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ORIGINAL RESEARCH ARTICLE

A Proposal for the Cause of the Next Great Pandemic and Recommendations for Preparing to Survive It

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ABSTRACT

May 11, 2023, marked the end of the federal COVID-19 Public Health Emergency. COVID-19 resulted in the death of almost seven million people. After such an ordeal, it is normal to feel a sense of relief, the need to relax. Some are afforded this luxury but not so for those who must prepare us for the next pandemic. A pandemic of the same, or greater, magnitude is not statistically expected for some time. Yet, it is a fact that the next pandemic can occur at any time. Thus, we must be ever vigilant and in a state of constant preparation. The benefits of such preparation will be greatly enhanced if the most likely type and magnitude of the next pandemic can be anticipated. The author believes that there are signs pointing to this source.

In pandemic preparation the worst-case scenario employed by many planners is based on the 1918 Spanish influenza. The highest mortality estimates indicate that the pandemic resulted in the death of between 50 and 100 million people. It is difficult to imagine a more intense pandemic. Yet we must. While the 1918 pandemic was the most intense we have experienced, it is certainly not the most intense that we can experience.

"Disease X" is a placeholder name which represents a hypothetical pathogen that the World Health Organization lists as a priority disease on its R&D Blueprint which is a global strategy and preparedness plan. The author believes that it is both naïve and dangerous to employ the 1918 pandemic as a worst-case scenario. It is necessary to think beyond this level. Granted when one does so one is venturing into hypothetical territory. Yet, this must be done to even have a chance at adequately preparing for the next pandemic. This article proposes avian influenza as Disease X. The virus is known but is not currently transmissible between humans. If this becomes possible (and nature is working to make this a reality) the estimated death toll can be expected to exceed a world-changing 1.3 billion.

While this article looks at avian influenza as Disease X it also recommends the preparations necessary to be made for the global society to even hope to survive it.

Keywords: Virus, Influenza, Pandemic, Preparedness, Avian, Disease "X"

Introduction

The world has just weathered a great global pandemic which at times tested its collective ability to effectively respond. COVID-19 resulted in the deaths of almost seven million people worldwide and altered society, perhaps permanently. Many, at various levels and in various capacities, engaged the virus in battle over the course of years. Thus, no reasonable person can debate whether these individuals should be entitled to breathe a collective sigh of relief and relax. Sadly, while they might be entitled to some respite the same cannot be afforded them. Their viral opponents take no holidays.

It is true that a pandemic of the same magnitude experienced during COVID is not statistically expected for some time. The sobering fact is that the next pandemic, of the same or greater intensity, can occur at any time. Thus, we must be ever vigilant and in a state of constant preparation. The benefits of such preparation will be greatly enhanced if the most likely cause, type, and potential magnitude of the next pandemic can be anticipated.

In influenza pandemic preparation the upper end of the influenza severity scales employed by many planners is based on the 1918 Spanish influenza. The implicit argument is that a pandemic of this magnitude is the worst we can expect to face. Unfortunately, this is incorrect. There is nothing that makes this the case. The uppermost estimate of the number of people who died from the 1918 influenza is 100 million. Granted, it is difficult to imagine a more intense pandemic. Yet we must. While the 1918 pandemic was the most intense <u>we have</u> experienced, it is certainly not the most intense that <u>we may</u> experience.

The author believes that it is both naïve and dangerous to employ the 1918 pandemic as a worst-case scenario for planning purposes. It is necessary to think beyond this level. Granted when one does so one is venturing into hypothetical territory. Yet, this must be done to even have a chance at adequately preparing for the next great pandemic.

This article proposes that avian influenza could be the source of this next great pandemic. The virus is not, for the most part, currently transmissible between humans. However, this article will demonstrate that if this does become possible (and nature is working diligently to make this a reality) the estimated death toll can reasonably be expected to exceed 1.3 billion people, dwarfing the effects of the 1918 influenza. After making this case the author proceeds to provide recommendations for preparations to be made if global society hopes to survive such an event.

Methods

The author published an article in 2013 relating to pandemic preparations focusing upon the need to have in place triage protocols for allocating scarce resources which changed allocation schemes as the intensity of the influenza pandemic increased in order to maximize the societal benefit of such resources.[1] The manner of allocation will vary depending upon then intensity of the pandemic being faced. In this earlier article it was first noted that in modeling future pandemics for planning purposes, the 1918 influenza data were invariably employed as the "worst-case scenario". It was claimed that this practice was naïve, dangerous and capable of rendering existing protocols useless in the face of a mega-pandemic. An ethical sliding scale to guide triage protocols based upon the severity of the pandemic was proposed and the scale contemplated as an upper limit a pandemic greater in intensity than 1918 influenza pandemic.

The author observed and studied the events of the COVID-19 pandemic and saw that responsive systems around the globe were at various times stretched to the point of breaking. This raised concern since the intensity of the COVID pandemic was nowhere near that of the 1918 influenza, which so many of the pandemics response protocols employed as its upper limit. This meant that most of the world was not prepared for a pandemic of a magnitude which planners acknowledged could occur and for which it was said they had prepared. The fear was that COVID had actually lowered the bar and that the goal would become to prepare for the next COVID pandemic and not a pandemic equal in severity to that or 1918 or worse yet, a foreseeable pandemic of an intensity surpassing that of 1918.

The author reexamined and updated his research regarding pandemic preparation and protocols. It was found that not much had changed regarding severity preparation from the time of his original article. The 1918 influenza was still invariably the upper limit employed on intensity scales.

