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MINIREVIEWS

The Threat and Response to Infectious Diseases (Revised)

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Abstract The threat from microorganisms is complex, and the approaches for reducing the challenges the world is facing are also multifaceted, but a combination approach including several simple steps can make a difference and reduce morbidity and mortality and the economic cost of fighting infectious diseases. This paper discusses the continually evolving infectious disease landscape, contributing factors in the rise of the threat, reasons for optimism, and the policies, technologies, actions, and institutions that might be harnessed to further reduce the dangers introduced by pathogens. It builds upon and updates the work of other authors that have recognized the dangers of emerging and re-emerging pathogens and have explored and documented potential solutions.

Keywords Emerging infectious diseases · Antibiotic resistance · Strategic

Introduction

In just the past year, the United States has been bombarded with headlines on the dangers of infectious diseases: "HIV 'Epidemic' Triggered by Needle-Sharing Hits Scott County, Indiana [1];"

"American with Ebola Now in Critical Condition [2];" "Seasonal Flu Vaccine Even Less Effective than Thought: CDC [3];" "'Superbug' Outbreak at California Hospital, more than 160 Exposed [4];" "Deadly CRE Bugs Linked to Hard to Clean Medical Scopes [5];" "Painful Virus [Chikungunya] Sweeps Central America, Gains a Toehold in U.S. [6]."

The Ebola outbreak that began in 2014 and the measles outbreak initiated at Disney World in particular brought the threat of "exotic" infectious diseases back to the American and global consciousness. This coupled with the fact that the most commonly circulating strains of the influenza A virus H3N2 drifted [7] from that used in the 2014–2015 influenza vaccines serve as reminders that the threat from microorganisms is continuously evolving and is persistent.

The threat of emerging and re-emerging pathogens has been discussed in the scientific literature, the medical community, by policy makers, and the general public over the past 70 years, but much of the discussion was among directly affected populations and their caregivers. General interest flourished after a series of events in the 1990s and early 2000s. In 1992, a report by Russian General Kuntsevich followed by Boris Yelstin's decree in April of that year to end all offensive biological weapons programs revealed that the former Soviet Union had an extensive biowarfare program and that facilities and expertise still existed which would enable Russia to unleash deadly pathogens on the world [8]. In 1996 when Shoko Asahara, the spiritual leader of a Japanese religious cult, was arraigned, the magnitude of the organization's attempts to deploy anthrax in 1993 was exposed [9]. In October 2001, the United States was transfixed by the first bioterrorism attacks on its own soil: envelopes containing *Bacillus anthracis* spores were sent through the mail to targets ranging from media companies to government officials [10]. Five people died and thousands were treated with prophylactic antibiotics. The attacks and other attempted and planned attacks, along with widely publicized outbreaks such as West Nile Virus in 1999 [11] and severe acute respiratory syndrome (SARS) in 2003 [12], brought the topic of infectious disease to the forefront. In addition, more incessant threats such as

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influenza and lower respiratory infections continue to kill and cause economic harm through lost productivity and hospitalizations. Furthermore, zoonotic diseases such as salmonella and listeria, which represent more than two-thirds of emerging and re-emerging diseases [13], raise the visibility of the economic and human and animal health issues caused by pathogens. In April 2015, the Sabra Dipping Company voluntarily recalled about 30,000 cases of hummus potentially contaminated with *Listeria monocytogenes.* At the same time, Blue Bell recalled nearly 30 products also similarly contaminated. While there were no known casualties as a result of the Sabra contamination, authorities in Kansas and Texas reported that three deaths in each state might be attributed to the Blue Bell incident [14].

The threat from microorganisms is complex, and the approaches for lowering the challenges the world is facing are also multifaceted, but several simple steps can make a difference. This paper will discuss the emerging infectious disease landscape, contributing factors in rise of the threat, reasons for optimism, and the actions, policies, technology, and institutions that might be harnessed to further reduce the dangers introduced by pathogens. It builds upon the work of other authors who have recognized the dangers of emerging and re-emerging pathogens and have explored and documented potential solutions [15–17].

Emerging Infectious Disease Landscape

Microorganisms pose health and economic threats and may pose a strategic threat if a large percentage of the population is overcome or if the potential transmission of infectious diseases across borders causes an increase in tension among state allies or enemies. One organism alone, *Clostridium difficile,* is estimated to cost the United States between $1 and $3 billion per year [18], with its primary impact on American children [19]. Initially identified in the early 1900s as a commensal organism in the digestive tract, *C. difficile* infection (CDI) has only been recognized as a significant threat to pediatric health over the last decade [19]. The threat to both children and adults is global. Infections since 2003 have become more common, more acute, less treatable by standard therapy, and more likely to reoccur [20]. Initially, the *C. difficile* infections were associated with the use of the antibiotic clindamycin, but fluoroquinolones and cephalosporins are currently the more likely cause of disturbed gut microbiota, which increasingly lead to colonization with ribotype 027, a severe variant of *C. difficile* [20].

According to the Centers for Disease Control and Prevention (CDC), emerging infectious diseases are those "whose incidence in humans has increased in the past two decades or threatens to increase in the near future [21]." While there may be debate about the specifics, for the purposes of this article, re-emerging and emerging diseases are distinguished as follows: re-emerging diseases are those that were known to impact humans or animals in the past and were thought to be brought under control with zero or few infections in the past several decades. These include infections resulting from changes or evolution of existing organisms and changes in the geographic distribution of an organism or populations affected by the organisms. Previously unrecognized (in the past several decades) infections are considered emerging. According to this definition, *C. difficile* would be considered an emerging pathogen as its dangers were not recognized when it was first identified.

Other outbreaks and trends of concern include the following: tuberculosis (TB), while no longer among the 10 leading causes of death in 2012, was still among the 15 leading causes, killing over 900,000 people in 2012 [22]. In the United States, while overall TB incidence is decreasing, it is still a large problem for foreign-born residents and for the homeless population at a cost of nearly $ 50 million per year [23]. Lyme disease caused by the spirochete *Borrelia burgdorferi* was recently recognized as an epidemic. The disease is difficult to diagnose, causes long-term disability if untreated, and may impact as many as 1000,000 people in the United States [24]. More than 40 % of Lyme disease patients continued to exhibit symptoms after six months, and for 10 % of infected people, symptoms continued for more than three years [25].

The spread of diseases such as multidrug resistance *Acinetobacter* in at-risk populations is also of increasing concern. "Within the last 15 years, members of the bacterial genus *Acinetobacter* have risen from relative obscurity to be among the most important sources of hospital-acquired infections. The driving force for this has been the remarkable ability of these organisms to acquire antibiotic resistance determinants, with some strains now showing resistance to every antibiotic in clinical use [26]." *Acinetobacter* resistance to drugs such as imipenem and ampicillin/sulbactam increased 25 % from 2003 to 2008 [26].

Leptospirosis, one of the most widely distributed zoonotic diseases worldwide, is an emerging public health concern particularly in large urban centers of developing countries [27]. It is also important in the United States in humans, pets, and wildlife. Experts believe incidence in humans is underreported, but the CDC estimates that 100–200 leptospirosis cases occur annually with approximately half of those in Hawaii [28]. In 1998, 775 triathletes in Illinois were exposed to Leptospirosis of which 110 became symptomatic [28], representing the largest human outbreak in the United States. Recently, cases in pets have caused concern in California [29], Michigan [30], and Florida [31]. More than a quarter of the tested deer population in Michigan was infected with the disease [30].

