Multiple Infections and Lung Damage Models Imply Strategies for Containing The COVID-19 Pandemic

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ABSTRACT

The COVID-19 pandemic threatens human lives mainly due to rapid disease development that cannot be held in check reliably. To address this difficulty, we explore infection and host response kinetics and their influencing factors. In kinetics, all influencing factors affect viral reproduction, immune response, and lung damages by their accumulating effects in the entire disease course. From existing data, we deduced a two-phase infection model, multiple infection modes, and a progressively degrading lung damage model. From exploring the model behaviors, we propose double tenth reduction strategies for containing the pandemic. The first strategy is reducing incidence rate from the current level to one tenth by avoiding exposures that could result in widespread damages to lungs and taking measures for reducing disease severity to that of a cold. The second strategy is reducing death rate from the current level to one tenth for infected patients by using multiple factors health optimization method. The models imply different treatment strategies for patients at different stages. In the early stage or before virus has spread to the whole lungs, measures are taken to slow down viral reproduction and slow down reinfections; and, after the virus has infected the whole lungs, the focus is maintaining blood micro-circulation and preserving functions of all major organs. The double tenth reduction strategies are expected to generate a series of chain reactions that favor containing the pandemic. Some reactions include a big reduction of the amount of viral discharges from infected patients into the air, the avoidance of

panic, chronic stress and emotional distress, and cross-infections which are expected in quarantines. The double ten reductions would make the disease manageable and tolerable.

INTRODUCTION

At the time of writing this article, there are 75,285 total cases, with 2,009 deaths in 26 countries [1]. At least 29 countries have reported cases. In the U.S., 15 infection cases were reported in Arizona, California, Illinois, Massachusetts, Texas, Washington, and Wisconsin [2]. After the outbreak of the COVID-19 virus, the research community seek strategies to contain the pandemic.

We note a pattern of similar diseases. The outbreak of SARS in 2003 led to a near pandemic with 8096 cases and 774 deaths reported worldwide, resulting in a fatality rate of 9.6% [3]. Since the outbreak of MERS in April 2012 up until October 2018, 2229 laboratory-confirmed cases have been reported globally, including 791 associated deaths with a case-fatality rate of 35.5% [4]. In the past, we have seen outbreaks of Ebola, Chikungunya, and Zika [5].

Coronavirus is an RNA virus, which can mutate rapidly. The genetic plasticity of RNA viruses is one of the main obstacles for the control of the diseases they cause [6]. Even if vaccine is available, vaccine is expected to have only partial protection due to the direct exposure of lung cells to viral particles [7]. Difficulties to contain such a pandemic is implied in consistent failure to control influenza viruses. Influenza virus transmission is promoted by low temperature based on guinea pig model of influenza virus transmission. The mechanism(s) by which temperature and humidity alter transmission outcomes remains unclear, but may include multiple effects acting at the level of the host, the virus, and the respiratory droplet [7, 8].

We previously discussed strategies for reducing damages to lungs in infected patients [7]. What is more important is containing the pandemic because it affects people life, disrupts world trade order and casts uncertainty in human life. We noted that final resolution of the infection depends on immune responses, while risk of death and degree of disability depend on the severity of infection and efforts of reducing lung damages. Some important factors are initial infection severity or mode of infections, viral reproduction speeds, immune responses, waste removal balance, etc. The first two factors depend on viral-host interactions, and a large number of factors; and waste removal efficiency depends on inflammation degree, lung micro-network condition, and organ capacities. One important factor is health-seeking behavior, which plays a key role in controlling influenza [9.1]. While influenza could be caused by non-coronavirus, the dynamics of infection and disease processes are presumed to be similar to those of COVID-19.

We explore strategies for reducing infection chances and death rate. We then consider how the double reductions lead to favorable chain of reactions.

MODEL DEVELOPMENT

A. Knowledge and Facts Considered in the Models

Following knowledge and facts are considered and relied upon in developing our multiple phase infection modes and lung damage models.

1. Viral infection steps and immune responses

Yoo et. al provide a review of knowledge of viral infection, and host responses [11]. The review summarizes current understanding of the triggering of innate and adaptive immune responses to infection, viral clearance, damages restoration, and virus–associated other sequelae. However, the current knowledge is limited to disease mechanisms viewed from a static point of view. No attempts have been made to evaluate their speeds and the impact of their speeds. In real cases, what can make differences to disease outcomes is the order of those different events, their timings, their relative speeds, and factors that affect their speeds.

2. Lung damages

Lung damage in SARS has been extensively discussed [12]. On gross examination, the lungs were edematous and increased in weight. In most cases, they showed extensive consolidation.

During the first phase of the disease (7 to 10 days), the lungs display extensive edema, glossy membrane formation, collapse of alveoli, scaling of alveolar epithelial cells, and fibrous tissue in alveolar spaces. Features of fibrous organization of diffuse alveolar damage (DAD) appear after about 10 to 14 days, such as interstitial and airspace fibrosis and pneumocytic swelling. When in 2 to 3 weeks, dense septal and alveolar fibrosis were seen. A direct correlation is observed between the extent of fibrosis and the duration of the illness.

DAD can progress to organizing pneumonia, which may result in permanent pulmonary fibrosis or resolve with the restoration of normal lung structure and function. The outcome depends on host factors, the severity of lung injury, and whether or not the inciting cause is corrected. Free radical damage from high levels of oxygen is common cause of DAD in severe patients.

Above findings are confirmed in a COVID-19 case report [13]. The patient had dry cough on Jan 14 (day 1 of illness) but kept working until Jan 21. The patient died from a sudden cardiac arrest later. Histological examination showed bilateral DAD with cellular fibromyxoid exudates. The right lung showed evident

desquamation of pneumocytes and hyaline membrane formation. The left lung tissue displayed pulmonary oedema with hyaline membrane formation suggestive of early-phase ARDS. Interstitial mononuclear inflammatory infiltrates, dominated by lymphocytes, were seen in both lungs. Multinucleated syncytial cells with atypical enlarged pneumocytes characterized by large nuclei, amphophilic granular cytoplasm, and prominent nucleoli were identified in the intra-alveolar spaces, showing viral-induced structural changes. Overactivation of T cells, manifested by increase of Th17 and high cytotoxicity of CD8 T cells, accounts for, in part, the severe immune injury in this patient.

3. Classical infection probability model

Infection chances are studied by classic model using MOI. MOI is the ratio of the number of virus particles to the number of target cells present in a defined space. 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. The probability that a cell will absorb n virus particles or bacteria when inoculated with a particular MOI can be calculated for a given population using a Poisson distribution [14]. When an MOI of 1 (1 viral particle per cell) is used to infect a population of cells, the probability that a cell will not get infected is P(0) = 36.79%, and the probability that it be infected by a single particle is P(1) = 36.79%, by two particles is P(2) = 18.39%, by three particles is P(3) = 6.13% and so on. As the MOI increases, the percentages of cells infected with at least one viral particle also increases: 1.0, 63.2%; 3.0, 95.0%; 5.0, 99.3%; and 8.0, 100.0%.

