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Emergence of Novel Human Infections: New Insights and New Challenges

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Background

New human infections have continued to come forth over the last decade. This discussion will focus on the period from 2006 to 2016. Given the importance of the severe acute respiratory syndrome (SARS) as the harbinger of coronaviruses such as the Middle East respiratory syndrome (MERS), some discussion of SARS is also included. The phenomenon of emerging infections has been constant with the majority of human infections reflecting the introduction into humans of zoonotic pathogens.

Over the last decade, great progress has been made in defining more fully how emergence occurs. In fact the emergence of new infections has expanded the paradigms of microbiology in a number of ways, which will be highlighted here. Specifically: (1) it is now well appreciated that influenza can migrate directly from avian sources to humans, and the appreciation of the actual directness of 'species jumping' has moved forward; (2) new infections have also introduced uncertainty in transmission dynamics with emphasis on super-spreader events as well as nosocomial transmission; (3) infectious particles are not confined to those organisms which contain genetic material; (4) a new paradigm such as 'Planetary Health' may be necessary for defining these trends; and (5) global preparedness and response is not in place for the next pandemic. For further background information, the reader is referred to the original article on this phenomenon (Kimball, 2008). A general discussion of antimicrobial resistance and xenotransplantation is not included in this discussion as they were thoroughly covered in the original article. Antimicrobial resistance will be covered in detail in another article of this volume. Nonetheless they continue to be important considerations.

Respiratory Pandemics: Highly Mobile, Highly Unpredictable

While it has long been appreciated that the majority of human pathogens arise from zoonotic sources, the directness of the path from animal to human has become clear. Ideally detecting pathogens in animals could be seen as a harbinger for human outbreaks. In fact this has been a working hypothesis of major US Agency for International Development (USAID) funding to their pandemic agents program. However, recent outbreaks of influenza, SARS, and MERS coronavirus (CoV) demonstrate how emerging infections are shifting this longstanding paradigm. They lend further urgency to this area of research. In addition, these outbreaks have challenged our understanding of transmission dynamics. Empirical observation has shown that there is not a single transmission force 'number' which completely characterized the spread of infectious diseases. This further complicates efforts to control infection within populations.

Influenza

In 2009, a cluster of high mortality influenza cases was detected in Mexico. An observational study of 899 patients hospitalized in Mexico between late March and 1 June 2009 showed that

pandemic (H1N1) disproportionately affected young people. Fifty-eight patients (6.5% of those hospitalized) became critically ill, with complications including severe acute respiratory distress syndrome and shock. Among those who became critically ill, the mortality rate was 41% (Domínguez-Cherit et al., 2009). The pandemic and its management have been the subject of an in-depth analysis commissioned by the World Health Organization (WHO), and that analysis proved prescient in more recent global outbreak events such as Ebola (WHO, 2005).

This cluster heralded a global pandemic and the declaration by WHO of a Public Health Emergency of International Concern (PHEIC). It occurred in the context of a decade of planning for a potential H5N1 outbreak, which included WHO updating its pandemic guidance (Pandemic Influenza Preparedness and Response, 2009). In 1997 a small but lethal cluster of influenza occurred in children in a Hong Kong nursery. Of the 18 cases, 6 died (Mounts et al., 1999). Science shifted its understanding of influenza and recognized that flu could come directly from birds to humans. In fact H5N1, which emerged in 2003, acquired the popular moniker of 'Bird Flu.' The outbreak was curtailed through active surveillance, changes in practice, and poultry culling of live markets in Hong Kong. However, the outbreak proved a harbinger of more widespread recognition of 'Bird Flu.' H5N1 was identified through active surveillance of poultry and wild birds; waterfowl were particularly affected. Human cases were sporadic but carried a very high mortality rate (estimated at 60%) (Webster et al., 2006).

Although the virus proved difficult to transmit to humans, case fatality was high. As of February 2011, about 500 laboratory-confirmed human cases had been reported to the WHO from 15 countries; about 60% of reported cases were fatal.