West Nile Virus (WNV) is another zoonotic disease of concern, and the US population and health practitioners have become more aware of this disease over the past decade. Birds

carry the virus, which is then transmitted by mosquitoes to humans, horses, and other mammals. Disease symptoms range from fever to neurological complications, such as encephalitis or meningitis. Mortality is observed mostly in older and immunocompromised individuals. In 1999, WNV was introduced to the United States, and its range soon extended across North America [32]. Not only is the number of WNV outbreaks increasing but also novel strains are emerging, which display higher virulence. WNV has also developed sophisticated avoidance mechanisms to avoid its elimination [33].

Noroviruses are the leading cause of foodborne disease outbreaks worldwide and may soon eclipse rotaviruses as the most common cause of severe childhood gastroenteritis, because rotavirus vaccine use is becoming more prevalent [34]. Norovirus rapidly undergoes genetic mutations and recombinations so that new epidemic strains are constantly evolving. Although norovirus infection is generally not fatal, infections in children, the elderly, and the immunocompromised can cause morbidity and even death. Research into a vaccine or treatment has been impeded by the lack of a cell culture or small animal model. However, vaccines based on norovirus capsid protein virus-like particles show potential and may become broadly available through transgenic expression in plants [34].

Vibrio vulnificus, a common gram-negative bacterium in warm coastal waters globally, is an emerging pathogen [35, 36]. Up to 30 million vulnerable Americans are at risk when consuming raw or improperly prepared seafood tainted with *V. vulnificus* which can cause primary septicemia [36]. Additionally, all individuals are at risk of serious wound infection that may lead to secondary septicemia [37, 38]. Even with antibiotic treatment, half of patients may die from primary septicemia and a quarter from secondary [36, 37]. Other environmental organisms of concern include the waterborne pathogen that causes Legionnaires' disease, *Legionella* bacterium; *Naegleria fowleri*, which causes amebic meningoencephalitis; other Mycobacterium (hospital environment) such as *Mycobacterium abscessus* and M.*massiliense* in lung disease; the mosquitoborne Chikungunya virus and the tickborne Bourbon virus.

In addition to causing acute illness, research has uncovered links between infectious diseases and cancer. In one study by Wu et al. [39], researchers found measurable differences in fecal microbiota between healthy individuals and those with colorectal cancer as determined by pyrosequencing of the 16S rRNA gene V3 region. As early as 1981, researchers found that hepatitis B surface antigen (HBsAg) carriers had a greater incidence of primary hepatocellular carcinoma (PHC) than among non-carriers [40].

The list of emerging and re-emerging pathogens could fill up a tome. These organisms vary in virulence and distribution, but all of them share common characteristics in that the incidence or virulence or both are increasing and humans must find methods of preventing, detecting, and treating them. To combat infectious disease, it is important to understand the factors that are working to increase the occurrence and severity of infections.

Factors in the Rise of the Threat of Microorganisms

Human behavior has a large impact on the creation of environments where microorganism can evolve and mutate. These changes can sometimes make organisms more infectious and/or virulent. Examples include the following: antibiotics in the environment through overuse and misuse; changes in sexual norms; patterns of drug use and incarceration; global climate change; human incursion into new environments; and changing patterns of human interactions with wild and domesticated animals; expanding travel patterns; vaccination avoidance; and population concentrations in large cities. Recent cases are used to illustrate how differences in human behavior have modified the threat from bacteria and viruses.

Antibiotic Resistance

The problem of antibiotic resistance is threefold: there has been a rise in the number or identification of resistant bacterial strains; the pipeline for the development of new medicines to treat infection dried up significantly over the past 20 years; and the most significant problem is the lack of stewardship of existing antimicrobials. These issues have led to a reduction in the efficacy and number of responses available to physicians and their patients. The biological processes that lead to resistance are extremely complicated and not fully understood, resulting in sometimes limited progress in the control and treatment of resistant microorganisms and the diseases they cause [41] despite recognition of the problem nearly a century ago. Davies and Davies [41] compiled a list of "suberbugs," which have increased pathogenicity and are more impervious to treatment. Their list includes the following: Multidrug-resistant (MDR) *M. tuberculosis;* nosocomial (hospital-linked) infections *with Acinetobacter baumannii, Burkholderia cepacia, Campylobacter jejuni, Citrobacter freundii, Clostridium difficile, Enterobacter* spp., *Enterococcus faecium, Enterococcus faecalis, Escherichia coli, Haemophilus influenzae, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Salmonella* spp., *Serratia* spp., *Staphylococcus aureus, Staphylococcus epidermidis, Stenotrophomonas maltophilia,* and *Streptococcus pneumoniae*. Their list does not include the New Delhi Metallo-beta-lactamase-1 (NDM-1) resistant strains discussed below. As the authors point out, in addition to the direct human toll, treatment is often more costly [42] when resistant organisms are involved. In fact, the issue has become so acute that new terms have developed over the past

decades: microorganisms that are pan-drug resistant (PDR) or extremely drug resistant (XDR).

One of the most widely dispersed antibiotic resistant organisms is *M. tuberculosis.* Worldwide, this organism is often resistant to multiple drugs, and in 2009, completely drug-resistant forms of tuberculosis were reported in citizens of four countries: Afghanistan, Azerbaijan, Iraq, and Iran [43]. In many organisms, such as enteric bacteria which are acquired both in community and hospital settings, resistance (often to β-lactam antibiotics in this case) spreads through horizontal gene transfer on plasmids; however, there have been no documented cases of this in tuberculosis, where all resistance occurs by spontaneous mutation [40]. Multidrug resistant *Pseudomnas aeruginosa* is also of concern as it is deadly and widespread [44, 45]. *M. tuberculosis* is one example of the multitudes of resistant organisms. Other widespread and dangerous bugs include *Staphylococcus aureus* (66.4 per 1000 inpatient prevalence rate in 2010 [46]) and *C. difficile* (in 183 US hospitals in 2011, *C. difficile* was the most commonly reported pathogen causing 12.1 % of health care-associated infections and *Staphylococcus aureus* caused the second highest percentage, 10.1 %. *Klebsiella pneumoniae* and *Klebsiella oxytoca* 9.9 % and *Escherichia coli* 9.3 % followed closely behind [47]). At a single hospital in 2010 and 2011, resistant *Acinetobacter baumannii* infected 13.5 % of patients who were not previously infected [48].

Infections with resistant organisms are harder to control; standard treatments are less effective; illness and hospital stays are longer; and mortality is higher. Gram-positive organisms resistant to antibiotics were the first concern, but resistance in gram-negative organisms emerged: gram-negative bacteria resistance increases faster than in gram-positive bacteria [49], and there are fewer antibiotics in the pipeline that work against gram-negative bacteria [50].