In this model, an implied assumption is each virus has the same probability to enter into any of target cell. The model does not take into account the speed of each infection. As we will show, disease outcome depends on the race between an apparent viral reproduction and immune response, and the immune-caused damages are related to their phase lag. Second, we have observed that the lungs have about 600 million alveoli (range: 274–790 million), and exposure to virus sources is not uniform. Due to differences in geometry, locations, and blood local circulation condition, an exposure to viral particles source could result in one, several, tens, hundreds, to millions infections or different parts of infections. Thus, the classic Poisson model cannot be used to model kinetics.

4. Independent action hypothesis and collective infection

One classical assumption is independent action hypothesis (IAH): every virus particle operates independently from other viral particles [15]. Zwart et al. developed a probabilistic framework for testing this hypothesis and demonstrated that two virus–insect systems tested, IAH is supported by the data. The mathematical model is mainly based on Poisson distribution. This model concerns only probability outcome. Like in a drawing trial, the model does not take into account any factors that alter infection probability in a real time and factors that affect specific cells, a portion of cells, or the entire lungs. This model

finding however provides support that infection could be caused by a single virion.

Increasing evidence indicates 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]. Those properties imply that infection requires a higher concentration of viruses, and may require more time to form infectious structure.

5. 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 [18]. 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) [18]. The study also establishes that viral infection time depend on viral concentration. Airborne exposure time is inversely related to virus gene copies. Based on the assumption that one TCID 50 is equivalent to about 300 PCR-detectable IAV RNA copies. The study establishes that infection time and concentration is 1 min for 11,161–281,250, 30 mins for 372–9,375, 1 hour for 186–4,688, 3 hours for 62–1,563, and 8 hours for 23–586.

The particle size of influenza A virus was studied [19]. Influenza A virus was detected in all particle size ranges in quantities ranging from 5.5x10(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). PRRSV was detected in all size ranges except particles between 0.7 and 2.1 µm in quantities ranging from 6×10(2) (0.4-0.7 µm) to 5.1×10(4) RNA copies/m(3) (9.0-10.0 µm). Porcine epidemic diarrhea virus was detected in all particle sizes and in higher quantities than IAV and PRRSV ranging from 1.3×10(6) (0.4-0.7 µm) to 3.5×10(8) RNA copies/m(3) (9.0-10.0 µm). In the case of IAV and PRRSV, viruses were isolated from particles larger than 2.1 µm.

Porcine epidemic diarrhea virus (PEDV) can travel a long distance [20], air samples were collected both from a room containing infected pigs and at various distances from the outside of swine farms experiencing PEDV outbreaks. Infectious PEDV was found in the air from experimentally infected pigs and genetic material of PEDV was detected 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 [21]. 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 [21].

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 [22]. 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.

B. Limitations In Existing Concepts and Research Methods

To find strategies to contain the pandemic, we need to examine concepts and methods used in current research.

To predict whether an infection takes place, an accepted method is using a known range of TCID 50, which is the number of viral particles that induce infection in 50% of inoculated tissue culture cells. This number may be far too higher than what could cause an infection. In a single cell organism, 50% may be a reasonable number for determining chance of individual infection. However, it is not a suitable number. In a multicellular organism, as long as one cell is infected, the virus may cause the disease. If one person is infected, the disease could be passed onto others by chain of infection.

Probability model based on Poisson distribution makes an assumption that virus infects cells at the same probability. This model does not consider how fast an infection can take place and what alter the speed of infection process. In reality, viral particle number always affects viral infection speeds. The number or viral concentration affects the chance for viruses to contact a target cell. When thousands of viruses “dance” on a cell, the time for completing the first viral entry is shorter than the time required for one virus particle to enter the cell.

Small probability theory is widely used in statistical analysis in medicine. Any method that is based on the small probability theory (e.g., 5%) cannot be used as a measure to break up the chain of infection for a pandemic. If the method could result in false results by a small chance, the method cannot contain the pandemic.

Weather an influenza can be transmitted by airborne particles and what concentration can cause infection has been studied for years [23]. No conclusion has been reached. Lack of conclusion is not surprising because nature does not create diseases by a binary scale, which is imposed by human will. Whether airborne particles transmit viruses depend 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, and even luck. Nevertheless, those animal model studies provide useful information that allows us to understand viral exposure risks.

For the above reasons, strategies intended to extinct viruses will be extremely difficult. The virus may transmit by airborne particles; may infect animals, and may stay in human body for restarting a new outbreak. For a similar reason, a cure by using vaccine and a synthetic drug would depend on luck. The rapid mutations can defeat acquired immunity; and belated immune responses may fail to protect certain persons who have been infected before.

Reasonable strategies comprise two lines of measures. A first line of measures is preventing and substantially reducing infection incidences. They naturally include everything that can be used in medicine, but include everything else. If infection incidence rate is reduced to one tenth relative to the imagined background, the pandemic can be controlled easily. Second line of measure is reducing the death rate. If the death rate is reduced to one tenth of the current rate or blow 1%, the risk of the disease will be tolerable. Since death rate and infection modes are related, some measures may affect both. If a measure can make infections less severe, infected patients collectively discharge less amount of airborne particles into the air. This will have an effect of making infection source smaller. When the overall infection rate and death rate are reduced to tolerable, people will not be panic; quarantine is not necessary; cross-infection in quarantines can be avoided; and mind will become the powerful component for fighting the disease.

Medical treatments are developed without considering viral concentrations, viral exposure duration, route of infection, host conditions, host-viral interactions, the phase lag between viral infection and immune responses, the stage of the disease, etc. Such treatments cannot effectively contain the pandemic because those factors actually determine infection chances, disease spreading, disease severity, and death risk.

C. Hypothetical Viral Infection Modes

Since our focus is on speed of viral infection and reproduction and the speed of damage process, we need to consider all probable modes of infections. Based on indications found in studies and news reports [12, 13, 24, 25, 26. et al], we propose most probably infection modes and then explore how different modes affect disease progression speeds and final outcomes.

1. Particles containing viruses enter the nose, they are trapped by nose hairs, thrown out by the centrifuge force generated by nasal turbinates, trapped by mucus and propelled by cilia vibrations. The particles that land on the respiratory track are finally destroyed by macrophages that reside on the membrane. If a small number of viruses enter cells, they are destroyed by host response. No infection takes place.

2. All facts are same as scenario 1, except that some virus particles enters epithelial cells of bronchi, and, with a time delay, they start reproducing and discharging cell content to blood. There was no independent infections in the lung. The viruses from discharged cells get into the bloodstream and activate the

adaptive immunity. The virus from the blood is accompanied by rapidly increased antibody concentration to contain viral reproduction.

