



Pandemic control - do's and don'ts from a control theory perspective

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Specialty type: Medical laboratory technology

Provenance and peer review:

Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

P-Reviewer: Ait Addi R, Morocco; Khidhir ZK, Iraq

Received: March 16, 2022

Peer-review started: March 16, 2022

First decision: June 16, 2022

Revised: July 6, 2022

Accepted: August 10, 2022

Article in press: August 10, 2022

Published online: September 20, 2022



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Abstract

Managing a pandemic is a difficult task. Pandemics are part of the dynamics of nonlinear systems with multiple different interactive features that co-adapt to each other (such as humans, animals, and pathogens). The target of controlling such a nonlinear system is best achieved using the control system theory developed in engineering and applied in systems biology. But is this theory and its principles actually used in controlling the current coronavirus disease-19 pandemic? We review the evidence for applying principles in different aspects of pandemic control related to different goals such as disease eradication, disease containment, and short- or long-term economic loss minimization. Successful policies implement multiple measures in concordance with control theory to achieve a robust response. In contrast, unsuccessful policies have numerous failures in different measures or focus only on a single measure (only testing, vaccines, *etc.*). Successful approaches rely on predictions instead of reactions to compensate for the costs of time delay, on knowledge-based analysis instead of trial-and-error, to control complex nonlinear systems, and on risk assessment instead of waiting for more evidence. Iran is an example of the effects of delayed response due to waiting for evidence to arrive instead of a proper risk analytical approach. New Zealand, Australia, and China are examples of appropriate application of basic control theoretic principles and focusing on long-term adap-

tive strategies, updating measures with the evolution of the pandemic.

Key Words: COVID-19 pandemic; Control; Control theory; COVID zero; Flattening the curve

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Core Tip: Controlling an epidemic is a massive challenge due to the nonlinear systems involved and interactions that are hard to model and predict well. Therefore, any pandemic control policy must apply at least the basic principles of control theory, including having multiple measures simultaneously and having models and predictions to combat the time delay between exposure and symptom onset that could lead to loss of life and controllability of the pandemic. In addition, a control-theoretic-based policy needs to factor in a large set of mutual interactions between people, animals, and pathogens that includes media and social networks and their influence on people's behavior, including fake news and the viral spread of disinformation.

Citation: Tomov L, Miteva D, Sekulovski M, Batselova H, Velikova T. Pandemic control - do's and don'ts from a control theory perspective. *World J Methodol* 2022; 12(5): 392-401

URL: <https://www.wjgnet.com/2222-0682/full/v12/i5/392.htm>

DOI: <https://dx.doi.org/10.5662/wjm.v12.i5.392>

INTRODUCTION

Control theory has been developed for the control of dynamic systems in engineering. Its main principle of feedback control is to use the measurement of the output and/or the states of the system and their deviations from the desired levels or trajectories to reduce the deviations to zero and achieve stability [1]. Although mathematical control theory is being developed to control different engineering processes, dynamic feedback systems are often found in biology at different levels, from cellular to whole organisms[2]. For example, the pituitary axis is involved in hormonal level stability control *via* multiple negative feedback loops to maintain homeostasis under different external stressors from the interactions of the system (the organism) with the environment[3]. Termination of the stress response is one prime example. Sustaining constant levels of different hormones and blood sugar are other examples (blood sugar needs to be at constant levels with the variability of demand for it from various physical and intellectual activities, especially in humans)[3]. Therefore, pandemic control is a natural area of application of control theory to achieve a certain level of disease prevalence, being zero or another appropriate level that does not burden healthcare systems. Sadly, many implemented pandemic control policies are not developed in accordance with the main principles of control theory, leaving suboptimal results and increased incidence of deaths from infectious diseases and financial losses in healthcare systems.

