A Review of the Emerging Literature on SARS-CoV-2 and COVID-19

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Introduction

Coronavirus Disease 2019, or COVID-19, quickly developed from a 'bad flu' into a global pandemic from the end of 2019 through 2020. The goal of this paper is to present a scientific view of COVID-19's rapid rise, as well as the response mounted against it, both in research laboratories and in government intervention. To simplify an extraordinarily large body of research into a manageable amount given resources available, four specific topics were focused on:

1. The origins of SARS-CoV-2 in animal populations and the specific vector species from which the first human was infected.
2. The mode of infection and its biological impact on humans.
3. Potential treatments to COVID-19, both those that treat an infected individual and those that prevent infection.
4. The effects of public health policies, social distancing, masks, etc. on disease transmission.

Origins of SARS-CoV-2

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the virus responsible for causing Coronavirus Disease 2019 (COVID-19), is a betacoronavirus, the same genus of virus as Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome (MERS) [1, 2, 3]. SARS-CoV-2 shares ~80% of its genome with SARS-CoV but even less with MERS [4]. SARS-CoV-2 and the original SARS virus share their mode of infection, the spike protein, and their most likely place of origin, bat populations [4, 5]. Bats have been implicated as hosts to many emerging and known zoological viruses, although bats themselves do not always transmit the viruses directly to humans. Viruses that come from bat populations have been known to enter human populations from a different species entirely by cross species transmission (CST). This means that even though COVID-19 shares 92% of its genome with a known bat coronavirus,

RaTG3, and therefore likely originated in a bat population, the vector that first infected humans with COVID-19 may not have been a bat [6].

Another instance in which a secondary vector was responsible for infecting humans was the MERS virus [7]. MERS's ancestral home is in bat populations, but only after the virus infected camels in Saudi Arabia did humans become exposed to the virus, via their camels [7]. Despite research into SARS-CoV-2 and its potential host species, none has yet to be confirmed [8]. Not all bats share the same viruses, but there is evidence showing that bats may all share a resistance to viruses, because their immune systems do not react to them with as great inflammation as other mammals' immune systems do [9].

Another type of virus found in bats is the betacoronavirus group [10]. Betacoronaviruses appear to be inherently zoonotic, or at least zoonotically inclined, as five of them have infected humans, with three having such great effect that they were labeled epidemic or potentially epidemic [11]. A recent study showed that betacoronaviruses with zoonotic potential can be found in wild animals the world over [12]. This means that another coronavirus like SARS-CoV-2 could cause another global pandemic if given the opportunity to infect a person. The way to counter this, as suggested by Ping Yu in a study on bat coronaviruses, is to limit human/wildlife interaction while simultaneously pursuing further research into bat related coronaviruses that have zoological and pandemic potential [13]. The ability to prepare for and develop vaccines against new viral threats is directly linked to knowledge of those viruses before and as they cross the species barrier by infecting humans.

SARS-CoV-2 in the Body and the Biological Impact of COVID 19

SARS-CoV-2 is spread via direct person to person contact. Respiratory droplets containing virus particles, thought to be the main form of transmission, are released by infected

individuals through oral and nasal expulsions [14, 15]. Coughing and sneezing are both well-known forms of respiratory droplet production, but recently speaking and especially singing have been identified as greater sources of droplets [16]. These droplets are spread by both symptomatic and presymptomatic individuals with COVID-19 infections [17]. Stadnytskyi et al. (2020) found that, over an hour, these droplets fall in a reverse exponential curve decreasing rapidly at first and slowly leveling out [17]. The virus infects the lungs first, then may infect other organs [18]. The colon is a potential target for initial infection as well, but such an infection has yet to be proven to take place before a lung COVID-19 infection [19].

