Treatment Strategies for Reducing Damages to Lungs In Patients with Coronavirus and Other Infections

(Preprint for comments, NOT published)

Jianqing Wu[1], Ph.D., J.D. and Ping Zha[2], M.D. (Chi. Med.)

Correspondence: tempaddr2@atozpatent.com

1. End the Incurable Era (Independent researcher for cause), P. O. Box 689, Beltsville, MD 20704. www.igoosa.com.

2. Independent Researcher (Not affiliated with any entity), can be reached by using the above address.

Keywords: coronavirus, SARS, MERS, viral reproduction, immune response, lung infections, lung damages, cold flu Fluenza, deep breath exercises, diet, emotion stress, lifestyle

ABSTRACT

We conducted many model simulations to understand the causes of the damages of coronavirus to lung tissues and constructed a diagram showing viral development, immune response and damage accumulation curves. We found that main causes are (1) the phase lag between the viral reproduction process and a belayed immune response, (2) the direct viral damages and massive collateral damages which are mainly caused by belated immune responses, and (3) further tissue damages triggered by accumulated wastes in lungs. We deduced from those causes that the key strategies for preventing lung damages include avoiding direct lung infection, altering host-virus interactions, promoting immune responses, diluting virus concentrations in lung tissues by promoting viral migration to the rest of the body, maintaining waste removal balance, protecting heart function and renal function, avoiding other infections, reducing allergic reactions and other inflammation, etc. We finally discussed how to use dietary, medical, emotional, lifestyle, environmental, mechanical factors, etc. to alter disease outcomes. We show why true benefits of those factors cannot be determined by randomized controlled trials, and why the multiple-factor optimization approach can be highly effective by examining organ usable capacity in the cause of death. This treatment protocol using water, air, salt, sound, temperature, emotion, exercise, etc. can be the most powerful cures for viral and non-viral lung infections because they do not depend on molecular specificity and are freely available to anyone.

          1   See supplemental Information

INTRODUCTION

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% [1]. 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% [2]. Viruses emerge and re-emerge globally. In the past, we have witnessed outbreaks of Ebola, Chikungunya, and Zika [3]. With each new outbreak, lives are lost, and economy was disrupted. The handling of such outbreaks is inherently difficult. It is hard to decide what must be done. It is argued that recent slow response of the World Health Organization to the 2014–2015 Ebola outbreak [4]. Excessive responses can also cause unnecessary worries and population panics.

The emerging coronavirus outbreak in Wuhan is caused by a new type of coronavirus distantly related to the SARS coronavirus (SARS-CoV) [5]. With an increasing number of new cases of infection reported in China and other countries, the world is seeking cures for the virus. At this point in time, 27 countries have confirmed coronavirus cases, and 12 countries have reported suspected cases, the outbreak has already placed the world on a public health alert, and adversely affects business, traveling, imports and exports, etc. Given the suspected long infection time, full containment will depend on temperature.

Containing the outbreak by breaking chain of infection seems very hard for this virus. This war has been fought for some time [5.1] and there is no simple cure for various reasons. First, RNA viruses have a highly error-prone polymerase used for genome replication, and individual RNA genomes within a species generally differ by many nucleotides from the average genome sequence [6, 7]. When its genetic composition changes, existing drugs may lose effectiveness. This new virus add another disease onto endemic human coronaviruses. Two other coronaviruses, OC43 and 229E, were discovered in the 1960s but had circulated in cows and bats, respectively, for centuries. The other two, HKU1 and NL63, were discovered after the 2003-2004 SARS outbreak, also after circulating in animals. Second, after a large number of human beings have been infected, some of them may carry the virus in a dormant state. When they are in suitable conditions, the virus may erupt. Finally, drugs do not work on every person due to drug resistance and unique personal physiological conditions. The early media reports reflect that the virus is not responsive to existing drugs. Some patients died within a few days. The lack of cure may still happen to a small number of individuals even if good drugs or effective vaccines are found. For those reasons, we explore alternative and complementary remedies that do not depend on chemical specificity and that can be used when no drug can cure the viral infection.

RESULTS

A. Phase Lag Between Viral Development and Immune Response

2
See supplemental Information

The risk of the virus lies in the phase lag between viral reproduction course and the immune response. This problem is particularly severe when initial infection takes place in the lungs.

The epithelial surface of the alveoli is composed of alveolar type I and type II cells. Alveolar type I cells comprise 96% of the alveolar surface area. These cells are extremely thin, thus, minimizing diffusion distance between the alveolar air space and pulmonary capillary blood. It is expected that virus can be attached and enter those cells. After a virus has entered into an epithelial cell, it may stay dormant for some time before it starts replicate itself. After the virus has reached to certain number in terms of a volume fraction, the virus is released. Some of the viruses may get into the bloodstream while some attach to nearby cells and repeat the same process. Those virus traveling in the blood will reach the bone marrow to activate B cells. The activated B cells will reach the secondary immune organs to generate clones. While the exact time for completing the virus reproduction cycle is unknown for this virus, the reproduction time for other viruses such as bacteriophage is from tens minutes to several hours. Unless, the host cells can hold the virus in a dormant state, the virus can quickly infect many layers of the cells in a time window that is required to generate a meaningful concentration of the virus in the blood stream.

1. Model for a single infection point in a lung

If the virus infects one alveolus, the virus may quickly destroy it. The air space of alveolus which are in close proximity (0.2) µm to pulmonary capillaries. The air space is exchanged around 10 to 15 times a minute. If the virus infects any part of the alveolus, it may destroy it in several minutes to hours. There are about 600 million alveoli in the lungs. In an adult, the lungs weigh approximately 1000 g. Lung volume is about 6000 mL. The height of a normal adult lung is 24 to 27 cm. If a single point is infected by the virus, the viruses would pass a distance of 12 cm from the center to the edge. If the virus transmits by cell-cell direct contact, the virus would have to travel through about 12000 cells assuming that each cell layer has 10 um size. If the infection takes 10 minute to 60 minutes, the total time would 2000-12000 hours (83-500 days). If immune response starts working in 4 to 6 days, a single point infection can cause limited damage. In this model, we did not consider the potentially required collective infection mechanisms and virus concentration, and virus spreading by blood is neglected.

After the alveoli and lung tissue are destroyed, the alveoli cannot support the bronchial tubes. The tubes collapse and cause a blockage, which traps air inside the lungs. Because there are fewer working alveoli, less oxygen will be able to move into the bloodstream. The lung function is diminished.

2. Model for multiple-point simultaneous infections

Adult lungs have about 600 million of alveoli. If the 600 million alveoli are infected at substantially the same time by the viruses. If the viruses stay in a

dormant state, they do not get blood stream in a meaningful number. After the viruses change from a dormant state to a reproduction state, they may destroy each of the alveoli in one single production cycle. The viruses may destroy the whole lung in as short as one or a few hours. In this model, the immune system is completely in dark, without aware of the viral invasion or at least did not have time to respond. The infected person may die shortly.

In reality, true simultaneous infections of all alveoli are unlikely. Most cases involve multiple points infection from two points to N points. The more infection points in the lungs, the more faster and serious damages the virus can cause. We attribute the infections of patients who die within one to several days after initial sign of symptoms to multiple points infections in the lungs. We found that the number of infection points in the lungs are critically important and must be considered in preventive measures. We can estimate that a phase lag is between 4 days to a week between the viral reproduction curve and the immune response cure. MERS-CoV in the Saudi Arabia outbreak develops the disease after 6.2 days, and continued releasing the virus for 13.17 days on average. This number is consistent with 4 days to a weak phase lag.

3. A model for non-lung initiated infection

If the virus enters into the body through the digestive track, body cuts or any other locality other the lungs, the virus must go through a long process. This long path causes a delayed infection of lungs and alters the outcomes of the race between viral development and immune response.

When infected cells release viruses from infected cells, the released virus particles arrive at the lungs and also arrive at the bone marrows at substantially same time. When first batch of viruses attach to lung cells, the immune system has started activating B cells. In the model 1, when the initial infection takes place in the lungs, the immune system is not aware of the viruses at all. In this model, when the virus has reached the lung cells, the immune system is already in the process of activation.

A much important factor is caused by differences in virus concentration. In the models 1 and 2, the initial virus concentration is presumed to be high enough to infect the lung cells. The virus concentration carried in blood is much lower. An adult weighing 150 to 180 pounds should have about 1.2 to 1.5 gallons of blood in the body. This is about 4,500 to 5,700 mL. If the first infected cell releases viruses into the blood stream, the virus particles are diluted by the blood. We use half blood volume 2,550 mL to account for incomplete dilution or non-complete mixing. If the virus concentration from the releasing cell is used as a reference and the total cell volume is 1,764 um (the mean volume). The total dilution factor for virus concentration is estimated to be is about 1,500,000,000. Now, we consider the viral concentration rise due to viral reproduction. With viral reproduction, more and more cells release viral particles into the bloodstream. Assuming that the early infected site has a million of releasing cells, the virus concentration from the circulating blood would be still diluted by

1,500 times. The actual concentration is much lower because the immune system starts destroying viruses in the blood. Therefore, virus concentrations brought by blood must be millions of times more diluted.