Time delay as a factor in pandemic

One of the main characteristics of an ongoing epidemic is that any implemented measure will have an effect with pure time delay. Even full quarantine that stops transmitting in a matter of a single day will leave many infected people in their incubation periods, who will get sick with an unavoidable delay, depending on it. The presence of asymptomatic transmission as in coronavirus disease-19 (COVID-19) means that if they are not found and isolated in time, they will still be able to transmit it in their households during quarantine - and thus, the measure will have a delay in its effects, which will increase the number of infected, sick, and deceased people[4]. The presence of time delay in a dynamical feedback system leads to old and less usable information in the feedback that has to stabilize it, thus decreasing the stability margins and introducing oscillatory behavior of the output. This is known from the beginning of control theory with the work of James Clerk Maxwell on governors[5].

So, how do we deal with a time delay? One mechanism is with modeling and prediction - making decisions about implementing specific policies at a current level and a projected level. For example, suppose we want to keep the number of occupied hospital beds under a certain threshold. In that case, we do not wait until it is reached to implement the policy. Instead, we rely on modeling and forecast to tell us when it is the last possible moment to implement without reaching it. This approach in Proportional-Integral-Derivative (PID) control uses its derivative part to make linear extrapolations and to use projections to compensate for the older information in the feedback loop due to pure time delay. Stability can be either improved or worsened by predictions. However, too much reliance on the future can decrease stability due to model errors and amplification of noise to signal ratio, just as the derivative part of the PID controller increases high-frequency noises. The future may not happen, and we must be

careful not to base the policy solely on unreliable models with long-term predictions.

Controlling unstable systems

Although the pandemics have been perceived as stable processes that eventually lead to endemic situations, that is not so. Every pandemic brings existential risk to the species that it attacks[6]. Stability can be achieved at a population level as small as zero - far from the desired level that we aim to control. Thus, this system is deemed unstable[7]. The risk of loss of life due to pandemics is fat-tailed. It is worse even than the risk of nuclear war[8,9]. As the history of the plague shows, other possible scenarios, such as endemics, may result in periodic oscillatory behavior without a significant decrease in mortality[10]. Unlike stable systems, an unstable system cannot be left unregulated, so the concept of "no policy" cannot be implemented with the expectation of achieving any measurable results in either death rate, hospitalizations, or economic growth targets. Pandemics must be controlled.

Controlling nonlinear systems

The basic and most often used epidemiological models that capture the dynamics of epidemics are nonlinear. Thus, a system that includes the pathogen and the population has to be considered a nonlinear system.

A significant difference between linear and nonlinear systems is that the principle of superposition does not hold for the latter - the result of a linear combination of inputs is not a linear combination of outputs. In other words, if we put inputs U_1 and U_2 to a system separately and archive outputs Y_1 and Y_2 , the result of the input $aU_1 + bU_2$ will not be $aY_1 + bY_2$. This decreases the predictability of the behavior of nonlinear systems. Its direct consequence is that the size of inputs defines a nonlinear system's behavior - doubling the input will not double the output.

Studying the influence of a given set of inputs over the system does not provide us with information for other sets of inputs - we cannot construct the combination of outputs due to the variety of inputs. An example, in pandemic control - implementing policy to decrease the prevalence of a disease depends on the prevalence level - the higher the number of active cases, the longer it will take to reach the desired aim due to the diversity.

WHAT ARE THE MEASUREMENT GOALS IN THE COVID PANDEMIC

Aims of the pandemic control system

To assess proper from improper methods for pandemic control, we need to know what our aim is. Do we want to minimize the lost number of lives? Instead, do we want to keep the healthcare system working and minimize only the collateral damage from the pandemic? Do we want to minimize short-term economic loss of value, or do we want to reduce long-term loss? Do we want to preserve the population's overall health for long-term goals related to spending on healthcare or other incentives to do so?

Any viral pandemic poses risks to the long-term health of a population. For example, children born second or third in a family have substantially increased exposure to respiratory disease than the first-born child, which has long-term consequences for their educational level and labor market outcomes [11]. Similar long-term outcomes were seen with 1918 influenza[12]. Minimizing long-term health damage thus coincides with the number of infected, which controls mostly the number of deceased where no specific treatment is available.

