JMMCB | Journal of Marketing Management and Consumer Behavior

Public Health Intervention Framework for Reviving Economy (2): Use of Personalized Measures Beyond the Epidemiological Model Limits

Jianqing Wu [a,*], Ping Zha [b]

[a] *Ph.D., J.D., Healthier World (a new entity), P. O. Box 689, Beltsville, MD 20704. www.igoosa.com.*
[b] *M.D. (Chi. Med.), Healthier World.*

ARTICLE INFO

Article History
Submitted 25 Feb 2022
Accepted 01 Mar 2022
Available online 23 Mar 2022

JEL Classification
TBD

Keywords
Coronavirus
COVID-19
Public Health Intervention
Revive Economy
Disease Severity
Epidemiological Model
R0

ABSTRACT

We previously proposed a public intervention framework concept that would allow people to resume personal and economic activities. We showed that intervention measures are used in a quantitative scale to reduce transmission probabilities and disease severity. In this article, we systematically examine the origin, assumptions, performance and limitations of epidemiological models from different angles used in published research. We found that nearly all model assumptions fail to hold or are remote from reality; R0 is a variable depending on a large number of factors or has no utility in guiding treatment options; personalized intervention measures are vitally important due COVID-19 transmission characteristics, but current epidemiological models are unable to accurately assess the true benefits of personalized intervention measures. We found that poor performance of the models is attributed to flawed assumption that health/disease properties can be treated as transferable properties. The flaw creates a fiction that disease properties such as infection probabilities and death risks can be transferred from any vulnerable person to any other person in the population, and thus severely limits societal ability to fight the pandemic. We finally show that the benefits of personalized mitigation measures could be determined directly by using variable Ri values for infected persons (or nodes) together with assessment of death rate and disability rate; the attempt of avoiding the disease by defeating all potential transmission probabilities is unrealistic; but mitigating disease severity for specific persons is more feasible and reliable. A most reliable strategy for reviving economy should include personalized protective and mitigation measures for improving personal health.

Journal of Marketing Management and Consumer Behavior

*Corresponding Author:
tempaddr2@atozpatent.com

INTRODUCTION

In the first article [1], we proposed a public intervention framework concept for reviving economy. In that framework, intervention measures may include altering host, viral and environmental factors. Since all infection properties are continuous quantitative properties, intervention measures are used in a quantitative manner to achieve better performance. Naturally, all biological properties including viral actions, immune responses, disease severity, etc. can be evaluated on a quantitative scale to achieve higher accuracy. However, personalized measures cannot be assessed by using epidemiological models or population trials, and thus have been dismissed from public intervention measures and thus severely limit society ability to fight the pandemic. In this article, our objective is to find suitable methodology for evaluating the true effects of personalized measures. We consider why the pandemic cannot be bright under control solely by reducing number of contacts and changing contact nature due to the unique transmission characteristics of the virus. The purpose of this study is to assess the benefits of personalized mitigating measures, which is anything such as lifestyle, personal activities, avoidance skills etc that can help to mitigate disease severity. We have proved that the benefit of any treatment cannot be determined by adding measured properties from different persons [1b] We will systematically examine assumptions used in epidemiological models, key presumptions used in population trials, common model parameters, and mathematical operations in the epidemiological models. We also show where the effects of personalized mitigating measures are carried in the epidemiological models. Finally, we propose an empirical method for characterizing the true beneficial effects of personalized measures on personal disease outcomes and the pandemic outcome without using complex models.

THE LIMITATIONS OF EPIDEMIOLOGICAL MODELS

In this study, our purpose is finding flaws in the epidemiological models, we cannot do the same kind of routine experiments. Rather, we collected data and research findings from published research articles and review articles, and analyzed them without being constrained by research models and model presumptions. Since we do not accept the assumption that statistic is right approach in medical research, we are not constrained by any search method which is important in studies within the acceptable research model. Indeed, we found articles by focusing on mainly subject relevance. For example, if we want to examine the affect of contact, we find a sufficient number of articles on the contact. We do not need to exhaust searches because when we can find enough articles on a subject, there is no need to find all. To determine the performance of the public health intervention framework, we need to use a suitable model for assessment. We first examine the classical basic reproduction number, R0.

A. Origins of the Epidemiological Model

The basic reproduction number (R0) was first introduced in the field of demography [2], where this number was used to count offspring. In this model, the offspring can be measured by the two-value scale because the investigator did not concern how offspring might differ. R0 was originally called the basic case reproduction rate when George MacDonald introduced the concept into the epidemiology literature in the 1950s [3-6]. The concept of the original model can be shown in Figure 1. R0 was used as an indicator of the contagiousness or transmission ability of infectious and parasitic agents. When R0 was adopted for use by epidemiologists, the objects being counted were infective cases [6]. Based

on the mathematical model, an outbreak is expected to continue if R0 is larger than 1 and to end if R0 is less than one [7] (since R0 is unstable, it would depend on Rt). R0 does not reflect disease severity; but disparities in disease severity between different patients are especially large for COVID-19 [9, 10]. Due to difficulties in counting the number of cases, R0 is nearly always estimated retrospectively from antibody-testing data or by using mathematical models [8].

B. Assumptions in Epidemiological Model for COVID-19

The epidemiological models were found to be poor generally [8, 11]. We examine stated and implied assumptions and found the following flaws:

1. No stable R0 exists for a disease agent

R0 is an estimate of contagiousness that is a function of human behavior and biological characteristics of pathogens. R0 is the average number of secondary cases per infectious case in a population made up of both susceptible and non-susceptible hosts. For such a number to have meaning, the key assumption is that all persons are identical or sufficiently similar. This assumption can be found from the model development history. R0 was introduced into the epidemiology literature in the 1950s [2-5], differences between individual persons were not understood at that time. The assumption that all human beings are identical has been refuted by overwhelming evidence. The first human genome sequences were published in February 2001 by the Human Genome Project [12], and the role of heritable phenotype changes became research subjects even further later [13, 14]; emotion and stress are found to affect disease outcomes through the immune system [15-24]. The role of emotion and chronic stress in cancer was discovered after 1980s [25-29]. The effects of acute and chronic psychological stress in heart attack risk were found later [30, 31]. Stress can make humans more susceptible to infection, and short-term stress negatively affects wound healing [32, 33], increases the pro-inflammatory response in caretakers of Alzheimer's patients [34], and negatively affects infectious respiratory diseases [35-38]. In addition, obesity can increase disease vulnerability through the immune system [39-42], and malnutrition affects infectious diseases [43-54]. Those cases show that human beings differ in three genome, phenotype and emotion. A body of evidence shows that human beings cannot be treated as identical or nearly identical. Personalized medicine concept was proposed in medicine in 2012 [55-56].