The spread of H5N1 was geographically broad with extension into Nigeria and throughout Southern and SE Asia in waterfowl and in domestic fowl. Extensive planning for a potential pandemic was put into place given the apparent proximity of the threat and the high mortality in humans. Veterinary and human health collaboration was a central precept of this planning in the 'One Health' concept (Heymann and Dixon, 2013). The H5N1 threat did not materialize despite the high level of circulation in birds. Preparedness in SE Asia in particular included tabletop exercises, culling of birds through rapid response, and at least one joint investigation carried out between Laos and Thailand.

In this setting, H1N1 ran its course, with a milder clinical syndrome (although it is estimated that the global death toll was 284 000). The pandemic of H1N1 precipitated some confusion as well as competition for access to antivirals and vaccines. In the aftermath of these contentious discussions, new policy initiatives were put into place. This included the 'Pandemic Influenza Preparedness' (PIP) (WHO) plan which took some years to negotiate. It balances access to new viral strains for vaccine production with access to these vaccines for poor countries. The Fineberg Commission to examine an

'after action' performance of the International Health Regulations (IHR) was central to potential reform as well. This will be more fully discussed below.

In 2013 a new influenza virus, H7N9, was isolated from patients in the People's Republic of China. Isolates were both from birds and from humans. Although 571 cases occurred globally with 212 deaths, international spread was limited to two countries. The national response to this epidemic was very strong which is a key to control (discussed below).

Severe Acute Respiratory Syndrome

The 2009 influenza pandemic also followed another global respiratory emergency, SARS. The etiology of SARS (a new coronavirus) was not known in late 2002 when cases and deaths began to occur in Guangdong province of the People's Republic of China. Initially misdesignated as a chlamydial pneumonia early in the course, public alarm mounted as antibiotics proved futile in treatment.

Between November 2002 and July 2003, a total of 8427 probable SARS cases were reported from 29 countries with 813 deaths for a mortality rate of 9.6% (MMWR, 2003). SARS effectively demonstrated the potential mobility of respiratory pathogens. While SARS was declared poorly transmissible, it effectively jumped continents in travelers and infiltrated populations through nosocomial spread. In contrast to influenza, which is highly transmissible, SARS still requires direct exposure to bodily fluids for transmission. However, SARS shifted the scientific paradigm of zoonotic transmission more fully – with incrimination of wet markets vending civet cats initially thought to be the source. This initial assessment has proved less robust in terms of 'reservoir' for new human pathogens as discussed below.

SARS also challenged our understanding of transmission dynamics. For reasons that remain unclear, a single infected person who spent a single night in a hotel in Kowloon resulted in geographically broad transmission. The concept of a 'super-spreader' was popularized (Lloyd-Smith et al., 2005). This phenomenon was also described in a second scenario in Beijing (Shen et al., 2004). Traditionally infection has been characterized by a 'reproductive rate' which is essentially the rate at which an infectious case replaces itself. If the rate is 1, then there will be no spread, as the infection will simply stay the same absolute number as the index case recovers. However, if the rate is higher (i.e., >1), then spread into the population will occur as a single case infects multiple individuals so the number of cases increases. Super-spreaders seem to have high infection rates although the overall rate for the pathogen in question may be low. This has, of course, changed our assumptions for modeling disease spread in populations.

Middle East Respiratory Syndrome Coronavirus

Following the 2009 H1N1 pandemic (and the avian influenza emergence of 1997) and the SARS pandemic of 2003, a new virus emerged on the Arabian Peninsula. MERS-CoV is a new human pathogen that also causes pneumonia and respiratory distress. The story of MERS is less history and more present in terms of defining its epidemic potential. It reinforces the need for 'One Health' collaboration between veterinarians, clinicians, and public health specialists, making use of their relative expertise.

