Global Biosecurity in a Complex, Dynamic World

Biosecurity is emerging as a major global health priority for which innovative and unprecedented solutions are needed. Biosecurity is a challenging biocomplexity problem involving multifaceted processes such as interactions between humans and nonhuman biota, anthropogenic environmental and ecological factors, and socioeconomic and political pressures. Key to an effective biosecurity strategy will be fundamental understanding of evolutionary, anthropogenic and environmental driving forces at play in transmission and perpetuation of infectious diseases. Biosecurity solutions will depend on increased support of basic biomedical research and public education, enhanced healthcare preparedness, alternative strategies for ensuring safety, and improved interagency cooperation regarding global health policy. © 2008 Wiley Periodicals, Inc. Complexity 14: 71–88, 2008

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BIODEFENSE AND BIOSECURITY: WHERE IS THE "REAL" THREAT?

I t is widely accepted by historians that there are certain dates upon which history seems to pivot, turning points that forever change the course of future events. The momentous months of September and October 2001 mark such a critical period in our recent history. Our world as we knew it shifted, not just for the United States, but all nations. As a consequence, defense against bioterror agents came to the forefront as a major health priority in the U.S. and elsewhere. Indeed, we were still reeling from the impact when SARS swept across the globe in 2002–2003, followed closely behind by the still ongoing worldwide spread of avian flu and the concomitant fear of it transforming into a human flu pandemic on the scale of that experienced in 1918. But, these events are only at the pinnacle of a mounting number of impinging natural and imposed biohazards (Table 1) [1–5]. Importantly, these manmade and natural events have revealed a number of glaring gaps in our knowledge about infectious diseases, their transmission and perpetuation, and how to effectively combat them.

Existing and looming biological threats have now made biosecurity, which includes biodefense, the most pressing global health priority. In a rapidly changing world, biosecurity is at the intersection of every sphere of medical, biological, ecological, socioeconomic, and political system. Although one might argue that the

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TABLE 1

The Human Cost of Biological Threats

Bioterrorism casualties:
   22 cases/5 deaths total in 2001 from anthrax (perpetrator still at large)
   >2,000 hospitalized/18 deaths *total* in 1994-5 from sarin gas (Aum Shinrikyo)
   751 cases/0 deaths *total* in 1984 from *Salmonella* (Rajneeshee)
   1 death in 1978 from ricin (assassination of Georgi Markov)
Natural casualities:
   300–500M cases/2 million deaths *per year* from malaria world-wide
   76M cases/325,000 hospitalizations/5,000 deaths *per year* from foodborne illnesses in USA
   8–10M cases/2 million deaths *per year* from tuberculosis world-wide
   >60M cases/>20M deaths *total* from HIV/AIDS world-wide, >0.5M deaths in USA
   ~170M cases/10,000 deaths *total* from hepatitis C in USA
   5–15% illnesses/110,000 hospitalizations/36,000 deaths *per year* from influenza in USA
   50,000 deaths *per year* from septic/toxic shock from infection in USA (mortality rate ~77%)
   8,096 cases (confirmed)/774 deaths *total* from SARS reported to WHO from 29 countries in 2002–2003, 27 cases (confirmed)/0 deaths in USA
   381 cases/240 deaths *(so far)* from Avian Flu H5N1 in Asia and Eurasia

Shown are selected list of biological threats that are currently impinging on our biosecurity along with the estimated number of incidences.

principal difference in the infectious disease threat today versus say 10, 25, or 50 years ago is bioterrorism, the resources spend on preparing for a bioterror attack is viewed by most scientists as grossly exorbitant [6], particularly considering the small numbers of individuals who have been or could be affected by this type of attack and considering the relatively low medical relevance or prevalence of the diseases caused by the limited number of high-priority bioterror bioagents, the so-called "category A select agents." And, while admittedly the preparedness and surveillance measures put in place for one has certainly helped to protect against the other (the improved global response to and curtailment of SARS coming after the anthrax bioterrorist attacks is a prime example of this), most scientists feel that the limited resources available from an already overburdened system should instead be used for studying and preparing against the looming and potentially more devastating infectious disease threats from natural or accidental exposure [7], which could affect millions of people and animals and could have huge health and economic consequences. And thus, while the threat of bioterrorism must be considered, many scientists propound that the focus should be on the more urgent and dire problem of biosecurity, rather than just bioterrorism.

