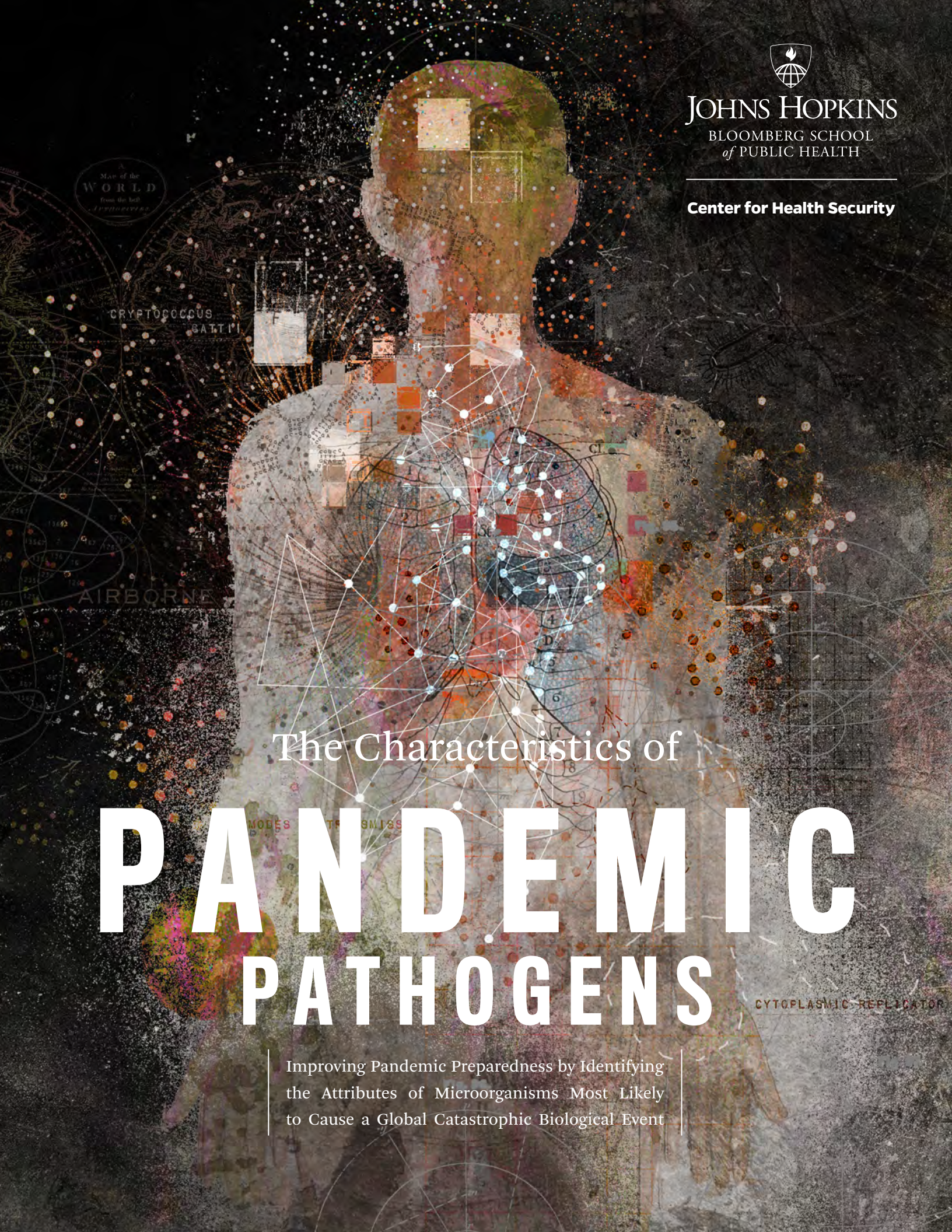
JOHNS HOPKINS
BLOOMBERG SCHOOL
of PUBLIC HEALTH
Center for Health Security
The Characteristics of
PANDEMIC
PATHOGENS
Improving Pandemic Preparedness by Identifying the Attributes of Microorganisms Most Likely to Cause a Global Catastrophic Biological Event

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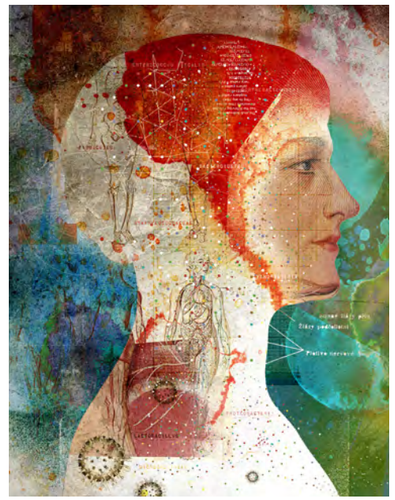

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The Characteristics of PANDEMIC PATHOGENS

Background and Purpose of Report

The Johns Hopkins Center for Health Security conducted this study to elucidate the characteristics of naturally occurring microorganisms that constitute a global catastrophic biological risk (GCBR).

GCBRs are defined as "those events in which biological agents—whether naturally emerging or reemerging, deliberately created and released, or laboratory engineered and escaped—could lead to sudden, extraordinary, widespread disaster beyond the collective capability of national and international governments and the private sector to control. If unchecked, GCBRs would lead to great suffering, loss of life, and sustained damage to national governments, international relationships, economies, societal stability, or global security."

The overarching aim of the study was to provide an inductive, microbe-agnostic analysis of the microbial world to identify fundamental principles that underlie this special category of microorganisms that have potential to cause global catastrophe. Such principles could refine pandemic preparedness by providing a new framework or lens through which to survey the threat landscape of infectious diseases in order to better anticipate, prepare for, and respond to GCBR threats.

Basis of Recommendations

There are several characteristics likely to be common to GCBR-level pandemic pathogens.

Irrespective of the biological class of a pathogen, several attributes are likely to be essential components of any GCBR-level pathogen. These traits include efficient human-to-human transmissibility, an appreciable case fatality rate, the absence of an effective or widely available medical countermeasure, an immunologically naïve population, virulence factors enabling immune system evasion, and respiratory mode of spread. Additionally, the ability to transmit during incubation periods and/or the occurrence of mild illnesses would further augment spread.

Although most classes of microbe could evolve or be manipulated in ways that would cause a catastrophic risk to humans, viruses—especially RNA viruses—are the most likely class of microorganism to have this capacity.

Among the various classes of microbes, many possess some or all of the characteristics necessary to be identified as a GCBR. However, several features of viruses make this class of microbial agents the most likely to cause GCBRs. Viruses possess higher capacity for genetic mutability due to both the structure of their genomes and the generation time for replication in which large numbers of progeny virus are created each day. Additionally, the inability of a virus to be countered with a broad-spectrum antiviral—compared with bacteria, fungi, and parasites—makes viruses the more likely cause of a GCBR.

Within the viral class, RNA viruses merit special concern chiefly because of their higher mutability compared to DNA viruses.

