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Algorithm for Pandemic Prediction and Prevention

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Abstract

The world remains under-prepared to predict, detect, respond, and even less prevent pandemics. Yet, the cost of failing to control them and the associated ravages (health, familial, social, economic, political) is far greater than the cost of prevention. Transmissible from animals to humans through direct or indirect contact or through food, water, and the environment, more than 70% of all new, emerging, or re-emerging diseases affecting humans at the beginning of the 21st century are zoonotic. This is the most opportune time to address the prevention and management of health crises such that the world has witnessed and continues to witness with COVID-19. Highlighting global health security, strengthening multi-disciplinary engagement and multi-sectorial coordination while emphasizing the importance of financial preparedness will be paramount for facing future health threats. Improvements in early warning and detection, timely data sharing, laboratory testing, and joint outbreak response capacities (in human health, animal health, and wildlife sectors) will create and strengthen the mechanisms necessary to effectively detect and respond to emerging zoonotic threats, prevent pandemics, and thereby enhance global health security. After a brief perspective from past pandemics, I will identify the root cause(s) of pandemics from the ancestral domestication of plants and animals to the present times in which we live on a microbially-unified planet. As a result of the emphasis on flus, I will stress that all our present guidelines for pandemic response are still based on influenzas whereas coronaviruses are different types of viruses. I will briefly present the several organizations that are pursuing a global health agenda and will lastly focus on the new paradigm of “one world-one health”, or better “one-world, one *eco*health” paradigm that, together with the Global Human Virome Project, has the potential to be the beginning of the end of pandemics. Lastly, I will offer some remarks regarding the state of research in the field and the use of epidemiological modeling (i.e. mathematical biology) to assist in health policies decision-making.

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1. Introduction

Infectious disease threats have the potential to endanger lives, disrupt families and societies, and wreck havoc on economies (travel, trade, food supply, etc.). Outbreaks do not respect national boundaries, do not discriminate between different ethnicities, religions, social or economic status, and can spread rapidly jeopardizing the health, security, and prosperity of all world countries. It is in each country's security interest to strengthen global health security and manage the risk of infectious disease outbreaks.

In 1992, the (U.S.) Institute of Medicine [1] published a report on the resurgence and emergence of infectious diseases, identifying the following causes: “*human demographics and behavior, technology and industry, economic development and land use, international travel and commerce, microbial adaptation and change, and breakdown of public health measures... “* in short, all human activities! It suggested “*better surveillance, vaccine and drug development, vector control (primarily through better pesticides), and human behavioral changes (sexual relations, antibiotic use)*”. Surprisingly, it did not mention regulating land use, working for more equitable economic developments, health insurance, or paid sick leave.

More than 15 years later, in 2008, the World Health Organization (WHO) published a review of evidence related to the social determinants of health. It recommended "*improvements of daily living conditions, including the circumstances in which people are born, grow, live, work, and age...*" , and "*to tackle the inequitable distribution of power, money and resources, and the structural drivers of these conditions (globally, nationally, and locally).* Further, 5 years hence, after the outbreaks of SARS and H5N1, it stated that the most important progress was "*genome-associated advances in microbial detection and treatment, improved disease surveillance, greater awareness of emerging infectious diseases, and the complicated variables that underlie emergence*". Unfortunately, none of the serious causes were addressed including the rapidity and scale of changes associated with human activity and climate and environmental change, … which should give us pause.

According to the WHO, more than 70% of pathogens capable of causing symptoms in, and even killing, humans originate in animals. The world remains under-prepared to predict, detect, respond, and even less prevent infectious disease outbreaks, whether such outbreaks are naturally occurring, accidental, or deliberately released. Physical distance alone no longer provides protection as pathogens can move from one point on Earth to almost any other place in the world within 36 hours. Yet, the cost of failing to control outbreaks, ruining and losing lives, destabilizing the social fabric, and decimating economies is considerably greater than the cost of prevention.

What is happening? I will explore these circumstances in the following sections, identify the root cause(s) of pandemics, emphasize that all our present guidelines for pandemic response are still based on influenza, and focus on the new paradigm of "one world-one health", or better "one-world, one *eco*health" that, together with the Global Human Virome Project, has the potential to be the beginning of the end of pandemics by predicting, preventing, and arresting their interminable succession. Lastly, I will offer some remarks regarding the state of research in the field and on decision- making health policies driven by epidemiological modeling (or mathematical biology).

2. On the Origin of Pandemics

The interface between humans, animals, and the environments we share can be a source of diseases impacting public health and the social and economic well-being of the world's population. Transmissible from animals to humans through direct or indirect contact or through food, water, and the environment, more than 70% of all new, emerging, or re-emerging diseases affecting humans at the beginning of the 21st century are zoonotic (i.e. originated in animals). Notable reminders of how vulnerable the increasingly interconnected world is to the global impact of new emerging diseases include [2]-[4]:

- HIV/AIDS;
- Influenzas: including:
  ◦ Influenza A (H1N1); ◦ Influenza B (Yamagata); ◦ Avian influenza (the H5N1 strain); and ◦ H7N9.
- SARS (Severe Acute Respiratory Syndrome);
- MERS (Middle East Respiratory Syndrome);
- MERS-CoV (MerS Coronavirus);
- Ebola;
- Marburg; and
- Nipah: without forgetting the current
- COVID-19.

Several of these outbreaks have spread extensively in human populations, causing global epidemics (pandemics). The speed with which these diseases can emerge and spread presents serious public health, socio-economic, and development concerns. It also underscores the need for the development of comprehensive disease detection and response capacities, particularly in "hot spot" areas such as Central Africa, South and Southeast Asia, and Latin America where a confluence of risk factors may contribute to disease emergence.