MERS was first reported in 2012 as a case report of a patient in an ICU with severe respiratory disease from Jordan (Hijawi et al., 2013). At the time of this writing, 1321 cases and 466 deaths have been reported to the WHO, with an average case fatality ratio of 35%. In one epidemiological analysis, the case fatality ratio for primary cases was 74% (95% CI, 49–91), whereas for secondary cases, it was 20% (95% CI, 7–42) (Alsolamy, 2015).

Like its coronavirus cousin, SARS, MERS-CoV has demonstrated agile spread within hospitals (Oboho et al., 2015) and across continents. In 2015 a large outbreak occurred in South Korea (Cowling et al., 2015). That outbreak was characterized by a mortality rate of about 20% among 186 cases, 33 were fatal. It also featured 'super-spreading' events. In fact a single case housed in the emergency room with persistent cough was linked to 81 cases in one hospital (Kucharski, 2015).

To summarize, the recent episodes of respiratory infectious diseases related to influenza, SARS-CoV, and MERS-CoV have demonstrated increasingly direct links between animal and human infections, agile intercontinental geographic spread, and complex transmission dynamics including 'super-spreader' events. Transmission within health-care settings has also been a prominent feature. These characteristics have challenged traditional assumptions about the pathogenesis and epidemiology of infectious diseases.

Beyond Biology: Auto-replicating Proteins

Traditionally microbiology has held that microbes (bacteria, viruses, protozoa, fungi, etc.) are organisms that replicate through genetic mechanisms. That replication is a major factor in the illness in humans these agents cause. Recent emerging infectious events have brought an additional complexity into that decades' old assumption.

New Biology-Prions

A new form of a human neurodegenerative disease that emerged in Britain in the 1990s was linked to the emergence of bovine spongiform encephalitis (BSE) in cattle ('mad cow disease'). This link was demonstrated through multiple case-control studies. The biological proof of a common etiology came somewhat later (Hill et al., 1997).

Prions are not microbial life in the traditional sense. They are 'autocatalytic proteins' or proteins that make change. In the instance of 'transmissible spongiform encephalopathies' (TSEs) of mad cow disease (BSE), sheep 'scrapie,' elk chronic wasting disease, as well as in the human diseases of Creutzfeldt-Jakob disease (CJD), new variant Creutzfeldt-Jakob disease (vCJD) and kuru, these changes occur in the central nervous system.

While the new vCJD epidemic related to ingestion of infected beef from BSE-affected cows has waned due to enhanced global surveillance and animal husbandry practices, research into prion disease continues. It appears that despite their lack of genetic material, prions do undergo mutation and strain diversification in response to selective pressures (Collinge et al., 2007). Soberingly, it is believed that some humans (estimated 1 in

4000 Britons) silently carry pathogenic prions for many years. This risk persists and creates safety concerns for blood transfusions and organ transplantation.

The story of BSE demonstrated the limitation of the traditional assumption that genetic reproduction of pathogens is necessary for infection as outlined above. The UK beef industry had historically been a relatively stable one when fragmented among many smaller farms across the British Isles. To protect this industry, the government maintained a tariff on the imports of competing products from abroad. With the explosion of global trading in beef after World War II, coincident with refrigerated transport, and the movement toward global free trade, the United Kingdom negotiated a timetable under the General Agreement on Tariffs and Trade to scale down tariffs on beef, which heightened competition in the UK beef industry and increased pressure for more efficient and less costly production methods.

Against this backdrop, innovation in rendering was introduced into the slaughterhouses of the United Kingdom. The rendering or processing of carcasses of cows and other animals after the edible and usable bits of flesh and meat have been cut away has been done for centuries. And for decades, UK farmers used the meat and bone meal from rendering as a protein source for beef cattle. Historically, the rendering process was similar to pressure cooking – applying very high temperatures for very long times so eventually even the bones broke down into powder. It was an expensive, fuel-consuming, and time-consuming process. When a new cold vacuum extraction method of rendering was introduced requiring lower temperatures (i.e., less energy) and less time, it seemed a win–win situation considering the increasing pressure on the UK beef industry in the face of global competition. But sometime after the new rendering practice was introduced into the United Kingdom, the prion disease known as mad cow disease emerged. The new process, discovered by UK beef industry, was not effectively disinfecting for prions. Existence of prion disease was unknown prior to its dramatic emergence, first in cows and then in people. The context is important to appreciate. Somehow the streamlining of the rendering process played a role. British scientists tested the new process by deliberately introducing animals with mad cow disease and assaying the resulting meat and bone meal product. They found that the newer rendering process does not remove the infection, whereas the older process did.