It has been argued by many that there is no better creator of new highly potent biological threats than nature itself. However, there is also little doubt that anthropogenic environmental, socioeconomic, and ecological influences can have devastating impact on the extent and severity of the outcome of these natural biological hazards. Risks to public health come from diverse scenarios ranging from epidemics to outbreaks during natural disasters to accidental exposures through poor food processing to deliberate releases or fear thereof (Table 2). Finding solutions to these challenging biocomplexity problems will require integrated, multilevel, flexible, and interdisciplinary approaches that stretch traditional concepts. Key to an effective global biosecurity strategy will be improved detection, prevention, treatment, and management of infectious diseases, but also better understanding of the intrinsic and extrinsic factors that contribute to their virulence and influence their transmission, prevalence, and perpetuation. Thus to achieve this, we first need a better understanding of the critical evolutionary, anthropogenic, and environmental driving forces that contribute to natural and man-made biological threats.

WHAT ARE THE BIOSECURITY THREATS?

To gain a sense of the potential impact of biological threats on biosecurity, it is best to begin by considering the source and nature of the biological agents that pose biosecurity risks (Table 3). Manmade biological threats come in two flavors, deliberate and accidental. The concept of intentionally using biological agents as weapons is nothing new to warfare, and we are all aware of the American, Russian, and other state-sponsored programs to develop biological agents as "weapons of

TABLE 2

Biological Threats Come from Diverse Sources

Manmade Threats	Natural Threats
Accidental	Persistent or resurgent infectious diseases
Unintentional release	Multidrug-resistant pathogens
Anthropogenic environmental or ecological impact	New or reemerging pathogens
Food processing, preparation, or distribution	Human-to-human, epizonotic, zoonotic, food, or water-borne transmission
Non-malicious intentional release or introduction	High-impact infectious diseases
Deliberate (the "Terror effect")	Foreign animal zoonoses
State-sponsored bioweapons; WMD, "weapons of mass destruction"	Invasive Alien Species
Bioterrorism–groups or individuals; WMD, "weapons of mass disruption"	Animals
	Plants
	Insects

mass destruction" (WMD). These state-sponsored WMD programs have been largely dismantled [8], and instead the concept of using biological agents as bioweapons has now been usurped by individuals or small groups acting as terrorists engaged in a different form of warfare, where these agents are perhaps more accurately described as "weapons of mass disruption" (still WMD). We experienced a vivid and horrible display of this new brand of WMD with the anthrax attacks of 2001, in which the U.S. Postal System was utilized to dispense deadly disease, but even more notably, fear and turmoil.

The cost of mounting a response to this new WMD has been enormous, not only in terms of billions of U.S. taxpayers' dollars, particularly directed toward biodefense (Table 4), but also in countless man-hours expended in ramping up other areas of security and healthcare preparedness and in the astounding disruption of lifestyle (e.g. inconveniences caused by intensified travel-related security measures). A growing number of scientists feel that the bioterror threat is exaggerated [7] and that it is highly unlikely that any terrorist organization, foreign or domestic, could on their own develop from scratch a bioweapon capable of

causing mass casualties. Instead, it is more likely that the potential terrorists would steal or procure existing material and deploy it on a much smaller scale. In contrast, manmade threats resulting from inadvertent release, accidental contamination, or even from non-malicious intentional introduction of biological agents represent much more measurable concerns with known likelihood of risk.