The reproduction number was developed several decades before the three-dimensional differences in human beings were understood. All of those factors imply there is no fixed average R0 in reality. Computed R0 values depend on human host conditions, infectious agents, epidemiological data and mathematical models. Lack of consistency of R0 is shown in a large number of studies dated after 1950's. More than 20 different R0 values (range 5.4–18) were reported for measles for various areas and periods [57], and a review in 2017 identified feasible measles R0 values of 3.7–203.3 [58]. The wide ranges highlight the effects of cultural, social-behavioral, and environmental factors. The effective reproduction number can also be specified at a particular time t which can be used to trace changes in Rt [59, 60]. We have demonstrated here that R0 is not a unique concept for characterizing the inherent property of disease agent [8]. The R0 is so erratic and highly variable. This is why that whether pandemic changing direction is based on Rt. Due to this nature, Rt and R0 may be used exchangebly.

2. Over simplified "susceptible persons" definition

Great differences in personal health and susceptibility to COVID-19 infection are hidden in erratic and widely variable R0 values. This means that society generally cannot, with limited exceptions, rely on this model in evaluating the benefits of personalized measures for personal protection. The mass-action assumption that all individuals are equally likely to become infected used in compartmental models also fail [8]. In Maryland, almost 48% deaths are of the vulnerable persons in nursing homes [61, 62].

3. New cases do not depend on time, and models lack real speed element

New cases do not depend on time or time is not considered although the word rate has a speed-like meaning [63]. The model recognizes the rate element only indirectly. If the disease course and transmission time window are fixed, a large R0 would tell rapid growth of new cases. This implies faster growing speed. However, the model does not address speed of the disease course for an infected person, and how faster the disease is transmitted to others. Even in a complex compartmental model, time is used only as a parameter for the population, but not for the disease course of a person [78]. Due to lack of real speed component, the model lacks must lack utility on any intervention measures to be directed to altering the kinetics of disease course. Humans resist the virus largely by innate immune responses [64] and the adaptive immune response [65-69]. In reality, R0 must be influenced by the speed competition between early viral activities and innate immune responses.

4. Most models generally do not consider disease severity

When a model is used to characterize transmission rates for COVID-19, data fitting is weighed by infection cases. However, transmission rates are not the most important part of this disease. Disease severity is far more complex than live-or-dead two outcomes. Some patients have no symptom, some have mild symptoms, some have severe symptoms, and some die and a super majority of infections will resolve without severe symptoms [9, 10]. If all infection is like a mild flu, the pandemic would not exist. R0 is heavily influenced by mild infection cases. The ratios between death risk and infection risk are low for healthy persons but are much higher for vulnerable persons. Disease severity is related to belated immune responses, and severe immune damages that are caused by belated and overly intense immune responses [70]. R0 could not take into account anything about viral replication speed and adaptive immune response [71]. When the disease is defined only in two statuses, all factors influencing disease severity between the two statuses are not model parameters. Even if death rate is used as a model parameter, the model is unable to take as model parameters all factors that influence death rate.

5. Oversimplified transmission contacts

In epidemiological models, contacts are not-defined or insufficiently defined [71]. The probability of transmission per contact is not an inherently fixed number because contacts can vary by types, manner, duration, intense levels, present health condition, etc. The probabilities of infection depend on environmental factors such as ventilation, temperature, humidity, etc. Since contacts cannot be defined in reasonable accuracy, the model is not very useful in determining how contacts affect personal outcomes and population outcome. Probability of transmission per contact is really a random variable that depends on a large number of variables.

6. Ignoring differences in transmission routes

Transmissions by skin contacts, blood, inhalation and other transmission routes are expected to have completely different disease consequences [72]. This is not considered in models. In reality, different transmission routes cause different disease severity. Some persons may get the virus by contact involving soft tissues; some may get it by blood or vector; some may get the virus by inhalation. Thus, transmission routes affect R0 and pandemic outcome, but could not be addressed by model parameters. Transmission routes and viral amounts are predicted to affect disease initiation, development, and death risk.

7. An implied assumption that health/disease properties are transferable

Due to influences of the population research model, the epidemiological model uses an implied assumption that all health properties can be summed and averaged [8, 71]. One well known example is the Survival Function [8], which always produces the average number of secondary individuals infected by a single infected individual in the same class. This averaging operation implies that disease from person A is same as disease of person B and curing X% a population is treated as same regardless of who are actually cured. R0 is actually a mathematically determined special average value. The Next-Generation Method [8] also depends on mathematical operation. When the model counts new cases or determines disease-specific death rate, it actually has an implied assumption that a disease property is transferable. It is true in all models we have examined, This assumption does not have a problem if the model is used to predict the effects of strong intervention measures.

The mathematical operation has a serious problem when the intervention has a weak effect. The transfer of infection from one person to another causes different consequences to involved persons. Since the model allows for swapping disease statuses and outcomes between different persons, such a model must lack sensitivity for assessing validity of the personalized measures for specific persons. The data mathematically derived from a population cannot be used to advance personal benefits [73]. This problem should be seen from the car repairing model: most mechanical properties such as coolant flow, engine power, engine speed, load capacity…. can be added up for cars across different makes and models, but cannot be applied to any particular car in car repairs. The obvious reason is that multiple systems or components must work precisely in balance. The coolant flow cannot be altered according to the population-derived average. This requirement is very similar to a human body where organ functions must be in precise balance. All human health properties are intensive properties that must be confined to each person.

The non-transferable nature of health properties can be shown in a hypothetical example. To improve vitamin A supply, its levels in blood for a sample of a population can be determined together with the mean and a standard deviation. The population mean may be used to determine the total amount of Vitamin A required for correcting vitamin A deficiency for the population. Since the vitamin levels actually vary among persons, the amounts of Vitamin A supplement intakes cannot be determined on the basis of the population mean but on the basis of actual vitamin level in each person. If the same amount of vitamin A supplement based on the population is indiscriminately used by all persons, the amount is insufficient to those with very low vitamin levels but may intoxicate those with high vitamin levels. The health property values derived mathematically from a population cannot be used as the basis for correcting subtle imbalance. This limitation has not been recognized before [8, 71, 74].

Mathematical operations of health/disease properties are not improper if they are used to eliminate measurement errors, provide ballpark estimates, predict disease courses, or provide policies supports in some aspects. They may be used to predict how strong public intervention measures affect the pandemic course [74-77]. The failure of this assumption is distinctively associated with treatment of diseases that arise from subtle imbalance. This balance requirement is another version of the long-held notion that diseases must be treated by using matched treatments but not randomized treatments. Any properties derived from population data cannot be used to optimize personalized measures for correcting subtle imbalances.