Efforts to create viral catalogs are not synonymous with nor necessarily effective as tools of pandemic preparedness.

Major resource-intensive efforts are currently under way to develop a global virome to catalog as many viral species on the planet as possible. The rationale behind these projects is to develop a full understanding of the breadth of the viral world and to be able to develop better situational awareness of looming threats. The scientific value of such an undertaking is substantial and without question.

However, these efforts will not necessarily translate into better pandemic preparedness, given the sheer numbers of viruses that will be catalogued without a clear means of prioritizing them, the fact that most identified viruses will pose little to no threat to humans, and the recognition that, while a viral cause of the next pandemic is most likely, there is no guarantee it will not be caused by another class of pathogen. The cost-effectiveness of a global viral catalog for diminishing pandemic threats may be less than that of systematically pursuing diagnoses of infectious disease syndromes, as discussed below.

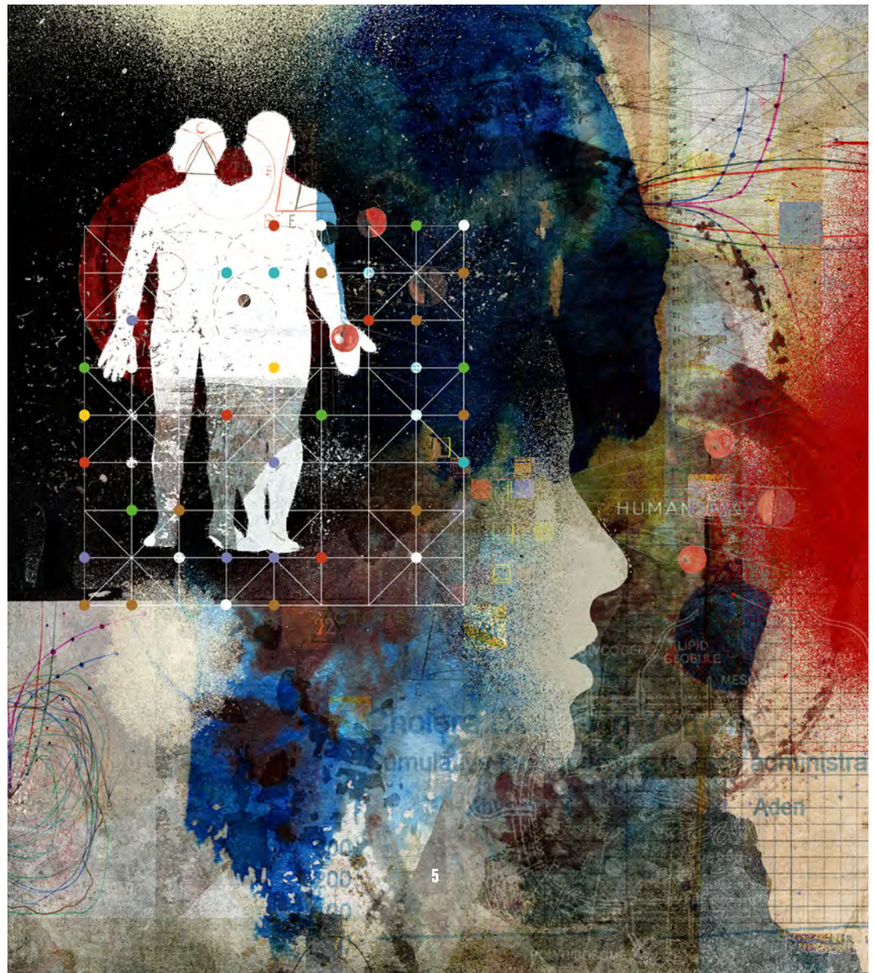
Pursuing diagnoses of infectious disease syndromes provides situational awareness of pathogens that could evolve into pandemic threats.

Aggressive diagnostic testing of infectious disease syndromes such as atypical pneumonia, central nervous system infections, and septic shock in strategic and sentinel locations around the world and over time may provide insight into new or changing patterns of infection. Such a practice would be a radical departure from standard practices in both the developed and the developing worlds, in which syndromic clinical diagnosis, basic microbiological testing, and empiric therapy are often the rule. With the heightened availability of more sophisticated diagnostic testing in both developed and developing nations, it is increasingly possible to have greater insight into the microbiological causes underlying many common infectious syndromes that currently are not routinely pursued to a specific microbiological etiology. Illuminating this biological dark matter that is present in hospitals and clinics worldwide will not only improve treatment but would focus pathogen discovery efforts on established damage-causing microbes.

Human factors and/or the occurrence of complex disasters can elevate pathogens to GCBR levels.

During an outbreak situation, early decisions regarding vaccine policy, resource mobilization, and countermeasure deployment made by political and scientific leaders can be decisive in the control of an outbreak and could prevent many of the downstream cascading effects that affect the healthcare and other sectors. Conversely, decisions—both scientific and political—that lead to harmful or erroneous actions could deepen the consequences of an epidemic or worsen a GCBR.

Additionally, as infectious disease outbreaks occur within a larger sociopolitical, geographic, environmental, and economic context, the presence of concomitant complexities can exacerbate an outbreak and confer GCBR-level status on a microbe that is unable, on its own, to possess such destructive capacity. For example, the record-breaking 2017 outbreak of cholera in Yemen, though not rising to the level of a GCBR, was significantly magnified by the presence of war. Therefore, it is important to realize that outbreaks caused by pathogens not categorized as GCBR-level risks could rise to that level through synergy with external factors.