There have been a number of recent high-profile incidences that illustrate the havoc, alarm, and economic consequences that can result from widespread distribution of contaminated food because of accidental introduction of harmful microbes during food processing. What previously was seen only sporadically, such as at church socials, family gatherings or community picnics, moved abruptly into the public's eye with the large-scale problem of undercooked fast-food hamburger meat contaminated with *E. coli* O157:H7, a toxin-producing bacterium that causes dysentery-like diarrhea and can cause kidney failure and death, especially in children and the elderly. This dangerous microbe has since been associated with over 400 multistate or multination outbreaks of contaminated food, including meat, radish sprouts, apple juice, let-

tuce, and most recently spinach. Late last summer, *E. coli* O157:H7 contamination of prepackaged fresh spinach led to 204 cases of illness across 26 states, with 104 hospitalizations, 31 kidney failures, and 3 deaths [9]. The outbreak, which was traced back to spinach obtained from a few fields in California [10], shook consumer confidence and cost the industry an estimated $150M in economic losses [11].

There are many other examples of how the spread of natural threats can be greatly facilitated by our modern technologies, practices, and behaviors. Viruses such as the Marburg and Ebola viruses, first discovered in the 1960s and 1970s, are examples of biological agents responsible for recently emerged diseases [12]. Ebola and Marburg viruses are considered to be zoonotic diseases that are transmissible by close contact with animal species, but their spread has been facilitated by conditions in the country of outbreak, including political upheavals, reuse of needles, and cultural burial practices. Zoonotic diseases are often perceived as only a problem of developing countries, where there is much closer contact with animals, both domestic and wild. However, living with animals is not limited to the third world. Consider how many Americans alone live

TABLE 3

A Selected List of Bioagents of Particular Concern to Biosecurity

Toxins	**Viral Diseases**
Botulinum neurotoxins (*Clostridia*)	Avian and pandemic flu (influenza A virus)
Naturally occurring botulism (paralysis)	Continually emerging due to antigenic drift (high mutation rate)
Ricin (plant toxin)	Currently H5N1 avian flu is pandemic, epizoonotic
Accidental poisoning, has been used as a bioweapon	No current confirmed human-to-human transmission (but feared)
Endotoxin (LPS)	SARS (severe acute respiratory syndrome, corona virus)
Toxic shock, septic shock, major persisting problem	Newly emerged epizoonotic, human-to-human transmission
Toxin-mediated bacterial diseases	Pox (small pox, monkey pox, mouse pox, others)
Anthrax (*Bacillus anthracis*)	Small pox eradicated through massive vaccine campaign
Endemic in areas, recently used as a bioweapon	Small pox developed as bioweapon, other poxes endemic in places
Diphtheria	HIV (human immunodeficiency virus)
Reemerging despite vaccination	Recently emerged, sexually transmitted (mostly) disease
Pertussis (whooping cough)	Currently pandemic, combined with TB = rapid death sentence
Reemerging despite vaccination	Hemorrhagic Fever (Ebola, Dengue, West Nile, others)
Cholera (*Vibrio cholerae*)	Continually emerging, newly emerged
Endemic in parts of world, currently in 7th major pandemic	Vector-borne, endemic in parts of world, pandemic
E. coli 0157:H7, *Shigella* (dysentery)	Hepatitis C
Sporadic outbreaks, contaminated food and water	Recently emerged, ~170 million cases (10,000 deaths/yr in USA)
Contaminated processed foods	Foot-and-mouth disease (Picornavirus)
Other bacterial diseases	High-impact (economically) foreign animal disease
Plague (*Yersinia pestis*)	Pandemic, highly contagious
Endemic in places, sporadic outbreaks	**Prion Diseases**
Tuberculosis (*Mycobacterium*)	Mad Cow disease (bovine spongiform encephalopathy)
Pandemic, multidrug resistance major problem	Newly emerged in 1980s, zoonotic
Gonococcal/meningococcal (*Neisseria*)	Transmissible to humans (variant Creuzfeldt-Jacob Disease)
Persisting, newly emerging social diseases	Chronic Wasting Disease (CWD)——zoonotic, currently only in cervids
"Flesh-eating bacteria" (*Staphylococcus/Streptococcus*)	**Invasive Alien Species**
Nosocomial, multidrug resistant	Non-indigenous plants, animals, pests
Fungal diseases	Agriculture and ecosystem devastation
Candidiasis (*Candida*)	Economic cost in billions per year
Invasive, common nosocomial infection among the immunocomprised	
Histoplasmosis (*Histoplasma*)	
Common among the immunocomprised	
Parasite Diseases	
Malaria (*Plasmodium*)	
Persisting, largest population of infected individuals	
Cryptosporidiosis (*Cryptosporidium*)	
Newly emerged, water-borne	