C. Limitations of the Population-Based Approach

Epidemiological research methodology reflects the thinking of population research model. R0 reflects an implied assumption that all persons are identical.

R0 is actually pooled from a large number of different Ri values. Even for an infected person and all persons exposed to the infected person, the actual Ri value would depend on an overwhelming number of environmental and social-cultural factors [8, 71, 74]. Although R0 is sensitive in evaluating strong intervention measures, the model cannot be used to evaluate personalized measures. The model actually dismisses from its model parameters all health properties such as age, heart disease, lung disease, obesity, immune problems, diabetes, emotional condition, other risk factors, etc [7, 8, 78]. The model does not pay attention to differences in transmission routes [78].

We show that the best population performance cannot be achieved by selecting intervention measures using the population approach. The principle illustrated in the vitamin A example also reveals problems in formulating personalized mitigating measures. Due to great disparities between individual persons, any single measure directed to personal health of some persons would appear to have little or no effects on the population [73]. Increasing social distance in personal interactions has little or no benefit because its beneficial effects on a small number of persons are diluted by the lack of beneficial effects on the majority of people. Similarly, intervention measures to correct a health problem of some persons is neutralized by negative effects on others [73].

Due to the inherent limitations of the population approach, the epidemiological models are useful for studying strong intervention effects such as locking down city, personal isolation or quarantine [8, 71, 78], and mask-wearing (out in closed public places such as groceries stores, trains, planes, ships, offices, etc), highly effective vaccination [74, 75, 76], and antiviral drugs.

Intervention measures that can be studied by current epidemiological models may be unable to stop transmission, as shown in Figure 2. Diagnostic methods can cause about 30% errors [79]; CDC estimated that 25% of infected persons may have no symptom, but the nursing facility viral test results showed that more than half of residents with positive test results were asymptomatic at the time of testing [80, 81], and incubation times can differ from one day to potentially more than 14 days [82]. Like other influenza, acquired immunity may have limited protection [70]; re-infection may be prevented in a short term in an animal study [83] but this finding cannot explain a relapsed disease which was confirmed [84]. If viral test results could be wrong by 30% chances, isolation and removal cannot achieve intended benefits. Each of the false negative persons has varying time windows to transmit the virus to other persons before the person develops symptoms for removal. Before the first generation of infected persons develop symptoms and removed, some of them have already

transmitted the virus to a second generation of persons. It is impossible to break the chain of transmissions by tracing and isolating infected persons.

D. The Limitations of Mathematical Models

The estimated values of R0 depend on numerous decisions made by the modeler and many model parameters [8, 74, 78, 85-87]. Furthermore, many of the parameters included in the models are merely guesstimates [8, 78, 88, 89]. This problem becomes more obvious for complex models that use more model parameters [74, 89]. Thus different models with different assumptions produce different R0 values even when they are computed by using same epidemiological data [8, 74, 86, 90, 91]. Mathematical models have limited utility for predicting future cases in a long time period. It is also found that obtaining R0 from empirical contact-tracing data collected by epidemiologists and using this R0 as a threshold parameter for a population-level model could produce misleading estimates of the infectiousness of the pathogen, the severity of an outbreak, and the strength of the medical and/or behavioral interventions necessary for control [86]. Even a fairly complex model constructed for COVID-19 does not include model parameters for personalized measures [78], but uses about 20 parameters with 8 initial parameters. The model would not take into account personalized factors that progressively reduce Ri with time.

DETERMINE TRUE BENEFITS OF PERSONALIZED MEASURES

Due to the limitations of mathematical models and population methods, personalized protective and mitigating measures cannot be assessed. Therefore, we explore personalized measures outside the epidemiological model limits and the population research framework.

A. Benefits of Personalized Measures Can Be Seen in the Transmission Network

We could look at how infection cases grow by examining transmission chains as shown in Figure 3. In a new breakout, if an initial infection is not stopped, the infection causes R1 new infections. For each newly infected person, the virus then infects R2 persons; this would result in R1*R2 cases in the second generation and R1*R2*R3 cases in the third generation. However, due to personal, social, and environmental variations, the persons in R1 are different; and R2 has different values, depending on the infected persons. Thus, we use variable Ri such as R2.1, R2.2, R2.3, R2.4, R2.5, R2.6 to denote specific infection cases. When Ri is used for a specific infected person, its realized value would depend on all exposed or contacted persons even though many of contacted persons do not got the disease. The final numbers of infected persons, the number of deaths, and the number of disabled persons in each of the infection node must depend on the performance of all people who have contacted the infected person.

The benefits of the measures can be evaluated without using a complex model. All patients from patient 0, to R1 and R2 form a series of transmissions and infections. There might be other series of transmission chains which are not shown. This figure provides a hint that preventing the infection zero could stop all series of infections, and preventing the infection at R2,3 could have the effect of stopping 20 infections, but do not stop the some of the persons from being infected by any of other series of transmission chains. Some persons could be infected by any of multiple chains of infections, but one or more personalized measures may block or hide multiple infection chains from appearing in the network. A person may be exposed to the virus by multiple contacts, and may escape one, two, and even

several contacts. This is why personalized preventive and mitigation measures are crucially important.

Personalized measures have both personal benefits and population benefits. A large number of personalized measures can be taken by all people to reduce contact number, the transmission probability for each contact, and disease severity of each infected person. Those measures reduce Ri for each infection node. Since the population performance of the personalized measures is a refection of all personal cases, reductions in all individual Ri values for all persons must lead to a reduction in the average R0. Even if the measures do not reduce the total infection number and case growth rate for the population, they can still reduce death rate and disability rate. If the six deaths are avoided in Figure 3, the intervention measures are successful.

B. Explore Personalized Measure Benefits Beyond The Model Limits

Mitigating measures may be tailored to persons to achieve best results because all personal contacts, personal resistance to the virus, human host responses to the disease, etc. greatly differ. Personalized approach essentially avoids the weakness in the population methods. As we have shown that the best performance cannot be achieved by using same measures to all persons, a best population outcome can be achieved by finely adjusting personalized measures for all persons. All personal outcomes contribute to the outcome of the population. If a person has better health, the person will not become infected, is infected at a lower probability, or gets the disease in a lower severity. Personalized measures contribute to a better population outcome by reducing each Ri and death risk of each infected person in the transmission network. The outcome of the population is better as compared a hypothetical reference without using the personalized measures.