The author explored the existing influenza viruses currently capable, or capable of mutating into a virus capable, of producing a pandemic exceeding in intensity the 1918 influenza. The author examined governmental and organizational data to make this assessment (i.e., data from the Centers for Disease Control and Prevention, World Health Organization, etc.). As explained herein, it was determined that the top contender was avian influenza. Reports regarding this strain and movement towards human-to-human transmissibility were tracked. The data regarding past infection and mortality rates of various strains of influenza, and those rates thus far accumulated relating to avian influenza, were extrapolated to model the impact of a pandemic of the avian influenza if it were to become transmissible among humans. These rates were then applied to the global population. The resulting estimates of this process was that the world could possibly experience approximately 1.3 billion deaths if the avian influenza became easily transmissible between humans.

The purpose of this article is to serve as a call against complacency and being lulled into a false sense of security now that COVID has been controlled. It is also a call for a change in our preparation for influenza pandemics based upon its possible magnitude. We must prepare for pandemics which exceed the intensity level of the 1918 influenza. If the protocols which used this pandemic as its upper level of intensity in designing response strategies to survive the same, then why did our infrastructure struggle so greatly with the handling of COVID-19 (a much less severe pandemic)?

Discussion

The world most recently faced the COVID-19 pandemic. This fact affords us no protection. There is no "off time" when it comes to pandemic preparations. The fact that we suffered through COVID-19 does not mean that we cannot be struck with yet another large-scale pandemic this year or the next.

If today a person on the street was asked what comes to mind when they hear the term "pandemic", the response will most likely be

"COVID-19". It is fresh in all of our minds. Academics have spilled much ink considering COVID-19. Through 2021, the published literature on COVID-19 exceeded 211,000 papers, books, and documents.[2] The purpose of this writing is not to add to this corpus. Rather, it is intended as a call against complacency. Many writings focus on preparing for the next pandemic caused by a coronavirus variant. This preparation is too limited.

Worldwide there has been a total of 696,010,839 cases of COVID-19 with 6,921,356 deaths. In the United States we experienced 108,728,769 COVID-19 cases with 1,176,843 deaths.[3] The war on COVID-19 was declared as having officially ended on May 11, 2023, when the federal COVID-19 Public Health Emergency was withdrawn.[4] A relatively small number of cases persist due, in part, to the COVID-19 variants. COVID is here to stay unfortunately but no longer in pandemic form. The COVID-19 pandemic was a great disaster and responsible for much suffering and sorrow. The belief espouse here is that if we fail to learn from that experience the pain, suffering and sorrow will have been for naught.

Looking Beyond COVID-19

The COVID pandemic being "over" the experts are now called upon to prepare for the next pandemic and that preparation cannot be made assuming that the next pandemic will be of the same magnitude as the last. We must prepare to do battle with an unknown enemy of unknown strength and whose weaknesses we do not yet know. It is likely that the pandemic will be viral. The virus makes a formidable opponent, a shapeshifter capable of altering its form in mid-pandemic. The National Academy of Medicine (the "Academy") released a series of four reports in 2021 related to the COVID-19 pandemic.[5] It was granted that COVID-19 had been "terrible". However, the admission was accompanied by a warning. The Academy cautioned that, "Yet, from an epidemiological perspective, COVID-19 does not represent a 'worst-case' scenario, such as the 1918-1919 influenza, which resulted in at least 50 million deaths worldwide."[6] COVID-19 has killed almost 7 million people globally.[7] The sobering fact is that the next great influenza pandemic could be far worse.

How Much Time Do We Have?

It is both reasonable and prudent to expect that an influenza of a severity surpassing that of the 1918 influenza will occur. In fact, it is not a matter of if one will occur, but rather when it will hit. Duke University published a study in 2021 in the *Proceedings of the National Academy of Sciences* claiming that statistics suggest that large pandemics are more likely than previously thought.[8] *Science Daily* in its article discussing the findings stated that Duke, "found the probability of a pandemic with similar impact to COVID-19 is about 2% in any year, meaning that someone born in the year 2000 would have about a 38% chance of experiencing one by now [2021].[9] And that probability is only growing." In the case of the Spanish flu the probability of a pandemic of similar magnitude occurring ranged from 0.3% and 1.9% per year. These figures mean that it is statistically likely that a pandemic of such extreme scale would occur over the next 400 years.[10] This makes it sound like there is not much to be concerned about.

However, the data also shows that the risk of intense outbreaks is growing rapidly greatly reducing the above-referenced number. Based on the increasing rate at which novel pathogens such as SARS-CoV-2 have spread in the human population in the past 50 years, the study estimates that the probability of novel disease outbreaks will likely grow three-fold in the next few decades.[11]

Employing this increased risk factor, the researchers estimate that a pandemic similar in scale to COVID-19 is likely within the span of 59 years. They also calculated the probability of a pandemic capable of eliminating all human life to be statistically likely in the next 12,000 years. The authors of the study claim that this fact highlights the need to adjust perceptions of pandemic risks and expectations for preparedness.[12]

It should be remembered that pandemics are equally probable in any year of the statistical span. Gabriel Katul, Ph.D., is one of the researchers and authors of the study. He explained that, "When a 100-year flood occurs today, one may erroneously presume that one can afford to wait another 100 years before experiencing another such event. This impression is false. One can get another 100-year flood the next year."[13]

An Error to Avoid in Preparing

In modeling future influenza pandemics, the 1918 influenza datum are often employed as the worst-case scenario – the "upper-end of the severity scale." This is both scientifically naïve and dangerous and may render resulting protocols useless in the face of more severe pandemics. For instance, what if what we are facing is not an H1N1 variant but rather an H5N1 strain of avian influenza which has finally mutated to make it easily transmissible among humans? The death toll from such a pandemic would dwarf the numbers of both COVID-19 and the 1918 influenza. Thus, we must think beyond what we have experienced and focus upon what we could possibly experience.[14]

Influenza Viruses

There are four types of influenza viruses:

Influenza A – this is the type of influenza that can infect humans and many animal types. This virus, together with influenza B, causes seasonal influenza epidemics in people (together they give us the "flu season"). However, influenza A viruses are the only influenza viruses known to cause pandemics. Such pandemics occur when a novel type A influenza virus emerges that infects people, has the ability to spread efficiently among them, and against which people have little or no immunity.[15]

Influenza type A is the most significant to public health officials, and those involved in the provision of health care due to its ability to cause an influenza pandemic. These viruses are classified into subtypes according to the combinations of two different surface proteins: hemagglutinin (H) and neuraminidase (N). There are 18 different hemagglutinin subtypes and 11 different neuraminidase subtypes. With these numbers, 198 different combinations are possible. Thus, although 130 influenza A subtype combinations have been identified in nature, primarily in wild birds, there are potentially many more influenza A subtype combinations given the propensity for virus reassortment. Reassortment is a process by which influenza viruses trade gene segments. Reassortment can occur when two influenza viruses infect a host at the same time and exchange genetic information.[16] Depending upon the origin host, influenza A viruses can be classified by researchers as avian [A(H1N1) and A(H9N2)], swine

[A(H1N1) and A(H3N2)], or other types of animal influenza viruses.[17]

Influenza A is constantly circulating globally. The virus is particularly prevalent during the winter months due to the increased humidity and closer contact between hosts, permitting easier transmission of the virus. Wild birds and poultry are reservoirs for the virus and many subtypes such as H5N1 are epizootic and panzootic, meaning prone to outbreak in birds that are far reaching particularly in South East Asian countries such as China.[18]

Influenza B – this type of virus circulates among human populations and is responsible, along with influenza A, for seasonal epidemics.[19]

Influenza C – this type of virus can infect both humans and some animals (i.e., pigs). However, the infections are generally relatively mild and rarely reported.[20]

Influenza D – this type of virus primarily affects cattle (and may spillover to other animals) and are not currently known to infect or to cause illness in people.[21]

Pandemic Influenza

The term "endemic" is most commonly used to describe a disease that is prevalent in or restricted to a particular location, region, or population. An "epidemic" disease is one "affecting many persons at the same time, and spreading from person to person in a locality where the disease is not permanently prevalent."[22] The World Health Organization (WHO) further specifies epidemics as occurring at the level of a region or community.

When compared to an epidemic disease, a "pandemic" disease is an epidemic that has spread over a large area, that is, it is "prevalent throughout an entire country, continent, or the whole world."[23] The WHO more specifically defines a pandemic as "a worldwide spread of a new disease." In March 2020, the WHO officially declared the COVID-19 outbreak a pandemic due to the global spread and severity of the disease.[24] While"pandemic" can be used for a disease that has spread across an entire country or other large landmass, the word is generally reserved for diseases that have spread across continents or the entire world.[25]

Certain conditions favor a pandemic. First, there must be a new influenza A virus that arises from a major genetic change (e.g., an antigenic shift). This virus must find a susceptible population possessing little or no immunity. The virus must be transmitted efficiently from person to person. It must be virulent with the capacity to cause serious illness and death. Finally, the virus will be most successful if it rapidly and frequently mutates to new forms that may not be recognized by the human immune system.[26]

Pandemic influenza differs in many important respects from the seasonal flu. It is capable of sustained transmission among humans and, as a result, causes a global outbreak. Since the hosts possess little natural immunity, pandemic influenza will affect significantly more people than seasonal flu.[27] There have been at least 10 recorded flu pandemics during the past 300 years.[28]

Past Influenza Pandemics

1918 – this is the year of the onset of the Spanish influenza pandemic. (H1N1) Despite the name the disease likely did not start in Spain. Spain was a neutral nation during the war and did not enforce strict censorship of its press, which could therefore freely publish early accounts of the illness. As a result, people falsely believed the illness was specific to Spain, and the name Spanish Flu stuck.[29] Estimates vary but it is claimed that between 20 and 100 million died worldwide from the virus.

The virus arose in February 1918 and spread rapidly throughout the Spring. The first wave disappeared in early Summer. A second wave appeared in August 1918. Between the first and second waves the virus mutated. Influenza viruses mutate rapidly and frequently. The new variation may not be recognized by the population's acquired immunity.[30] Thus, new variations may be deadlier or less deadly than the previous variation. What's more, new variations may be more or less contagious.

The second wave appeared almost simultaneously in many cities around the globe. It had mutated into an exceptionally lethal variation. Over 90% of the total deaths occurred during the second wave.[31] It had a significant effect on the war effort in combatant countries. For instance, not a single United States troop transport ship was sunk during the entire war but thousands died from influenza on the ships bound for Europe. The second wave infected between 30-50% of the world population. Ten percent of those developed massive pneumonia and of these 60% died. In many cases death occurred in 24 hours or less.[32]

The 1918 influenza was different from those that would follow. The so-called "Hong Kong" flu would attack for the most part the very young, the very old, and the debilitated while the Spanish flu killed a disproportionately large percentage of previously healthy young adults.

The "Asian" and "Hong Kong" flus arose through reassortment (mixing) of the genetic matter between avian and human viruses.[33] It seems that the Spanish flu virus is a pure avian virus that developed the unique ability to infect humans easily by human-to-human contact. In a typical flu season, during the lesser pandemics, most deaths are due to secondary bacterial pneumonias. In the 1918 pandemic, many deaths were due to an exceptionally lethal primary viral pneumonia.[34]

1957 - this is the year of the onset of what is commonly referred to as the Asian influenza pandemic (H2N2 – a lineal descendant of the 1918 H1N1 virus).[35] Estimates vary but it is claimed that between 0.7 – 1.5 million died worldwide. This flu was relatively mild.

