Will lockdowns, social distancing and other measures stop the pandemic? Really?

Are antivirals and vaccines likely to work?

A science-based harsh truth of the Covid-19 pandemic:

What, in reality, may await us in the future

F. Javier Enriquez, M.D., Ph.D., specialized in immunology of infectious diseases and epidemiology, with more than 35 years of scientific and clinical research experience in the U.S. and Europe, shares openly key aspects of the COVID-19 global outbreak. What happened, what is happening and what could happen in the future.

Inspired by the interview that I recently had with Dr. Herrera de la Fuente and keeping the same format, here I answer many of the questions that have been posed to me (from many countries) since the COVID-19 health crisis began.

"… we are taking a far too narrow approach to managing this outbreak of a new coronavirus… The economic crisis that is advancing towards us will not be solved by a drug or a vaccine." *R. Horton. Lancet 09/2020*

Key points

In an outbreak caused by a highly contagious microorganism, coupled with a long incubation period and with the majority of those affected showing mild symptoms or being asymptomatic, a confinement of less than 100% of the population will not stop contagion.

This summer there is no resurgence of COVID-19 or new outbreaks, but it is the continuation of the same global outbreak, of the same epidemic in each geographical region.

Innate immunity is the first line of defense against infection.

Innate immunity is possibly responsible for most of the asymptomatic or mildly symptomatic COVID-19 cases. It has nothing to do with herd immunity.

As of 09/2020, COVID-19 has likely elicited immune responses in more than 25 million confirmed cases worldwide; too few to create herd immunity that would require protective immunity in more than 60%, 70% or 80% of the population. However, no knowledgeable scientist can assert a precise percentage.

Because of the reasons below, COVID-19 vaccines are likely to fail in generating herd immunity.

Innate immunity helps to mount strong adaptive immune responses (antibodies and T cells, among others). Both, innate and adaptive immune response possibly account for the COVID-19 cases with mild or moderate symptoms.

Different types of COVID-19 vaccines are being developed by numerous institutions and pharmaceutical companies. Their chance of success or efficacy may be similar to influenza virus vaccines.

The effectiveness of the influenza vaccines is highly variable. In general, they reduce the risk of infection in children and the rate of hospitalizations and risk of death in elderly populations. In several studies there is no evidence of protection among healthcare workers. The effect in the general population is not known with certainty.

In the development of any viral vaccine there is a significant difference between the immune responses detected in the laboratory of the vaccinated subjects and the actual protection rate against the disease.

No one can predict what the true protection rate of a COVID-19 vaccine will be in the general population.

Like the influenza virus, COVID-19 can exhibit discrete changes on its structure, called "antigenic drift" or significant changes, called "antigenic shift." When these changes happen, the adaptive responses of the immune system does take time to get organized and the infection spreads causing disease.

Seasonal influenza outbreaks are caused by an antigenic drift of the virus.

The 1918 influenza pandemic was caused by an antigenic shift of the virus.

Influenza vaccines are developed with virus samples from the previous year’s outbreaks, prior to the antigenic drift of the virus that will cause the future outbreak. That is why influenza vaccines are not 100% effective. In some people, arouse a cross immunity and their effectiveness is moderate and variable. In other people they are ineffective.

COVID-19 vaccines now in development are likely to work like influenza vaccines if variants of the COVID-19 virus emerge after an antigenic drift.

None of the vaccines will work if variants of the COVID-19 virus emerge after an antigenic shift.

Continuing with restrictive measures in the coming months, undetected positive COVID-19 cases will infect people who have not previously been exposed to the virus. The current preventive measures will only perpetuate the inevitable.

If COVID-19 exhibits drastic antigenic changes or "antigenic shift" we will not have a global outbreak but a true pandemic and probably with very different morbidity and mortality characteristics that we have witnessed in 2020.

Knowing: a) the basic mechanisms and the heterogeneity of immune responses, b) the biology of viruses recently adapted to infect new host species, c) the similarity of these viruses with others that exhibit similar patterns of attributes and behaviors, d) the reliable efficacy of therapies and immunizations in general populations, and e) the patterns of plagues and epidemics of the past, it is highly doubtful to infer that the measures currently taken will stop the health crisis.

