COVID-19: viral characterization, pathophysiology and prevention

COVID-19: caracterização viral, fisiopatologia e prevenção

COVID-19: caracterización, fisiopatología y prevención viral

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Abstract

Introduction: There are seven known species of human coronavirus capable of causing respiratory diseases. The most recent is SARS-CoV-2, the etiologic agent of COVID-19. Objective: To evaluate the main characteristics of SARS-CoV-2, the pathophysiology of COVID-19 and the main measures for prevention and containment of disease progression. Methods: An integrative review was carried out between 2003 and 2020, based on: PubMed, Medline, SciELO, LILACS and Google Academic, using the descriptors: COVID-19, coronavirus, novel coronavirus, human, SARS virus, outbreak disease, viral pneumonia, all listed in MESH and DECS. Results: Of the 65 selected articles, 28 met the inclusion criteria. Conclusion: SARS-CoV-2 is an RNA virus whose protein S is involved in adsorption to the target cell membrane. It is transmitted through contact with contaminated surfaces, secretions or aerosols. In these, it remains viable for three hours, and up to three days on surfaces. Frequent hand washing, disinfecting surfaces, not sharing personal items, social distance of two meters and wearing facemasks when leaving home are recommended. Non-severe patients should be isolated at home for 14 days. Healthcare professionals should use PPE and be careful with potential sources of contamination, including urine and feces of patients during hygiene.

Keywords: SARS-CoV-2; Severe Acute respiratory syndrome; Pandemics.

Resumo

Introdução: Há sete espécies conhecidas de coronavírus humanos capazes de causar doenças respiratórias. O mais recente é o SARS-CoV-2, o agente etiológico do COVID-19. Objetivo: Avaliar as principais características do SARS-CoV-2, a fisiopatologia do COVID-19 e as principais medidas de prevenção e contenção da progressão da doença. Métodos: Foi realizada uma revisão integrativa entre 2003 e 2020, com base em: PubMed, Medline, SciELO, LILACS e Google Academic, utilizando os descritores: COVID-19, coronavirus, novel coronavirus, human, SARS virus, outbreak disease, viral pneumonia, todos listados em MESH e DECS. Resultados: Dos 65 artigos selecionados, 28 atenderam aos critérios de inclusão. Conclusão: SARS-CoV-2 é um vírus de RNA cuja proteína S está envolvida na adsorção à membrana da célula alvo. É transmitido por contato com superfícies contaminadas, secreções ou aerossóis. Nestes, permanece viável por três horas e até três dias em superfícies. Recomenda-se lavagem frequente das mãos, desinfecção de superfícies, não compartilhamento de objetos pessoais, distância social de dois metros e uso de máscaras na saída de casa. Pacientes não graves devem ser isolados em casa por 14 dias. Os profissionais de saúde devem usar EPI e ter cuidado com as fontes potenciais de contaminação, incluindo urina e fezes de pacientes durante a higiene.

Palavras-chave: SARS-CoV-2; Síndrome respiratória aguda grave; Pandemia.

Resumen

Introducción: Hay siete especies conocidas de coronavirus humanos capaces de causar enfermedades respiratorias. El más reciente es el SARS-CoV-2, el agente etiológico de COVID-19. Objetivo: Evaluar las principales características del SARS-CoV-2, la fisiopatología del COVID-19 y las principales medidas para prevenir y contener la progresión de la enfermedad. Métodos: Se realizó una revisión integradora entre 2003 y 2020, basada en: PubMed, Medline, SciELO, LILACS y Google Academic, utilizando los descriptores: COVID-19, coronavirus, nuevo coronavirus, humano, virus SARS, brote de enfermedad, neumonía viral. , todos listados en MESH y DECS. Resultados: De los 65 artículos seleccionados, 28 cumplieron los criterios de inclusión. Conclusión: el SARS-CoV-2 es un virus de ARN cuya proteína S participa en la adsorción a la membrana celular diana. Se transmite por contacto con superficies, secreciones o aerosoles contaminados. En estos, permanece viable durante tres horas y hasta tres días en superficies. Se recomienda lavarse las manos con frecuencia, desinfectar superficies, no compartir objetos personales, distancia social de dos metros y usar máscaras al salir de casa. Los pacientes no graves deben aislarse

en casa durante 14 días. Los profesionales de la salud deben usar EPP y tener cuidado con las posibles fuentes de contaminación, incluida la orina y las heces de los pacientes durante la higiene.

Palabras clave: SARS-CoV-2; Síndrome respiratorio agudo severo; Pandemia.

1. Introduction

Coronaviruses (CoVs) are members of the order Nidovirales, family Coronaviridae, subfamily Coronavirinae. They encompass four genera: alpha- (α-CoVs), beta- (β-CoVs), gamma- (γ-CoVs) and delta-coronaviruses (δ-CoVs). The first two genera infect mammals and the last two, mainly birds, though some may also infect mammals (Corman et al., 2019; Wang & Chi, 2003). The genera are further subdivided in species according to their genetic, antigenic and host particularities (Cui et al., 2019; Wang & Chi, 2003).

There are seven pathogenic CoV species in humans (HCoV), which cause respiratory diseases with possible evolution to viral pneumonia, severe respiratory syndrome and death (Corman et al., 2019; Cui et al., 2019; Wang & Chi, 2003; Woo et al., 2010). The last three identified species are associated to severe respiratory syndrome outbreaks in the last two decades: Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), responsible for severe acute respiratory syndrome (SARS-2003); Middle East Respiratory Syndrome Coronavirus (MERS-CoV), which causes Middle East respiratory syndrome (MERS-2013); and the more recently identified Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), the etiologic agent of Coronavirus Disease 2019 (COVID-19) (L. Chen et al., 2020; Corman et al., 2019; Wang & Chi, 2003; Woo et al., 2010).