1968 - this is the year of the onset of what is commonly referred to as the Hong Kong flu (H3N2). Estimates vary but it is claimed that 1 million died worldwide. This represented a new generation of the 1918 viral descendants. However, the impact was so mild that in some locations there were fewer influenza deaths than occurred in certain non-pandemic years.[36]

2009 - this is the year of the onset of the so-called Swine Flu pandemic. Estimates vary but it is claimed that between 151,700 and 575,000 died worldwide.[37]

Ethical Paradigm Shift Based Upon The Intensity of the Pandemic

Public health emergency preparedness and response has been defined as "the capability of the public health and health care systems, communities, and individuals, to prevent, protect against, quickly respond to, and recover from health emergencies, particularly those whose scale, timing or unpredictability threatens to overwhelm routine capabilities."[38] In a disaster situation, the focus of medical care shifts from the needs of the individual (from the focus on individual autonomy) to the needs of the community (to a focus on realizing utilitarian goals) so that the greatest good for the greatest number becomes the measure.[39] This represents a paradigm shift for most health care providers. The physician's primary duty in clinical medicine is to promote the well-being of individual patients. A shortage of resources in a public health emergency may require physicians to withhold or even withdraw treatment from a patient against their own clinical instincts, and the wishes of the patients who otherwise might survive. The notion that public health concerns could shape life or death clinical choices for individual critically ill patients is foreign to most clinicians and their patients.[40]

It should be noted that based upon the intensity of the pandemic the "instrumental value" of patients may be considered in making allocation decisions involving limited vital resources (i.e., in triage situations).[41] Instrumental value, in the triage context, refers to considering the potential future contributions a person might make to society.[42] Essentially, it is a recognition that certain individuals, by virtue of their roles, skills, or functions, might be particularly crucial to the ongoing response to the crisis, or to societal recovery and functioning.[43]

Pandemic Intensity Models Using the 1918 Influenza as the Upper Limit

The following categories are those most often found on Pandemic Intensity Scales:[44]

Mild Severity- This would be equivalent to the seasonal flu.

Definition – "Mild" refers to the early phase of an outbreak of a health emergency where cases are limited in number and geography.

Characteristics – The outbreak is limited to certain regions or demographics. Healthcare facilities are adequately equipped to cope with the outbreak. Public concern is moderate, and there is no significant disruption in daily life.

Potential Indicators – Less than 1% of the regional or national population is affected. Less than 50% of the ICU beds and regular beds are occupied by crisis-related cases in affected regions. There is no reported shortage of critical resources (i.e., personal protective equipment [PPE], medications, etc.). Elective surgeries might be postponed, but critical care resources are still plentiful.

Ethical Implications – Ethical challenges are minimal. The emphasis is on standard medical care without any specialized triage based on instrumental value. However, healthcare workers in affected regions might still receive priority for PPE and similar items given their current "frontline" role.

Morbidity and Mortality - Such annual outbreaks result in 3 to 5 million cases of severe illness and about 290,000 to 650,000 respiratory deaths.

Moderate Severity – Similar in intensity to the 2009 H1N1 Pandemic.

Definition – "Moderate" means that the health crisis has spread more widely, affecting larger populations, possibly on a national scale. The disease has spread nationally but globally affected numbers remain moderate.

Characteristics – There is a rising rate of cases, possibly with a higher severity or mortality rate. Initial shortages of specific resources may emerge (e.g., specialized drugs or PPE). There is a more pronounced public concern, leading to changes in behavior like voluntary social distancing or localized lockdowns.

Potential Indicators – Between 1% to 5% of the regional or national population is affected. 50% to 75% of the ICU beds and regular beds are occupied by crisis-related cases in most affected regions. Initial shortages are reported, especially in "hot spots" (e.g., less than a month's supply of PPE in affected areas). There will most likely be voluntary or localized lockdowns. There is noticeable economic slowdown, and public behavior changes.

Ethical Implications – The beginnings of ethical dilemmas surface. While the priority might be given to front line workers for specific treatments, the general public might have concerns about fairness. Initial considerations might emerge about prioritizing healthcare workers and first responders for treatments or prophylactics (like vaccines), based on the argument of reciprocity (as a reward or quid pro quo for their service which exposes them to a higher risk of infection) and their potential to benefit many others.

Morbidity and Mortality - It is estimated that the death toll would be between 123,00 and 203,000.

High Severity – Similar in intensity to the 1957 Asian Flu (H2N2) or the 1968 Hong Kong Flu (H3N2).

Definition – "High" means that the health crisis is severe, with rapid spread and high case numbers. The disease has become a global pandemic.

Characteristics – There is a significant global spread with varying regional impacts. There is a strain on global and national healthcare resources with a potential for shortages in affected areas. There is a rising rate of cases, possibly with a higher severity or mortality rate. The rapid development and distribution of a targeted vaccine becomes a priority.

Potential Indicators – Between 5% and 15% of the regional or national population is affected. 75% to 95% of the ICU beds and regular beds are occupied by crisis-related cases. Hospitals are at or nearing capacity. Ventilators, ICU beds, and medications are scarce. There might be a need for makeshift hospitals or care facilities to be erected. Widespread shortages of critical resources are reported, with urgent international or national appeals for supplies. There are mandatory national lockdowns, a large economic recession, travel bans, and public fear.

Ethical Implications – Ethical challenges become more pronounced. The concept of instrumental value plays a greater role in triage protocols. Beyond healthcare workers and first responders, other "essential" roles might be identified based upon societal need. For instance, this could include utility workers, food supply chain workers, and other groups or individuals critical to societal functioning. Pre-established triage committees might begin to oversee the allocation of resources. Instrumental value becomes a significant triage factor again significantly influencing decisions about ICU admission and ventilator allocations. Assume that there is a shortage of ventilators and a young nurse and an elderly person with no described "instrumental" profession both need one. The ventilator might be allocated to the nurse and not only based upon age or prognosis, but also based on his instrumental value to the ongoing crisis response.[45]

Morbidity and Mortality - The 1957 pandemic resulted in an estimated 1-2 million deaths, while the 1968 pandemic variant caused around 1 million deaths.