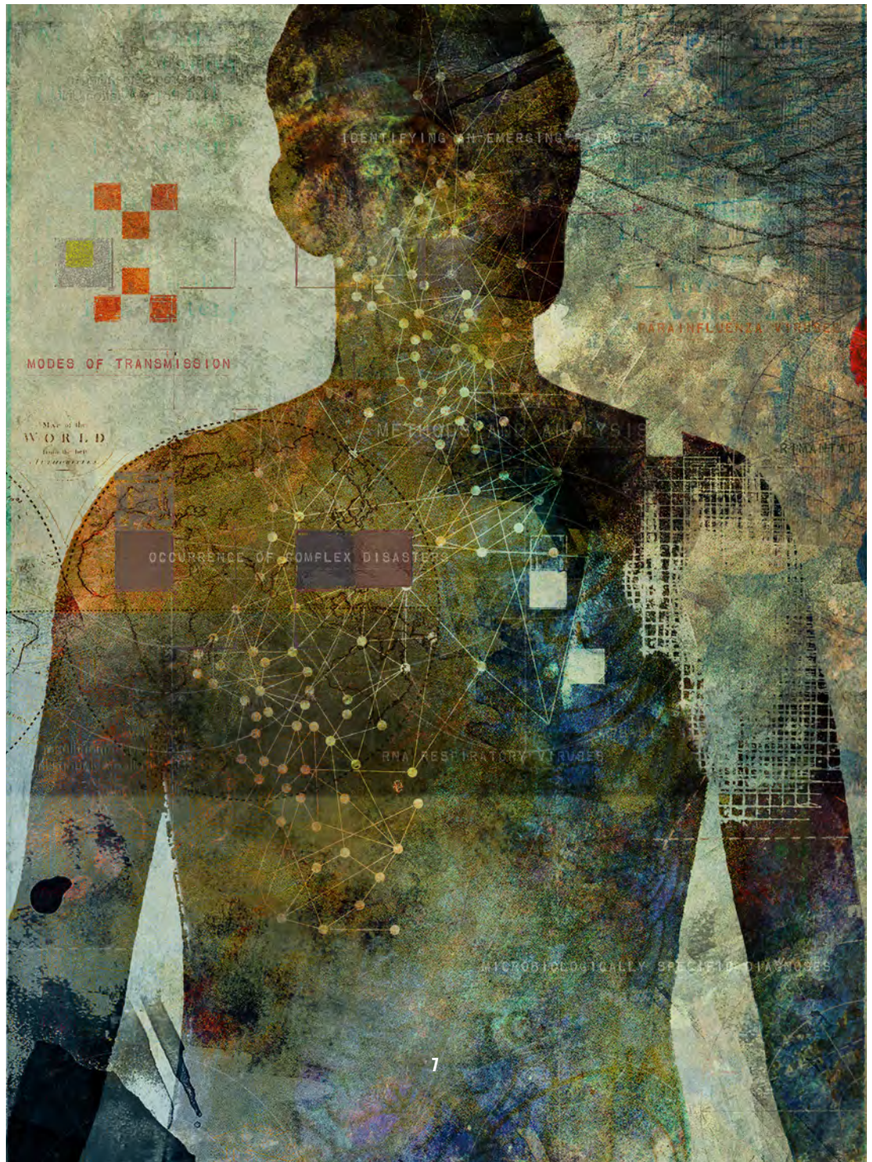


Recommendations to Prepare for GCBR-level Microbial Threats

Preparing for GCBR-level microbial threats as a class is a complex endeavor, with many facets, challenges, and priorities. The following are recommendations that emerged from this study:

- Preparedness against GCBR-level threats should first be focused on those pathogens with the characteristics that are most likely to result in GCBRs. But the work should be flexible enough to encompass new knowledge of pathogens and resist focusing entirely on lists of specific proscribed potential microbial agents. The most probable naturally occurring GCBR-level threat that humans face is from a respiratory-borne RNA virus, and so this class of microbes should be a preparedness priority. However, because other classes of microbes (viral and other) still possess some ability to incite a GCBR-level event, they will continue to merit significant study and appropriate preparedness efforts.
- Historical pathogen list–based approaches should not stand as permanent fixed ideas that stultify thinking on pandemic pathogens. An active-minded approach that seeks to root the pandemic potential of pathogens in their actual traits is one that will foster more breadth in preparedness and proactivity. Incorporating this approach would require a major change in thinking and resource allocation.
- Given the greater concern for respiratory-borne RNA viruses, improving surveillance of human infections with this class of viruses should become a higher priority. Currently, such a system exists for influenza, but other viruses, such as parainfluenza, coronavirus, and RSV, are not given the dedicated resources necessary to track their epidemiology, clinical characteristics, and microbiological traits. Future efforts could build on the success of influenza surveillance and incorporate additional high-priority viruses.
- An increased emphasis on developing a specific pipeline of antiviral agents for RNA respiratory viruses would add resilience against these potential GCBR agents. Today, no such antiviral agents exist outside of influenza that possess high efficacy. Broad-spectrum therapeutics should be pursued given their potential value, even if the likelihood of identifying such medicines remains low. Narrow-spectrum agents should be pursued because of the increased likelihood of identifying candidates.
- Vaccines against RNA respiratory viruses should be pursued with increased priority, as no highly efficacious vaccines, including against influenza, are commercially available today. Vaccines could be used to quench nascent outbreaks or to pre-vaccinate target populations. Ongoing efforts to create a universal flu vaccine should continue and be supplemented, given the risk of a novel influenza A virus to cause a GCBR.
- A clinical research agenda for optimizing the treatment of respiratory-spread RNA viruses should be funded by pharmaceutical companies and medical research agencies and pursued by clinical centers. Important research questions regarding supportive and adjunctive therapy, intensive care unit interventions, and antiviral therapy should be addressed and answered. As many of these viruses circulate and cause disease, there is an opportunity to systematize their study in order to prepare for a GCBR from this class. From these efforts, treatment protocols could be developed for various syndromes caused by this class of microbes that could be relied on for routine clinical care as well as during an emergency outbreak situation.
- Research that could increase the pandemic potential or risk of respiratory-borne RNA viruses or the orthopox viruses should undergo special review, given the potential consequences. Such work should be performed under the appropriate biosafety level protocols.

- Pursuing microbiologically specific diagnoses of infectious disease syndromes in strategic or sentinel locations around the world should become more routine, especially now that diagnostics are becoming more powerful and available. Since it is unclear where the next pandemic pathogen will appear and because there are countless undiagnosed severe infectious disease syndromes (including sepsis, pneumonia, meningitis, and encephalitis) in every hospital and clinic in the world, we need to do more to understand these causes of undiagnosed infectious syndromes, some of which may be the result of a novel GCBR-level agent in its first forays into humans or a changing spectrum of illness in a known agent.



INTRODUCTION

The recent emergence of severe infectious diseases with pandemic potential has triggered much interest in understanding the broader pandemic threat landscape. A substantial proportion of infectious disease preparedness activities have, to date, focused on a historical list-based approach constructed around biological warfare agents and on recent outbreaks (eg, SARS).[1,2] But such an approach is not proactive or forward-looking and will inherently fail to account for agents not currently known or those without historical precedent. Activities that are solely limited to list-based approaches may foster a static non–active-minded approach to the problem and hamper preparedness and lessen resilience. This type of approach was adopted by the United States, and many other nations have followed suit.

For this project, the explicit focus was on threats that pose a global catastrophic biological risk, or GCBR.

WORKING DEFINITION OF GCBR

The Center published a working definition of global catastrophic biological risks—or GCBRs—to facilitate discussion and stimulate critical thinking and work on the topic:

"Those events in which biological agents—whether naturally emerging or reemerging, deliberately created and released, or laboratory engineered and escaped—could lead to sudden, extraordinary, widespread disaster beyond the collective capability of national and international governments and the private sector to control. If unchecked, GCBRs would lead to great suffering, loss of life, and sustained damage to national governments, international relationships, economies, societal stability, or global security."[3]

Given the potentially severe public health consequences of pandemic events, there should be a vital interest in developing and maintaining a flexible, rapid, and robust response capability for pandemic potential emerging infectious diseases (EIDs) by multiple stakeholders, both in and out of government.[4-7] Such an approach should be—but is not now—adaptable to new threats and not exclusively wedded to prior historical notions. A new framework based on probative analysis of the actual traits required by a GCBR-level pandemic pathogen could provide such a basis for developing this type of adaptability.