The preventive measures taken by the vast majority of the countries were short-sighted. It would have been more prudent to consider the possible consequences of the measures 5, 10 and 20 years in the future.

Yes, the preventive measures protected many now, but the future victims, for various reasons, will be many more.

With or without restrictions and incomplete confinements, the global outbreak will run its course.

The "new normality" is restricting and will continue to restrict freedom, violating basic human rights. The "new normality" will rule people repressively, like a pseudo-Sharia code of law.

Now is the time for all of us and our governments to prepare with a long-term view, aware of the doubtful effectiveness of vaccines and antivirals and anticipating the worst case scenario: 1) Invest now in strengthening the infrastructure of health systems to be able to serve the large number of affected. 2) Provide recommendations with sound scientific bases to high-risk populations and the general population so they can voluntarily decide their actions. 3) Avoid mandates that will detrimentally and uselessly affect millions of people.

In a couple of decades there may be articles, essays, books and documentaries examining the strategies carried out globally in 2020 to circumvent the severity of the COVID-19 global outbreak and pointing that instead they contributed to unleash the full virulence potential of the microscopic tiger, and that they provoked serious and long-lasting sociological, psychological and economic catastrophes.

In the context of past pandemics, has the global response against COVID-19 demonstrated progress in controlling the spread of a virus?

It is very difficult to regard anything as an advancement just yet. Social distancing, lock-downs and masks were measures taken because the medical world had no formal and agreed-upon response. There is no telling as to the long-term efficacy of these measures. This question can only be answered with confidence in a couple of decades. However, my feeling is that the measures taken lack long-term foresight and may come back to haunt us.

How the preventive measures taken may come back to haunt us?

The measures taken followed recommendations from the World Health Organization and advisors to government authorities and ministries of health of multiple countries. Those recommendations were based on the possible short-term impact of the outbreak. In my opinion, the measures did not consider the potential long-term consequences with regard to how infectious diseases evolve in host populations, how virulence evolves and how our immunity adapts in response to infectious agents, such as COVID-19. The measures did not consider that there are two categories of disease interacting within specific populations: infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and an array of non-communicable diseases present in high-risk populations, resulting in disparate immune responses and immunity patterns. According to some scholars, this is not a pandemic, but a syndemic. I will leave aside the impact on social, psychological, and economic aspects as those are not my fields of expertise.

The virus is highly contagious but in the majority of the confirmed cases the severity of disease ranges from low to asymptomatic. The problem lies with the few, but significant cases where the disease is devastating with pneumonia, severe acute respiratory syndrome, or aberrant immune responses that cause clotting pathologies with significant sequelae or death. Approximately 5% of infected people require intensive therapy and in them the fatality rate can be up to 40%. As we know, the worst affected are the elderly and those with comorbidities (chronic pulmonary disease, cardiovascular diseases, diabetes, etc.). There is a good chance that unprepared health care systems worldwide would have been completely overwhelmed had lockdowns, social distancing and other COVID-19 measures not been taken. If social distancing, confinement and other measures had not been implemented,

clinics and hospitals not prepared for the large number of patients would not have been able to cope. In many countries, medical and paramedical personnel have fought heroically to treat patients at risk of contracting the disease themselves and spreading it to their families. The world was simply not prepared for a crisis of this size. Now, it seems that experts in epidemiology of infectious diseases, virology and immunology from numerous institutions worldwide must weigh in to highlight the possible consequences beyond the immediate future.

Why? What will happen, say, later this year?

I cannot tell what will happen. I can, however, anticipate what may not happen based on the biology of host-parasites interactions.

During an epidemic, or a pandemic, of an infectious disease caused by a highly contagious pathogen and with a long incubation period, social distancing, general closure of social activities and, in essence, lock-downs of less than 100% of the population at risk cannot stop the progression of contagion completely. As soon as the aforementioned measures are relaxed, the course of the epidemic will continue its course and the virus will infect people who were not previously exposed. These will not be resurgent clusters or outbreaks, but the continuation of the same global outbreak, the same "pandemic." How widespread this will be is anyone's guess.