Extreme Severity – This would be an intensity of the 1918 Spanish Flu (H1N1).

Definition – "Extreme" is the upper limit on most influenza severity scales and is intended to represent the pinnacle of crisis severity.

Characteristics – There is a rapid global spread with high mortality and morbidity rates across different age groups. It overwhelms healthcare systems globally. There are severe societal disruptions, with widespread lockdowns, economic downturns, and societal fear.

Potential Indicators – The healthcare system is overwhelmed in multiple countries. Cases far outweigh available medical resources. More than 15% of the regional or national population is affected. Over 95% of the ICU beds and regular beds are occupied by crisis-related cases. Makeshift hospitals will be set up and triage protocols activated. There are severe shortages and rationing protocols will be in place. Healthcare workers will be forced to make critical decisions on resource allocation.

Ethical Implications – There is a severe shortage of medical resources. Decisions are not just about who to admit, but potentially about who to remove from life-saving treatment to give another a better chance at survival. At this level, instrumental value takes on a critical role. There is a sharp focus on maximizing societal benefit. This might entail not just considering one's current role, but potential future contributions as well. Triage becomes severe with instrumental value becoming paramount, encompassing broader considerations. This might now include teachers (i.e., for post-crisis education), engineers (for infrastructure rebuilding), and others. For example, assume that a makeshift hospital has one 1CU bed remaining. Two patients enter the hospital at the same moment – a middle-aged truck driver and a young biologist researching the disease. Both have similar medical prognoses. The bed might be allocated to the biologist, recognizing the potential long-term benefit of their research. In another scenario, a country might ensure that its agricultural experts receive early vaccines, anticipating future food shortages and recognizing their role in post-crisis food security.[46]

Morbidity and Mortality - The 1918 pandemic had between 20 and 100 million deaths. However, in 1918 the world's population was just 1.8 billion and today stands at 8.1 billion[47] (4.5 times greater). Adjusting the numbers to consider the population difference, the numbers become between 90 and 450 million deaths.

An Influenza Outbreak <u>Exceeding</u> in Severity the 1918 Influenza Pandemic ("Disease X")

Disease X is a hypothetical pathogen that the WHO first included in its 2018 R&D Blueprint.[48] The R&D Blueprint is a global strategy and preparedness plan that allows for the rapid activation of research activities during epidemics. It is a framework to facilitate diagnostics, vaccines, and therapies during an outbreak. However, Disease X does not refer to a specific pathogen, but rather represents the concept of an unknown pathogen that could cause a future epidemic or pandemic. The idea is to recognize the inevitability of unexpected diseases and the importance of being prepared for unknown threats, not just the known ones. Including Disease X on the Blueprint emphasizes the need for flexibility in response and research platforms that can be adapted or modified to confront unexpected or unknown pathogens. It serves as a reminder that the next big threat might not be from a known source and that preparedness is key.[49]

The 1918 pandemic is often cited as the most severe in recent history in terms of global reach, mortality rate and the sheer speed at which it spread.[50] As stated, most influenza intensity scales use this pandemic as the upper limit, worst-case scenario. However, it is necessary to think beyond this level of intensity. Granted when one goes beyond the intensity of the 1918 pandemic one is venturing into hypothetical territory. Yet, this is necessary. In order to do so one would most likely have to consider a combination of influenza strains which come together to create a novel virus which spreads faster than previously imagined between humans and with greater lethality.[51]

Again, Disease X would need to represent a novel pathogen, at least with regard to the infection of the human population. It must also be extremely efficient in its mode of transmission, most probably it would be airborne. An airborne transmission mode that could spread over long distances would be more devastating than droplet transmission. For instance, consider the measles virus, which can remain airborne in a room for up to two hours after an infected person departs.[52]

Disease X would need to have a very high basic reproduction number (RO) meaning that each infected individual, on average, spreads the disease to many others. The RO of the 1918 influenza is estimated to have been between 1.4 and 2.8.[53] Finally, it should have a long asymptomatic period where people are contagious but do not yet show symptoms. Individuals being capable of spreading the virus without showing symptoms would seriously challenge containment efforts. Disease X might mutate at a rate that makes it difficult to develop a singular effective vaccine. If the pathogen has animal reservoirs (like bats, or rodents which are not as easily destroyed as, let's say, birds), it could be challenging to eradicate the reservoir sources, leading to potential recurring outbreaks.[54]

A Possible Candidate for Disease X – Avian Influenza

Worldwide, the number of potential pathogens is very large, while the resources for disease research and development (R&D) is limited. To ensure efforts under the WHO's R&D Blueprint are focused and productive, a list of diseases and pathogens are prioritized for R&D in public health emergency contexts. A WHO tool determines which diseases pose the greatest public health risk due to their epidemic/pandemic potential and/or whether there is no or insufficient countermeasures. At present, the priority diseases are:

- Crimean-Congo hemorrhagic fever
- Ebola virus disease and Marburg virus disease
- Lassa fever
- Middle East respiratory syndrome coronavirus (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS)
- Nipah and henipaviral diseases
- Rift Valley fever
- Zika
- "Disease X" - This represents the knowledge that a serious international epidemic could be caused by a pathogen currently unknown to cause human disease.

