based vaccine candidates. Models of the human ACE2 protein in transgenic mice and rhesus monkeys have been well-mapped for the creation of a vaccine, and some SARS-CoV-2 vaccine candidates are already entering the clinical trial stage.⁵³ In Seattle, USA, the first human trials for a vaccine candidate began on March 16, 2020, with just four volunteers.⁵⁴ The vaccine candidate contains a harmless genetic code, copied from the SARS-CoV-2 virus that causes disease. Recombinant interleukin-7 (IL-7) therapy is also being investigated, as this protein plays a significant function in the reproduction and maturation of lymphoid cells.⁵⁵

Conclusion

Global migration, changes in climate, and evolving human-animal interactions are possible factors that may enhance the COVID-19 pandemic. Travelers are at high risk of acquiring the infection, and most countries with high numbers of cases have placed travel bans on foreign travel. We have provided a summarized review of the COVID-19 pandemic as a potential agent for traveler's infections, worldwide.

Abbreviations

COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; RNA: Ribonucleic Acid; PHEIC: Public Health Emergency of International Concern; WHO: World Health Organization; ORFs: Open-reading Frames; S: Spike; E: Envelope; M: Membrane; N: Nucleocapsid; IgG: Immunoglobulin G; IgM: Immunoglobulin M; RT-PCR: Reverse Transcriptase-Polymerase Chain Reaction; ACE2: Angiotensin-Converting Enzyme 2; CDC: Centers for Disease Control and Prevention.

Ethics Approval and Consent to Participate

Not Applicable

Competing Interest

Authors declares that there is no significant competing financial, professional, or personal interests that might have affected the performance or presentation of the work described in this manuscript.

Availability of Data and Materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' Contribution

Victor B. Oti conceptualized and designed the study. Victor B. Oti and Marina Ioannou searched the literature and prepared the manuscript. All authors reviewed the manuscript and approved the final manuscript.

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