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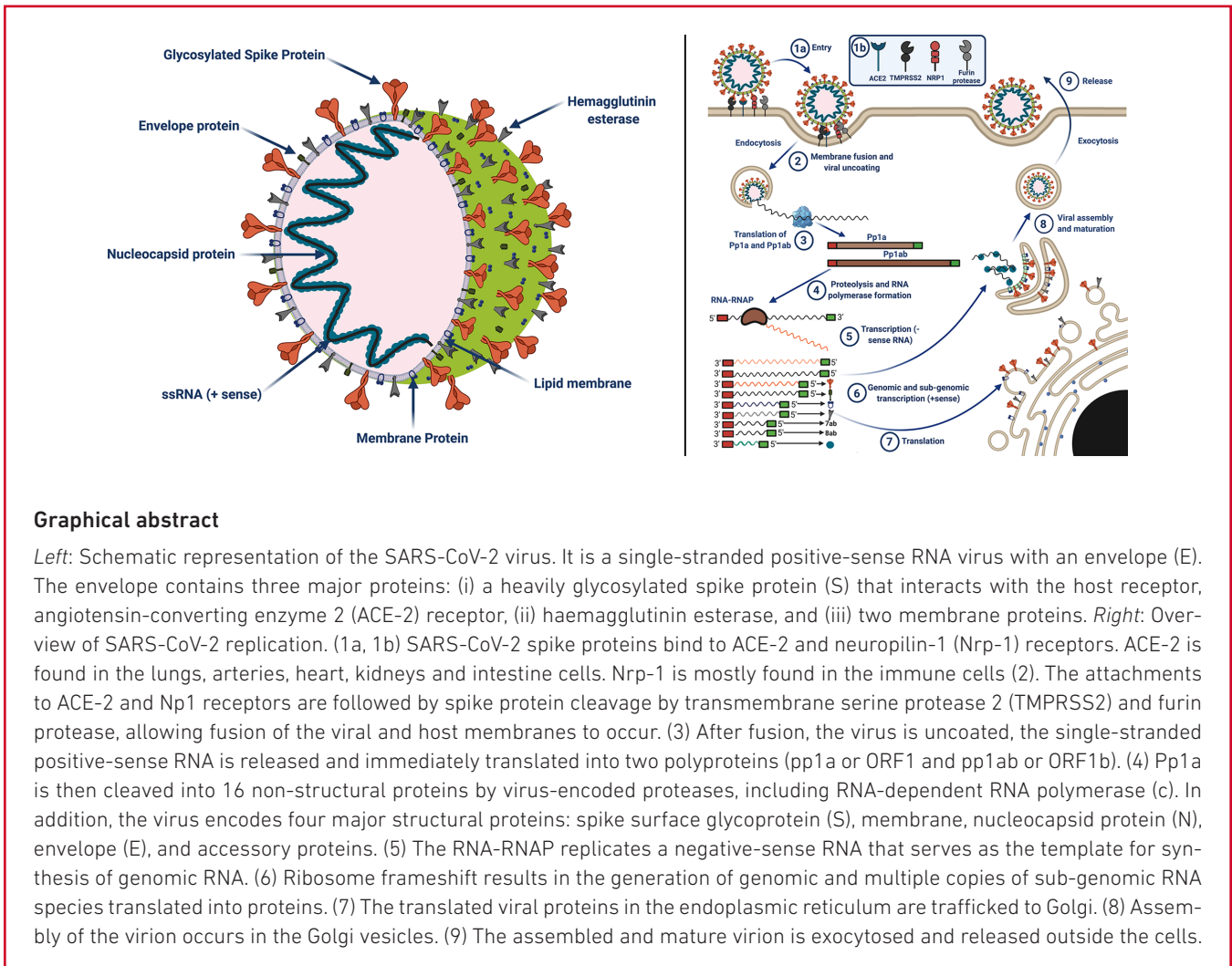OF MEDICAL
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JMM Profile: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

