New Coronavirus (COVID-19) pandemic: complexities resulting in a tragedy.

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Abstract

A striking aspect of COVID-19 is the difference in the outcome of the infection between different countries, and different ethnic groups within one country. We surveyed the literature on SARS-CoV-2 complemented with comparative publications on SARS-CoV and other coronaviruses to capture the current understanding of virus – host interactions including virus subtypes, transmission, zoonotic aspects, and potential host determinants.

Keywords: covid; covid-19; SARS-CoV-2; zoonosis; ethnic disparities; health care disparities; virus strains; virus subtypes; virus variants

Introduction

The novel coronavirus, SARS-CoV-2 which causes COVID-19, has caused many deaths and has put even more patients in intensive care, and therefore induced much anxiety around the globe. The COVID-19 disease started in Wuhan, China at the end of 2019 and has since become a pandemic affecting all countries globally.

Globally, and in the US, we have built biomedical response teams - from basic scientists, clinical trial persons, epidemiologists, clinical response teams, to the physicians, from public health officials, hospitals to biotech and pharmaceutical companies - all are trained to run towards the crisis. We are also trained in networked, coordinated collaborations that ultimately enable the clinical response team to come up with the optimal answer to a disease as dangerous and fear-inducing as COVID-19.

Our current limitations are limiting quantities of protective clothing and equipment for health care workers [1, 2], and beds in hospital floors / wings / buildings that are dedicated to a highly communicable infectious disease staffed by well-equipped personnel. Intensive care equipment specifically reserved for the highly communicable infectious disease including ventilators are also limiting for a large concurrent number of patients, globally (schematically presented in Fig.1).

To add to the health-related fears, our global economy is built on contact, travel and personal interaction. COVID-19 is having a major economic impact, for small and large businesses alike. Therefore, the health care task force is now also asked to address the COVID-19 issue in order to get the economy back on its feet.

To understand the effects of the SARS-CoV-2 infection, we performed a literature review on the material published since January 2020, and added a review of manuscripts on SARS-CoV and other coronaviruses for comparative biology assessment.

SARS-CoV-2.

Virus RNA analysis indicates that the virus developed from a bat reservoir and used a mammalian intermediate host to mutate into a human specific virus [3-5]. Virus genome analysis suggests that there are at least two types of SARS-CoV-2 [6,7]. Three independent science groups have concluded that there is one haplotype that is older, more closely related to the bat viruses, and could have been circulating prior to the Wuhan strain. The region of origin in China of this older subtype remains uncertain, and this virus type potentially causes less severe disease, or spreads at lower frequency [6-8]. The Wuhan subtype SARS-CoV-2 is evolutionary younger, caused the outbreak of severe pneumonia cases in Wuhan and spreads extremely fast [6-8]. These assertions are under debate [9,10] because the variation between the haplotypes is relatively minor, and different biological behavior between the two SARS-CoV-2 types has not been confirmed experimentally [9]. Another independent group has also analyzed virus genomes and concludes that there is a subtype that has emerged in Wuhan prior to the outbreak of the Wuhan pneumonia, and that the prior subtype is closer to the bat genomes and distinct from the subtype that caused the Wuhan pneumonia outbreak [11]. Current PCR tests are designed to identify SARS-CoV-2 [12], but they do not distinguish between SARS-CoV-2 subtypes. Whole genome analysis of SARS-CoV-2 has been used to trace the origin of infectious outbreaks in certain geographic regions to virus sources. In all four studies that have inferred an ancestral type and a later type that caused the Wuhan outbreak, both types of SARS-CoV2 were later traced and sequenced throughout the world (e.g. United States [6-8,11], Japan [6-8,11], Australia [6-8,11], Korea[7], Taiwan[7], England [7]). Therefore, even if there are SARS-CoV-2 types that cause different outcomes in the host (subclinical, or mild vs. severe disease), this cannot be inferred by geographical location, but will have to be investigated using personal whole-genome virus analysis studies.

Analysis of the virus sequence, structure and cell infection studies have identified the SARS-CoV-2 protein, spike protein, that binds to the cellular receptor, ACE-2 angiotensin converting enzyme-2 [3, 5, 13]. The crystal structure of the spike protein identified key differences between SARS-CoV-2 and SARS virus in the receptor binding site [14, 15]. In addition to receptor binding, virus entry requires proteolytic cleavage of ACE2 or spike protein by a cell surface bound cellular protease, most prominently transmembrane protease serine 2 (TMPRSS2) [16]. The proteolytic cleavage of spike protein is essential for virus entry into the cells [16, 17].