C. Get More Benefits By Using More Personalized Measures

In the classical epidemiological model, many model parameters and most case data are accepted in a two-value scale. In reality, all viral properties, health properties and intervention measures (with limited exceptions) have bell-shaped probability density profiles or other kind of probability density distributions. When any such a property is converted into a two-value scale, a small tail always falls outside the two-value flipping point. There are always some bad outcomes. A strategy for defeating this natural error is creating higher safety margins: (1) a larger distance may be used for social distancing between an immune-suppressed person and an infected person because the immune-suppressed person has diminished antiviral ability; (2) high-quality masks are worn by people who are exposed to the virus for long time each day and this could reduce the total number of viral particles that leak into the respiratory track in a time-dependent manner; (3) for people with extensive personal interactions, face-shield may be used to reduce the amount of the virus that could reach the face and the respiratory track; (4) comprehensive measures may be taken to reduce risk of outbreak in nursing homes because old people are more vulnerable to the virus; (5) for facilities that are of strategical importance, intervention measures cannot rely on viral test statuses and tracing contact histories. In addition, better personalized protective measures and multiple layers of the measures may be used to offset errors attributable to poor test sensitivity, insufficient incubation time, asymptomatic infections, etc.

Reducing death risks can have great beneficial impacts on the population outcome. As shown in Figure 4, by using proper measures, the disease severity of an infected person can be reduced; and the infected person may have reduced viral discharge and shortened infectious period. A person with mild symptoms or short duration would generate fewer

infection cases than the same person would if he had severe and long lasting disease. The mitigation measure taken by the infected person could reduce risks of getting infection in the node of transmission.

D. Improve Personal Overall Health As The Fundamental Measure

If a virus is deemed to co-exit with human beings, stopping an early infection is not a final success. Stopping a seed or early infection has the effect of stopping all infections in many generations, but it cannot stop some of the persons from infected by different series of infection chains (they could become members of other infection nodes). Considering unavoidable successive exposures, the most reliable mitigation measure is improving personal health as a fundamental solution. How an infected person transmits the virus to people depends on their age, personal health, risk factors, immune system condition, etc. After a person is exposed to the virus, whether the virus can enter cells and thrive also depends on antiviral responses and viral amounts [64, 65]. An initial infection may be controlled by innate responses. Thus, people can improve their resistance to viral infection and reduce disease severity. In each node in the transmission network, the health condition of the infected person and all exposed persons must affect the finally realized Ri value. The total number of contacted persons may be a lot more than realized infected persons. Many of them are not infected and their good outcomes can be attributed to their health conditions, host responses, innate immunity, prudent interaction manners, plus social and environmental factors. In sum, a small Ri would be due to the good health conditions of the uninfected persons. If all people improve their resistance to the virus, the number of infected persons could be further reduced. When a disease is already endemic, lowering the basic reproduction number below 1 may no longer be a viable control measure [8].

E. Personalized Benefits Are Hidden in Epidemiological Models

The epidemiological models cannot accurately show benefits of personalized measures. We will show where the benefits are hidden.

1. The benefits of personalized measures can be revealed by making plus and minus changes to model parameters

As we have shown, epidemiological models cannot be directly used to assess the benefits of personalized measures. However, the models can be used to assess relative benefits of personalized measures in some cases. It is possible to determine disease outcome by reducing transmission rate by a certain percent, as it was done in a study, where epidemiological models show 10% reduction in transmission rate can reduce hundreds of thousands of deaths [92]. Such a method may also be used to predict money saved [93]. When a model is used to determine incremental benefits, most errors affecting the baseline is expected to drop out. However, one difficulty is that most personalized measures cannot be uniformly applied to all people and directly used as model inputs. Additional step of work must be done to establish how personalized measures quantitatively reduce transmission probabilities or other relevant model inputs. Moreover, personalized measures must be tailored to persons on basis of their health conditions such as obesity, inactivity, immune problems, chronic diseases, etc.

2. Benefits of personalized measures are hidden in a reduced R0 value

The benefits of personalized measures may be reflected in a reduced R0 value but their contributions cannot be determined. The effects of personalized measures are carried in the epidemiologic data. If a significant number of people in the population have improved

their resistance to the virus and improved their survival probability from infection, there will be fewer infection cases and fewer deaths. The computed R0 would become smaller. Moreover, personalized measures affect R0 through the following known factors: (1) Epidemiologic triad (agent, host, and environmental factors) [94] affect R0. This means that pre-exposure physiological changes, post exposure remedial measures, and multiple factors treatments are important; (2) The value of R0 is a function of human social behavior and organization, as well as the innate biological characteristics of particular pathogens [71]; (3) policy environment, various aspects of environment, and other factors that influence transmission dynamics and, thus, are relevant for the estimation of R0 values [94]; and (4) any factor having the potential to influence contact rate, including population density, social organization, seasonality, frequencies of human–human or human–vector interactions in a time or space [8, 71, 74]. All of those factors affect the average R0 through influencing individual Ri in the transmission network. In reality, there is no way to determine the contribution of personalized measures on the reduced R0.

3. Benefits of personalized measures may be falsely rejected as errors

One biggest problem is that epidemiological models are unable to take different values for different persons. When a mitigation measure is weak, compared with other influencing factors, it may exhibit as having no effect; and when one single mitigation measure is used among many influencing factors, the true benefits of the measure cannot be determined [73]. Also, if only 5 of one hundred persons use the mitigation measure, even though the five have benefited from it, the benefit cannot be revealed in the population outcome. To show this problem in an example, additional distance, prior-exposure mitigation measures, heightened protection, and post-exposure remedies may have little additional benefits on those who are healthy. True benefits can be found only on vulnerable persons. This is why population trials will eliminate all weak factors improperly. The worst problem is that when a personalized protective and mitigation measure has both positive and negative benefits on different persons, positive benefit will be neutralized by negative benefit due to mathematical averaging. Wearing masks by an infected person is predicted to increase viral redistribution or re-infection of healthy tissues within the lungs, but wearing masks by uninfected person in a public building can provide the best protection [96]. The negative benefits of mask-wearing by infected persons are hidden in the population data.

DISCUSSION

Public health intervention measures cannot break the chain of infection reliably due to asymptomatic persons, poor viral detection sensitivities, varying incubation times, etc. If asymptomatic person can restart an outbreak because the person can infect many persons before the infected person is identified and removed. The attempt of stopping chain of infection by conducting tests and removal is deemed to fail. Because of psychological impacts of death threats, small outbreaks cause population panic and thus disrupt economy.