The epicenter of the COVID-19 pandemic was the city of Wuhan, province of Hubei, China. It began in December 2019, with a few cases of pneumonia, of similar severity to SARS, in patients who had recently visited Wuhan's wet market. In January 2020, the Chinese Center for Disease Control and Prevention (CDC) detected a new species of coronavirus in patients with severe respiratory tract complications: the etiologic agent of COVID-19, which was named SARS-CoV-2 by the International Committee on Taxonomy of Viruses. In January 30th 2020, the World Health Organization (WHO) declared a Public Health Emergency of International Concern. Quickly, the disease spread to several countries and, by the end of February 2020, all continents had confirmed cases. In March 11th, the WHO declared COVID-19 a pandemic.

In Brazil, the first COVID-19 case was confirmed in February 26th, 2020 (WHO,

2020c). By the way, Brazil, as well as other countries, continues growing in new cases and deaths up to this date. The worldwide scientific community has been working incessantly to increase our knowledge of SARS-CoV-2 and the physiopathology of COVID-19, and to gather data to allow implementation of effective actions to reduce spread (WHO, 2020b). Therefore, it is crucial to understand the main characteristics of SARS-CoV-2 and the physiopathology of COVID-19, and to describe the main preventive measures that reduce COVID-19 spread.

2. Methods

We performed an integrative review of the PubMed, Medical Literature Analysis and Retrieval System Online (Medline), Scientific Electronic Library Online (SciELO), *Literatura Latino-Americana em Ciências da Saúde* (LILACS) e Google Academic databases, between 2003 and 2020. The following keywords were used: 'COVID-19', 'coronavirus', 'novel coronavirus, human', 'SARS-COV-2', 'SARS virus', 'outbreak disease' and 'viral pneumonia', all listed in MeSH. The following inclusion criteria were used in this review: on-topic full articles, related to humans, available online, free access and preferably published in English or Portuguese.

3. Results and Discussion

Our search yielded 65 papers, of which 28 fulfilled the inclusion criteria. Thirty-seven papers were excluded due to repetition, similar topics, incomplete materials, publication in other languages or not falling within the scope of this study.

Among the 28 selected papers, 24 (85.71%) are from 2020; 2 (7.14%), from 2019; 1 (3.57%) from 2009 and 1 (3.57%) from 2008 (Table 1).

Table 1. Papers selected for integrative systematic review.

AUTHORS	TITLE	GOAL	CONCLUSION/EVIDENCE
Schwartz & Graham, 2020	Potential Maternal and Infant Outcomes from (Wuhan) Coronavirus 2019-nCoV (SARS-CoV-2) Infecting Pregnant Women: Lessons from SARS, MERS, and Other Human Coronavirus Infections	This communication reviews the medical and clinical findings from coronavirus infections in pregnant women in order to anticipate how the newly discovered 2019-nCoV might affect maternal and infant morbidity and mortality.	Coronaviruses can also result in adverse outcomes for the fetus and infant, including intrauterine growth restriction, preterm delivery, admission to the ICU, spontaneous abortion and perinatal death. Unlike some viral infections, notably Ebola virus and Zika virus, the likelihood of intrauterine maternal-fetal transmission of coronaviruses is low – there have been no documented cases of vertical transmission occurring with either SARS or MERS. Additional clinical research on the treatment of SARS, MERS, and the new coronavirus 2019-nCoV is necessary if we are to understand the potential risks and benefits of novel therapies and new vaccines in pregnancy. This research will be critical in improving the care, and even saving the lives, of pregnant women in the current as well as future outbreaks.
Jin et al., 2020	Virology, Epidemiology, Pathogenesis, and Control of COVID-19	The review discusses the virology, clinical and molecular epidemiology, diagnosis, pathogenesis, and potential therapeutics for treatment of this infection.	SARS-CoV-2 looks similar to SARS and MERS. The main mode of transmission is by inhaling respiratory droplets and indirect or direct contact, and the infection is estimated to have an average incubation period of 5.2 days and an R0 of 2.2. The most common factors behind mortality are old age and concomitant illnesses. There are no specific antiviral treatments or vaccines. It is necessary to develop more interventions that allow effective control of viral infection. The pandemic potential of human CoVs remains a major threat to global public health.
Wu et al., 2020	Complete genome	To characterize the genome of a	Next generation metagenomic RNA sequencing identified a novel RNA