In the early stage of infection, the contraction of viruses released from lung cells are expected to be more than more than a billion times higher than the concentration of viruses that are originated from a non-lung infection and brought by blood.

4. Phase lags between lung-initiated and non-lung-initiated immune response

An initial infection may be in the lungs or a non-lung tissue such as the digestive track. When an infection is initiated in a lung, the viruses can directly damage lung cells soon after they start reproduction cycles. They may start cell-to-cell transmission without giving the immune system a meaningful chance to respond. The immune system is not activated for this virus before at least some infected cells have released the viral content that has reached the bone marrow. Moreover, activation also depends on various conditions and existence of co-factors.

B cell activation occurs in the secondary lymphoid organs (SLOs) such as the spleen and lymph nodes [*8*]. Antigens that activate B cells with the help of T-cell are known as T cell-dependent (TD) antigens and include foreign proteins. B cell response to these antigens takes multiple days. Then activated B cells participate in a two-step differentiation process that yields both short-lived plasmablasts for immediate protection and long-lived plasma cells and memory B cells for persistent protection [9]. The first step, known as the extrafollicular response, occurs outside lymphoid follicles, but still in the SLO.

The above model implies that before antigen stimulation, receptors diffuse through the membrane coming into contact with Lck and CD45 in equal frequency, rendering a net equilibrium of phosphorylation and non-phosphorylation. It is only when the cell comes in contact with an antigen presenting cell that the larger CD45 is displaced due to the close distance between the two membranes. This allows for net phosphorylation of the BCR and the initiation of the signal transduction pathway. Of the three B cell subsets, FOB cells preferentially undergo T cell-dependent activation while MZ B cells and B1 B cells preferentially undergo T cell-independent activation [9].

In a first step, activated B cells proliferate, undergo immunoglobulin class switching, and differentiate into plasmablasts that produce early weak antibodies mostly of class IgM [10]. In a second step, activated B cells entering a lymphoid follicle and forming a germinal center, which is a specialized micro environment where B cells undergo extensive proliferation, immunoglobulin class switching, and affinity maturation directed by somatic hypermutation [11]. These processes are facilitated by TFH cells within the GC and generate both high-affinity memory B cells and long-lived plasma cells [9]. Resultant plasma cells secrete large amounts of antibody and either stay within the SLO or, more preferentially, migrate to bone marrow [11]

          5   See supplemental Information

When the lung is infected first, the virus has not reached the SLO yet; and even if some viruses got into the bloodstream, they have been diluted by blood by a billion times. It is highly unlikely for such viruses to reach a required concentration that can reliably activates B cells. Second, the antibody activation often requires co-factors and various conditions. Thus, even if a sufficient number of viruses is around a B cell, the B cell may be not activated due to missing co-factors or breached conditions. Finally, the cloning process naturally takes time for the antibody to reach a level that has a practical meaning. Multiple-day delays are recognized by consensus. In coronavirus, patents die within the first week after the appearance of symptoms. We estimate that the delays are about 4 to 7 days on most patients, but longer delays may be found on those with compromised immune systems. In those patients who died quickly, the virus might have infected and destroyed a bulk part of the lung tissues before the immune system has generated a sufficient number of antibodies in the bloodstream.

5. Infections by viruses carried in blood and by cell-cell direct contact

In direct cell-to-cell infection, the high viral population or high viral concentration in the lung cells can quickly infect and kill lung cells. The discharges from a releasing cell may contain thousands of copies of viruses, which have a high chance to infest its neighbor cells. Some discharges that are close to capillaries or good blood flow path is diluted by the blood, and may become less lethal to other tissues. While it is not known what is the minimum concentration required for infect host cells, it is unlikely that highly diluted viruses can infect host cells [12, 13, 14]. The infested cells will repeat the same process. The viruses will quickly destroy the lungs. However, viruses from blood is highly diluted and under immune system attack are unable to enter a lung cell. When more and more viruses are released from infected cells, the virus concentration arises. However, the antibody concentration is expected to increase even faster and ultimately bring the virus population under control.

Fluid from blood circulation dilutes protein concentration and reduce viral activities in lung tissues. During the replication, hundreds to thousands of proteins assemble around the viral nucleic acid to form a protein shell capsid. It was found that the palmitate adducts on coronavirus S proteins are necessary in assembly and also in positioning the assembled envelope proteins for maximal infectivity. Intuitively, a good blood circulation in the lung tissue hinders the protein from forming the assembly and also dilute palmitate. The good blood flow also affects host cell stress response, which was described in a study [29].

The virus concentration difference at tissue localities is the most important factor that is most probably responsible for different outcomes among different infection routes.

6. A system diagram for reducing damages to lungs

Based on the behaviors of the above models, all findings are shown in Figure 1.

                    See supplemental Information
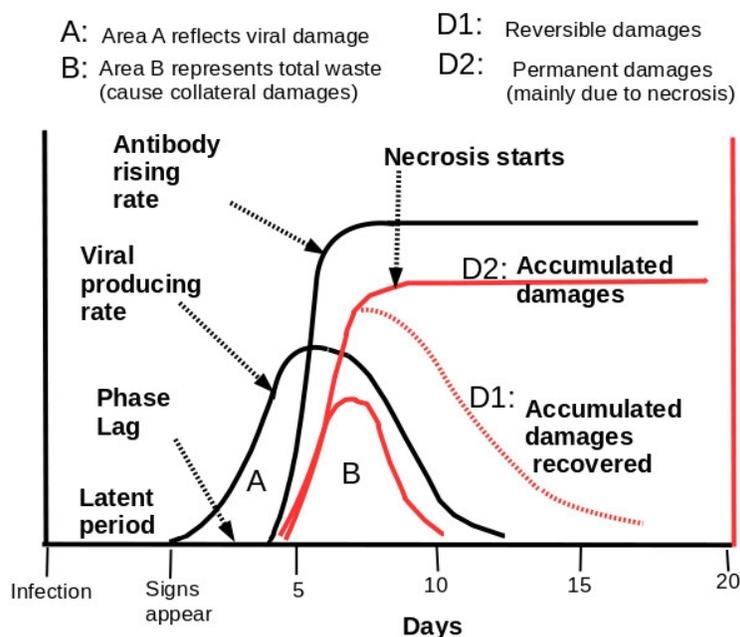
Figure 1 shows that the virus starts reproducing after a latent period. The antibody reproduction starts after a delay. After the time of activation, antibodies will rise rapidly. The immune system starts bringing down the viral reproducing speed. The size of area A reflects the total viral population and the direct damages by the virus to the lungs. After the war between the immune system and the virus starts, the tissue produces wastes at rates which first increase, then level off, and finally decline consistent with reduced virus population. The area B reflects total wastes from the immune response. The accumulated damages are designated by D1 and D2. If blood circulation in the tissue is maintained, the damage is irreversible as shown in D1. However, if the produced wastes are accumulated, they cause tissue inflammation and tissue swelling, which eventually lead to tissue necrosis. As shown in D2, the damages from tissue necrosis are largely irreversible.

The difference of infection routes on the phase lag between the virus infection in the lungs and the immune response is the main reason for disparity in observed severity of infections. This difference implies fighting strategies. Any measures are directed to slowing down viral development speed and increasing the immune response. The strategies are using everything that can be found to reduce areas of A and B, and taking additional measures to prevent tissue necrosis.

B. Collateral Damages Caused by Immune Responses and Strategy

If the immune response is boosted up before the virus has caused sufficient damages, the disease will resolve quickly without signs of damages. However, if

  See supplemental Information

the virus has invaded into and infected a sufficiently large portion of lung cells, the immune response will wage a large scale war against the virus and infected cells. It is expected that the great inflammation will occur and massive cell wastes, virus debris and metabolic products are generated. If they are not promptly removed, they cause severe inflammation and tissue swelling. The swelling will further degrade micro circulation condition in the tissues.

1. The main battles against the virus

Virus can kill lung cells directly. This damage is controlled by altering viral production cycle or the size of A. In the belated war against the virus, the immune system kills infected cells and virus in the following ways.

One type of T cell is called a cytotoxic T cell because it kills cells that are infected with viruses by releasing toxic mediators. Cytotoxic T cells have specialized proteins on their surface that help them to recognize virally-infected cells. These proteins are called T cell receptors (TCRs). Each cytotoxic T cell has a TCR that can specifically recognize a particular antigenic peptide bound to an MHC molecule. If the T cell receptor detects a peptide from a virus, it warns its T cell of an infection. The T cell releases cytotoxic factors to kill the infected cell. When the cell dies, it release cell debris, virus debris and possible survival virus.