When inhaled or otherwise taken into the body, SARS-CoV-2 cannot infect cells and begin replication unless it comes in contact with a special kind of cellular transport protein, the Angiotensin-Converting Enzyme 2, or the ACE2 receptor [20]. This receptor is found on cells in the lungs, kidneys, heart and intestines [21, 22]. ACE2 expression is highly expressed in intestinal cells, which indicates that intestinal cells are a likely target for SARS-CoV-2 infection [19]. Gastrointestinal (GI) symptoms (such as abdominal pain and diarrhea) have been observed in 20-50% of COVID-19 patients, which further indicates that the virus influences the GI tract [23, 24, 25]. Some studies have found SARS-CoV-2 RNA in stool samples from infected patients without finding active virus in the samples, yet conflicting studies have found active SARS-CoV-2 in stool samples [26, 23]. Intestinal Epithelial Cells (IECs) are the cells in the intestine that often targeted by intestinal viruses [19]. Zang et al. (2020) found that SARS-CoV-2 could infect IECs, but simulated human colonic fluid quickly rendered the virus inactive and therefore noninfectious [19]. Their findings meant that even if virus particles from a COVID-19 colon infection were to be excreted, they would be noninfectious [19]. Given the previously mentioned studies that found live virus within the feces of COVID-19 patients, however, the fecal to oral route cannot be disregarded [23].

The SARS-CoV-2 virus uses its spike glycoprotein, a specially made protein also present in the SARS coronavirus, to invade the ACE2 receptor and infect the cell [27]. The immune system's response to this varies by the individual affected, but when the response is poor, a cytokine storm may occur [28, 29]. This uncontrollable release of pro-inflammatory cytokines may lead to damage in the affected organs because of the intense swelling and even lead to multiple organ failure [28]. The COVID-19 symptom with the highest mortality rate, however, is Acute Respiratory Distress Syndrome (ARDS) [28, 30]. ARDS is treated with supportive care, and cytokine storms are treated with anti-inflammatories, but the best treatment for COVID-19 continues to be prevention [31, 28]. This is especially important because those at highest risk of dying from COVID-19 are also those who get infected at the highest rates [32].

COVID-19 infections and mortality are both age related. Younger people disproportionately get infected at a lower rate with decreased severity of symptoms, while older people get infected at higher rates, experience more severe symptoms and have higher mortality rates [32]. In addition, fatalities are highest in those with comorbidities, including diabetes, hypertension and cancer, making prevention all that much more important for the at-risk population [32].

Treatments for COVID-19

Prevention through quarantine, social distance and face masks is possibly the most currently relevant of treatments for the public, as such practices affect everyone who participates in a country that requires such preventative measures [15]. Prevention is only one of many diverse approaches the scientific community is taking to solve the problem. Other, more invasive, treatments attempt to disable COVID-19 after an infection has already begun, such as the two lead peptidomimetic aldehydes created by Dai et al (2020) that are meant to bind to the main protease of SARS-CoV-2 and incapacitate the virus [33]. There are also supportive care treatments administered to patients to assist their immune systems in fighting off the virus, such as ventilators used for ARDS patients [28].

The two main kinds of treatments undergoing research, however, are anti-inflammatories and vaccines. Acalabrutinib, a Bruton Tyrosine Kinase (BTK) inhibitor, acts as an anti-inflammatory by preventing BTK from activating and signaling macrophages [34]. When administered to 19 hospitalized COVID-19 patients, they all regained some degree of oxygen function. Tocilizumab, another anti-inflammatory, was used on COVID-19 patients who were in in either severe or critical condition

[35]. These patients all saw a drop in temperature the day they received their Tocilizumab treatment, and they all regained lung function to an extent. Though the success of both of these anti-inflammatories seem to point to anti-inflammatories being the answer to COVID-19, the solution is not so simple. New studies show that while some patients may experience cytokine storms, others experience ineffective immune systems that require support to prevent being overwhelmed by the virus [36, 37]. More research is required to fully understand why both anti-inflammatories and immune system boosters are effective at treating the same virus in different people.

