CURRENT PERSPECTIVE ON DETERMINANTS AND DETERRENTS OF COVID-19

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ABSTRACT

Introduction*: COVID-19, the infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has left several countries grappling with a devastating pandemic. Developing an effective COVID 19 vaccine may be possible but there are significant issues with public distrust and vaccine hesitancy. Public health efforts aimed at testing symptomatic patients, and other preventative measures, however, these efforts have been unable to significantly curtail the pandemic. There is a paucity of research that comprehensively focuses on determinants and deterrents to identify critical knowledge gaps. This review aims to focus efforts on strategies to contain the virus.*

Materials and methods: *Google Scholar, PubMed, and archives of preprints were searched with the following terms "COVID-19", "SARS-CoV-2", "2019-nCoV", "epidemiology", "determinants", and "deterrents." The reference lists of articles were examined for relevant studies.*

Results: *All age groups are susceptible and can transmit the virus. Individuals with severe outcomes include but are not limited to age 65 years or older, male sex, ethnic minorities, and the presence of comorbidities. Misinformation on social media and other traditional information sources is a risk factor for COVID-19 morbidity and mortality. Indoor and outdoor aerosolization of SARS-CoV-2, asymptomatic, pre-symptomatic transmission, and incubation period of over 14 days in some infected individuals have been reported. Widespread rapid SARS-CoV-2 population screening and contact tracing are methods of effective containment including proper use of facemasks in crowded outdoor or indoor spaces, installation of HEPA filters, regular hand hygiene, and physical distancing measures. Simple cost-effective measures include opening doors and windows of buildings where possible.*

Conclusion: *Achieving herd immunity with a vaccine may be difficult because of misinformation. A potential incubation period of over 14 days is the bane of Covid-19 current control strategies. More research is needed including investigating the long-term effects of Covid-19 particularly in children, and fecal aerosol transmission. Evidence-based information and the identified infection prevention measures should be advocated.*

Keywords: *COVID-19, pathogenesis, risk factors, determinants, deterrents.*

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Introduction

COVID-19, the infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has left several countries and territories grappling with a devastating pandemic. Genetic studies found that SARS-CoV-2 shares almost 80% and 50% sequence identity with SARS-CoV and Middle Eastern Respiratory Virus Coronavirus (MERS-CoV) respectively[1]. The genetic variations between SARS-CoV and SARS-CoV-2 translate into differences in infectivity and immune response[2, 3]. As of 13th August 2020, COVID-19 global confirmed cases were 20,634,064 and 749,576 deaths[4]. However, the Center for Disease Control (CDC) reported that it is likely that greater than 10 times more SARS-CoV-2 infections occurred than the reported number of cases in some sites[5]. In comparison to MERS-CoV or SARS-CoV, SARS-CoV-2 has a lower case-fatality rate (CFR) but spreads more efficiently, making it difficult to control[6]. CFR is the ratio of the number of deaths divided by the number of confirmed (preferably by nucleic acid testing) cases of the disease. A better estimate of COVID-19 fatality is infection fatality risk (IFR), which is the ratio of deaths divided by the number of actual in-

fections with SARS-CoV-2. Nucleic acid testing is limited and currently available primarily to people with significant indications of and risk factors for COVID-19 disease, and because a large number of infections with SARS-CoV-2 result in mild or even asymptomatic disease, the IFR is likely to be significantly lower than the CFR. A study estimated the IFR for 5 age groups; <25years 0.011; 25-44 years 0.12; 45-64 years 0.94; 65-74 years 4.67; 75+ years: 13.83 during March 22-May 16, 2020. The overall estimated IFR was 1.45%. In particular, weekly IFR was estimated as high as 6.1% for 65-74 year-olds and 75+ year-olds: 17.0%[7]. These rates depict the gravity of COVID-19 among the older population and the significance of preventative measures in elderly residents and other long-term care facilities. As the world grapples with the COVID-19 pandemic, curative pharmacotherapeutics are still not available but potential effective vaccines are awaiting emergency use authorization. Previous attempts to produce effective vaccines for SARS-CoV or MERS failed[8].