Our analysis supports the conclusion by Li et al. that "... in almost every aspect that matters, R0 is flawed" [8]. R0 from most models is not a measure of the disease severity or the rapidity of a pathogen's spread through a population and thus could not address the most important aspects of the disease. The models are especially poor for COVID-19 because they focus on disease transmissions, which are the less important part of the disease. Thus, intervention measures finely adjusted by focusing on infection cases are not necessarily the best for mitigating death rate and disability rate.

All epidemiological models use an assumption that all health properties are transferable between individual persons. This presumption always fails if they are used as guidance for formulating treatment methods for individual persons. The failure of this assumption is directly responsible for transferring death risks from a small number of distinctive vulnerable people to the whole population and cause society to ignore the fact that disease severity varies from no-sign to death. This fact implies there is a great room for interventions. When the death rate is sufficiently low, occasional outbreaks will not disrupt economy. The non-transferable nature of disease/health properties implies that personalized measures must be formulated for specific persons.

Epidemiological models cannot differentiate differences between different persons. Naturally, personalized measures are nearly always falsely rejected. Their true benefits may be falsely rejected as a result of averaging positive and negative benefits. With limited exceptions, R0 should not be used to evaluate personalized measures. Some epidemiological models may be used to study relative benefits by determining the reduction in one or more model parameters. Personalized measures can also be hidden in R0 through modeled epidemiological data, but are not correctly recognized. The true beneficial effects of personalized measures are considerable if we just see disparities in personal disease outcomes and effects from altering model parameters in published studies.

It has been suggested that wearing masks in public area in combination with complementary public health measures could stop community spread [95]. Due to a high R0 and invisible transmissions, an active person expects to be in multiple infection chances. It would be hard to escape from all infection chances. The best strategy for surviving from the pandemic is using personalized protective and mitigation measures to increase personal resistance to the viral and reduce disease severity when infected. We have found that multiple personalized measures can be used to break the limits of population approach [73].

It is hoped that a simple, accurate, and useful measure like R0 can be found [8]. However, in light of personalized medicine concept and the extremely complex personal, social, cultural, and environmental factors, such a measure may not exist. Due to the complexity of infection routes, target tissues, host antiviral responses, innate immunity responses, and adaptive immune responses, the most effective measures against this pandemic must include personalized measures.

FUTURE RESEARCH DIRECTIONS

The study found that personalized preventive and mitigation measures should not be ignored in the fight against the COVID-19 pandemic. Personalized measures have been ignored obviously because existing research methods cannot positively affirm their benefits. This is clearly a mistake. Governments should foster a population belief that ultimate personal disease outcomes highly depend on a range of personal preventive and mitigation factors. Future research should be directed to all aspects of those factors that could affect personal disease outcomes. Best personalized measures can be developed only by focusing on the conditions of specific persons.

CONFLICT OF INTERESTS

None

ADDITIONAL INFORMATION

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

REFERENCES

1. Wu, JQ, and Zha P. Public Health Intervention Framework for Reviving Economy Amid the COVID-19 Pandemic (1): A Concept. Preprint (www.osf.io) 2019 Available from https://osf.io/hjgw8
1b. Wu J, Zha P. Clinical Trials and Reductionist Approach Preclude Cures for Chronic Diseases Due to Flawed Presumptions. Preprints 2020, 2020090572 Doi: 10.20944/preprints202009.0572.v1.
2. Heesterbeek JAP. A brief history of R0 and a recipe for its calculation. Acta Biotheor. 2002;50:189–204.
3. MacDonald G. The analysis of equilibrium in malaria. Trop Dis Bull. 1952;49:813–29.
4. MacDonald G. The epidemiology and control of malaria. London: Oxford University Press;1957.
5. Fine PEM. Herd immunity: history, theory, practice. Epidemiol Rev. 1993;15:265–302.
6. Dietz K. The estimation of the basic reproduction number for infectious diseases. Stat Methods Med Res.1993;2:23–41.
7. Diekmann O, Heesterbeek JAP, Metz JAJ. On the definition and the computation of the basic reproduction ratio R0 in models for infectious diseases in heterogeneous populations. J Math Biol. 1990;28:365–82.
8. Li J, Blakeley D, Smith RJ. The failure of R0. Comput Math Methods Med. 2011;2011:527610.
9. CDC, Severe Outcomes Among Patients with Coronavirus Disease 2019 (COVID-19) — United States, February 12–March 16, 2020. The report was posted online on March 18, 2020 as an MMWR Early Release. Weekly/March 26, 2020/69(12);343-346.
10. Verity R, Okell LC, Dorigatti I et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis. Lancet Infect Dis 2020. Published Online March 30, 2020. Available from https://doi.org/10.1016/S1473-3099(20)30243-7
11. Devine M. Another blow dealt to public faith in scientific models: Devine. Apil 25, 2020. Available from https://nypost.com/2020/04/25/coronavirus-models-deal-another-blow-to-faith-of-americans-devine/
12. Pennisi E. The human genome. Science. February 2001;291 (5507): 1177–80.
13. Misteli T. Beyond the sequence: cellular organization of genome function. Cell. February 2007;128 (4): 787–800.
14. Bernstein BE, Meissner A, Lander ES. The mammalian epigenome. Cell. February, 2007;128 (4): 669–81.
15. 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.

16. 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.
17. McCann SM. Neuroimmunomodulation: Molecular aspects, integrative systems, and clinical advances. Ann N Y Acad Sci, 840,1-1998 May 1.
18. Dhabhar FS. Effects of stress on immune function: the good, the bad, and the beautiful. Immunol Res. 2014 May;58(2-3):193–210.
19. Webster Marketon JI, Glaser R. Stress hormones and immune function. Cell Immunol. 2008 Mar-Apr;252(1-2):16–26.
20. 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.
21. Bakunina N, Pariante CM, Zunszain PA. Immune mechanisms linked to depression via oxidative stress and neuroprogression. Immunology. 2015 Mar; 144(3): 365–373.
22. Hu D, Wan L, Chen M, Caudle Y, LeSage G, Li Q, Yin D. Essential role of IL-10/STAT3 in chronic stress-induced immune suppression. Brain Behav Immun. 2014 Feb; 36:118–127.
23. 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.
24. Schakel L, Veldhuijzen DS, Crompvoets PI, et al. 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
25. Cross J, Emotional expression in cancer onset and progression, Soc. Sci. Med. Vol. 28. No. 12 pp. 1239-1248, 1989.
26. Moreno-Smith M, Lutgendorf SK, Sood AK. Impact of stress on cancer metastasis. Future Oncology 2010;6(12):1863-1881.
27. Sloan EK, Priceman SJ, Cox BF, et al. The sympathetic nervous system induces a metastatic switch in primary breast cancer. Cancer Research 2010;70(18):7042-7052.
28. Lutgendorf SK, Sood AK, Anderson B, et al. Social support, psychological distress, and natural killer cell activity in ovarian cancer. Journal of Clinical Oncology 2005;23(28):7105-7113.
29. Lutgendorf SK, DeGeest K, Dahmoush L, et al. Social isolation is associated with elevated tumor norepinephrine in ovarian carcinoma patients. Brain, Behavior, and Immunity 2011;25(2):250-255.
30. Brydon L, Magid K, Steptoe A. Platelets, coronary heart disease, and stress. Brain Behav Immun (2006) 20: 113–119.
31. Sundquist J, Li X, Johansson SE, Sundquist K. Depression as a predictor of hospitalization due to coronary heart disease. Am J Prev Med (2005) 29: 428–433.
32. Kiecolt-Glaser JK, Marucha PT, Malarkey WB, Mercado AM, Glaser R (1995) Slowing of wound healing by psychological stress. Lancet 346: 1194–1196.
33. 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.
34. Kiecolt-Glaser JK, Preacher KJ, MacCallum RC, Atkinson C, Malarkey WB, Glaser R (2003). Chronic stress and age-related increases in the proinflammatory cytokine IL-6. Proc Natl Acad Sci USA 100: 9090–9095.
35. 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.