	characterization of a novel coronavirus associated with severe human respiratory disease in Wuhan, China	new coronavirus associated with severe human respiratory disease in Wuhan, China.	virus from the family *Coronaviridae* designed WH-Human-1 coronavirus (WHCV). Phylogenetic analysis of the complete viral genome (29,903 nucleotides) revealed that WHCV was most closely related to a group of Severe Acute Respiratory Syndrome (SARS)-like coronaviruses (genus *Betacoronavirus*, subgenus *Sarbecovirus*) previously sampled from bats in China and that have a history of genomic recombination. This outbreak highlights the ongoing capacity of viral spill over from animals to cause severe disease in humans.
Zeng et al., 2008	Structure of coronavirus hemagglutinin-esterase offers insight into corona and influenza virus evolution	Analyze the influenza and coronavirus hemagglutinin esterases (HEs) and their evolutionary role.	The authors report the crystal structure of a coronavirus (CoV) HE in complex with its receptor. CoV HE arose from an influenza C-like HE fusion protein (HEF) and the plasticity of its receptor-binding site is related to evolutionary flexibility conferred by functional redundancy between HE and its companion spike protein S. Our findings offer unique insights into the structural and functional consequences of independent protein evolution after interviral gene exchange and open potential avenues to broad-spectrum antiviral drug design.
Malik et al., 2020	Emerging novel coronavirus (2019-nCoV)-current scenario, evolutionary perspective based on genome analysis and recent developments	Provide an overview of 2019-nCoV in its current scenario, comparative analysis to the previously reported CoVs, evolutionary perspective (genome analysis) and recent advances in vaccines and therapies.	The recent nCoV outbreak highlights the hidden reservoir of wild animals from deadly viruses and the possible threat of overflowing zoonoses. Successful attempts at virus isolation have opened the door to the development of better diagnostics and effective vaccines. A report emerged from China, where scientists claimed the successful isolation of the 2019-nCoV virus in the Vero and Huh7 cell lines of infected patients. Subsequently, by assisting in further research to design rapid diagnostics and vaccine development for nCoV, scientists at the Peter Doherty Institute for Infection and Immunity in Melbourne, Australia, have also been successful in cultivating the Wuhan coronavirus in cell culture.

Jiang et al., 2020	An emerging coronavirus causing pneumonia outbreak in Wuhan, China: calling for developing therapeutic and prophylactic strategies	Determine the SARS-CoV2 genome, as well as describe the viral protein Spike, in order to develop neutralizing antibodies against the virus.	It may take several months or even years to research and develop neutralizing antibodies against 2019-nCoV infection. One of the quick approaches is to evaluate the currently available SARS-CoV neutralizing antibodies with cross-neutralization activity and protection against 2019-nCoV infection. Once identified, these cross-neutralizing antibodies can be readily developed for the prevention and urgent treatment of 2019-nCoV infection.
van Doremalen et al., 2020	Aerosol and surface stability of SARS-CoV-2 compared to SARS-CoV-1	Analyze the aerosol and surface stability of SARS-CoV-2 and compare it with SARS-CoV-1.	The results indicate that the transmission of SARS-CoV-2 aerosol and fomite is plausible, since the virus can remain viable and infectious in aerosols for hours and on surfaces for days. These findings echo those with SARS-CoV-1, whose forms of transmission have been associated with nosocomial and over-propagation events, and provide information for pandemic mitigation efforts.
Yang et al., 2020	The deadly coronaviruses: The 2003 SARS pandemic and the 2020 novel coronavirus epidemic in China	Provide a brief summary of the epidemiology and history of SARS – as lessons learned. To review the epidemiology, pathogenesis, clinical characteristics, diagnosis and treatment of those infected with SARS-CoV-2 to better understand the virus and suggest strategies for prevention, treatment and management.	We can always improve the treatment of global pandemics or epidemics. From the lessons learned during the SARS epidemic and now the SARS-CoV-2 epidemic, we can almost provide a roadmap for responding to future outbreaks. The development of a coronavirus vaccine is a critical step in prevention, but it may not be effective for future strains and we need to be ready for the next epidemic.

Brasil, 2020	Coronavírus (COVID-19): Sobre a doença	To disseminate crucial information about COVID-19.	COVID-19 is the disease caused by SARS-CoV-2. COVID-19 may vary from simple cold-like symptoms to severe pneumonia. Transmission occurs from one sick person to another through close contact. Diagnosis is performed with real time RT-PCR or immunological tests. The main preventive measures are: frequent handwashing, the use of 70% gel ethanol, cover nose and mouth when sneezing, avoid touching the face, not sharing personal objects, social distance of 2 m and the use of facemasks. Sick patients must isolate at home for 14 days and go to the hospital only if they experience shortage of breath
People's Republic of China, 2020	General Office of National Health Commission & State Administration of Traditional Chinese Medicine: Diagnostic and treatment protocol for Novel Coronavirus Pneumonia	Review the diagnostic and treatment protocol for new coronavirus pneumonia (experimental version 7).	When isolated and cultured in vitro, 2019-nCoV can be found in human respiratory epithelial cells in about 96 hours, however it takes about 6 days for the virus to be found if isolated and cultured in Vero E6 and Huh-7 cell lines. Transmission of the virus happens mainly through respiratory droplets and close contact. There is the possibility of aerosol transmission in a relatively closed environment with long-term exposure to high concentration aerosols. As the novel coronavirus can be isolated in feces and urine, attention should be paid to these in contaminated environment that may lead to aerosol or contact transmission. A suspect case has any of the epidemiological history plus any two clinical manifestations or all three clinical manifestations if there is no clear epidemiological history.

Ianiro et al., 2020	Screening of faecal microbiota transplant donors during the COVID-19 outbreak: suggestions for urgent updates from an international expert panel	Analyze the impact of the COVID-19 pandemic on stool banks.	Before each donation, it is suggested to track (FDA): a donor's travel history to outbreak areas, cohabitation with infected individuals and the presence of typical symptoms of COVID-19 in the 30 days prior to the collection of feces for donation. Alternatively, donor feces should be stored and quarantined for 30 days prior to use and released only if the donor has no symptoms. In endemic countries, the RT-PCR assay should be considered in all donors. Stool banks should check donors' health status retrospectively before using frozen stools, according to local epidemiology, to avoid possible potential spread of SARS-CoV-2.
United States of America, 2020	Fecal Microbiota for Transplantation: New Safety Information - Regarding Additional Protections for Screening Donors for COVID-19 and Exposure to SARS-CoV-2 and Testing for SARS-CoV-2	The safety alert informed health care providers and patients of the potential risk of transmission of SARS-CoV-2 by FMT.	Because of the potential risk of transmission of SARS-CoV-2 via Fecal Microbiota for Transplantation (FMT), the FDA has determined that additional protections are needed for any investigational use of FMT, whether under an Investigational New Drug Application (IND) on file with the FDA or under FDA's enforcement discretion policy. Stool donor screening, testing of the stool donation or stool donor for SARS-CoV-2 virus or RNA and conveying to the FMT recipient that healthy, asymptomatic stool donors may potentially be infected with SARS-CoV-2.