This is not intended to be an exhaustive list, nor does it indicate the most likely causes of the next epidemic. The WHO reviews and updates this list as needs arise, and methodologies change.[55]

Most humans are in contact with animals in one way or another. A zoonotic disease is a disease or infection that can be transmitted naturally from vertebrate animals to humans or from humans to vertebrate animals. More than 60% of human pathogens are zoonotic in origin. This includes a wide variety of bacteria, viruses, fungi, protozoa, parasites, and other pathogens.[56]

Avian Influenza

Since 1996, the highly pathogenic H5N1 avian subtype has developed the ability to be transmitted from poultry to humans, Previously, it was understood that people could only be infected with H1,H2 and H3 variations. This spill-over demonstrates the high risk imposed by random mutations in the hemagglutinin and neuraminidase glycol proteins, from which the subtypes get their H and N classifications. So far there is no human-to-human transmission of H5N1, but this is not true of avian influenza subtype H7N9, which emerged in 2013 and has been found in a limited number of suspected cases in people who were then found to have infected family members.[57] In any event, both of these types have high mortality rates and little is understood about these mutations, making them unpredictable. They have high pandemic potential and must be considered high risk and a strong candidate for Disease X.[58]

While many subtypes of avian influenza can infect birds, not all are pathogenic or capable of infecting humans. H5 and H7 subtypes are the most known to mutate from low pathogenicity to high pathogenicity forms in birds. When this mutation occurs, outbreaks in poultry can be devastating, with mortality rates nearing 100% in some cases. The most concerning strains for human infections so far have been H5N1, H7N9, and H5N8, among a few others. Direct contact with infected birds or their secretions is the most common mode of transmission to humans. Aerosol transmission, especially in environments like wet markets, is also a risk. The fecal-oral route, especially in water sources shared by wild and domestic birds, is a significant transmission mode among birds. The symptoms in humans can range from mild flu-like symptoms to severe respiratory distress, multi-organ failure, and death. The severity often depends on the viral strain, and the age and health of the individual.[59]

Avian influenza appears to be very adept at jumping continents and species. The H5N1 strain was first discovered in 1996 in geese bred on a farm in southern China. Since that time, it has ravaged the population of captive, commercial birds, prompting the slaughter of tens of millions of turkeys, chickens and other poultry in an effort to deprive the contagions of hosts. Carried by infected wild birds, especially geese, swans and gulls, the virus has also gained a foothold in various types of mammals which includes a small number of humans for whom it has proven lethal. The most feared outcome would be mutation facilitating human-to-human transmission. This event could trigger a pandemic of untold magnitude.[60]

Since 2020, when a new variant of the H5N1 strain emerged in Europe, outbreak numbers that typically ebb and flow have been persistently elevated. Health experts claim that the new version, clade 2.3.4.4b, is especially efficient at spreading among birds, both domesticated and wild, and the mammals that prey on or scavenge them.[61] It spread to the Americas in 2021 and 2022. In the UK, there have been 23 infections in wild animals, including in red foxes, Eurasian otters and harbor seals, through July 4, 2023. Dozens of domestic cats and five dogs have been infected in Europe.[62] Twelve fur farms in Finland, housing more than 50,000 foxes, minks and raccoon dogs, have reported cases.[63] Almost 3,500 sea lions in Peru succumbed to the infection. In the US, H5N1 has been detected in mountain lions, bobcats, bears, dolphins, skunks, raccoons, and other animals.[64]

Since the beginning of 2020 through July 14, 2023, there were 17 confirmed cases of H5N1 in humans according to the WHO. This number includes four infections in people with no symptoms detected through a proactive surveillance system implemented in the UK. All were thought to have contracted the infection via direct contact with sick birds or contaminated surfaces. Although case numbers are modest, the death rate among humans is not: of 878 people known to have been infected from 2003 through July 2023, 458 died[65] (a mortality rate of 52%).

The question then is if the avian flu could become the next pandemic, the Disease X. Unlike the COVID virus, the H5N1 variants currently circulating do not bind easily to receptors found in cells in the human respiratory tract, the prime reason why human infections have thus far been so rare. However, when H5N1 does take hold of a human, it progresses more quickly to the lungs – a major reason for its lethality. As reported by even the popular media, if the virus was to mutate to become easily transmissible among humans, it is said that the number of deaths could dwarf the nearly seven million confirmed deaths caused by COVID as of mid-September 2023.[66]

The fact that it has spread so widely throughout the world is particularly troubling from a public health standpoint. More problematic is the fact that the virus is affecting countries with limited experience in detecting and tracing the virus.

Researchers have discovered a subtype of the avian flu virus endemic to the poultry farms in China. These are said to be undergoing mutational changes which could increase the transmissibility of the disease to humans raising further concerns of a potential pandemic.

Research results have been published in *Cell* and report on the characterization of a human isolate – from a patient – of the H3N8 avian influenza virus. Employing laboratory mice and ferrets as models for human infection, the study found that the virus has undergone several adaptive changes, to cause severe animal infections and making it transmissible by the airborne route between animals. In humans the H3N8 virus infection has been found to cause acute respiratory distress syndrome and can even be fatal. The virus is widespread in chicken flocks; however, the features permitting it to be transmitted from animals to humans are poorly understood. Almost 59 million commercial birds have been culled as of the end of May 2023. This makes the outbreak the broadest of this type of avian flu since it was identified in China in 1996.[67]

Vaccines

The virus's proliferation and high mortality rate have prompted questions about two types of possible vaccines; those for bids and those for humans. H5N1 kills almost all of the birds it infects; among people in reported case since 2003, the death rate has been 52%.

The US has stockpiled H5N1 flu shots in the event of a crisis. But several experts claim that it would prove insufficient should this particular type of avian influenza begin infecting people.[68] The shots have only been administered in trials and were derived from strains that circulated in 2004 and 2005.[69] The virus has mutated since then.

Additionally, if necessary, developing a better tailored vaccine for the current strain would be quite complicated. Flu vaccines are grown or created in one of two ways. The first employs chicken eggs. The process requires individually inoculating each egg with a modified virus and this, of course depends on an ample supply of healthy chickens to produce the requisite number of eggs. Death of laying hens = drastic reduction in the number of eggs = inadequate quantity of vaccine to fight the modified strain.