The increase in the number of naturally occurring outbreaks over the past 15 years (e.g., influenza, Ebola, Zika, and Rift Valley fever) and the risk posed by an accidental or deliberate release of pathogens highlight the critical need for robust prevention, detection, and response mechanisms. Infectious diseases can spread across species, and indeed many human diseases have animal origins. Achieving global health security requires a sustained, coordinated, multi-disciplinary and multi-sectorial approach that incorporates an understanding of the linkages between human, animal, and environmental health.

Now, more than ever before, the world should recognize this moment as the most opportune time to highlight global health security and emphasize the importance of financial preparedness for health threats to better prevent and manage health crises that the world has witnessed with the COVID-19 pandemic. Improvements in early warning and detection, timely data sharing, improved laboratory testing, and enhanced outbreak response capacities in the human health, animal health, and wildlife sectors will be of paramount importance. They will create and strengthen the mechanisms necessary to effectively detect and respond to emerging zoonotic threats, and thereby enhance global health security.

Now, global patterns of zoonoses reflect social and ecological changes that go well beyond individuals and communities. If we look over the natural history of zoonoses and their emergence or re-emergence in the early 21st century, the general causes are a mixture of the following factors:

- Human's creation of new urban or agricultural ecosystems: in the ruins of older, non-human dominated ecosystems. Ebola, Marburg, Chagas, SARS-CoV, and SARS-CoV2 emerged in part because people invaded new territories where other animals and their microbes have lived in some rough kind of harmony for millenia.
- Economies of scale and monocultures in agriculture: have created ideal conditions for the generation of epidemics of avian influenza, salmonellosis, and SARS-CoV2.
- Fast global travel and unfettered free trade: have fostered the spread of epidemics.
- Loss of biodiversity.
- Social inequity.
- Marginalization of poor people.
- Rapid sprawl of slums: with bad housing, inadequate water, and standing sewage.
- Climate change: is contributing to the destabilization of ecosystems and the dispersal of animals and microbes into new areas.

They have irremediably created ecosystems that change the patterns of old infectious diseases and create opportunities for new ones.

3. A Brief Perspective from Past Pandemics

All pandemics are zoonotic viral diseases, the viruses having jumped directly from their animal habitat to humans or indirectly from animals to other animals to humans. Some of them, mostly the influenzas took the direct route from chickens or pigs to people. Others, such as Ebola, SARS, and COVID-19 took a circuitous route from bats, pausing at “rest stops” in one or two other animals (civets, monkeys, perhaps pangolins) before finding their ways into humans.

SARS CoV-2 was predictable in some limited sense. There were reports, briefings, warnings about viruses bearing traces of their animal origins and of emerging infectious diseases... but, for various reasons, they have not been heeded. Nonetheless, the manner in which COVID-19 spread to (and in many cases killing) older people, immunocompromised people, but also younger adults or even infants and children has taken us all by surprise. It should not have been so!

To be sure, endemics, epidemics, and pandemics have been with us since the beginnings of time. Actually, the word “epidemic” appeared for the first time in Homer's Odyssey in about the 8th Century BCE. It had connotations of “indigenous” or “endemic”. Later, in 430 BCE, Hippocrates gave it a medical slant by referring to physical syndromes (i.e., groups of symptoms that may refer to unknown diseases) that occurred in particular places and times. The description of the Plague of Athens (429-426 BCE) by Thucyclides that claimed an estimated death toll of 75,000-100,000 people is considered to be one of the earliest accounts of a disease epidemic. After the discovery of bacteria in the 19th century, specific terms were used for specific diseases such as “epidemics of cholera”. Nowadays, multi-country outbreaks of various diseases are called epidemics - pandemics being a step beyond, at least in terms of numbers and geographical extent.

Before 2020, the only WHO-declared pandemics were in:

- 1918: the Spanish flu (75 million deaths);
- 1968: the Hong Kong flu (1 million deaths); and
- 2009: the H1N1 swine flu (only 18,500 deaths although mathematical models suggested 150,000-575,000).

This overlooks the Black Death (75-100 million deaths or 30% of Europe's population), and the six choleras, especially the Third (1 million deaths) and the Sixth (> 800,000 deaths). According to the WHO, as of 15 March 2021, there were 119,603,671 confirmed COVID cases and 2,649,722 resulting deaths, these numbers further climbing as days, weeks, and months pass. But, what is a pandemic?

4. But, Officially, what is a Pandemic?

There are two generally accepted definitions of a pandemic:

A. **The World Health Organization (WHO)'s definition:** For the WHO: “(a pandemic is) *an epidemic occurring worldwide, or over a very wide area, crossing international boundaries, and usually affecting a large number of people*”.

Aside from its vague and subjective attributes, this definition includes nothing about virulence so that a disease may become pandemic without being a serious killer. Conversely, a serious killer, even one appearing in different parts of the world, may not necessarily be classified as a pandemic. Thus, for example, SARS and even HIV/AIDS were never officially declared pandemics! Also, “seasonal epidemics” of influenza are not pandemics.

The WHO classifies pandemics in six categories spanning the spectrum from exclusive transmission between animals to exclusive transmission between humans. After waves of the disease go around the world, fewer people get sick and die with each subsequent wave, either because humans have built immunity or/and because the agent evolved through the processes of mutation and natural selection as the agent moves in with our species to a more sustainable life.

B. **The (U.S.) Centers for Disease Control & Prevention (CDC)'s definition:**

For the CDC: “*An influenza pandemic is a global outbreak of a new influenza A virus that is very different from current and recently circulating human seasonal influenza A viruses. Pandemics happen when new (novel) influenza A viruses emerge, which are able to infect people easily and spread from person to person in an efficient and substantial way. Influenza pandemics are uncommon; only occurred during the 20th century*”. Again, while the newness of the influenza virus is explicitly emphasized, and the characteristics of the transmission are addressed, this other definition likewise says nothing about virulence and speaks only of an influenza A virus. It is dated and was not prescient regarding the COVID19 pandemic. How are pandemics classified?