WHO, 2020a	Health topics: Coronavirus – Symptoms COVID-19	Describe the symptoms of COVID-19.	COVID-19 affects different people in different ways. Most infected people will develop mild to moderate illness and recover without hospitalization. Most common symptoms: fever, dry cough, tiredness. Less common symptoms: aches and pains, sore throat, diarrhea, conjunctivitis, headache, loss of taste or smell, a rash on skin, or discoloration of fingers or toes. Serious symptoms: difficulty breathing or shortness of breath, chest pain or pressure, loss of speech or movement.
Xydakis et al., 2020	Smell and taste dysfunction in patients with COVID-19	Discuss anosmia, with or without dysgeusia, as symptoms frequently associated with severe acute respiratory syndrome (SARS-CoV-2) coronavirus infection.	The authors observed that traditional nasal cavity manifestations, as seen in other upper respiratory infections, are commonly absent in patients with COVID-19. SARS-CoV-2 does not appear to generate clinically significant nasal congestion or rhinorrhea. This observation suggests a neurotropic virus that is site-specific for the olfactory system. Although labelled as a respiratory virus, coronaviruses are known to be neurotropic and neuroinvasive. Anosmia, with or without dysgeusia, manifests either early in the disease process or in patients with mild or no constitutional symptoms.

Galván Casas et al., 2020	Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases	To describe the cutaneous manifestations of COVID-19 and to relate them to other clinical findings.	We provide a description of the cutaneous manifestations associated with COVID-19 infection. These may help clinicians approach patients with the disease and recognize paucisymptomatic cases.
Letko et al., 2020	Functional assessment of cell entry and receptor usage for lineage B b-coronaviruses, including 2019-nCoV	Develop an approach for the rapid screening of beta-CoV lineage B, such as SARS-CoV and the recent 2019-nCoV, for the use of receptors and their ability to infect cell types of different species.	The findings suggest 2019-nCoV is capable of using human ACE2 as efficiently as SARS-CoV, which may help explain the human-to-human transmissibility of this virus. More studies are needed with the full spike sequence and, ideally, a viral isolate.

Yang & Shen, 2020	Targeting the Endocytic Pathway and Autophagy Process as a Novel Therapeutic Strategy in COVID-19	Discuss the implication of the endocytic pathway and the autophagy process in the infection of pathogenic β-CoV (including SARS-CoV-2) and the therapeutic potential of directing these processes.	At present, while the exact role of autophagy remains debatable, there is overwhelming evidence suggesting that the endocytic pathway plays a key role in mediating viral entry for many CoVs including SARS-CoVs, MERS-CoVs and possibly SARS-CoV-2. As a result, several inhibitors targeting the endocytic pathway appear to have the therapeutic potential in treatment of COVID-19, including a lysosomotropic agent chloroquine and a clathrin-mediated endocytosis inhibitor chlorpromazine.
Hoffmann et al., 2020	SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor	To understand the endocytosis mechanism in SARS-CoV-2 infection and the host cell factors involved.	SARS-CoV-2 infection depends on host cell factors ACE2 and TMPRSS2 and can be blocked by a clinically proven protease inhibition.

Sanders et al., 2020	Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review	To summarize current evidence regarding major proposed treatments, repurposed or experimental, for COVID-19 and provides a summary of current clinical experience and treatment guidance for this novel epidemic coronavirus.	The COVID-19 pandemic represents the greatest global public health crisis of this generation and, potentially, since the pandemic influenza outbreak of 1918. The speed and volume of clinical trials launched to investigate potential therapies for COVID-19 highlight both the need and capability to produce high-quality evidence even in the middle of a pandemic. No therapies have been shown effective to date.
Chen et al., 2019	Severe Acute Respiratory Syndrome Coronavirus Viroporin 3a Activates the NLRP3 Inflammasome.	To examine the role of protein 3a in the activation of the NLRP3 inflammasome.	SARS-CoV 3a protein is sufficient to activate the NLRP3 inflammasome in macrophages initiated by lipopolysaccharides. Protein 3a ion channel activity was essential for 3a-mediated secretion of IL-1β. K$^+$ efflux and mitochondrial reactive oxygen species were important for the activation of the NLRP3 inflammasome induced by SARS-CoV 3a. These results highlight the importance of viroporins, viral proteins that form transmembrane pores, in the activation of the virus-induced NLRP3 inflammasome.

Yang, 2020	Cell Pyroptosis, a Potential Pathogenic Mechanism of 2019-nCoV Infection	Discuss the relationship between 2019-nCoV infection and cell pyroptosis and present a potential hypothesis.	2019-nCoV likely causes cellular pyroptosis, especially in lymphocytes, by activating the NLRP3 inflammasome. However, further studies on morphological changes in lymphocytes and leukocytes and classical and non-classical expressions of cell pyroptosis markers at the nucleic acid and protein levels are still needed.
Shin et al., 2019	Immune Responses to Middle East Respiratory Syndrome Coronavirus During the Acute and Convalescent Phases of Human Infection	Investigate the spectrum of immune responses that occur in patients with MERS during the initial period of infection.	The results show an association between the early response of CD8^{+} T cells and the severity of the infection and also provide basic information that can help prepare effective control strategies for MERS in humans.