Cosgrove et al. [51] performed a meta-analysis of studies published between 1980 and 2000 on the impact of methicillin resistance on mortality. These studies included nearly 4000 patients, a third of whom were infected with methicillin resistant *Staphylococcus aureus* (MRSA). Mortality was significantly lower in the group infected with susceptible bacteria. In another study, Cosgrove's group found that MRSA bacteremia also increased median length of hospital stay by almost 30 % and not surprisingly (given the longer stay), increased hospital charges from an average of $19,212 to $26,424 [52]. A prospective study found similar results in hemodialysis patients at the Duke University Hospital [53] as did a study on orthopedic patients [54]. Vancomycin-resistant enterococci (VRE) [55] and Enterobacter species resistant to third generation cephalosporins [56] showed a similar trend; however, penicillin- and cephalosporin-resistant *Streptococcus pneumonia* results were dissimilar, and the authors surmised that this might be due to the specific use of vancomycin [51].

Chemicals in daily use may also change microorganism susceptibility to antimicrobial agents. For instance, it has been regularly demonstrated in the laboratory that resistance to triclosan, an antimicrobial agent used in many household products including hand sanitizer, and cross-resistance to antimicrobials increases with use of triclosan containing products; however these results have not yet been observed in the community. Based on the available evidence, the risk of potential antimicrobial resistance outweighs the benefit of widespread triclosan use in antimicrobial soaps [57].

Resistance is not something that can be conquered: bacteria with their relatively short lifespans can mutate quickly; however, with knowledge of the 20,000 resistance genes of 400 types [41], it may be possible to stay one step ahead of resistance and find new ways to treat bacterial infections.

Sexual Norms, Drug Use, and Incarceration

Other changes that have impacted infectious disease distribution and prevalence are changes in sexual norms, drug use, and incarceration. Needle sharing itself can spread infections, and the use of drugs can affect sexual and risk taking behavior which can put people in jeopardy [58]. While homophobia is decreasing in the United States and worldwide, homophobia has been one of the major social determinants of infection particularly with HIV/AIDS and other sexually transmitted diseases. For example, men sleeping with men accounted for 53 % of new HIV infections in 2008 [59]. Historical legal restrictions, which are now being relaxed in this decade, had ostracized gay people, limiting their self-identification and therefore efforts to target gay communities for education and prevention as well as diagnosis and treatment efforts.

Injecting drug users account for 12 % of new HIV infections often due to inadequate access to sterile needles and syringes and addiction treatment programs [59]. As noted below, drug use also changes behavior which also leads to increased transmission. Drug use and incarceration patterns go largely hand-in-hand. In part because of the United States hard line on drug use, United States incarceration rates are the highest in the world with minorities accounting for a disproportionate percent of the prison population. Incarceration rates disrupt community and sexual relationships and compound poverty issues, amplifying the exposure of communities and individuals to HIV infection and other infections [59]. In a second example, methamphetamine use has been shown to affect a person's judgment and may lead to unsafe behaviors such as reduced condom use, multiple partners, and increased drug injection. Methamphetamines also increase physical susceptibility because their use dries mucosa intensifying chafing and abrasions, which, in turn, allow microorganisms to enter the body during sexual and other activity [58, 60].

Overuse and Misuse of Antibiotics in Animals

Aquaculture contributes to the pollution of rivers, bays, and even our oceans with antibiotics and antibiotic resistance genes (ARGs). From China to the United States, antibiotics and ARGs have been found in surface water of all types. For example, in the coastal water of the Bohai Bay, China, fluoroquinolones, macrolides, sulfonamides, tetracyclines and chloramphenicoles, and polypeptides were found at concentrations up to several micrograms per liter with higher concentrations where human activity was concentrated [61]. In a review, comparing aquaculture and land animal production with the respect to type, mechanism, and quantity of antibiotic resistance, Done, Venkatesan, and Halden [62] found that aquaculture was similar to terrestrial agriculture in terms of the resistance mechanisms, that 39 antibiotics used in aquaculture are important in human health, and that pathogens isolated from the farmed fish were resistant to multiple antibiotics.

Improper Disposal of Medicines

Due to improper use and disposal of antibiotics, the presence of antibiotic-resistant organisms and genes in natural waterbodies, wastewater, and treated municipal water has been widely demonstrated and reviewed [63–66]. Without additional treatment, this water is commonly used on crops; humans and animals then consume the products, and serious outbreaks have occurred that are difficult to treat because the microorganisms do not respond to commonly used antibiotics [63–66]. Pruden et al. [66] found concerning levels of ARGs in Colorado (United States) dairy lagoon water, irrigation ditch water, river sediments, treated drinking water, and recycled wastewater. Ramsden et al. [67] similarly found antibacterial resistance in municipal wastewater treatment plants. Zuccato et al. [68] discovered that the concentrations of atenolol, bezafibrate, clofibric acid, cyclophosphamide, diazepam, erythromycin, furosemide, lincomycin, oleandomycin, ranitidine, salbutamol, spiramycin, and tylosin were in the nanogram per liter range in river or drinking water or river sediments in several sites in Italy. Munir et al. [69] examined the presence of antibiotic-resistant genes and bacteria in several types of wastewater effluents in Michigan and found that advanced water treatment systems such as membrane bioreactors were significantly more effective than conventional wastewater treatment at removing the tetracycline-resistant gene *tet*O and sulfonamide-resistant gene (Sul-I) as well as tetracycline and sulfonamide-resistant bacteria. Anaerobic digestion and lime stabilization treatment of wastewater was more effective than the conventional dewatering and gravity thickening methods for removing antibiotic-resistant genes and bacteria [69]. Burch et al. [70] were able to significantly reduce the concentrations of the ARGs *tet*(A), *tet*(W), and *erm*(B) using conventional wastewater treatment (aerobic); however, removal of *intI1* required batch treatment, while the others required relatively long-term semi-continuous treatment. *Tet*(*x*) increased in concentration.

Travel Patterns

According to the World Bank, nearly 70 million travelers visited the United States and approximately one billion people traveled globally in 2012 [71]. The incidence of tuberculosis in the United States is largely due to foreign visitors and citizens and residents born in other countries [23]. Another, travel related resistance threat emerged in the United States in 2010 when three patients were reported to have the gene for New Delhi metallo-beta-lactamase (NDM-1), an enzyme that destroys beta-lactam antibiotics including commonly used penicillins, cephalosporins, and carbapenems. The first case was reported in India in 2009 [72], and to date, India and Pakistan have reported the most instances of NDM-1, but the gene is spreading globally, and cases have now been detected in many countries, including Great Britain, Canada, Sweden, Australia, Japan, and the United States. Antibiotics are widely used in India and some researchers [73] have demonstrated that overuse of carbapenems led to the development of NDM-1 [71]. Research also points to medical tourism as a cause [74–77]. NDM-1 is a newly identified problem, only recognized since about December 2009 in the medical literature, but it is only one example of diseases transmitted through medical tourism which is defined as travel to a country to get medical care that is not available or is more expensive in one's own country. Precise data on the economic value and the number of patients seeking medical procedures are not easily available. In 2009, Smith et al. [75] estimated that approximately four million patients crossed borders seeking treatment. In 2011, guidelines to unify definitions of medical tourism and methodologies for reporting its extent were published and accuracy of the types and amounts of medical tourism may improve in the near future [76]. A greater potential threat is related to the increasing travel of immunocompromised patients. Lortholary et al. [77] illuminated the fact that as more and more people are living with HIV, having organ transplants, using immunodilators, or suffering from diabetes, more individuals are infected when traveling. The authors suggested preparations and responses to prevent severe illnesses when traveling.