Disease eradication

The goal to eradicate a disease globally is the most ambitious and often includes eradication *via* immunization, as with measles or polio[13]. Although local eradication, as seen in China, can be successful for prolonged periods, the pandemic control policy needs to be adapted continuously to respond to the mutating virus from widespread outside of the country or region that implements the policy[14].

Chinese control policy implements multiple different key elements from control theory to achieve this success, such as early response, traffic control, and predictive mechanisms: Early and rapid response that allows the local reaction to a local cluster without disrupting the socio-economic activity. Delay is the critical variable in the economic costs of any pandemic control strategy - costs increase exponentially over time. Fast and complete isolation of exposed individuals includes extensive data analysis to locate all registered infected contacts automatically, so contact tracing is ahead of the transmission chain. This is the *predictive part* of the control mechanism - who is in incubation and will spread the disease next time? Why is the need for prediction?

Due to asymptomatic spreading in the case of COVID-19, all exposed individuals need to be isolated, which needs to happen before some of them display symptoms to rapidly break the chain of transmissions for up to two incubation periods. For this strategy to work, both in government and people, compliance is needed. Excessive community involvement, government funding, motivation

mechanisms, and constraint mechanisms require serious investment and may be at odds with the political system in a given country, such as data privacy protection policies and traffic restrictions. A control system designed to achieve local zero policy also controls people and their motivation and compliance, which can be expensive and hard to achieve or require actions incompatible with specific legal systems. A high technology approach is also beyond the reach of many countries with smaller budgets for pandemic control.

Although the local disease zero policy is possible and is still successful in China, it has been used before, as in the SARS pandemic in 2003, which was eradicated[15]. It is unstable until global eradication is achieved.

Disease containment

Due to various restrictions in implementing pandemic response, sometimes "flattening the curve" is the main goal - to avoid hospital system overburdening, which can cause excessive deaths due to lack of hospital treatment for other diseases and the infected during the pandemic. This also aims to sustain the long-term quality of healthcare due to the hazardous effects of infections among medics, nurses, and staff and the impact of accumulated fatigue for prolonged periods of overburdening.

Measures and effects

Although different measures suit different regional specifics during a pandemic, countries with multiple standards have seen the most robust outcome[16,17].

This is in line with the basics of control theory - having more degrees of freedom in a controller satisfies many constraints while maintaining stability[18]. Thus, redundancy improves robustness - stability in the face of changing parameters of the system, such as the pathogen transmissibility and severity of disease.

In contrast, in countries with poor outcomes of pandemic control, such as Iran, multiple control mechanisms are broken due to socio-economic conditions, including education, economic disparity, and lack of coherent response from the healthcare community due to limited evidence and scientific controversies, which lead to premature actions from the government towards reopening[19].

Still, when implementing multiple different measures, some key measurements need to be highlighted as high-priority ones.

One very effective non-pharmaceutical intervention for that aim is to localize traffic - reducing interstate traffic in the United States substantially affects deaths and intensive care unit admissions[20]. In addition, the estimation of imported cases shows their significant influence in the case of COVID-19[21].

Another cheaper measure is the use of protection such as masks which are highly effective in decreasing case counts and mortality in multiple different ways, including socio-cultural norms and improvement of long-term behavior during pandemics[22]. For countries with limited budgets, universal mask-wearing must control any respiratory disease pandemic.

Another key and high-priority measure that has a high cost that we already described - rapid response to newly found cases and predictive approach to contact tracing - isolates exposed individuals before they become contagious. This is the golden standard that is difficult to achieve for many already described reasons. However, any effort on contact tracing will impact the health prevention of the infected (early discovery and treatment).