Viruses can also be removed from the body by antibodies before they get the chance to infect a cell. Antibodies recognize viruses and bind to them. This binding cripples the viruses, causing virus particles to stick together as agglutinated viruses. A virus-bound antibody binds to receptors, called Fc receptors on the surface of phagocytic cells and triggers a mechanism known as phagocytosis, by which the cell engulfs and destroys the virus. Antibodies can also activate the complement system, which opsonises and promotes phagocytosis of viruses. Complement can also damage the envelope (phospholipid bilayer) that is present on some types of virus.

Interferons prevent replication of viruses, by directly interfering with their ability to replicate within an infected cell. They also act as signaling molecules that allow infected cells to warn nearby cells of a viral presence – this signal makes neighboring cells increase the numbers of MHC class I molecules upon their surfaces, so that T cells surveying the area can identify and eliminate the viral infection.

Killing viruses is the ultimate goal for controlling the infection. However, no matter how the viruses are killed, the end products are cell debris, virus debris, and toxic metabolic products. If the infection is severe, the volume of the wastes from the tissue is high. The viral activity, the immune response, and the wastes can all cause distress to lung cells. In this phase, the virus population is in decline, but the wastes rise. If the wastes are not removed, blood micro circulation is blocked and slowed, the lungs are unable to maintain the migration of antibodies from blood to the lungs, and those large T cells cannot be migrated

          8   See supplemental Information

to the lung cells. Therefore, we will examine how waste removal rates affect lung tissues.

2. A model for toxic wastes balance

We found that maintaining the waste removal balance is critically important in mitigating lung damages. In any given time, if the viral population is increased by dN and if the lung does not remove the increased viruses completely, it will be accumulated. In each incremental time, the virus created is more than virus removed from the tissue, it will be accumulated over time. The total number of accumulated virus is the sum of all surplus virus particles in all of the incremental times. The failure to maintain virus particles must be fatal if the time is long enough. This rule must be true to all toxic substances in a living being that lives for an in-definitive time.

We note however that virus production speed are not at constant. The invaded viruses first stay latent for a period of time. Then, the viruses picks up their reproduction speed slowly and than grow exponentially. The reproduction speed is expected to slow down and level off when the virus production has consumed required materials. Despite this reproduction curve. One thing must be true is that the lungs must remove all produced wastes including virus debris, and related by-products promptly. If they are not removed through blood circulation, they must be brought out by other means. Coughing, running nose, and other discharges can remove extra wastes when blood circulation would not maintain the waste balance. In patients with severe lung distress, even those secondary means are unavailable due to degraded energy metabolism.

The crucial importance of maintaining the waste removal balance is implied in the steady state theory. Adverse outcomes from failure to maintain the input and output balance are common for complex machines such as cars and planes. If the heat generated in each combustion cycle is more than that removed, the engine eventually is ruined by accumulated heat.

Even just a 1% imbalance results in damages with time. For a small lung tissue that can produce waste at 100% per hour. If the tissue can remove all of them, the tissue can keep the original waste amount W if the lung maintain this balance in a steady state. If the lung can remove 99% or produced waste but fails to remove 1% in each hour, and one hundred hour later (four days later), the tissue would have the amount of equivalent to W + the full amount generated in one hour. This is an ideal case that cannot be true. This accumulated wastes may cause tissue damages and cause much series of immune response. The immune system attempts to attack virus, virus debris, cell debris in a highly concentrated area. If the wastes are timely removed and distributed to the whole body, the battle is found in all part of the body that are not vital to human life.

The speed at which lungs are damaged can be rapidly sped up by vicious cycles caused by the lungs, heart and kidneys interactions. The wastes include virus debris, host cell debris, and any other metabolic products. They intoxicate

lung tissues, cause severe inflammation, and cause the tissue to swell. The swelling of lung tissues further degrades the blood flow condition in the tissue. This diminished blood circulation further reduces the lung capacity to remove metabolic products, virus and cell debris, and degrades lung muscle ability to breath. The blood circulation is dominated by much slower diffusion processes. The lack of blood in the lung tissues results in poor energy production and thus dramatically reduces lung ability to uptake oxygen. Reduced oxygen degrades energy metabolisms in the whole body. Now, the heart will reduce the ability to pump, the kidneys will have reduced capacity to process waste, and the liver cannot perform its functions of filtering the blood, detoxifying chemicals and metabolizing drugs. The degraded system's blood circulation will further impair the lung's ability to function and makes lung muscles even weaker. As long as this waste removal balance is not restored, the body viciously degrades to the point that one or more organ functions reach below the threshold of death. Due to the vicious interactions, the lungs may may fail to remove 1% of produced wastes in the first hour, 2% ten hours later, 3% twenty hours late, etc. Any mathematical model will show that a slight imbalance in removing metabolic wastes will result in disastrous results.

One possible strategy is to slow down the immune response. The immune system augments initially very slowly, and raises antibody producing speed exponentially. However, the final resolution of the disease depends on immune responses. So, slowing down the immune response is not a sound strategy (except in life-threatening cases). Besides, the body normally scales down the antibody production speeds quickly after the infection is brought under control. This leaves only one strategy that can be used in the clinical setting: removing antigens and all metabolic wastes from the tissue as fast as possible. Other sources of inflammation must be addressed because they are presumed to attribute to the swelling of lung tissues and cause additional damages to the lung tissues by making lung micro-circulation worse.

C. Controlling Points Are the Phase Lag and Lung Micro-circulation

To reduce the risk of death, two control points are to reduce the phase lag between viral development and immune responses (the areas A and B), and improve the blood micro-vascular circulation in the lung tissues. Despite lack of direct evidence for the Wuhan coronavirus, host cell physiological state is presumed to affect the viral development speed and the immune response speed in humans.

Based on other data, it generally take 4 to 6 days to detect antibodies. This delay would depend on where the initial infection is. In MERS-CoV cases, some patients may not develop strong antibody responses even after 4 weeks of illness [15]. The great differences in the phase lags imply that the viral life reproduction cycles are sensitive to many factors in host cells. In the CoV, envelope is involved in critical aspects of the viral reproduction cycle [16]. This property provides a hint that many things can be used to disrupt the formation of the envelope.

Moreover, the various host-virus interactions discussed in the cited article can be explored to inhibit or slow down the viral reproduction speed. After the use of Chinese medicine in SARS patients, it is found that glycyrrhizin, a compound found in liquorice roots, was reported to have a good in-vitro activity against SARS-CoV [17].

The phase lag highly depends on the relative concentrations of the viruses in the infection site and the manner of infections. Virus infection depends on contact chance. In bacteriophage, the host quantity, which dictates the average time for a phage to find and infect an uninfected host, and the host physiological state affects the rate by which the phage progeny are assembled/matured. Studies indicate that intra-host viral population diversity may be a prerequisite for a virulent infection [18, 19, 20]. Serial passage of a virus in laboratory animals is often used to increase pathogenicity of the virus for that host in order to generate a laboratory model of the disease [21, 22]. Viral spread is often mediated by structures that simultaneously vehicle groups of viral genomes, such as polyploid virions, aggregates of virions, virion-containing proteinaceous structures, secreted lipid vesicles, and virus-induced cell-cell contacts. The requirement of high concentration is reflected in the multiplicity of infection concept, which has been traditionally defined as the ratio of infectious viral particles to susceptible cells in a given space or alternatively, the average number of viral genomes that initiate an infection [12]. The co-delivery of multiple viral genomes to the same target cell can be further facilitated by direct contacts between cells [12, 23-26]. Multi-genome infectious structures may promote mutually beneficial interactions between different variants of a virus at the intracellular level [27, 28]. RNA viruses have a highly error-prone polymerase used for genome replication, and individual RNA genomes within a species generally differ by many nucleotides (nts) from the average genome sequence [6, 7]. Thus, the coronavirus has high genomes diversity. This property implies that in collective infection is an important mean of infection. The collective infectious mechanism implies that high concentration of viruses is a required condition for infecting cells. This is applicable to subsequent cell-to-cell infections and infections by blood-carried viruses.

The health condition of the lungs affects the virus infection and spread. The lung health depends on nutritional balance. In any time, blood circulation must maintain the nutritional balance and the waste removal balance. If those balances are lost, the lungs slowly be damaged for lack of essential nutrition and poisoning of toxic substance. Replication of coronavirus induces the Unfolded Protein Response and other cellular stress responses in infected cells, triggering innate immunity and antiviral signaling pathways. The translational control it is targeted and subverted by various coronaviruses at different levels via different mechanisms [29]. It can be assumed that lung health affects the host ability to resist virus infection. Increased virulence was associated with the efficiency of interaction of the spike protein and the viral receptor on the rat cells, increased age of the rodent and mutations in the viral genome [30]. Viruses get protein from the host cell membranes to form the virus envelope. The capsid and the

 11 See supplemental Information

envelope play many roles in viral infection, including virus attachment to cells, entry into cells, release of the capsid contents into the cells, and packaging of newly formed viral particles. Those facts imply that virus-and-host interactions affect viral reproduction timing and viral reproduction speeds. A large number of factors can be used to alter the viral initial time and reproduction speed and reduce the area A in Figure 1.