Infections spread within the United States from travel as well. For example, during the period from 2004 through 2011, 96 *Cryptococcus gattii* infections were reported to the CDC. *C. gattii,* an environmental fungus typically prevalent in tropical and sub-tropical regions, can cause an uncommon infection of the lungs and/or the central nervous system in those who inhale the fungus. More than 86 % of the cryptococcosis

cases occurred in people who had traveled to the Pacific Northwest. The infection was fatal for 33 % of the patients [78].

Stunted Antibiotic Pipeline

Many factors have reduced the number of new antibiotics approved in the United States each year as well as reduced domestic production including demanding Food and Drug Administration (FDA) regulations, the cost and time to market of development, the consolidation in the pharmaceutical industry, and the lack of financial impetus to produce and distribute antibiotics, which are generally used on a one-off basis versus drugs used to treat chronic conditions such as statins, Viagra, and allergy medications.

In a May 2012 speech, Janet Woodcock, the Director of the Center for Drug Evaluation and Research (CDER), acknowledged that new antibiotics were not sufficient to address growing antibiotic resistance and that FDA's approach to approval was a significant factor [79]. The FDA introduced new regulations for clinical trials at the beginning of the twenty-first century, which led to a cooling of antimicrobial development in the pharmaceutical industry [80]. First, the newly required approach doubled the cost of phase III clinical trials, already a substantial barrier for development. In phase III, it is expected that testing will include pairs of relatively large (usually >750 total subjects per study) groups of people conducted for the selected pathogen at the relevant body location(s). This has become challenging as new antibiotics focus on particular pathogens including resistant pathogens, making it difficult to enroll large numbers of patients [81]. In part because of the cost of the new regulations, Eli Lilly, Bristol-Myer Squib, Glaxo SmithKline, Proctor and Gamble, Roche, and Wyeth left the development business [7, 79]. In addition, while the amount of antibiotics prescribed has continued to grow, the market value has not changed and was estimated at $32 billion in 2010 [79] as compared to a $19.7 billion market in 2012 for statins alone [82]. Companies are getting out of the market because the regulatory burden is high, antimicrobials are typically used for short periods of time, public pressure is building to lower use, and the medicines are often subject to price controls outside of the United States [79, 83].

While development has slowed, in the past 15 years, 22 new antibiotics have been brought to market. Two approved more recently, fidaxomicin and bedaquiline, have new modes of action. Fidaxomicin was shown to effectively treat *C. difficile* [84]. Because the financial incentives are few, much antibiotic production has been outsourced from the United States to India, China, and other countries where labor, raw material, and energy costs are lower [85]. In fact, it has been more than 10 years since the active ingredient for penicillin was last manufactured in the United States. This presents a significant strategic problem for the United States in the case of an outbreak, particularly during times of conflict or worldwide scarcity.

Global Climate Change

Global climate change is increasingly accepted as causing extreme, unusual weather patterns [86]. Changing weather patterns can impact the presence of infectious agents in many ways. For instance, in May and June 1993, an initially unidentified disease killed ten people in the Four Corners region of Arizona and New Mexico. At the outset, 70 % of the patients died of the infection, and after the medical staff developed enhanced protocols, the death rate was only reduced to 40 %. Scientists isolated a hantavirus [87], and later, researchers determined that an unusually wet spring led to increased rodent carrier density which in turn impacted human infection rates; however, these factors alone are not enough to explain persistent hantavirus infection in the southwestern United States [88]. Ecosystem changes and human interactions with the environment may increase the transmission of infectious disease [89]. For instance, three studies found robust correlations between the threat to humans from West Nile virus and low bird diversity in the United States [89–91].

The spread of emerging infectious diseases among animals has significant human health and economic costs. Zoonotic diseases kill more than two million people per year and transmission occurs from both wild and domesticated animals [92]. Halsby et al. [93] reviewed the English literature with respect to infectious diseases caused by pet store animals and found 57 discussions of infections related to pet shops. The most commonly observed diseases were Salmonellosis and psittacosis: other diseases such as tularemia were also identified. The human animal interaction has impacted civilization throughout history. According to Daszak et al. [94], "Parallels between human and wildlife emerging infectious diseases (EIDs) extend to early human colonization of the globe and the dissemination of exotic pathogens. In the same way that Spanish conquistadors introduced smallpox and measles to the Americas, the movement of domestic and other animals during colonization introduced their own suite of pathogens. The African rinderpest panzootic of the late 1880s and 1890s is a paradigm for the introduction, spread, and impact of virulent exotic pathogens on wildlife populations. This highly pathogenic morbillivirus disease, enzootic to Asia, was introduced into Africa in 1889. The panzootic front traveled 5000 km in 10 years, reaching the Cape of Good Hope by 1897, extirpating more than 90 % of Kenya's buffalo population and causing secondary effects on predator populations and local extinctions of the tsetse fly." More recently, bovine tuberculosis, while responsible for only 22 cases of human tuberculosis in the UK, prompted the slaughter of tens of thousands of cattle in the first decade of the twenty-first century [95]. In 2015, throughout the United States, domestic poultry

and wild birds have been suffering from a highly pathogenic strain of avian influenza (HPAI) H5 [96]. Through June 17, 2015, more than 48 million birds were put to death. The cost of the government response is tagged at $500 million primarily to fund the work of 3400 staffers and contractors [97]. On the commercial side, analysts used economic models and found that for a million dollars in direct losses there are $1.8 million in overall economic losses. In mid-May direct losses in poultry production were estimated at $113 million leading to overall losses of more than $300 million [98]. Transmission to humans in the United States has not been detected, although related viruses have caused serious illness and death around the world [97].

Typically, people have focused on wildlife diseases that affect human health and agriculture. Recently, researchers, policy makers, and others have begun to pay attention to wildlife infectious diseases, because a number of endangered species including birds, amphibians, and invertebrates [99] are impacted [94].

Human's Changing Relationship with the Environment

"Deforestation and ensuing changes in land use, human settlement, commercial development, road construction, water control systems (dams, canals, irrigation systems, reservoirs), and climate, singly, and in combination have been accompanied by global increases in morbidity and mortality from emergent parasitic disease [100]." Lyme disease is a prime example of how human destruction of the environment (forests) can lead directly to increased risk for disease exposure. Allan, Keesing, and Ostfeld [101] found that as forest patch size decreased *Ioxdes* nymphal infection prevalence and nymphal density with increased, resulting in a noticeable rise in the density of infected nymphs and concluded that habitat fragmentation affects human health.

Changing Patterns of Human Interactions with Wild and Domesticated Animals

As humans change or destroy the local environment, they tend to interact with or disturb wildlife populations, creating further instances for exposure to infectious diseases. Goldberg et al. [102] found increased rates of interspecific gastrointestinal bacterial exchange between people and nonhuman primates when humans visited chimpanzee and ape habitats. Chimpanzees carried antibiotic-resistant bacteria although there had never been treatment with antibiotics.