Fewer reports indicate that SARS-CoV-2 can utilize another cell entry way via CD147 [18, 19]. CD147 exhibits a different expression pattern, which includes leukocytes, erythrocytes and skeletal muscle. T cells have been reported to be infected by SARS-CoV-2 via membrane fusion [20]. However, blood samples have been mostly negative for virus RNA [21], therefore it is not clear how frequently the CD147 virus entry or the membrane fusion pathways are utilized.

Management.

The most important management tool is social distancing (closure of schools, universities, restaurants, art institutions, sports, limiting gathering in groups, delaying elections, distancing between individuals, limiting travel) [22, 23]. Currently, there is not yet any specific treatment available for COVID-19. To bridge the time until specific treatment becomes available, drug libraries have been scanned to identify candidates that could be repurposed for COVID-19 [24, 25], and new potential drug candidates were identified (e.g. remdesivir). Despite still ongoing or inconclusive clinical trials [26], antiviral treatment is regularly used in China [27, 28], Singapore [29], many European Countries [30], and in the United States [31, 32]. A global clinical trial of these drugs has just been announced by the World Health Organization [33].

Prophylactic treatment is being evaluated in clinical trials [34]. This could be considered for health care workers, persons at high risk, their caretakers and families who live in hot-spot areas, and who have been in contact with persons who tested positive.

Vaccine. Clinical vaccine trials have just started in the United States [35], and others are planned globally and in the United States [36]. However, no vaccine is expected to be available for at least one year. The strategy used for the human vaccines relies on recombinant molecular biology technology to create recombinant viruses / virus epitopes. Even in the case that the vaccines may induce immune responses that are not fully protective, they will aid in boosting the response to virus challenge.

Transmission. ACE2 and TMPRSS2 co-expression is most frequently observed in epithelial cells, for example in the tracheal, bronchi and alveoli, as well as intestinal epithelial cells [37]. This expression pattern corresponds to an aerogenic transmission which is also supported by detection of the virus in pharyngeal swabs, and sputum (Fig.1 schematic). Additionally, oro-fecal virus shedding occurs to a lesser degree and lower frequency, and virus is detected in stool samples even in the absence of diarrhea [21, 38]. A consequence of the presence of fecal SARS-CoV-2 RNA and the environmental stability of the virus [39] is the detection of virus RNA in sewage, for example measured close to the Amsterdam Airport and in other cities in the Netherlands and Massachusetts [40-42]. The detection of virus RNA in wastewater can be used as a means to understand the presence of the virus in the population [40-42]. Experimental spiking of coronaviruses to wastewater has demonstrated virus stability for 1-3 days [43]. Based on these experimental studies and virus

transmission tracking of the previous SARS virus (SARS-CoV) [44, 45], water and wastewater aerosols could also be potential routes of transmission of the current SARS-CoV-2 [46, 47].

Using the previous SARS-CoV data to derive a modeling framework, the current SARS-CoV-2 outbreak was analyzed. This indicate that fecal-oral transmission (e.g. via aerosol droplets from wastewater) has played a role in amplifying the epidemic in Wuhan, but not the less severe outbreaks in Singapore and Taiwan [48]. However, direct experimental studies of infectious SARS-CoV-2 in feces or wastewater are not available yet.

Tests.

Diagnostic tests are based on the detection of virus RNA or antibodies specific for SARS-CoV-2 [49]. Current limitations of the test for virus RNA are that these tests are rather slow, and do not distinguish between virus sub-types. Antibody assays are designed with the receptor binding site of spike protein, or the nucleocapsid protein of SARS-CoV-2 as antigens (baits) [50, 51]. These antibodies are expected to be virus neutralizing because they reduce virus replication. Antibody tests will identify people who have already undergone SARS-CoV-2 infection. Furthermore, the identification of neutralizing antibodies can be used for therapeutic purposes by engineering these antibodies in vitro for passive immunization of person affected with COVID-19.

Zoonosis.

COVID-19 started as a zoonosis. The precursor of SARS-CoV-2 developed in bats. Perhaps climate change that affects reproduction and feeding behaviors [52], and fungal disease prevalence in bats may have caused more replication and mutation of coronaviruses in these animals [53]. The closest relative to SARS-CoV-2 infected an intermediate host, most likely a mammalian host.