Zika Virus: Emergent Intergenerational Risk?

Zika virus emerged in sub-Saharan Africa in the late 1940s. It is a close cousin of dengue virus and in the same family as yellow fever. All of these viruses are transmitted to humans through the bite of a mosquito. All of these diseases are clinically mild, but occasionally severe causing fever, rash, and joint pain. Unfortunately all of these diseases have become globally distributed. Zika is the most recent arrival in the Americas. It has circulated in Asia for some time (Chen and Hamer, 2016).

While clinically relatively mild, epidemiologic studies in Brazil have suggested a link between Zika virus and severe birth defects in newborns. Viral infection in early pregnancy appears to be associated with microcephaly, which is associated with profound brain injury in newborns.

Again, the emergence of a new infectious disease is pushing the boundaries of biomedical knowledge. In the absence of certain prevention or treatment options, the government of Brazil has gone as far as advising women not to become pregnant (McNeil, 2015).

Antimicrobial Resistance in Small Packages

The emergence of antimicrobial resistance has continued to be a major concern. In 2008 a new enzyme in gram-negative bacteria was detected which caused broad antibiotic resistance. This enzyme was produced by mobile genes that travel on plasmids. Plasmids are small circular DNA (genetic) packages, which are distinct from the DNA of the bacteria itself. These are mobile, with the ability to be taken in across classes of bacteria if and when they confer a selective advantage for survival, as in the case of antimicrobial resistance. The new enzyme NDM-1 (New Delhi metalloproteinase-1) was traced to an infection that occurred in patients who had been treated in India. A more complete study of the epidemiology of this enzyme in gram-negative bacterial isolates from the subcontinent suggested a broad range of gram-negatives were affected (Kumarasamy et al., 2010).

This new biology, which was first described for extended spectrum beta lactamase (ESBL) resistance in the 1990s, has provoked renewed concern in antimicrobial resistance. 2011 was declared by the WHO as the year to address antimicrobial resistance. The pharmaceutical pipeline is bereft of new antibiotics to address this challenge. Chillingly another new pan-resistant plasmid has been reported from China, which is resistant even to the last line of defense, the polymixin class of antimicrobials (Liu et al., 2015). This report included isolates from pigs at slaughter, retail pig and chicken meat, and humans. Again, the specter of intensive agriculture fostering new biological threats calls for careful study. The isolates were largely from areas of intensive porcine agriculture in China. Figure 1 indicates sites sampled for polymixin plasmid resistance.

Reservoirs in Nature Links?

The question of where new infections lurk in nature has been an active area of research. As noted above, the initial reservoir for SARS coronavirus was thought to be civet cats which are domestically raised for food in China. However, further investigation has suggested that there may be a single host involved in many emergent diseases. In an elegant demonstration of interdisciplinary research, Han et al. (2015) have recently published a persuasive article on the role of bats in emerging infections. Whether or not the theses of the article prove true with further research, the work provides additional evidence of how extremely powerful interdisciplinary research can be toward solving the puzzles of emergent diseases in humans. In discussing the spillover of viruses from bats to humans, the authors write:

Factors that contribute to the intrusion of bats into human living environment can be summarized into a 'push' and a 'pull'