Virus can spreed by cell-to-cell contact. The details for this coronavirus is unknown now, but mechanisms for other viruses provide useful hints. In solid tissues, effective cell-to-cell transfer can occur in the absence of specific cell signaling structures if viral budding is concomitant with attachment/entry into a neighbor cell [31]. In HIV-1 and other retroviruses, viral glycoproteins located in the cell surface stimulate the establishment of filopodes, which are used as bridges for cell-to-cell spread [32]. Several lines of evidence indicate that cell-to-cell virion passage through virological synapses is a major route of intra-host viral dissemination for HIV-1, human T cell leukaemia virus 1 (HTLV-1), and hepatitis C virus [33-39]. HTLV-1 uses virus-containing biofilm to spread virions between neighbor cells [36]. In vaccinia virus and other poxviruses, newly assembled viral particles remain associated to the surface of the infected cell, where they induce actin polymerization and the production of cellular projections that enhance viral transmission to neighboring cells [40]. Multiple genomes initiate a new cell infection [41].Viral population diversity plays a role in its adoption to new host environment [41.1].

The immune system responses can be altered by using a large number of factors. Immunocompetence of a host is determined by many factors such as age, pregnancy, and nutrient intake of various types (42-49). Studies suggest that both malnutrition and obesity adversely affect the ability of a host to mount a robust innate and adaptive immune response to viral infections (46, 50-59). Low zinc level, commonly reported in the elderly, impairs immune function, decreases resistance to pathogens, and is associated not only with increased incidence and duration of pneumonia, increased use and duration of antimicrobial treatment, but also with increased overall mortality in the elderly [59.1]. Those factors can be used to reduce areas A and B as well as the magnitudes of cures D and avoid the D2 curve appearance in Figure 1.

The virus can cause various level stress [60]. Stressful events can influence the functioning of the immune system [61, 62, 63]. Several systematic reviews and meta-analyses have shown that particularly chronic stress suppresses protective immune responses and promotes pathological immune responses, including inflammatory responses [64, 65, 66, 67, 68, 69]. These immune alterations can be expressed as slower wound healing [65, 66], impaired responses to vaccines [64], and progression of infectious and immune-mediated diseases [64, 70, 71]. Moreover, host immunocompetence influence viral virulence during in vivo passage; and some study on Stress-Reducing Interventions can improve immune responses [73], thus reducing area B and avoiding curve D2 appearance.

In the Saudi Arabia MERS-CoV outbreak, the chance of survivals among confirmed cases were associated with younger age, breathing ambient air, not being transferred to the intensive care unit and not receiving renal replacement therapy [74]. The observed age-related morbidity can be explained by weakened immune system and poor blood circulation which is resulted from less physical activity common among the elderly. The compromised vascular system will also affect the virus reproduction, the immune response, and the ability to survive. Above all, the most important factor is blood circulation rate in the lung tissue.

D. Practical Measures for Reducing Damages To Lungs

To reduce areas A and B and prevent D2 curve appearance, the strategies further include improving micro circulation in the lung tissue, improving the renal function, avoiding and reducing other sources of inflammation, reducing physical activities, avoiding using allergic foods, improving the vascular system, and changing immune response characteristics. Even based current knowledge, hundreds of factors can be used to alter final outcomes. We now summarize key measures in the following table.

Table 1 Treatment measures for reducing damages to lung tissues and raising the usable organ capacity.

Measures	Application Details	Known Mechanisms	Our Reasons and Mechanisms (A, B, effect on D2 and D1)
Drink a lot water	Drink two or three times of water one normally drinks	MOI and corrective infection.	The vital role of virus concentration in infection elimination (A and B, D2→D1)
Take reasonable amounts of salts	Take moderate salts to maintain electrolyte balance	Not recommended, but some doctors advice it	Salt is essential for maintaining the CNS function; and an increased ionic strength in the body fluid can help remove the virus and cell waste more easily, See n1. (B, D2→D1)
Keep emotional calm	Emotional distress suppresses immunity	It is found in a large number of studies concerning many diseases.	Severe emotional distress can divert the CNS resources and make less resources for regulating the immune system (A, B, D2→D1)
Vitamins C, A, K, B, etc and other	Use vitamins to improve immune system, & host	There are a large number of studies on vitamins, etc; however long-term	We favor using fresh and pollutant-low vegetables and fruits to void catalysts, pollutants, and over-used

nutrients	defense.	over-use is not good.	imbalance (A, D2→D1). Large doses are used for short term.
Do deep breathing exercise	In the early phase when the lungs are capable, do deep breath exercise for 2-8 hrs a day.	Medical evidence starts emerging. It can improve oxygen in blood by up to 30%.	The exercise improves energy metabolism, increases lung blood micro-circulation, facilitates waste removal, and the enlarged lung motions promote waste removal (A, B, D2→D1).
Improve air quality	Improve air quality or improve ventilation.	Increase oxygen by 2% to 5% is a significant factor; and avoid secondary infections from other patients is vitally important.	Reduce viral level in the air may disrupt potential interactions between different viruses from air; substances from natural air may affect virus-cell interactions.
Utter sounds	Based on six sounds deep breathing exercise (used for more than 1000 years)	Collective infection, and formation of protein envelope, etc requires a calm environment; sound-inducing vibrations disrupt required condition.	It disrupts a calm environment, improves blood circulation, promotes waste removal, stimulates the nerve signal transmission, etc. Take time to get a result (B, D2→D1)
Relaxation	Try to relax in the whole body, especially lungs.	Many studies found that relaxation can help health by affecting blood vessels.	Relaxation can cause a few percents of expansion of blood vessels, reduce blood flow resistance, and improves blood circulation (A, D2→D1).
Avoid physical exercise while infected.	When the lungs are under distress and experience shortness of breath, avoid physical activities.	This is used in medicine for its entire history.	When the lung usable function has reached to a disability level, any physical exercise will produce more metabolic wastes, and further degrade the waste removal balance (D2→D1).
Use warn foods such as ginger, date, etc.	A class of foods can make people warn.	(Some indirect emerging evidence)	Warn foods can improve blood circulation, improve immune cell migration and waste removals (A, D2→D1).

    14   See supplemental Information

Ginseng	Ginseng is commonly used to extend life in critical time.	The effect is similar to steroids which can improve energy metabolism.	In certain cases, it can improve energy metabolism, and improve the usable capacity of lungs, kidneys and heart. However, avoid long-term use (B, D2→D1).
Steroids and oxygen	Steroids and oxygen are routinely used in treating lung infections	Improve energy metabolism and improve lung micro-circulation	It is important to prevent or mitigate damages to lung tissues for patients who have experienced shortness of breath (B, D2→D1)
Anti-inflammation foods and herbs	A large number of foods and herbs can reduce inflammation	Inflammation is the cause of all chronic diseases.	Although medicine separates infection from inflammation, they play a similar role in the organ usable function and waste removal (A, B, D2→D1)
Avoid other-infections	Avoid other infections before this infection is resolved.	Collective infection theory; burden on immune system; and B cells exclusivity, etc.	Other infections can bring down the usable organ function; and other inflammation makes lung micro-circulation worse (B, D2→D1).
Eat anti-virus foods such as garlic, onion, etc.	Garlic, onion, shallot, leek, chive are used to fight virus and improve the heart.	A large number of studies show they have many roles but lack direct evidence on cold-related viruses.	We accept well known working mechanisms, but reject the conflicting or inconclusive findings from controlled trials (A, B, D2→D1).
Physical exercise before infection	Do regular exercise one hour a day	Improve the vascular system and micro circulation in all major organs.	Exercise increases blood flow capacity by 2X to 3X (one feels NO shortness of breath when running at typical marathon speed) (A, B).
Reduce heavy metals & pollutants	Many heavy metals and pollutants can suppress immunity	There are a large of studies show direct and indirect evidence of their roles on immunity	The major risk of death is caused by a delayed immune response. If it is reduced to two days, the infection might appear as a small cold. It is a best preventive measure prior to infection.

Those measures can be used to make two areas A and B (Figure 1) smaller. If those measures are used in time, in good combination, it is possible to prevent or reduce damages to lung tissues substantially or completely.

Per our personal research experience, we found that salt raises ionic strength and reduces the viscosity of biological materials. Protein sols can be dissolved when salt is added. Thus, salt is used to improve waste removal balance (not killing viruses). For patients who are unable to cough and have no lung discharges, waste removal must be regarded as the first priority. Any additional measures such as continuous deep-breathing, uttering sounds, maintaining warn temperature, eating hot foods, generate mechanical vibrations, etc. may be considered. Bringing the body into a relaxing state can improve blood flow significantly through enlarging vessel diameters.

