

Association of COVID-19 Disease Severity with Transmission Routes and Suggested Changes to Community Guidelines

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ABSTRACT

In the war against the COVID-19 pandemic, the world is experiencing severe resource constraints. Although transmission routes are well understood, we suspect that they cause different disease consequences. We evaluate them in different forms to understand how they affect infection rates and disease severity. In determining how they affect disease outcome, we evaluated target tissue vulnerability, functional role, defense mechanisms, viral concentration, infection vicinity to target vital tissue, and host factors. We found that direct lung infection is the most lethal transmission route followed by bronchi infection. Transmissions by physical contacts, foods, and blood by low viral concentration (as expected in normal human activities) pose lower or much lower risks unless the infection is followed by subsequent lung exposures. After adding transmission route, treatment timings, and improper treatments into the list of known risk factors, we found that death rate and disability rate for young or healthy persons are nearly zero. We show that population based medical model improperly shifts nominal death rate from few vulnerable people to the population resulting in unnecessary population panic, and such panic is responsible for shutting down human activities and the world economy. Finally, we examined limitations in population-based mitigating measures and proposed for governmental and private adoption community guidelines, which are mainly

to enable vulnerable people avoid exposures, prevent non-vulnerable people from serving as viral transmitters, get rid of high-risk exposure modes in working environment, improve safety for people in buses, ships and planes, and reduce death and disability rates for infected people.

INTRODUCTION

At the time of writing this article, there are 125,048 total cases, with 4613 deaths in 26 countries [1]. At least most countries have reported cases. In the U.S., 1215 infection cases were reported in 43 states [2]. So the rate of increase of new cases are so fast that the pandemic causes public concern. After the outbreak of the COVID-19 disease, the world is trying to find methods to contain the pandemic. The biggest problem is that no nation can meet the rapidly rising demand for resources.

In order to best use resources for mitigating the pandemic and treating patients, we believe it is time to revisit some basic epidemiological concepts. CDC guidelines for influenza use an implied presumption that disease severity for an influenza is same, as shown in FIGURE 5 [3]. This presumption has been widely accepted in population-based medicine. In most studies, disease severity is found to depend on the virulence of the influenza virus strain and the immune competence and previous influenza exposures of the patient [4].

We believe that transmission routes play a critical role for COVID-19 disease outcomes. We found that the presumption was never approved but is refuted by findings in research articles on infection diseases. Specific host factors greatly enhance the efficiency with which certain influenza virus-infected persons transmit disease to subsequent, susceptible hosts so-called "superspreaders" [5, 6]. While this study did not focus on transmission routes, transmission route may be a hidden factor. Higher levels of TNF- α and IL-6 were also significantly associated with more efficient airborne transmissibility, which ranged from 67-100% for the human isolates to 0% for the H5N1 strains [7].

Early research before 1966 in human subjects demonstrated that airborne influenza virus, inhaled as an aerosol, was more infectious than virus applied via liquid droplets into the nose [8]. There is difference between aerosol and intranasal inoculation. The results indicate high infectivity via either route, but intranasal inoculation by liquid leads to about 20 times lower infectivity than when the virus is delivered in an inhalable aerosol, probabilities of infection by either aerosol or sedimentating droplets are approximately equal. Droplet transmission results in a slightly higher illness risk due to the higher doses involved [9]. The relative importance of the transmission routes have been debated intensively, but it still remains unclear if any route is dominant [10, 11]. Despite the immense importance of their findings, no further work has been

done, and U.S. CDC 2017 Community Guidelines for influenza still reflects the obsolete presumption.

The mystery appeared in animal infectious disease again. The critical role of transmission routes was reflected in *Actinobacillus pleuropneumoniae*, a bacterium causing respiratory problems in pigs [12]. In this study, each paired test, one pig was inoculated intranasally with 5×10^6 CFUs of *A. pleuropneumoniae* strain 1536 and housed together with a pig which is exposed by contact. Disease severity in inoculated pigs were higher compared to contact pigs. The survival days of some inoculated pigs were only 2 to 4 days as compared with 21 days of the contact-infected pigs. Inoculated pigs had observable lung or pleurisy lesions. In addition, disease severity was positively associated with bacterial load in inoculated pigs, and bacterial load. This finding implies the role of infection location relative to the lungs.

The critical roles of transmission routes clearly reflected in an animal model study involving enterovirus A71 [13]. The clinical symptoms and survival rate of the mice depend on intracranial and venous injection. When a viral strain CMU4232 is injected intracranially, induced viral infection was mainly limited in the brain; but when the virus is introduced by venous injection, the virus spread to heart, lungs, intestine, and muscles. It appears that the neurovirulence of the CMU4232 is weak, and naturally the venous injection is more lethal. A similar trend is observed for viral strain CDV-Isehara. When the virus is introduced by venous injection into experimental mice, the viral load was reduced by more than half, but increase viral concentration in heart, lung and muscles. The disease outcome depends on the damages to different organs. This study showed that viral concentrations in organs depend on injection routes while disease severity depends on how the virus causes damages in affected organs [13].

