

The sweeping tide: SARS-CoV-2 and Covid-19

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Project

Overview:

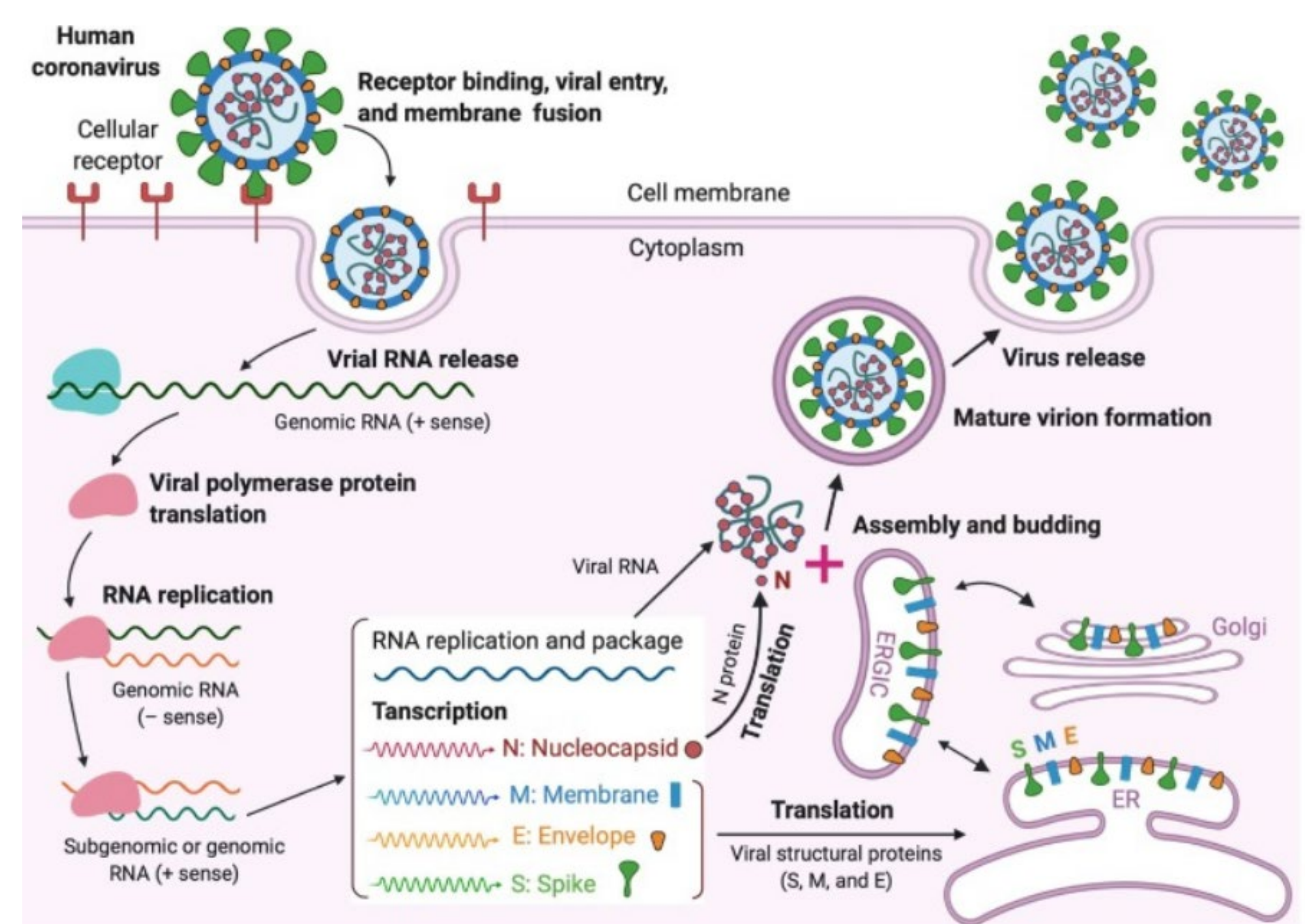
The Coronaviridae are a family of positive sense single stranded RNA viruses from which severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), otherwise known commonly as The Coronavirus or novel coronavirus, hails from (Phan et al). This family consists of viruses enveloped in lipoprotein, with a single strand of positive sense RNA. Characteristic of the Coronaviridae are the coronae or crowns which decorate the surface. These peplomers are responsible for mediating a degree of virulence-i.e. hemagglutination, fusion, and binding-making them a popular target for immunization (Medical Virology 1994). Several serotypes of the Coronaviridae cause the common cold (Corman et al). In this overview of the incumbent pandemic of the most recent novel coronavirus dubbed SARS-CoV-2, World Health Organization (WHO) guidelines and conventions will be used to reference the appropriate entity: SARS-CoV-2 for the virus and Covid-19, the diseased by infection of the virus. SARS-CoV-2 was implicated in infamous infections in December 2019 from a wet market in Wuhan, Hubei in China (WHO). Following this, a mere 44 patients were reported, 11 of which were in critical condition as of January 3rd 2020 (WHO). A public health emergency was declared in the US in early February of 2020. However, the earliest stay at home order in California came about in mid March with subsequent closure of many public facilities including university campuses as per the American Journal of Managed Care. At the time of authoring this piece, over 30 million individuals have been affected with over half a million deaths just within the US (CDC). Covid-19 has reached record notoriety with the infection of the President of the United States in early October, showing that nobody is untouchable. Interestingly, the vast majority of those testing positive are asymptomatic. A recent study showed that 76% of those testing positive in a single event were asymptomatic, which poses an intriguing quagmire where spreaders might be hidden (Lan et al, 2020). This review will aim to identify some key characteristics of this novel coronavirus at the molecular, clinical, and epidemiological levels.