The second way would be to employ mRNA manipulation that would not require eggs. The creators of the process, Katalin Kariko and Drew Weissman, were jointly awarded the Nobel Prize in Physiology or Medicine for 2023 for their mRNA vaccine discoveries that made highly effective COVID vaccines possible and for such vaccines to be manufactured so quickly.[70] It is not known if the technology could respond timely to a novel virus triggering a new pandemic.[71]

What is the possible death toll from an Avian Influenza Pandemic?

The most striking aspect of H5N1 is its high mortality rate. As previously mentioned, there have been 878 people known to have been infected from 2003 through July 2023, of these 458 died (a mortality rate of 52%). Unlike many circulating strains, H5N1 has a lower age curve, with the median age of infection being 19 (possibly because the infections have been largely among bird farm workers who skew younger). This is more similar to the Spanish Influenza, in which 50% of deaths were adults between 20 to 40. In contrast, H7N9 has a lower case fatality rate of 40% in which two-thirds of deaths were in people over the age of 50 but even so significantly higher than seasonal and even Spanish influenza.[72]

Several research teams have worked on the difficult problem of reconstructing the global health impact of the Spanish Flu. The range of published estimates is particularly wide. The widely cited study by Johnson and Mueller (2002) arrives at a very high estimate of at least 50 million global deaths. But the authors suggest that this could be an underestimation and that the true death toll was as high as 100 million.[73] Patterson and Pyle (1991) estimated between 24.7 and 39.3 million died from the pandemic.[73] A more recent study by Spreeuwenberg et al. (2018) concluded that earlier estimates were too high. Their own estimate is 17.4 million deaths.[74]

Pre-pandemic world population in 1918 is estimated to have been 1,832,196,157 people. The estimates of 50,000,000 deaths published by Johnson and Mueller implies that the 1918 influenza killed 2.7% of the world population. And if it was in fact higher – the 100 million estimated as suggested by the authors, then the global death rate would have been 5.4%. (50,000,000 deaths/1,832,196,157 = 0.02729; if death count twice as high: 0.05458).

The world population currently stands at approximately 8.1 billion people. If a pandemic of the severity of the 1918 pandemic were to occur today applying the above percentages to the population, the death toll would be between 221,049,000 (8,100,000,000 x 0.02729) and 442,098,000 (8,100,000,000 x 0.05458) people.

However, it is clear that human-to-human transmission of avian influenza will create a pandemic of greater magnitude than the 1918 influenza. Assume the following: a world population of 8.1 billion; an exposure rate of 60%; 50% of those exposed develop the flu; and a mortality rate of 55%.

8,100,000,000 x .60 = 4,860,000,000 x .50 = 2,430,000,000 x .55 = 1,336,500,000 deaths

Employing the assumed percentages, the avian influenza pandemic could produce 1,336,500,000 deaths. This number is little more than an educated guess. It assumes many things such as human-to-human transmissibility. The percentage of people exposed to the virus and who develop the influenza will certainly vary. The fatality rate is also forecasted from past pandemics. There will certainly be collateral deaths as the world attempts to cope with the disaster. The number of deaths the computation yields is equal to 16.5% of the world population. Even if the assumptions are in error and turn out to be double the actual numbers, the result would still be 668,250,000 deaths. This would still be equal to 8.25% of the world population. A more sobering thought is that the hypothetical might, in fact, be understated.

Societal and Economic Ramifications

Global trade and economy will be greatly affected. There will most likely be a complete halt or severe disruption of international trade. A world-wide economic depression greatly surpassing the 1930's Great Depression in terms of duration and depth should be expected. The meaning of national wealth might shift from GDP to things more highly valued in this environment such as industrial output to health infrastructure and research capabilities. The capitalist structure could be questioned, leading to experiments with alternative economic models, such as universal base income.

It is an understatement to say that there would be social disruption. Societal functions would break down, with essential services such as law enforcement, fire services, and waste management becoming sporadic or nonexistent. There could also be a disruption in agricultural output and food distribution. This could lead to global food shortages and even famine. Similarly, water supplies might break down, leading to a secondary crisis.

The pandemic would be mentally devastating. This should be considered when planning. Beyond the immediate physical health threats, a global mental health crisis could arise due to prolonged isolation, loss, societal breakdown and lack of access to needed medications.

Some have speculated that there would be an urban exodus.[75] People would flee the crowds and the violence of the urban areas and seek places where they could grow/raise their own food. Significant population decline could also lead to further societal restructuring.

Unforeseen Global Implication

The pandemic may cause shifts in geopolitical power. Nations previously considered superpowers might be severely weakened, either due to the disease's impact or economic collapse, leading to unexpected powers shifts on the global stage. This event might prompt the formation of new geopolitical alliances based, for instance, on mutual aid during the crisis, while old alliances might be strained or broken.

This might prompt an increase in the use of technology. In an effort to control the spread of the pandemic, there might be an unprecedented rise in surveillance, potentially leading to permanent changes in the concept of privacy and other norms and rights.

Environmental and Planetary Health

As stated above, we could be dealing with cities that have become human-abandoned landscapes. Vast areas of land previously dominated by humans could evolve into new ecological niches, leading to rapid evolution and speciation. Some species, previously thought to be on the brink of extinction, might make surprising comebacks in human-reduced environments. Certain species might thrive in the absence of human interference, while others, dependent on human-created environments, might suffer. Significant drops in industrial activity and transportation could lead to temporary drops in greenhouse gas emissions. However, this might be followed by aggressive industrial activity in an attempt to recover, resulting in spiking emissions.

If the urban exodus should occur, major cities could experience significant decay if they remain uninhabited or less populated for extended periods. Nature might begin reclaiming those areas, leading to a unique urban ecosystem.

Preparing for an Avian Influenza Pandemic

Preparing for the pandemic resulting from the avian influenza mutating to become much more capable of transmission among humans means preparing for the unknown. While it is certainly challenging to prepare in advance for an unknown threat, the idea is to have systems in place in advance that can be rapidly mobilized and adapted to any infectious threat (even those, especially those, of any substantial size). The following is a list of the broad measures and strategies that are either already in place, or which may be implemented, to guide the preparations for the next great pandemic.