My deepest concern is not what may occur later this year, but what potentially may happen later on.

I think it is now when we need to re-examine the preventive strategies taken and decide how to minimize the long-term impact. Continue social distancing, lock-down of whole populations, mandatory use of facemasks, antiseptic gels, etc.? Close bars, cafes, restaurants, shops, gyms and public events? Enhance the infrastructure of clinics, emergency care units, hospitals and confine only high-risk populations? How to identify those healthy adults and young adults who may be potentially at risk of a severe disease or death?

Good questions, but what should be the course of action?

There is not one simple answer and I do not imply to have a solution. There must be a careful re-evaluation of the policies that will be implemented in the next few weeks and months, considering multiple disciplines. Those in charge of making the decisions that affect millions of people must weigh the recommendations of experts. The experts must deeply consider epidemiology of infectious diseases, virology, immunology, history of the patterns of plagues and epidemics of the past, the evolution of virulence. Professionals of other areas should also provide their

recommendations as the consequences of the new policies will be far reaching.

What exactly does all that mean?

I would need to elaborate on some basic aspects of these disciplines to put everything in context. This is crucial because it is OUR future.

Infectious agents that have evolved in hosts tend to produce mild diseases and hosts mount immune responses that do not completely get rid of the infection. Two examples are the intestinal parasites: the helminth (worm) *Ascaris lumbricoides* and the tapeworm *Taenia solium*. These infectious organisms and the hosts have adapted to each other as long as the infections are intestinal. On the other hand, when the hosts of infectious microorganisms, such as COVID-19, are "new", several possible scenarios can occur, such as:

1) **The infectious agent cannot colonize or infect the host**, as is the case with feline leukemia virus in humans. The virus is not adapted enough to colonize and infect us.

2) **The microorganism enters the host, can infect cells or tissues temporarily, but cannot reproduce** and dies shortly after. Helminth parasites of the genus *Anisakis* that infect fish can sometimes be found in dishes prepared from raw fish that are consumed by humans. The parasites cannot find "fishness" in people and thus, migrate to the upper part of the digestive tract, penetrate the gastric wall causing gastritis, and eventually die after a few days.

3) **The parasite colonizes and infects the host**. By parasite I mean all potentially infectious agents: viruses, bacteria, fungi, rickettsiae, protozoa, or helminths. I leave prions out because they are a different story. If colonization and infection of the parasite in these "new" hosts takes place, **virulence tends to be high**, as was the case during bubonic plague or yellow fever epidemics of the past.

What is virulence?

Virulence means the relative ability of a microorganism to cause disease and consists of two attributes: **infectivity**, that is, the ability of an organism to invade and colonize their hosts, and **pathogenicity**, that is, the degree of damage or the severity of the disease produced. An example of this scenario was the bubonic plague that ravaged mankind in ancient and medieval times. The bacterium *Yersinia pestis* (named after Yersin, the bacteriologist, a disciple of Pasteur, who discovered it in 1884) quickly adapted to invade and

colonize (i.e. infect humans) with high pathogenicity (i.e. severe disease with high mortality rate). Another example is the protozoan (one cell) parasite *Plasmodium falciparum* that causes severe malaria in Africa. The parasites have the ability to reach the brain and cause cerebral malaria. The trend is that over time, evolutionarily speaking or through several generations, virulence decreases. On one hand infectious agents tend not to kill or damage their hosts too much, since without them it is difficult for them to survive. On the other hand, host immune responses tend to tolerate infectious agents by mounting milder responses that do not get rid of the parasites completely. This is the general, common evolution of host-parasite interactions, that is, the co-evolution of parasites and hosts.

Not everything is black and white, since multiple factors are involved, such as the genes and genetic characteristics of infectious agents, the genes that code for anti-parasite immune responses in hosts, the infective dose (i.e. the number of parasites involved in colonization), the nourishment and health of the hosts, etc. For example, the dog helminth *Toxocara canis* rarely infects humans, but when it does, the larvae travel to the eyes where they eventually die, in part due to the host's immune response, causing blindness in unfortunate humans, usually children.