3. All facts in scenario 2 plus the following: a small number of viral particles enter the lung alveoli because the first line defense mechanisms fail to retain, capture, or inactivate them. The viral particles in alveoli dance on the epithelial cells. After various delays, they make entries and, after delays, they start reproducing. Disease severity depends on the number of alveoli involved and the number of infection cells in each alveolus. Infected alveoli are injured. If a sufficient water leaks out in an alveolus, it collapses. Only a small number of alveoli is involved, symptom is mild.

4. All facts in scenario 3 except that a large number of alveoli are infected. A large number of alveoli collapse as a result of leaked fluid or discharged cell contents, the lungs are unable to maintain normal function; and the patient experiences shortness of breach. The severity depends on the scale of damages to alveoli. Additional or independent infections may take place on brochini and other body parts.

5. All facts in scenario 1 except that a small number of alveoli are infected. Disease severity depends on how fast the viruses from the lungs reinfect other alveoli, and whether other alveoli are infected by independent viruses.

5a. All facts in scenario 5 plus the fact that other alveoli are reinfected by viruses from the prior infected alveoli. Disease severity depends on how fast the viruses reinfect other alveoli.

5b. All facts in scenario 5 plus the fact that alveoli are infected by external viruses independently. Disease severity depends on the scale of successive infections, and the timings of their infections.

6. A large number of alveoli are infected by external viruses in a very short time window. If bronchi is not infected, the patient experiences dry cough. If bronchi is also infected, the patient produces web discharge. The lungs may fail quickly. Disease severity depends on the portion of alveoli involved and their timings of infections.

7. The facts in 5, 5a, 5b, and 6, plus the fact that the patient is burdened by other inflammation. A bad secondary cold, allergic reaction of foods, the side effect of synthetic drugs, excessively high oxygen administration, and extremely poor environment conditions such as low temperature and high humidity.

8. The facts in 7 plus senior age. Old people’s lung functions have declined by as much as 30% compared with young people; their blood vessels are less elastic so that they can retain more white blood cells which are responsible for the failure of pulmonary circulation.

The above infection scenarios are summarized in the following table followed by a list of influencing factors.

Table 1 Two Phases Infections, Repeating Infections, and Influencing Factors (A temporary scheme subject to change)

Modes of Infections	Infection Phases and Sites	Defense Mechanisms & Timings	Influencing Factors
1 (no risk)	Bronchi exposure; no infection	Innate immunity	Micro-vascular network, health condition, temperature, humidity, RIGHT nutrition, etc.
2 (mild)	Bronchi infection	Innate immunity and acquired immunity	Same as 1 above
3 risky	1st: bronchi 2nd: lung	Innate immunity and acquired immunity	Time lag between two infections; viral concentration, particle form, exposure, micro-vascular network, patient health, temperature, humidity, blood pH, etc.
4 (risky)	1st: bronchi 2nd: lung large scale.	Innate immunity and acquired immunity	Same as 3 above.
5 (risky)	1st: lungs (limited) Opt: bronchi	Innate Immunity acquired immunity	Viral concentration, particle form, exposure, micro-vascular network, patient health, temperature, humidity, blood pH, etc (as common factors)
5a (deadly)	1st: lung (limited), successive infections	Innate immunity (2nd infection take place after acquired immunity develops)	Poor air ventilation, improper manner and repeating exposure to self-virus; plus common factors.
5b (more deadly)	1st: lung: limited 2nd: lungs (independent Infections)	Innate immunity (2nd infection take place before acquired immunity develops)	Continue exposures, poor air ventilation, lack of protection, plus common factors.
6 (very deadly)	1st: lung: (whole lungs)	Innate immunity (dry cough as the initial signs, acquired immunity	Extensive exposure, lack of protection, repeat exposures in short time, especially under cold and humid

		is too late).	environment, plus common factors.
7 (very deadly)	Any of 5, 5a, 5b, 6 plus inflammation-aggregating factors.	Innate immunity; acquired immunity.	use of inflammation-triggering foods, synthetic drugs, plus respective factors mentioned for each scenario.
8 (most deadly)	7 plus senior age	Innate immunity; acquired immunity.	In addition to the above factors, reduced usable organ capacity, and reduced blood vessel elasticity

We assume that viruses may exist in airborne particles, some of which are capable of reaching and landing on alveoli. Some viral particles enter the lung alveoli notwithstanding the general belief that most particles cannot enter the lungs. The viruses may land on one to N epithelial cells of alveoli. Most of them cannot immediately enter cells, but may stay there. With time passing and by strike of luck, a virus may make an initial entry into a cell. Infections may take place in one to M alveoli. Since we concern viral spread speed, the number of infected cells and the number of initially infected alveoli are both important.

If the lungs inhale a large number of airborne particles, more of the alveoli may be filled with airborne particles, and more viruses may enter epithelial cells. High viral concentration can provide better chances for viruses to enter cells because they provide more contact opportunities. Regardless of how the viruses act in the initial infection, high concentration increases the infection speed in terms of number of entries per unit time. The time from the exposure to viral entry is noted as Te.

After a virus has entered a cell, the virus stays in the cell for time (Tl). In this time, the virus adopts itself to the cell. Host condition affects the time length.

Some of the infected cells may discharge viruses or transmit viruses by cell-to-cell contact. Some viruses get into bloodstream and travel to bone marrows to activate adaptive immunity. It takes 4 to 6 days to develop detectable antibody concentration that have a power to protect the lungs. However, some patients may not develop strong antibody responses even after 4 weeks of illness [26.1].

If the number of initial infections is very limited, the viral population is expected to grow slowly. The damage to the lungs would be localized in a short time window. If a large number of alveoli are infected at substantially same time, the disease is expected to progress rapidly. We expect to see great differences between one seed site, thousands of seed sites, and millions seed sites.

Other organs and cell types that may be infected include mucosal cells of the intestines, tubular epithelial cells of the kidneys, neurons of the brain, and several types of immune cells, and certain organs may suffer from indirect injury [12, 13]. However, we focus on the lungs in this study because lung damages are the common causes of death and disability.

D. Repeated Infections and Development of Chronic Disease

In the kinetic analysis framework, infection speed and immune response speed are critically important. We cannot assume that infections of a limited number of alveoli are same as the infections of a large number of exposed alveoli. The importance of their infection timings is not any less simply because a final result is that all alveoli will be infected. Studies show that lungs in the patient have different localized damages [13]. What is critically important is how much time it takes to spreed viruses from a limited number of alveoli to substantially all alveoli. Moreover, the number of initial infection sites and their spatial allocations have great impacts on viral development speed. A uniform distribution of infection points in the whole lungs is worse than centralized infections of the same number in a part of the lungs. The total disease time courses vary from a few days to more than month, but ultimate damages tend to reach the entire lungs. We suspect that different infection modes are responsible for different outcomes.