PURPOSE, METHODS, AND ANALYSIS

Purpose

The Johns Hopkins Center for Health Security (the Center) conducted this study to develop an expert assessment of the traits most likely to be possessed by microorganisms that constitute a global catastrophic biological risk. The results of this analysis could be used to inform preparedness and prediction activities with respect to emerging and reemerging infectious disease threats with the potential to cause severe global spread.

Methods and Analysis

Review of published literature and previous reports

The Center project team surveyed current biomedical literature on the topic of emerging infectious disease characteristics, the pathogenic potential of microbes, and related topics. The literature review was microbe- and species-agnostic, encompassing all classes of microorganisms and host species. The literature review was accomplished with extensive PubMed searches on these subjects. Relevant US government policy and strategy were reviewed.

Interviews

The Center project team interviewed more than 120 technical experts (listed in Appendix A) who work in and are intimately knowledgeable about this field. Interviewees were drawn from academia, industry, and government. Our goal was to ascertain the experts' views about the essential traits needed for a pathogen to become a GCBR, to contextualize historical outbreaks in light of these traits, and to determine which currently known infectious disease agents possess such characteristics.

Pandemic Pathogens Meeting

The Center project team completed a preliminary analysis that synthesized the results of our literature review and expert interviews. Those findings were used to design and facilitate a meeting held on November 9, 2017, that included many of those who had been interviewed for this project. The meeting was held at the Johns Hopkins Center for Health Security in Baltimore, MD. The purpose of the meeting was to gain additional insight and input into the project analysis, examine assumptions, and test possible recommendations. Participants included representatives of US and foreign academic institutions, the federal government, and other independent subject matter experts. Attendees are listed in Appendix B.

Conclusions

This final report presents the Center's assessment of the traits most likely to be possessed by a GCBR-level pandemic pathogen, informed by our expert interviews, literature review, and the views of meeting participants or sponsors who met on November 9, 2017, at the Center. Based on these traits, the assessment describes the classes of pathogens most likely to become GCBRs. The findings and recommendations in this report are those of the Center and do not necessarily reflect the views of those who were interviewed or who attended the meeting at the Center.

Funding

This project was funded in whole with funds from the Open Philanthropy Project.

BASIS 1: There are several characteristics likely to be common to GCBR-level pandemic pathogens.

The Alchemy of a Pandemic Pathogen

When a pathogen has the capacity to cause a pandemic, it will possess several attributes that, in combination, elevate its status above that of a microbe that is capable of causing only sporadic or limited human infections. These traits can be divided into several categories: mode of transmission, timing of transmission, host population factors, and intrinsic microbial characteristics. Many of these characteristics have been captured and are reflected, in equation form, by Casadevall.[8]

Modes of Transmission

Microbes have varied routes of transmission, ranging from blood and body fluids to vector-borne to fecal-oral to respiratory (airborne and respiratory droplet). While each mode of transmission is capable of causing large outbreaks if sustained human-to-human transmission is possible and left unchecked, certain modes of transmission are more amenable than others to intervention. For example, the spread of an infectious disease caused by blood and body fluid transmission can be halted with infection control measures such as gloves or gowns.

Of the various modes of transmission, the respiratory route is the mechanism most likely to lead to pandemic spread. This is chiefly due to the fact that interventions to interrupt this method of spread are more difficult to implement when the simple and universal act of breathing can spread a pathogen. The prolific spread of influenza, pertussis, measles, and rhinoviruses are testament to this fact.[9]

By contrast, although pathogens spread by the fecal-oral route, such as *Vibrio cholera* and the hepatitis A virus, can generate explosive outbreaks, even a modicum of sanitary infrastructure can quench the outbreak.

Vector-borne outbreaks are a special case of a nonrespiratory spread agent. Indeed, the only postulated extinction of a mammalian species by an infectious organism, the Christmas Island rat, was caused by a vector-borne trypanosome.[10] For most of the agents that use this class of transmission, the spread is limited by a geographically and climatologically restricted vector habitat. Humans can protect against vectors, and they can change where they live, but the Christmas Island rat could not. These factors have generally served to limit the pandemic potential of microbes that are spread by vectors.

Exceptions to this general limitation of vector-borne viruses include microbes spread by *Anopheles* and *Aedes* mosquitoes. Pathogens spread by these mosquitoes have higher pandemic potential, given the geographic breadth of their spread. For example, most of sub-Saharan Africa is hospitable to the malaria-transmitting *Anopheles* mosquitoes, while residents in 75% of US counties—as well as half the world's population—are regularly exposed to *Aedes* mosquitoes that serve as vectors for high viremia flaviviruses and alphaviruses. Such phenomena are borne out by the prolific spread of dengue, chikungunya, and Zika.[11,12]

Timing of Transmission

The onset and duration of the period when a person is contagious during an infection also plays a major role in spread. Diseases that are contagious during a late stage of infection, when infected people are very sick and therefore have more limited opportunities for spread, may be delimited in their spread. On the other hand, diseases that are contagious prior to symptom development, during the incubation period, or when only mild symptoms are present have greater opportunities for spread as infected individuals are able to conduct their activities of daily living with little or no interruption.

Modeling studies with simulated outbreaks have shown that the presence or absence of this timing of transmission factor can be decisive in whether an outbreak can or cannot be controlled. If a microbe is contagious before a person is seriously ill while the disease is still incubating, then there is higher potential for pandemic spread. Historical examples reinforce this idea, as the only human infectious disease to be vanquished from the planet—smallpox—was one that was not contagious during the incubation period.[13] By contrast, a microbe such as the influenza virus, which is contagious prior to symptom development and has a wide range of clinical severity, is able to infect widely and is not amenable to control.[14]

Host Population Factors and Intrinsic Microbial Pathogenicity Characteristics

Microbial pathogenicity cannot, in reality, be separated from host characteristics. As elucidated by Pirofsky and Casadevall's host damage framework, disease is a complex interplay between a host immune system and a microbe.[15] In congruity with this paradigm, host features and microbial pathogenicity are discussed together.

For a microbe to cause a GCBR-level pandemic, it will be necessary for a significant proportion of the human population to be immunologically naïve to the agent so that the microbe would have a high number of susceptible humans to infect. Additionally, large quantities of a sufficiently effective countermeasure (vaccine or antimicrobial agent) would not be available. Immunologic naïveté would be expected with a zoonotic pathogen. The microbe, correspondingly, would have to possess the ability to evade the host immune response through virulence factors, immunological camouflage, or other features that allow a productive infection to ensue.

Additionally, human receptors that are utilized by a pandemic-causing microbe would likely be widespread in the population, facilitating permissive infection in the majority of humans. Receptors may also provide target organ tropism for the agent, allowing severe disease to occur (eg, lower respiratory tract, central nervous system).

