The Future of Humanity and Microbes: Impact of Emerging Infectious Diseases on Global Health and Economies

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Abstract: Infectious diseases have affected humans since the first recorded history of man. Infectious diseases cause increased morbidity and a loss of work productivity as a result of compromised health and disability, accounting for approximately 30% of all disability-adjusted life years globally. The world has experienced an increased incidence and transboundary spread of emerging infectious diseases due to population growth, urbanization and globalization over the past four decades. Most of these newly emerging and re-emerging pathogens are viruses, although fewer than 200 of the approximately 1400 pathogen species recognized to infect humans are viruses. On average, however, more than two new species of viruses infecting humans are reported worldwide every year most of which are likely to be RNA viruses. Establishing laboratory and epidemiological capacity at the country and regional levels is critical to minimize the impact of future emerging infectious disease epidemics. Improved surveillance and monitoring of the influenza outbreak will significantly enhance the options of how best we can manage outbreaks to both treat as well as prevent spread of the virus. To develop and establish an effective national public health capacity to support infectious disease surveillance, outbreak investigation and early response, a good understanding of the concepts of emerging infectious diseases and an integrated public health surveillance system in accordance with the nature and type of emerging pathogens, especially novel ones is essential. There are important tools with which to fight outbreaks: a clear case definition, an aware health care system, and an informed public. The influenza outbreak in India should be further researched to determine the virulence and potential threat of the virus. Real-time surveillance, getting organized, and depositing these sequences, can help in planning a better strategy to respond to the virus.

Keywords: infectious diseases, emerging infection, microbes, global health, seasonal influenza, public health surveillance system, H1N1 Virus, HIV / AIDS, ebola, hepatitis C, mers-coV, zoonotic pathogens, cost of human economic development, burden of disease, mutation

1. Introduction

Humans have lived with emerging and re-emerging pathogens since before the dawn of civilization. The situation is worse now than in past decades or centuries because there are billions more of us and some of our activities allow such infections to appear and flourish. Moreover, our mobility within and between countries is conducive to the rapid spread of microorganisms. Similar observations hold true for animals and plants, with frequent consequences for human health. Emergent infection is recognized as a global threat. At least 17 million die annually from infectious diseases. Of these, the South-east Asia Region accounts for almost 41 per cent, or 7 million deaths. Emergent infection is recognized as a global threat. These diseases are the leading causes of death globally. According to an estimate, during the last two decades, over thirty new and highly infectious diseases have been identified. These include HIV/AIDS, Ebola, Hepatitis C, MERS-CoV, etc. In developing countries, the burden of disease caused by emerging and re-emerging infectious diseases not only places a great strain on the already stretched health services, but also adds to the socio-economic burden of families and individuals. In South East Asia, emerging diseases include HIV infection, cholera, tuberculosis, malaria, dengue hemorrhagic fever, viral hepatitis, meningitis and Japanese encephalitis. Examples of re-emerging infectious diseases are plague and Kala-azar. The most important factors that are responsible for emergent infection include the increasing number of people moving across the world, overcrowding in cities resulting in poor sanitation and the increased exposure of people to disease causing agents.¹

Modern civilization dates from approximately 10,000 BC. It took until 1830 for the world population to reach 1 billion persons; however, from there the world population doubled in the next 100 years and reached 6 billion 70 years after that. By the end of 21st century the world population could be between 14 and 18 billion.

In the global human population, the emergence of over 335 infectious diseases between 1940 and 2014 has been reported. The emergence of these pathogens and their subsequent spread has caused an extremely significant impact on global health and economies ¹–⁶. Previous efforts to understand patterns of EID emergence have highlighted viral pathogens (especially RNA viruses) as a major threat, owing to their often high rates of nucleotide substitution, poor mutation error-correction ability and therefore higher capacity to adapt to new hosts, including humans. [Fig 1 a,b]

Every year there are around 600 million travelers. Some will already be carrying pathogens; others will be traveling to areas in which they will suffer unintended exposure to, for them, new pathogens that, potentially, they can introduce to their communities upon their return home.
The majority of pathogens involved in EID events are bacterial or rickettsial (54.3%). This group is typically represented by the emergence of drug-resistant bacterial strains. Viral or prion pathogens constitute only 25.4% of EID events. The percentage of EID events caused by other pathogen types is 10.7% for protozoa, 6.3% for fungi and 3.3% for helminths.

The majority (60.3%) of EID events are caused by zoonotic pathogens (those which have a non-human animal source). Moreover, 71.8% of these zoonotic EID events were caused by pathogens with a wildlife origin—for example, the emergence of Nipah virus in Perak, Malaysia and SARS in Guangdong Province, China. The number of EID events caused by pathogens originating in wildlife has increased significantly with time, controlling for reporting effort, and they constituted 52.0% of EID events in the most recent decade (1990–2000). Zoonotic EIDs represent an increasing and very significant threat to global health. Vector-borne diseases are responsible for 22.8% of EID events. Our analysis reveals a significant rise in the number of EID events they have caused over time. This rise corresponds to climate anomalies occurring during the 1990s, adding support to hypotheses that climate change may drive the emergence of diseases that have vectors sensitive to changes in environmental conditions such as rainfall, temperature and severe weather events. EID events caused by drug-resistant microbes (which represent 20.9% of the EID events in our database) have significantly increased with time, controlling for reporting effort. This is probably related to a corresponding rise in antimicrobial drug use, particularly in high-latitude developed countries.

2. EIDs: Hidden ‘cost’ of Human Economic Development

Perhaps no human activity is as conducive to emergence of infectious diseases as warfare, a human behaviour that, measured by the number of people involved, becomes more extensive every century. The 20th century has been the bloodiest in history. There have been 150 wars in the second half of the century, resulting in more than 20
million deaths, two-thirds of them civilians. The prospects for less warfare are not good. Ethnic, religious, racial and tribal strife will be exacerbated by population growth, overcrowding and rivalries over increasingly depleted natural resources. Disease emergence is largely a product of anthropogenic and demographic changes, and is a hidden ‘cost’ of human economic development. Wildlife host species richness is a significant predictor for the emergence of zoonotic EIDs with a wildlife origin, with no role for human population growth, latitude or rainfall. The emergence of zoonotic EIDs from non-wildlife hosts is predicted by human population density, human population growth, and latitude, and not by wildlife host species richness. EID events caused by drug-resistant microbes are affected by human population density and growth, latitude and rainfall. The pattern of EID events caused by vector-borne diseases was not correlated with any of the environmental or ecological variables we examined, although we note that the climate variable used in this analysis (rainfall) does not represent climate change phenomena.

The economic impact of new, emerging and re-emerging infectious diseases can be enormous. The 1991 cholera epidemic in Peru cost that country an estimated $770 million. The plague epidemic in India cost that country $1.8 billion. BSE in the United Kingdom cost more than $6 billion. By the year 2000, the overall costs to Thailand and India on account of AIDS have been estimated at US$ 9 billion and 11 billion, respectively. The global cost of SARS has crossed $30 billion. Infectious diseases like malaria and AIDS act as a massive societal brake, slowing both economic and human development.1

3. Burden of Disease

Collectively, infectious diseases are the second leading cause of death globally, following cardiovascular disease, but among young people (those under the age of 50) infections are overwhelmingly the leading causes of death. In addition, infectious diseases account for nearly 30 percent of all disability-adjusted life years (DALYs), which reflect the number of healthy years lost to illness.7

As we eradicate diseases such as polio and smallpox, something else emerges and takes their place. This is the nature of the perpetual challenge of infectious diseases. Multiple factors reflect in some measure the encroachment of human civilization on the environment and on the microbial species that inhabit our environment. The human species lives in a delicate balance with microbial species; there is an ever-present tension between the two. If we perturb this balance, microbes almost always figure out a way to counterbalance the effect. Lyme disease emerged as we developed land near forests; changes in social structure and human behavior contributed to the emergence of HIV/AIDS; and monkeypox emerged in the United States when people started adopting exotic pets such as Gambian rats.