We show why multiple factors can be used jointly to treat the infection. We have proved that randomized controlled trials are not a suitable method for studying week and slow-delivering effect as long as one interfering factor of a similar effect exists in the human body. We found that when N factors can be used, each with the same benefit, the real total benefit of N factors is more than what would be detected for one single factor in a controlled trial (by $(1/g)k$ times); and statistics for conducting hypothesis is off by more $(1/g)k\sqrt{k}$ times, making findings from randomized controlled trails meaningless [75]. When many factors are used to slow down viral infection, reproduction and migration, speed up immune responses and promote virus distribution in the body.

Moreover, we further justify the use of multiple factor health optimization by a model for death cause analysis. A person dies when the usable organ function reaches a threshold of death, which is independent of organ functional reserve. Based on the vascular capacity, the usable lung capacity is reduced from the highest value (100%) to about 20% as the death threshold. We found that a large number of factors affect the usable capacity in an additive manner; and that each of the factors can raise usable lung function [76]. Tens to hundreds of things may be used to preserve some of the surplus 80% heart function. This is the first instance that we use multiple factors to address an acute infection. The bottom line is the lung damages are NOT caused by anything in a binary manner.

Emotional health or absence of emotional stress is vitally important in controlling the virus. We note that findings from studies on improving immune responses are weak. However, emotion is a kind of things that can be studied by controlled trails. When many interfering factors exist, the errors used in statistical analysis have been raised by two to several folds, thus, the statistical conclusions are meaningless and should be ignored. The effectiveness of measures entirely depend on individual persons. If a patient uses it correctly, it may make a big difference. If the patient lacks heart in it, it may have little benefits. Moreover, we propose a general model on how the central nervous system keeps the disease state. The mind state is in constant balance with the body state. Health cannot be achieved without achieving mind health [77]. We showed there that even negative findings from a controlled trial does not

        16   See supplemental Information

preclude its benefits on specific patients. A treatment, which gives 50% negative responses, 40% positive responses, and 10% neutral responses, is a good treatment for those 40% patients if the treatment is correctly used only on those matched patients. We hold that health conditions, treatment responses and death risks found from other people have nothing to do with those of a particular person.

Air quality is a vital factor in fighting lung infections. Air in a poorly ventilated room contains 1% to 5% lower oxygen level than fresh air from nature. Air containing less oxygen but more bacteria, viruses and harmful substances must be bad to lung-infected patients because oxygen uptake speed and infections are treatment focuses. Simultaneous viral and non-viral infections burden their immune systems. If a person has five types of viruses to fight, the immune system has to split their "troops" (the immune cells) to fight all five battles against all five viruses. This single factor may be responsible for some deaths in some treatment settings. When fresh air is not available, the healthcare industry should think how to remote from air viral particles and restore the oxygen level to the natural level.

In the clinical setting, the ultimate strategy is to save lung tissues from direct rival damages and collateral damages. When shortness of breath is noted, a presumption is that blood circulation in the lungs is severely impaired and tissue damages may be in the process. Using corticosteroids and improving oxygen can prevent further damages [78]. One case reveals that severe lung tissue changes took place in a weak after an initial infection and that most severe damages might occur in three to several days after obvious breathing shortness. They found that corticosteroids were associated with considerable improvement in oxygen saturation and pulmonary infiltrates, etc. We attribute its benefits to reducing damages from immune responses because the immune system is in a state of producing massive number of antibodies. Our waste removal model sheds some light on the rapid speed at which the lung tissues are damaged.

Each of the listed measures can make a decisive difference if it is correctly used on a right person. For example, increasing water intake by one time (1X) may bring out wastes by more than a few to tens percents; using salt in reasonable amounts may help remove more viral debris and dead cell wastes in a given time. Emotional factor can make differences in some patients. Vitamins and essential nutrients for the immune system (but not for the virus) may shorten the phase lag by one to two days and thus make a difference; deep breaching can improve energy metabolism by as much as 30% (for experienced, it may improve more); and avoiding exercise may save MET values by up to 70%; relaxation exercise can reduce blood circulation by 10% to 30%; avoiding a secondary infection can reduce burden on the immune system, reduce viral burden on lungs, kidneys and heart, and help maintain the waste balance in the lungs. Warn foods such as ginger, date, citrus, etc are known to improve blood circulation and energy production; anti-inflammatory and antivirus foods such as

garlic, onion, shallot, leek, and chive are also good, regardless of conclusions in past studies.

When the lungs lose some functions, the heart and the kidneys reduce their usable capacities due to degraded energy metabolism caused by diminished oxygen supplier. The degraded blood circulation in the lung tissues and increased amounts of wastes will make the lungs worse. Even a small deficiency in the early stage can progressively degrade the performance of the lung. If this problem is not firmly addressed and brought under control, damages to lung tissues and other organs are inevitable. Serious damages are irreversible. However, lungs always suffer the most damages because they are battle fields of the immune system. Oxygen, steroids and certain herbs may effectively mitigate lung damages by improving micro circulation. For localized lung infections, damages may be done to infected localities even before severe shortness of breath is felt; but a severe and degrading breath difficulties should be presumed to be caused by severely impaired micro-circulation. Those measures or other measures must be used to improve lung micro circulation to prevent damages to the lungs.

Keeping the body warn is important because cold may invite different infections. This is not a small factor because temperature affects blood circulation. One most important reason we believe is that people tend to contract the vessels at low temperatures, and this effect is expected to reach all capillaries in all organs. Cold-initiated discomfort is not felt on body surface, but often in the heart, lungs, etc. Voiding additional antigens is important because each B cell can bind to only one type of antigen. If the person suffers multiple infections, the immune system is over burdened and lack biological resources.

When the viral reproduction curve and the immune response curve have a few days of phase lag, it is possible to starve some viruses in the early stage by limiting materials that are essential to viral reproduction and then boost nutrition to promote the immune system after the immune response starts. The old thinking to get better nutrition may be not the best strategy for some patients. In the early stage, resource limitation may be an effective factor for slowing down early viral development. However, one difficulty is to correctly find the infection time. If one knows that he has been exposed to the virus, it may be worthwhile to impose specific nutritional restriction for a few days and then improve nutritional supply for promoting the immune system.

As we noted that many studies failed to find evidence that those things are effective to cold or to this virus. Some studies even reached negative conclusions. The only evidence those studies rely on is data from randomized controlled trials and statistical conclusions. In each of such studies, a treatment or factor is studied without regarding the differences in application timing, patient conditions, and other problems. However, we can find their effects by studying their ingredients and working mechanisms. For example, glucosinolates found in garlic (as well as cruciferous vegetables) have an antibiotic-like effect and help ward off bacterial, viral, and fungal infection in the intestines and other

parts of the body. This compound can fight herpes simplex types 1 and 2, human rhinovirus type 2, parainfluenza virus type 3, vaccinia virus, and vesicular stomatitis virus. There is no evidence that garlic can fight coronavirus. However, garlic is known to have numerous indirect effects. It has antioxidant activity, lipid (cholesterol and triglyceride) lowering, platelet aggregation inhibition, enhancement of fibrinolytic activity, prolongation of bleeding and clotting time, and prevention of LDL oxidation. It also possesses anti-inflammatory properties, hypoglycemic actions, digestive effects and cleansing actions. As a whole, garlic can improve micro circulation in the lungs, improve the immune function. or promotes the holistic health.

Although age is a known risk factor in lung infections in virtually all studies. This factor can be overcome. We noted that the total time for recovering from a cold or flu can be reduced to hours or less than a day as compared with several weeks. Similarly, we noted from personal experience that severe seasonal allergic reactions to pollen can be corrected by adjustment to lifestyle. We explain those changes by the waste removal balance. Antigens enter the body in variable speeds. If the body is unable to remove them and their metabolic products through circulation, the body must remove them by discharging fluid from running nose, sneezing, and coughing. Those symptoms are compensatory activities necessary to restore the waste-removal balance. The imbalance can be restored in the alternative by improving micro-circulation efficiency. A large number of isolated stories can be found reflecting the importance of improved micro-circulation. By maintaining the waste removal balance, the body can avoid severe collateral damages to lung tissues.

Most of the listed measures can be used independent of medical treatments. We have made clear that inaction is not an option, and that miracles happen only in a small number of patients. When medical treatments are unavailable, do everything possible to reduce A and B areas and improve the waste removal. Upon a suspected infection or earliest signs, keeping body warn avoiding exposure to low temperature, drinking more water containing moderate amount of salt, doing deeping breath continuously with focus on the lungs, uttering sound when doing deep breath (using the Shi sound or all six sounds for the entire exercise), consuming hot foods, inflammation-reducing foods (and herbs if you can find); do not use any drug to stop coughing, do not try to avoid coughing (but avoid coughing that poses risks to others), and avoid other infections in the narrow time window. Depending on how much effort is made, the person may be able to reduce A and B from a few percents to completely. If large scale lung tissue necrosis is avoided, most lung functional reserve may be saved or later recovered.

Preventive behavioral responses can affect outcomes of population. Due to the difference in the risks, if one must be infected by the virus, then infection by a non-lung body parts may change outcomes. This should be studied before it can be used in real persons. When vaccine is unavailable, it can be life-saving measure if it is used correctly together with other protective measures.