with pets, sleeping with them, and even kissing them. It is interesting to consider that measles virus is closely related to canine distemper virus [13, 14], suggesting that at some point a dog–human transmission occurred or a common ancestral virus may have infected both.

Of particular and growing concern are high impact, foreign animal diseases, such as mad cow and foot-and-mouth diseases (Table 5). Bovine spongiform encephalopathy (BSE), commonly known as mad cow disease, is a fatal, progressive neurodegenerative disease of cattle caused by an infectious form of misfolded protein called a prion [15]. Transmission of BSE occurs when healthy animals come in close contact, usually through ingestion, with prion-containing tissues from animals that have the disease. The first probable occurrence in cattle was in the early 1980s, possibly as a result of feeding cattle meat and bone meal that contained scrapie-infected sheep products. Scrapie is a prion disease of sheep and goats. Industrial cattle-farming practices in Europe prior to 1987 used rendered meat and bone meal, instead of the more common soybean meal used elsewhere, as a protein supplement in cattle feed. In

Cost of Biosecurity to Taxpayers

Research/Disease Areas ($M)	FY 2003 Actual	FY 2004 Actual	FY 2005 Actual	FY 2006 Actual	FY 2007 Estimated	FY 2008 Estimated
Anthrax	219	249	183	150	117	111
Antimicrobial resistance	181	203	217	221	221	220
Biodefense	1,554	1,629	1,696	1,766	1,731	1,723
Emerging infectious diseases	1,362	1,807	1,872	1,857	1,853	1,835
Food safety	208	294	329	316	315	312
HIV/AIDS	2,718	2,850	2,921	2,902	2,903	2,905
AIDS, pediatric	318	280	279	276	275	274
AIDS, vaccine	405	452	511	566	564	571
Immunization	1,059	1,585	1,438	1,438	1,438	1,430
Infectious diseases	2,441	3,055	3,188	3,132	3,118	3,085
Influenza	57	113	164	207	222	233
Lyme disease	30	28	27	24	24	24
Malaria	72	89	104	98	100	101
Malaria vaccine	23	30	44	35	45	45
Smallpox	99	324	187	149	125	142
Tuberculosis	122	137	158	150	150	149
TB vaccine	13	18	26	22	22	21
Vaccines	1,066	1,610	1,450	1,449	1,486	1,507
Vector-borne diseases	296	419	447	464	462	457
West Nile virus	37	43	43	85	42	63

Shown are the actual or projected portions of the NIH annual budgets for the years 2003–2008 devoted to selected areas pertinent to biosecurity.

the early 1980s, a change in the rendering process in the U.K., in which a lower sterilization temperature was used for the steam boiling step in the process, is thought to be the major contributing factor to an increase in prions in the cattle feed that resulted in the BSE epizoonotic outbreak. The UK epidemic peaked in 1993 with nearly 1,000 new cases per week, and by the end of 2005 there were over 184,000 cases of BSE confirmed in the U.K. [16, 17].

BSE attracted particular attention because it now appears that it can also be transmitted to humans that consume tainted meat. Since the first reported case in 1996, at least 188 people, 160 in the U.K. and 28 elsewhere, have died of a disease with similar neurological symptoms to BSE, called variant Creutzfeldt-Jakob disease (vCJD) [18]. For many of the vCJD cases, there is direct evidence that they

had consumed tainted beef years before. The connection between BSE and vCJD has a wider impact than just food safety—blood, tissues and organ donation programs are also affected and anyone having exposure to BSE is a potential carrier [19]. Because of the long incubation period for prion diseases (years to decades), the full extent of the human vCJD outbreak is still not fully known, although the number of new cases appears to be declining. The long incubation period also makes testing for the disease in animals difficult because most livestock are slaughtered long before noticeable symptoms occur or even before plaques in the brain can be readily detected during inspection by necropsy.