It has been suggested that developing an effective COVID 19 vaccine looks promising but there are still significant issues with public distrust and vaccine hesitancy [9, 10]. In addition, research suggests IgG levels and neutralizing antibodies in a high proportion of individuals who recovered from SARS-CoV-2 infection start to decrease within 2-3 months after infection making the arguments for herd immunity weak[11, 12]. Therefore, public health efforts aimed at testing symptomatic patients, and other preventative measures. However, these efforts have been unable to significantly curtail the spread of the pandemic[13]. Given the accelerated transmission of SARS-COV2 and the associated remarkable morbidity and mortality, it is important to leverage evidence from prior research. There is a paucity of research that comprehensively focused on determinants and deterrents to identify research gaps. This review aims to focus efforts on developing research and health strategies to contain the virus, reduce hospitalization and mortality.

Materials and methods

Google Scholar, PubMed, and archives of preprints were searched with the following terms in all combinations and without date restrictions until August 2020: "COVID-19", "SARS-CoV-2", "2019-nCoV", "epidemiology", "determinants", and "deterrents." Hand searching of reference lists in each journal article found was also done. Relevant articles published after 1 December 2019 were included.

The titles of retrieved articles were reviewed by the author to eliminate studies that did not meet the inclusion criteria of determinants and deterrents of COVID-19 before the full review of abstracts and full-text of selected studies.

Results and discussion

Virology and pathogenesis

SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA genome beta coronavirus of the family Coronaviridae[14, 15]. Coronaviruses that spread to humans included several common cold viruses, such as hCoV-OC43, HKU and 229E5[6]. However, animals including camels, cattle, cats, pangolins and bats, are known intermediate hosts of coronaviruses[16]. The intermediate hosts of SARS-CoV and MERS-CoV are the civet and camel. Pangolin has been identified as a possible intermediate host of SARS-CoV-2, because of the high sequence identity (99%) between pangolin origin CoVs and SARS-CoV-2. Besides, SARS-CoV-2 also demonstrated a high sequence identity to some bat CoVs (96%)[16, 17].

In human to human transmission, the nasal surfaces are the primary site of infection by SARS-CoV-2 due to its comparatively high Angiotensin-Converting Enzyme 2 (ACE2) concentration[18]. The nose has a range of innate defense responses due to exposure to high but variable doses of environmental agents, producing a spectrum of innate defense responses. The innate defense responses might explain the different types of clinical syndrome of COVID-19[19]. Studies suggest that an oral-lung aspiration axis may be the primary mechanism of infection in the lower airways[20, 21]. Secretions in the nasal cavity are moved from the nasal surface backward by mucociliary action and accumulate in the oral cavity where it mixes with oropharyngeal or tonsillar fluid[22]. At night, an infected individual may aspirate a high concentration of virus that exceed the threshold needed to initiate infection into the deep lung, through micro-aspiration or gastro-esophageal reflex-associated aspiration[21, 23].

Besides, trachea secretions containing the virus may accumulate in the oropharynx through mucus clearance in enough concentration and later aspirated into the deep lung[24]. Oropharyngeal aspirates contain enzymes with or without inflammatory mediators that might make alveolar cells susceptible to infection.

Aspiration of SARS-CoV-2 into the lungs is consistent with the patchy, bibasilar infiltrates seen on chest computed tomography (CT) scan in COVID-19[21]. SARS-CoV-2 mechanism of action exploits the angiotensin-converting enzyme 2 (ACE2), part of the renin-angiotensin-aldosterone system (RAAS). The virus binds to ACE2 and its normal process is altered through multiple mechanisms[25].

The interaction between ACE2 and COVID-19 is based on two possible pathways (i) the SARS-CoV-2 mechanism of infection by direct viral tissue damage and (ii) the regulatory role of ACE2 during RAAS overreaction and dysfunctions of immune responses (cytokine storm)[3]. Although COVID-19 causes significant respiratory infection, it is also responsible for other extrapulmonary conditions such as thrombosis and inflammation, injuries to the heart, liver, intestines, kidneys, and genitals. ACE2 is present in many extrapulmonary tissues.

Transmission pattern

Transmission is usually from an infected asymptomatic, presymptomatic, and symptomatic person to uninfected individuals. Research suggests that presymptomatic transmission exposure occurred 1-3 days before the infected patient develops symptoms[26]. Asymptomatic infection is common and contributes to undetected transmission.