The host immune responses are a key factor in the virulence of the infectious agent. During this COVID-19 global outbreak the communication media and social networks spread information, a few times correct, about antibodies, herd immunity, etc., but the immune responses against parasites (virus, rickettsia, bacteria, fungi, protozoans or helminths) are intricate and become even more complex the more we learn about them.

Does it mean that with a strong immune response the microbe decreases its virulence?

Yes, since it is a component of the co-evolution of parasites and hosts. The host's immune response is a key factor in virulence. The media and social networks have spread information about antibodies, about herd immunity [as of 09/2020, COVID-19 has probably aroused immune responses in more than 25 million confirmed cases worldwide; too few to create herd immunity that would require protective immunity in more than 60%, 70% or 80% of the population, although no knowledgeable scientist can assert a precise percentage, but immune responses against parasites, that is, infectious agents of all kinds, are intricate and increasingly complex the more we learn about them.

For example, in 1348, when the bubonic plague (buboes or inflammation of the lymph nodes or lymph nodes, since the *Yersinia pestis* bacteria replicated there) devastated the populations of Asia, the Middle East and Europe, the cause was the high virulence of the bacteria, transmitted by the

flea *Xenopsilla pestis* or by person to person. The human to human transmission was, like COVID-19, through the upper respiratory tract (fomites or small saliva droplets) causing lung colonization, replication of bacteria in the lungs causing pneumonia, respiratory failure and cyanosis (bluish or black discoloration of the skin due to lack of oxygen) hence the name Black Death. These consequences were the result, in part, due to the poor of ineffective immune responses of the host. In other words, from the human immune system perspective, the bacteria were “new” and difficult to fight.

Since COVID-19 is also "new" for humans, do we have ineffective responses against the virus?

In some people it is extremely effective. In others, the response takes time to establish and they have symptoms of the disease for a time. In others, the response is initially ineffective or goes berserk, causing problems that exacerbate the disease in addition to other concomitant problems. That is why there are many people in ICUs (intensive care units) as well as a significant number of deaths.

Why are there variable outcomes of the immune response in different people if the immune systems are fighting the same virus?

To understand the intricate spider web of immune responses, I need to make a concise summary of the basic characteristics and working mechanisms of the immune system. The basic function of the immune system is to recognize and destroy the enemy. For the immune system the enemy is anything that is identified as "non-self." Everything that is not part of oneself is perceived as an enemy that must be destroyed.

Let's imagine the immune system as an army with generals, colonels, captains and a whole spectrum of soldiers specialized in hand-to-hand combat by multiple mechanisms. These are subtypes of white blood cells in the blood and lymph, differentiated from precursors in the bone marrow. When an invader, such as a virus, enters the body, it is detected by foot soldiers who are constantly circulating the body through the blood. These soldiers, like macrophages (macro = large, phage = eat) engulf and eat the virus, killing it and breaking it into small pieces. Then these cells bring to their surface portions of these pieces, like trophies displayed by warriors from a primitive tribe, and present these trophies to B cells. The B cells process information from the small pieces of the virus, that is, its configuration and structure, and go to work like a weapons factory in times of war. Every day, each B cell produces millions and millions of antibodies, also called immunoglobulins. Imagine antibodies as ballistic missiles that specifically recognize each piece of the virus. Let's say they are like specific magnets against each part of the uniforms or portions of the invader that the macrophages engulfed and tore apart, such as a bacterial wall, a viral capsid, or the cuticle of parasites ; in