EFFICACY OF PANDEMIC CONTROL MEASURES IN COVID-19 PANDEMIC

When the COVID-19 pandemic began in 2019, precautionary measures started to be taken worldwide to limit the increasing number of cases. However, countries demonstrated that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission could be gradually retard or stopped. Effective strategies have been developed because the entire scientific and medical community cooperated in identifying cases and developing strategies for diagnoses, therapies, and vaccines. As a result, quick identification of close contacts, and testing and confirming symptomatic and asymptomatic patients have begun. Thus, all institutions' multidisciplinary approaches and collaborative work have led to containment and case management[23].

The main strategies for mitigating the COVID-19 pandemic are based on measures of social distance and health system reinforcement. Many countries have introduced strict lockdowns due to the widespread virus transmission in the community. However, prolonged strict lockdowns have various unfavorable social, economic, and health effects. Permanent lockdowns are not a long-term solution to limiting the COVID-19 pandemic. Lockdowns have reduced the effective reproduction number (R)[24]. But developing all kinds of resources to test and confirm all cases and using other non-therapeutic prevention will prevent SARS-CoV-2 transmission[17,25,26].

Prolonged strict lockdowns can lead to more deaths forward in time and can do more damage than benefits. Not all models analyzing lockdowns consider the potentially possible effects on other diseases. In England and Wales, cardiovascular deaths at home have increased by 35% compared to 2014-2019 [27]. In Italy, mortality from myocardial infarction increased 3 times in March 2020 during the blockade

period compared to the same period in 2019[28]. However, we must consider that lockdowns are not worse than the epidemic. Plenty of literature on the subject shows the effectiveness of lockdowns. Here, the variable that makes a lockdown good or bad is its duration. That is why China makes theirs within 28 d with the help of the strategy described here. An increase in infarcts can be a confounding variable with the disease because it causes such mortality directly and indirectly.

There is also a reduced hospitalization rate for the acute coronary syndrome. The most likely reason is people's fear of infestation with SARS-CoV-2 in hospitals[29,30]. Most of these deaths reported at the time were not due to COVID-19[27]. Children and adolescents are also not spared from the unfavorable effects of lockdowns. The interruption of the educational process and the lack of socialization caused even more problems[31].

The economic effects are expected to lead to rising unemployment and poverty in the long term[32]. Therefore, careful planning is necessary, but the positive results of any decision must exceed the negative effects on the people. Furthermore, all measures must be based on scientific facts and evidence to be as correct as possible to the situation when they are taken to achieve the long-term goal[33].

Hospital preparedness has been one of the main strategies of governments. Still, even the best health care system cannot cope if the viral transmission and infections continue too long. Therefore, increasing the number of beds, adapting infrastructure and redistributing human resources and equipment, implementing measures to protect healthcare staff and patients, and training staff are essential measures to tackle the COVID-19 crisis[34].

In Europe, governments have mobilized special funds to increase labor capacity and equipment. However, even in regions with high resources, such as the USA and Italy, hospitals and intensive care units came under tremendous pressure from the first wave of the disease. There have been situations with difficult decisions to prioritize cases based on patients' age, comorbidities, and health status[35,36]. The hospital overcrowding and pressure on the health care system led to the first lockdown, which imposed severe restrictions on movement worldwide. Therefore, even if significant financial resources were allocated to hospitals' preparation, that would not be enough to mitigate the effects of the pandemic unless other measures are taken.

Initial mortality data were based on confirmed COVID-19 cases, but actual mortality from COVID-19 was established later[37].

A significant part of infected people is undetected because they are asymptomatic or usually do not seek medical attention. In addition, significant differences in the percent of mortality have been found between different age groups[38]. Therefore, many patients with confirmed COVID-19 will not need to be hospitalized, especially the younger ones.

Primary health care can play a crucial role in unburdening hospitals. Previous data have shown that access to family doctors helps treat patients. They can become the first line of defense in diagnosing and preventing COVID-19[39,40]. Thus, severe patients will be referred to hospitals, while those with mild COVID-19 will be treated at home. A well-coordinated and planned process of primary health care will ensure control of the disease spread and identification of vulnerable groups that need to be protected. Early detection of COVID-19, monitoring during isolation, individual risk assessment, treatment of mild COVID-19 cases, and timely identification of worsening conditions could be priorities for family physicians.