The proportion of asymptomatic infections reported ranges from 4% to 41%[27]. A study conducted in an entire non-institutionalized Spanish population found asymptomatic cases represent between 21.9% and 35.8% of all SARS-CoV-2 infections[28]. The presence of asymptomatic and presymptomatic transmissions of SARS-CoV-2 increases the challenges of current COVID-19 preventative measures based on early detection and isolation of symptomatic persons. This finding reinforces the importance of rapid detection and isolation of confirmed SARS-CoV-2 cases and quarantine of their contacts

The role of children in the transmission of the virus has been under intense scrutiny especially as public health restrictions are relaxed and children return to classrooms. Children younger than 5 years with mild to moderate COVID-19 have high amounts of SARS-CoV-2 viral RNA in their nasopharynx compared with older children and adults[29]. Previous research demonstrates that SARS-CoV-2 spread efficiently and children of all ages are susceptible to SARS-CoV-2 infection and might play an important role in transmission[26, 30].

A study suggests children under the age of 10 years spread the virus at about half the rate of adults but children between 10-19 years old spread it at a similar rate as adults[31].

Modes of transmission

Direct transmission occurs between nearby individuals (within 1 meter) or in direct contact with one another. Droplets that are produced when an infected person coughs or sneezes may land in the mouths or noses of people who are nearby or possibly be inhaled into their lungs[32]. Airborne transmission occurs when an infected individual with coronavirus emits tiny particles (aerosols) bearing the virus when they cough, sneeze, talk, sing, or breathe[33]. The aerosols defy gravity, remain suspended in the air for many hours or even days indoors or long-distance outdoors[32, 34]. Larger aerosolized droplets (>5 μm) remain in the air for only a short time and travel only short distances, generally <1 meter. However, strong airflow such as from air-conditioning could move droplets further. Virus-laden small (<5 μm) aerosolized droplets can remain in the air and travel long distances, >1 meter. Depending on the weather, droplets could travel up to 20 feet in five seconds[35, 36]. A recent study found infectious SARS-Cov-2 RNA on aerosols in Wuhan's hospitals[37] and outdoor in northern Italy[38] suggesting a strong possibility of indoor and outdoor airborne transmissions. Also, aerosolization of fecal matter containing coronavirus when toilets are flush has been reported[39]. Coronavirus survives in the digestive system, and evidence of the virus has been found in human waste[40]. The water droplets from a flushed toilet could travel as high as three feet into the air, however, this could be even higher when a toilet is used frequently, such as in a densely populated area[39]. More research is need but there is good reason to put the lid down before flushing and to treat fomites and air in public toilets as potentially contaminated. Environmental contamination with SARS-CoV-2 increases the possibility of indirect transmission through fomites. Objects might be contaminated directly by droplets or through contact with an infected individual's contaminated hands and transmitted through unhygienic practices[41]. The evidence on vertical transmission is inconclusive. Perinatal transmission of COVID-19 is unlikely to occur if measures to avoid exposure to any source of infection are instituted[42]. However, a neonate born to a pregnant woman with COVID-19 pneumonia tested positive for SARS-CoV-2 infection 36 hours after birth at Wuhan Tongji Hospital[43].

Clinical manifestation and disease severity

The incubation period of COVID-19 is usually 2-14 days but there is evidence that 10% of patients with COVID-19 developed symptoms after 14 days of infection[44]. This has implications for current prevention measures. About 96% of patients with symptoms reported either a fever, cough, or shortness of breath and about 45% experienced all three. Cough was the most common symptom, fever was the next, and shortness of breath was more commonly associated with patients on admission[45].

A range of other symptoms have been reported but changes in smell or taste were more commonly reported by women than by men[45, 46]. Younger patients tend to report altered mental status[47]. More research is needed to investigate the impact of COVID-19 on the brain. Sudre, Lee[48] classified the symptoms of COVID-19 into six categories that predict disease severity and the need for dedicated medical support:

• Category 1 with no fever: headache, loss of smell, muscle pains, cough, sore throat, chest pain, no fever.