essence, the enemy's surface. By sticking to that portion of the invader, the antibodies neutralize or stick to it to tag them in order to call or attract cells such as "activated" macrophages that are more efficient at engulfing and destroying than the initial macrophages. Antibodies can also call a series of molecules that are virtual chemical bombs that destroy everything around the attached antibodies. Antibodies also call or attract other fighters called cytotoxic T cells. These are kamikaze cells that release granules filled with various types of chemical weapons that destroy everything around the antibody. Likewise, antibodies attract more cell types such as eosinophils monocytes dendritic cells plasma cells neutrophils or basophils. The organization of the type of soldiers that will be used for each battle and war is done through multiple messages encoded in the form of molecules called cytokines. This entire spectrum of elegant immune responses is called "adaptive or acquired immunity." The main characteristics of acquired or adaptive immunity are:

inducible (induced by the enemy, that is, any molecule or entity recognized as not-self), The whole orchestration, organization and performance of the immune response are induced by that “enemy” recognized as non-self.
specific (the war is directed exclusively towards the detected enemy), and
have memory (the immune system stores the enemy's characteristics in specific cells).

When the immune system detects that particular enemy for a second or subsequent times, it mounts an anamnestic response. That is, a response that is faster, stronger, specific and longer lasting than the first response to that particular non-self invader. These are the principles behind immunizations or vaccinations. A vaccine against a virus, such as smallpox, poliomyelitis, or measles is made from inactivated virus, dead virus or portions of a virus that are administered to the person or animal to be immunized. When the immunized or vaccinated individual is actually infected by the virus, the memory of the immune system is activated and mounts an aggressive immune response with a good part of its army. This response is anamnestic, that is, rapid, specific and more energetic. This is part of the reason we do not see among us smallpox victims or children in wheelchairs or with steel support on their legs to help them walk due to sequela of poliomyelitis.

In view of these solid immune responses, let’s pose the questions again: why do some people infected with COVID-19 develop serious diseases and die?
Inversely, why do the vast majority present a mild disease?
Why are a significant proportion of COVID-19-infected people asymptomatic?

We can start by asking a question with a more fatal disease. Why in the Middle Ages there were asymptomatic people during the devastating bubonic and black plagues when in some communities the death toll surpassed 25%, 33% and even 50%? The explanation is, in part, due to another type of immune response:: innate immunity.

Innate immunity involves a complex network of cells and molecules that constitute the first line of defense of our body against all that is recognized as non-self. Innate immunity exists in invertebrate and vertebrate animals and includes in its arsenal tools to trigger inflammation, activation of a series of molecules collectively called "complement," phagocytes, innate lymphoid cells and NK cells (natural killer cells). There are also multiple types of lymphoid cells, lymphocyte precursors, and various types of molecular platforms, "sensors," and receptors such as those curiously named by their discoverers with amazingly peculiar names and acronyms (eg, Toll-like receptors, RIG-I-like receptors inflammasomes and cGAS) that awaken the maturation of pro-inflammatory cytokines. Innate immunity works in minutes, lasts for days, and precipitates multiple adaptive or acquired responses that last for a long time.

To add another piece to this complex puzzle, the strength or weakness of the innate and adaptive immune responses differ from person to person because we have distinct genetic make up. Different genes in each of us code for specific components of each immune response branch. These are important reasons for the difference in immune responses and susceptibility in each of us towards an infectious microorganism.

Now that we know the nature and heterogeneity behind the variability of these responses, in order to protect ourselves, do we need to rely on the number of vaccines and antivirals currently under development?

First of all, we must be aware that the outbreaks started at the end of last year. Many companies jumped on the bandwagon just this year to develop vaccines and therapies, some of them with innovative technologies such as viral nucleic acid-based vaccines. Thus, let's put everything into perspective. Reviewing the medical literature of antivirals and vaccines developed for, say, influenza virus over several years, might provide us with a more realistic picture of what may occur with COVID-19 therapeutic and prophylactic endeavors. Data from well designed and powered, randomized, double blind, placebo controlled studies of some antivirals to treat influenza virus infection. The effectiveness of neuraminidase inhibitors such as oseltamivir or zanamivir or M2 protein inhibitors such as amantadine or rimantadine reduce the time of relief of symptoms or fever by 16.8 hours, 1.5 days or 24 hours, respectively, or the results are inconclusive. More reliable evidence of their effectiveness is when antivirals are administered prophylactically (8% protection). Do we really expect that an

antiviral, such as remdesivir, will be developed short term to treat COVID-19 infections in a more effective and safe than those antivirals to treat influenza virus infections? There is still no evidence, even with remdesivir.