Approximately 75 percent of emerging pathogens are zoonotic (communicated by animals to humans). When humans encroach upon a rainforest, they become exposed to viruses and other microbes that they otherwise would not have encountered. HIV/AIDS, avian influenza, monkeypox, Nipah, SARS, and Ebola are all the result, to a greater or lesser extent, of interactions with animals that led to the emergence and re-emergence of deadly diseases.

Two fundamental characteristics of microbes allow them to circumvent our attempts to control them. Whereas human generations occur approximately every two decades, those of microbes occur in minutes, allowing them to rapidly replicate. Microbes also can mutate with each replication cycle. Their ability to replicate and mutate gives them the advantage of selectively circumventing human interventions, be they antimicrobials, vaccines, or public health measures. In our battle with microbes we have an intellect and a will. We use these to implement public health measures, biomedical research, and technological advances. In essence the human species uses its intellect and will to contain, or at least strike a balance with, microbial species that rely on genes, replication, and mutation.

4. Recent Trends in H1N1 in India

According to Ministry of Health (Government of India) figures, the total number of persons who have died of the disease till April 5, 2015 is over 2123 while a total of 35000 cases have been reported from all 36 states and Union Territories except five. The only ones untouched by swine flu with no cases or deaths are Arunachal, Meghalaya, Sikkim, Tripura and Lakshadweep. In Gujarat, which is one of the worst-affected states, the swine flu toll has climbed to 436 while the number of affected persons was 6,544. The number of deaths due to the virus in Rajasthan, Maharashtra and Madhya Pradesh was 426, 431 and 309, while that of those affected is 6,642, 4,749 and 2,233 respectively. In Karnataka, swine flu has killed 85 people and affected 2,866, while it has taken the lives of 77 in Telangana, 56 in Punjab, 53 in Haryana, 38 in Uttar Pradesh, 26 in West Bengal, 23 in Himachal Pradesh, 22 in Andhra Pradesh, 20 in Chhattisgarh, 24 in Jammu and Kashmir, 14 in Kerala, 12 in Uttarakhand and 16 people in Tamil Nadu. In Delhi, the toll has risen to 12 with the number of affected persons at 4,158.8,9

As per a ministry of Health (India) study, 34 per cent of the 723 swine flu deaths that were analysed had occurred in the age group 30-45 years followed closely by those in the 45-60 bracket, who accounted for 32 per cent of the fatalities, 17 per cent of the deaths occurred in the age group 18-30 years while 12 per cent of the casualties were in the 60 and above category. The ministry also said that among the victims, 50.35 per cent were women while 49.65 per cent were male. It also found that in Gujarat and Rajasthan, more than 50 per cent deaths had occurred among people with co-morbid conditions while in Karnataka it was more than 72 per cent. Several patients who died also had high risk factor involved and they suffered from other chronic diseases including diabetes, TB, chronic lung disorder.

According to the World Health Organisation (WHO), most seasonal influenza in the northern hemisphere is being caused by influenza A (H3N2) virus, which accounted for 87.5% influenza A cases. Of the more than 26,000 blood
samples tested by the WHO, the pandemic 2009 swine flu virus accounted for 12.5% cases.8,9

5. New Mutations

The swine flu virus in India may have acquired mutations that make it more severe and infectious than previously circulating H1N1 strains. The study by Massachusetts Institute of Technology (MIT) contradicts previous reports from Indian health officials that the strain has not changed from the version of H1N1 that emerged in 2009. MIT researchers found that the recent Indian strains carry new mutations in the hemagglutinin protein that are known to make the virus more virulent. Hemagglutinin binds to glycan receptors found on the surface of respiratory cells and the strength of that binding determines how effectively the virus can infect those cells.

In the past two years, genetic sequence information of the flu-virus protein hemagglutinin from only two influenza strains from India has been deposited into publicly available influenza databases which make it difficult to determine exactly which strain is causing the new outbreak and how it differs from previous strains. However, those two strains yielded enough information to warrant concern. Sasisekharan and Kannan T, a research scientist in MIT’s Department of Biological Engineering, compared the genetic sequences of those two strains (of 2014) to the strain of H1N1 that emerged in 2009 and killed more than 18,000 people worldwide between 2009 and 2012. One of the new mutations is in an amino acid position called D225, which has been linked with increased disease severity, researchers said. Another mutation, in the T200A position allows hemagglutinin to bind more strongly to glycan receptors, making the virus more infectious, the study found. More surveillance is needed to determine whether these mutations are present in the strain that is causing the current outbreak, which is most prevalent in the Indian states of Gujarat and Rajasthan and has infected more than 20,000 people so far. The Ministry of Health (India) is likely to take up the issue with the Indian Council of Medical Research (ICMR) since the latter has been saying till now that there have not been any mutations.10

Pandemic Influenza A(H1N1) 2009, currently the most common circulating strain of influenza virus globally, first caused illness in Mexico and the United States in March and April, 2009. It continues to spread globally with more than 340,000 laboratory confirmed cases and over 4100 deaths reported to WHO as of 27 September 2009. The 2009 novel A H1N1 virus appears to be of swine origin and contains a unique combination of gene segments that has not been identified in the past. The molecular analysis of the novel H1N1 virus has re-assorted segments from American swine, Eurasian swine, Avian and Human virus. It has not been previously detected in pigs or humans. It is an enveloped RNA virus and belongs to the family orthomyxoviridae. The size of the virus is 80-200 nm /0.08 -0.12 micron in diameter. There are three types of influenza A virus, namely A, B & C. The virus contains two surface antigens H (hemagglutinin) and N (neuraminidase).

The Influenza A virus is unique among the viruses because it is frequently subjected to antigenic variation. When there is a sudden complete or major change, it is called a shift, and when the antigenic change is gradual over a period of time, it is called a drift. Antigenic shift appears to result from genetic recombination of human with animal or avian virus, providing a major antigenic change. This can cause a major epidemic or pandemic involving most or all age groups. Antigenic drift involves “point mutation” in the gene owing to selection pressure by immunity in the host population. Antigenic changes occur to a lesser degree in the B Group Influenza viruses. Influenza C appears to be antigenically stable.

A confirmed case of pandemic influenza A (H1N1) virus infection is defined as an individual with laboratory confirmed new influenza A (H1N1) virus infection by one or more of the following: real-time RT-PCR, viral culture, four-fold rise in new influenza A(H1N1) virus-specific neutralizing antibodies. Where influenza viruses are known to be circulating in a community, patients presenting with features of uncomplicated influenza can be diagnosed on clinical and epidemiological grounds. All patients should be instructed to return for follow-up, should they develop any signs or symptoms of progressive disease or fail to improve within 72 hours of the onset of symptoms.