Long et al., 2020	Antibody responses to SARS-CoV-2 in patients with COVID-19	To study antibody responses to SARS-CoV-2 in patients with COVID-19.	We report acute antibody responses to SARS-CoV-2 in 285 patients with COVID-19. Within 19 days after symptom onset, 100% of patients tested positive for antiviral immunoglobulin-G (IgG). Seroconversion for IgG and IgM occurred simultaneously or sequentially. Both IgG and IgM titers plateaued within 6 days after seroconversion. Serological testing may be helpful for the diagnosis of suspected patients with negative RT-PCR results and for the identification of asymptomatic infections.
Lippi & Plebani, 2020	The novel coronavirus (2019-nCoV) outbreak: think the unthinkable and be prepared to face the challenge	Describe the possible reasons for the high capacity for viral mutation and the importance of early detection to reduce the spread of the disease.	Regardless of the underlying nature of these three recent coronavirus outbreaks, the most reasonable steps to prevent the unfavorable consequences of viral epidemics on humanity involve the development of active surveillance programs, along with laboratory preparation to address new environmental problems and biological challenges.

| Li et al., 2020 | Updated approaches against SARS-CoV-2. | Summarize current knowledge about the potential treatment for SARS-CoV-2 based on emerging basic and clinical data. | Considering the possible therapeutic strategies: inhibition of virus entry / fusion, interruption of virus replication, suppression of excessive inflammatory response, treatment with convalescent plasma, vaccine, combination of traditional Chinese and Western medicine, the authors anticipate that therapeutic drugs that directly target SARS-CoV-2 are more effective. In addition, vaccines are critical for preventing and limiting transmission of COVID-19. In addition, strong preclinical and clinical studies are needed to determine the safe and effective treatment for COVID-19. |
| WHO, 2009 | Infection-control measures for health care of patients with acute respiratory diseases in community settings – Trainer's guide | Inform healthcare professionals to recognize symptoms of ARD, identify measures to be used to provide safe healthcare in a clinical setting (regularly in an epidemic or pandemic) and control infection in healthcare facilities. | The spread of the virus causing SARS was amplified in health-care settings, where 55–72% of probable cases occurred, and health-care workers were severely affected. While the virus causing SARS was not known to be circulating in human populations at the present time, it is possible that it is present in animal hosts and may re-emerge in humans in the future. Among the lessons learned from the SARS epidemics are the need for preparation of healthcare facilities and to pursue a culture of safe practice to prevent and control the spread of infections associated with healthcare. |

Kampf et al., 2020	Persistence of coronaviruses on inanimate surfaces and their inactivation with biocidal agents	Summarize data on the persistence of some coronaviruses on different types of inanimate surfaces and present efficacy of commonly used biocidal agents.	Human coronaviruses can remain infectious on inanimate surfaces for up to 9 days. Disinfecting the surface with 0.1% sodium hypochlorite or 62% and 71% ethanol significantly reduces coronavirus infectivity on surfaces within 1 min of exposure time. A similar effect is expected against SARS-CoV-2.
Brasil, 2020a	Protocolo de Manejo Clínico do Coronavírus (COVID-19) na atenção primária à saúde	Define the role of APS/ESF services in the management and care of COVID-19; make available instruments to clinically orient first-line healthcare professionals of the public healthcare system (SUS) in view of COVID-19 community transmission in Brazil.	The clinical management of COVID-19, as well as its symptoms, signs and diagnostic, were summarized. The following tools for clinical management were discussed: fluxogram, case identification, preventive measures, stratification of flu-like syndrome severity, management of mild to moderate cases, notification procedures, clinical monitoring, community preventive measures, active surveillance support and recommendations to special groups. Fast-track flow model forms were also presented for use in primary care.

Source: Authors.

Characteristics of SARS-CoV-2

Seven species HCoVs were identified: HCoV-NL63, HCoV-229E, HCoV-OC43, HCoV-HKU1, MERS-CoV, SARS-CoV and SARS-CoV-2 (Jin et al., 2020; Schwartz & Graham, 2020). They are all α or β-CoVs of zoonotic origin (most in bats, except for HCoV-OC43 and HCoV-HKU1, of rodent origin), with respiratory and GI tract tropism; some species also infect the kidneys (Jin et al., 2020; Malik et al., 2020). They cause respiratory diseases of different severities (Table 2).

Table 2. HCoV genus, species and associated respiratory disease.

GENUS	SPECIES	ORIGIN	ASSOCIATED RESPIRATORY DISEASE
α-CoV	HCoV-NL63	bats	
α-CoV	HCoV-229E	bats	Light respiratory tract infections
β-CoV	HCoV-OC43	rodents	
β-CoV	HCoV-HKU1	rodents	Pneumonia
β-CoV	MERS-CoV	bats	Severe viral pneumonia
β-CoV	SARS-CoV	bats	Severe respiratory syndrome
β-CoV	SARS-CoV-2	bats	

Source: Authors.