36. 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.
37. 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 Jul;10(7),1206-12.
38. Peña J, Chen-Harris H, Allen JE, et al. Sendai virus intra-host population dynamics and host immunocompetence influence viral virulence during in vivo passage. Virus Evol. 2016 Jan; 2(1): vew008.
39. Monteiro R, Azevedo I. Chronic Inflammation in Obesity and the Metabolic Syndrome, Mediators of Inflammation, 2010, pii:289645.
40. Nieman DC, Henson DA, Nehlsen-Cannarella SL, et al. Influence of Obesity on Immune Function, Journal of the American Dietetic Association, 1999; 99: 294–9.
41. Kanneganti TD, Dixit VD. Immunological Complications of Obesity, Nat Immunol, 2012;13:707–12.
42. Smith AG, Sheridan PA, Harp JB, et al. Diet-Induced Obese Mice have Increased Mortality and Altered Immune Responses when Infected with Influenza Virus, Journal of Nutrition, 2007;37:1236–43.
43. Levander OA. Nutrition and Newly Emerging Viral Diseases: An Overview, Journal of Nutrition, 1997;127: 948S–50S.
44. Beck MA, Williams-Toone D, Levander OA. Coxsackievirus B3-Resistant Mice Become Susceptible in Se/Vitamin E Deficiency, Free Radical Biology and Medicine, 2003;34:1263–70.
45. Beck MA. Selenium and Vitamin E Status: Impact on Viral Pathogenicity, Journal of Nutrition, 2007;137: 1338–40.
46. Beck MA, Handy J, Levander OA. Host Nutritional Status: The Neglected Virulence Factor, Trends in Microbiology, 2004;12:417–23.
47. Beck MA, Levander OA, Handy J. Selenium Deficiency and Viral Infection, Jourrnal of Nutrition, 2003;133: 1463S–7S.
48. Beck MA, Nelson HK, Shi Q, et al. () Selenium Deficiency Increases the Pathology of an Influenza Virus Infection, The FASEB Journal 2001;15: 1481–3.
49. Nelson HK, Shi Q, Van Dael P, et al. Host Nutritional Selenium Status as a Driving Force for Influenza Virus Mutations, The FASEB Journal, 2001; 15: 1846–8. 10.1096/fj. 01-0115fje.
50. Alice M, Tang ES, Semba RD. Nutrition and Infection, in: Kenrad E., Nelson CMW, editors. (edn.) Infectious Disease Epidemiology: Theory and Practice, 3rd eds. Burlington, MA: Jones & Bartlett Learning; 2013.
51. Chandra RK. Nutrition and The Immune System: An Introduction, American Journal of Clinical Nutrition. 1997;66: 460S–3S.
52. Keusch GT. The History of Nutrition: Malnutrition, Infection and Immunity, Journal of Nutrition.2003;133: 336S–40S.
53. Ritz BW, Gardner EM. Malnutrition and Energy Restriction Differentially Affect Viral Immunity, Journal of Nutrition. 2006;136:1141–4.
54. Schaible UE, Kaufmann SH. Malnutrition and Infection: Complex Mechanisms and Global Impacts. PLoS Medicine. 2007;4: e115.
55. Ogino S, Fuchs CS, Giovannucci E. How many molecular subtypes? Implications of the unique tumor principle in personalized medicine. Expert Rev Mol Diagn. 2012;12(6): 621–8.
56. Ogino S, Lochhead P, Chan AT, et al. Molecular pathological epidemiology of epigenetics: Emerging integrative science to analyze environment, host, and disease.