The pandemic influenza A (H1N1) virus differs in its pathogenicity from seasonal influenza in two key aspects: as the majority of the human population has little or no pre-existing immunity to the virus, the impact of the infection has been in a wider age range, in particular among children and young adults, and the virus can infect the lower respiratory tract and cause rapidly progressive pneumonia. On 26 September 2011 WHO has adapted a new nomenclature as Influenza A (H1N1) pdm09. A higher risk of severe complications from this virus has also been reported in individuals who are obese particularly in those who are morbidly obese.

Following its emergence in March 2009, pandemic A (H1N1) virus spread rapidly throughout the world. The world is now in post-pandemic period. [Fig 2,3]
6. Seasonal Influenza

Influenza occurs in all countries and affects millions of people every year. Its behavior is unpredictable. It may occur in several forms. It may smolder in a community without clinical recognition, being manifest only by serological surveys. It may occur in pandemics every 10-40 years due to major antigenic changes. In between pandemics, epidemics tend to occur at intervals of 2-3 years in case of influenza A.

Seasonal influenza kills about 250,000 to 300,000 people each year throughout the world. Superimposed on this yearly cycle is the ever-present threat of an influenza pandemic. A pandemic occurs through exposure to a microbe for which there is no baseline immunity in the population. The worst influenza pandemic in history occurred in 1918–1919. There were 40 million deaths throughout the world and a half-million deaths in the United States. Unlike the seasonal flu that typically kills the elderly, the 1918 pandemic killed young people as well. Even though they were fundamentally healthy, 20-, 30-, and 40-year-old people were dying because they had no background immunity to the virus, and the virus was particularly virulent. Influenza virus strains are designated by the composition of their hemagglutinin and neuraminidase proteins. Virtually every year, the sequence of the prevalent strain mutates slightly in a process known as drift. A drift from an H3N2 Panama strain to an H3N2 Fujian strain (as occurred in the 2003–2004 influenza season) represents a relatively minor mutation; if you were vaccinated or are immune to a Panama strain, you would also harbor some degree of cross-reacting, baseline immunity to a Fujian strain. However, an antigenic shift occurs when an influenza strain emerges that is substantially different from anything to which the population has been previously exposed. In 1918, H1N1 first appeared; in 1957 H2N2 emerged, and in 1968, we first saw H3N2. Outbreak of H5N1 was reported in 2003 and has affected poultry in 50 countries and caused human infections in 15 countries.

Over the past few years, many more influenza strains have emerged with the capability of infecting humans. The H5N1 strain likely evolved from a few flocks of chickens in Hong Kong (where it was first noticed in 1996 and infected a small number of humans in 1997) to the situation today where it has infected numerous flocks, as well as wild birds throughout Southeast Asia. Hundreds of millions of birds have been infected; more than 100 million chickens have died or have been culled to slow the spread of the H5N1 virus. If a few birds are infected, there is a problem, but not a big problem. When more birds are infected, the problem is getting bigger. When the virus jumps to humans, the problem is getting even more serious. If it jumps to significant numbers of humans, the threat becomes more serious still. Infectious diseases cause increased morbidity and a loss of work productivity as a result of compromised health and disability, accounting for approximately 30 percent of all disability-adjusted life years globally.
The world has experienced an increased incidence and transboundary spread of emerging infectious diseases due to population growth, urbanization and globalization over the past four decades. Most of these newly emerging and re-emerging pathogens are viruses, although fewer than 200 of the approximately 1400 pathogen species recognized to infect humans are viruses. On average, however, more than two new species of viruses infecting humans are reported worldwide every year most of which are likely to be RNA viruses.1

Emerging novel viruses are a major public health concern with the potential of causing high health and socioeconomic impacts, as has occurred with progressive pandemic infectious diseases such as human immunodeficiency viruses (HIV), the recent pandemic caused by the novel quadraple re-assortment strain of influenza A virus (H1N1), and more transient events such as the outbreaks of Nipah virus in 1998/1999 and severe acute respiratory syndrome (SARS) coronavirus in 2003. Other emerging infections of regional or global interest include highly pathogenic avian influenza H5N1, henipavirus, Ebola virus, expanded multidrug-resistant Mycobacterium tuberculosis and antimicrobial resistant microorganisms, as well as acute hemorrhagic diseases caused by hantaviruses, arenaviruses and dengue viruses.1

To minimize the health and socioeconomic impacts of emerging epidemic infectious diseases, major challenges must be overcome in the national and international capacity for early detection, rapid and accurate etiological identification (especially those caused by novel pathogens), rapid response and effective control. The diagnostic laboratory plays a central role in identifying the etiological agent causing an outbreak and provides timely, accurate information required to guide control measures.

Six major factors, and combinations of these factors, have been reported to contribute to disease emergence and re-emergence: (i) changes in human demographics and behavior; (ii) advances in technology and changes in industry practices; (iii) economic development and changes in land use patterns; (iv) dramatic increases in volume and speed of international travel and commerce; (v) microbial mutation and adaptation; and (vi) inadequate public health capacity.1

EIDs are divided into four categories based on the nature and characteristics of pathogens or infectious agents causing the emerging infections. The categorization is based on the patterns of infectious disease emergence and modes leading to the discovery of the causative novel pathogens. The factors or combinations of factors contributing to the emergence of these pathogens also vary within each category. Likewise, the strategic approaches and types of public health preparedness that need to be adopted, in particular with respect to the types of public health laboratories that need to be developed for optimal system performance, will also vary greatly with respect to each category of emerging infectious diseases.

Category 1: ‘known’ infectious pathogens/agents occur in new ‘niches’ Emerging infectious diseases under this category are subcategorized into 1a, 1b and 1c. Subcategory 1a covers known pathogens that occur in new ecological niches/geographical areas. A few past examples belonging to this subcategory are the introduction and spread of West Nile virus in North America; Chikungunya virus of the Central/East Africa genotype in Reunion Island, the Indian subcontinent and South East Asia; and dengue virus of different serotypes in the Pacific Islands and Central and South America. Factors that contributed to the occurrence of emerging infectious diseases in this subcategory include population growth; urbanization; environmental and anthropogenic driven ecological changes; increased volume and speed of international travel and commerce with rapid, massive movement of people, animals and commodities; and deterioration of public health infrastructure. Subcategory 1b includes known and unknown infectious agents that occur in new host ‘niches’. Infectious microbes/agents placed under this subcategory are better known as ‘opportunistnic’ pathogens that normally do not cause disease in immunocompetent human hosts but that can lead to serious diseases in immunocompromised individuals. The increased susceptibility of human hosts to infectious agents is largely due to the HIV/acquired immune deficiency syndrome pandemic, and to a lesser extent, due to immunosuppression resulting from cancer chemotherapy, anti-rejection treatments in transplant recipients, and drugs and monoclonal antibodies that are used to treat autoimmune and immune-mediated disorders. Subcategory 1c includes known and unknown infectious agents causing infections associated with iatrogenic modalities. Some examples of emerging infections under this subcategory include therapeutic epidural injection of steroids that are contaminated with Exserhelium rostratum and infectious agents transmitted from donor to recipients through organ transplantation, such as rabies virus, West Nile virus, Dandenong virus or Acanthamoeba.