SARS-CoV-2 is an enveloped, positive-RNA strand virus of spherical or oval appearance, with 60-100 nm diameter. Its 29.9 kb genome has 5' (265-nucleotide) and 3' (229-nucleotide) end sequences. Similarly to SARS-CoV, open reading frame 8 (ORF8) is located between the ORFs of the membrane (M) and nucleocapsid (N) genes (Jin et al., 2020; Wu et al., 2020). The virus is covered by two types of spike proteins: glycoprotein spikes (S) and haemagglutinin esterase (HE), whose redundancy in target cell adhesion is adaptative (Zeng et al., 2008). SARS-CoV-2, therefore, is composed of five protein structural groups: spike glycoproteins (S), membrane (M), envelope (E), nucleocapsid (N) and haemagglutinin esterase (HE) (Jin et al., 2020; Malik et al., 2020) (Figure 1). In addition, they produce several replication proteins (Malik et al., 2020).

Figure 1. SARS-CoV-2 structure.
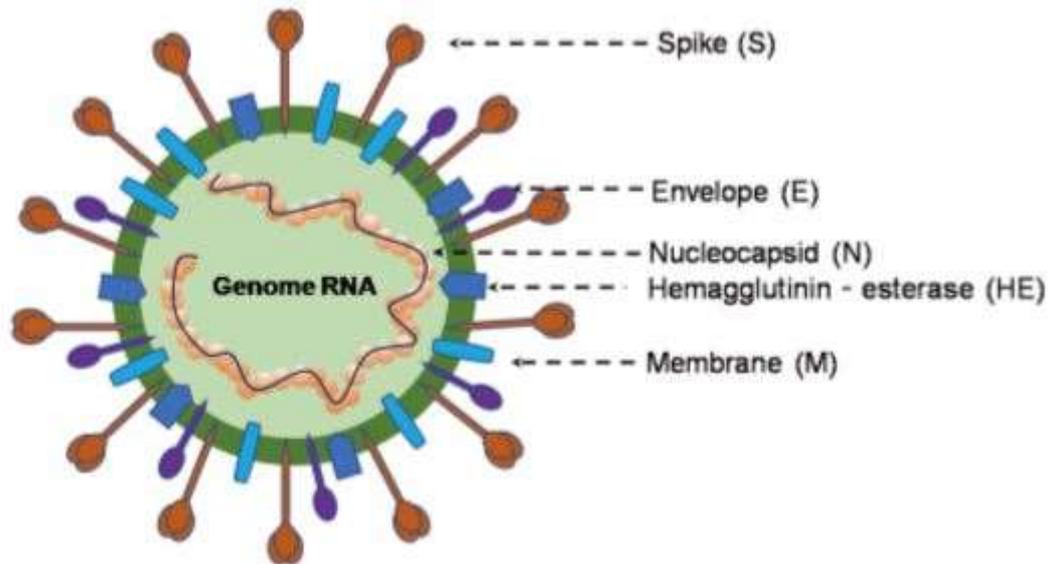
Source: Authors.

There is some variation between CoVs among these structures; HE is present exclusively in β-CoVs, where it acts on cell receptors (Malik et al., 2020; Zeng et al., 2008). Protein S is crucial for adsorption and immune system stimulation. A SARS-CoV-2 phylogenetic study showed that its 1,282 aminoacid-long S protein is longer than those of other HCoVs of the same subgenus. It is divided in two subunits, S1 and S2 (Jiang et al., 2020; Malik et al., 2020) (Figure 2), and S1, which contains both N terminal (NTD) and receptor binding (RBD) functional domains, is responsible for virus binding to the host cell (Jiang et al., 2020). When compared to SARS-CoV, SARS-CoV-2 S1 protein has three short insertions in the NTD and four changes in the receptor binding motif, in the internal region of the RBD (Malik et al., 2020; Wu et al., 2020). S2 has three functional domains: a fusion peptide (FP) and heptad repeats 1 and 2 (HR1 and HR2). It changes its conformation to insert FP into the target cell membrane (Jiang et al., 2020).

Figure 2. Molecular representation of SARS-CoV-2 spike
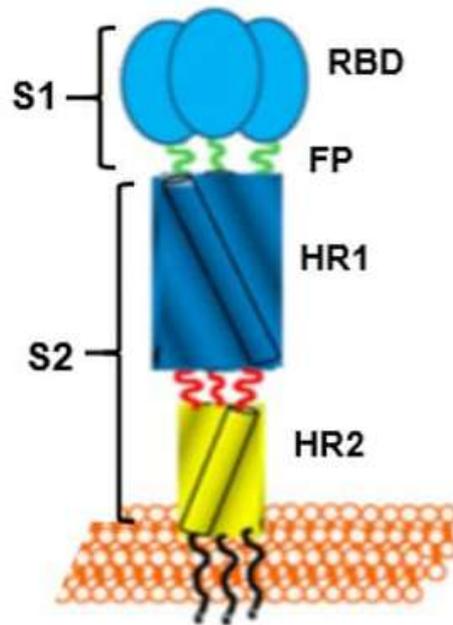
Source: Authors.

SARS-CoV-2 is quite environmentally stable. Viable particles are detected 72h after application onto surfaces such as plastic and stainless steel; 24h on cardboard; 4h on copper and for 3h in aerosols. These conditions dramatically increase its dissemination potential (van Doremalen et al., 2020).

Physiopathology of COVID-19

COVID-19 has already infected more than 3 million people worldwide (WHO, 2020b). Among these, it is estimated that 80% are asymptomatic, while 20% will have required hospital support due to respiratory difficulties and 5%, mechanical respiratory support (Brazil, 2020b; Y. Yang et al., 2020).

SARS-CoV-2 is transmitted through contact with contaminated surfaces, through inhalation of aerosols containing viable viral particles or through contact with emissions or secretions from contaminated individuals (Brazil, 2020b; People's Republic of China, 2020). It was also detected in urine and feces samples from infected patients, though further studies are required to clarify the transmission potential of these pathways (Ianiro et al., 2020; People's Republic of China, 2020). Some countries, such as the US, have already preemptively adopted triage protocols for either fecal microbiota transplantation samples or

donors (Ianiro et al., 2020; United States of America, 2020).