The other main treatment being researched to combat COVID-19 is the vaccine. Vaccines have shown promise in the prevention of COVID-19 in preliminary studies using rhesus macaques as human substitutes [38]. The macaques tolerated the vaccines reasonably well and did not get infected a second time when exposed to the virus 6 weeks after the initial infection. Additionally, another study using rhesus macaques found that after infection with COVID-19, the monkeys appeared to be immune to reinfection, further validating the first study [39]. Unfortunately, both were small and relatively short studies, which makes the scope of their findings limited. Human trials for vaccines are underway in several countries, but none have been completed. The downside to making vaccines for viruses is that they must be updated frequently. The flu vaccine, for example, must be remade and redistributed every year because the flu mutates and evolves so rapidly [40]. Fortunately, COVID-19 does not mutate as fast as other viruses do because of certain editing enzymes it possesses [41]. This means that a COVID-19 vaccine will be all that more useful.

Efficacies of Public Policies

Effectiveness of Public Health Policy varies around the globe. The Chinese Government claims to have had remarkable success in halting the spread of COVID-19 within their own borders using masks and quarantining strategies [15, 41]. In contrast, most other countries have handled the virus outbreak poorly. The United States federal and local governments have asked and ordered facial masks to be worn and social distancing practiced [42, 43, 44]. Despite these rules and requests, the United States of America (USA) continues to have the highest number of COVID-19 cases in the world

[41]. It should be noted that despite having the most cases, the USA is ranked 10th in deaths per capita globally [41]. A wide variety of reasons are at play regarding the USA's performance, it may be that not all citizens comply with what is asked of them, but it may also be due to misinformation or poorly designed public policies regarding COVID-19. In New York City, for example, lockdown and social distancing were required for a full month before masks were, and their COVID-19 cases rose seemingly exponentially in that time [15]. Yet within two weeks of requiring masks to be worn, the number of new COVID-19 cases each day began to fall [15]. Italy faced a similar situation, with similar results [15]. Taken together, social distancing without face masks is inferior to social distancing with face masks.

Masks clearly made a difference when worn and used with social distancing, as can be seen in New York City and Italy. Yet not all masks are created equal. The respiratory mask, or N-95 mask, is meant to prevent the wearer from inhaling virus particles and from exhaling them beyond the N-95 mask, as it is meant to be sealed with air only entering the mask through the filter [45, 46]. The standard surgical mask is meant to protect the wearer from outside droplets from entering the nose and mouth while simultaneously catching microscopic particles that leave the wearer's mouth, but it does not seal and thus does not protect the wearer as well as the N-95 mask does [46, 47]. Cloth masks are not nearly as effective as surgical masks, blocking roughly a third of the particles a surgical mask does [47]. However, they do reduce the number of exhaled particles, so it is better to wear a cloth mask than none at all to prevent COVID-19 transmission [47].

Conclusions and Further Lines of Inquiry

Despite the best efforts of many scientists, the original vector remains unknown. What is known is that bats and other animals are known carriers for betacoronaviruses that can mutate to infect humans. The right response to the COVID-19 crisis is not to find the bat population COVID-19 came from and destroy it, but rather to assume that all bats carry the potential for deadly diseases within them. Only by preserving land for bats to live on and respecting those boundaries can another crisis like COVID-19 be averted.

COVID-19 infects certain organs using the ACE2 receptor, but the specific effect it has

on those organs and the body as a whole is still under study. Conflicting articles have been peer-reviewed and published regarding the effect of coronavirus infection on the human body, and controversy and corrections are expected given the novelty of the virus and the explosion of research on it [23, 26]. What is known is that the virus mainly affects the lungs and colon, distinctly infecting the lungs first then moving onto the colon [19, 21, 22]. Colon-first infections have yet to be proven but remain a possibility [19].

Treatments for COVID-19 are still undergoing testing and clinical trials. These treatments may come quickly but could also not be ready for public consumption for years to come. The most effective treatment for COVID-19 continues to be prevention over medicine. The best public policies therefore are those that encourage prevention, such as making masked social distancing a requirement for all during any time outside the home or quarantining specific outbreaks of COVID-19 until transmission in an area drops below an acceptable threshold. In addition, surgical masks should be encouraged as the optimal mask to wear, and cloth masks discouraged unless surgical masks are unavailable.

Acknowledgements

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