Mod Pathol. 2013;26(4): 465–84.
57. Anderson RM. Directly transmitted viral and bacterial infections of man. In: Anderson RM, editor. The population dynamics of infectious diseases: theory and applications. London: Chapman and Hall; 1982. p.1–37.
58. Guerra FM, Bolotin S, Lim G, Heffernan J, Deeks SL, Li Y, et al. The basic reproduction number (R0) of measles: a systematic review. Lancet Infect Dis. 2017;17:e420–8.
59. Nishiura H, Chowell G. The effective reproduction number as a prelude to statistical estimation of time-dependent epidemic trends. In: Chowell G, Hyman JM, Bettencourt LMA, Castillo-Chavez C, editors. Mathematical and statistical estimation approaches in epidemiology. Dordrecht (the Netherlands): Springer Netherlands; 2009. p.103–21.
60. Mercer GN, Glass K, Becker NG. Effective reproduction numbers are commonly overestimated early in a disease outbreak. Stat Med. 2011;30:984–94.
61. Associated Press. Coronavirus outbreaks like 'wildfire' at US nursing homes under lockdowns: Measures including a ban on visits and daily health screenings of staffers either came too late or were not rigorous enough. Thu 2 Apr 2020. Accessed from https://www.theguardian.com/world/2020/apr/02/coronavirus-outbreaks-us-nursing-homes-lockdowns.
62. Janney E, MD Coronavirus: Nearly 48 Percent Of Deaths Are In Nursing Homes: Nursing homes are a hot spot for the new coronavirus in Maryland, according to new data provided by the Maryland Department of Health. Apr 29, 2020. Accessed at https://patch.com/maryland/baltimore/md-coronavirus-nearly-48-percent-deaths-are-nursing-homes
63. Heesterbeek JAP, Dietz K. The concept of R0 in epidemic theory. Stat Neerl. 1996;50:89–110.
64. Handfield C, Kwock J, and MacLeod AS. Innate Antiviral Immunity in the Skin. Trends Immunol. 2018 April; 39(4): 328–340.
65. Yoo J-K, Kim TS, Hufford MM, Braciale TJ. Viral infection of the lung: Host response and sequelae. J Allergy Clin Immunol. 2013 December; 132(6): doi:10.1016/j.jaci.2013.06.006.
66. Nutt, SL, Hodgkin, PD, Tarlinton, DM, Corcoran, LM. The generation of antibody-secreting plasma cells. Nature Reviews Immunology. 2015;15 (3): 160–71.
67. Park WB, Perera RA, Choe PG, et al. Kinetics of serologic responses to MERS coronavirus infection in humans, South Korea. Emerg. Infect. Dis. 2015;21:2186–2189.
68. MacLennan, ICM; Toellner, K-M; Cunningham, AF, et al. Extrafollicular antibody responses. Immunological Reviews. 2003,194:8–18.
69. Shlomchik, MJ, Weisel, F. Germinal center selection and the development of memory B and plasma cells. Immunological Reviews. 2012; 247 (1): 52–63.
70. Wu, JQ and Zha, P. Treatment Strategies for Reducing Damages to Lungs in Coronavirus and Other Lung Infections. Preprint(https://ssrn.com) February 6, 2020. Available from http://dx.doi.org/10.2139/ssrn.3533279
71. Delamater PL, Street EJ, Leslie TF, Yang YT, Jacobsen KH. Complexity of the Basic Reproduction Number (R0). Emerging Infectious Diseases January 2019; Vol. 25, No. 1.
72. Wu, JQ and Zha, P. Association of COVID-19 Disease Severity with Transmission Routes and Suggested Changes to Community Guidelines. March 13, 2020. Preprint (https://www.preprints.org). Available from https://www.preprints.org/manuscript/202003.0246/v1
73. Wu, JQ and Zha, P. Randomized Clinical Trial Is Biased and Invalid In Studying Chronic

Diseases, Compared with Multiple Factors Optimization Trial. November 4, 2019. Preprint (https://www.ssrn.org). Available from http://dx.doi.org/10.2139/ssrn.3480523
74. Ridenhour B, Kowalik JM, Shay DK. Unraveling R0: considerations for public health applications. Am J Public Health. 2014;104: e32–41.
75. Anderson RM, May RM. Infectious diseases of humans: dynamics and control. Oxford: Oxford University Press; 1991.
76. Anderson RM. The concept of herd immunity and the design of community-based immunization programmes. Vaccine. 1992;10:928–35.
77. Plans Rubió P. Is the basic reproductive number (R0) for measles viruses observed in recent outbreaks lower than in the pre-vaccination era? Euro Surveill. 2012;17:22.
78. Tang B, Wang X, Li Q, et. al. Estimation of the transmission risk of 2019-nCov and its implication for public health interventions. 27 Jan 2020. Preprint (https://www.ssrn.org). Available from https://ssrn.com/abstract=3525558
79. Yang Y, Yang M, Shen C, et al. Evaluating the accuracy of different respiratory specimens in the laboratory diagnosis and monitoring the viral shedding of 2019-nCoV infections. medRxiv preprint. Available from doi: https://doi.org/10.1101/2020.02.11.20021493
80. Ma J, Lew L, Jeong-ho L. A third of coronavirus cases may be 'silent carriers', classified Chinese data suggests. 22 Mar, 2020. South China Morning Post. Accessed from https://www.scmp.com/news/china/society/article/3076323/third-coronavirus-cases-may-be-silent-carriers-classified.
81. Arons MM, Hatfield, KM, Reddy SC, et al. Presymptomatic SARS-CoV-2 Infections and Transmission in a Skilled Nursing Facility. NEJM.org. April 24, 2020. Available from DOI: 10.1056/NEJMoa2008457
82. Lauer SA, Grantz KH, Bi, Q, et al. The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application. Ann Intern Med. 2020;172(9):577-582. doi:10.7326/M20-0504
83. Bao L, Deng W, Gao H, et al. Reinfection could not occur in SARS-CoV-2 infected rhesus macaques. March 14, 2020. Preprint at bioRxiv. Available from https://doi.org/10.1101/2020.03.13.990226
84. Chen D, Xu W, Lei Z, et al. Recurrence of positive SARS-CoV-2 RNA in COVID-19: A case report. Int J Infect Dis. 2020 Apr; 93: 297–299.
85. Keeling MJ, Grenfell BT. Individual-based perspectives on R0. J Theor Biol. 2000; 203:51–61.
86. Breban R, Vardavas R, Blower S. Theory versus data: how to calculate R0? PLoS One. 2007;2:e282.
87. Artalejo JR, Lopez-Herrero MJ. On the exact measure of disease spread in stochastic epidemic models. Bull Math Biol. 2013;75:1031–50.
88. Khan A, Naveed M, Dur-E-Ahmad M, Imran M. Estimating the basic reproductive ratio for the Ebola outbreak in Liberia and Sierra Leone. Infect Dis Poverty. 2015;4:13.
89. Roberts M, Heesterbeek H. Bluff your way in epidemic models. Trends Microbiol. 1993;1:343–8.
90. Bani-Yaghoub M, Gautam R, Shuai Z, van den Driessche P, Ivanek R. Reproduction numbers for infections with free-living pathogens growing in the environment. J Biol Dyn. 2012;6:923–40.
91. Nishiura H. Correcting the actual reproduction number: a simple method to estimate R0 from early epidemic growth data. Int J Environ Res Public Health. 2010;7:291–302.
92. Roberts MG. The pluses and minuses of R0. J R Soc Interface. 2007;4:949–61.