Symptoms may appear between days 5 and 14 of infection; the most common are fever, dry cough and tiredness. Less commonly, there may be pain, sore throat, diarrhea, conjunctivitis, headache, anosmia or ageusia, skin rashes or discoloration of fingers or toes. More severe symptoms may include difficulty breathing, chest pain or pressure, aphonia or loss of movement (Galván Casas et al., 2020; WHO, 2020a; Xydakis et al., 2020). Some risk factors are associated with increased susceptibility to infection: chronic respiratory tract disease, diabetes, cardiovascular disease, cancer, obesity and tobacco use (Jin et al., 2020).

SARS-CoV-2 binds angiotensin II-converting enzyme (ACE) for entry into the human organism (Letko et al., 2020). ACE is widely expressed in the nasal mucosa, bronchi, lungs, heart, esophagus, kidneys, stomach, bladder, ileum and testicles (Jin et al., 2020; N. Yang & Shen, 2020). The main protein in this process is protein S and its two subunits: S1 binds the receptor and S2 facilitates cell membrane fusion, mediated by the target cell's type 2 transmembrane serine protease (TMPRSS2) (Hoffmann et al., 2020; N. Yang & Shen, 2020). Once internalized, the virus first induces protein synthesis of the replicase-transcriptase complex, then synthesizes RNA with its RNA-dependent RNA polymerase (Sanders et al., 2020). Finally, there is synthesis of structural proteins, assembly and exocytosis of new viral particles (Sanders et al., 2020) (figure 3).

Figure 3. SARS-CoV-2 viral cycle and mechanism of infection.
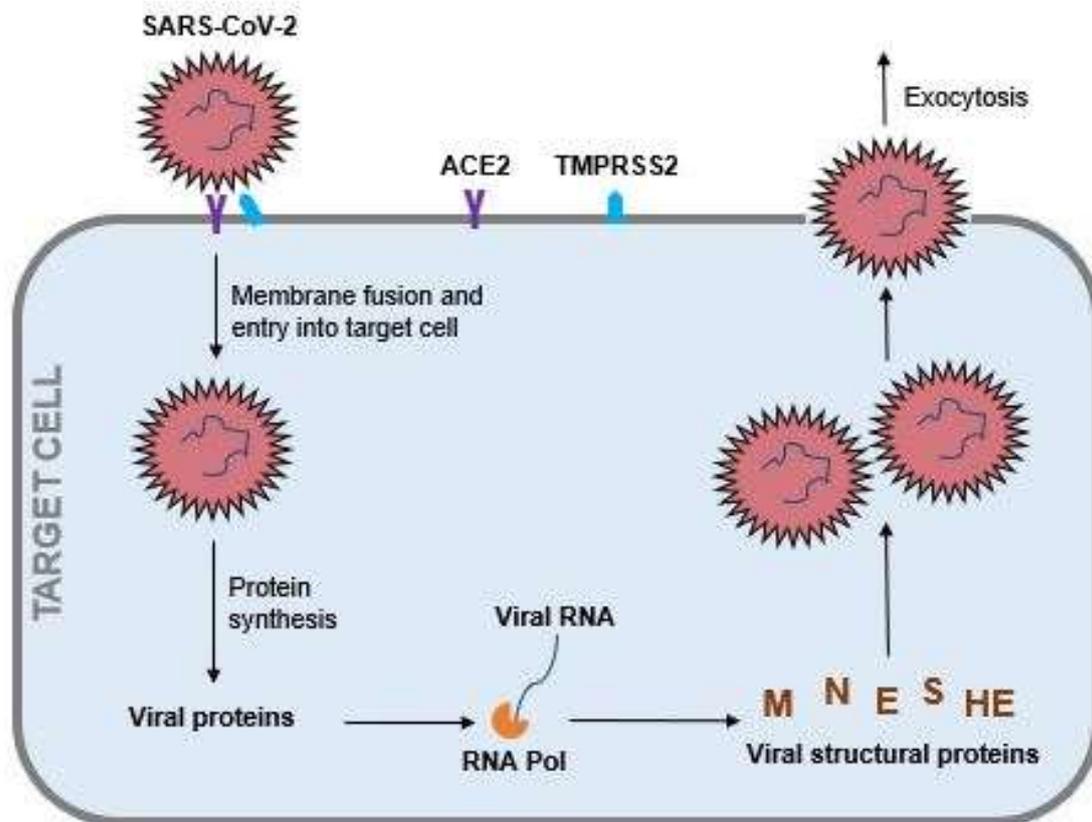
Source: Authors.

The virus has 14 ORFs, which codify several proteins: non-structural (pne1-pne10 and pne12-pne16), structural (S, HE, E, M and N) and accessory (3a, 3b, p6, 7a, 7b, 8b, 9b and orf14) (Jin et al., 2020; Y. Yang et al., 2020). Viroporin 3a may change cell membrane permeability to favor viral release (Y. Yang et al., 2020). It also activates caspase signaling through the nod-like receptor family, pyrin domain-containing 3 (NLRP3) sensor, an inflammatory regulator also called inflammasome, which induces macrophage interleukin-1β (IL-1β) and interleukin 18 (IL-18), triggering lysosome-dependent cell death, or pyroptosis (I.-Y. Chen et al., 2019; Y. Yang et al., 2020). This process leads to cell membrane rupture and migration of leukocytes to the site of infection (Y. Yang et al., 2020). There are indicia of pyroptosis in COVID-19, such as increased IL-1β in the sera of SARS-CoV-2-infected patients, and that it might target mainly lymphocytes, which could explain the lymphopenia commonly seen in these patients (M. Yang, 2020). Therefore, the intense inflammatory response and consequent exacerbated pyroptotic activity might be one of COVID-19's pathogenic mechanisms (M. Yang, 2020; Y. Yang et al., 2020).