The lungs perform both inhaling and exhaling breath cycles [16]. When the lungs exhale, they drive air from lung alveoli space and to trachea. The air exits from the nose. However, some of the exhaling air remains in primary bronchus, trachea and nostrils as the dead space. Each breath volume is about 500 mL for an an adult, with a dead space of about 150 mL. When the lungs inhale, external air inhaled is mixed with the air in the dead space. Due to limited size of breath, the inhaled air could reach only the tertiary bronchi; and most particles are trapped on bronchi membrane; some pass into alveoli as airborne particles by alveoli ventilation. Breathing cycles are like pumping actions to spread viruses from infected cells to uninfected cells and from infected alveoli to non-infected alveoli.

Before infected cells start discharging cell contents, outgoing air may contain viruses in very low concentration equivalent to that of the background air. After the patient shows signs of infection, exhaled air contains viruses. Tidal (normal) breathing can contain virus [23.1]. Exhaled influenza virus RNA generation rates range from 3.2 to 20 influenza virus RNA particles per minute (<28,800 RNA copies/day) and over 87% of particles exhaled were under 1 μm in diameter. In a closed space, the viral concentration can rapidly rise. In each inhaling cycle, the viral particles are diluted by 3.3 times. Normal breathes redistribute about 1 to 6 RNA particles per minute within the lungs.

Most viruses are prevented by the first line defense. Those that land on alveoli may be killed by alveoli macrophages. The lungs have about 20 million macrophages, they may be able to take care of a small number of virus particles.

It is a riddle how they move around and reach viral particles. Other viruses that have landed on alveoli lose activity for other reasons. Those that survive stay for a period of time before reproducing. The first-phase infection takes place without activating the immune system; but the reinfections are caused by discharged viruses. At the time of reinfections, some discharges get into the bloodstream. Soon after successive reinfections take place, the reinfecting viruses encounter rapid immune response.

The impacts of reinfections depend on viral concentrations in the first exposure, previously infection degree, inflammation degree, lungs' remaining capacity, and the immune response timing. Reinfections at early stages may affect more of alveoli due to weak immune responses. A large scale of simultaneous reinfections are lethal. Reinfections at a late stage may have limited effects. The immune system catches up with the viral reproduction speed and eventually the contain the viral reproduction.

Controlling successive infections is important in several situations. If patient immune systems are compromised, reinfections can cause more viral damages. If the lungs have been impaired with reduced lung usable function, a large scale of reinfections can cripple additional alveoli and may further depresses lung functions to threshold of death. Widespread reinfections cause more serious inflammation and make the lungs more consolidated. This may result in completely jammed pulmonary circulation. Due to widespread swelling, it is impossible to dilate blood vessels because there is no room for them. Reinfections can be more serious if ambient air contains additional virus particles or different viral genome types. To improve outcome, air must be well ventilated so that viral concentrations are lower enough to substantially slow down reinfection process.

The first-phase infection may comprise many individual infections at different times. We regard them as the first phase infection as long as they take place before the immune response is sufficiently powerful. The second phase infection may also comprise individual infections at different times. After the reinfections start, self-generated viral contractions are much higher than viral concentration in the ambient air.

It is anticipated that infections in some patients will become chronic diseases. Chronic diseases may be caused by immune compromise, excessive poor micro-vascular system, and formation of local structures which prevent the immune cells from clearing viruses completely.

E. Progressively Degrading Lung Damage Models

When lung alveoli are filled with water, the alveoli collapse due to the surface tension of water [17]. Alveoli can also be damaged by depositing viscous materials.

1. Inflammation-driven progressive lung damage model

All immune cells pass through capillaries by deforming themselves and squeezing through [26]. There is a great size discrepancy between the mean diameter of circulating leukocytes (6-8 μm) and that of the pulmonary capillaries (~5.5 μm). Except platelet (4 μm), all other white blood cells including HL-60 cells (10.2 μm), erythrocyte, monocyte, and neutrophil (all at about 7.5 μm), and lymphocyte (6.3 μm) are bigger than the mean pore size of capillaries. The study found that retention time depends on cell stiffness and cell size in a complex manner. The study provides several hints: First, cell retention time depends on elasticity of capillaries. Second, the micro-vascular network of capillaries can be jammed: when the fluid contains particles of different sizes, they can jam the pores. Finally, the fluid viscosity is an important factor. For example, platelets aggregation can raise flow resistance even though platelets are smaller than the pores.

A large number of resident macrophages are found in all kinds of diseased tissues [12, 13, 27, 28]. Asbestotic lesions are characterized by macrophagic accumulation, fibroblast proliferation, and collagen deposition. The accumulation of a large number of macrophages can be attributed in part to their large size (15-20 μm). The origin and differentiation cues for many tissue macrophages, monocytes, and dendritic cell subsets in mice, and the corresponding cell populations in humans, remain unclear [24]. Migration of monocytes is similar to elastic cats squeeze through expansible small door holes. After monocytes enter the tissue, some of them cannot get out due to increased friction. Some become larger macrophages. The tissue is like a filter to catch them. Figure 1 shows how the retention of white blood cells is responsible for damages to the lungs.

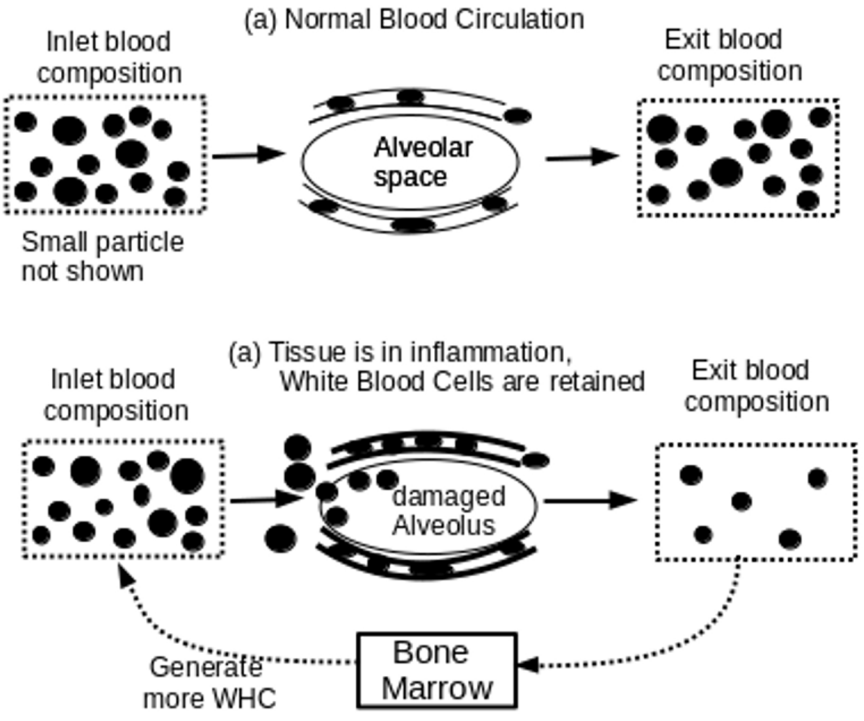

Figure 1, diagram (a) shows how white blood cells squeeze through capillary network with much smaller pores. Diagram (b) shows that when the tissue is in inflammation, the wall of capillaries is changed and the white blood cells will met with more friction. Some large white blood cells are retained and thus result in higher local blood pressure. Initially, water leaks out from the blood vessels and passes through inter-cellular or interstitial spaces to reach the space of the alveolus. When local blood pressure rises further, white blood cells break the blood vessels and squeeze between epithelial cells to get into the space of the alveolus.