The cited studies indicate that disease severity depends on transmission routes. Best preventive methods cannot be developed without understanding the true risks of each of transmission routes. If a serious disease is caused by most lethal transmission route, the most effective measure is to avoid such transmission route. It is especially important when the health systems have been stretched to limits and the world is running out of resources.

ANALYSIS AND RESULTS

A. Background Knowledge

1. Classical infection probability models

Per classic model, the actual number of viruses or bacteria that enter any given cell is a statistical process: some cells may absorb more than one infectious agent while others may not absorb any [14]. This implies that as the viral

concentration increases, the percentages of cells infected with at least one viral particle increases. Cells infected by at least one virus increase when more virus particles are present. Studies showed that virus may operate independently from other viral particles [15]. More recent studies found that viral spread is often facilitated by groups of viral genomes, such as polyploid virions, aggregates of virions, virion-containing proteinaceous structures, secreted lipid vesicles, and virus-induced cell-cell contacts. These multi-genome structures may promote virus-virus interactions and the evolution of social-like traits [16, 17, 18, 19]. Those properties imply that infection requires certain concentration of viruses, and may require more time to form infectious structures.

2. Airborne viral particles and their transmission

Bacteria and viruses can travel through the air. When someone sneezes or coughs, tiny mucous droplets filled with viruses or bacteria scatter in the air. The expelled air can travel at the speed of 75-100 miles per hour [20]. In air samples collected from a school during an influenza season, influenza A virus was detected in densities ranging from 2.0×10^{-1} to 1.9×10^4 (gene copies m^{-3} air) [21]. Infection could be caused by exposure to the air containing 23-586 for 8 hours. Influenza A virus can exist in all particle size ranges in quantities ranging from 5.5×10^2 (in particles ranging from 1.1 to 2.1 μm) to 4.3×10^5 RNA copies/ m^3 in the largest particles (9.0-10.0 μm) [22]. Porcine epidemic diarrhea virus was detected from 1.3×10^6 (0.4-0.7 μm) to 3.5×10^8 RNA copies/ m^3 (9.0-10.0 μm). Porcine epidemic diarrhea virus (PEDV) can be detected in a room containing infected pigs and at various distances from the outside of swine farms experiencing PEDV outbreaks [23]. Infectious PEDV was found in the air from experimentally infected pigs up to 10 miles downwind from naturally infected farms at the concentration of 7.98×10^3 .

Viruses were detectable in association with aerosolized particles. Proportions of positive sampling events were 69% for PEDV, 61% for HPAIV, and 8% for PRRSV. For all 3 viruses, higher numbers of RNA copies were associated with larger particles [24]. Influenza virus RNA was detected in air samples collected between 1.5 and 2.1 Km away from the farms with viral levels significantly lower at 4.65×10^3 RNA copies/ m^3 [26]. Pigs can be a source of infectious aerosols of Influenza A virus. Such aerosols can be exhausted from pig barns and be transported downwind to a long distance [27]. Some of these viral particles are infectious. The viral concentration depends on viral source and distance from the source. The viral concentration is 5.71×10^7 in oral fluid, 8.32×10^4 inside air, and 4.57×10^4 in exhaust air. Relative to oral fluid, virus in inside air is diluted by about a thousand and exhausted air has a further lower viral concentration.

Tidal (normal) breathing can contain virus [27]. Exhaled influenza virus RNA generation rates range from 3.2 to 20 influenza virus RNA particles per minute and over 87% of particles exhaled were under 1 μm in diameter. In each inhaling cycle, the viral particles are diluted by 3 to 4 times. Normal breathes

redistribute about 1 to 6 RNA particles per minute within the lungs. In a closed small room, the viral concentration can rapidly rise (add about 28,800 RNA copies/day for influenza virus per day). Patient's cough and sneezing may generate far more viruses.

Those animal studies establish that viruses from infected persons can travel long distance and it is impossible to totally avoid them. The chain of infection cannot be broken by identifying and controlling infected persons alone. To break the pandemic, additional measures must be taken to reduce disease outcomes.

B. Main Generic Viral Travel Paths

Before we consider the impacts of the transmission routes on disease severity, we examine how viruses travel to the lung tissues. The following three paths are most important.