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Graphical abstract

Left: Schematic representation of the SARS-CoV-2 virus. It is a single-stranded positive-sense RNA virus with an envelope (E). The envelope contains three major proteins: (i) a heavily glycosylated spike protein (S) that interacts with the host receptor, angiotensin-converting enzyme 2 (ACE-2) receptor, (ii) haemagglutinin esterase, and (iii) two membrane proteins. *Right*: Overview of SARS-CoV-2 replication. (1a, 1b) SARS-CoV-2 spike proteins bind to ACE-2 and neuropilin-1 (Nrp-1) receptors. ACE-2 is found in the lungs, arteries, heart, kidneys and intestine cells. Nrp-1 is mostly found in the immune cells (2). The attachments to ACE-2 and Np1 receptors are followed by spike protein cleavage by transmembrane serine protease 2 (TMPRSS2) and furin protease, allowing fusion of the viral and host membranes to occur. (3) After fusion, the virus is uncoated, the single-stranded positive-sense RNA is released and immediately translated into two polyproteins (pp1a or ORF1 and pp1ab or ORF1b). (4) Pp1a is then cleaved into 16 non-structural proteins by virus-encoded proteases, including RNA-dependent RNA polymerase (c). In addition, the virus encodes four major structural proteins: spike surface glycoprotein (S), membrane, nucleocapsid protein (N), envelope (E), and accessory proteins. (5) The RNA-RNAP replicates a negative-sense RNA that serves as the template for synthesis of genomic RNA. (6) Ribosome frameshift results in the generation of genomic and multiple copies of sub-genomic RNA species translated into proteins. (7) The translated viral proteins in the endoplasmic reticulum are trafficked to Golgi. (8) Assembly of the virion occurs in the Golgi vesicles. (9) The assembled and mature virion is exocytosed and released outside the cells.

Abstract

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus is the cause of an infection known as coronavirus infectious disease 2019 (COVID-19). COVID-19 has become a global source of morbidity, mortality and social disruption since its emergence in East Asia in late 2019 and subsequent pandemic spread. Typical symptoms include cough, sore throat, fever, and sudden loss of taste and smell. Persistent, post-infection sequelae have been noted in a minority of cases. Severe complications and deaths occur mostly in older adults. Laboratory confirmation can be performed by viral RNA and antigen detection in nasal swabs or by detecting specific neutralizing antibodies. There is no effective and approved antiviral treatment, but several vaccines with favourable safety and efficacy profiles are being used in mass vaccination programmes. Vaccine-based COVID control should be seen as an addition to existing hygiene measures such as physical distancing, increased hand hygiene, cough etiquette, and barrier protection with personal protective equipment for frontline healthcare workers and other high-risk professions.
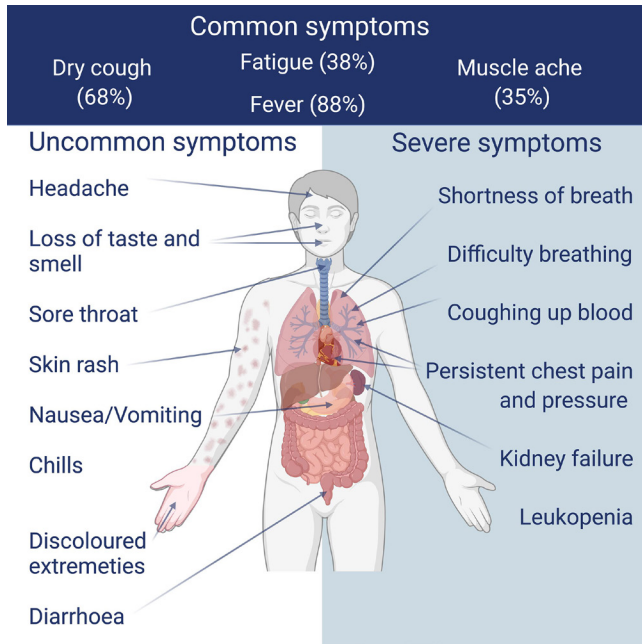
Fig. 1. COVID-19 symptoms [9]. Infection with the SARS-CoV-2 virus results in many symptoms 2–14 days after exposure, and the disease is referred to as COVID-19. The most common symptoms of COVID-19 are fever (88%), dry cough (68%), fatigue (38%) and muscle ache (35%). The severe form of COVID-19 can be fatal.
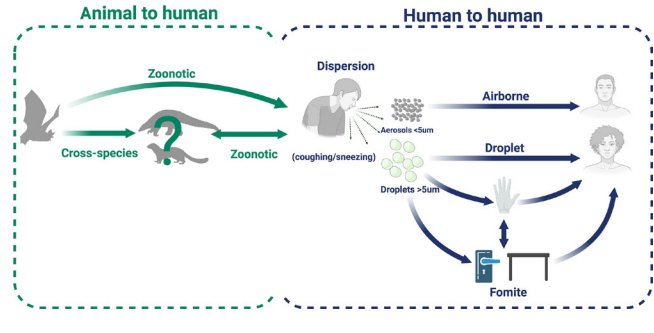