There is no evidence exactly how SARS-CoV-2 migrated to humans and acquired the ability to spread from human to human. Additional direct observations of the zoonosis include a small but measurable virus load in two dogs in Hong Kong, China, perhaps transmitted by their human owners [54]. Further, the Bronx Zoo in New York, United States, had one tiger that tested positive for SARS-CoV-2 [55]. The test was performed because several tigers and lions in the zoo showed dry coughs and the animal handler presented as asymptomatic SARS-CoV-2 carrier. Because humans usually stay at distance from tigers and lions, there may be a possibility that the animal's food (raw meat) or water may have become virus positive and this is how the virus was transmitted. Reports from China identified house cats with antibodies against SARS-CoV-2 [56] and from Belgium identified two virus positive cats [57]. Experimental infection studies from independent groups have demonstrated that house cats can be infected by the airway route, and that they can transmit the virus to co-housed cats [58, 59]. Social distancing may be a suggestion to pets, for example, dog runs were closed in New York City as of April 6, 2020 due to potential overcrowding. There are few feral cats in big cities like New York City, and therefore, cats or other pet animals are currently not considered a virus reservoir that would amplify the infection risk for humans [60].

There are no reports that livestock like pigs, chicken or cattle are infected by SARS-CoV-2. However, experimental infection studies were only performed via the airway route, the oral infection route was not explored, and systematic testing of meats and poultry is lacking [58, 59]. On the other hand, comparative analysis of the ACE-2 binding site for the SARS-CoV-2 spike protein [61], and a cell transfection study with pig ACE-2 [5] has suggested that livestock could be potentially infected. Livestock meat processing plants in the United States have had a spike of SARS-CoV-2 positive workers in many states, forcing the plants to close [62]. It is possible that infections occurred

because of humans working together in close proximity. Regardless of infection source, food products could potentially become contaminated because of the environmental stability of the virus (Fig.1 schematic), although this has not been demonstrated. International public health organizations recommend to cook meat and eggs [63, 64].

Risk.

Many chronic conditions increase the risk for COVID-19 including hypertension, cardiovascular disease, diabetes, cancer, autoimmune disease [22, 27, 29, 65, 66]. In many of these cases, the underlying disease causes changes that predispose for severe outcome. In others, COPD, nicotine inhaled via cigarette or perhaps also e-cigarette smoking has been shown to increase the expression of ACE-2 in the airways [67, 68], thereby providing more cellular targets of SARS-CoV-2.

The highest risk for COVID-19 is posed by group living of mostly elderly people in a nursing home or retirement home, where many of the residents may not survive COVID-19 [69]. The age of the persons in group housing is not the determinant of the increased susceptibility to being infected with SARS-CoV-2. Group housing of groups of persons of mixed age on cruise ships has resulted in multiple outbreaks of COVID-19 [70]. Large groups of younger persons living at close quarters on naval ships are also at increased risk for becoming infected with SARS-CoV-2, some of whom developed COVID-19, and consequently died [71]. Perhaps people living at close proximity, the high risk of SARS-CoV-2 infection is determined by the multiplicity of routes of transmission that SARS-CoV-2 can take (inhalational person to person, environmental, oro-fecal).

Other groups that were generally considered to be at high risk, are not at increased risk, among them children [72] and pregnant women [73]. In those groups, SARS-CoV-2 infection can occur but there is a substantial percentage of sub-clinical or mild infection [72, 73]. Additionally, among

patients affected with chronic lung diseases, some are not over-proportionally represented among COVID cases, these include asthma [74], and pulmonary arterial hypertension [75]. A search for studies demonstrating clear anti-viral activity of common drugs taken for these conditions has not yielded clear positive data. Therefore, one explanation for the observed data in these patient groups is that infectious disease prophylaxis is routinely and stringently performed as part of the daily management, because any infectious disease could cause a major exacerbation with severe consequences.

Some ethnic groups are at high risk for severe COVID-19, in the United States persons of African American and Hispanic descent in comparison with persons of Caucasian descent [76]. Currently there is no scientific evidence to support genetic resistance that would be the major determinant of this disparity based on polymorphisms in the ACE2 gene [77]. Instead, social and health care disparities are likely the reason for the disparate outcome to SARS-CoV-2 [76,78].