1. Most lethal path - viral particles entering lung tissues directly

After particles containing viruses enter the nostrils, they are trapped by nose hairs, thrown out by the centrifuge force generated by nasal turbinates, trapped by mucus in bronchi, and propelled out by cilia vibrations. The particles landed in the lungs may be engulfed by resident macrophages. In normal cases, it is generally believed that particles cannot reach lung tissues. Notwithstanding all barriers and defense mechanisms, it is a matter of probability for a small portion of viral particles to go through the air ways to reach the inner spaces of alveoli. This route should be presumed to exist if the air contains sufficiently high concentration of small virus-containing particles.

2. Secondary transmission path to the lungs

The viral particles that land on the respiratory track finally enter epithelial cells of the track. The virus adapts to the tissue environment, and starts reproducing. They may transmit by cell-to-cell-contact. If the infection point is sufficiently close to the lungs, the virus may reach the lungs before the acquired immunity is able to inhibit viral reproduction.

A second presumed risk from this viral travel path is that viruses generated in the initial infected site become airborne particles in normal breathing cycles, and a part of them stay in the air of the dead space; and when the air is breathed back, the viral particles are distributed to uninfected lung alveoli. Thus, the viruses can sequentially attack lung alveoli at different times. While reinfection is an inevitable result, what can make differences is the speed of the reinfection process and degree of viral redistribution.

3. A delayed blood transmission

The significance of transmission by physical contact at a distant site would depend on the viral transmission through blood. If virus enters from a cut, the virus enters the bloodstream directly or get into bloodstream after they have

successfully reproduced and discharged viral content. By blood transmission, they infect other organs and cell types that may include mucosal cells of the intestines, tubular epithelial cells of the kidneys, neurons of the brain, and several types of immune cells [28, 29, 30]. However, they are not causes of death of COVID-19 patients and some damages might be the consequences of lung damages.

C. Factors That Determine Disease Severity

In this article, disease severity is rated by death rate and disability rate although many other factors could be considered.

Disease severity for different transmission routes cannot be determined by conducting clinical experiments because the disease posts death risk. Due to the impacts of a large number of variables and their interactions, randomized controlled trials are not suitable methods. Thus, we have to develop a common-sense approach to appraise the degree of risks for transmission routes.

Disease severity of infections caused by viral transmission routes depends on functional importance of target tissue [13], defense structure to viral infections, viral concentration [12, 15,16,17,18] or viral dilution factor, the phase lag between viral reproduction process and immune responses [4], vicinity of the infection to the lung tissue [12], and physiological and physical condition of the tissue.

1. Lungs are a vital organ. Disabling lung function for as short as two minutes can result in death. They are known as the most vulnerable organs because their alveoli are open to the air which normally contains a large number of microorganisms. Lung functional insufficiency can be a serious aggravating factor. The importance of lung function must be appraised by looking at the value relative to the threshold of death.

2. Protective structure. Due to the need to reduce resistance to oxygen and carbon dioxide exchanges, lung cells especially those epithelial cells in the inner alveoli cannot contain strong protective structures as on normal skin cells. In addition, alveoli must be deformable, the inner epithelial cells cannot be fortified by fibrotic materials. The inner lung cells are much weak and fragile. Thus, they are more vulnerable to viral attacks.

3. Viral concentration at an infection site. Viruses overcome all physical barriers and defense mechanisms by numbers. Even if they have reached the lung cells, they may be engulfed by macrophages or lose their activity as a result of host responses. A depletion in alveolar macrophages resulted in worsening of influenza disease in ferrets infected with a 2009 influenza H1N1 pandemic isolate, including higher viral loads, greater inflammatory cell infiltrates, and upregulated pro-inflammatory cytokines and chemokines [31]. This finding is anticipated. Normal lungs have about 20 million macrophages so that there is only about one macrophage for about every 20 alveoli. It is possible that some

viruses may land on alveoli inner spaces that have no macrophages. Other defense responses may also fail.

For a given viral source, the concentration of viruses that initially land on one or more cells can differ by great margins. If virus is introduced from a cut, the viral concentration is diluted by great degree. An adult weighing 150 to 180 pounds has about 1.2 to 1.5 gallons of blood in the body. This is about 4,500 to 5,700 mL. If a cut is introduced with a small amount of viral particles. We use half blood volume 2,550 mL to account for incomplete dilution or non-complete mixing. The total dilution factor is more than a billion. The chance of direct infection by small number of viral particles in blood circulation is extremely small. Upon entering the blood stream, they are most probably destroyed by white blood cells.

The importance of blood role in inhibiting infection is implied by skin boil healing. If a boil is formed in skin, the infection may resolve very slowly. However, if the boil center is punched by a needle, viruses or bacteria are discharged and blood passes through infected area. The infection resolves rapidly. This fact implies that blood has strong anti-infection effects or efficient blood circulation helps resolve the infection.