5. Schwabe’s Classification of Pandemics

While all classifications may be useful, they may not represent the whole truth. Based on animal reservoirs and natural cycles, Carl Schwabe provided a classification that included four categories:

- Direct zoonoses: includes many food-borne agents;
- Cyclozoonoses: have maintenance cycles that require more than one vertebrate species but no invertebrates;
- Metazoonoses: require both vertebrates and invertebrates; and
- Saprozoonoses: depend on inanimate reservoirs or development sites.

While it has served well scientific researchers and public health advocates, the above classification may not apply to pandemics and zoonoses in the 21st century's context of globalization, climate change, ecological collapse, species extinctions, human overpopulation, huge economic and political disparities, and unintended consequences of well-meaning interventions. All of these issues must be encompassed at once. But, first, what are the root causes of pandemics?

6. Identifying the Root Cause(s) of Pandemics

A. In the beginning

Hunting began with our ancestors around 8 million years ago, forever changing the way that we would interact with the microbes in our world. Hunting and eating flesh with its attendant blood, saliva, urine, feces,...spattering into the orifices of human bodies (eyes, nose, mouth, any open sores or cuts...) provided the perfect opportunity for direct entry of viruses into their bodies. In as much as hunting represented a milestone for our 8- million-year old ancestors, it had equal importance for the world of our microbes. Once in the body, microbes, like toxins, have the potential to negotiate their way through different levels of a food web, increasing interaction with their prey and increasing contact with their prey's own microbes (this is called *biological magnification*) [2]-[4].

Within the small mobile hunter-gatherer lifestyle that our ancestors led prior to domestication, acute viruses could not survive for long unless they were microbes that we shared with other species. As our African ancestors migrated to different environments, their microbial repertoire and their lives changed. Genomic studies indicate that our ancestors had low population densities that did not favor a great spread of infectious agents. This population bottleneck led to a *microbe bottleneck* with an accompanying loss in microbial diversity. Later, the particular combination of larger population sizes, sedentary groups of humans, and the growing populations of domestic animals would play a central role in transforming the relationship between humans and microbes.

When it comes to domestication, microbes were a triple hit to our ancestors: (1) they provided sufficiently close contact with a small set of domesticated animals, allowing their microbes to cross over to us; (2) domestic animals provided a regular and reliable bridge to wild animals, giving their microbes increased opportunities to cross into us; and (3) they permitted us to have large and sedentary communities that could sustain microbes.

We must also recognize that viruses and other microbes are phenomenally successful. They are the oldest form of life on Earth and together comprise 60% of the Earth's living matter. Most are beneficial or cause no great harm to humans and their livestock, and we live in symbiosis with them. But, some are a formidable and constant challenge to humanity.

B. After the beginning

After the beginning, came the domestication of plants and animals. Each animal (wild and domestic) has its own microbial repertoire, and when concentrated on a farm or in a house or herd, these microbes thrive. Domestic animals have contributed novel microbes to humans in different ways. Since each of these species had its own pre-domestication repertoire, the initial close contact of farming led to an early exchange of its microbes to those of humans.

Of the microbes that originated in our domesticated animals, many entered into humans thousands of years ago, at or near the time we domesticated them. This enhanced the microbial repertoire of our ancestors during the climax of domestication 5-10,000 years ago. Over time, this has further changed.

Over the thousands of years of interaction, our microbes have reached a sort of microbial equilibrium with domestic animals. Nonetheless, these animals still contribute to our microbial repertoire and continue to feed us new microbes. These microbes derive not from the domestic animals alone but also from the wild animal species that they are exposed to. Our domestic animals act as microbial bridges permitting new agents from wild animals to make the jump into us. For example, the Nipah virus can enter humans with or without pigs; its reservoir is the “flying fox” bat (scientific name: *Pteropus*). It can further spread from human to human.

Additionally, pathogens can jump between wild animals, domestic animals, human hosts but also even plants, emphasizing the complex way that animal domestication and plant growing can provide new avenues for pathogens to pass into people. As villages and towns formed around agricultural centers, they did not do so in isolation but became interconnected communities of towns, providing the first opportunity in human history for an acute virus to persist permanently in the human species.

The biodiversity of animals, plants, and fungi supported by tropical rain forest systems is higher than any other ecosystems on land. The savanna habitat houses fewer animals and a lower diversity of microbes capable of infecting humans, which in turn contributed to lower microbial repertoires for our ancestors. The diversity of animals between the forest and the savanna also played a role in microbe diversity and repertoire. The loss of microbial diversity in our early ancestors and the resulting decrease in their genetic defenses would make us susceptible to the microbial repositories that our ape cousins maintained during our own microbial cleansing.

We now live in a microbially-unified planet. This radically mobile world gives infectious agents a truly global stage on which to act. We no longer live on a planet where pockets of life persist for centuries without contact with others. The impact of smallpox on New World populations (in the16th century) is the most dramatic known example of the way that the connections formed by shipping can influence the spread of microbes (~ 90% of the Mayas, Aztecs, and Incas were decimated by smallpox brought by boats during the European colonization). Each of the major transportation advances would alter connectivity between populations, and each would have their own impact on the spread of new microbes. For microbes, the transportation revolution was really a connectivity revolution. These technologies created links that forever changed the nature of human infectious diseases including, critically, how efficiently they spread. HIV is among the most notable example of the impact that road proliferation has had on the movement of microbes. Proximity to roads increases a person's risk of acquiring HIV. Roads also provide the mechanism for different types of HIV to encounter one another in a single co-infected individual and swap genetic information. Roads and other modes of transportation can also help ignite pandemics [2]-[4].