Category 2: ‘known’ infectious pathogens/agents of a ‘new biologic’ phenotype (new subtypes or strains). Examples of past emerging infectious diseases under this category are antimicrobial resistant microorganisms (e.g., Mycobacterium tuberculosis, Plasmodium falciparum, Staphylococcus aureus) and pandemic influenza due to a new subtype or strain of influenza A virus (e.g., influenza
virus A/California/04/2009(H1N1)). Factors that contribute to the emergence of these novel phenotype pathogens are the abuse of antimicrobial drugs, ecological and host-driven microbial mixing, microbial mutations, genetic drift or re-assortment and environmental selection. Accidental or potentially intentional release of laboratory manipulated strains resulting in epidemics is included in this category.

Category 3: ‘novel’ infectious pathogens/agents. Some examples of novel pathogens causing epidemics are Ebola virus, Marburg virus, Hendra virus, Nipah virus, SARS coronavirus and HIV. Most, if not all, novel pathogens under this category are spillovers of zoonotic pathogens. These spillovers are directly or indirectly due to an enhanced intensity and increased frequency of mixing at the interface between wild-life animal reservoirs carrying the ‘novel’ zoonotic pathogens and humans or peri-domestic animals. Factors that lead to the spillovers and emergence of these novel pathogens are human population expansion, economic development, changes in land use patterns, modifications to natural habitats, and changes in agricultural practices and animal husbandry. Human behavior, such as wildlife trade and translocations, live animal and bush meat markets, consumption of exotic foods, development of ecotourism, access to petting zoos and ownership of exotic pets, also plays a significant role in the transfer of pathogens between species.

Category 4: ‘old/known’ diseases of ‘unknown’ etiology due to ‘unrecognized’ pathogens. It is further classified into two subcategories: category 4a covers acute illnesses, and category 4b focuses on chronic sickness. Some recent examples of infectious diseases that affect humans under category 4a include acute respiratory illnesses due to human metapneumovirus, human bocavirus, human coronaviruses (NL63, HKU1), new human polyomaviruses (KI, WU), novel orthoreoviruses (Melaka virus, Kampar virus, HK23629/07) and Saffold virus. Examples of infectious diseases under category 4b are gastritis and peptic ulcers due to Helicobacter pylori, Kaposi sarcoma due to human herpesvirus and chronic hepatitis due to hepatitis virus C and G. Advances in scientific knowledge and technology have contributed substantially to the discovery of these infectious etiological agents.

8. Lack of Preparedness

Recent outbreaks, such as SARS in China and 32 other countries, the plague episode in India, Ebola hemorrhagic fever in Zaire, leptospirosis in Nicaragua, and Ebola in Africa in 2014, depict the limited global capacity to rapidly diagnose and respond to emerging disease threats.

New microorganisms capable of causing disease in human continue to be detected. Whether an emerging microorganism develops into a public health threat depends on factors related to the microorganisms and its environment, or the infected human and his/her environment. Such factors include ease of transmission between animals and people and among people, potential for spread beyond the immediate outbreak site, severity of illness, availability of effective tools to prevent and control the outbreak, and ability to treat the disease. Some of the new agents detected in the past 25 years are now genuine public health problems on a local, regional or global scale.1,24

There is no single factor responsible for emergence of new, infectious disease, and the re-emergence of old ones. Factors responsible for EIDs as identified by Board on Global Health (BGH) and the Institute of Medicine (IOM), include: microbial adaptation and change, human demographics and behavior, international travel and commerce, economic development and land use, technology and industry, breakdown of public health measures, human susceptibility to infection, climate and weather, changing ecosystems, poverty and social inequality, war and famine, lack of political will, intent to harm, a global political commitment is rather vague.1,24

EIDs are a significant burden on global economics and public health. Their emergence is thought to be driven largely by socio-economic, environmental and ecological factors. EID origins are significantly correlated with socio-economic, environmental and ecological factors, and provide a basis for identifying regions where new EIDs are most likely to originate. They also reveal a substantial risk of wildlife zoonotic and vector-borne EIDs originating at lower latitudes where reporting effort is low. Global resources to counter disease emergence are poorly allocated, with the majority of the scientific and surveillance effort focused on countries from where the next important EID is least likely to originate.1,24

9. Public Health Surveillance System

Effective early detection, identification, characterization, containment, control and ultimately prevention of the emerging infectious diseases will require a good, functional national public health surveillance system. The system needs to be well supported by a network of primary public health and clinical/medical diagnostic laboratories that are coordinated by a national public health reference laboratory with real-time and harmonious communication between the laboratories and epidemiological surveillance units.

10. Challenges and Issues

Confronted with the great diversity of these emerging pathogens and the equally diverse mechanisms and factors that are responsible for their emergence, there is an urgent need to develop a network of diagnostic laboratories, especially in countries where epidemic infectious diseases are likely to emerge. This network should include local laboratories with basic clinical laboratory capabilities, provincial and national public health diagnostic laboratories with greater capability to diagnose known pathogens and support effective laboratory-based surveillance, and a centralized national reference laboratory that can provide laboratory training and quality control for diagnostic assays for the network of diagnostic laboratories in the country. Ideally, the national reference laboratory should have state-of-the-art laboratory technology and be able to identify and characterize novel
pathogens with specialized university laboratories and foreign institutes that can provide backup capability, but more importantly, the national reference laboratory should be able to conduct research for the development of new diagnostic technologies to detect and identify novel pathogens, especially those classified as category 4. The US system, which includes local and state public health laboratories that conduct diagnoses of known pathogens, the Centers for Disease Control and Prevention and university laboratories that provide research and reference activities, is a good model. Delay in the diagnosis of epidemics can cause substantial economic losses and social disruption and prevent containment or control as a result of the implementation of inappropriate control measures or a delay in implementing the appropriate control measures. Public health analytical diagnostic laboratories (both primary and clinical) should adopt a generic approach and serve as the initial or first entry point for the investigation of the causative pathogens in the event of an infectious disease outbreak or the occurrence of any fatal illness with clinical suspicion of infectious etiology. 26-34

Public health laboratories must have the capability to support the expanded scope and sophistication of public health activities brought about by a rapid increase in population and social, demographic and ecological changes, in addition to the factors mentioned above. In countries with limited resources, an interim centralized national public health diagnostic laboratory can take on some of the roles and functions of a national reference laboratory, especially in supporting laboratory training and quality assurance. For countries without such an idealistic centralized public health reference laboratory, an in-place system of networking should be developed to link to regional and international high-end laboratories or WHO Collaborative Centers to rapidly identify and characterize novel pathogens and provide other specialized laboratory diagnostic reagents, assays or validation. In addition, each region should have a regional center for reference and research to help the national reference and/or diagnostic laboratories train and maintain laboratory quality control. The US Centers for Disease Control and Prevention is a major WHO collaborative partner and provides laboratory service not only for the American region, but also for many other countries in the world. 26-34 [Fig 5]

Figure 5: Organizational interrelationship and linkages of public health diagnostic, reference and research laboratories within a country


Because of the increased likelihood of epidemic diseases caused by novel pathogens, diagnostic laboratories serving as the primary entry point of investigation should be able to take a more generic approach in pathogen detection, isolation and identification.