Genomic structure:

The linear (+)ssRNA genome of Coronaviridae consists of approximately 27-33kb, and comes with a 5' cap and 3' poly A tail, reflective of post transcriptional modification found in the eukaryotes which they infect (Medical Virology 1994). SARS-CoV-2 is roughly 30 kb long and two thirds of that codes for nonstructural proteins. Given that this is a mRNA strand, the genome has a 5' untranslated region and a 3' poly A tail (Fehr et al, 2015). Viral replication methods shared by all genera of coronaviridae include polymerase complex jumping, whereby the RNA-dependent RNA polymerase (RdRp) constantly switches template strand, leading to the intrinsically high mutability of the family (Payne, 2017). SARS-CoV-2 shares approximately 50% of its genome with the earlier MERS-CoV and approximately 77.5% similarity with the more recent SARS-CoV (Kim et al). The genome of coronaviridae historically encodes for 7-10 ORFs, however, with alternative cleavage of transcript RNA, many more proteins are produced, and the production of subgenomic units allows for an increasingly complex mosaic expression pattern (Payne, 2017). A high volume, almost two thirds of the proteins, are non structural. Of these non-structural proteins, some interesting components are IFN antagonists, membrane remodelers, single stranded binding proteins (SSBP), RdRp, helicases, and endonucleases which concertedly assist in production of virions (Payne, 2017). Virtually all products inhibit a robust immune response. Of the 28 proteins identified in SARS-CoV-2, 16 of the structures have been described, half of which are novel (Rana et al, 2020).

Viral molecular biology:

SARS-CoV-2 encodes for four major structural proteins integral for survival: Membrane, Spike, Nucleocapsid, and Envelope (Schoeman et Fielding). The envelope protein is small yet plays a role in budding and assembly of envelope, as in the absence of E protein, virions fail to form (Li, 2016). The nucleocapsid (N) is helical in shape and this single species of protein interacts with the ssRNA(+) genome to tightly pack it within the viral envelope (Masters). The envelope is made of a heptad arrangement and the glycosylated spike protein (S), which grants the virion the classical crown shape, is integral to receptor mediated entry (Yuan et al). The trimeric S protein is divided into S1 and S2 subunits, where the former is for receptor binding, and the latter for membrane fusion. The protein is heavily glycosylated which produces a shielding effect and since the envelope is derived from golgi membrane in SARS-CoV-2, the glycosylation is dependent on golgi machinery, making antibody development and immunogenicity problematic during an incumbent infection. However, due to the inert nature of the region coding for the amino acids at those glycosylated regions, this may be a viable candidate for vaccine development. The shielding effect of N-linked glycoproteins is observed to a lesser effect in influenza, and not at all in HIV (Yasunori et al). For spike protein mediated fusion to occur, the S1 subunit which is most distal to the virus is in constant conformational transition until it binds the target receptor (Belouzard et al, 2012). Once bound to the target receptor, in the case of SARS-CoV-2 this receptor is angiotensin converting enzyme II, then host cell proteases cleave the S1 subunit, allowing the S2 subunit to undergo conformational change and facilitate membrane fusion (Shang et al, 2020. Hoffman et al, 2020). Cleavage of the S1 subunit occurs at a peripheral motif by host cell serine proteases (Piva et al, 2020). Once fusion occurs, interestingly, the nucleocapsid (N) protein is involved in cellular arrest, diverting all machinery to virion production (Payne, 2017). The membrane (M) protein, which is a glycosylated protein integral to virion formation, is implicated in modulation interferon release, leading to increased inflammation (Masters, 2006).