4. The phase lag between viral reproduction curve and immune response curve. Viral infections are eventually controlled by the acquired immunity. What is critically important is the race between viral reproduction and immune response. It takes 4 to 6 days to develop detectable antibody concentration that has power to protect the lungs. However, some patients may not develop strong antibody responses even after 4 weeks of illness [32]. Physical barrier and tissue structure may also affect disease outcomes by influencing phase lag between the viral reproduction and the immune response.

5. The infection vicinity. The distance between the infection site and the lung cells is presumed to be important because viruses can reach the lung cells by cell-to-cell spreading, redistribution of airborne particles, and, to a less extent, blood circulation. There is a big difference between an infection at top bronchi and one at tertiary bronchi. Infections at lower bronchi may reach the lung tissues in short times.

6. Host conditions can vary from person to person. For lungs, temperature, air humidity, pressure, mechanical condition, etc. are important. All those factors affect the efficiency of oxygen-carbon dioxide exchange.

D. Multi-Factor Model for Predicting Disease Severity for Transmission Routes

1. Prediction of transmission routes

We consider how the above-mentioned factors affect disease severity. We do not use classical transmission routes, but use generic forms that are most important to COVID-19. We consider lung direct infection, bronchi infection, oral

infection, skin (cut) and skin (fomite) and blood. The effects of other transmission routes can be inferred.

All transmission routes are evaluated by using lung tissues as a reference. Functional factor means how the target tissue is compared with the lung tissue. Structure factor means structural barrier against viral activities. Dilution factor means how viruses are diluted when they travel from an original infection site to lung tissues. Additional defense means the body's resistance against the virus transmitting from an infected site to lung tissues; and immune response means the phase lag between viral reproduction process caused by the infection and the immune response activated by the same infection. Vicinity factor tells the distance between the infected site and lung tissues. Host factors indicates sensitivity of the virus to certain host conditions. All of those properties are for COVID-19 virus, whenever possible.

Table 1. The Effects of Key Factors on Disease Severity

| Viral Entry Routes | Function Factor | Struct. Factor | Dilution Factor | Add. Def. & Imm. Resp. lag | Vicinity Factor | Host Factors | Overall Disease Severity |
|----------------------|-----------------|----------------|-----------------|----------------------------|-----------------|-----------------------|--|
| (1) Lung Cells | Vital | Fair | No | NA/Long delay | In the lungs | T, H, P, manner, etc. | Most severe disease |
| (2) Bronchi | Not vital | Poor | Some | Poor, shortened delay | Depend | (Differ) | High chance, disease severity depends on successive lung infection and timing. |
| (3) Oral track | Not vital | Good | (very large) | Better/long delay | Long distance | (Differ) | Low if reinfection by air is avoided |
| (4) Skin (Infection) | Not vital | Best | (very large) | Best, shorten delay | Long distance | (Differ) | Very low |
| (5) Skin (cut) | Not vital | Best | Mil. to bil. | Fair, shortest delay | Distant | (Differ) | Very low unless viral concentration is too high |
| (6) Blood (Vector) | Vital | Good | Mil. to bil. | Fair, shortest delay | Distant | (Differ) | Very low unless viral concentration is too high |

The above table shows that direct exposure of lungs to the virus is the worst infection route from all aspects. Lung tissue is critically important to sustaining life, and has limited protective structure. Virus attacks lung cells without meaningful dilution, and innate immunity is not powerful enough and the acquired immunity has a delayed response; the vicinity factor is unfavorable to the lungs because viruses can spread by cell-to-cell contact. Finally, host factors

such as low temperature, high humidity, etc. can aggravate disease severity, and breathing can cause the virus to be redistributed to different lung cells, and the whole lungs before the immune system can generate meaningful antibody concentration.

Upper respiratory tract symptoms are less common in some patients, indicating that the cells targeted by the virus might be located in the lower airway [33]. When lungs are infected first, the viral reproduction may cause severe damage to lungs before the acquired immune response is activated. From the incubation time of influenza viruses, the incubation period is only one to two days in humans [40]. This implies that a widespread lung damages would take place within a time window that is far shorter than the time required to activate the acquired immunity. We note that some patients died in short times but not officially reported.

All other transmission routes are less lethal for one or more reasons. All infection caused by routes 2 to 5 may be followed by secondary lung infections, re-information of patient own viruses, and infection of additional external viruses. The severity attributable to such secondary infections would depend on lung functional capacity, the scale of preexisting damages, and the phase lag between the triggered lung infection and the immune response.

Bronchus is not a vulnerable organ but its infection can lead to lung infection. Its severity would depend on the timing of later-induced lung infection relative to the response of acquired immunity. Oral infection may impose less risk to lung infections. However, its severity depends on redistributing the viral particles to lung cells. The normal breathing can redistribute viruses like pumping them to the whole lungs. Among healthy adults, the amount of respiratory particles exhaled while coughing or breathing can vary greatly from person to person, suggesting that some individuals may indeed shed infectious virus much more efficiently than others [35, 36]. The speeds of reinfection depend on a large of lifestyle factors, environmental factors, speedy treatments of initial infection and personal habits and manners. Infection of a mouth sore is expected to be mild unless the patient has a habit to use mouth to breathe so that exhaled viral particles are sucked back to the lungs.