11. The New Global Health

Global health is multidisciplinary, encompasses many elements besides development, and requires coordination of multiple parties, rather than direction by one organization or discipline. Global health reflects the realities of globalization, especially the increased movement of persons and goods, and the global dissemination of infectious and noninfectious public health risks. Global health is concerned with protecting the entire global community, not just its poorest segments, against threats to health and with delivering essential and cost-effective public health and clinical services to the world’s population. A fundamental tenet is that no country can ensure the health of its population in isolation from the rest of the world, as articulated in the Global Health Strategy of the United States Department of Health and Human Services. 35
Three overlapping themes determine global health action: development, security, and public health. These themes provide the humanitarian and political bases for engagement by high-income countries in health matters internationally: for development, to promote health for stability, prosperity, and better international relationships; for security, to protect their populations against internal and external health threats; and for public health, to save lives worldwide and at home. Despite different requirements, organizations and agencies involved must adapt to global trends in socioeconomic development, fertility, population, and urbanization.11

Of 214 countries categorized by the World Bank, only 36 (17%) were classified as low-income countries (gross national income per capita in 2011 <$1,025 per year), 26 of which were in Africa. Economic growth is moving some low-income countries toward middle-income status, and some of the greatest imbalances in wealth may now be within rather than between individual countries. With socioeconomic development, basic health indicators improve but so do countries’ abilities to shoulder more of their own health expenditures. A clear correlation exists between countries’ gross domestic product and their health indicators, such as mortality rates in children <5 years of age (highest in low-income countries) or life expectancy (highest in high-income countries). Development raises living standards, accompanied by improvement in basic services and drivers of health, such as nutrition and food security; access to potable water and sanitation; maternal and child health interventions, including family planning; and basic education, especially for women. The fundamental responsibility for development agencies, and their greatest contribution to health, is poverty reduction. Since 1980, the world’s population has increased by nearly 60%; from 7 billion today, global population is projected to reach 9.3 billion by 2050 and 10.1 billion by 2100.36-46

Health security captures the need for collective action and preparedness to reduce vulnerabilities to public health threats that transcend borders. Earlier optimism predicting the end of infectious diseases was replaced by recognition of the threat to global health from emerging infectious diseases and widespread antimicrobial drug resistance. The pandemic of HIV/AIDS, repeated outbreaks of Ebola and Marburg virus infections, rapid international dissemination of severe acute respiratory syndrome and pandemic influenza, international spread of several foodborne pathogens, and the intentional transmission of anthrax all convincingly illustrated global vulnerability. Surveillance and laboratory capacity through strong national public health institutes are essential components of functioning health systems that provide the basis for health security. Ensuring ability to detect, investigate, diagnose, and rapidly contain public health events of concern wherever they occur requires commitment to global health capacity development in all countries and widespread and supportive public health networks.36-46

Public health agencies have a major role in strengthening specific areas of health systems, such as health information systems and surveillance, laboratory capacity, workforce skills, operational research and evaluation, and capacity for preparedness and program implementation.

12. Infectious Disease Priorities

Recent estimates of the global incidence of disease suggest that communicable diseases account for 19% of global deaths. In Africa, 76% of deaths are still attributable to communicable, maternal, neonatal, or nutritional causes, compared with 25% in the entire world; conditions relevant to MDGs 4, 5, and 6 are responsible for 42% of years of life lost. Focus on infectious diseases remains necessary to prevent their global spread or recrudescence, save lives, enhance economic development, and increase health equity. There is increasing pressure to use resources for biomedical interventions with the strongest evidence of efficacy.36-46 Lack of access to water and sanitation highlights some of the greatest inequities in global health. Approximately 1 billion persons worldwide do not have clean drinking water, and 2.5 billion persons have to openly defecate, which is an affront to human dignity. Surveillance will have to be strengthened globally to track exposure to risk factors for the major causes of disability and death, disease outcomes, and health systems responses.4

13. Disease Burden Estimates for Infectious Diseases

Baseline comprehensive estimates of infectious disease (ID) burden are needed for effective planning and prioritizing of limited public health resources. The impact of every adverse event on health can be measured by the number of life years lost due to premature death and the number of life years lost due to disability. The latter requires measuring the impact of disease on quality of life using disability weights. Both the number of life years lost due to premature death and the number of life years lost due to disability are estimated by use of a reference that reflects an ideal health goal, and add up to a disability-adjusted life year (DALY). The dynamics of ID transmission occurs in widely differing time scales depending on the pathogen. Clearly, infections that spread on the time scale of the average generation time of a population will be closely linked to changes in demography, social and behavioral changes, and the implementation of preventive measures. ID can influence a population's demography by affecting mortality and therefore average life expectancy, or by influencing fertility rates. On the other hand, demography also influences the transmission of ID by determining the relative sizes of susceptible and vulnerable populations. Prevention programs such as mass vaccination tend to increase the average age at which an exposure to infection takes place and therefore increase the probability of severe complications for some diseases. Demographic flow leads to shifts in the immune status of entire populations, possibly resulting in increasing risks of large outbreaks in vulnerable population groups. Recent advances in mathematical and statistical methods for studying IDs will provide new tools for future disease burden estimation. Dynamic transmission models will be used to describe temporal dynamics of outbreaks and the impact of large-
scale intervention measures. Bayesian statistical methods for parameter estimation provide tools for combining data from various sources into a consistent estimate, allowing the weighting of evidence according to its perceived reliability. Combining dynamic transmission models that include demographic modeling with Bayesian estimation methods will be the methodological toolkit for future burden estimates for ID.55-57

14. Emerging Trends in Flu

The flu epidemic of 1918 started as a mild disease in the spring, called the “3-day fever”. Most victims recovered in a few days; there were few deaths. Then in the fall, it turned into something far more severe. It was the same flu strain, but it had become more virulent. Some victims died within hours. Healthy young adults were as susceptible as children and the elderly. It affected remote villages as well as urban areas. It attacked 1/5 of the world’s population, one-fourth of the US population, and killed 50 million people.

Wartime conditions may have favored the evolution of a more virulent strain. In peacetime, the sicker stay put and the mildly affected move around. In the trenches, the mildly affected stayed on duty and the sicker were sent on crowded trains to crowded field hospitals. Today, places with social upheaval might have similar effects favoring a virulent strain.

In February 1976 a strain of H1N1 influenza similar to the 1918 strain killed a soldier at Fort Dix. Officials feared a pandemic and over-reacted. In actuality, the H1N1 strain was limited to the Fort Dix area and quickly died out, and another related strain only persisted until March. Nevertheless, a swine flu vaccine was developed and was given to 48,000,000 Americans, 22 percent of the population. The vaccination program was stopped in December after 532 cases of paralysis from Guillain-Barré syndrome were linked to the vaccine and 25 people died. It had been a false alarm, and more people died of the vaccine than of the disease. The risk of getting Guillain-Barré from the vaccine was approximately 1 in 100,000.

Between April 15 and July 24, 2009, there were 43,771 confirmed and probable cases of H1N1 influenza (“swine flu”) in the USA. There were 5011 hospitalizations and 302 deaths, 39 PERCENT among those aged 25 to 49, in contrast to the usual flu where 90 percent of the deaths are in people over age 65. For comparison, the more common strains of flu have been killing around 36,000 people a year in the US. Swine flu has been declared a phase 6 pandemic by the World Health Organization: that is a measure of its spread, not of its severity.