Just in the U.S., for example, the volume of domestic air travel predicts the rate of spread of influenza. International travel also plays a vital role. When travel is lower, the peak of the influenza season comes later because, when there are fewer travelers, it takes longer for the virus to spread. The transportation revolution has created an interconnectivity unprecedented in the history of life on our planet (> 50,000 airports, > 20 million miles of roads, > 700,000 miles of train tracks, >100,000s of ships and boats in the oceans at all times). It has:

- Fundamentally changed the ways that animal and human microbes move around our planet;
- Radically changed the speed with which microbes can travel;
- Brought populations together: allowing agents that could not previously sustain themselves with low population numbers to flourish;
- Permitted completely novel diseases to emerge; and, frighteningly,
- Extended the range of animal viruses.

These technologies have created a single interconnected world – a giant microbial mixing vessel for infectious agents that previously stayed separate and stayed put, altering forever the way in which we will experience epidemics and ushered us into the pandemic age. Further, while we lament about disappearing animal and insect species, we rarely think about the trillions of various yeasts, fungi, and bacteria for which they are home. These “refugees” from those lost habitats are coming back to haunt us!

C. The case of COVID-19 transmission

COVID-19 is a hybrid-type of outbreak. It is both a “common-source outbreak” with so far a continuous exposure (time will tell if it will recur) and a “propagated outbreak” spreading from person to person wherein infected individuals become independent reservoirs leading to further exposures. It propagates:

- **Airborne:** the infection spreads by droplet nuclei or dust in the air. Without the intervention of winds or drafts, the distance over which airborne infection takes place is short, say 10-20 feet (so-called “social – more accurately physical - distancing”). It can also be transmitted by
- **Contact:** wherein the disease agent is transferred directly by biting, sucking, chewing or indirectly by inhalation of droplets, drinking of contaminated water, traveling in contaminated vehicles; and
- **Horizontal transmission:** spreading laterally to others in the same group and at the same time.

Note: On 4/28/2020, three cases of animals (1 dog, 2 cats) affected by COVID-19 have been reported. The causes are unknown and may include either an infected person or an asymptomatic person (owner, family member, etc.). These are the first reports of person-to-animal transmission. It is now time to review the current international guidelines for response to a pandemic.

7. Current Guidelines for Pandemic Response are based on Influenza

As a result of the emphasis on flus, all our guidelines for pandemic response are based on influenza. They are embodied in all the WHO and other official publications. Yet, while there are vaccines and approved therapeutics for the flu, as of now, they have just recently been developed for the SARS-CoV2 virus that caused COVID-19. Thus, to consider only the most current pandemics:

A. WHO Publication: 2019 Novel Coronavirus (2019- nCoV) - "Strategic Preparedness and Response Plan"

After conducting a situation assessment consisting of an epidemiological overview as of 11
1 February 2020, the WHO made a risk assessment after due consideration of the following pertinent factors:

- The likelihood of further spread through human-to-human transmission: including transmission within families and within healthcare settings within the pandemic's epicenter (City of Wuhan, Province of Hubei, China), and in several cities outside China;
- The potential impact on human health: the virus can cause severe illness and death, although most cases appeared to be mild; and
- The effectiveness of current preparedness and response measures.

On the above basis, the WHO assessed the risk to be very high for China and high at the regional and global levels. It further recommended a strategic preparedness and response plan to "*stop further transmission within China and to other countries, and to mitigate the impact of the outbreak in all countries*". This plan naturally included the following traditional measures:

- Limiting human-to-human transmission;
- Identifying, isolating, and caring for patients early;
- Identifying and reducing transmission from the animal source(s);
- Addressing crucial unknowns: clinical severity; extent of transmission and infection; and treatment options;
- Accelerating the development of diagnostics, therapeutics, and vaccines;
- Communicating critical risk and event information to all communities;
- Countering misinformation; and
- Minimizing social and economic impact: through multifactorial partnerships.

It is interesting that, departing from its own definition of a pandemic, the WHO finally mentioned "severity"!

B. WHO Publication: 2017 - "Pandemic Influenza Risk Management"

Although it can be applied to all infectious diseases, this earlier document was used by WHO during SARS-Cov2 even though it preceded that outbreak. It is aimed at "managing disaster risks" and helping countries assess risks so they can make more informed decisions. It has 4 phases:

- Inter-pandemic;
- Alert;
- Pandemic;
- Transition; and

then another Inter-pandemic. The document assumes that whenever we are not in a pandemic, we are in an inter-pandemic. According to this document, there is no non- pandemic phase in our future! We have always lived between pandemics and always will! We must progress beyond this mold and be able to predict and prevent future pandemics.

Fortunately, the WHO is not the only organization interested in, and pursuing, a global health agenda. Let me briefly address these other organizations which, in my view, may optimistically provide the solution to the problem at-hand of predicting, preventing, and eventually eradicating future pandemics.

8. Selected Organizations pursuing a Global Health Agenda

A. The (U.S.) Government Global Health Security Strategy (GHSS)

In close cooperation with its international partners, this program aims to prevent, detect, and respond to infectious disease threats at home and abroad, whether naturally occurring, unintentional, or deliberate.

Together with the (U.S.) National Security Strategy, the (U.S.) National Biodefense Strategy, and the Executive Order on “Advancing the Global Health Agenda to Achieve a World Safe and Secure from Infectious Disease Threats”, the GHSS strengthens global health security, including accelerating the capabilities of targeted countries to prevent, detect, and respond to infectious disease outbreaks domestically and globally [5].

B. The (U.S.) Agency for International Development (USAID)

Together with its partners and subcontractors (government agencies, universities, national research & development centers, private research organizations, and others), the (U.S.) Centers for Disease Control & Prevention (CDC), and the Global Health Security Agenda (GHSA), the USAID has the following programs [6]:

- **USAID: EPT-1 (2009-2014), EPT-2 (2014-2019) - “Emerging Pandemic Threats (EPT) Program“**

This multi-million dollar global program was designed to predict, identify, and respond to (but, surprisingly not prevent and eradicate) the threat posed by emerging infectious diseases. It consisted of two phases. The first phase (dubbed “EPT-1”) aimed to “aggressively pre-empt or combat emerging infectious diseases that could spark future pandemics”. It was composed of four complementary projects operating in 20 countries: PREDICT, PREVENT, IDENTIFY, AND RESPOND – with technical assistance from the CDC. It draws on expertise from across the animal and human health sectors to build local, national, and regional “One Health” capacities for early disease detection, laboratory-based disease, disease diagnosis, rapid response and containment ,and risk reduction. The particulars of each of these projects are provided in Appendix 1.