Infection started with skin lesion is limited if the person has normal immune system. After an infected skin lesion starts producing viral particles and release the virus into bloodstream, the virus might have activated the acquired immune response. Moreover, discharged virus is diluted by bloodstream by millions to billions times and most viral particles are destroyed by circulating white blood cells before they can settle down in lung cells. If the virus gets into the bloodstream, the dilution and responsive action of white blood cells would control the virus. Infection started at an eye cannot have lethal impact to the lungs unless lungs are reinfected by own virus or independent source of virus.

2. Collaborative Evidence of The Effects of the Transmission Routes

Some viruses are transmitted vertically. Zika virus, for example, can infect a fetus via the placenta, while HIV can pass through breast milk.

Evidence of lack of vertical transmission

In a study, nine women with COVID-19 gave birth to health babes without sign of infection. In all nine cases, amniotic fluid, cord blood, breast milk, and the newborn babies tested negative for the virus. Even though, the babe directly used the blood of mother, virus in the mother blood could not infect newborns. While the data is small, there is no reason to question its validity. A large controlled trials do not provide better evidence because it cannot be applied to any specific person in any specific condition. This study is contrary to early observations that two babes got the virus at the birth. However, vertical transmission may be caused by post delivery contamination.

Indications of the “shutting down city” measures in China

Since January 23, 2020, China started “shutting down cities” which comprises blocking street exits and entrances, stopping public transportation, prohibiting public gathering, shutting down shops, closing schools and business, limiting personal activities, and limiting family shopping frequencies. In less than two months, new case incidence rate was dramatically reduced by almost 10 folds. The measure has the biggest impact in reducing people exposure to air polluted by virus. They significantly reduce personal contact frequencies, but also increases personal physical contacts for administrative activities. For example, people must show personal IDs, process papers before making trips, etc. Finally, since they must buy foods and necessities, the chances of contacting virus from foods, groceries, and daily products are not eliminated. The rapid drop in new disease incidence rates seems to show that the biggest benefits are gained from reducing frequencies of exposure to airborne particles and droplets.

One potential transmission route is fecal-related transmission. In Hong Kong, there was a huge outbreak of SARS due to an infected individual who lived on the top of an apartment building whose sewage had a blockage and caused many new cases on people living on the floors below. There are several possible ways of transmission. The blockage in the sewer is thought to have subsequently contaminated the bathing area so that people contacted viral particles in the polluted area. This is unlikely due to great dilution and the unfavorable path. While one single viral particle could cause infection in theory, that happens at extremely low probability. One possible route is that viral particles from the infected person room might have gotten into the apartments below and were breathed into lungs. If virus was originated from the patient’s feces and got into the air.

Transmission routes in health-care professionals

Most lethal infections happened among doctors treating eyes, ears nose and throat in the early time. Many doctors got infected before the virus was identified. This tends to be consistent with airborne viral parties because other

physical contact cannot explain the differences between those doctors and other doctors.

In the personal isolation cases, what is most effectively changed is reducing the chance of breathing air in the vicinity of infected persons. There was no way to stop indirect physical contacts. Viruses are transmitted by contacting foods, water, medicine, and other things between the patient and care-givers. We did not see reports that care-givers in such situations are infected. If they do, the most probably route of transmission is independent exposure to viral-containing particles in the air.

After the health care professionals in China started using strict protection measures, the incidence rate among health care professionals became extremely low. We also saw news that doctors who took certain preventive herbal soups seem to have better resistance to the virus.

In a case, four family members were infected sequentially and died within a few days. The original report did not tell details about their protection, we assume that breathing air in an infected patient is the most probable route. In comparison, a woman who had taken care of her infected mother for more than 20 days did not get infection. Her important protection is wearing double masks when she was with her mother. Despite the use of other protective measures such as disinfectants and protective uniforms, complete avoidance of physical contact of virus was impossible.

Other reported serious cases

Based on self-reported stories, the most probable infection routes are breathing air in a rail way car, taking a train for long hours, playing cards with people, taking public buses, taking a public elevator, shopping in poorly ventilated shops, eating in restaurants, etc. Among all those known situations, a common element is that they inhaled viral-polluted air, airborne particles, viral-polluted dusts, etc. [Sup. N1]

White self-reported cases generally may not be used as reliable evidence, some cases do have very strong probative value. The first Hangzhou patient who got the COVID-19 after he made a business trip to Huanan provided convincing evidence. In that trip, he and many coworkers did similar business activities and lived same personal lives in same locations. The only difference is that he took a train when he came back from the trip from Huanan. All his coworkers went back by flight and did not get the virus.