Influenza viruses are spread from person to person primarily through large-particle respiratory droplet transmission. Transmission via large-particle droplets requires close contact between source and recipient persons, because droplets do not remain suspended in the air and generally travel only a short distance (less than or equal to 1 meter) through the air. Contact with respiratory-droplet contaminated surfaces is another possible source of transmission. Airborne transmission (via small-particle residue [less than or equal to 5µm] of evaporated droplets that might remain suspended in the air for long periods of time) also is thought to be possible, although data supporting airborne transmission are limited. The virus is also transmitted by infected people who cough or sneeze into their hands and then touch other people or objects before washing their hands. The typical incubation period for influenza is 1—4 days (average: 2 days). Most healthy adults may be able to infect others beginning 1 day before symptoms develop and up to 5 to 7 days after becoming sick. Some people, especially young children and people with weakened immune systems, might be able to infect others for an even longer time.

The risk for H1N1 transmission through breast milk is unknown. However, with seasonal flu, it seems that the virus does not usually get into the blood stream and cross into breast milk. Sick women who are able to express (pump) their milk for bottle feedings by a healthy family member should be encouraged to do so if their doctor or other health care provider agrees. A mother who is taking antiviral medications (drugs that fight viruses) to prevent or treat H1N1 infection can still breastfeed if her health care provider agrees.

Influenza viruses cause disease among persons in all age groups. Rates of infection are highest among children, but the risks for complications, hospitalizations, and deaths from influenza are higher among persons aged 65 years and older, young children, and persons of any age who have medical conditions that place them at increased risk for complications from influenza. Estimated rates of influenza-associated hospitalizations and deaths varied substantially by age group in studies conducted during different influenza epidemics.

15. Laboratory Diagnosis

The 2009 influenza pandemic is the first pandemic in the molecular era and the first to occur in the face of extensive pandemic preparedness activities that have been undertaken globally since the emergence of the highly pathogenic H5N1 influenza A virus. Although commercially available rapid influenza diagnostic tests (RIDTs) vary widely in their reported sensitivities, their high specificities and positive predictive values during peak influenza season allow early confirmation, facilitate timely treatment decisions, and enable improved patient care by limiting additional and often unnecessary diagnostic and therapeutic interventions (including hospitalizations) in these patients. Moreover, their lower cost and minimal to no technical complexity render them particularly useful in low-complexity laboratories and low-resource and point-of-care settings.51,52 Pyrosequencing has emerged as a useful sequencing technique in recent years. This technology has been used successfully to identify and detect molecular markers of antiviral resistance in seasonal H1N1 and H3N2 influenza viruses, H5N1 virus, 2009 H1N1 influenza A virus, and influenza B viruses. The method is employed by the CDC for detection of antiviral resistance directly in clinical samples and is used in combination with NAi assays to detect novel or previously known molecular markers of resistance. Advantages of
pyrosequencing-based assays include (i) a rapid turnaround, with results available in less than 5 hours; (ii) help in discovering previously unknown markers of resistance by identifying new mutations within the area of the genome that is sequenced by a given assay; and (iii) increased sensitivity. Pyrosequencing can reliably, accurately, and quantitatively detect mutants present at as low as 5 to 10% prevalence in mixed viral populations, in contrast to Sanger sequencing, which requires mutants to be present at levels of ≥50 percent to be detected. Rapid sensitive quantitative detection makes this technology particularly valuable for antiviral resistance testing in a clinical context. Sensitive and timely detection of resistant mutants directly in clinical specimens, which are often obtained serially from immunocompromised patients, who are at highest risk for emergence of such mutants while on sequential or combination antivirals, would enable timely therapeutic changes. If minor resistant populations identified early in the course of infections are shown to have clinical and phenotypic significance, further studies to optimize drug doses for prophylaxis and treatment would have the potential to advance the current knowledge and management of antiviral resistance in influenza virus.

A confirmed case of pandemic influenza A (H1N1) 2009 virus infection refers to a person with an acute febrile respiratory illness with laboratory confirmed influenza A (H1N1) 2009 virus infection at WHO approved laboratory by one or more of the following tests: Real Time PCR, Viral Culture, Four-fold rise in influenza A (H1N1) virus specific neutralizing antibodies.

A valuable advantage of Real-time RT-PCR-based assays is that many clinical laboratories with molecular capabilities already have the infrastructure and expertise required for development and implementation of assays using an RT-PCR-based format. A short turnaround time of 3 to 4 hours, automation, and high throughput are added benefits. A potentially important feature of real-time RT-PCR assays is their increased sensitivity over that of pyrosequencing assays. A recent study described the development of a real-time PCR assay that reliably detected mixed populations at percentages down to 0.1 percent H274Y variant component or 1% wild-type component in viral nucleic acid extracts. Assays with such excellent analytical sensitivities offer the advantage of detecting mutations in samples with viral loads that are too low to be detected by pyrosequencing. Another advantage of assays with high analytical sensitivities is the ability to confirm or refute the role of mutations identified in cell culture-propagated isolates but not in original samples. A novel Q136K mutation in the NA gene, reported to confer zanamivir and peramivir resistance, was identified in 9 prepandemic H1N1 virus isolates but not in their original clinical specimens. Similar detection of mutations (D151G/N) that potentiated the effect of the H274Y mutation on NAI susceptibility and conferred cross-resistance to all 4 NAIs tested was noted by pyrosequencing for viruses propagated in MDCK cells but not in matching clinical specimens. This discrepant detection in isolates but not clinical specimens suggests that the variants either occurred in very small proportions in the primary clinical specimens, below the limits of detection of pyrosequencing (~5 to 10 percent), or reflected genetic variability introduced during passage in culture. Detection of mutants in viral isolates should be evaluated in the context of the number of passages, which is often not known or may be high in surveillance or research studies but would be important for interpreting results for clinical purposes. Comprehensive studies of virologic resistance at the genotypic and phenotypic levels, along with clinical correlation, would be required to facilitate accurate validation of novel molecular determinants as well as help determine accurate assay cutoffs for clinically relevant resistance.51,52

NAI resistance in the 2009 H1N1 influenza A virus remains rare (<1%), with the majority of this being observed in immunocompromised patients with prior exposure to the drug. All resistant isolates analyzed to date have been reported to have the H275Y mutation. The recent precedence of unexplained emergence and rapid global spread of oseltamivir resistance in the prepandemic H1N1 virus unrelated to drug usage, should serve as a reminder to maintain constant vigil for similar trends in currently circulating and any future novel subtypes. Zanamivir resistance has been reported rarely, with just one resistant influenza B virus reported for a zanamivir-treated immunocompromised patient. To date, none of the 2009 H1N1 influenza A viruses have been reported to be resistant to this drug. Diagnostic criteria will need to be developed and standardized for interpreting test results for clinical use, particularly for tests with excellent sensitivity for minor resistant variants.51,52

16. Role of Genetics in Studying Infectious Diseases

Characterizing novel or re-emerging infections is aided by the availability of pathogen genomes. When a pathogen crosses over from animals to humans, or an existing human disease suddenly increases in incidence, the infectious disease is said to be ‘emerging’. Genomic studies have contributed to better understanding of EIDs and their spatiotemporal spread. Sophisticated statistical methods have been developed to uncover the epidemiological features of infectious diseases based on the genealogy of their sequences. There is also growing effort to integrate genomic analysis with analysis of epidemiological data. In recent cases of EIDs, genomic data have helped to classify and characterize the pathogen, uncover the population history of the disease, and produce estimates of epidemiological parameters.53-66 Detecting characterizing and responding to an EID requires coordination and collaboration between multiple sectors and disciplines. Laboratory-based research helps to characterize the pathogen and its interactions with host cells, but is less useful for quantitative understanding of population-level disease dynamics. Modeling approaches enable a large number of hypotheses to be tested, which might not be logistically or ethically feasible in laboratory and field experiments. In addition to characterizing past
disease dynamics, modeling future trends informs decisions regarding outbreak response and resource allocation. Modeling plays an especially important role in epidemiological studies of infectious disease spread, because the transmission of infectious disease between individuals is not directly observable. At the individual level, transmission times and who infected whom are typically unknown. And at the population level, disease burden needs to be inferred from observable data. Sequencing pathogens can confirm suspected cases of an infectious disease, discriminate between different strains, and classify novel pathogens. In addition to examining individual pathogen sequences, multiple sequences can be analyzed together using phylogenetic methods to elucidate evolutionary and transmission history. Just as mathematical models of disease transmission help to capture the epidemiological properties of an infectious disease, modeling the molecular evolution of pathogen genomes is important for phylogenetic methods.