Primary healthcare and home care are taken together with more measures that are selective and are the only realistic long-term strategy to mitigate the COVID-19 pandemic.

Controlling the extended pandemic system, with an account for communications impact on behavior, several countries have successfully reduced COVID-19 cases and deaths by maintaining these results for a long time with long-term maintenance of some of the measures related to masks, social distancing, and control of imported cases. The success depends on the reaction and resolution of the governments and how the information has been presented to the public. Unfortunately, there is no universal communication policy for providing information during a prolonged crisis. But if the right, comprehensive, and scientific information reaches the citizens, it also will help control and mitigate the pandemic. Clear and accurate messages made by medical and scientific professionals delivered through appropriate platforms (media, social networks, and other non-government organizations) will ultimately lead to long-term success. But this is a complicated process and much depends on maintaining public confidence.

An overall policy can be outlined, including a communication strategy to refute the available disinformation with scientific data and evidence and different variants to clarify the importance of vaccination programs during the COVID-19 pandemic.

In December 2020, data showed that New Zealand had 420 reported cases and 5 deaths per million population. In the United States, there were 51655 cases and 937 deaths per million. Australia also reported lower numbers for the second week of December 2020 than other European countries - 1094 cases and 35 deaths per million population[41,42].

One of the main factors contributing to Australia's success was its geographical isolation and consensus among political circles and scientific councils on public health about the measures. A multidisciplinary group was formed, including experts from the country's eight leading universities [43]. The aim was to prepare an independent report to acquaint the entire government with the country's situation and give recommendations and guidelines for managing the crisis[44]. They pro-

posed a strategy in which communication in public health is paramount to tackling the pandemic and involves both politicians and communities

There are various recommendations for communication during a crisis. It is imperative to provide specific information on what to do and avoid for certain periods. Clear rules are essential when some restrictions are stringent. There must be absolute consistency in the messages and maximum reliability of the data provided to the public. The field's specialists and scientists should be used, although the public trust in them is not by presumption[45]. Confidence can be quickly lost if the expert is politically committed.

Politicians should listen to the community's needs and concerns when communicating. People are more likely to follow the pieces of advice if they understand the logic behind them. Therefore, explaining why specific actions are critical, beneficial, or problematic is essential. In addition, information concealment can motivate people to look for information elsewhere, promoting belief in rumors, misinformation, and conspiracy theories[46]. There is always uncertainty in crisis management, so there should be no illusion of false security for people because trust will be undermined[47].

People must also be allowed to get involved in the action. This means that communication must be attended to by appropriate measures to favor changes in the behavior and motivation of the population [48]. People are more likely to comply with quarantine if they have the financial and economic resources to endure a period of unemployment. The role of the government is to call for public solidarity and sustainability[49]. Fear and stress are reduced when people are part of a group and are supported. Then work, responsibilities, home life, and even helping others are often at the forefront of their minds.

The outbreak of the COVID-19 pandemic showed another lousy feature of humanity - its lack of faith in science and the scientific community. As a result, we have witnessed the rise of misinformation and conspiracy theories[50,51]. Transparent providing of factual information prevents susceptibility to emerging misinformation and conspiracy.

In combat against misinformation, specific techniques are used to reduce the spread of fake news significantly[52,53]. But again, public trust in government and health institutions is the most important and protective factor against people looking for opportunities for conspiracies[50].

Another critical factor that plays a crucial role in mitigating and controlling the COVID-19 pandemic is vaccination[13,54-58]. Several vaccines have already been approved and available, but vaccination campaigns in some countries are going slowly. It was assumed that the presence of collective immunity would control the pandemic[56]. However, suppose high morbidity, high mortality and adverse economic effects should be avoided. In that case, the vast part of the population must acquire immunity through vaccination but not through past infection. While the global eradication of COVID-19 may prove very difficult to achieve[13,58], successful vaccination programs can focus on regional elimination in the short term. Vaccinations will therefore have a critical impact on the dynamics and management of the COVID-19 pandemic.