Since antivirals are not that promising, would it be more realistic to hope that vaccines against COVID-19 will protect us from infection?

As I mentioned earlier, there are effective vaccines against several viral infections that successfully prime the immune system to trigger potent adaptive immune responses upon real viral challenge. It has been noted that in people infected with COVID-19 there are strong immune responses involving CD4+ and CD8+ type T cells and antibodies. The vast majority of vaccines in development against COVID-19 focus on the protein S (for or "spike") and on the RBD "receptor-binding domain," which is the component in viruses required to adhere to angiotensin-converting enzyme 2 (ACE2)2, as a way of attach and infect host cells. Let's picture RBD as a fuzzy part of a tennis ball that sticks like Velcro, in a molecularly specific manner, to (ACE2)2 on the surface of a host cell and, once adhered, the virus injects its nucleic acids into the cell to reproduce. The clinical trials evaluate the successful vaccine candidates by measuring specific anti-COVID-19 antibodies and CD4+ and CD8+ T cells. However, the ideal manner to rationally evaluate the actual efficacy of a vaccine would be to compare the infection rates between vaccinated and non-vaccinated individuals, but this takes time. Testing exclusively the antibodies and cell immune responses mentioned in a laboratory does not provide us with the true protective abilities of a vaccine in a population.

The development of various types of anti-COVID-19 vaccines of different types are being evaluated by numerous institutions and pharmaceutical companies. Their likelihood of success could be similar to those of influenza virus vaccines. The influenza vaccines are developed with viral strains from previous years. Nobody can predict the antigenic structure of a current year influenza virus structure following the seasonal antigenic drift. Nevertheless, it has been reported in previous years that moderately reduced the risk of infection in children and the rate of hospitalizations and the risk of death in people over 65 years of age compared to those non-vaccinated of similar age. Some studies in health care workers found that moderately reduced both the number of febrile respiratory illnesses and the number of reported days of work absence, but the majority of studies are either inconclusive or show no effect. Careful analyses of most of the studies found no evidence. In addition, most of these retrospective studies do have some biases. It must be taken into account that influenza vaccines are very varied depending on the company, if the virus is live attenuated or inactivated, the strain of virus used, the year, the characteristics of the virus that served as immunogen, the type of vaccine developed, if it is univalent, trivalent, etc. Analysis of numerous studies or meta-analyzes have concluded that its effectiveness is variable.

The effect in the general population is not known with certainty. Likewise, mandatory immunizations lack scientific basis. To summarize, we do not know the true impact of an influenza vaccine in the general population.

Immunization strategies and selection of coronavirus components are carried out trying to detect components of the virus that arouse immune responses that generate neutralizing antibodies that prevent the adhesion of viruses to cells and/or specific CD4+ and CD8+ T cell responses to destroy the virus. Ideally, the effectiveness of a vaccine should be evaluated by comparing the infection rate in vaccinated with non-vaccinated populations. In the last decades a vaccine can be approved to go on the market if it only awakens the development of antibodies or specific cells in laboratory tests. Now they are being assessed in a hurry (at pandemic speed) because of the current crisis. There is a **significant difference between the immune responses triggered by vaccine detected in the laboratory and the actual protection rate**. No one can predict what the protection rate of a COVID-19 vaccine will be in the general population.

Here I must elaborate on another variable that will significantly influence the efficacy of a vaccine. Multiple microorganisms that cause infections have developed strategies to change their antigenic structure, that is, the proteins on their surface (their uniform) to evade hosts' immune systems detection and responses. When the influenza virus exhibits discrete changes, called antigenic drift, our acquired immune responses do not have the complete picture of to evade hosts' immune systems detection and responses. In other words, the response is called cross immunity. These changes (antigenic drift) of the virus are the cause of annual influenza outbreaks. When the changes of the virus are significant, called "antigenic shift," the immune system does not recognize it at all and takes even longer to mount an adaptive anti-viral immune response. When the immune response is finally organized, the virus has replicated in an exaggerated way in the airways. This was the cause of the 1918 pandemic that took the lives of dozens of millions of people worldwide. In many cases, the deaths were caused by pneumonia-causing bacterial infections, secondary to the actual viral infections.This means that, after the antigenic changes in its structure, or change of uniform, the influenza virus succeeded in evading the immune response of its hosts.