When tissue is in inflammation, the endothelium actively participates in controlling blood flow, and affect permeability, leukocyte infiltration, and tissue edema [29, 30]. The changes in epithelial cells disrupt blood homeostasis by increasing capillaries resistance. Other changes include flow dysregulation, thrombosis, and capillary leak [29]. The elevated local blood pressure causes the blood to break epithelial cells and get into alveolar spaces. The capillary leak results in swelling of the tissue and thus has an equivalent effect of reducing capillary deformity or elasticity. The blood that has leaked into inter-cellular spaces causes the tissue to swell, reduce rooms for capillaries to expand and add more resistance to blood flow. The reduced capillary elasticity results in retention of white blood cells at faster speeds.

If the inflammation is of a limited degree, the slower migration speed has an effect of extending white blood cells' dwell time so that they have more opportunities to encounter and engulf infected cells and foreign matters.

If the inflammation is not resolved or too severe, the lung blood circulation condition becomes worse and worse. The inflamed tissue keeps retaining white blood cells. By perpetual accumulative effects, white blood cells are accumulated on the inflamed tissue leading to high flow resistance. A reduction of the white blood cells in the blood then causes bone marrows to generate more white blood cells [13]. When newly arrived cells travel through the infectious lungs, they are again caught and retained. The leaked blood and accumulated white blood cells eventually occupy substantially all volume spaces in the lungs. Extruded blood fills all voids in the lungs, the flow resistance of the lungs reaches the maximum, the maximum flow resistance makes normal pulmonary circulation impossible. The end result is inevitable heart failure or multiple organs failure.

The worst damage is on lung alveoli [12, 13]. Each alveolus is surrounded by a capillary network. Most alveoli are filled with viscous materials and white blood cells. If a sufficient number of alveoli have been filled by extruded blood materials, the lungs become consolidated. The patient cannot breathe and die.

The severe inflammation inevitably leads to congestion of lung tissue. Healthy lungs are highly elastic and have ample rooms for capillaries to expand during breathing cycles. After the white blood cells are caught and accumulated in alveolar spaces, the lung circulation become worse and worse due to reduced elasticity attributed to tissue swelling. Normal blood circulation in local tissues is increasingly replaced by extremely-slow diffusion process. As a result, some lung cells die from lack of energy and oxygen. When high concentration of oxygen is administrated, free radicals may cause additional damages to lung cells. To fill the dead tissue, lungs generate fibroblastic cells.

Many other mechanisms may be attributed to tissue damages. Examples include apoptosis, innate immunity, and ER stress response that may be modulated by human coronavirus [35]. During viral infections, apoptosis is induced as one of the host antiviral responses to limit virus replication and production [35]. Both the host and the virus can manipulate innate immune mechanisms as a form of defense or evasion strategy [36, 37]. In cases of prolonged and irreversible ER stress, apoptosis mechanisms are triggered [38]. During viral infections, ER stress response is induced. The utilization of the ER elicit immense burden, causing the host to mount unfolded protein response as its antiviral response [39]. Those mechanisms do not explain the large number of accumulated white blood cells, extruded viscous materials, and their locations.

2. Lung damages induced by insufficient lung function

If the lungs are unable to perform required functions, degraded energy metabolism speeds up lung deterioration and leads to failure of major organs such as heart, kidneys, and liver. Those processes are shown in Figure 2.

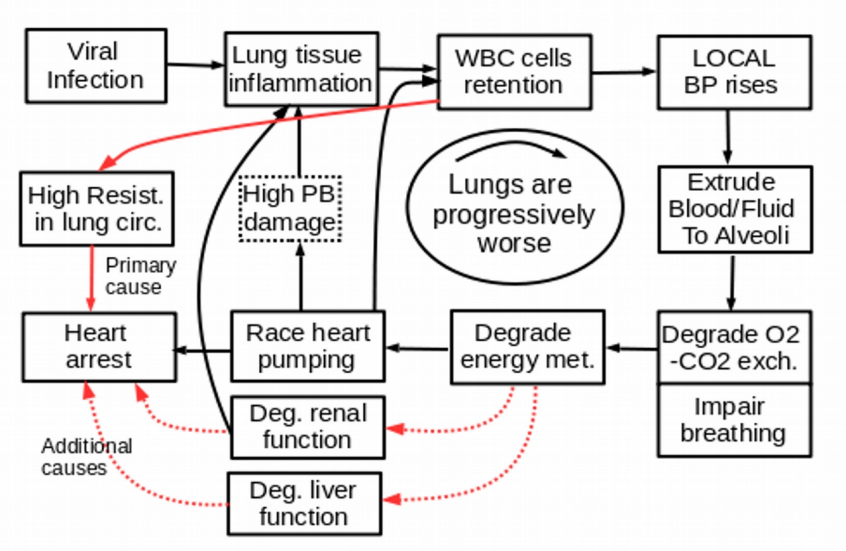

Figure 2 shows how viral infection triggers the retention of white blood cells and causes damages to alveoli as indicated by the round circular arrow. The

damages to alveoli results in higher flow resistance and degrade energy metabolism. The increased flow resistance and impaired heart, renal and liver function inevitably result in heart failure (as indicated by red arrows).

If a small portion of the alveoli are infected, only the infected alveoli may be damaged in the early time. The damaged alveoli cannot be compressed and expanded as normal. They add mechanical resistance to breathing processes. However, people can survive with only part of functional lungs [31-33]. If inflammation is limited, inflammation-triggered poor blood circulation may damage the infected tissue and some surrounding tissues. The potential damages could be predicted by looking at the blood flow pattern.

Severe and irreversible damages to lungs are triggered by extensive and widespread infections. When a sufficient number of alveoli are infected by the virus, the virus-caused inflammation causes white blood cells to accumulate in infected tissues. The inflammation causes the lungs to further reduce function. The inflammation-driven process steadily brings the lung's usable function down, but may not necessarily cause immediate lung failure.

If the inflammation drives the lung function to below the threshold (40% of the maximum or whatever threshold for the person), the lungs are unable to deliver required oxygen. Oxygen insufficiency affects all major organs including the heart, the liver, and the kidneys. The heart will have less power to pump and the kidneys have a diminished capacity to clear inflammation and metabolic wastes. The inflammatory wastes and metabolic by-products are accumulated at faster rates, and, in turn, further promote inflammation. The degraded blood circulation results in accumulation of more white blood cells and more metabolic wastes, and cause more damages.