          19   See supplemental Information

The discussed measures are based well known knowledge that might exist long ago. Since this virus is new, a large number of specific properties are not fully understood, and we do not know how to use those newly discovered properties to fight the virus. Any of the properties that have been known [79-89] or discovered in the future may be employed to alter the phase lag and waste removal efficiency in the lungs and thus reduce risks to damage the lungs. Reading from those articles, we found that even physical activities, environment pollutants, body physical condition (such as obesity), emotional state, etc. can alter outcomes because they affect areas A and B, and the waste removal balance.

We believe that the most promising fact-acting cures are herbal formulations. Good herbal formulations must address lung, heart, liver and kidney function at same time. The herbs are used to reduce areas A and B substantially and dramatically improve waste removal capacities shown in the Figure 1. Some formulations have appeared at the time of wring this article, we will include them in an updated version or Supplemental Document when more information is available.

Future measures may be used to disrupt one or more viral activities such as formation of the conformation of the protein envelope, cooperative infection activities, nutritional supply, host-virus interactions, etc. We hope that hundreds to thousands of new factors will be discovered in the future and add them to this treatment framework.

E. Limitations of The Study

This study was performed by applying data from related viruses. Thus, absolute numbers found in all computation examples tell only trends but cannot be used as absolute values. No data can be directly used on persons without adjustments. Personalized medicine mean use a treatment according to specific persons and diseases, but never by random applications. The treatment strategies are useful to all viruses that can infect lungs because most of the measures do not depend on molecular specificity. They are expected to be useful to SARS, coronavirus, Fluenza. Etc. Some of them can be used to ward off common cold or bacterial infections.

We initially had no plan to disclose our knowledge in a search article; but the coronavirus outbreak in Wuhan urged us to write this article. Despite lack of time in preparing this article, the key points for controlling lung damages are beyond challenge because they are obvious now. Most of suggested measures such as deep breathing exercises, sound uttering, relaxation, emotional management, etc. in the multiple factor optimization approach were known long before, and have been used by one of the authors for years. Most of those treatment options are part of people lifestyle and health wisdom. They do not pose additional risks (Those clinical measures are clearly indicated). We initially thought it may take several months to write this article. However, we found that medical basic research has discovered all key data and knowledge that we need

20
See supplemental Information

and this allows us to build ballpark models to explore viral infection and immune response processes. This article will be periodically updated to correct abundant errors and omissions.

FUNDING STATEMENT

The author(s) declared that no grants were involved in supporting this work.

ADDITIONAL INFORMATION

Additional information is provided in a supplemental document and some information may 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 academic exchanges is permitted by default; if anyone wants to translate the article into other languages, please let us know, we will grant the permission.

REFERENCES

1. World Health Organization WHO. Summary of probable SARS cases with onset of illness from 1 November 2002 to 31 July 2003 2003. Available from: http://www.who.int/csr/sars/country/table2004_04_21/en/index.html.

2. World Health Organization WHO. WHO MERS-CoV Global Summary and Assessment of Risk, August 2018 (WHO/MERS/RA/August18) 2018. Available from: http://www.who.int/csr/disease/coronavirus_infections/risk-assessment-august-2018.pdf?ua=1.

3. Parvez, M.K.; Parveen, S. Evolution and Emergence of Pathogenic Viruses: Past, Present, and Future. Intervirology 2017, 60,1–7.

4. Burkle, F.M. Jr. Global Health Security Demands a Strong International Health Regulations Treaty and Leadership From a Highly Resourced World Health Organization. Disaster Med. Public Health Prep. 2015, 9, 568–580.

5. Liu SL and Saif L. Emerging Viruses without Borders: The Wuhan Coronavirus. Viruses 2020, 12, 130; doi:10.3390/v12020130

5.1 Jian Zheng, Stanley Perlman Immune responses in influenza A virus and human coronavirus infections: An ongoing battle between the virus and host.

Curr Opin Virol. Author manuscript; available in PMC 2019 Feb 1. published in final edited form as: Curr Opin Virol. 2018 Feb; 28: 43–52. Published online 2017 Nov 21. doi: 10.1016/j.coviro.2017.11.002

6. Domingo E. (1997) 'RNA Virus Evolution, Population Dynamics, and Nutritional Status', Biological Trace Elements Research, 56: 23–30.

7. Domingo E., Holland J. J. (1997) 'RNA Virus Mutations and Fitness for Survival', Annual Review of Microbiology, 51: 151–78.

8. Murphy, Kenneth (2012). Janeway's Immunobiology (8th ed.). New York: Garland Science. ISBN 9780815342434.

9. Nutt, Stephen L.; Hodgkin, Philip D.; Tarlinton, David M.; Corcoran, Lynn M. (2015-01-01). "The generation of antibody-secreting plasma cells". Nature Reviews Immunology. 15 (3): 160–71. doi:10.1038/nri3795. PMID 25698678.

10. MacLennan, Ian C. M.; Toellner, Kai-Michael; Cunningham, Adam F.; Serre, Karine; Sze, Daniel M.-Y.; Zúñiga, Elina; Cook, Matthew C.; Vinuesa, Carola G. (2003-08-01). "Extrafollicular antibody responses". Immunological Reviews. 194: 8–18. doi:10.1034/j.1600-065x.2003.00058.x. ISSN 0105-2896. PMID 12846803.

11. Shlomchik, Mark J.; Weisel, Florian (2012-05-01). "Germinal center selection and the development of memory B and plasma cells". Immunological Reviews. 247 (1): 52–63. doi:10.1111/j.1600-065X.2012.01124.x. ISSN 1600-065X. PMID 22500831.

12. Sanjuán R. Collective infectious units in viruses Trends Microbiol. 2017 May; 25(5): 402–412. Published online 2017 Mar 3. doi: 10.1016/j.tim.2017.02.003.

13. Shirogane Y, Watanabe S, Yanagi Y. Cooperation between different variants: A unique potential for virus evolution. Virus Res. 2019 Apr 15;264:68-73. doi: 10.1016/j.virusres.2019.02.015. Epub 2019 Feb 26.

14. Leeks A., Segredo-Otero E.A., Sanjuán R., West S.A. Beneficial coinfection can promote within-host viral diversity. Virus Evol. 2018;4/2

15 Park W.B., Perera R.A., Choe P.G., Lau E.H., Choi S.J., Chun J.Y., Oh H.S., Song K.H., Bang J.H., Kim E.S., et al. Kinetics of serologic responses to MERS coronavirus infection in humans, South Korea. Emerg. Infect. Dis. 2015;21:2186–2189. doi: 10.3201/eid2112.151421.

16. Schoeman D and Fielding BC. Coronavirus envelope protein: current knowledge. Virology Journal (2019) 16:69.

17. Cinatl J, Morgenstern B, Bauer G, Chandra P, Rabenau H, Doerr HW. Glycyrrhizin, an active component of liquorice roots, and replication of SARS-associated coronavirus. Lancet 2003a;361:2045-6.

           22   See supplemental Information

18. Vignuzzi M., Stone J. K., Arnold J. J., et al. (2006) 'Quasispecies Diversity Determines Pathogenesis Through Cooperative Interactions in a Viral Population', Nature, 439: 344–8.

19. Kuss S. K., Etheredge C. A., Pfeiffer J. K. (2008) 'Multiple Host Barriers Restrict Poliovirus Trafficking in Mice', PLoS Pathogens, 4: e1000082.

20. Gutiérrez S., Michalakis Y., Blanc S. (2012) 'Virus Population Bottlenecks During Within-Host Progression and Host-To-Host Transmission', Current Opinion in Virology, 2: 546–55.

21. Aronson J. F., Herzog N. K., Jerrells T. R. (1995) 'Tumor Necrosis Factor and the Pathogenesis of Pichinde Virus Infection in Guinea Pigs', The American Journal of Tropical Medicine and Hygiene, 52: 262–9.

22. Tiwari A., Patnayak D. P., Chander Y., et al. (2006) 'Permissibility of Different Cell Types for the Growth of Avian Metapneumovirus', Journal of Virological Methods, 138: 80–4.

23. Vassalli JD, et al. Direct cell-to-cell transmission of vesicular stomatitis virus. J Cell Sci. 1986; 85:125–131.

24. Sattentau QJ. The direct passage of animal viruses between cells. Curr Opin Virol. 2011; 1:396–402.

25. Zhong P, et al. Cell-to-cell transmission of viruses. Curr Opin Virol. 2013; 3:44–50.

26. Sherer NM, et al. Retroviruses can establish filopodial bridges for efficient cell-to-cell transmission. Nat Cell Biol. 2007; 9:310–315.