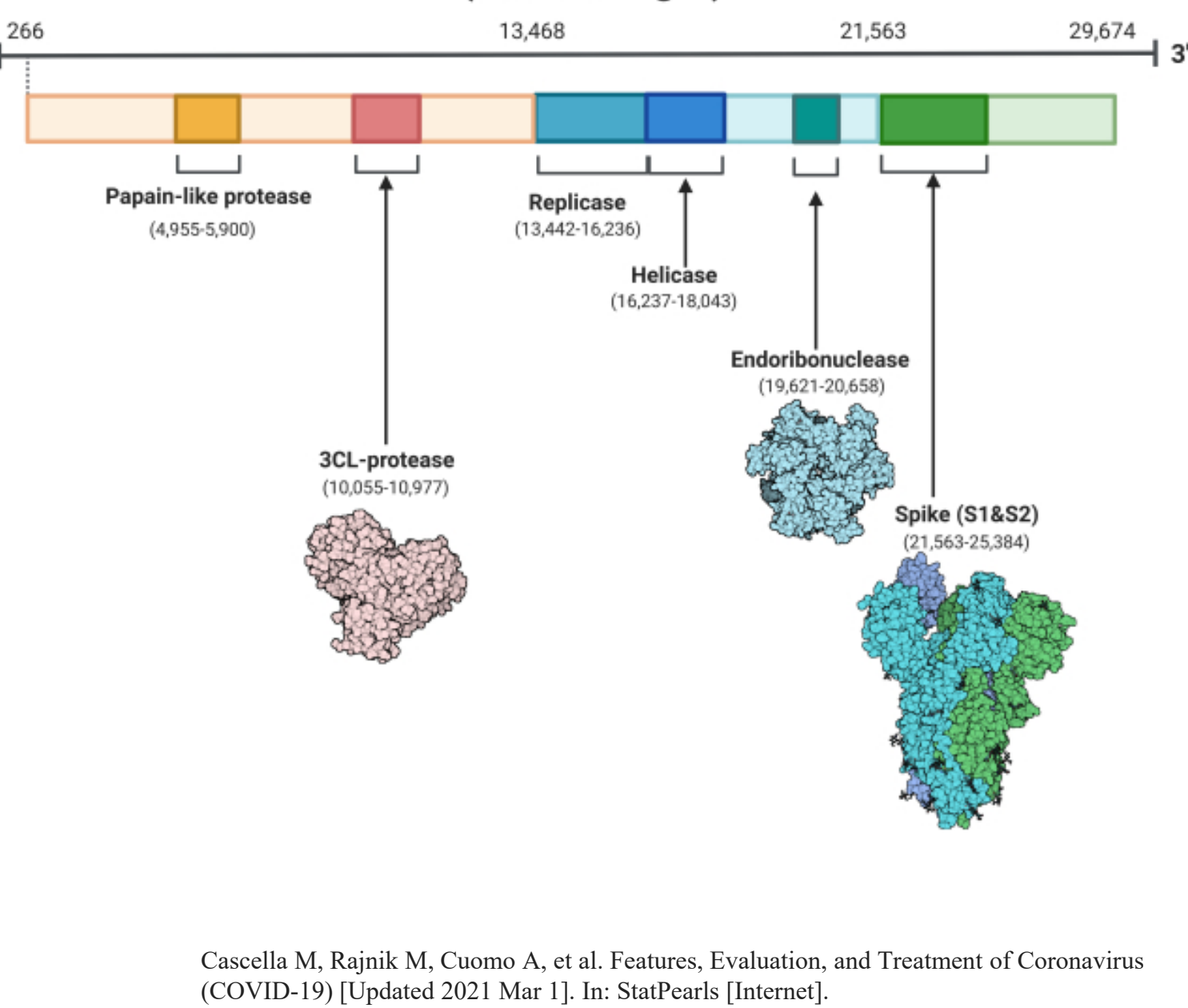


Jiang, Hillyer, et al. Neutralizing Antibodies against SARS-CoV-2 and Other Human Coronaviruses. Science and Society vol 41 issue 5 355-359. May 2020

COVID-19 in the clinic:

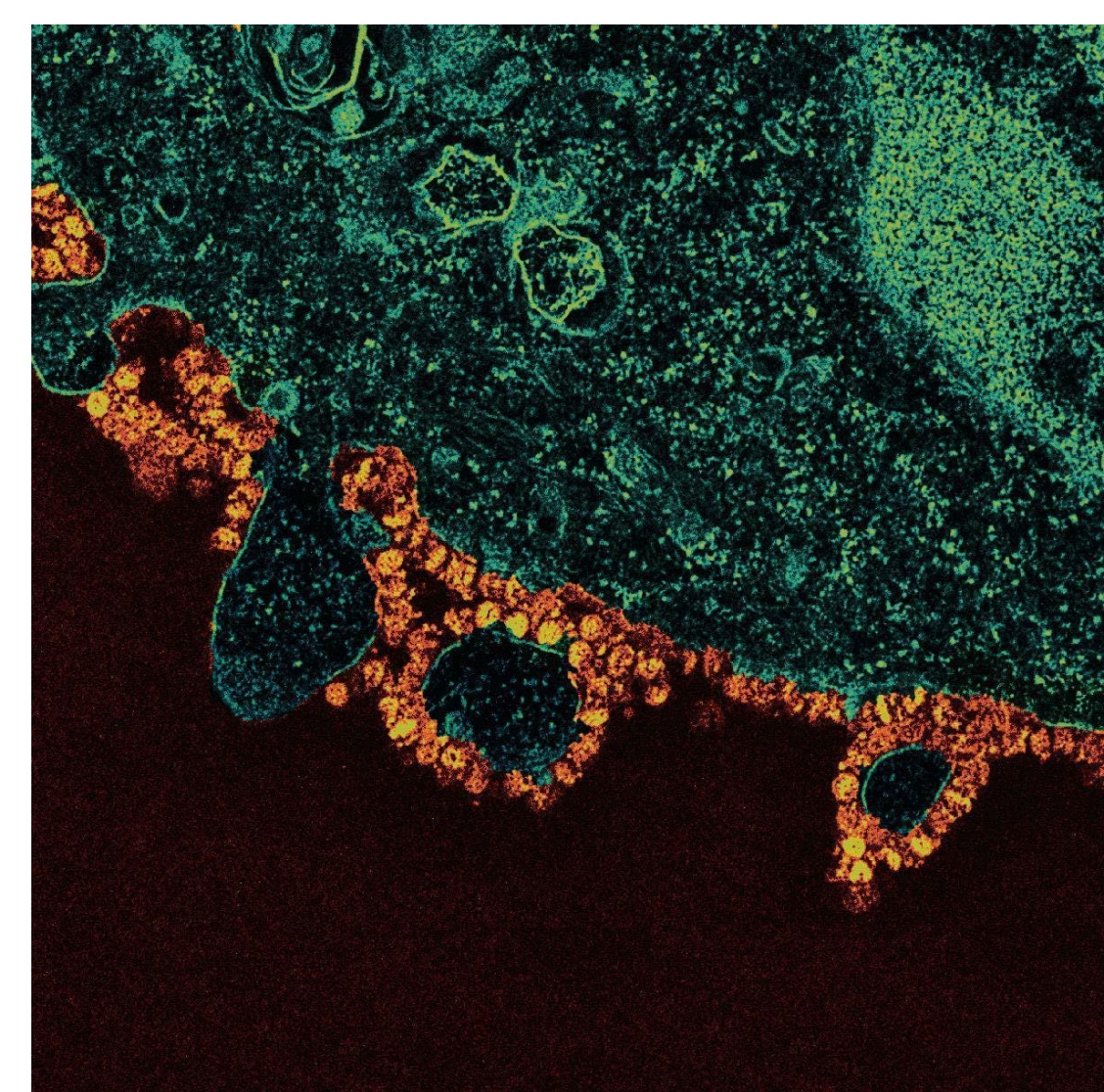
As per the Covid-19 treatment guidelines from the NIH, patients who have a mild illness show typical upper respiratory and flu-like symptoms of fever, cough, sore throat, malaise, headache, muscle pain, but also gastrointestinal symptoms of nausea, vomiting, and diarrhea, as well neurological symptoms of anosmia. Patients with a moderate to severe illness will have decreasing oxygen saturation, dropping below 94%, and can necessitate oxygen administration, as well as antibiotics for a secondary bacterial pneumonia (Covid-19 treatment guidelines). Critical cases could necessitate homeostasis control with blood pressure assistance, renal support, and breathing support in the form of ventilators. Patients who test positive for Covid-19 are shown to have an increased hospitalization rate, with a 5 fold increased chance of death once admitted to the hospital (Ioannou, 2020). A concerning metric is the prothrombin time which is highly reduced in Covid-19 patients, which shows hypercoagulation that could contribute to the severe respiratory disease and pulmonary function loss that is typical of acute Covid-19 cases (Han et al, 2020). Viable SARS-CoV-2 particles exist on steel and plastic for up to 72 hours, though perish on copper after 8 hours, and are undetectable on cardboard after 24 hours (Van Doremalen et al, 2020). Of note, viable times are greater than twice as long as SARS-CoV-1 (Van Doremalen et al, 2020). The CDC recommends using 7-8% sodium hypochlorite bleach solutions or greater than 70% alcohol solutions for non-porous surface cleansing. *In vitro* application of commercial alcohol solutions, including gels, liquids, and foams, were shown to have a 3 log₁₀ reduction in viral titer; there were 1000 x less viral particles after applications which is in line with CDC guidelines (Leslie et al, 2020). Masks are of vital importance, with 70% decrease in viral titer when both parties or just the spreader were masked-this emphasizes the use of proper personal protective equipment or PPE (Ueki et al, 2020). Some of the virulence of Covid-19 can be attributed to the molecular components of a SARS-CoV-2 virion. The N protein, apart from its function of associating with viral RNA, is a potent interferon antagonist which limits systemic response to infection, and also is a prothrombinase which is potentially responsible for the high incidence of clotting in Covid-19 patients (Perlman et Netland, 2009). Mortality with Covid-19 is shown to be due to predominantly respiratory failure secondary to pneumonia as per over half of cases evaluated post mortem (Elezkurtaj et al, 2020). A large majority suffered from renal failure necessitating dialysis and a third from multiorgan failure (Elezkurtaj et al, 2020). Pulmonary embolisms were present in a quarter of patients examined (Elezkurtaj et al, 2020). This is concerning as acute respiratory disease affects all across the board