To minimize the impact of pandemic threats on human health and economic and social stability, the second phase of the program dubbed (EPT-2”) built on the lessons and knowledge acquired from EPT-1 and brought heightened focus to places and practices that not only enable new microbial threats to “spill over” but also potentiate their spread. It aimed to pre-empt or combat at their source newly emerging diseases of animal origin that could threaten human health. It also directly improved the capacity of more than 20 focus countries in Africa and Asia to prevent, detect, and respond to infectious disease threats.

EPT-2 helped develop and improve predictive models for early identification of viral and other biological threats in resource-poor “hot spot” regions. It also enhanced regional, national, and local capacities for surveillance, laboratory diagnosis, and field epidemiology in both the animal- and human-health sectors in these areas. These efforts would ultimately minimize the risk for the emergence and spread of new pandemic disease threats.

The EPT-2 program was managed by USAID with technical collaboration from the CDC, the WHO, and the Food & Agriculture Organization (FAO). In addition to these partnerships, USAID had awarded three new projects to provide additional technical support to developing countries.

Unfortunately, by late 2019, just before COVID-19, the EPT program had run-out its initially-planned and funded lifetime and was terminated. Beyond economic and political considerations, I very much hope that the EPT program will be resuscitated and reactivated for years to come. (Note: The new U.S. administration that took office on 20 January 2021 restored in a limited way the PREDICT component.)

- **USAID (2020-2025) “STOP Spillover Project”**

On 9/30/2020, the USAID launched its “Strategies to Prevent Spillover”, a 5-year, $100 million project to anticipate and address threats posed by the emerging zoonotic diseases that pose the greatest risk of jumping from animals to humans. The project will play a significant role in the implementation of the U.S. Government's Global Health Security Strategy (GHSS), including support for the Global Health Security Agenda (GHSA). It will be implemented by a consortium of cross-disciplinary experience headed by Tufts University. It will contribute directly to the reduction of future outbreaks from known zoonotic viruses. It will also develop and institutionalize innovative, country-specific, and sustainable approaches to prevent future outbreaks, focusing on strengthening national capacity in a limited number of targeted countries.

Considering that more than 70% of emerging infectious diseases originate from animals, STOP Spillover is a critical next step in understanding and addressing the risks posed by zoonotic diseases that can "spillover" - or be transmitted - from animals to humans. Outbreaks can start - and stop - at the country level, and that early, country-level and country-led interventions are key to preventing or reducing the impact of outbreaks.

- **USAID/CDC**

CDC activities funded by the USAID focused on pathogen detection as well as outbreak investigation and response. Specific activities included:

- Strengthening surveillance and laboratory capacity;
- Enhanced monitoring for zoonotic pathogens: in people with frequent contact with wildlife;
- In-service Field Epidemiology Training Programs (FETP); and
- Supporting outbreak response: when requested.

To further enhance coordination and link to CDC’s expertise, two CDC technical officers had been seconded to USAID to directly manage the EPT projects that were focused on One-Health, pre-service epidemiology training, and laboratory capacity- building. Again, unfortunately, this particular activity of CDC has been terminated at the same time as that from USAID.

C. The (U.S.) CDC’s Global Disease Detection Operations Center (GDDOC)

The GDDOC monitors disease outbreaks and other health emergencies of potential international importance, historically providing verification and early warning of more than 300 outbreaks per year.

9. The “One-World, One-Health” and “One-World-One-*ECO*Health” Paradigm for predicting and preventing New Pandemics.

A steady wave of interconnectedness among humans and animals has created a perfect storm for new pandemics. Yet, the interconnectedness among humans that now exists through communication and information technology gives us an unprecedented capacity to catch outbreaks early. When combined with advances in our ability to study the diversity of the tiny life forms that cause epidemics, this makes us optimistic about the future of predicting pandemics.

Fortunately, the following organization is still alive and viable, pursuing the wider agenda of “One-World, One-Health”, better yet “One-World, One-*eco*Health” paradigm, not merely just “One-Health”.

Launched in 2014 by nearly 30 countries, international organizations, and private sector companies, the Global Health Security Agenda (GHSA) serves as “*a catalyst for progress toward the vision of attaining a world safe and secure from global health threats posed by infectious diseases*” [7].

As of September 2018, GHSA comprised: 65 participating countries representing nearly 6 billion people; 9 international and regional multilateral organizations and institutions; non-governmental sector partners, including over 100 private companies, non- governmental organizations, and academic institutions. It has grown to 69 countries and is anticipated to include more than 100 by 2024. These countries have come together to achieve the vision of a world safe and secure from global health threats posed by infectious diseases. It addresses priorities and gaps in efforts to build and improve country capacity and leadership in the prevention and early detection of, and effective response to, infectious disease threats. It emphasizes the need for strong multi-sectoral engagement, including human and animal health, agriculture, security, defense, law enforcement, development assistance, foreign affairs, research, and finance sectors among others.

At its October 2017 GHSA Ministerial Meeting in Uganda, GHSA member countries present supported the “Kampala Declaration” to extend GHSA for an additional five years (to 2024), acknowledging that significant work remains to be done to fully achieve and sustain health security. (For more details about the GHSA membership and agenda, refer to its website: www.ghsa.org.)

In 2020, in the context of globalization, climate change, ecological collapse, species extinctions, human overpopulation, huge economic and political disparities, and unintended consequences of well-meaning interventions, the above paradigm needs to be further extended to account for as many of these factors as possible or feasible.