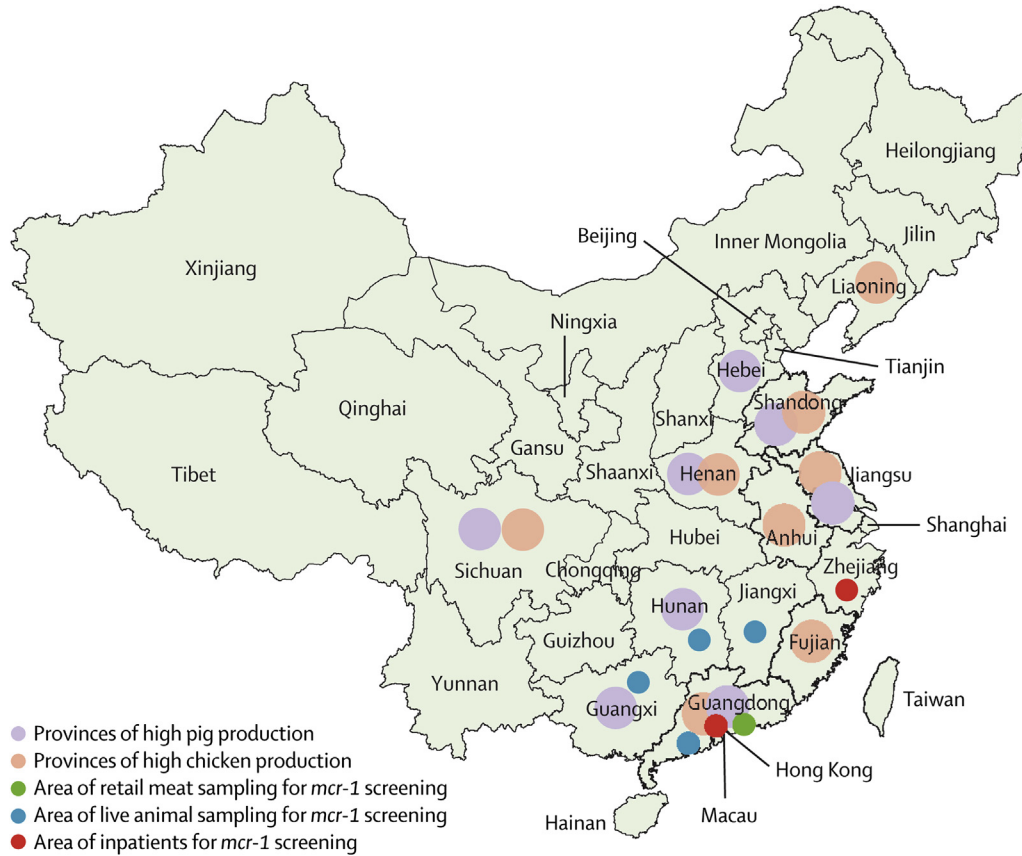


Figure 1

(Brüssow, 2012). A ‘push’ refers to the enormous demand for more space and resources brought by the human population explosion, which leads to the destruction of bat habitats and shortage of food. Natural environmental changes, such as typhoons and droughts, can also place stresses on bats. A ‘pull’ involves the living environments built by humans, characterized by urbanization, intensive agriculture and food animal breeding, which attracts bats into human living environments for an abundant of food supply.

So coming full circle, this discussion highlights the critical importance of further understanding these events of ‘species jumping’ or ‘spillovers,’ given the pressures will only augment rather than abate. Infections potentially housed in bats as their natural reservoir (from Han and colleagues) is shown in Table 1.

It is an impressive array, which brings us to consider how indispensable further understanding in these interactions is to gain insight into emergent human infections.

Table 1 Summary for selective bat-borne viruses

Virus	Putative host	Intermediate host	Modes of transmission	Drivers
Nipah virus	Flying foxes	Pigs	Close contact with sick ones, drinking date palm juice, contact with pigs	Climate changes, changes of farming practices (dual land use), transportation of pigs as merchandise, social/cultural practices, habitat destruction
Hendra virus	Flying foxes	Horses	Contact with horses	Climate changes, urbanization, social/cultural practices
SARS-CoV	Horseshoe bats	Palm civets	Slaughtering, farming of wildlife	Economic growth, desire for game meat, wildlife trading in wet markets, international travel
MERS-CoV	Bats ^a	Dromedary camels	Direct contact with camels, consumption of camel milk/meat	Not known
Ebola virus	Egyptian fruit bats	Nonhuman primates	Slaughtering, hunt for bush meat	Preference for bush meat, burial practices, poor health-care practice

^aSpecific bat species not identified.