Case fatality rates (CFRs) need not be inordinately high to cause a GCBR-level event, as evidenced by the 2.5% CFR reported for the 1918 influenza pandemic—the event closest to an actual human GCBR in the modern era.[16] A low but significant CFR adheres to the host density threshold theorem. According to this commonly held theorem, a microbe that kills too many of its hosts will run out of susceptible hosts and be extinguished.[17] While this may be true of pathogens that are closely linked to one host species, it is not applicable to sapronotic diseases such as amoebic encephalitis and cholera (in certain contexts), which can infect and kill without jeopardizing future transmission or survival. Indeed, many extinction-level amphibian infectious diseases are sapronotic in nature, such as the chytrid disease of salamanders and frogs.[18]

Additionally, a GCBR-level event may not confer direct mortality. Reproductive effects (ie, in the manner of rubella or Zika) or carcinogenic effects (eg, HTLV-1) could, in many ways, be highly detrimental to the future of humanity, as they could lead to significant curtailment of lifespans and diminishing birth rates, which could ultimately result in significant population collapse.[19,20]

BASIS 2: Although most classes of microbe could evolve or be manipulated in ways that would cause a catastrophic risk to humans, viruses—especially RNA viruses—are the most likely class of microorganism to have this capacity.

Given the right context, any microbial organism could be thought of as a GCBR risk. However, the most likely manifestation will be a virus, and among the viral groups, those whose genomic composition is RNA have the most potential to become GCBRs.[21]

Bacteria: Broad-spectrum Antimicrobials Limit Pandemic Potential of Pathogens

Historically, bacterially caused infections such as plague have had incredible impacts on the human species.[22] However, the development of antibacterial therapies, beginning with the sulfonamides in 1935 and then penicillin in 1942, have severely limited the ability of this class of microbes to cause a GCBR-level pandemic. In addition, the relatively slower speed of replication and accumulation of mutations also disadvantages this class over viruses. For example, a human infected with the hepatitis C virus (an RNA virus) produces trillions of virions per day, whereas the doubling time of *Yersinia pestis*, the cause of plague, is 1.25 hours.[23,24]

The public health crisis of multiple-drug-resistant bacteria, such as carbapenem-resistant Enterobacteriaceae (CRE) and others, is very alarming.[25] The spread of these bacterial agents, for which few if any treatments exist, threatens the entire practice of modern medicine, from cancer chemotherapy to joint replacement therapy. However, these organisms, which have variable attributable mortality, tend to be unable to efficiently infect human hosts that are not compromised or hospitalized. As such, the risk to the general public is constrained.

Large outbreaks of cholera and plague at the time of this writing (2017) represent true public health emergencies in Yemen and Madagascar, but their spread reflects severe infrastructure deficiencies caused by war and supply constraints rather than true global pandemic risk.[26,27]

Fungi: Thermal Growth Restriction Limits Pandemic Potential

Fungi represent prolific pathogens outside of the mammalian species. Outbreaks of chytrid fungal disease in frogs and salamanders as well as snake fungal disease represent true existential threats to affected species.[18] However, fungi are largely thermally restricted, and only limited members of this class of microbes can infect warm-blooded organisms such as mammals.[28] Indeed, a fungal filter is hypothesized to have existed and may be partly responsible for mammalian warm-bloodedness. The success of the mammalian-adapted fungus that causes white-nose syndrome in bats is facilitated by the lower body temperature that occurs during their hibernation.[29]

Human infections with fungi tend to be severely damaging only in an immunocompromised host. The human innate immune system contends with countless fungal spores that are present in every breath of air. As such, many endemic fungal diseases, such as histoplasmosis or coccidioidomycosis, do not cause harm in the majority of immune-competent humans infected. Even newly emerging fungi such as *Candida auris* and *Cryptococcus gattii* are largely subject to this limitation.[30,31] One of the most widespread fungal outbreaks—the Exserohilum fungal meningitis outbreak—was abetted by direct injection of a contaminated medical product into the spinal region of humans, which is not a usual mechanism of infection.[32]

Without thermal adaptation (which might be feasible with deliberate manipulation), fungi, many of which are sapronotic and do not rely on or need mammalian hosts, will not constitute a pandemic threat to humans.

Prions: Select Transmission Characteristics Limit Pandemic Potential

Prions—transmissible infective proteins—are one of the most fascinating and understudied of infectious agents. These agents, which are responsible for diseases such as kuru and new variant Creutzfeldt-Jakob disease (vCJD, the human form of "mad cow disease") in humans, cause scrapie, chronic wasting disease, and bovine spongiform encephalopathy in other mammalian species.[33]

Though highly damaging to humans and other species they infect, prions require specific conditions for spread. New variant Creutzfeldt-Jakob disease was to date the most highly publicized outbreak of a human prion disease; it resulted in 229 human cases tied to the consumption of beef products primarily in England in the 1990s and 2000s.[34] Other modes of transmission of CJD tied to iatrogenic spread via contaminated surgical instruments or cadaveric hormone products ceased once protective measures were put in place.[35] Kuru, a geographically restricted prion disease, was spread via human cannibalism in Papua New Guinea, and the outbreak abated once that practice was ended in the 1960s.[36]

The transmission characteristics of prion diseases are such that very extraordinary circumstances, on par with human cannibalism or massive food contamination, must be present for a GCBR-level risk to be present for humans. Additionally, and almost by definition, such an event would be slow-moving (prions were once known as "slow viruses").

Protozoa: Delimited Pandemic Pathogen

Protozoal organisms have the distinction of being the only infectious disease to have caused the extinction of a mammalian species. The Christmas Island rat, unable to outrun its vector, was felled by a vector-borne trypanosome (*T. lewisi*) during the early 20th century on the Australian island.[10] Human forms of trypanosomiasis have not risen to such a level of concern.

Human protozoal infections have exerted tremendous pressure on the species, and it is hypothesized that half of all humans who have lived died of malaria, which still kills approximately half a million humans annually.[37] However, the development of antimalarial compounds and vector avoidance strategies have proved successful when they are able to be employed appropriately, and they have relegated malaria to a pathogen whose impact is amenable to control. Nonetheless, one aspect of malaria is of particular concern: the development and spread of artemisinin-resistant forms, which render treatment extremely challenging with little to no effective antimalarial agents left for use. Largely confined to specific regions of Asia, such as Cambodia and Myanmar, this organism poses severe treatment challenges, and, if it were to spread to Africa, could represent a continent-level biologic risk.[38]

Other Microbial Classes Have Delimited Pandemic Risk

Amoeba, ectoparasites, and helminths all have delimited pandemic risk, as they are constrained by pathogenicity, transmissibility, or both. Clonally transmissible tumors—such as the notable devil facial tumor disease in Tasmanian devils—are rare occurrences in humans, with restricted modes of transmission (maternal-fetal, organ transplantation).