93. Pellis L, Ball F, Trapman P. Reproduction numbers for epidemic models with households and other social structures. I. Definition and calculation of R0. Math Biosci. 2012;235:85–97.
94. Lloyd-Smith JO, Schreiber SJ, Kopp PE, Getz WM. Superspreading and the effect of individual variation on disease emergence. Nature. 2005;438:355–9.
95. Howard J, Huang A, Li Z, et al. Face Masks Against COVID-19: An Evidence Review. Preprint (www.preprints.org). 12 April 2020. Available from doi:10.20944/preprints202004.0203.v1
96. Wu, JQ and Zha, P. Mask Is a Double-edged Sword in the Fight Against COVID-19 Pandemic. Preprint (www.ssrn.com). March 28, 2020. Available from http://dx.doi.org/10.2139/ssrn.3563851
97. Johnson R. The 10 epidemics that almost wiped out mankind. Business Insider. 2011 Sep 19. Accessed on May 1, 2020. Available from http://www.businessinsider.com/epidemics-pandemics-that-almost-wiped-out-mankind-2011-9

Figures

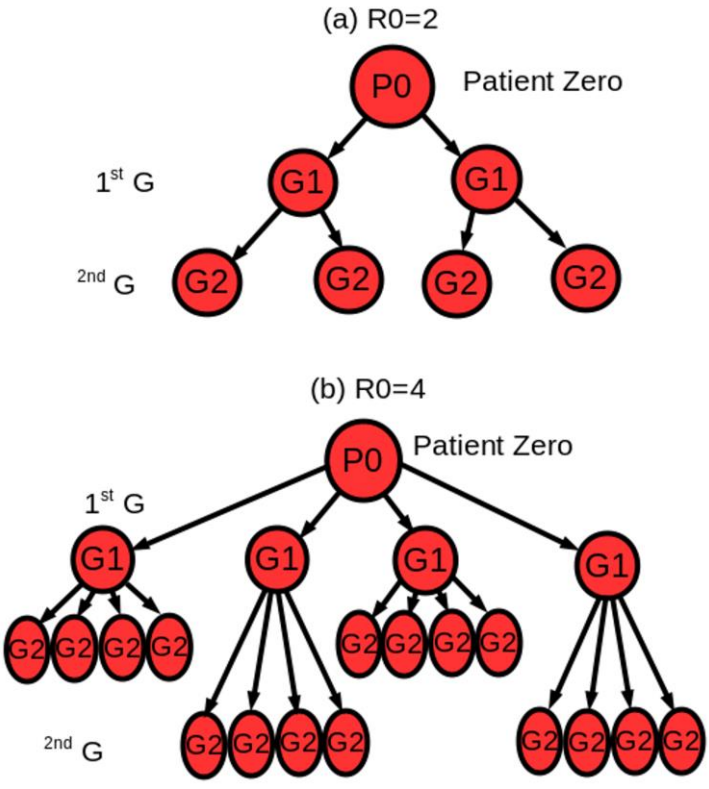

Figure 1. Hypothetical models, (a) R0=2 and (b) R0=4

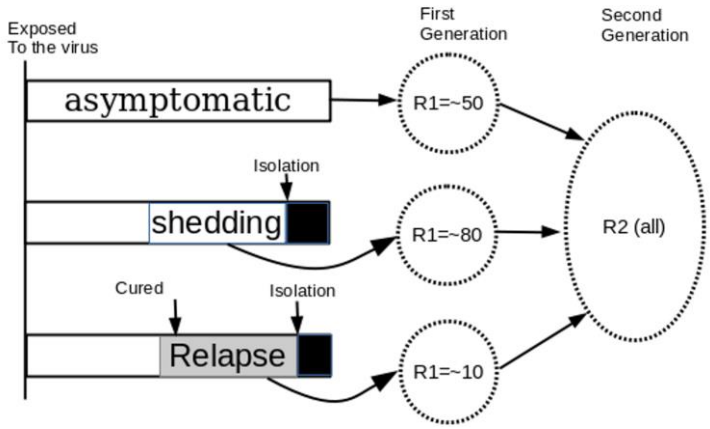

Figure 2. The COVID-19 virus can transmit from person to person in advance of detecting, tracing and personal isolation. The virus can transmit by asymptomatic infected persons before symptoms appear, and thus detecting infected persons followed by removing them is not effective means to stop viral transmission.

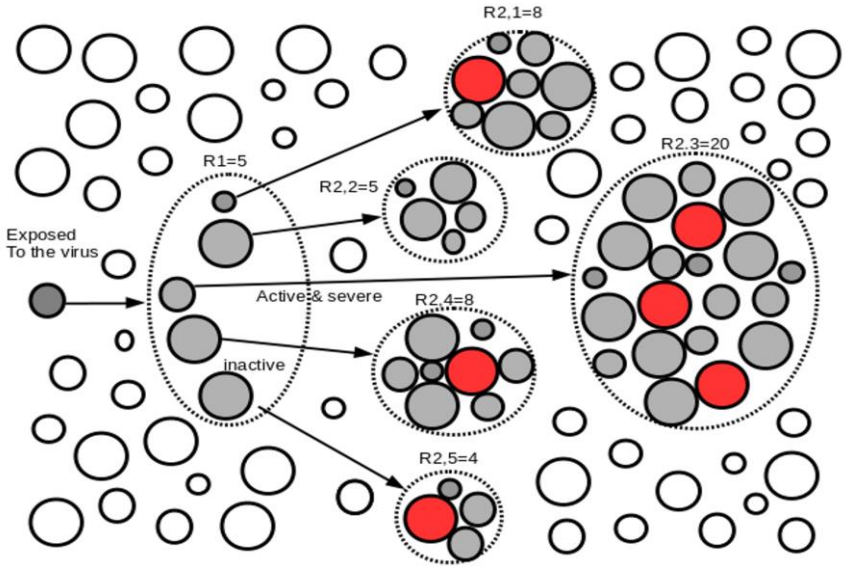

Figure 3 shows a transmission network from the patient zero, to the first generation of infected persons and the second generation of infected persons. The sizes of circles represents vulnerability and disease severity of infected persons. The red ball denotes death of the infected person.

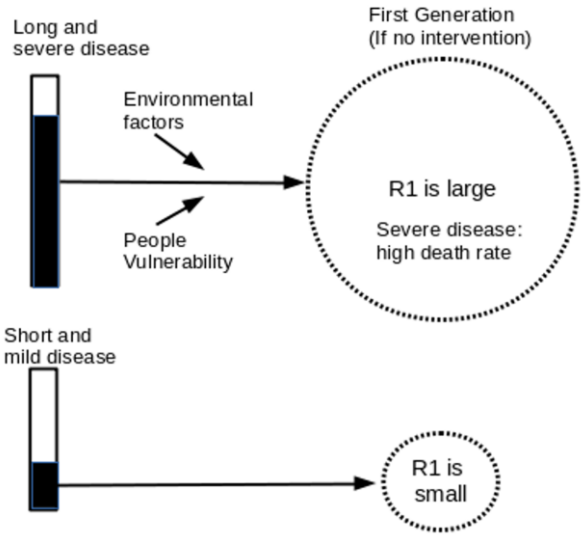

Figure 4. Disease severity affects both R0 value and death rate. Current models do not have suitable model parameters for disease severity. If measures are directed to reducing disease severity, different measures are applied to different persons.