Interplay of Infection with Human-Made Factors

So what explains the apparent increased pace of emergence of new human infections? Is it simply that we are more able, with our new technologies, to detect them? Or are there forces at work that are fostering this trend?

The stories of BSE and nvCJD recounted above were outlined because the United Kingdom, although a small country, has excellent epidemiologic, statistical, laboratory, and clinical acumen. While cases of BSE and nvCJD were not confined to the United Kingdom, the origin of emergence was tracked and described relatively efficiently.

But, what of influenza? The potential contribution of intensive poultry and swine agriculture to the emergence of influenza A emergence was outlined in my earlier article for this publication. Research over the past decade has continued to provide evidence of this risk. As intensive practices have spread to developing countries, the assurance of biosecurity has become less sure as noted in the discussion (above) of polymyxin resistance through plasmids in pigs and humans. While many new strains of influenza arise in wild birds (particularly waterfowl), the link to human populations appears to be through domestic poultry (Leibler et al., 2009).

However, other anthropogenic mechanisms are also at play. Without the global 'mobile' environment of travel and trade, emergence would remain a largely local phenomenon. However, as we saw with the influenza discussion above that is not the case. Nor was it the case with SARS or with MERS-CoV. International tourism surpassed 1.1 billion arrivals in 2013 according to the World Bank (World Bank International Tourism). After a slump in global trade during the global recession exports of food in 2014 reached nearly \$1.5 trillion in value for selected countries where data were available. This, of course, does not include all of global trade, which has surpassed \$3 trillion in value (Merchandise Trade by Product). Guarding against transcontinental transmission in food or through human travel is a complex undertaking, with safeguards at the source the most likely answer. However, research, testing, and demonstration of effective measures remain wanting.

Finally, climate change, largely attributed to human activity, seems to be readjusting the boundaries of mosquito borne diseases. The recent incursion of Zika into Brazil is attributed to the *El Niño* weather pattern now in force in that geography. While *El Niño* oscillation is not directly attributable to human activity, the shifting of such natural oscillations and their severity may well be.

In his landmark 1993 book *Planetary Overload: Global Environmental Change and the Health of the Human Species*, Anthony J. McMichael outlines the human-generated stress on natural systems (McMichael, 1993). He posits that food will become increasingly scarce for the human community. The macroecologic effects of human activity on climate, water, food, agriculture, pollution, and human health are well described, but the systematic link between the macrolevel (what we can see) and what is occurring on the microlevel remains an important area of research. To address the emergence of new pathogens, we need more precise knowledge about the mechanisms that form the critical pathway to emergence.

A follow-up report to the landmark IOM Report, *Emerging Infections, Microbial Threats to Health: Emergence Detection and*

Response was published in 2003 (Smolinski et al.) (*Microbial Threats to Health*). Additional factors of emergence were examined in this report: human susceptibility to infection, climate and weather, changing ecosystems, poverty and social inequity, war and famine, the lack of political will, and intent to harm. Thus the original 6 factors grew to 13. While enriching the discussion and description of emergence, this proliferation of factors also created overlapping domains within factors; for example, climate and weather are an integral physical science aspect of ecosystems, the failure of political will is integral to the neglect of public health systems, and so forth. From an analytic point of view, the need for in-depth study of factors and how they actually work has become critical for scientific insight into public health protection.

McMichael has suggested the term 'the anthropogenic epoch' to describe our contemporary situation. In other words, human kind is changing the nature of our environment in unprecedented ways. More recently the Rockefeller-Lancet Commission has suggested the new scientific discipline of 'Planetary Health' as a unifying concept to bring the disparate strands of life sciences, and ecology more closely together to foster interdisciplinary research and insight (The Rockefeller Foundation, 2015). The key to success will require intense investment in transdisciplinary research which brings in disparate databases and talents into risk analysis.