Vaccination Avoidance

Many of the factors discussed above coexist to increase the threat from microorganisms. The antivaccine lobby, especially in the United States, has led to a significant decline in the vaccination rates of infants and children, particularly among specific demographics despite the overwhelming success of vaccines in the fight against vaccine-preventable diseases. For instance, in 1950 (pre-vaccine), 319,124 cases of measles were reported with 468 mortalities. In 2011, there were 211 cases of measles but no deaths. Similarly in 1950, 5796 cases of diphtheria were reported resulting in 410 deaths. In 2011, there were no reported cases of diphtheria [103]. Up to two % of parents in the United States refuse vaccination completely for their children with up to 19 % more who are cautious or elect to delay vaccination [103]. The reduction in vaccination coverage is typically attributed to the lack of perceived threat due to the success of vaccination, combined with false medical research and media reporting [103].

The reduction in vaccination rates has resulted in the highest number of cases of measles in the United States since it was declared eliminated in 2000 [104]. While native measles has been eliminated in Canada, several measles cases are imported each year by international travelers and due to inadequate vaccination, these cases often lead to secondary spread. In the first five months of 2014, 103 cases in five provinces from 21 known importations occurred through infected travelers arrived from the Philippines, India, the United States, Thailand, Pakistan, Italy, and the Netherlands [105]. Travel patterns in Canada are exemplary of much of the world. In 12 years, international travel (excluding travel to the United States) more than doubled from 4.5 million to 11 million trips [106, 107]. If the antivaccine trend does not abate, and in conjunction with widespread global travel, the threat from diseases once thought under control may pose a significant threat to the population.

Influenza outbreaks kill and hospitalize more than 100,000 Americans each year. The predominant strategy in the United States is to encourage all eligible populations to get vaccinated; however, for the 2014–2015 flu season, more than half of influenza A (H3N2) viruses had drifted from the H3N2 vaccine virus. This mismatch leads to decreased vaccine effectiveness [7]. It may also discourage individuals from getting the flu vaccine in the future.

Urbanization

Population growth, urbanization, and travel along with deterioration in public health infrastructure have contributed to the resurgence of infectious diseases. Dengue fever provides a prime example of the intersection of the triad. While dengue viruses were dispersed throughout the tropics in the first half of the twentieth century, epidemics were infrequent because urban populations were comparatively small, and the viruses and mosquito vectors were transported on ships versus the air transport of today. The travel of both goods and people during World War II set the stage for the spread of dengue fever. In the post war era with unparalleled urban growth and travel,

serious epidemics occurred more frequently. Scarcely 40 years later, dengue hemorrhagic fever became a principal cause of hospitalization and mortality in the pediatric population throughout Southeast Asia [108].

Biowarfare and Bioterrorism

With respect to the intentional use of microorganisms as a weapon, the United States and the world have an outmoded threat-view focused on Soviet era biological weapons, but travel, medicine abuse, and the lack of a US capability to approve and manufacture new antimicrobial and antiviral agents have changed many dimensions of the threat as discussed above. With the dissolution of the Soviet Union, the fact that the US biological weapons program ended decades ago, and the intellectual, medical, manufacturing, and weaponization knowledge needed to start a bioweapons program, the threat from naturally occurring organisms is far greater than the threat of bioterrorism or biowarfare in 2015.

Hope for the Future

Death and Illness

The threats of infectious diseases dwarf that of terrorism and other asymmetric threats to human life. Approximately three million people died in 2012 due to lower respiratory infections [22], and infectious diseases are the major cause of death of children under five. "The most important pathogens are rotavirus for diarrhea and pneumococcus for lower respiratory infections [109]." However, there is hope that new antibiotics will be identified and developed. Recent research such as that performed by Ling et al. [110] found new ways to identify antibiotics [111] in the environment and companies are beginning to invest again. Under the direction of Dr. Kim Lewis, Ling and colleagues identified teixobactin. To do this, the team used the novel screening method to examine 10,000 strains. In both in vitro and in vivo tests, teixobactin was demonstrated to be operative, without major side effects, against the organisms that cause common illnesses such as pneumonia, tuberculosis, and staph infection, diseases which sicken more one million Americans yearly. While teixobactin was effective against diseases of public health concern, it was ineffective against gram-negative bacteria. Teixobactin binds on several targets triggering cell wall break down. The ability to bind on multiple sites lessens the chance of early Teixobactin resistance. In addition to developing the new antibiotic, the researchers commercialized the screening technology, which can examine organisms that cannot typically be cultured in the lab [111]. Researchers are also developing techniques to enhance the impact of probiotics in fighting infections and other diseases such as cancer [112].

Reasons for Optimism

While recent events bring the threat of microorganisms to the forefront of the public mind, the work of doctors, researchers, public health professionals, and other experts have continued unabated for decades. These attempts include scientific, technological, policy, and commercial attempts to reduce or eliminate the deaths and other losses caused by pathogens.

To a large extent, these efforts have succeeded. In 1900, the average lifespan in the United States was 46.3 for men and 48.3 for women, and one of the predominant causes of death was infectious disease. By the end of the century, lifespan had increased to 73.8 for men and 79.5 for women [113]. In 1848, infectious diseases accounted for more than half of all deaths: in 1971, this percentage was reduced tenfold [114]. The increases in life expectancy have been distributed across the world, although some areas have benefitted more than others from breakthroughs in sanitation, nutrition, and medical advances. One of the primary contributors to the reduction in the death rate was the reduction of infant deaths due to infectious diseases. Prior to the mid-1930s, infectious disease played the predominant role in infant mortality with half of the 100 (out of 1000) infant deaths due to pathogens [115, 116]. By 2014, the United States infant mortality rate had decreased to 6.1 per 1000 live births [117]. Also in the United States, in the mid-nineteenth century, foodborne and waterborne diseases such as typhoid, cholera, and dysentery resulted in 214 deaths per 100,000. These diseases were eliminated in the United States by the early 1970s [114]. One noteworthy exception to the steady progress in increased life expectancy is due to an infectious disease: HIV/AIDS decreased life expectancy dramatically in parts of Africa over the past 30 years [118].

The leading causes of death and illness have shifted from infectious and parasitic diseases to noncommunicable diseases and chronic conditions. With the introduction of widespread antibiotics [119, 120] in the 1940s and antivirals in the late 1980s [121], a new era of public health was ushered in, and the death rate due to infectious diseases accounted for less than 20 % of mortality worldwide [22]; however, the optimism was short lived. Even before there was prevalent proof that bacteria could quickly evolve to thwart antibiotics, evidence indicates that bacteria exhibit resistance in nature even without human pressure [122]; however, mechanisms of resistance impacting disease treatment were first noticed in the late 1930s with regards to the use of sulfonamides [41]. Due to overuse, underuse, and incorrect disposal, antibiotic resistance has become a worldwide threat to public health [41]. In addition, the cost and difficulty in developing new antibiotics has stunted the pipeline. Finally, environmental [89], behavioral, and other physical and cultural changes have fostered situations where new pathogens can emerge and old enemies re-emerge or spread to new locations. Global climate change is

altering where species thrive, and more localized or temporary changes modify infectious disease risk to humans as well.