3. Findings for other viruses

A study used H5N1 (an influenza virus) ferret infection models to show that breathing in the virus was more likely to produce clinical infection than swallowing contaminated liquid [37]. Severe disease develops in H5N1 virus-infected ferrets irrespective of exposure route. The ability of H5N1 virus to cause diffuse CNS infection [38] has been attributed in part to spread via different

cranial nerves into the CNS [39]. Its result may be due to the facts that infection severity is mainly determined by the damages in the CNS, and 10(6) 50% egg infectious doses (EID 50) may obscure the impacts of infection in other locations.

E. Known Risk Facts For Severe COVID-19 Diseases

In a study to understand epidemiological and clinical characteristics of patients with COVID-19 [56], 191 patients were included in this study, of whom 137 were discharged and 54 died in hospital. The subjects are all adult inpatients (≥ 18 years old) with laboratory-confirmed COVID-19 from Jinyintan Hospital and Wuhan Pulmonary Hospital (Wuhan, China) who had been discharged or had died by Jan 31, 2020. The following data are extracted:

(1) Among the 54 that died, average age is 69 with age range of 63-76.

(2) Among the died patients, 48% had hypertension; 31%, diabetes; 24%, coronary heart disease; and 7%, chronic obstructive lung disease.

(3) Time from illness onset to hospital admission are 11 days with range of 8-15. This implies that the high death rates may be attributed to lack of care in the early stage. Due to novel nature, most people may not use self-help measures.

(4) The time from illness onset to fever and cough is about one day; and time to shortness of breath is about 6 days from initial onset. It takes additional two to three days to see sepsis, and additional 1-3 days to see ARDS. The corticosteroids treatments maintain their lives for about one week thereafter.

The age ranges for those died were 63-76 and the survivals are 45-58. The data does not represent the population or most individual persons. Patients were excluded for being still in hospitalization or not being diagnosed. It is implied that patients must have been treated resulting in sufficient medical records. It is impossible to include patients who died without visiting hospitals, on their ways to hospitals or soon after arriving at hospitals. It naturally does not include all patients who experienced the disease as mild influenza. Young people are grossly unrepresented and health people are most probably not among the study subjects. The death number from this study cannot be used to determine death rate in any way.

The risk factors can be used to estimate relative risks for different people. After an adjustment is made against those three factors, the odd of dying from the disease for young and healthy adults is much lower. If anyone dies, it is most probably due to improper treatments, really bad exposures or a series of mishaps.

Laboratory data were extracted from electronic medical records and compared between survivors and non-survivors. The data records show the following trends:

(1) D-dimmers in those died is about 9 times of the survivals. This implies there might be a blockage of an artery in the lungs.

(2) Serum ferritin ($\mu\text{g/L}$) in those died is 3 times of that in the survived.

(3) Interleukin-6 (IL-6) for the died is 2 times of that for survivors.

(4) High-sensitive cardiac troponin I in those died is 7 times of those survived. It may be attributed to myocardial damage, kidney failure, heart failure, subarachnoid haemorrhage and pulmonary embolus.

(5) Lactate dehydrogenase in those died is about 2 times of that of the survived. Elevated level usually indicates tissue damages, which has multiple potential causes. An elevated level might be caused by infection, sepsis, myocardial infarction, lung infarction, acute kidney disease, acute liver disease, severe shock, and hypoxia [57]

The lab data showed that most of those died started showing tissue damages starting at day 4 of the initial symptom. Serum ferritin and lactate dehydrogenase might has risen soon after the first onset signs. Those lab tests data show that the lungs sustain structural damages and may be followed by heart damage.

By combining above risk factors with bad exposures, bad treatments, and improper care, we estimate that the combination of all risk factors cover nearly all death probability.

F. Challenges to Existing Medical Practices

Due to influence of the binary concept in medicine, viral latency has been treated as a constant for a virus. CDC Community Mitigation Guidelines treat seasonal influenza latent period as 3 days by relying on a study finding [40]. This number is useful as a ballpark parameter which depends on a set of specific conditions. However, we must presume that latency greatly varies, depending on infection route, viral concentration, host conditions, etc.

Exposed household members of symptomatic persons (with confirmed or probable pandemic influenza) should stay home for up to 3 days (the estimated incubation period for seasonal influenza) [40]. The guidelines use the population approach that regards the disease as same for all people without regarding the differences in personal health, age, transmission routes, lifestyle and work environment, and viral variations. This approach is used for COVID-19 guideline. In reality, each of those properties is a random variable with wide dispersion.