Fig. 2. SARS-CoV-2 transmission. Based on genome sequence analyses, the human SARS-CoV-2 virus appears to have originated from bats and may have circulated in several intermediate hosts (viverrids and mustelids) before jumping to humans. Airborne viruses, especially those that are less than 5 µm in size, suspended in the air through talking, coughing and sneezing, are the leading form of human-to-human transmission. Droplets larger than that 5 µm fall onto the ground, and fomites probably contribute to viral transmission. Poor hand hygiene has also been associated with transmission, especially in healthcare settings.

HISTORICAL PERSPECTIVE

Coronavirus infectious disease 2019 (COVID-19) was first described in Wuhan Province, China, in 2019. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus was isolated shortly afterward, its designation distinguishing the virus from other Betacoronaviruses, including the original SARS-CoV and the Middle East respiratory syndrome (MERS) viruses. 'Corona' in Latin refers to a crown and is used because the spike proteins encircling the main body of the virus give it the appearance of a solar corona or crown.

CLINICAL PRESENTATION

The typical course of SARS-CoV-2 infection starts with an asymptomatic incubation period (5–6 days, maximum range 1–14) [1]. This period is followed by a symptomatic stage of varying duration then a convalescent period, which can be prolonged. Some people do not develop any symptoms. In around 80% of cases, COVID-19 is a mild illness, most commonly with fever and cough (Fig. 1). Other symptoms include sore throat, fatigue, shortness of breath, headache, myalgia, loss of smell and taste, chills, vomiting, and diarrhoea. Emergency warning signs include trouble breathing, persistent chest pain, confusion, an inability to stay awake, and bluish discoloration of the lips and face. Symptom progression differs from influenza. The median duration of symptoms before hospital admission is 4 days (interquartile range 1–8). A significant factor contributing to COVID-19 deaths is acute respiratory distress syndrome (ARDS), which is caused by the release of large quantities of chemokines and proinflammatory cytokines. This 'cytokine storm' results in extensive damage and leads to multiple organ system failure (MOSF) and, eventually, death. For recovering cases, clinical features such as loss of taste and smell, debilitating lethargy, tachycardia, and palpitations may persist for weeks or even months, contributing to a condition known as 'long COVID'.

MICROBIAL CHARACTERISTICS

The novel Betacoronavirus SARS-CoV-2 is a positive-sense ssRNA virus. SARS-CoV-2 has close genetic similarity to bat coronaviruses, suggesting a zoonotic origin (Fig. 2). The genome of the SARS-CoV-2 varies from 29.8 to 29.9 kb and encodes ten genes. The virus has little genetic diversity but some clades have distinctive transmission properties and are known as variants of concern (VOCs). These include B.1.1.7, B.1.351 and P1 first recognised in the UK, South Africa and Brazil, respectively. The

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virion has a diameter of 50–200 nm and four structural proteins: N (nucleocapsid), M (membrane) and E (envelope) proteins in the viral envelope, and a highly glycosylated S (spike) protein that enables attachment to the host's angiotensin-converting enzyme 2 (ACE2) and neuropilin 1 (NRP1) receptors, leading to subsequent fusion with and entry into host cells.