While NDM-1 strains are difficult to treat, many of them remain sensitive to an older, seldom used antibiotic, colistin, or aztreonam [123, 124]. Several clinical trials on combatting *C. difficile* infections have been completed; however none of the tested vaccines have garnered FDA approval. These trials include: A Study To Investigate A Clostridium Difficile Vaccine In Healthy Adults Aged 50 To 85 Years, Who Will Each Receive 3 Doses Of Vaccine, clinical trial number NCT02052726; Evaluation of a 3-dose Vaccination Regimen With One of Three Ascending Dose Levels of Clostridium Difficile Vaccine With or Without Adjuvant in Healthy Adults Aged 50 to 85 Years, clinical trial number NCT01706367; and Safety, Tolerability, and Immunogenicity Study of a Clostridium Difficile Toxoid Vaccine in Healthy Adult Volunteers, clinical trial number NCT00127803 (a total of 15 studies were found on www.clinicaltrials.gov when searching for '*C. difficile* vaccine [125].' Improvements are needed in dosage and timing to achieve high level immunity, however the investment required is large with estimates ranging from $500,000, 000 to $1000,000,000 [126] to take a vaccine or antibody, respectively, through clinical trials. Until a vaccine is developed, antibiotics will be used to treat infections. Fidaxomicin, the first new antibiotic approved by the FDA to treat CDI was approved in May 2011. It was shown to be as effective as oral vancomycin, previously the only FDA-approved therapy for mild-to-moderately severe CDI. Vancomycin is expensive and resistance in Enterococci is a concern. Oral metronidazole has been used by the medical community off label (it was approved for the treatment of certain anaerobic bacteria and parasites); however, relapse was observed in a quarter of patients within a month following treatment. Fidaxomicin, in addition to being as effective as standard treatment, is a narrow spectrum antibiotic, allowing patients to maintain healthy native gut microbiota [127, 128].

On a larger scale, according to the World Health Organization (WHO), HIV mortality was reduced from 1.7 million in 2000 to 1.5 million in 2012, and diarrhea fell from one of the top five causes of death to number seven, with a similar number of deaths to HIV/AID in 2012 [22]. Tuberculosis distribution has declined since the turn of the century, in part because of the reach of the WHO's Directly Observed Therapy Short-Course strategy and the implementation of the stop TB partnership plan [129]. Malaria cases and mortality has been meaningfully reduced by over 670 cases and four million people respectively over the 12 years between 2001 and 2013 through the use of artemisinin-based drugs, distribution of insecticide-treated bed nets, and indoor residual spraying of insecticide [130]. This demonstrates that research, infrastructure, and other health-based investments have improved prevention and response to infectious diseases. All of this comes at a cost: between 2012 and 2014 governments including the United States, the UK, Australia, Canada, France, and Germany and large non-profits and international institutions such as the Gates Foundation and the Global Fund contributed more than $32 billion to the fight against HIV/AIDS and nearly $20 billion for international maternal and child health, which is in large part funding for vaccination [131].

In addition, President Obama has recognized that infectious diseases pose a national security threat. On September 16, 2014, in his weekly address [132], the President stated, "So this is an epidemic that is not just a threat to regional security—it's a potential threat to global security if these countries break down, if their economies break down, if people panic. That has profound effects on all of us, even if we are not directly contracting the disease. And that's why, two months ago, I directed my team to make this a national security priority."

Because the challenges of new and re-emerging infections are complicated, a combination of science and technological advances, policy initiatives, and cooperative institutions are required. To make a significant difference, the United States and other countries must invest in technology and have systems capable of making these advancements available to those who need them, build technology development, and public health infrastructure; put in place policies and institutions that encourage these investments both in the public and private sectors. The success of programs such as the Malaria Initiative that combine these approaches is self-evident, but more needs to be done. An illustrative, but not complete, discussion of recent and additional proposals/initiatives is below.

Response: Actions, Policies, Technology, and Institutions

The United States, other countries, states, and international institutions have taken many steps to combat the threat. Below are many of the important efforts and characteristics needed for resilience to the microbial threat.

Most importantly, it is critical to have a well-defined leader who is responsible for directing and monitoring progress as well as communicating risks. In President Obama's September 2014 Executive Order [133], he directed the "National Security Council staff, in collaboration with the Office of Science and Technology Policy, the Domestic Policy Council, and the Office of Management and Budget to coordinate the development and implementation of Federal Government policies to combat antibiotic-resistant bacteria [133]." The President also created both a Task Force and an Advisory Council; however, he did not put a single individual in charge. Identifying and developing a central, qualified, trusted person in charge of coordinating the investments in research, infrastructure and outreach; policies to incentivize

behaviors to improve medicine development, infection control in medical and community settings; and communicate risks and responses in a directed and trusted manner at the federal government level, will enhance accountability and the likelihood of success. During times of low or chronic threat (e.g., flu season), the named person can develop a trusted relationship with the public, the medical and public health communities, the pharmaceutical industry, the defense department, international peers, and others involved in infectious disease response and defense. This is particularly difficult in diverse countries with divided political parties. A history of purposeful and innocent ethical lapses and scientific mistakes have contributed to a lack of trust such as the inaccurate flu vaccine in the 2014–2015 season and the confusing messages from the Texas hospital and the CDC on Ebola in 2015. When a man traveled from Africa and came down with a high fever and other symptoms, he was sent home by the hospital with antibiotics for two days [134]: Ebola was not well diagnosed in Texas.

One of the last trusted public health officials was the Surgeon General under Ronald Reagan, Dr. C. Edward Koop. By the time he stepped down in 1989, he had become a household name, a rare distinction for a public health administrator. "Dr. Koop issued emphatic warnings about the dangers of smoking, and he almost single-handedly pushed the government into taking a more aggressive stand against AIDS [135]." Dr. Anthony Fauci, Director of the United States National Institutes for Allergy and Infectious Disease, has been a source of trusted and accurate infectious disease related information recently with regards to the Ebola outbreak of 2014. Fauci is a natural leader for the US infectious disease/public health message, "He is someone who is really trusted by all the different organizations and people surrounding the AIDS challenge, ranging from the scientific community, the academic community and the activist community," according to Louis Sullivan, M.D., secretary of Health and Human Services during the first Bush administration and president emeritus of Morehouse School of Medicine in Atlanta. "I don't know of anyone as broadly accepted by all those disparate groups [136]." The head of the CDC can also be a valuable spokesperson, but the CDC may have lost some of the public's trust during the Ebola crisis [137]. To centralize response, President Obama appointed Rob Klain as the Ebola Coordinator. He was neither a doctor nor a scientist, and he left the job after six months, while Ebola was still spreading in Africa. While additional capability was developed at medical centers in the United States under Klain's tenure, there were few noticeable signs of progress; he was not open to the media [138]; and likely as a result, was not embraced by the public. If the President chose a well-respected individual with healthcare and pharmaceutical industry expertise to serve in the White House to coordinate policies, funding and messages from NIH, the CDC, the Department of Defense, the State Department, state public health agencies, and other national and international institutions involved in the chain of prevention, detection, and treatment of infectious disease, it would be optimal.