Conclusions. Complexities of transmission, the potential of different responses due to variations in the virus and the zoonotic aspects of SARS-CoV-2 are perhaps the most underappreciated aspects of the COVID-19 pandemic. The management of the pandemic is aimed at protecting these persons who are at risk and also elderly persons [65] and to avert mortality – which could strike anyone infected with SARS-CoV-2. It is important to note that COVID-19 can develop in persons younger than 45 years of age and in children [79,80]. Specific treatments and specific vaccines for SARS-CoV-2 are still many months away and therefore, a big fear concerns the global economy which depends on the health care system's ability to mitigate COVID-19 now. We also have to keep in mind of living in a global world like a village now, only having national crisis plans are not enough, international collaborative plans should be available for the management of SARS-CoV-2.
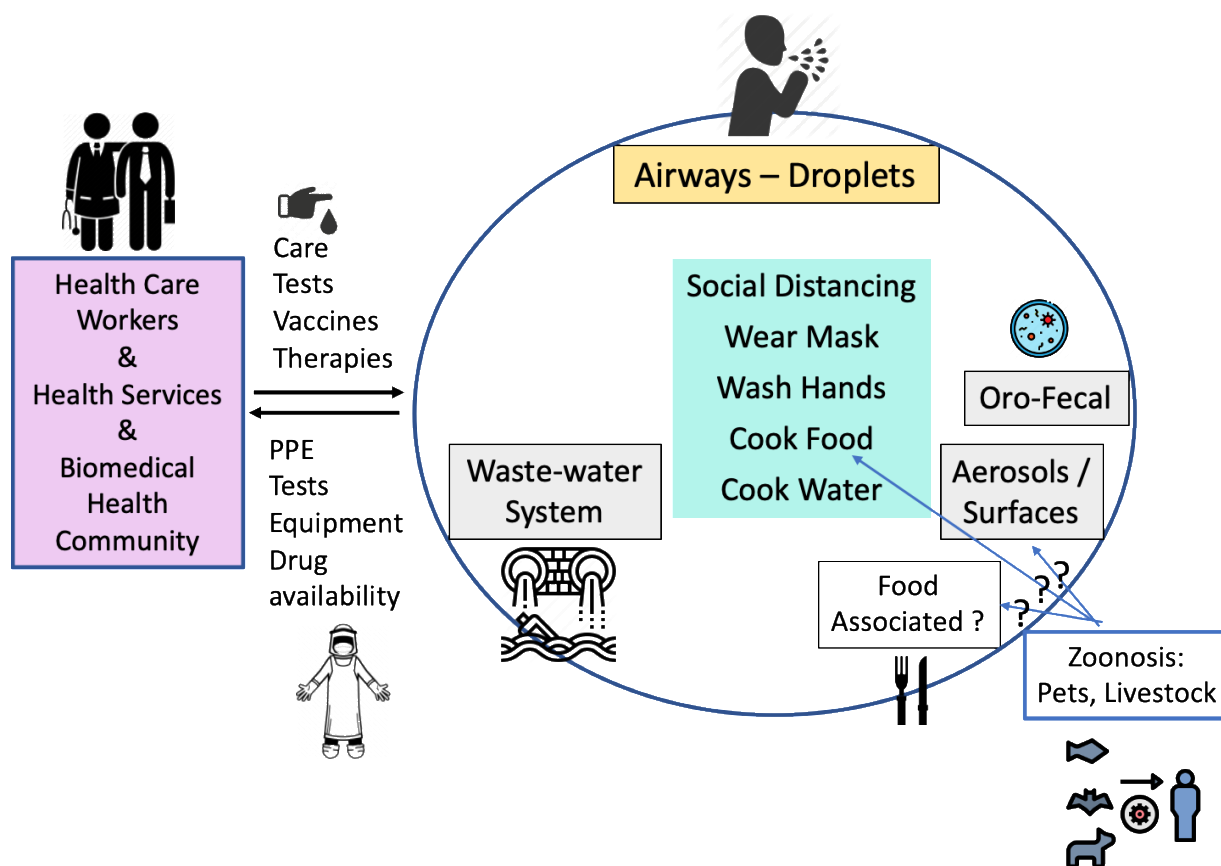
Figure 1: COVID-19, schematic of measures to control spreading and infection.

Established measures and pathways are denoted by text boxes and arrows, while pathways needing

further studies are indicated by '?'.

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