CLINICAL DIAGNOSIS, LABORATORY CONFIRMATION, AND SAFETY

Clinical diagnosis
Clinical diagnosis of COVID-19 is difficult due to the high proportion of asymptomatic infections, the variable rate of onset of symptoms (Fig. 1), and the range of diseases with similar clinical features. At present, the most helpful diagnostic pointers are contact with another confirmed case or travel to a pandemic-affected locality in the previous 14 days.

Laboratory confirmation
Laboratory confirmation of COVID-19 is usually by detection of one or more SARS-CoV-2 targets using an RT-PCR assay. The most common clinical specimens are oro-, nasopharyngeal or combined oronasopharyngeal swabs. Other samples used include saliva, tracheal secretions and bronchoalveolar lavage fluid. False-negative PCR results occur and are most likely during the asymptomatic period or due to other pre-analytical considerations such as unsuitable swab material or poor collection technique. Saliva samples and self-collected oronasopharyngeal swabs have lower sensitivity than swabs collected by a trained worker. False positives infrequently arise due to contamination during laboratory processing. Positive results with low or borderline PCR activity occur during the convalescent period. These do not necessarily indicate the presence of infective viruses after more than 8 days from the onset of symptoms and may represent the shedding of viral RNA fragments.

Alternative methods of confirming a diagnosis are viral isolation in tissue culture and demonstration of a rising antibody titre. Rapid antibody tests have yet to be validated for use in the detection of asymptomatic and pre-symptomatic infection. Antibody responses may be absent after PCR-confirmed infection, particularly in individuals with mild or asymptomatic infections. Rapid antigen tests are considered a potential point-of-care option, along with other emerging rapid test methods that could be used either with higher test frequency (e.g. daily) or in combination with established tests to boost sensitivity.

Laboratory safety
It is critical to adhere to recommended procedures for the safe handling and processing of samples from COVID-19 patients. Clinical laboratories follow national and local guidance based on pathogenic potential, transmission risks and treatment, and risk assessment activities. The UK Advisory Committee on Dangerous Pathogens designates SARS-CoV-2 as a Hazard Group 3 pathogen. Similarly, the World Health Organization (WHO), Centers for Disease Control and Prevention (CDC), and Australian Government Department of Health classify SARS-CoV-2 as a Biosafety Level-3 (BSL-3) pathogen. However, non-propagative diagnostic laboratory work is permitted at Biosafety Level-2 (BSL-2) [2].

TREATMENT AND RESISTANCE

Treatment
Despite the many candidate agents under evaluation, there is, as yet, no effective, approved antiviral treatment for COVID-19. Currently, hospitalized patients are provided respiratory support and drugs such as dexamethasone to suppress the cytokine storm. Promising results were observed in some early clinical trials of treatment with Remdesivir, dexamethasone, convalescent plasma and some novel anti-inflammatory agents. Further clinical trials have produced conflicting results. No antiviral or adjunctive treatment can be recommended outside of a properly conducted clinical trial.

Resistance
None has been reported.

PATHOGENIC STRATEGIES

Host range
SARS-CoV-2 is a human pathogen whose genome bears a close resemblance to bat coronaviruses. Infections have been reported in various mammals, including domestic and wild cats, dogs, monkeys, ferrets, pangolins, hamsters and mink (Fig. 2).

Transmission
Person-to-person transmission of SARS-CoV-2 is from an infected subject via droplets, direct physical contact, indirect contact via fomites and possibly in aerosols (Fig. 2). Most estimates of the reproductive number (R0, number of secondary cases arising through transmission from an index case) are from 2 to 3. Much higher estimates have been reported. New SARS-CoV-2 variants such as the UK variant strain B 1.1.7 appear to have enhanced transmission without reducing virulence and may prove even more challenging to control.