Diverse habitats, which buffer against disease, are resilient (meaning they have the ability to adapt and change and continually reorganize themselves in the context of a changing world). In the same way, we will have to adapt and live in symbiosis with the ecosystem.

If the climate and the environment were stable, we could develop public health and management strategies to deal with diseases where they occur endemically. By altering the climate and the environment, we are changing the baseline and encouraging diseases to spread into new areas. Our ability to adapt is being undermined by the way in which we continually change the environment in which we are trying to adapt. In other words, the success of responses to one disease problem is very much connected to how we solve a whole lot of other problems.

Some institutions or organizations that are active in this paradigm are:

- The International Resilience Alliance: it has contributed a great deal to our ability to develop appropriate response and management strategies that will provide both ecological resilience and human well-being;
- WHO and its sister The World Organization for Animal Health (*Organisaion Internationale contre les Epizooties,* OIE);
- The International Association for Ecology and Health (IAEH);
- EcoHealthAlliance;
- EcoHealth International;
- The Communities of Practice in Ecosystem Approaches to Health (COPEH): examples are COPEH-Canada, COPEH-Latin America and the Caribbean;
- *Medecins sans Frontieres* – Doctors without Borders (MSF/DWB);
- *Veterinaires sans Frontieres* –Veterinarians without Borders (VSF/VWB); and others.

10. The Global Human Virome Project: The Beginning of the End of Pandemics?

On May 1, 2020, the CDC announced a new initiative to study the coronavirus genome. At least 75 U.S. public health, academic, and commercial institutions will be brought together in an effort to hasten research into how it is spreading in the U.S. and how to fight it. Tiny mutations accumulate in the genetic code of a virus as it replicates, and identifying those changes helps scientists track transmission patterns and outbreaks. A goal is to standardize the information that should accompany each sequence, such as where and when a sample was taken. These are crucial details for making use of the data, and it is hoped that sharing the results of genetic research on the coronavirus will help scientists create vaccines and treatments.

But, looking beyond COVID-19, would the Global Human Virome Project (GHVP), with its aim to sequence the genome of all known and to be discovered viruses truly be the beginning of the end of future pandemics? Let me examine this issue beginning with a brief outline of the project itself.

A. The GHVP

As we already know, new and deadly viruses have already highlighted our vulnerability on a global scale to emerging diseases, many of these having massive health and socio-economic costs. Looking to many past and present spillovers of pathogens from animals to humans, it appears that inadequate preparedness and vigilance have led to humans being sentinels for animal diseases. Further, the absence of basic data on the pathogens reservoir resulted in costly delayed diagnosis and preventable morbidity and mortality. This was the case with novel strains of influenza, Ebola virus, Marburg virus, Dengue virus, AIDS, tuberculosis, and other infectious zoonotic pathogens, such as malaria, rabies, Zika, or Lyme disease. Further, the countermeasures we developed utilizing our limited adaptive toolkit (mostly therapeutics and vaccines) have often been ineffective as they were outpaced by the speed and spread of emerging daughter (mutated) viruses.

After decades of reacting to each of the past pandemics, we remain only marginally better protected against the next ones. In this, we are undermined by our poor understanding of the diversity and ecology of viral threats, and of the drivers of their emergence. One promising idea is to develop a global atlas of pathogens that are, as yet, unknown but might threaten humanity already or are likely to evolve into clear threats. Such an atlas would be a foundational necessity for anticipating and reducing the threats, but it would also be ambitious and costly, even if it was restricted initially to viruses [8]-[11].

The Prince Mahidol Awards Conference in 2018 in Bangkok, Thailand, highlighted the importance of the topic: "*Global trends indicate that new microbial threats will continue to emerge at an accelerating rate, driven by our growing population, expanded travel and trade networks, and human encroachment into wildlife habitat".* Most emerging viruses are zoonotic, that is, transferred between vertebrates and humans. Estimations show that there are more than 1.5 million (Note: This number is uncertain; other sources put it at 1 million) mammalian and waterfowl viruses, spanning across 25 viral families. Compared with the more than 260 viruses known in humans, the unknown viruses represent 99.9% of potential zoonoses. These viruses usually remain undetected until they cause disease in humans.

The GHVP was officially launched in 2018 to help identify the bulk of the viruses that threaten us and to provide timely data for public health interventions against future pandemics. Much like map-making for newly-discovered continents, the GVHP would be a pathway to improve our capacity to detect, diagnose, and discover viruses that potentially pose threats to human populations, particularly in low-income and middle-income countries. Between 631,000 and 827,000 (actually one million or more) unknown viruses might be zoonotic and, thus, have the potential to infect humans after spillover from host animal populations. The big idea is to gradually build a global atlas of most of the planet's naturally-occurring potentially-zoonotic viruses by systematically creating the missing maps. Broadening the knowledge base on viral sequences, geographical ranges, and host distributions would provide vital intelligence about humanity's formidable microbial enemy. Additionally, the GHVP would complement ongoing efforts, such as the "**Coalition for Epidemic Preparedness Innovations**", the "**International Vaccines Task Force**", and the "**World Bank's REDISSE Program"** for surveillance and preparedness capacity-building projects.

The three specific benefits that the project would provide are:

- Early warning of future threats;
- Data to improve prevention and reduction of these threats; and
- Inputs for advance preparation of responses: for unexpected outbreaks of unknown diseases.

However, there is a debate in the scientific community about whether the animal-human infectious disease nexus warrants substantially more funding, science effort, and global policy discussion [12]-[14].