but those with underlying comorbidities such as hypertensive disease, diabetes, and established pulmonary, cardiac, or renal disease are at higher risk for mortality (Sanyaolu et al, 2020). As per the Covid-19 treatment guidelines, Remdesivir is the only antiviral approved by the FDA for Covid-19. There has been some attempt at using HIV protease inhibitors unsuccessfully. Hydroxychloroquine was put on trial in China with some efficacy, and molecularly, the antimalarial is shown to prevent viral entry in vitro but the lack of in vivo studies limits the true validity of this treatment (Sanders et al, 2020). The efficacy of some nucleoside analogues for preventing viral replication is limited or null in vitro, eliminating their promise (Sanders et al, 2020). The use of monoclonal antibodies in limited studies has shown success, with a prominent modulator being IL-6, and serum treatment with immunoglobulins has been standard for other outbreaks like H1N1 and Ebola, making it a promising treatment for Covid-19 (Sanders et al, 2020). As of late November, a number of vaccines, per the CDC, are in phase 3 of clinical trials. The most recent being the Pfizer vaccine which aims to deliver mRNA and per the statement from BioNTech on 11/18/20, this will have a greater than 95% effectiveness. Moderna also aims to create a mRNA vaccine with efficacy of 94.5%. Novavax is aiming to create a spike protein vaccine with adjuvant.

Single Stranded RNA genome of SARS CoV-2 (~30kb length)



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Left is transmission EM of Covid-19 virions and host cells and right is a scanning electron microscopy image. Images are courtesy of Hong Kong University, from the La Ka Shing Image.

Epidemiology:

As per the CDC, minority populations are disproportionately affected by Covid-19, with a ratio of infection for hispanic/latino populations being 7.4 to white individuals in the age range of 18-49. Per the CDC, hispanic/latino individuals are more likely to be afflicted by Covid-19 by a factor of 4.3. This may be due to access to proper protective equipment, medical education, or a culture about disease. The CDC reports that hispanic individuals tend to be averse to medical intervention, which may contribute to their increased risk for Covid-19. A more concerning issue is that hispanics have a lower average socioeconomic status when compared to non-hispanic whites in the US, as well, there is a concern for access to health insurance (Escarce et Kapur, 2006). Factors including language, acculturation, and region confound this, though it is interesting that the Asian population is not as extensively affected considering similar factors; Asian-Americans are at an average twice as likely to contract Covid-19, as reported by the CDC, though this tapers off to a factor of 1 when individuals reach 65 and above. The CDC also reports a higher mortality rate in Asian, Hispanic, and Black populations.