While inflammation is the initial culprit, the usable capacity of the heart, the kidneys and the liver affect the ability to resolve inflammation. When inflammation-driven damage is coupled with heart, kidneys and liver deterioration, the lungs degrade faster. When the whole lungs severely swell, the flow resistance of the capillaries network is high. The blood pressure in the pulmonary arteries is expected to rise; and eventually pulmonary flow resistance is too high to maintain. It is inevitable that the heart fails due to excessive pulmonary flow resistance and lack of energy in the heart. The strategy is improving blood circulation as early as possible in the entire disease course.

Even if lungs fail to maintain blood circulation by a small margin initially, the condition can degrade as more and more white blood cells are added into the tissue. Thus, the lungs' condition becomes worse and worse with time. When the lung circulation is sufficiently bad, lung cells die and their voids are filled by fibroblastic cells [12, 13], which have no function but add resistance to breathing force.

This model implies that lung damages could be triggered by viral damages without immune responses. Before acquired immune response has reached

sufficient level, virus-induced inflammation may be enough to cause white blood cells retention, leading to eventual lung failure and heart arrest.

This lung damage model explains the vital role of temperature in lung micro circulation. The flow of blood in the capillaries is controlled by precapillary sphincters near arterioles, or by the sizes of capillary pores. When temperature is lower, blood vessels and capillaries in lung tissues are constricted [33.1]. A lower temperature results in smaller pore sizes of capillaries. A lower temperature also reduces the blood's viscosity and slows down blood circulation. Temperature is a critical factor in preventing infection, reducing the severity of infection, promoting recovery, and reducing damages to lungs.

The model also explains the role of humidity in disease outcomes. The role of humidity on influenza is known [8]. When the COVID-19 outbreak took place, it was a cold and humid season. Humidity affects alveoli ventilation. When the humidity is high, water molecules coming from alveoli cells cannot be brought out fast enough. Thus, more water molecules stay on the inner walls of alveoli. For those alveoli with fluid leakage, high air humidity hinders disease recovery. The water layers on alveolar walls also interfere with oxygen-carbon dioxide exchange and thus adversely affect the lungs by degrading energy metabolism.

The model can explain the role of blood viscosity, mechanical vibrations, and salt role. A large number of factors affect blood viscosity. Those factors affect the disease development in the entire disease courses.

The model can explain the role of mechanical activities. It is a common sense that objects jammed at a bottleneck of a bag can be facilitated by making mechanical vibrations. A suitable degree of activities and motions can disrupt the machinery used in RNA replication. This effect can be inferred from its impact on cell cycles in dinoflagellates [42]. COVID-19 requires formation of envelop proteins [43]. We believe that the formation of envelop could be disrupted by mechanical vibrations. This is in accord with the observed vulnerability of obese persons to many viruses presumably due to lower physical activities.

The model can explain the roles of heart, lung, liver and kidneys. Their functional capacities determine how well patients can tolerate viral-caused inflammation. Old people are more vulnerable to lung infection because their usable lung function has been reduced by about 30% when they reach the age of 90 [31-32], and their blood vessels are less elastic.

The model also explains the role of chronic stress and emotional distress on disease outcomes [66-75]. When person is in relaxed state, the blood circulation is improved.

Due to differences in influencing factors, some patients die with a few days after experiencing first signs, some can survive for much longer times, most people can recover, and some have little or no symptoms. The differences can be explained by the cumulative effects of above-mentioned factors [76].

F. Future Recurrent Lung Infections

The unique structure of lungs make them especially vulnerable to infections. We predict that a person could be infected by the same or similar viral species after the prior infection has resolved. After an infection has resolved, the antibody concentration declines rapidly. While small number of B cells exist as memory cells, they provide limited benefits. Assuming that a massive of airborne viral particles are inhaled into the lungs, infections can take place at multiple sites without the full protection of the immune system. It is possible that exposure to high concentration of the same virus may cause serious diseases.

Some patients die within only a few days after the initial signs of infection. This is because infection starts on the side of cells that are away from blood flow. In contrast, viral infections of other organs are originated by viruses that are traveling in blood. Hepatitis C, HIV, etc. travel through blood. In those cases, the activation of the cellular immunity takes place before the virus starts infecting target cells.

STRATEGIES FOR CONTAINING THE COVID-19 PANDEMIC

A. Strategies for Mitigating Lung Damages

From the infection modes and the lung damage models, we found there are many intervening points that could be used to alter outcomes.

1. From exposure to the virus to experiencing the first signs, most viruses cannot enter the lungs and some of them may take time to complete entries. Many potential methods could be used to reduce the number of infections. While the whole lungs will be infected by the virus, intervening measures can delay viral reproduction process and thus reduce damages to the lungs.

2. Effort to stop sequential exposure to external viruses. Before any virus is released to the bloodstream, the body is still vulnerable to continuous infection in the lungs. Breathing infected air only one time is better than breathing 100 times. Exposure to an infectious environment for many days is worse than exposure for one day.

3. Adjust body conditions in the latent periods. Viral reproduction requires interactions between viruses and hosts [10, 16.3, 35, 40, 41], but none of the current knowledge has been used in treatments. In multiple factors health optimization approach, it is not required that selected factors have definite effects as defined by a binary scale.

4. Mitigate or slow down re-infections by patient-self-originated viruses. Ultimately, most of the lung cells are infected by re-infections, but what is critically important is how fast the viruses spread the whole lungs. Good

emotion, good air ventilation, warn body temperature, low air humidity, and good life manners can slow down the reinfection. If the reinfection time is extended from several hours to a few days, it could make difference. The slower reinfection speed will result in fewer viral particles and less viral damages. Sequential infections cause less physical stress on the whole lungs than synchronized large-scale infections. Delays in successive infections result in reduced viral burden and reduced level of inflammation, thus reducing lung damages and risk of death.

5. Think about everything that could be used to improve the waste removal balance and encourage white blood cells to pass through infected tissue. Controlling parameters are temperature, air humidity, body hydration, mechanical motions, and protection of the heart, lungs, liver, and kidneys. Those measures can be used in the entire course of disease.

(1) Temperature is the most important factor. It affects blood stricture, blood viscosity, blood vessel pore size, etc. Keeping warn is the most important thing in the fight against cold, influenza and any lung infection. Keeping warn is important before exposure, during exposure, in the latent time, in the fight, and during recovery.

(2) Low humidity facilitate removal of water layer on the alveolar walls and promotes oxygen uptake and thus improve the lungs' function to maintain waste removal balance and mitigate the congestion of immune cells/white blood cells in lung tissues.