27. Andino R, Domingo E. Viral quasispecies. Virology. 2015; 479–480C:46–51.

28. Ciota AT, et al. Cooperative interactions in the West Nile virus mutant swarm. BMC Evol Biol. 2012; 12:58–12.

29. Fung S, Liao Y, Liu DX. Regulation of Stress Responses and Translational Control by Coronavirus. Viruses. 2016 Jul; 8(7): 184. Published online 2016 Jul 4. doi: 10.3390/v8070184

30. Nagata N., Iwata N., Hasegawa H., et al. (2007) Participation of both host and virus factors in induction of severe acute respiratory syndrome (SARS) in F344 rats infected with SARS coronavirus. Journal of Virology, 81: 1848–57.

30.1. Edward B. Thorp, Joseph A. Boscarino, Hillary L. Logan, Jeffrey T. Goletz, Thomas M. Gallagher. Palmitoylations on Murine Coronavirus Spike Proteins Are Essential for Virion Assembly and Infectivity. J Virol. 2006 Feb; 80(3): 1280–1289. doi: 10.1128/JVI.80.3.1280-1289.2006

See supplemental Information

30.2. Dawn K. Krueger, Sean M. Kelly, Daniel N. Lewicki, Rosanna Ruffolo, Thomas M. Gallagher. Variations in Disparate Regions of the Murine Coronavirus Spike Protein Impact the Initiation of Membrane Fusion. J Virol. 2001 Mar; 75(6): 2792–2802. doi: 10.1128/JVI.75.6.2792-2802.2001

30.3. Thorp EB, Boscarino JA, Logan HL, Goletz JT, Gallagher TM. Palmitoylations on murine coronavirus spike proteins are essential for virion assembly and infectivity. J Virol. 2006 Feb;80(3):1280-9

31. Vassalli JD, et al. Direct cell-to-cell transmission of vesicular stomatitis virus. J Cell Sci. 1986;85:125–131.

32. Sherer NM, et al. Retroviruses can establish filopodial bridges for efficient cell-to-cell transmission. Nat Cell Biol. 2007; 9:310–315.

33. Álvarez RA, et al. Unique features of HIV-1 spread through T cell virological synapses. PloS Pathog. 2014; 10:e1004513.

34. Agosto LM, et al. HIV cell-to-cell transmission: effects on pathogenesis and antiretroviral therapy. Trends Microbiol. 2015; 23:289–295.

35. Komarova NL, et al. Synaptic transmission and the susceptibility of HIV infection to anti-viral drugs. Sci Rep. 2013; 3:2103.

36. Gross C, Thoma-Kress AK. Molecular mechanisms of HTLV-1 cell-to-cell transmission. Viruses. 2016; 8:74.

37. Pais-Correia AM, et al. Biofilm-like extracellular viral assemblies mediate HTLV-1 cell-to-cell transmission at virological synapses. Nat Med. 2010; 16:83–89.

38. Xiao F, et al. Hepatitis C virus cell-cell transmission and resistance to direct-acting antiviral agents. PLoS Pathog. 2014; 10:e1004128.

39. Graw F, et al. Quantification of hepatitis C virus cell-to-cell spread using a stochastic modeling approach. J Virol. 2015; 89:6551–6561.

40. Dodding MP, Way M. Nck- and N-WASP-dependent actin-based motility is conserved in divergent vertebrate poxviruses. Cell Host Microbe. 2009; 6:536–550.

41. Miyashita S, et al. Viruses roll the dice: the stochastic behavior of viral genome molecules accelerates viral adaptation at the cell and tissue levels. PLoS Biol. 2015; 13:e1002094.

41.1. Borucki M. K., Allen J. E., Chen-Harris H., et al. (2013a) 'The Role of Viral Population Diversity in Adaptation of Bovine Coronavirus to New Host Environments', PLoS One, 8: e52752.

42. Levander O. A. (1997) 'Nutrition and Newly Emerging Viral Diseases: An Overview', Journal of Nutrition, 127: 948S–50S; Beisel W. R. (1996) 'Nutrition

  See supplemental Information

in Pediatric HIV Infection: Setting the Research Agenda. Nutrition and Immune Function: Overview', Journal of Nutrition, 126: 2611S–5S.

43. Beck M. A., Williams-Toone D., Levander O. A. (2003) 'Coxsackievirus B3-Resistant Mice Become Susceptible in Se/Vitamin E Deficiency', Free Radical Biology and Medicine, 34: 1263–70.

44. Beck M. A. (1996) 'The Role of Nutrition in Viral Disease', The Journal of Nutritional Biochemistry, 7: 683–90.

45. Beck M. A. (2007) 'Selenium and Vitamin E Status: Impact on Viral Pathogenicity', Journal of Nutrition, 137: 1338–40.

 46. Beck M. A., Handy J., Levander O. A. (2004) 'Host Nutritional Status: The Neglected Virulence Factor', Trends in Microbiology, 12: 417–23

47. Beck M. A., Levander O. A., Handy J. (2003) 'Selenium Deficiency and Viral Infection', Jourrnal of Nutrition, 133: 1463S–7S.

48. Beck M. A., Nelson H. K., Shi Q., et al. (2001) 'Selenium Deficiency Increases the Pathology of an Influenza Virus Infection', The FASEB Journal, 15: 1481–3.

49. Beck M. A., Shi Q., Morris V. C., et al. (1995) 'Rapid Genomic Evolution of a Non-Virulent Coxsackievirus B3 in Selenium-Deficient Mice Results in Selection of Identical Virulent Isolates', Nature Medicine, 1: 433–6.

50. Alice M., Tang E. S., Semba R. D. (2013) 'Nutrition and Infection', in: Kenrad E., Nelson C.M.W., editors. (eds.) Infectious Disease Epidemiology: Theory and Practice, 3rd edn. Burlington, MA: Jones & Bartlett Learning.

50.1. Chandra R. K. (1997) 'Nutrition and The Immune System: An Introduction', American Journal of Clinical Nutrition, 66: 460S–3S.

50.2. Keusch G. T. (2003) 'The History of Nutrition: Malnutrition, Infection and Immunity', Journal of Nutrition, 133: 336S–40S.

50.3. Nelson H. K., Shi Q., Van Dael P., et al. (2001) 'Host Nutritional Selenium Status as a Driving Force for Influenza Virus Mutations', The FASEB Journal, 15: 1846–8. 10.1096/fj. 01-0115fje.

50.4. Ritz B. W., Gardner E. M. (2006) 'Malnutrition and Energy Restriction Differentially Affect Viral Immunity', Journal of Nutrition, 136: 1141–4.

50.4. Schaible U. E., Kaufmann S. H. (2007) 'Malnutrition and Infection: Complex Mechanisms and Global Impacts', PLoS Medicine, 4: e115.

51. Kanneganti T. D., Dixit V. D. (2012) 'Immunological Complications of Obesity', Nature Immunology, 13: 707–12.

52. Karlsson E. A., Beck M. A. (2009) 'Diet-Induced Obesity Impairs The T Cell Memory Response to Influenza Virus Infection', The FASEB Journal, 23: 110–3.

53. Karlsson E. A., Sheridan P. A., Beck M. A. (2010) 'Diet-Induced Obesity Impairs the T Cell Memory Response to Influenza Virus Infection', The Journal of Immunology, 184: 3127–33.

54. Mito N., Hosoda T., Kato C., et al. (2000) 'Change of Cytokine Balance in Diet-Induced Obese Mice', Metabolism, 49: 1295–300. [PubMed]

55. Monteiro R., Azevedo I. (2010) 'Chronic Inflammation in Obesity and the Metabolic Syndrome', Mediators of Inflammation, 2010, pii:289645.

56. Nieman D. C., Henson D. A., Nehlsen-Cannarella S. L., et al. (1999) 'Influence of Obesity on Immune Function', Journal of the American Dietetic Association, 99: 294–9.

57. Kanneganti T. D., Dixit V. D. (2012) 'Immunological Complications of Obesity', Nat Immunol, 13: 707–12.

58. Smith A. G., Sheridan P. A., Harp J. B., et al. (2007) 'Diet-Induced Obese Mice have Increased Mortality and Altered Immune Responses when Infected with Influenza Virus', Journal of Nutrition, 37: 1236–43.

59. Aroor A. R., DeMarco V. G. (2014) 'Oxidative Stress and Obesity: The Chicken or the Egg?' Diabetes, 63: 2216–8.

59.1. Junaidah B. Barnett, Davidson H. Hamer, Simin N. Meydani. Zinc: a new risk factor for pneumonia in the elderly? Nutr Rev. Author manuscript; available in PMC 2011 Jan 1. Published in final edited form as: Nutr Rev. 2010 Jan; 68(1): 30–37. doi: 10.1111/j.1753-4887.2009.00253.x

60. Hawryluck L, Gold WL, Robinson S, Pogorski S. Galea S, Styra R. SARS Control and Psychological Effects of Quarantine, Toronto, Canada. Emerg Infect Disv.10(7); 2004 JulPMC3323345, 10 (7),1206-12

61. Steptoe A, Hamer M, Chida Y. The effects of acute psychological stress on circulating inflammatory factors in humans: a review and meta-analysis. Brain Behav Immun. 2007 Oct;21((7)):901–12.