B. GHVP cost estimate and its justifications

The projected cost estimate for the GHVP is in the range: US$ 1.2 – US$ 3.4 billion over a 10-year period. In perspective, it is modest in at least four regards [11]:

- Even a single regional disease outbreak can result in considerable human illness and death and cost $10's of billions in productivity, trade, economic growth, and social welfare: over $53 billion for the 2014–15 Ebola outbreak in west Africa. Further, the economic cost of a pandemic of a novel influenza (or other readily transmissible viral disease) has been conservatively estimated as $80 billion annually when averaged over a century. By contrast, a maximal expenditure of $400 million a year on the GHVP would be equivalent to just 0.5% of the ongoing annual economic risk of $80 billion from a pandemic influenza (and other readily transmissible viral disease);
- Analyses of viral risks would increasingly become possible as data is collected;
- The viral atlas might yield large co-benefits since concentrated research in one area often leads to unforeseen benefits elsewhere; and
- The project would create an international partnership that cuts across political adversaries for a common cause.

11. On Health Policy Decision-Making driven by Epidemiological Modeling (Mathematical Biology)

To make science-based decisions regarding the containment and abatement of the current pandemic, policymakers have resorted to epidemiological modeling (or mathematical biology). Based on experiences with past epidemics, increasing knowledge of the SARS-Cov2 virus, and the drivers of the current pandemic, several modelers have used their models to numerically simulate how the disease spread and, unfortunately, may continue to spread. (This is much like weather and climate prediction as they are well know to all.) These science-based predictions can be (and have been) applied to various geographical locales and even globally (see Appendix 2 for a quick description of the several models currently in use.) First, however, it must be kept in mind that these are only mathematical/statistical simulations that aim to mimic but may not actually describe reality. Further, all models and their results are beset by their underlying assumptions, the uncertainties of the data employed to run them and, at times, the lack of critical data. For example, at the start of an epidemic, the following parameters:

- The average proportion of infected people who die and the number of people that can be infected by one person (so-called reproduction number, R0);
- The number of days the virus takes to infect a person (so-called incubation period);
- The number of asymptomatic people who can still spread the virus;
- The proportion of people having natural immunity to the virus; etc.

are all imprecisely known. The decision comes as to which model to choose. The answer would be to use more than one (perhaps even all) available model(s), hoping they will lead to consistent results. However, although projections might not diverge wildly depending on the approach chosen, it is natural to wonder how reliable any of the simulations are. Indeed, many scientists have voiced their reservations or even objections and disapprovals of them especially since during an epidemic, it is hard to get data — such as on infection rates — against which to judge a model's projections. In addition, the uncertainties associated with the validity and accuracy of the tests administered and the resulting numbers of cases and deaths reported (in other words, our whole surveillance system) may be questionable and in need of further research. Further, reliance on the models can lead to drastic measures on society as a whole (allowing the disease to spread while protecting the oldest in society; ability of the healthcare infrastructure to handle the number of infected people; social/physical distancing; widespread testing; the use of pressurized oxygen outside intensive care units versus invasive mechanical ventilators that require such units; contact tracing; lockdowns, etc.). It behooves us to develop as accurate and predictive models as possible. To avoid too much reliance on any one model, policy makers and governments should take advice from several modeling groups. Nonetheless, the models represent a useful quantitative tool that has assisted policymakers and guided the responses of the various countries and the world to the current pandemic.

12. New Research Vistas

Research is essential for understanding how pathogens spread and cause disease, and to generate safety and efficacy data to support regulatory decisions on clearance, approval, licensure, and emergency use. Recent outbreaks of diseases such as Lassa fever, Ebola, Zika, and Nipah have highlighted gaps in the knowledge base needed to optimally stem the outbreak. These gaps can be addressed through the integration of infectious disease research into global preparedness and response activities. Research during an emergency response is often the only available and most effective opportunity for determining the safety and efficacy of a vaccine, therapeutic, or diagnostic (which may expedite licensure and access to safe, and effective countermeasures).

Since 2015, global institutions such as the WHO and the World Bank, and public-private partnerships have been responding to deficiencies in research by ensuring integration of research into global health security preparedness and response efforts. The 2015 World Health Assembly-mandated WHO reform included the development of a WHO Research and Development Blueprint for pathogens with epidemic and pandemic potential.

In the area of epidemiological simulation, it would be necessary to conduct retrospective analyses to assess the actual performance of the models and inform on updating them and their simulations. The codes, models, data, and results should also be open and made available to many.

13. Summary and Conclusions

Promoting global health security to detect and mitigate outbreaks early should remain a core tenet in global health security. It can help prevent the spread of human and animal infectious diseases and protect populations. Furthermore, investments that focus on prevention and preparedness are far more cost-effective than responding to infectious disease epidemics.

To maximize global health security and preparedness for infectious disease threats, all countries must address global health security challenges.

Unfortunately, the world remains under-prepared to detect, respond, and prevent infectious disease outbreaks, whether such outbreaks are naturally occurring, accidental, or deliberately released. Yet, the cost of failing to control outbreaks, losing and ravaging lives, destabilizing the social fabric, and decimating economies is considerably greater than the cost of prevention.

Transmissible from animals to humans through direct or indirect contact or through food, water, and the environment, more than 70% of all new, emerging, or re-emerging diseases affecting humans at the beginning of the 21st century are zoonotic. Several of these outbreaks have spread extensively in human populations, causing pandemics. The speed with which these diseases can emerge and spread presents serious public health, socio-economic, and developmental concerns. It also underscores the need for the development of comprehensive disease detection and response capacities, particularly in “hot spot” areas such as Central Africa, South and Southeast Asia, and Latin America where a confluence of risk factors may contribute to disease emergence.

Improvements in early warning and detection, timely data sharing, laboratory testing, and joint outbreak response capacities in the human, animal health, and wildlife sectors will create and strengthen the mechanisms necessary to effectively detect and respond to emerging zoonotic threats, and thereby enhance global health security.

We now live in a microbially-unified planet. This radically mobile world gives infectious agents a truly global stage on which to act. Each of the major transportation advances altered connectivity between populations, and each had their own impact on the spread of new microbes. For microbes, the transportation revolution was really a connectivity revolution. These technologies created links that forever changed the nature of human infectious diseases including, critically, how efficiently they spread.