(3) Increase water intake to reduce blood viscosity. A large number of other factors can be used to reduce blood viscosity. Certain foods and herbs can be used to reduce platelet aggregation. Right level of salts can reduce blood viscosity. Intake of more water with moderate salts can increase the ability to disperse viral-generated wastes, cell debris and metabolic by-products into the circulating blood.

(4) Increase mechanical vibrations of lungs. Sound-uttering, an ancient healing art, can help lungs relax, thus facilitating the passing of white blood cells through the capillaries network. It is best used in early phrase, after the reinfection phase, and during the recovery phase. However, sound uttering in the reinfection time windows may facilitating viral spreading. One best bet is avoid uttering violent and explosive sounds in the reinfection time window.

(5) Normal breath does not generate high viral concentration that pose serious risk of causing reinfections of non-infected part. However, after at least some infected cells have discharged cell contents, couching and sneezing generate high-concentration viral sources for self-reinfection. In the early phrase, patients should avoid coughing, sneezing, and violent throat clearing activities as much as possible or taking any valid measures to inactivate viruses that are inhaled back. Such attempts can slow down viral spread speed. After the

whole lungs have been infected, coughing can generate force to improve micro-circulation to facilitate white blood cells to pass through.

The benefits of deep breathing exercise can be explained in light of the damage models. The expansion and contraction of thoracic cage and the diaphragmatic movements can increase the force to squeeze liquid surrounding alveolar tissue from the arterial side to the venous side; breath-induced mechanical vibrations facilitate the passing of immune cells through alveolar tissues; active motion of the exercise can raise lung local temperature with triple benefits including making blood more fluidity; the increased air exchange improve alveolar ventilation and thus brings out more of the leaked water from alveolar spaces; and finally, exercise can improve the function of the CNS or the brain region that regulates lung functions. Viruses harm the lungs for the entire disease time, the exercise can be used to offset some of the adverse effects in the entire time period.

Deep breathing exercises have been used in China, India, Japan, Korean, etc. as primary healing art for thousands of years. This exercise can work with other measures to further improve micro-circulation.

In a kinetic scale, vitamins A, C, E, antioxidants, selenium, etc. protect cells from the injuries of free radicals [30]. Human lifestyle and body condition also have great effect on human ability to resist viral diseases [44-55]. Lifestyle and body condition also affect human vulnerability to viral infection [56-65]. Given the observed impacts, influencing factors are expected to have great impacts on disease outcomes.

B. Strategies For Reducing Incidence Rate and Death Rate

Attempt to contain the COVID-19 pandemic by breaking the chain of infection could be difficult. Virus can travel up to 10 miles. In animal infection cases, no direct contact exists between different animal farms but epidermic can pass from a farm to another. Even though viruses are slowly inactivated when they travel in air, one cannot expect all of viral particles lose infectious power. An “extincted” virus may be revived by animals carrying it. This risk is implied by related virus SARS-CoV, which can transmit through species such as Himalayan palm civets, raccoon dogs, Chinese ferret badgers. Moreover, 60 novel bat coronaviruses were identified in bats in various regions of the world [34]. A new outbreak may be restarted by patients who carry the virus as chronic infections. Vaccine is expected to have only partial protection due to expected delays in immune responses and viral mutations. So, it would be as difficult as containing an influenza outbreak. We believe that any attempts of controlling viral sources could depend on luck.

We proposed double-tenth reduction strategies to contain the pandemic. The main promise of this strategy is that disease process is addressed in a quantitative manner rather than in a binary scale. The double tenth reduction strategies are reducing incidence rate from an imagined background rate to one

tenth and reducing the current death rate of infected patients to one tenth. When incidence rate is reduced to one tenth, the total disease population can be reduced dramatically. When the death rate is reduced to one tenth or below 1%, a disease would be like a bad influenza. The double reductions will generate a series of positive chain of reactions. When the death rate is tolerable, people will not be panic, cross-infection in quarantine is avoided, and adverse impacts of panic, emotional distress will not aggravate the pandemic. Deaths attributed to cross-infections in hospitals, improper and wrong treatments, and unexpected adverse side effects will be minimized. The changes will contribute to further reduction of death rate.

The infection modes and damage models imply two different strategies. In the early phase before the virus has infected the whole lung and the patient organs still have ample redundant capacities, the measure is inhibiting, slowing down viral reproduction, viral spread and viral reinfection. Anti-viral drugs in late stages should be avoided after the patient organ capacities have declined to disability levels or near death threshold. Instead, a sound strategy is taking measures to reduce tissue inflammation and maintaining blood circulation.

The modes of initial infection and repeating infections are vitally important. One cannot avoid viruses in a city where a large number of people have been infected. Existing knowledge of the chain of infection is insufficient. One cannot evaluate risk of infections according to a simple yes-or-no rule. The chances of infection depend on viral source, viral concentration, viral activity level, manner of routes, times of exposures, duration of exposure, host condition, health conditions, post-exposure measures, post-infection protective measures, etc. Overwhelming factors could be used in several days before exposure to several days after exposure. One or more properly used measures could make differences. General guidance can be developed for preventing against direct lung infections. Detailed guidance can be tailored for this virus when more knowledge about the virus is known.

The most important strategy is to avoid massive viral exposure in a short time window. People should learn avoiding direct exposure to air containing fresh droplets and airborne particles, avoid breathing air from the vicinity of infected patients, and reducing exposure duration. In an outbreak reason, reduce time in public places, avoid getting too closer to strangers, walk away from air containing coughed droplets. Stores, schools, and hospitals should take measures to reduce human density or improve air ventilation. If fresh air cannot be provided, a ventilation system should be used to filter out viral particles from the air. A reduction of viral concentration and removal of large particles from air must make differences even though they may not be reflected in infection incidence rates.

Based on the disease time window from a few days to more than a month, a large number of measures could be used to make differences. If an infection takes about 20 days to destroy the lungs, the person has the same 20 days to

make differences. An adverse outcome is the result of accumulated effects of viral-induced damages. The patients can have the same time window to deliver accumulative effects of useful measures. However, in a small number of cases, patients die within one to two days of earliest signs. It would be difficult to intervene because they might have compromised immune systems.

In dealing with suspected patients, doctors and patients should focus on degrading signs and must take measures to arrest further degradation. Some patients died because they did nothing for several days or weeks. The strategy is not replacing a first measure with a second measure when the first measure appears to fail. It is possible that the second measure could be worse, and the change may stop gradual improvement that could enable the patient to survive.

Properly chosen measures should not be disused simply because they appear to fail to work. They can slow down the infection and damaging processes. Every bit of incremental improvement influences disease kinetics to make differences, but their incremental benefits cannot be measured objectively or subjectively. The measures may help the patient survive longer. The additional time the patient gets allows the immune system to catch up. This is true even if final results are poor. In the fight against the infection, success or failure is a result of the speed race between viral reproduction and immune response and the time-accumulated effect of damaging process caused by impaired blood circulation. In this kinetic problem, delays in individual viral actions, advances in immune activities, and altered timings of individual immune activities must influence final outcomes. Their benefits should not be denied simply because the lungs are infected eventually or adverse outcomes follow in some cases. If irreversible damages have not taken place, the infection of the whole lungs will be resolved and local damages can be repaired by stem cells.