Critical manufacturing capabilities have moved overseas, particularly to India and China. The US Government could provide tax and other incentives and clear policies for approval for drugs, biologics, and manufacturing facilities to get manufacturing of key ingredients back to the United States. This would allow a faster and more certain response in times of emergency and the allow the government to initiate emergency medicine production under President Obama's March 2012 Executive Order [139]—National Defense Resources Preparedness for manufacturing and distribution of medicines during times of crisis and The Defense Production Act of 1950 as Amended [140].

International institutions are making significant efforts in preventing, detecting and responding to infectious diseases, and the continued work and support through the WHO, UN, NATO, the Pan American Health Organization, the G20, The CDC Global Health Initiative, and other domestic and international bodies will improve international surveillance, reporting, prevention, and response. Mechanisms for early reporting would avoid punishment such as travel bans for acknowledgement of dangerous infectious diseases within countries' borders. In addition, leaders in the United States would work to develop trusted relationships with peers in other countries. With more US foreign aid directed towards building public health infrastructure, the funds would have the primary impact of bolstering response and reducing transmission and casualties from infectious diseases within a country and secondary impacts of stabilizing societies (studies have shown that countries with healthy populations are more stable [141]). These outcomes would result in a safer and more secure world as there would be reduced disease transmission across borders. There are many existing global and domestic health initiatives such as the following: African Comprehensive HIV/AIDS Partnerships; Global Business Coalition on HIV and AIDS; Global Coalition on Women and AIDS; Global Fund to Fight AIDS, Tuberculosis and Malaria; Hope for African Children Initiative; Inter-Company for AIDS Drug Development; International Partnership Against AIDS in Africa; International pharmaceutical company initiative to support AIDS orphans (Step Forward); Maternal to Child Transmission; Multi-Country HIV/AIDS Program; President's Emergency Plan for AIDS Relief (PEPFAR); WHO Malaria Drug Partnership; Malarone Donation Program; Medicines for Malaria Venture; Multilateral Initiative on Malaria; Action TB Program; Eli Lilly Multi-Drug Resistance Tuberculosis Partnership; Partnership Against Resistant Tuberculosis; Sequela Global Tuberculosis Foundation; Stop TB partnership (Stop TB); The Global Alliance for TB Drug

Development; the CDC's Global Health Strategy; and many others summarized in the WHO Maximizing Positive Synergies Collaborative Group's assessment of interactions between global health initiatives and country health systems [142]. Lessons learned from this work can be utilized to further the goals of improving prevention and response to infectious disease.

A research and response focus on diseases we encounter in the modern era as opposed to an emphasis on old Soviet threats (unless the Intelligence Community identifies specific threats in the areas of bioterrorism and biowarfare) would enhance prevention and response capacities and funnel limited resources to current health and disease issues. Preparations for naturally occurring outbreaks will not only prevent deaths year to year, but will also help exercise countries to fight intentionally introduced diseases by developing policies, procedures, infrastructure, and new technologies that foster quick innovation and therefore response to any microorganism, natural or manmade.

Science and Technology

Each day, there are technological advances for preventing and combatting infectious diseases in addition to the progress specifically in medical research. For instance, adoption of advanced wastewater treatment systems can reduce exposure to antibiotics and ARGs. This can be accomplished by tax incentives and partial payment by the federal government when wastewater treatment systems are replaced and advanced systems are used. In 2014, $109 billion federal dollars were spent on water utilities (water supply or treatment) accounting for approximately one quarter of public infrastructure spending [143]. State and local governments spent $208 billion for the operation and maintenance of infrastructure double the spending on capital improvements ($112 billion). "Although state and local governments rely primarily on their own revenues to purchase capital, federal grants also are an important source of funds. Since 1960, federal grants have accounted for one-third or more of the capital spending on infrastructure by states and localities. That share was considerably larger from the mid-1970s through the mid-1980s as a result of federal support for water utilities after passage of the Clean Water Act in 1972 [143]." A renewal of this investment, with a focus on improving water treatment to remove antibiotics, ARGs and other pollutants and destroying resistant organisms, would expand the positive results. Regulations limiting the concentrations of antibiotics and ARGs in treated municipal water, if enacted, in concert with meaningful financial penalties for those violating these standards, may significantly reduce the risk of population exposure. This can be difficult because the source of the contamination is often hard to identify.

Current antiviral drugs have several disadvantages including their specificity, toxicity and expense. Researchers at the Charles Draper Stark Laboratories developed DRACO (Double-stranded RNA Activated Caspase Oligomerizer). In lab-grown cells, DRACO killed 15 different viruses, including ones that cause the common cold, influenza, polio and dengue fever with minimal effects on healthy cells [144]; however, there is still much work to be done before this drug can be FDA approved and used by the general public. Vectored vaccines use a live-vaccine made with a partial pathogen. They have been developed against SARS-CoV and demonstrated in mice, but the safety of vesicular stomatitis virus vaccine (VSV) in humans requires further research. Newcastle disease virus, a host range-restricted virus, has been developed as a vaccine vector for intranasal immunization against emerging pathogens [145].

Science informs advances in drug development. For instance, authors reviewed a variety of genome sequence and gene knockout data for *Acinetobacter* spp., with a focus on the critical systems to find the most appropriate sequences to target for therapies [146]. This is just one early example in the explosive field of bioinformatics. In 2004, in recognition of the importance of bioinformatics as a tool to diagnose and develop therapeutics for infectious diseases, the National Institute of Allergy and Infectious Diseases established four Bioinformatics Resource Centers (BRCs) to collect, store, and share bioinformatics information on bacteria, viruses, eukaryotic pathogens, and invertebrate vectors of human pathogens.

As with the factors involved in the rise of the threat the responses are interrelated. The FDA is, and must continue to, evolve its policies and regulations in the approval process so that research can proceed to the stage where drugs and biologics are ready for human use. This is discussed in more detail in the Policies section below.

Policies

Because infectious diseases do not respect borders, it is in the strategic interest of the United States, the European Union, and other countries with developed public health systems to invest in global public health infrastructure. This requires both a long-term investment as well as an acute response capability. President Obama recognized both of these in the fall of 2014. First on September 24, 2014 at the Global Health Summit, President Obama discussed long-term capacity building: "We, collectively, have not invested adequately in the public health capacity of developing countries." "This speaks to a central question of our global age—whether we will solve our problems together, in a spirit of mutual interest and mutual respect, or whether we descend into the destructive rivalries of the past. When nations find common ground, not simply based on power, but on principle, then we can make enormous progress. [147]" A few weeks later,

President Obama discussed the acute strategic needs, "As I have said from the start of this [Ebola] outbreak, I consider this a top national security priority. This is not a matter of charity—although obviously the humanitarian toll in countries that are affected in West Africa is extraordinarily significant. This is an issue about our safety [148]." The President also signed the Executive Order on Combating Antibiotic-Resistant Bacteria in September of 2014 [133].