Global Surveillance and Reporting:

Especially true of avian influenza is the need to enhance and maintain global systems with the ability to quickly identify and report outbreaks. This includes improving laboratory capacity and diagnostic tools, especially in regions known for the virus. Already in place is the Global Outbreak Alert and Response Network (GOARN), a collaboration coordinated by the WHO, and which plays a key role in monitoring and responding to outbreaks.[76]

R&D Blueprint: The WHO's R&D Blueprint aims to speed up the availability of diagnostic tests, vaccines, and treatments during emergencies. It focuses on both known high-threat infectious agents and the unknown potential threats (e.g., Disease X). It is designed to fast-track the development of effective tests, vaccines, and medicines during pandemics.[77]

Flexible Research Platforms: There is a need to develop research platforms that can be quickly tailored to new pathogens as necessary. For example, vaccine platforms like the mRNA technology, discussed above, and which was crucial for the rapid development of COVID-19 vaccines, should continue to be improved so that they might be potentially adapted to effectively fight the avian influenza pathogens.[78]

Stockpiling: Some countries and organizations maintain stockpiles of essential medical supplies, treatments, and vaccines that can be quickly deployed during an outbreak. The Global Health Security Agenda (GHSA) emphasizes the importance of countries having a national framework for stockpiling and deploying essential medical countermeasures. The question is the amount that should be stockpiled. If the avian pandemic contemplated here becomes a reality probably no amount of supplies capable of stockpiling would be sufficient. But not being able to do everything, does not mean that one should do nothing.[79]

Strengthening Health Systems: It is vital to build robust health systems, especially in vulnerable regions, to help ensure that outbreaks can be detected and managed early. Some of these should be made mobile to allow them to be moved when and as needed or, depending on circumstances, exported to another country which has been harder hit or whose health care system is less capable of coping.[80]

Simulation and Training: Regular drills and simulation exercises should be conducted at local, national, and global levels to ensure that responses are coordinated and effective. One such exercise was "Event 201," a pandemic exercise, which took place in October 2019 and was hosted by Johns Hopkins Center for Health Security, World Economic Forum, and the Bill & Melinda Gates Foundation. If something of this magnitude hits, borders may melt away and individuals will begin identifying simply as members of the same species attempting to survive.[81]

Collaboration and Information Sharing: An environment should be fostered where countries and organizations freely share information about disease outbreaks without fear of economic or political repercussions. International Health Regulations (2005) are intended to help the international community prevent and respond to public health crises.[82]

One Health Approach: The interconnectedness of human, animal, and environmental health must be recognized. Many emerging diseases come from animal reservoirs (including avian influenza), so monitoring and understanding these interfaces can provide early warning. The WHO, in coordination with the Food and Agriculture Organization of the United Nations (FAO) and the World Organization for Animal Health, follows a One Health approach recognizing this interconnection between people, animals, plants, and their shared environment.[83]

Funding: It is necessary to secure continuous investment in research on emerging infectious diseases, funding rapid response teams, and maintaining preparedness infrastructure. The Coalition for Epidemic Preparedness Innovations (CEPI) was established to finance and coordinate the development of new vaccines.[84]

Regulatory Frameworks: There must be regulatory pathways that can expedite the review and approval of diagnostics, treatments, and vaccines during emergency situations. The WHO's Emergency Use Listing (EUL) procedure allows for the accelerated assessment of medical products during emergencies.[85]

Public Education and Communication: It is necessary to build public trust and ensure transparent, accurate communication that can lead to more effective responses and compliance by the populace with public health measures. Risk communication and community engagement (RCCE) is a critical component of emergency response, as emphasized by the WHO.[86]

Global Partnerships: CEPI aims to drive vaccine development for emerging infectious diseases, including those of unknown magnitude. The Global Preparedness Monitoring Board (GPMB) monitors and advocates for preparedness activities globally.[8]

Conclusions

The phrase "Generals are always preparing to fight the last war" is often attributed to a number of historical figures (including Winston Churchill), but its origin remains murky.[88] One of the people most frequently associated with the quote is Ferdinand Foch, a French Marshal and the Supreme Allied Commander during World War I.[89] Still, it is challenging to locate a direct and authenticated source indicating that he, in fact, made this statement.

No matter, what is important about the observation is the sentiment it conveys. The quote means that military leaders and planners in preparing for the next war often focus on the strategies and tactics of the most recent conflict (especially if they were victorious), potentially rendering them ill-prepared for the nuances of a new, different type of war. We cannot be preparing for the last war. Rather, we must anticipate and prepare for the next. This thinking must be applied to our pandemic preparations.

Pandemics are the wars that governments, and public health officials, healthcare providers, and all first responders are called on to fight. Unlike a conventional war there are truly no "civilians" or "bystanders" in a pandemic. As was learned with COVID-19, all are participants, willingly or not, in the battle against a deadly virus. The experts must be ever-vigilant and in a state of perpetual preparation. Response protocols must always be in the process of modification and revision as new data is processed and assimilated. While preparations must be made annually for the seasonal influenza, additional preparations must also be made and continually modified to permit us to contend with the next great pandemic, which may emerge at any time.[90]

While the hypothetical used in this article paints a picture of immense challenges, it also hopefully points to possibilities for renewal, innovation, and evolution. Societies have faced calamities in the past and have often emerged transformed, sometimes for the better. The emphasis, as always, would be on human adaptability, resilience, and the unyielding spirit to innovate and overcome. The limits of human resilience, adaptability, and ingenuity would be tested. Specifics can and will vary, however the importance of proactive global cooperation, pandemic preparedness, and the need for robust healthcare and response systems cannot be emphasized enough.

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