Infection
SARS-CoV-2 uses ACE2 as a receptor for host cell entry. The virus co-opts host furin to cleave the spike protein, where its S1 protein subunit attaches to epithelial cells, and its S2 subunit enables membrane fusion. After fusion, an endosome forms around the virion, separating it from the host cell. The virion escapes from the endosome into the cell to force the production and dissemination of virus copies. A more recently discovered additional entry mechanism relies on the exposed carboxyl terminal of the S1 subunit binding to cell surface NRP1 receptors. These receptors are abundant in the nasal respiratory epithelia and can trigger epithelial cell entry of the virus.

Virulence factors
Insights into SARS-CoV-2 virulence are rapidly evolving. SARS-CoV-2 appears to have several virulence factors that promote

virion attachment, fusion and entry (S glycoprotein). Distinct SARS-CoV-2 clades vary between an aspartic acid (D) and a glycine (G) residue in the viral spike protein. This mutation may cause unstable viral machinery and alter viral fusion with the cell membrane. The endosome's double membrane shields the virus from detection by the host cytosol pattern-recognition receptors (PRRs), thus evading the innate immune response. The SARS-CoV-2 virion then escapes from the endosome and releases its RNA. The SARS-CoV-2 non-structural protein 1 (Nsp1) suppresses host gene expression by ribosome association. SARS-CoV-2 Nsp1 binds to the 40S ribosomal subunit and shuts down mRNA translation. The C terminus of Nsp1 binds to and obstructs the mRNA entry tunnel, blocking RIG-I-dependent innate immune responses that would otherwise assist clearance of the infection. In addition, viral proteins down-regulate the production of antiviral cytokines and type 1 interferon, delaying the development of an adaptive immune response and prolonging viral clearance.

EPIDEMIOLOGY, PREVENTION, AND RISK GROUPS

Epidemiology

COVID-19 has spread across the world since the detection of a case cluster of a severe acute respiratory syndrome associated with a wet market in Wuhan, China, during December 2019. Expansion of the initial outbreak occurred through international travel, leading to seeding in multiple distant locations and spread through the global population. There have been over 96 million cases at the time of writing, and over two million deaths, in over 215 affected countries. While some of the first affected countries have passed their peak caseload, few have avoided a resurgence and further COVID-19 case clusters. SARS-CoV-2 clades (strains) with greater transmission potential were detected in late 2020 and early 2021, including the UK-origin B 1.1.7 variant of concern (VOC). Other VOCs include those originating recently in South Africa and Brazil. Some of these VOCs have multiple mutations consistent with rapid viral evolution. It is still unclear whether these have lost or maintained the virulence of the parent lineage [3].

Prevention

In the absence of a universally available COVID-19 vaccine or effective chemoprophylaxis, the mainstay of prevention is a combination of physical distancing, enhanced hand hygiene and personal protective equipment, including disposable gloves, gowns, face masks and eye protection. There are additional measures for contacts of known COVID-19 cases, returning international travellers and suspected cases with symptoms. The details vary with evolving local epidemiology [4–8].

Risk groups

Severe and fatal outcomes are more frequent in the elderly. Children have milder symptoms than adults. In the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) (https://isaric.tghn.org/) study of clinical presentation of COVID-19 patients admitted to hospital, the median age was 73 years (interquartile range 58–82, range 0–104). In total, 60% were men and 40% women.

People older than 60 years or with underlying comorbidities such as diabetes, chronic lung or heart disease, and conditions compromise the immune system. The commonest comorbidities are chronic cardiac disease (31%), uncomplicated diabetes (21%), non-asthmatic chronic pulmonary disease (18%) and chronic kidney disease (16%); 23% had no reported significant comorbidity [3].

OPEN QUESTIONS

(1) What is the role of serology in COVID-19 diagnosis and seroprevalence studies?
(2) What is the basis of lasting protective immunity after SARS-CoV-2 infection?
(3) How do we confirm a case of COVID-19 is no longer infectious?
(4) What is the most effective vaccination method?
(5) Is there an effective antiviral for SARS-CoV-2?

Conflicts of interest
The authors declare that there are no conflicts of interest.

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