• Category 2 with fever: headache, loss of smell, cough, sore throat, hoarseness, fever, loss of appetite.

• Category 3 (gastrointestinal): headache, loss of smell, loss of appetite, diarrhea, sore throat, chest pain, no cough.

• Severe category 4 (fatigue): headache, loss of smell, cough, fever, hoarseness, chest pain, fatigue.

• Severe category 5 (confusion): headache, loss of smell, loss of appetite, cough, fever, hoarseness, sore throat, chest pain, fatigue, confusion, muscle pain.

• Severe category 6 (abdominal and respiratory): headache, loss of smell, loss of appetite, cough, fever, hoarseness, sore throat, chest pain, fatigue, confusion, muscle pain, shortness of breath, diarrhea, abdominal pain.

The first, second and third categories are associated with a 1.5%, 4.4% and 3.3% chance of needing breathing support such as oxygen or a ventilator. The last three categories of COVID-19 are severe types. In categories four, five, and six, patients need breathing support at a rate of 8.6%, 10%, and 20% respectively. These three severe categories would need ventilator support, with higher risk of mortality. Patients in the severe categories also tended to be older or with pre-existing conditions and weakened immune systems, compared to those in the first three categories. Only 16% of patients in category one required hospitalization, compared with nearly half of the patients in category six. Studies suggest that it takes more than 2-3 weeks after testing for the resolution of symptoms and return to usual health among persons with no chronic medical conditions. Older age and the presence of multiple chronic medical comorbidities were associated with severe or prolonged symptoms[49].

Interestingly, children have largely been spared the severe effects of COVID-19 but a small percentage who test positive develop a life-threatening condition called Multisystem Inflammatory Syndrome In Children (MIS-C). Most cases of MIS-C have features of shock, with cardiac involvement, gastrointestinal symptoms, and significantly elevated markers of inflammation, with positive laboratory test results for SARS-CoV-2[50]. The long-term effects of MIS-C are unclear.

Risk factors

Patients with chronic obstructive pulmonary disease, heart conditions, diabetes, chronic kidney disease, and obesity are six times more likely to be hospitalized, five times more likely to need intensive care, and twelve times more likely to die from the disease[51, 52]. Other factors associated with death included age >65 years, male sex, cancer, acute organ dysfunction, and admission to a hospital with fewer intensive care unit beds[53]. Patients with hypertension, which is the most frequent comorbidity, had significantly decreased survival and hypercholesterolemia is independently associated with mortality[54].

Smoking is a risk factor for the progression of COVID-19, with smokers having higher odds of COVID-19 progression than never smokers and an increased symptom burden[55].

Ethnicity and income inequality are independently associated with COVID-19 mortality[56]. Ethnic minority communities are more likely to be socioeconomically disadvantaged than white communities and often live in extended cohabiting families, engaged in high-risk jobs, potentially increasing the risk of virus transmission and more often have underlying health conditions[57, 58].

Blood type A is associated with a higher risk for COVID-19 infection and mortality while blood group O is associated with a lower risk of infection and mortality[59]. Blood type A was correlated with higher odds of testing positive for infectious disease[60]. However, a recent study found blood type is not associated with risk of progression to severe disease[61]. The evidence is inconclusive.

Misinformation about COVID-19 pandemic and unfounded claims that potential vaccines could

kill exist in social media[62]. Recent research suggests that areas with greater exposure to Fox News show downplaying the threat of COVID-19 experienced a greater number of cases and deaths[63]. Besides, COVID-19 misinformation in social media has been associated with deaths[64, 65]. The implication is that misinformation is a potential risk factor for COVID-19 morbidity and mortality.

Deterrents

Widespread rapid population testing to detect asymptomatic and presymptomatic cases is crucial in curtailing the spread of the virus.

Social distancing, quarantine, and isolation

Research suggests the peak attack rate in a population could be reduced by case isolation, household quarantine, school, university, and work closure[66, 67]. The Wuhan quarantine reduced transmission of COVID-19 cases from mainland China to other countries by about 77% by early February 2020[68]. Preventing international travel and land borders closures are effective in limiting the transmission of the virus when enforced for more than two weeks[67]. However, shutting down public transport was not associated with any additional benefits[65, 66].