Besides characterizing the genetics and evolution of a pathogen, mathematical models used in population genetics link demographic and evolutionary processes to temporal changes in population-level genetic diversity. The coalescent population genetics framework was developed so that demographic history could be inferred from the shape of the genealogy linking sampled individuals. More recently, the birth-death model has been applied to infectious diseases to infer epidemiological history from a genealogy. Given the link between pathogen evolution and disease transmission, there is a trend towards integrating both epidemiologic and genetic data in the same analytical framework.

Middle East respiratory syndrome coronavirus (MERS-CoV) first appeared in Saudi Arabia in 2012, and has since been reported in several neighboring countries in the Arabian Peninsula and on other continents. Unlike the 2014 EBOV outbreak, which is sustained by human-to-human transmission, there appears to have been multiple introductions of MERS-CoV into the human population. Identification of the animal reservoir is therefore crucial for establishing risk factors of infection and planning appropriate interventions to control the disease. Since bats are reservoirs for other coronaviruses, their being a reservoir host is possible. A 182-nucleotide-long region of the RNA-dependent RNA polymerase gene was found to be 100% identical between a viral sample from a patient in Saudi Arabia and from a bat nearby, though the region is known to be highly conserved. However, antibodies against human MERS-CoV have been detected in dromedary camels, the camel MERS-CoV genome is similar to human MERS-CoV, and there are reports of close contact between patients and camels. Phylogenetic analysis of coronavirus sequences from bats, dromedaries and humans indicate a bat origin, with dromedary camel as an intermediate host. With sequences collected over three decades from humans, pigs and birds, the origin of the pandemic H1N1 influenza A strain (pdmH1N1 or ‘swine flu’) was elucidated soon after emergence. Within two months of the first reported case of swine flu in humans, genomic analysis of the novel influenza strain had been carried out. A phylogeny was constructed for each of the eight genomic segments with sequences from humans, swine and birds. Comparison of these eight phylogenies revealed a complex history of reassortment with a mixture of gene segments from all three groups. The start of the pandemic was estimated to be the end of 2008 or early 2009, and the dates of the reassortment events leading to pdmH1N1 were also obtained.

Whole-genome sequencing of bacterial isolates is becoming more widespread, and can help to uncover genetic determinants of clinical severity, elucidate pathogen-host interactions, and quantify evolutionary rates at within- and between-host levels. Epidemiological investigations using bacterial genomes have also been possible. Even though bacteria acquire point mutations at a lower rate per base than viruses, longer bacterial genomes have provided sufficient genetic resolution for phylogenetic analysis.

The response to influenza outbreaks has improved markedly. The response was faster and more effective in terms of control strategies, stockpiling of antivirals, and vaccine development. These improvements also suggest advances in disease surveillance, transparency in reporting, and regional collaboration and cooperation. These trends also foreshadow better prospects for prevention and control of emerging infectious diseases. However, there are shortcomings since strategies failed to focus on high-risk groups, quantitative and measurable results (both direct and indirect) were unclear, and quantitative assessment is still lacking.

Compared to the fight against pandemic influenza A (H5N1) in 2003, the fight in 2009 was a marked improvement. Both direct results and indirect results of control strategies improved. A rapid-response stockpile of antivirals had been prepared in advance, and the stockpile was quickly delivered. Vaccines were also developed faster. The WHO also evaluated pandemic influenza (H1N1) 2009 after the pandemic. Therefore, the response to pandemic influenza improved significantly. However, there were shortcomings during response to the outbreak of pandemic influenza (H1N1) 2009. First of all, just like the strategies against pandemic influenza A (H5N1) in 2003, strategies against H1N1 also failed to pay enough attention to the younger population as a high-risk group. There is no evidence of a specific strategy focusing on the younger population beside the school closure mentioned above. Second, the evaluation needed to go further. The evaluation of H1N1 was a qualitative evaluation, lacking convincing quantitative evidence. The response to pandemic influenza outbreaks has improved markedly in terms of control strategies, stockpiles of antivirals, and vaccine development. These improvements also suggest advances in disease surveillance, transparency in reporting, and regional collaboration and cooperation. These trends also foreshadow better prospects for prevention and control of emerging infectious diseases. However, there are shortcomings since strategies failed to focus on high-risk groups, quantitative and measurable results (both direct and indirect) were unclear, and quantitative assessment is still lacking.
17. Effective Surveillance

Continuous surveillance of influenza viruses enables researchers to track viral evolution, identify amino acid mutations in key viral proteins governing their circulation, predict potential “outbreaks,” and assist in the development of various “outreach” approaches to treat as well as prevent further spread. Typically, influenza-genome data collected from field studies or research efforts are sequenced and submitted to GenBank and/or one or more specialized open-access databases. Open-access databases such as National Center for Biotechnology Information (NCBI) Influenza Virus Resource (http://www.ncbi.nlm.nih.gov/genomes/FLU/FLU.html), Influenza Research Database (http://www.fludb.org/), and EpiFlu (http://platform.gisaid.org/epi3/start) facilitate sharing of viral genome sequences and encourage collaborative research world over. An analysis of the publicly available influenza databases suggests that influenza monitoring has not yet reached sufficient levels to enable real-time surveillance. Despite the risk posed by these animals, the number of swine influenza sequences collected in the 2009–2015 period is insignificant, with notably no swine influenza strains deposited from India. These numbers highlight the irregular, reactive nature of the influenza surveillance response. Since 2009, HAs of the 2009pdmH1N1 lineage have gradually evolved and acquired mutations in the H1 antigenic sites (Sa, Sb, Ca, and Cb). Notably, strains carrying seven antigenic-site mutations appeared in 2013, which has implications for re-evaluation of the H1N1 vaccine component (A/California/04/2009). Importantly, the mutation K166Q at the “Sa” antigenic site discriminated strains that circulated before 2013 from those that circulated during 2014–2015. While the majority of strains that circulated before 2013 possessed Lys at 169, >80% of the strains that circulated after 2013, including the two 2014 Indian isolates, possessed a Gln. There needs to be genetic and phenotypic analysis of the virus and general dissemination of the data to ensure access to real-time information. For many strains, only the HA gene is sequenced, leaving the rest of the genome incomplete. This is because many of these efforts are part of research studies that focus on receptor binding or immune response. 67-70 One response to epidemic outbreaks is to identify vaccine strategies to abbreviate the time lag between advent of a novel virus strain and the manufacture of vaccine, such as through synthetic approaches or use of alternative vaccine formats, such as virus-like particles. Epidemiological modeling of influenza epidemic outbreaks may allow for such strategies, such as potentially targeting high-risk populations such as health care workers with a prophylactic long-lived antiviral to possibly mute outbreaks, allowing time for implementation of vaccine strategies. The use of antibody to treat influenza has some clinical experience to support efficacy. For example, a recent study evaluated the use of convalescent plasma in 93 patients with H1N1 2009 influenza in Hong Kong. 67-70