If vaccination programs are modeled and combined with disease dynamics and available virus transmission data, a very effective strategy can be obtained that will lead to the successful long-term management of COVID-19. Monitoring, testing, and isolation will remain important factors in controlling the COVID-19 pandemic. Still, the effectiveness of the vaccination program and the level of vaccination will outweigh these factors in eliminating and stabilizing the COVID-19 pandemic.

The proposed approaches to control in all possible directions are not without challenges. We have seen that many factors affect the management of a pandemic. In addition, SARS-CoV-2 is evolving quite rapidly, and the efficacy of the available vaccines against new strains can be much lower. Despite these challenges, the successful implementation of COVID-19 vaccination programs will lead to pandemic control and a return to everyday life.

CONTROLLING IMPORT OF CASES

One of the most important aspects of nonlinear systems is size-dependent behavior. Large systems are inherently harder to stabilize, while smaller systems are much more easily influenced. This explains the hierarchical nature of multicellular organisms with cells, tissues, organs, and systems with separate feedback control mechanisms for different levels[59]. Pandemics are interactions in nonlinear systems comprised of humans, other life forms, and pathogens. A straightforward way to control a pandemic better is to decrease its size. This can mean lowering prevalence in a given area or localizing the pandemics by breaking the dependencies between different world regions. This necessitates control of imported cases. Imported cases can sustain a pandemic even in the absence of local transmission, and failing to account for them will lead to inappropriate responses with measures that are not focused on targeting the imports and exert unnecessary harsh efforts on the community[60]. Controlling imported cases is much easier and more reliable to be done at the borders of a given region instead of doing it after the patient has arrived, which is essential. The latter requires a high-cost, high-tech approach, while the former does not. This is a standard practice in the Chinese response to both pre- and after case imports[61].

CONCLUSION

Although control theory has been developed for engineering, it has found applications in systems biology and pandemic control. It is an abstract, mathematical theory that can be used to analyze and control any dynamic system as long as the calculated measures have the means to be physically applied. The ongoing COVID-19 has been mainly a challenge for epidemiology and pandemic control. It is a novel type of pandemic with multiple different variants emerging consequentially, resulting from the varied responses in other countries and regions and the abandoning of principles of pandemic control in some of them.

However, we know what to do and what not, thanks to management theory and the real-world applications in countries such as New Zealand, China, Australia in zero COVID and Norway, Denmark, Finland, South Korea, and Japan in disease containment. Mathematical modeling has been crucial in pandemic control as means of prediction that allow rapid response to newly found clusters and proper choice of working measures such as social distancing, masks, control of imported cases, *etc.* In addition, localization of pandemic control has been crucial by dividing the world into smaller regions that are easier to manage.

Communication strategies and transparency have helped with compliance and the overall success of non-pharmaceutical interventions. Focusing on long-term health and economic results helped motivate large parts of the industry and the politicians to join the effort. These are the prosperous regions. In policies that fail, multiple causes exist - weak links at the government level and at the social and community levels, including the scientific community that leads to a slow and reactive approach. Measures that are being implemented and lifted too early, lack of consistency with policy, and lack of adaptivity diverged from the basic control theoretic principles.

FOOTNOTES

Author contributions: Tomov L and Velikova T designed the research; Sekulovski M, Miteva D, and Batselova T performed the research; Tomov T contributed analytic tools; Tomov T, Velikova T, and Batselova H analyzed the data; Tomov T, Sekulovski M, Miteva D, and Batselova H wrote the paper; Velikova T revised, supervised, and edited the paper. All authors revised and approved the final version of the manuscript.

Conflict-of-interest statement: All authors declare no conflict of interest for this article.

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S-Editor: Wang LL

L-Editor: Wang TQ

P-Editor: Wang LL

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