Space-adapted organisms (eg, salmonella that originates on Earth but spends time in the space station before coming back to earth) can exhibit enhanced virulence; however, they still are susceptible to antibiotic treatment and normal control measures: There is no evidence they pose greater epidemic risk than normal salmonella.[39] An alien microbe species that is obtained on Mars or meteorites and brought back to earth, one of the focuses of the planetary protection program at the National Aeronautics and Space Administration (NASA), were not deemed by our interviewees and meeting participants to be likely to pose a threat. And if such a species were found, it would be unlikely to be adaptable to an Earth-like planet environment, as adaptations to its home planet's markedly different environment would likely preclude adaptations to Earth. Even though the chances of serious biological risk posed by such a sample return are deemed to be low, there are many uncertainties, and the highest-level biocontainment procedures are being considered for specimens that might harbor such non–Earth-based organisms.[40]

Viruses: Several Factors Contribute to Heightened Pandemic Risk

Traditionally, viruses have been ranked at the highest level of pandemic risk, and dedicated preparedness efforts often focus solely on viruses. A disproportionate focus on viruses is justified, however, based on several aspects unique to the viral class of microbes.

The high rate of replication of viruses—for instance, over 1 trillion hepatitis C virions are produced per day in a human infection—coupled with the mutability inherent in such short generation times give viruses an unrivaled plasticity. This plasticity allows for host adaptability, zoonotic spillover, and immune system evasion.

The lack of a broad-spectrum antiviral agent—like ones available for bacterial and even fungal organisms—also confers a special status on viruses. With no off-the-shelf treatment available to contain a viral outbreak, containment, in its early stages, will be done in the absence of a medical countermeasure.[41]

There is a strong consensus that RNA viruses represent a higher pandemic threat than DNA viruses.[42] This assessment is derived from the fact that the stability of RNA as a genomic material is less than that of DNA, giving more genomic pliability to the RNA viruses. However, DNA viruses such as smallpox challenge this assumption, and concern exists surrounding the related risks of monkeypox viruses, which are increasingly spreading in the absence of a smallpox vaccine campaign.[43] As monkeypox outbreaks continue to occur with longer chains of transmission, employing smallpox vaccines in target populations might be considered.

Another aspect of viral characterization is the location of replication. Pandemic potential viruses have been shown in studies to be more likely to replicate in the cytoplasm of a cell.[44,45] This is postulated to be due to the higher affinity a virus must have for a particular type of host to be permitted entry into its nucleus, delimiting its zoonotic potential as it will be strongly tied to its usual host. In general, it is DNA viruses that tend to have a nuclear replication cycle, while RNA viruses have a cytoplasmic cycle. Strikingly, smallpox—historically one of the highest pandemic potential DNA viruses—is a cytoplasmic replicator, while influenza—one of the highest pandemic potential RNA viruses—has a nuclear replication cycle. The exceptions to these rules argue against any overly strict adherence to them.

Other factors that may affect a virus's pandemic and GCBR potential include a segmented genome (as exemplified by influenza viruses), genome size, and host viremia (eg, vector-borne flaviviruses). For example, the flu virus's segmented genome makes novel genetic assortment an eventuality, while a large genome may prevent nimble mutations. However, with each characteristic it is impossible to find a general rule, as exceptions abound.

Among currently studied viruses, the influenza A viruses, with special note taken of avian viruses such as H7N9, were almost universally thought to be of greatest pandemic risk based on historical outbreaks and viral characteristics.[46,47] Such an analysis is reflected in the Centers for Disease Control and Prevention (CDC) Influenza Rapid Assessment Tool (IRAT) ranking of H7N9 as the most concerning influenza virus strain.[48]

There are several viral groups other than the orthomyxoviruses (which include the H7N9 strain of influenza A) that are spread by respiratory routes, that possess RNA genomes, and that merit enhanced attention: paramyxoviruses (especially these 3 genera: respirovirus, henipavirus, rubulavirus), pneumoviruses, coronaviruses, and picornaviruses (especially these 2 genera: enterovirus and rhinovirus). Based on our analysis, it is from these viral groups that the most likely source of a GCBR-level threat will emerge.

BASIS OF RECOMMENDATIONS

BASIS 3: Efforts to create viral catalogs are not synonymous with nor necessarily effective as tools of pandemic preparedness.

There are currently several efforts under way by groups such as EcoHealthAlliance and Global Viral Forecasting to construct viral catalogs of as many viruses as possible. Funding is primarily from the US government via the United States Agency for International Development (USAID); costs are over $1 billion.[49] The explicit aim of these projects is to reduce the uncertainty of outbreaks by extensively cataloging as many viral species as possible, so that a virus that causes a disease is less likely to be truly unknown. At the meeting and interviews for this project, several experts expressed concern that, while efforts to catalog and sequence viruses indiscriminately would provide new scientific discovery, we should not expect that it will measurably improve pandemic preparedness. Broad viral sequencing would, doubtless, uncover many novel viruses.

However, the vast majority of discovered viruses will not have the ability to infect humans, let alone cause harm; only a few viruses possess this ability. And while a pandemic is most likely to be viral in nature, it is not the case that only a virus is capable of causing it.

There is no doubt that viral discovery undertaken by these projects has great scientific value and will lead to many new discoveries in virology; however, such findings, in themselves, will not be enough to have a direct impact on pandemic preparedness. This work would be better pursued with the objective of fundamental viral scientific discovery, rather than the goal of near-term improvement in pandemic preparedness.

BASIS 4: Greatly increasing specific diagnoses of infectious disease syndromes in clinical environments would provide more actionable, relevant information and would increase our chances of identifying an emerging pathogen with dangerous pandemic potential.

In the clinical practice of medicine, syndromic diagnosis—that is, making a nonspecific diagnosis, such as "sepsis," "pneumonia," or "viral syndrome," with little to minimal laboratory testing—is the norm. Specific diagnosis (ie, sending patient samples for definitive laboratory diagnosis) is often eschewed if it does not affect clinical management, is costly, is not revealed with routine tests, and/or if the patient recovers. This practice has become enshrined not only in resource-poor areas in which access to diagnostic testing may be limited, but also in resource-rich areas, like North America and Western Europe, where specific diagnoses are viewed as superfluous.

However, the yield from pursuing an etiologic diagnosis in infectious syndromes such as atypical pneumonia, sepsis, encephalitis, meningitis, and clinically significant fevers of unknown origin may be considerable, as it will provide important insight into the ongoing torrent of threats posed by the microbial world. By causing an infection with enough severity to come to medical attention, the culpable microbes have already established that they are damage-causing pathogens to humans—a feat that only a sliver of the microbial world can accomplish.[50] Many of these microbial diagnoses cannot be made through the routinely ordered diagnostics. Therefore, a special effort would need to be made to get to a microbial diagnosis. If that were to be done more frequently and at a more strategic level around the world, it would provide an opportunity to develop new situational awareness regarding which microbes are circulating and infecting humans—information that is clinically valuable in its own right and more attuned to uncovering GCBR-level pathogens than broad viral cataloging.