Recent outbreaks of diseases thought banished from the United States demonstrate the need for full vaccination. Several communities resist vaccination, and incentives to vaccinate will increase population safety and prevent those who cannot be vaccinated from coming down with vaccine-preventable diseases. One common incentive is the requirement to be vaccinated to enter public school. Waivers can be sought, but to boost the vaccination rates, state and local governments can reduce the numbers of exemptions provided. Mississippi has already followed this course, and it has the highest vaccination rates in the United States. Other potential policies include requiring exemption forms to be filed yearly; requiring parents to complete an education component; and requiring private as well as public school children to be vaccinated [149]. Several states are implementing one or more related measures. While only four states do not recognize a religious exemption from vaccinations, 33 states do not allow exemptions for personal reasons (all states allow exemptions for medical reasons). In part due to the 2015 measles outbreak, on July 1 of 2016 California will eliminate all non-medical vaccine exemptions. Pennsylvania is also pondering eliminating personal exemptions. Colorado has made the exemption process more burdensome [150]. Dina Fine Maron of *Scientific American* [151] suggested the following common sense approach: improved education and communication, sustain and enhance immunization outreach, maintain vigilance and rapidly contain imported infections.

Anthony Fauci proposed partnerships, among government, industry, and academia to develop additional timely solutions to the threat of new and resurgent infectious diseases [152]. One example of a successful academia-industry partnership is the response to the HIV/AIDS epidemic. AIDS was first recognized in the early 1980s and the death rate steadily increased through the mid-1990s when it was recognized as a worldwide epidemic. Research at and collaboration among academic institutions (including Wayne State University) and investment by the public and private sectors (Burroughs Wellcome which later became GlaxoSmithKline) led to the development of the antiretroviral treatments used today. The partnerships transformed a deadly infection into a principally chronic disease within two decades [153–155]. Partnerships now work to ensure prevention, testing, distribution of anti-HIV/AIDS drugs and treatment worldwide.

Over the years FDA has introduced innovations for the development and approval of pharmaceuticals including fast track, parallel track, orphan drugs, surrogate endpoints, non-inferiority [156]. According to the FDA Guidance [156], a non-inferiority (NI) study is used to demonstrate that the degree of inferiority of the drug being tested as compared to the control (an already approved drug) is less than the non-inferiority margin. Recently, to facilitate the development of biopharmaceuticals, a cross-industry group, including members from Astra Zeneca, University of Texas Medical School Houston and smaller pharmaceutical companies, proposed a tiered evidence-based regulatory approach. In this approach Tier A is the typical large Phase III approach and Tier D is equivalent to the Animal Rule, which states that "for drugs developed to ameliorate or prevent serious or life threatening conditions caused by exposure to lethal or permanently disabling toxic substances, when human efficacy studies are not ethical and field trials are not feasible, FDA may grant marketing approval based on adequate and well-controlled animal efficacy studies when the results of those studies establish that the drug is reasonably likely to produce clinical benefit in humans [157]." Tiers B and C rely heavily on preclinical data and combined animal and human pharmacokinetic and pharmacodynamic (PK–PD) data fully integrated into a limited clinical program [158].

In the *C. difficile* study discussed above, suggestions for prevention include: limit contact, limit inappropriate antibiotic usage, and increase surface cleaning. Handwashing with soap from dispensers with sealed refills instead of open refillable dispensers can lower the risk of infection [159] and is just one example of a common sense technique to prevent the spread of many bacterial infections. Another common sense response is increased monitoring. *Cryptosporidium parvum* did not appear to pose a risk until 400,000 people became ill, and approximately 100 people died of cryptosporidiosis in Milwaukee's water service area in 1993. Today, regulators and public health scientists are trying to identify microbes that pose a similar risk in the future. If these microbial contaminants occur in raw water supplies, they may need monitoring and treatment prior to these waters entering the potable water distribution system. The Contaminant Candidate List (CCL) developed by the United States Environmental Protection Agency outlines a series of biological contaminants of concern that are not currently regulated but may pose a threat. Should these contaminants move from the CCL to a regulatory framework, water supply utilities will incur added monitoring and testing of their water supply sources, and potentially added monitoring and treatment costs in their operations, but safety will likely increase as a result of these expenditures.

The article discusses many of the problems and solutions due to emerging pathogens with a focus on the impact and response in the United States. These challenges are exacerbated in less

well-off countries with poor sanitation, lack of access to preventative health care, unstable governments, or weak public health infrastructure. Awareness is key, and this and other articles are working to spread the message.

Special Note on the Zika Virus

The threat from emerging diseases is continuously evolving as evidenced by the recent appearance of the Zika virus. While the virus itself was isolated from the Zika Forest in Uganda in the first half of the Twentieth Century, it did not begin to take a serious human toll until 2015 when it traveled from the Pacific Islands to Brazil [160]: it is now considered a global threat, with its vector, the *Aedes* species mosquito living on all continents [161]. There have been more than one million cases in Brazil, and researchers noticed a surge in fetal microcephaly, a small head size for gestational age and sex indicating issues with brain growth, in Zika-prone locations [160]. It is now widely accepted that maternal infection with Zika can lead to serious consequences for a fetus. For most infected, the effects will be minimal, but in addition to the fetal effects Guillain-Barre increases have been associated with Zika infections. Reliable diagnosis is not yet widely available, but reverse-transcriptase polymerase chain reaction (RT-PCR) testing of serum in the first seven days after symptom onset or IgM-capture enzyme-linked immunosorbent assay (MAC-ELISA) analysis of samples are the most promising methods [158]. Animal models for further research, therapeutics and vaccines are required [160] to stop the negative impacts of the disease since the vector is widespread and difficult if not impossible to eradicate.

The general growing awareness of the threat posed by infectious disease because of travel, urbanization and all of the other factors described above combined with the serious consequences, primarily for pregnant mothers and their fetuses led to one of the fastest global responses to an infectious disease in the history of humankind. On April 6, 2016, President Obama announced that he would direct $589 million in Federal dollars remaining from the fund to fight Ebola to fight the Zika virus. The money will primarily be used for CDC and NIH research on the virus, its role in birth defects, and vaccines for prevention. Funds will also go to the formation of CDC response teams. This funding falls short of the $1.9 billion in emergency money President Obama initially requested, and the shortfall is likely to delay a complete, effective response. Internationally, the WHO designed and disseminated a global Strategic Response Framework and Joint Operations Plan, which can be accessed at http://www.who.int/emergencies/zika-virus/response/en/ .

Compare this to the response to Polio, an *Enterovirus* that causes few symptoms in the vast majority of cases, but can cause paralysis and even death in 1–2 % of cases. Though poliovirus circulated in the population for hundreds of years, it did not reach epidemic propositions until the early 1900s. It took nearly 100 years to develop a vaccine and implement widespread vaccination so that in 1994 polio was eradicated in the western hemisphere. Polio is now endemic in only three countries: Afghanistan, Nigeria, and Pakistan. More recently effective prevention and treatment options for HIV/AIDs did not take hold for decades. This timeline is now significantly reduced. Research is already underway on vaccines for Zika as well as prevention through vector control. We do not know exactly which microorganism will become the next virulent threat, but surveillance and monitoring, robust public health and research infrastructures, policies to encourage the approval of treatments and vaccines, and openness and communication will allow for the quickest responses possible to any emerging, currently unknown threat.

Acknowledgments Dr. Ralph Mitchell inspired me to look at the world in a new way, from the perspective of the tiny organisms that make the world what it is, but also threaten that world.

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