Serious respiratory symptoms are characteristic of COVID 19, which may develop

into severe viral pneumonia, acute respiratory syndrome and even death (Brazil, 2020b; WHO, 2020b). Viral pneumonias initially affect pneumocytes, then evolve into disseminated alveolar damage. Infected patients have several alterations in plasma cytokines: in the acute phase, there is increase of interleukin-6 (IL-6), which induces antibody formation; interleukin-10-induced protein (IP-10), which recruits activated T cells and monocyte chemoattractant protein-1 (MCP-1), which regulate macrophage migration (Malik et al., 2020). The submucosa shows hyperemia, punctual hemorrhage, edema and neutrophil and mononucleate infiltration, with fibrin and turgescent fluid accumulation. As the disease progresses, fibrocellular formations appear inside the alveoli, with multinucleated histiocytes and pneumocytes. Thus, CD4+ and CD8+ T lymphocytes stimulate interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α) production, causing infected cell lysis (Malik et al., 2020; Y. Yang et al., 2020). The activation of the immune response, especially that of active CD8+ T lymphocytes and monocytes, may lead to pulmonary and cardiovascular syndrome, interstitial pneumonitis, pulmonary edema and cardiogenic shock (Shin et al., 2019).

Severe endpoints are also related to intense viral replication, with intense pro-inflammatory reaction and highly increased T cell activation (Malik et al., 2020; Y. Yang et al., 2020). The initial damage caused to endothelial and epithelial cells favors vascular leaks. In addition, virus binding to ACE interferes with renin-angiotensin system function, increases pro-inflammatory cytokines and chemokines and triggers abnormal pyroptotic activity (Jiang et al., 2020; Jin et al., 2020).

As for the immune response, a study of 285 COVID-19 patients identified seroconversion to antiviral immunoglobulin G (IgG) in up to 19 days after the beginning of symptoms in all patients. Titers, both of IgG and of antiviral immunoglobulin M (IgM), reached a plateau up to 6 days after seroconversion (Long et al., 2020). These results highlight the role of serological tests as a diagnostical tool, though further studies are needed in order to identify potential neutralizing activity in these antibodies (Long et al., 2020).

Preventive measures

The lack of specific therapies against SARS-CoV-2 further underlines the need for prevention and care to be incorporated to the routines of the general populace, as well as healthcare professionals (Li et al., 2020; Lippi & Plebani, 2020).

One of the main measures is attention to hygiene though frequent handwashing with water and soap and 70% ethanol disinfection (figure 4), as well as sanitization of work

surfaces and environments with appropriate biocidal solutions – 70% ethanol, 0.5% hydrogen peroxide or 0.1% sodium hypochlorite (Kampf et al., 2020; van Doremalen et al., 2020; WHO, 2009). SARS-CoV-2 may also be inactivated with UV light, heating to 56 °C for 30 min or chloroform (People's Republic of China, 2020).

Figure 4. COVID-19 prevention recommendations.

Source: Authors.

Beside hand hygiene, the Brazilian Secretary of Health recommends to the general public: cover nose and mouth with a tissue or arm when coughing or sneezing; avoid touching the eyes, nose and mouth with unwashed hands; do not share personal use objects (such as cutlery, towels, plates and glasses); keep environments clean and well ventilated; rest and eat well; keep a minimum distance of 2 m (7 ft.) from any coughing or sneezing person; avoid unnecessary circulation and agglomerations; use handcrafted or improvised tissue facemasks, in case it is necessary to leave the house. This last guideline was proposed so as to prioritize healthcare professionals in the distribution of surgical and N95 masks, since personal protection equipment (PPE) is in a worldwide shortage due to the pandemic (Brazil, 2020b; WHO, 2020b).

Sick individuals with no severe symptoms must remain isolated at home and sleep in separate rooms, if they do not live alone. Patient and household member isolation must last for 14 days and, in the event any of them begin to show any symptoms, all must restart the 14-day period (Brazil, 2020b).

Early control measures are also recommended to healthcare professionals in direct contact with patients: respiratory barriers; PPE use: surgical facemask for routine procedures and N95 for procedures with risk of generating aerosols, gloves, protective glasses or face

shields and disposable gowns; frequent handwashing; clean and disinfect frequently touched objects or surfaces; keep at least 2 m (7 ft.) distance from other people whenever possible; supply suspected COVID 19 patients with facemasks and accommodate them in isolation in a well-ventilated room (Brazil, 2020a). It is important that professionals who deal with patients' personal hygiene be aware of the potential contamination risk with excretes (feces and urine), since the virus has been detected in these samples. The same risk is present in diaper-wearing children.

There measures aim to mitigate dissemination of the virus and to minimize mortalities. Considering the worldwide impact of the pandemic, particularly to healthcare systems and economies of affected countries, further research is needed to improve diagnostics, clarify the disease's physiopathology and aid development of effective therapies and vaccines (Brazil, 2020b; Li et al., 2020; Lippi & Plebani, 2020; van Doremalen et al., 2020; WHO, 2020b).

4. Final Considerations

Taken together, our results and discussion summarize concepts associated to viral characterization, pathophysiology and prevention in COVID-19.

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