62. Segerstrom SC, Miller GE. Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. Psychol Bull. 2004 Jul;130((4)):601–30.

63. McCann SM. NY Acad Sci; 1997. Neuroimmunomodulation: Molecular aspects, integrative systems, and clinical advances.

64. Dhabhar FS. Effects of stress on immune function: the good, the bad, and the beautiful. Immunol Res. 2014 May;58((2-3)):193–210.

          26   See supplemental Information

65. Walburn J, Vedhara K, Hankins M, Rixon L, Weinman J. Psychological stress and wound healing in humans: a systematic review and meta-analysis. J Psychosom Res. 2009 Sep;67((3)):253–71.

66. Webster Marketon JI, Glaser R. Stress hormones and immune function. Cell Immunol. 2008 Mar-Apr;252((1-2)):16–26.

67. Allen AP, Kennedy PJ, Cryan JF, Dinan TG, Clarke G. Biological and psychological markers of stress in humans: focus on the Trier Social Stress Test. Neurosci Biobehav Rev. 2014 Jan;38:94–124.

68. Pedersen AF, Zachariae R, Bovbjerg DH. Psychological stress and antibody response to influenza vaccination: a meta-analysis. Brain Behav Immun. 2009 May;23((4)):427–33.

69. Pedersen A, Zachariae R, Bovbjerg DH. Influence of psychological stress on upper respiratory infection—a meta-analysis of prospective studies. Psychosom Med. 2010 Oct;72((8)):823–32.

69.1. Nataliia Bakunina, Carmine M Pariante, Patricia A Zunszain. Immune mechanisms linked to depression via oxidative stress and neuroprogression. Immunology. 2015 Mar; 144(3): 365–373. doi: 10.1111/imm.12443

69.2. Dan Hu, Lei Wan, Michael Chen, Yi Caudle, Gene LeSage, Qinchuan Li, Deling Yin. Essential role of IL-10/STAT3 in chronic stress-induced immune suppression. Brain Behav Immun. Author manuscript; available in PMC 2015 Feb 1. Published in final edited form as: Brain Behav Immun. 2014 Feb; 36: 118–127. doi: 10.1016/j.bbi.2013.10.016

70. Cohen S, Janicki-Deverts D, Doyle WJ, Miller GE, Frank E, Rabin BS, et al. Chronic stress, glucocorticoid receptor resistance, inflammation, and disease risk. Proc Natl Acad Sci USA. 2012 Apr;109((16)):5995–9.

71. Lewis CE, O'Sullivan C, Barraclough J. USA: Oxford University Press; 1994. The psychoimmunology of cancer: mind and body in the fight for survival?

72. José Peña, Haiyin Chen-Harris, Jonathan E. Allen, Mona Hwang, Maher Elsheikh, Shalini Mabery, Helle Bielefeldt-Ohmann, Adam T. Zemla, Richard A. Bowen, Monica K. Borucki. Sendai virus intra-host population dynamics and host immunocompetence influence viral virulence during in vivo passage. Virus Evol. 2016 Jan; 2(1): vew008. Published online 2016 Apr 9. doi: 10.1093/ve/vew008

73. Lemmy Schakel, Dieuwke S. Veldhuijzen, Paige I. Crompvoets, Jos A. Bosch, Sheldon Cohen, Henriët van Middendorp, Simone A. Joosten, Tom H.M. Ottenhoff, Leo G. Visser, and Andrea W.M. Evers. Effectiveness of Stress-Reducing Interventions on the Response to Challenges to the Immune System: A Meta-Analytic Review. Published online 2019 Aug 6. doi: 10.1159/000501645: 10.1159/000501645

See supplemental Information

74. Al-Jasser FS, Nouh RM, Youssef RM. Epidemiology and predictors of survival of MERS-CoV infections in Riyadh region, 2014-2015. J Infect Public Health. 2019 Mar - Apr;12(2):171-177. doi: 10.1016/j.jiph.2018.09.008. Epub 2018 Oct 16.

75. Wu, Jianqing and Zha, Ping, Randomized Clinical Trial Is Biased and Invalid In Studying Chronic Diseases, Compared with Multiple Factors Optimization Trial (November 4, 2019). Available at SSRN: https://ssrn.com/abstract=3480523 or http://dx.doi.org/10.2139/ssrn.3480523. https://www.researchgate.net/publication/336699251

76. A_Multi-Factor Model for Estimating Relative Lifespans and Extending Health Spans https://www.researchgate.net/publication/337900952

76. Wu, Jianqing and Zha, Ping, A Cancer Theory: The Central Nervous System?s Adaptive Changes Make Chronic Diseases Incurable (November 4, 2019). Available at SSRN: https://ssrn.com/abstract=3480562; http://dx.doi.org/ 10.2139/ssrn.3480562; https://www.researchgate.net/publication/336775211

77. Won Mo Jang, Sanghyun Cho, Deok Hyun Jang, Un-Na Kim, Hyemin Jung, Jin Yong Lee, Sang Jun Eun. Preventive Behavioral Responses to the 2015 Middle East Respiratory Syndrome Coronavirus Outbreak in Korea. Int J Environ Res Public Health. 2019 Jun; 16(12): 2161. Published online 2019 Jun 18. doi: 10.3390/ijerph16122161

78. Zhong NS, and Zeng GQ.Our Strategies for Fighting Severe Acute Respiratory Syndrome (SARS) All ajrccm Issues. Vol. 168, No. 1 Jul 01, 2003

79. Maged Gomaa Hemida. Middle East Respiratory Syndrome Coronavirus and the One Health concept. PeerJ 2019; 7: e7556. Published online 2019 Aug 22. doi: 10.7717/peerj.7556

80. Snawar Hussain, Stanley Perlman, Thomas M. Gallagher. Severe Acute Respiratory Syndrome Coronavirus Protein 6 Accelerates Murine Hepatitis Virus Infections by More than One Mechanism. J Virol. 2008 Jul; 82(14): 7212–7222. Published online 2008 Apr 30. doi: 10.1128/JVI.02406-07

81. Snawar Hussain, Tom Gallagher. SARS-Coronavirus Protein 6 Conformations Required to Impede Protein Import into the Nucleus. Virus Res. Author manuscript; available in PMC 2011 Nov 1. Published in final edited form as: Virus Res. 2010 Nov; 153(2): 299–304. Published online 2010 Aug 26. doi: 10.1016/j.virusres.2010.08.017

82. Wang H, Yuan X, Sun Y, Mao X, Meng C, Tan L, Song C, Qiu X, Ding C, Liao Y. Infectious bronchitis virus entry mainly depends on clathrin mediated endocytosis and requires classical endosomal/lysosomal system. Virology. 2019 Feb;528:118-136. doi: 10.1016/j.virol.2018.12.012. Epub 2018 Dec 28.

                    See supplemental Information

83. Baumann C., Neubert W. (2010) 'Neuraminidase-Deficient Sendai Virus HN Mutants Provide Protection from Homologous Superinfection', Archives of Virology, 155: 217–27.

84. Jerzak G. V., Bernard K., Kramer L. D., et al. (2007) 'The West Nile Virus Mutant Spectrum is Host-Dependant and a Determinant of Mortality in Mice', Virology, 360: 469–76.

85. Xu R., Palmer S. G., Porotto M., et al. (2013) 'Interaction Between the Hemagglutinin-Neuraminidase and Fusion Glycoproteins of Human Parainfluenza Virus Type III Regulates Viral Growth In Vivo', MBiology, 4: e00803–13.

86. Anna Qin, Ting Zhong, Huajiao Zou, Xiaoya Wan, Bifeng Yao, Xinbin Zheng, Deling Yin. Critical role of Tim-3 mediated autophagy in chronic stress induced immunosuppression. Cell Biosci. 2019; 9: 13. Published online 2019 Jan 22. doi: 10.1186/s13578-019-0275-1

87. Steven A. Lowrance, Amy Ionadi, Erin McKay, Xavier Douglas, John D. JohnsonSympathetic nervous system contributes to enhanced corticosterone levels following chronic stress. Psychoneuroendocrinology. Author manuscript; available in PMC 2017 Oct 25. Published in final edited form as: Psychoneuroendocrinology. 2016 Jun; 68: 163–170. Published online 2016 Feb 26. doi: 10.1016/j.psyneuen.2016.02.027

88. Katherine V. Houser, Andrew J. Broadbent, Lisa Gretebeck, Leatrice Vogel, Elaine W. Lamirande, Troy Sutton, Kevin W. Bock, Mahnaz Minai, Marlene Orandle, Ian N. Moore, Kanta Subbarao. Enhanced inflammation in New Zealand white rabbits when MERS-CoV reinfection occurs in the absence of neutralizing antibody. PLoS Pathog. 2017 Aug; 13(8): e1006565. Published online 2017 Aug 17. doi: 10.1371/journal.ppat.1006565

See supplemental Information