Medicine is characterizing every health property in a binary scale. First, TCID 50 can introduce great uncertainty. In a multicellular organism, as long as one cell is infected, the virus may cause the disease. The infected person could pass the disease onto others. Probability model based on Poisson distribution is unrealistic because it does not consider infection speed and disease severity. In realty, speed decides disease outcomes. Small probability theory cannot be

trusted because an assurance of 95% probability correctness is not good enough to break up chain of infection.

Whether an influenza can be transmitted by airborne particles and what concentration can cause infection have been studied for years [35, 36]. The answer depends on a large number of factors such as viral nature, viral concentration, viral out-of-the-body time, exposure time, humidity and temperature, host health, etc. There is no definite simple answer. “Conflicting” conclusions regarding the relative importance of airborne, droplet, and contact-based spread among humans [41, 42] are natural. Diseases severity naturally depends on exposure to and thus immunity against influenza viruses, and immunocompromise affect influenza viral reproduction [43, 44, 45, 46, 47, 48]. When at least one variable is not controlled or omitted, studies naturally reach different conclusions.

Observational studies show that health properties are widely disperse. The estimated secondary attack rates range between 4% and 51% among household contacts of indexed influenza cases [49, 50, 51, 52, 53, 54]. Influenza virus could be detected in the exhalations of infected persons during normal tidal breathing or talking but not during coughing [55]. Later studies showed that respiratory particles by influenza patients were produced while breathing or coughing, but not both maneuvers side-by-side [34, 35, 36]. The scattering data and conflicts demonstrate that findings from population trials cannot be relied in the war against COVID-19.

G. Population-Based Medical Model Aggravates Disease Severity for the Population and Perpetuates the Pandemic.

The population-based disease control practices have severely limited societal ability to win the war against the COVID-19 pandemic. The above analysis shows that the disease poses serious risks only on certain vulnerable people, people with certain lifestyles or bad habits, or people with worst exposures.

The population approach is very unreliable in two main aspects. First, it shifts a mathematical death rate to irrelevant population. The “global death rate” for COVID-19 is less than 5%. When this death rate is applied to the population, it creates a false impression that anyone would die from the disease at the same chance. It improperly turns the population into potential victims of the pandemic even through such death rate has no relevance to the population or specific person. In reality, the true death rate for a bulky people such as young and healthy people is zero or near zero. Second, by focusing on single or few treatment options, it creates an impression that disease can be cured only by approved medical treatments. It causes patients not to use hundreds of factors as self assistance. So, patients can cling their hopes to magic cures that may not come. We have demonstrated that true cures are outside of medicine.

None of medical methods can contain the disease and cure the disease in a predictable way. Each diagnosis method has some false negative results. All concepts such as latent times are ballpark population-based numbers. They are imposed by human will, but do not reflect reality. Whenever, an infected person is not diagnosed or does not exhibit infection sign within the imposed time window, this person quickly spreads the virus to others and thus revive the chain of infection. Thus, an extinguished pandemic can be revived again and again. That means business will be shut down for two months, another two months.... And flight can be grounded to March 2020, and then to October 2020, then to March 2021. There will be no hope for reviving the world economy.

We have demonstrated by irrefutable evidence that disease severity on most people were aggravated by improper treatments, wrong health treatments, fears and panic, cross-infections, reinfection and successive infections, etc. Routine improper care and improper treatments make healthy people to suffer poorer outcomes, and turn the misapplied death prophecy into "reality". The approach is like imposing vulnerable people's death risks onto the healthy people and do numerous things incorrectly to make their diseases worse. When the situation is out of control, the only option is to halt personal life and cease business, and shut down economy. However, such measures are incapable of achieving long-term objective. China now experiences recurring small outbreaks after it starts resume business activities.

H. Proposed Changes to Community Guidelines

After the disease risk profile is known, governments should not rely on quarantines and traffic bars as the primary means to contain the outbreak or prevent future outbreaks.

It is clear that the virus will not vanish from the world. The ultimate strategy is mitigating disease severity for vulnerable people based on personal health, lifestyle, exposure routes, and work environment. Disease severity profile should be established for different people according to their age, health condition, lifestyle and work environment, and then corresponding measures are developed to reduce disease severity for them. After the disease severity for the vulnerable people is reduced to the level of influenza, COVID-19 becomes a mild influenza. We propose following community guidelines for governments and private organizations.

(1) Identify vulnerable people as the main protective target and study their risk factors for each vulnerable group, and develop detailed preventive and treatment measures for each group.

(2) Although children and young people are not vulnerable to the virus, they can carry the virus to spread them to those who are vulnerable. Sophisticated guidelines should be developed to prevent children and young people as viral middlemen transmitters.

(3) Systematically examine work environments as to ventilation condition, temperature and humidity, personal interaction modes and exposure risk levels, and remove or reduce arrangements or activity modes that might pose serious lung exposures.