Digital disease surveillance systems have the potential to aid in the monitoring of disease spread and communicating to public health practitioners and the public. If adopted by appropriate public health authorities, the data available through these systems can aid in timely detection and response, which is needed for disease control. These systems are typically built to enhance traditional indicator-based surveillance systems with the potential to aid in medical decision making, improve assessment of population response toward disease control (e.g., vaccination sentiments), understand disease spread relative to population density and movement, and aid in the early detection of disease events, including those emerging from remote regions. Computational approaches for influenza surveillance can be broadly categorized as active and passive. Active surveillance is defined here as the targeted collection of information from the population, such as crowd-sourcing using cell phone apps and participatory approaches. In contrast, passive surveillance can be described as the extraction of existing data from sources such as specific web pages using machine learning techniques (e.g., crawling and scraping). 71-74

The participatory surveillance systems typically collect some background information at time of registration and send surveys to registered participants at regular intervals, usually weekly, to gather data on disease symptoms experienced during the previous week. The symptoms data are processed and presented using maps or other methods aimed at informing the public of influenza-like illness activity levels. Ddata from these systems have been shown to have similarities in trends and peak timing when compared to reports from practitioner-based surveillance systems. Furthermore, data from these systems have also been used to assess vaccination coverage and inform epidemiological models for influenza-like illness. Web-based disease information resources are used by major public health organizations (such as the WHO) and states and local communicable disease investigators for regular surveillance activities. Although usual attributes for assessing surveillance systems based on the effectiveness of response have been deemed inadequate, there is some utility and potential impact of these systems on the public and global public health. 72-73 Internet-based data sources have been demonstrated to be valuable for detection, monitoring, and dissemination of information during recent influenza outbreaks. Digital disease detection systems have identified early reports of emerging influenza outbreaks. Internet-based systems can be used for monitoring disease activity and extracting epidemiologic data on cases during an outbreak. Digital disease surveillance systems can aid in the understanding of spatial spread of influenza epidemics. By mapping reports of influenza and influenza-like illness, the public and public health authorities can identify regions with the highest prevalence. Internet-based systems have been used to evaluate population health-seeking behavior and sentiments toward disease and disease control measures such as vaccination, which can be critical for the design and implementation of targeted control measures during influenza pandemics. These data can also enable a better understanding of changes in population behavior before, during, and after an outbreak. Novel data approaches such as high-resolution satellite imagery of disease-affected populations can provide a representation of how population behavior varies over time and can be used to
assess response to specific intervention strategies such as social distancing. Disease-related data extracted from different sources could be compared and integrated to improve surveillance. Data integration techniques using Bayesian ensemble and filtering methods have been shown to yield promising results both for influenza monitoring and prediction. The integration of diverse data sources or models based on a combination of different data types has the potential to improve estimates of influenza activity relative to a single system or data source. These systems and data sources have the potential to improve global public health by improving disease surveillance in data and resource poor regions.\textsuperscript{75,74}

18. Responding to the Challenge

The management of EIDs requires a proactive and planned approach to ensure the appropriate prevention and control of the spread of disease by health authorities. Strategic planning should include:

- Phase I (non-alert) is a routine, preparatory state. Critical sets of activities that should be operating include ongoing surveillance, routine reporting, clarity and definition of legal and ethical responsibilities, collecting and analyzing data and disseminating information.
- Phase II (alert) is the detection, confirmation and declaration of changes identified during non-alert conditions.
- Phase III (response) includes the ongoing assessment of information and the planning and implementation of an appropriate response, which includes the coordination and mobilization of resources to support intervention activities. These may include needs assessment, prioritization, the identification of barriers, contingency planning, communication strategies, research and development of vaccine, drugs, etc.
- Phase IV (follow-up) activities include re-evaluation, restructuring, reporting and continuing education, and redefining strategic parameters.

To effectively manage the spread of disease, it is the responsibility of the international community to have minimum standards in place for the development of information systems. This includes addressing the need for technology and ensuring the human capability to analyse and share information. A comprehensive communication strategy is required to ensure accurate, timely sharing of information. The communication plan should be established and disseminated. Specific communication strategies should address containment of new and re-emerging diseases. Communication to the public should be prompt, honest and focused on fully informing the public. Efforts to manage EIDs, particularly during outbreaks, suggest that there is frequently a lack of coordination and what appears to be a delayed response. A well-planned systematic response is required, which should include assessment of emergent infection, an evaluation of existing resource capacity and the formulation of a strategic and operational plan to ensure a coordinated intersectoral global response.

Key to the successful implementation of these activities is the adoption of a system approach such as continuous quality improvement. Strategic operational goals should focus on efficiency, equity, effectiveness, and economy.

The priority activities towards the prevention and control of emerging and re-emerging communicable diseases are: strengthening epidemiological surveillance, strengthening laboratory capabilities and services, establishment of a rapid response team, monitoring antimicrobial resistance, establishment of international disease surveillance networking and advocacy and mobilization of the international support.

19. Conclusion

As we struggle to keep a step ahead of the diseases that challenge us, we must develop partnerships among clinicians, researchers, government, and industry to detect and diagnose disease; to conduct basic, applied, and clinical research; to develop effective countermeasures; to manufacture vaccines and drugs to prevent and treat disease; and to deliver these therapies to the patients who need them. Today’s medical students will play an important role in all aspects of our efforts to combat infectious diseases. It is clear that we will rely heavily on fundamental science, its applications, intellectual capital, and research facilities in the ongoing struggle between microbes and humans, a challenge that is perpetual. To minimize the health and socioeconomic impacts of emerging epidemic infectious diseases, major challenges must be overcome in the national and international capacity for early detection, rapid and accurate etiological identification (especially those caused by novel pathogens), rapid response and effective control. The diagnostic laboratory plays a central role in identifying the etiological agent causing an outbreak and provides timely, accurate information required to guide control measures. Establishing laboratory and epidemiological capacity at the country and regional levels is critical to minimize the impact of future emerging infectious disease epidemics.

To develop and establish such an effective national public health capacity to support infectious disease surveillance, outbreak investigation and early response, a good understanding of the concepts of emerging infectious diseases and an integrated country and regional public health laboratory system in accordance with the nature and type of emerging pathogens, especially novel ones, are highly recommended. The influenza outbreak in India should be further examined to determine the virulence and potential threat of the virus. Improved surveillance and monitoring of the influenza outbreak will significantly enhance the options of how best we can manage outreach to both treat as well as prevent spread of the virus. The future of humanity and microbes likely will unfold as episodes of a suspense thriller that could be titled Our Wits Versus Their Genes.\textsuperscript{75} We can look forward with confidence to a considerable degree of freedom from infectious diseases at a time not too far in the future. Indeed, it seems reasonable to anticipate that within some measurable time, all the major infections will have disappeared.\textsuperscript{76} Real-time surveillance, getting organized,
and depositing these sequences, can help in planning a better strategy to respond to the virus.

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