As a result of the emphasis on flus, all our guidelines for pandemic response are still based on influenza. They are embodied in all WHO and other official publications.

Through its emerging pandemic threat program (terminated in December 2019), in collaboration from the CDC, the USAID pursued a “one-health” paradigm for predicting and preventing future pandemics. This paradigm has been expanded to the new paradigm “one-world, one-health” or better “one-world, one-*eco*health” that, together with the Global Human Virome Project, may hopefully represent the beginning of the end of pandemics.

However useful as they offer science-based assistance to health policy decision-making during epidemics/pandemics, epidemiological models remain limited in their mimicry of reality and beset by their basic assumptions and the lack of some critical data.

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Appendix 1 – The USA ID's Emerging Pandemic Threats Program

The particulars of each of the component projects of this program are as follows:

PREDICT focused on the detection and discovery of zoonotic diseases at the wildlife- human interface. Specific activities included:

- Strengthening surveillance and laboratory capacities: in order to monitor wildlife and people in contact with wildlife for novel pathogens that may pose a significant public health threat;
- Characterizing human and ecological drivers of disease spillover from animals to people;
- Strengthening and optimizing models: for predicting disease emergence and using this information to improve surveillance; and
- Supporting outbreak response: when requested.

PREVENT focused on characterizing the risks associated with disease transmission between animals and people and developing risk-mitigation strategies. Specific activities included:

- Characterizing specific practices and behaviors: for example, bushmeat hunting and butchering, raising wildlife for trade and consumption,... that expose people to zoonotic diseases; and
- Developing and deploying risk-mitigation strategies: including a tool for extractive-industry workers to decrease their exposure to emerging zoonoses.

IDENTIFY focused on strengthening laboratory capacity to safely diagnose and report common animal and human pathogens. Specific activities included:

- Improving laboratory assessment tools: to allow for better targeting of technical support and training;
- Developing and rolling out training modules: on diagnosing highly-infectious diseases;
- Improving laboratory management practices: related to biosafety and biosecurity; and
- "Twinning" laboratories: with laboratories in developed countries; and
- Expanding monitoring: of antimicrobial resistance rates among priority bacterial pathogens.

RESPOND focused on pre-service workforce training and strengthening outbreak response capacity. Specific activities included:

- Networking 34 Schools: of public health, veterinary medicine, and environment in both Africa and Southeast Asia to promote a “One Health” approach among future graduates;
- Developing an outbreak response algorithm: for health events where the cause has not yet been identified; and
- Supporting outbreak response: when requested.

At the country level, the EPT partners worked with governments and other key in- country and regional partners to enhance the understanding of viral distribution and key drivers of disease emergence from:

- Deforestation;
- Land use change;
- Wildlife trade; and
- Livestock product demands.

This information, along with other EPT investments, can strengthen and improve country-level capacities for routine infectious disease detection/surveillance and outbreak response as well as risk-mitigation strategies. The efforts were intended to safeguard human and animal health and livelihoods in locations in Africa, Asia, and Latin America where new pandemic threats are likely to emerge. It focused on:

- Helping these countries detect viruses with pandemic potential;
- Improving laboratory capacity to support surveillance;
- Responding in an appropriate and timely manner;
- Strengthening national and local response capacities; and
- Educating at-risk populations on how to prevent exposure to these dangerous pathogens.

Appendix 2 – Modeling and Numerical Simulation of the Coronavirus Pandemic

The underlying mathematical principles are the same for all models, *albeit* some variations may exist between the different modeling schools. I shall distinguish between the several models in existence:

Basic coronavirus models

All the basic models (also known by the acronym SIR) posit three main states:

- **S** (susceptibility to the virus);
- **I** (infection by the virus); and
- **R** (either recovery or death). Further, R is presumed to be immune to the virus so it can no longer pass on the infection. This group also includes people with natural immunity.

In mathematical parlance, S, I, and R are the three independent variables in the differential equations used for the simulation.

The basic SIR model makes two basic assumptions, namely:

1. The mixing of the population of the geographical region of interest (from a village to a city, to a region, to a country, to a group of countries, even to the world) is perfect and even; and
2. Until they recover or die, all people are equally infectious.

Then, this world is seeded with an infection and the results that unfold are studied and analyzed. Some limitations of this basic SIR model are immediately apparent. Thus:

- S should include asymptomatic as well as symptomatic people and the proportion of people with natural immunity to the virus; and people who have been exposed but are not yet infectious;
- R should also include partial recovery leading to reinfection (partial immunity after an initial episode of infection); and
- In any geographical area of interest, people are not perfectly and evenly mixed.

More advanced models

These models incorporate more detailed information on:

1. Population size;
2. Population density;
3. Population age, especially its proportion of old people;
4. Transport links;
5. Size of social networks; and
6. Healthcare provision.

With all this information folded in, people are subdivided into smaller groups (by age, sex, health status, employment, number of contacts, ...) to measure social mixing. Further, virtual copies of any geographical region of interest (city, country, region, or even the world) are built up using differential equations to predict the movements and interactions of population groups in space and time. These are, in turn, seeded with an infection and the unfolding results are analyzed and interpreted. Such quantitative predictions are used by policymakers during an emerging pandemic.

Stochastic models

These models inject some randomness in the simulations such as, for example, would someone in the R group infect an S person when they meet.

Other models also simulate people's activities in different ways:

Equation-based models

Here, individuals are sorted into population groups and groups are broken into smaller, more-representative social subsets to better reflect reality.

Agent-based models

Here, individuals move around and act separately on a given day or in an identical situation. These detailed models necessitate information on households, how individuals travel to work, what they do during their weekend, etc.

To minimize the impact of incomplete data and incorrect assumptions, modelers typically conduct hundreds of simulations by allowing the variables to vary within accepted ranges (called sensitivity analysis).