New Tools

While a full discussion is beyond the scope of this discussion, a number of new tools have come into use that allow more rapid diagnosis and response to newly emergent outbreaks. A few will be highlighted here.

Informal Disease Surveillance Networks

In addition to formal disease surveillance reporting a number of informal diseases, surveillance networks have arisen among countries which share common borders or work within a common economic bloc. These networks facilitate the flow of information across borders and allow collaborative investigations, tabletop exercises, and resource sharing on an ongoing basis. In postconflict areas such as the Mekong Basin, they contribute to health security (Gresham et al., 2013).

Modeling

Increasing sophistication of bringing disparate data sets together and creating models to understand possible scenarios has brought additional insight into prevention and control efforts for emerging diseases. Prediction of where outbreaks are most likely to occur remains a very imperfect science (Jones et al., 2008). Retrospective niche modeling has brought additional insight into how different factors may interact to foster outbreaks (Daszak et al., 2013).

Rapid Genomic Sequencing

Laboratory diagnosis of unknown agents has also advanced. During the SARS outbreak, the WHO convened an informal network approach to fully sequence the new agent in 1-month time (David, 2004). One group has put forward a vision of bringing full genomic sequencing into the

laboratories of developing countries (Aarestrup et al., 2012). Clearly the ability to quickly diagnose new agents without the necessity of culture would be an important advance. As importantly the integration of informatics linking genomic analyses to phylogenetic metadata would allow global tracking of agents.

Is the World Prepared?

As the boundaries of microbiology are stretched with new insights from emergent diseases, the ability of the people of the world to protect against pandemics is more important than ever. Global traffic and trade continue to grow, confounding national approaches with their international span.

In 2005 (following SARS) the WHO adopted the IHR (international health regulations). This is the only law with the force of an international treaty, which is in place to govern the conduct of countries during global security emergencies. The IHR outline 'core capacities' for national-level protection. It is not the optimal level for an emergent pandemic, but it is the minimum considered essential for global health security. The IHR implementation was to have been completed by all member countries by 2012. However, implementation has languished with only one-third of countries implementing and many not disclosing their status of implementation to the WHO in 2015.

After the 2009 influenza pandemic, an independent expert panel was convened to assess how the IHR functioned. That panel, lead by Dr Harvey Fineberg, then President of the Institute of Medicine, was explicit in outlining the gaps in global health security.

The world is ill-prepared to respond to a severe influenza pandemic or to any similarly global, sustained and threatening public-health emergency. Beyond implementation of core public-health capacities called for in the IHR, global preparedness can be advanced through research, reliance on a multisectoral approach, strengthened health-care delivery systems, economic development in low and middle-income countries and improved health status.

Fineberg (2014).

In 2013, Ebola (a known infection) emerged in Guinea. At the time of its appearance, none of the countries in sub-Saharan Africa had implemented the core capacities of the IHR (Kimball and Heymann, 2014). The outbreak went on to create pandemonium in the three most affected countries (Guinea, Liberia, and Sierra Leone) killing over 11 000 people (and afflicting more than 28 000) (ebola-situation). Infection was introduced in other countries, but onward transmission was limited. Following Ebola, the international systems are again under review. Initial observations remain distressingly similar to those made in 2009. With reform of the UN and WHO, once again underway, it will be important to follow through. Of particular importance as highlighted above is the interdisciplinary (and in the case of the UN interagency) nature of prevention, detection, and response to emergent threats. Despite the new technological tools, the ecological factors in emergence are ever gathering force. Clearly additional efforts are required. Emerging infections remain an intersectoral challenge with every indication they will continue to be with us over the coming decades.

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See also: Antimicrobial Resistance in a One Health and One World Perspective – Mechanisms and Solutions; Arboviruses; Ebola and Other Viral Hemorrhagic Fevers; Global Health Law: International Law and Public Health Policy; Influenza.

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