Going back to the COVID-19 efforts, I hate to be the bearer of bad news. COVID-19 is an RNA virus and like any other RNA virus can rapidly mutate. The vaccines now in development will likely **work moderately and variably as influenza** or rotavirus vaccines if variants of the virus emerge after an **antigenic drift**. It is likely that **none of the vaccines will work** if variants of the COVID-19 virus emerge after drastic changes in its antigenic structure or **antigenic shift**. Any vaccine produced prior to the viral antigenic change will induce immune responses to the virus prior to its mutation, but will prove ineffective to the newly mutated viral strains. Most RNA virus vaccine

manufacturers for farm animals present data showing significant protection against the corresponding experimental viral challenge, usually publications in peer-reviewed scientific journals are absent. or if present are not efficacious. Vaccines to other RNA viruses in humans are suboptimal or have variable degrees of efficacy, which decrease long-term.

Assuming that COVID-19 presents changes in its structure, what can we do? Should we continue confinement, social distancing and other measures?

Considering that COVID-19 virus is highly contagious and the majority of people infected exhibit a mild disease with varying, moderate symptoms or are asymptomatic. It is very likely that their innate immunity put the virus in check, even thought they might continue shedding viral particles. Because of COVID-19's long incubation period and the unknown number and location of asymptomatic carriers, a lock-down of almost 100% of the population must be necessary to put an end to contagion and stop the global outbreak. The current measures will delay the inevitable; they will delay transmission, but will not stop the course of the global outbreak as we have witness recently with the new localized outbreaks in some countries.

So, how long will the pandemic last?

Nobody can predict the pattern of infection dynamics COVID-19 will have with its "new" human host. Anyone claiming to know would be lying like a standard fortune teller. I think we need to think beyond the outcome of the current global outbreak. As in other plagues, epidemics and pandemics in history there are several possible scenarios for COVID-19: the current global outbreak may continue for months and then fizzle. Then the virus could go away and not come back for a long time or may return at any point in the future, spreading in a similar, milder or more severe form. The virus may also exhibit periodic antigenic drifts, producing seasonal outbreaks like the influenza virus. Adversely, the virus may undergo one or more antigenic shifts and cause outbreaks, epidemics or pandemics with similar morbidity and mortality rates or with more severe morbidity and higher mortality rates that could ravage us or future generations.

What is to be done?

It is necessary to re-analyze the preventive strategies taken and decide how to minimize the enduring impact of COVID-19 and the measures themselves. Due to the long incubation period or duration of infectivity coupled with the lack of knowledge of asymptomatic carriers, only a confinement of almost 100% of the population for the appropriate time would be necessary to mitigate infections and contain the global outbreak or "pandemic". This option is not viable. So far the costs caused by the global outbreak compounded by

the consequences generated by the restrictions will have a global impact for a long time. Knowing:
a) the basic mechanisms and the heterogeneity of immune responses,
b) the biology of viruses recently adapted to infect new host species,
c) the similarity of these viruses with others that exhibit similar patterns of attributes and behaviors,
d) the credible efficacy of therapies and immunizations in general populations, and
e) past pest and epidemic patterns, can we infer that current measures will stop the current health crisis? At the beginning of the global outbreak, the health systems in many countries were not prepared for that. It was a hard decision under an impending crisis. One exception was Sweden. Sweden followed the guidelines of their chief epidemiologists. Attempting to achieve herd immunity was never their goal as knew it was unrealistic. The big difference between other countries is that Sweden's governing is based on multiple administrative realms. Several institutions stand beyond the reach of ministries' authority and have the freedom to shape their actions regardless of the government's wishes. Thus, the Public Health Agency of Sweden (Folkhälsomyndigheten) had more say during the COVID-19 health crisis than did the government. The result was striking: Swedish mild mandates overlaid with voluntary measures achieved so far results highly similar to late-onset stringent mandates of other countries, although with more short-term healthcare demand and more deaths among the elderly. Swedish citizens had also higher levels of institutional and interpersonal trust.