Facemasks

There is an inverse correlation between the duration of implementation of facemask or respirator policy and per-capita coronavirus-related mortality. Countries without masking policies, had 54.3% increase in per-capita coronavirus-related mortality per week after patient zero, compared with 8.0% in countries with masking policies[69]. Previous studies indicate that both surgical masks and homemade cloth face coverings can reduce the aerosolization of virus into the air and on surfaces[69] and protect wearers from contracting the disease[70]. In case of shortages of surgical masks, a cloth face covering with at least two layers but three is preferable. Research indicates that a 12-layered cotton mask was as effective as a surgical mask and a single-layered cloth mask was not protective against beta-coronaviruses. Several factors determine the efficacy of cloth masks such as type of material, the number of layers, the arrangement of different layers, the frequency of washing, and if they are properly worn[21, 71]. N95 respirators should be used in healthcare settings. However, the adequate availability of personal protective equipment does not seem to completely reduce COVID-19 risk among health-care workers[72].

Ventilation

Sufficient and effective ventilation such as circulating fresh outdoor air to minimize recirculating indoor air, the use of high-efficiency particulate air (HEPA) filter particularly in public buildings, workplace environments, schools, hospitals, and nursing homes supplemented with airborne infection controls such as germicidal ultraviolet lights (UVC) have been suggested[73]. Other simple measures that could be adopted in buildings include opening both doors and windows to increase airflow rates where possible and installing carbon dioxide monitors to know if the air is being refreshed properly[74].

In vehicles, windows could be open and when air conditioning or heating system is used, the air should not be recirculated but set to include outside air. Treating patients in negative pressure systems with HEPA filter offers additional protection to healthcare workers utilizing noninvasive positive-pressure ventilation for patients[75].

Frequent cleaning of surfaces and handwashing

Viruses in droplets and aerosols that settled on fomites could get re-suspended in air, where they could lead to infection. Cleaning surfaces using vacuums with HEPA filter and frequently cleaning and disinfecting surfaces are strategies that may also help reduce fomite and secondary airborne transmissions[76]. Studies suggest that regular hand washing would lead to a decrease in peak infection rate of about 65% and a 29% reduction in total infection rate[65]. SARS-CoV-2 will not cause large outbreaks in communities with 90% uptake of handwashing, mask-wearing and social distancing measures that are 25% efficacious[77].

Evidence-based information provision

Accurate information provision via social media and traditional information sources serves as cues for individuals to follow health advice, develop favorable dispositions towards preventative measures, and acquisition of knowledge have been associated with protective behavior[65].

Pharmacotherapeutics

There are therapies for COVID-19 patients but have substantial limitations. Remdesivir is given to hospitalized patients. It does not provide a survival advantage but faster recovery in those who survive[78]. Dexamethasone is a potent corticosteroid that suppresses the immune system. It is used for se-

verely ill patients requiring oxygen support, but not for mild or moderate disease[79]. Another therapy is convalescent plasma but clinical trials have been inconclusive on efficacy. Still under study are monoclonal antibody therapies, favipiravir, and LAM-002A, previously tried in lymphoma treatment, which may interfere with viral attachment and be useful in early Covid-19. Regeneron an antibody cocktail has been granted emergency use authorization by the United States health regulators. Several vaccines are currently in clinical trials with two awaiting emergency use authorization and there is cautious optimism for future effective vaccines[77, 78].

Conclusion

Asymptomatic, pre-symptomatic transmission of SARS-CoV-2 and a potential incubation period of more than 14 days are the bane of Covid-19 pandemic control based on current public health strategies. The rapid spread across countries, outbreaks in countries that successfully reduced transmission and the ultimate need to relax current social distancing practices argue for widespread SARS-CoV-2 population testing and contact tracing. The findings also support the case for the public to use facemasks when in crowded outdoor or indoor spaces, use of HEPA filtration systems in crowded indoor spaces, regular hand hygiene, and physical distancing measures. However, misinformation is a potential risk factor for COVID-19 and could discourage vaccine uptake. More research is needed such as to investigate vertical transmission, the impact of blood type on disease severity, the long-term effects of Covid-19 particularly in children, and fecal aerosol transmission.

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