(4) Identify, examine, and study transmission risks for public buses, planes, trains, ships, etc. because most reported cases have been traced to travels. For the aviation industry, the final solution is to explore and develop methods to dramatically reduce lung exposures as the long-term solution.

(5) Identify, examine, and study transmission risks for public activities to determine what could be done to dramatically reduce exposure risks. This is especially important for schools, universities, and working environments.

(6) Reverse the CDC default rule that only infected people wear masks, but encourage both infected and healthy people to use masks. This is the only way to protect health people against airborne particles from unknown virus-carrying persons. Current CDC rule is against using masks “unless you are caring for someone who is sick (and they are not able to wear a mask)....”

(7) Teach the vulnerable people to learn protect themselves in cold/humid and outbreak seasons. They should understand risky exposures, recognize and avoid lethal exposures, and mitigate exposure’s impacts after event under various circumstances.

(8) In community guidelines, latent times, viral tests, and follow-up times should be used as inflexible parameters; and they cannot be trusted due to approximation nature.

(9) The most important factor for mitigating the pandemic is relieving public panic. Our lung damage mechanisms show that vascular stricture is the main reason for lung damages and learning relaxation can alter disease outcomes.

(10) The most important measure is public education to make people understand that early interventions are vitally important, doing nothing for several days is the biggest common mistake, and medical community should encourage potentially infected people to use self-help whenever possible especially if health care service is unavailable.

(11) Restore population health care wisdom by disclosing the true limitations of population-based medical model and treatments, the limitations of synthetic drugs, and true benefits of multiple factor optimization self-care method.

(12) Develop treatment protocols that can take full advantages of antiviral drugs, helpful diet, helpful lifestyle, environmental and physical factors, emotional management, etc. to achieve lowest death rate and lowest disability rate. We have pointed out that all factors that affect viral reproduction, immune

responses and lung micro-vascular conditions, etc. can alter disease outcomes. The public should be taught that a treatment protocol comprising several hundreds of factors is much more powerful than one fact treatment. Population is enabled to avoid exposures, learn how to mitigate disease severity for prior exposures, and learning to do things to reduce lung damages during treatment.

(13) A long-term strategy is improving the population health. Exercise can narrow the phase lag and the area between viral reproduction curve and immune response curve and the lungs ability to recover.

Conclusion

Animal studies, theoretical analysis, and personal observations of reported COVID stories provide consistent and irrefutable evidence in support of the finding that transmission routes and virus loads affect both transmission rate and disease severity. The contrary view is an unwarranted presumption that is contrary to reality. A proper presumption should be that both viral load and transmission routes affect transmission rate and disease severity. Disease severity depends on the vital function of target tissue, defense feature of the tissue, viral concentration, immune response timing, and host condition.

When all pieces of evidence are combined, an inevitable finding is that exposure of the lungs to airborne COVID-19 viral particles is the most lethal transmission while oral, physical contacts, blood and body fluid, etc. pose much lower risks as long as the viral concentration at the infection site is within what humans normally encounter. Therefore, the top priority in preventing and mitigating the disease is avoiding breathing in airborne particles and cough-generated droplets, and shortening the time of lethal exposure as much as possible. In explaining disparity of disease outcomes, one should keep in mind that the lungs can be successively infected by patient-generated viruses or independent sources of virus from the air. The reinfection is especially important before the acquired immunity has reached enough intensity to inhibit the viral reproduction or when the patient's lung function is approaching the disability level.

Resources should be diverted to lungs protection while for non-lethal transmission cases, the focus is avoiding or slow down secondary and successive exposures of lungs to the virus.

LIMITATION OF THE STUDY

We try to find answer to a very important question that has been debated for half a century with no resolution. Our final conclusion is based on a large number of findings from various animal model and observations for other viruses and infection agents. The contrary "evidence" is only presumption with zero

proof. When human trials cannot be run and randomized controlled trials are improper, our mixed approach is the only way to answer the question. Our approach satisfactorily reconciles seemingly conflicting and inconsistent results in medical literature. Thus, we are confident that the approach is right for addressing such a complex question. We used facts from patient stories only as collaboration. When this presumption causes society to drain limited resources and lose the war against the COVID-19 pandemic, the presumption should be rejected. The presumption may hold ONLY IF viral concentration is so high that it is able to infect the vital target organ(s) before acquired immune responses. Any additional research should be done to find more details. Duo to the urgency of this study, we did not have time to edit and polish the article, and omitted citations for facts we know are beyond dispute. Corrections to writing style, arrangements, and citations will be made in update.

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CONFLICT OF INTERESTS

None

ADDITIONAL INFORMATION

Additional information is provided in a supplemental document and some information will be stored in igoosa online database. This article may be used by any person for personal use as fair use; any use for research and development is permitted by default.

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