Now it is more advisable to consider possible consequences 5, 10 or 20 years in the future before jumping into implementing measures geared toward near-term solutions, especially now that we know the epidemiological patterns in children and young adults. Yes, the measures taken initially protected many now, but in view of the multiple reasons stated here, the future victims may be many more.

What to do now? Invest in strengthening the health systems' infrastructure to be able to serve the large number of people that will be affected. Provide recommendations to high-risk populations so they can **voluntarily** decide their actions. Do not restrict the youth. Keep schools and universities open. Of course there will be high rate of disease and death among the high-risk populations and there will be victims who do not belong to high-risk groups. The extraordinary cost of illness and death in human victims and of the investment may be a fraction of those to solve the consequences of the devastation that awaits us if the harsh restrictive measures continue.

The global outbreak will continue its course, like others in the past, with current measures or not. For how long should we continue as in the last months? Do we believe that an antiviral will be effective in treating those affected? Knowing the characteristics of COVID-19 as recombination and

potential antigenic changes, do we believe that a vaccine will paralyze the infection dynamics?

I would like people advising authorities in different countries to take into account the potential repercussions of the measures in the distant future. I wish to err, but maybe in a couple of decades there will be essays, articles, books and documentaries on the strategies carried out globally in 2020 to circumvent and evade the severity of the COVID-19 crisis and what could have been done to lessen the ravages for years to come. I am also referring to the ravages of another kind, such as economic, social, psychological at a global level, since today, in our globalized world, everything is interconnected.

It is essential and urgent now that the “experts” advising government authorities take into account the potential long-term repercussions of the measures to take. I do not expect politicians to be versed in the multiple disciplines that encompass our current conundrum. However, politicians and policy makers must use their ignorance and overcome the quandary to ask logical, pertinent and necessary questions to their advisors regarding the likely short- and long-term scenarios for each recommendation. Their decisions are paramount as they affected, are affecting and for years will continue to affect millions of human lives worldwide.

The "new normality" is a series of restrictive norms predicated by false prophets. The "new normality" is a violent, oppressive normality that will dislodge our freedom and infringe our basic human rights. To start with, we will continue dressing following a pseudo-Sharia-law unisex dress code.Considering everything that has affected and will continue affecting our lives by COVID-19 and, more than anything, the measures ordered to prevent contagion, one of the most damaged and less appreciated is the psychological harm to children. I would encourage sociologists, psychologists, economists, labor law attorneys, human rights scholars and other professionals to highlight the potential repercussions that the "new normality" is likely to have.

Just like physicians, who treat one patient at a time, have sworn the Hippocratic Oath, government authorities and politicians, whose actions affect whole populations, must swear a new Oath inspired by Thomas Sydenham: **“Do no harm.”**

Medicine has made tremendous leaps in recent past thanks to strict scientific methodology and evidence-based medicine. It is time to apply evidence-based epidemiology, virology and immunology for us and our children’s sake. The world was not prepared for a health crisis of these dimensions. It is now the time to prepare for worst-case scenarios with sizable investments to strengthen health care infrastructure and to recommend realistic, forward-thinking preventive measures based on solid science that people can

voluntarily take and not mandates that will negatively affect millions of people for a long time.

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eucracy. noun. *Politics.* A form just government without a profit agenda that practices peace and gets out of people's faces.*

antisperation. noun. *Politics*. A set of strategies used by a despotic government to evaporate the hope of its citizens. Example: *Faux-flag* events. *

avernocracy. noun. **1.** An extremely repressive government regime. **2.** A punitive government. 3. Hematocracy. **4**. *Informal*. A government from hell.*

* From the Lexinary: words that I coined in my novels thinking they were fiction