Such efforts should not be limited to exotic "hot spots" of disease emergence, but should be practiced in localities that are broadly representative of where these conditions occur. Particular hot spots of emergence due to the presence of unique risk factors may be higher yield overall, but they should not be the sole sites of investigation. Infectious disease emergence can occur anywhere, as evidenced by the 2009 H1N1 pandemic, which was first recognized as the etiology behind a mild pediatric upper respiratory infection in California, and West Nile Fever emerging in cases of undifferentiated encephalitis in the New York City metropolitan area in the late 1990s.[51,52]

Such a program would have significant cost and infrastructure implications in resource-constrained regions, so it would be most logical to set up sentinel or strategic sites for pursuing this level of microbial diagnosis in ways that are broadly representative. In developed nations such as the United States, these programs are available but underutilized because of lack of awareness or perceived lack of value by clinicians, for whom it will often not likely change therapeutic decisions.

BASIS 5: Human factors and/or the occurrence of complex disasters can elevate pathogens to GCBR levels.

Many participants in the project voiced the view that any microbe's pandemic potential could be substantially enhanced by human factors and poor preparedness, which could exacerbate a pathogen's spread or damage-causing potential.

Specific issues identified included gaps in hospital preparedness, medical countermeasure manufacturing capacity, medical countermeasure manufacturing locations, impacts on critical workforce members, and cascading effects on vital programs such as food production. For example, concentration of intravenous fluid manufacturing plants in Puerto Rico created massive shortages after a hurricane took the plants offline in 2017.[53] The inability of hospitals to surge to meet enhanced patient needs for ventilators or ICU beds is another potential constraint.

Human factors could also take the form of mistaken actions that are based on political considerations but are not supported by an evidence-based medical rationale, or scientific mistakes based on human error, such as misidentifying a microbe or misinterpretation of scientific or epidemiologic data. For example, early in the SARS outbreak, mistakes regarding the etiology of the viral agent occurred, and the 2014 West African Ebola outbreaks were initially thought to be cholera, delaying response efforts for months.[54]

Some participants were of the view that such factors as these would outweigh any intrinsic property possessed by a microbe or any physiologic vulnerability possessed by a human. Magnification by human error could cause delays in response or awareness, allowing a pathogen to spread wider and deeper into the population and rendering containment more difficult, sowing panic, and severely stressing the healthcare infrastructure of a region.

RECOMMENDATION 1: Preparedness against GCBR-level threats should have a focused approach with some flexibility.

Though the highest-ranked pandemic potential pathogens were RNA viruses spread via the respiratory route, it is important to distinguish between what is most likely and what is possible. RNA viruses spread via the respiratory route merit prioritization, but other classes of microbes, such as bacteria, fungi, and protozoa, should not be dismissed.

Since RNA viruses that are spread via the respiratory route have the characteristics that are most concerning in terms of their ability to cause global catastrophic threats, surveillance, science, and countermeasure development programs and efforts should logically allocate significant resources to them.

Except for influenza and certain coronaviruses, this is largely not the case. In addition, as we said above, other classes of infections should not be ignored given their pandemic potential characteristics.

Cultivating and maintaining expertise in the epidemiology, surveillance, and pathogenicity of all classes of microbes, with explicit incorporation of a One Health approach—which incorporates and integrates information from infectious diseases of plants, amphibians, and reptiles—will help foster the flexible and robust capacity needed for pandemic preparedness and GCBR work.

RECOMMENDATION 2: Historical pathogen list–based approaches should not stand as permanent fixed ideas that stultify thinking on pandemic pathogens.

Pathogen-based lists, both US and global, based on historical incidents and biosecurity preparedness activities, were responsible for galvanizing early activities in the field of pandemic preparedness and have helped drive many important contributions. But these lists tend to engender a static approach to pandemic preparedness by prematurely closing off the pandemic possibilities of agents not included in the original lists.

Lists, in effect, can become frozen in the minds of those in the field and may be viewed as exhaustive rather than as starting points. Additionally, inclusion in lists can also be sought for political (and not epidemiologic) reasons if inclusion carries with it the prospect of enhanced funding for a long-neglected endemic problem.

One of the chief rationales behind this project was to attempt to move away from a strict list-based approach when considering pandemic threats and to develop a framework firmly rooted in the facts of a microbe's biology and epidemiology. We propose that risk assessment be rooted in the actual traits that confer GCBR or pandemic risk on a pathogen rather than exclusively historical emerging infectious disease or bioweapons-based considerations. Such an approach would recognize the value of lists but also recognize their limitations. Lists should be modifiable based on the result of thorough medico-scientific analyses and less subject to the vicissitudes of politics or historical bias. These improvements will add rigor that, in the end, will serve to ground pandemic preparedness and GCBR-related activities more firmly.

RECOMMENDATION 3: Improving surveillance of human infections with respiratory-borne RNA viruses should be a higher priority.

As respiratory-borne RNA viruses have been identified as possessing heightened pandemic potential, it will be important to establish surveillance activities that reflect this concern. Currently, of the respiratory-borne RNA viruses, only influenza and certain coronaviruses receive high priority for surveillance.

While nascent efforts to understand coronaviruses, in the wake of SARS and MERS, exist, there is no systematic laboratory surveillance of coronavirus infections in humans. Similarly, no such program exists for rhinoviruses, parainfluenza viruses, RSV, metapneumoviruses, and similar viruses. Since this class of viruses is most likely to hold the future pandemic pathogen, constructing an influenzalike surveillance apparatus should be a priority.

Such an approach would focus on human infections, characterizing the epidemiology, virologic features, antiviral susceptibility (if applicable), and clinical manifestations in a fashion that mimics the extensive influenza surveillance conducted by the CDC and other international entities.

RECOMMENDATION 4: An increased emphasis on developing a specific pipeline of various antiviral agents for RNA respiratory viruses—both broad spectrum and virus-specific—would add resilience against potential GCBR agents.

Currently, outside of anti-influenza antivirals, there is only one FDA-approved antiviral for the treatment of respiratory-spread RNA viruses (ribavirin). Of the 5 FDA-approved influenza antivirals—amantadine, rimantadine, zanamivir, oseltamivir, and peramivir—all target influenza viruses specifically and have no activity outside influenza, with 2 influenza A–specific agents (amantadine and rimantadine) rendered virtually obsolete because of resistance. The other antiviral agent (inhaled ribavirin) is approved for the treatment of respiratory syncytial virus (RSV) but has very limited use due to poor efficacy and major toxicity concerns for both RSV and parainfluenza viruses.

There are currently no approved antivirals for any other respiratory-spread RNA viruses in the world. Prioritization of antiviral compounds against this group of viruses may lead to acceleration of drug development and (government and nongovernment) incentivizing programs. Such antiviral compounds would have an advantage over many other emerging infectious disease countermeasures: These viruses exact a considerable toll in the form of community infections each year, providing a basis for a traditional pharmaceutical market as well as one for emerging infectious disease.