According to news, four family members died within a few days, but many people survive from repeating exposure environments. The difference is how they respond in each of exposure instances. More specific protective measures for each of scenario should be developed. To contain the pandemic, people need to learn to avoid exposure, avoid serious exposures, turn an inevitable infection to a mild flu, mitigate an infection, and avoid doing things to turn a minor infection into repeated infections. What is a big mistake is doing nothing, doing too little, failing to make personal efforts, and awaiting for magic drugs and vaccines.

What a synthetic drug does is nothing more than whatever we have discussed above. Drugs may help slow down viral reproduction, maintain blood circulation, strength heart functions, etc. Patients should be advised that drug side effects can diminish the usable organ capacities of lungs, heart, liver and kidneys. When the lungs are under severe distress, even a moderate thrust by drug side effects can instantly cause death. Patients should not misplace their hope entirely in drugs and ignore measures that have beneficial effects with little risks.

The damage models demonstrate that maintaining blood circulation and waste removal balance is the central strategy. Herb formulations may be formulated to improve holistic health. Herbal formulations may include herbs that fight against virus and inflammation, promote waster removal, and strengthen the functions of all major vital organs. The focus is improving blood micro-circulation in lungs. Synthetic drugs may be used to dilate the blood vessels, but this should be used in the early stage. When the whole lungs are consolidated, there is no room for the blood vessels to expand.

Some medical treatments should be reexamined in the context of those models. Antiviral drugs are effective only in the early stage when the functions of major organs are strong; after the viruses have spread to the whole lungs, virus reproduction is limited by biological resources. Such a drug may only burden the lungs by its side effects. We also question the measure of using drugs to lower body temperature. Body temperature is controlled by substance interleukin-1 (or leukocyte pyrogen) in the hypothalamus of the brain. Interleukin-1 is released from blood leukocytes and tissue macrophages that have digested viruses and bacteria [17]. Thus, raising set-point of temperature has an expected benefits of improving blood micro-circulation and facilitates immune cells dissipate. Lowering the body temperature may be justified only in situations that excessive high temperature could damage the brain. However, a better strategy is maintaining the lungs at higher temperature but lowering the head's temperature by using a cooling bath. Using oxygen intake must be reasonable. While supply oxygen can improve lung function, it can cause widespread damage to tissue cells and make inflammation even severe. Using antiviral and anti-bacteria drugs in the later stage disease should be avoided.

People should consider preventive measures. Severity of the first phase infection depends on virus concentrations, virus activity levels, exposure duration, and host person's health conditions or innate immunity. The best strategies are strengthening the innate immunity, blood micro-circulation in the lungs, immune surveillance function as the long-term goal, avoid exposure to low temperatures and avoid excessive fatigues in an outbreak season, and strictly reduce total inhaled viral parties per day or instance to the minimum.

Airborne particles differ greatly in infection power and infection scale. Fresh droplets from the lungs of persons under infection are the most risky sources; droplets from mouse is the second; air exhaled from infected patients contain virus; dust generated from things that have been used by infected patients would depend on how viral particles are diluted. As a general rule, the viral concentration in the air polluted by powder generated from a small amount of patient discharges is dramatically diluted. In addition, the powder will lose infectious power with time. The decay of viral activity shapely depends on temperature. We recommend use of ballpark dilution factor. We use the fresh viral discharge from patients as a reference concentration. Any dilution by at least 1,000 times to a million times can make differences. Double dilution by a million time each can make viral source safe for health people.

Disease outcomes depend on viral concentration and time of the first infection. Exposure of the lungs to high concentration viral particles is the most dangerous. Per classical model, a low viral concentration and a long exposure time would achieve a similar level of infection. However, under this two phase infection model, extended duration of the infection has an effect of postponing some individual infection actions to later times. The delays cause some viral reproduction activities to take place after the immune system has been scaled up. Later infections are thus limited to epithelial cells of lungs. Therefore, disease severity cannot be predicted by the product of viral concentration and exposure time.

Lung infection and non-lung infection may be caused by two independent exposures. Their relative timings and routes are important. If a patient gets lung infection first and later gets an eyes infection from other source, the eye infection does not mitigate the lung infection. If the eye infection take place a few days before the lungs infection, the eye infection may work to shorten the phase lag between lung viral development and the immune response. If the lung infection is caused by virus released from the infected eye, the lung infection may be limited; if the eye infection is caused by lung infection, the eyes infection only add a burden to the immune system. If a person is expected to expose the lungs to high concentration of virus as a matter of course, a possible strategy is infecting the digestive track so that the immune system can protect the lungs.

Lung reinfection can intervened to slow down their speeds. Although immune system is expected to fight the infection, additional measure can be taken to reduce more reinfections or successive infections. This is important if the first infection is sufficiently serious that additional lung infections may further damage alveoli. Lung reinfection is particularly important when the patient lung function has declined to a disability level.

Duo to the phase lag between lung infection and immune response, maintaining strong innate immunity is the most important strategy. Since all immune cells migrate into lung tissues by squeezing themselves, improving lung micro vascular networks is the most important measure to mitigate damages to the lungs. This measure is useful before infection but take time to achieve it.

The high death rate is a result of lack of treatment experience. Most deaths happen because the medical community did not know much about the virus, the disease progression, and treatment strategies.

C. Policy Implications

Even through COVID-19 is novel, a great deal of related knowledge exists which could aid us in finding treatment strategies. Strangely, all basic research ends without exploring potential utilities of their findings. Temperature and humidity have been known for thousands of years, have been used in entire human histories, and have been confirmed in modern studies. They are still

omitted in modern treatments. The reason is that lifestyle, sleep, diet, exercise, physical activities, personal knowledge, etc. do not help vendors generate profits and randomized control trials generate confusing and false results. This leaves only one revenue: finding a magic drug or vaccine. The population-based medicine creates wrong perceptions by pooling data from different patients, with different disease stages, different health condition, and different severity, etc.

The risk of COVID-19 can be attributed to a small percent of persons with poor health or serious exposures. Poor disease outcomes are worsen by wrong or improper treatments, leading to population panic, which ultimately becomes one biggest aggravating factor. Cross-infections, repeating infections in poorly ventilated rooms, emotional distress, fears and stress, exposure to cold and humid environment, wrong treatments are mainly attributed to the high incidence rate and moderate death rate. Based on recovery stories and potential effects of a large number of influencing factors we have identified, disease outcomes can be easily altered. If the disease is not contained, the top priority is improving population general health AND learning how to avoid serious exposures. Temperature, humidity, exercise, environment factors, lifestyle, diet and herbs, and emotional health can be used in the most powerful protocol to contain the pandemic.

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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.

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