Pursuing not only broad-spectrum RNA antivirals, but also those specifically targeted to specific viruses such as RSV, would increase the likelihood of yield.

Nontraditional molecules, such as monoclonal antibodies and immunomodulators, should also be investigated for a role in the treatment and prevention of RNA virus respiratory infections.[55] Such adjunctive treatments may lead to improved clinical outcomes. To date, only one virally targeted monoclonal antibody is FDA-approved: palivizumab for prevention in high-risk infants.

RECOMMENDATION 5: Vaccines against RNA respiratory viruses, including a universal influenza vaccine, should be pursued with increased priority.

As with the above discussion regarding antivirals, the need for vaccines against respiratory-borne RNA viruses should also be prioritized. Currently, aside from influenza, for which a moderately effective but technically limited vaccine exists, there are no other vaccines for respiratory-borne RNA viruses. Experimental vaccines targeting RSV have made it to late clinical development only to fail.

Several important initiatives in this realm do exist and could be augmented to move beyond specific targets that have already been recognized. For example, the Coalition for Epidemic Preparedness Innovation (CEPI) has selected a coronavirus (MERS-CoV) and a paramyxovirus (Nipah) for vaccine development incentivizing.[56] Such a program could, in potential future iterations, select more vaccine targets from this group of viruses and even encourage the development of broadly protective vaccines against groups of viruses—for example, a vaccine that protects against all 4 strains of human parainfluenza viruses, both MERS and SARS CoVs, and both Hendra and Nipah viruses.

Additionally, the heightened interest at the National Institutes of Health (NIH) in a universal influenza vaccine in the wake of the moderately severe 2017-18 influenza season should be channeled to provide significantly increased resources to this endeavor.[57] As certain avian influenza viruses are of the highest threat tier, a universal influenza vaccine (even one that just protects against A strains) could substantially hedge against an influenza virus attaining GCBR status.

RECOMMENDATION 6: A clinical research agenda for optimizing the treatment of respiratory-spread RNA viruses should be funded by pharmaceutical companies, governments, and medical device companies and pursued by clinical centers.

As was evident during the 2009 influenza pandemic and subsequent influenza seasons, the treatment of influenza is suboptimal, despite evidence-based guidance. The status of the treatment for other respiratory viruses is even less defined.

While there currently is not a robust antiviral armamentarium against these viruses, there are important clinical questions that occur with their treatment that merit further study. For example, what adjunctive therapies are useful? What co-infections may be present? At what stage of illness are rescue oxygenation devices warranted? As many of these viruses are highly prevalent in the community and are frequently encountered by clinicians in both outpatient and inpatient settings, finding answers to these questions would render clinicians more adept at dealing with pandemic versions of these viruses.

With respect to influenza, there is a growing literature on the use of antiviral agents in combination with anti-inflammatory agents such as nonsteroidal anti-inflammatory agents (NSAIDs) and macrolide antibiotics.[58] Untangling the nuances of these treatment effects in order to develop robust guidance would have an impact on the ability to cope with an influenza-driven GCBR.

RECOMMENDATION 7: Special review is warranted for respiratory-borne RNA virus research that could increase pandemic risks.

Because of the higher likelihood that a GCBR-level threat might emerge from the group of RNA viruses with respiratory spread, special attention to research on these agents is warranted if the work could increase pandemic risks. While much research on this class of viruses is low risk, experimentation on antiviral resistance, vaccine resistance, and enhanced transmission, for example, could raise major biosafety concerns if a biosafety breach occurred. The 1977 appearance of the H1N1 influenza A strain was thought to have resulted from laboratory escape.[59] It is important to understand the kinds of work being performed with these agents and, in particular, to know of experiments that are being done or are being proposed that would result in increased pandemic risks. Those experiments should have their own special review and approval process that is consistent with the risks.

RECOMMENDATION 8: Pursuing microbiologically specific diagnoses of infectious disease syndromes in all locations globally should become more routine.

As unknown infectious syndromes abound in all locations, and any given infectious syndrome may have as its etiology a potentially unknown or unappreciated microbe, specific diagnosis should be a routine endeavor. Atypical pneumonias, central nervous system infections, and even upper respiratory infections often are treated without any etiologic agent being identified.

As diagnostic technologies and devices improve in breadth, speed, and ease of use, the increasing uptake of these devices will provide a new opportunity to enhance situational awareness of an infectious syndrome in any location where they are deployed. Such devices are currently being used in research projects in the developing world. The more routine use of devices, such as multi-analyte molecular diagnostic devices, has the capacity to provide a fuller picture of the microbiological epidemiology of any given syndrome, illuminating what has heretofore been biological dark matter.[60,61] Coupled with heightened surveillance of respiratory-borne RNA viruses, the ability to capture an early signal of a potential pandemic pathogen will be greatly enhanced.

To date, certain considerations have limited the uptake and use of these devices: cost, perceived lack of clinical impact, and constraints on hospital resources such as isolation beds. Impacts on hospitals might be noted in laboratory testing volume as well as costs. However, when these devices are viewed in the context of pandemic preparedness, the cost-effectiveness calculation should change. These considerations could be moderated if they are considered part of a hospital's emergency preparedness activities and not exclusively as clinical (they also have benefit for antibiotic stewardship activities in both inpatient and outpatient settings). In fact, the use of these devices should be considered on par with mechanical ventilators, vaccines, antivirals, and antibiotics in the context of pandemic preparedness. Pilot projects demonstrating the feasibility of procuring such devices for infectious disease emergency preparedness could be conducted.

FUTURE DIRECTIONS

As pandemic preparedness and prediction mature, the integration of data from new technologies will have the potential to have a significant impact on human resilience to GCBR-level threats. Employing new tools in an adaptable framework that seeks to highlight the features of highest priority classes of pathogens will yield new insights. As diagnostic technology rapidly advances, is simplified, and is widely distributed over the next decade, pandemic pathogens will be more readily identified at earlier stages worldwide, allowing preparedness activities to be more proactive.

CONCLUSION

This report is an expert assessment of the traits of GCBR-level pandemic pathogens. We found that it is possible to develop an adaptable open-ended pathogen-agnostic framework of pandemic pathogens that is based on their biologic and epidemiologic traits. We hope that such a framework will shift preparedness activities away from closed list-based approaches and foster a more active-minded approach to this problem that will, in the end, guard against such an event occurring or enable the mitigation of its most severe consequences.

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APPENDIX A: LIST OF EXPERTS INTERVIEWED

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Don Burke, University of Pittsburgh
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Nancy Cox, CDC
Donald Craven, Lahey Clinic Medical Center
Jim Curran, Emory University
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Peter Hotez, Baylor College of Medicine
Mike Imperiale, University of Michigan
Bruce Innis, PATH
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APPENDIX A: LIST OF EXPERTS INTERVIEWED

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A. Marm Kilpatrick, University of California Santa Cruz
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Sabra Klein, Johns Hopkins University
Tom Kziazek, UTMB
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