Although many foreign animal diseases are not of serious concern to human health (i.e. humans may be affected only very rarely through direct contact with infected animals), they do

TABLE 5

List of Potential Biological Agents that Pose Threats Against Animal Populations

Viruses
  Newcastle disease virus
  Foot and mouth disease virus
  Classical swine fever (hog cholera) virus
  Highly pathogenic avian influenza viruses
  African swine fever virus
  Venezuelan equine encephalitis virus
  Rift Valley fever virus
  Pseudorabies virus
Bacteria
  Bacillus anthracis (anthrax)
  Burkholderia mallei (glanders)
  Francisella tularensis (tularemia)
  Brucella species (brucellosis)
Toxin
  Botulinum toxin (from *Clostridium botulinum*)

pose considerable threat to our agricultural and food industries and could cost millions or even billions of dollars in economic and trade losses (hence their status as "high impact" diseases). Foot-and-mouth disease (FMD) is a highly contagious, sometimes fatal viral disease primarily of cattle and pigs, but it has a wide host range. FMD occurs worldwide, but a number of areas, including North America, Australia, New Zealand, Japan, most of Europe, and parts of South America have been FMD-free for some time, mainly due to eradication through rigorous vaccination and culling programs. However, in 2001, a major outbreak of FMD in the U.K. resulted in the slaughter of millions of animals, huge economic and trade losses estimated in the range of £20M, the temporary cancellation of sporting events and other outdoor events attended by farmers or those living in the country, and the implementation of strict policies on the sale and trade of livestock, as well as disinfection of all persons entering or leaving farming areas [20, 21]. Countries are recognized to be in one of three FMD categories: FMD present with or without vaccination, FMD free with vaccination, and FMD free without vaccination [22, 23]. Understandably, countries designated as FMD free without vaccination have the greatest export markets, so most developed countries have greatly enhanced their agricultural surveillance and trade policies to maintain their FMD-free status.

Innocuous introduction of foreign plants, animals, or insects can also have considerable ecological and economic impact on horticultural and agricultural industries. Kudzu, a member of the pea family that is native to Southeast Asia, is an example of an invasive alien plant species that has caused considerable damage since its introduction to the southeastern regions of the U.S., where it is sometimes referred to as "the plant that ate the South" [24]. Kudzu was first intro-

duced from Japan into the U.S. in 1876 at the Philadelphia Centennial Exposition, after which it gained some popularity as an ornamental shade vine. But, from 1935 to 1953, the Soil Conservation Service promoted its use as a means for controlling soil erosion. Once established with a root system that can reach depths of up to 12 feet, kudzu vines grow as much as a foot per day during a season with lengths up to 100 feet. Kudzu now covers over 1M hectares and poses a considerable threat to the otherwise high biodiversity of flora found in the South [25]. A tremendous amount of money and effort is spent each growing season to prevent the highly prolific kudzu from overtaking roads, bridges, powerlines, local vegetation, and even homes, barns and other buildings. It costs an estimated $500M annually in lost cropland and management resources [26]. For successful long-term control, the entire root system must be destroyed or the plant will grow back, and considerable effort has been made to find pesticides that can control this plant pest.

EVOLUTION AS A CRITICAL DRIVING FORCE IMPACTING BIOSECURITY

Key to an effective strategy to combat complex biological problems to ensure biosecurity will be a greater understanding of the driving forces that are important for transmission and perpetration of infectious disease and then the management and implementation of effective preventive or containment measures. The potential power of natural selection is obvious. Time and again we have seen how rapidly microbes can evolve in response to selective pressure, such that certain behaviors or genetic traits tend to be eliminated from the gene pool, while others are maintained or changed. As a consequence, new biological threats are bound to emerge as we impose our influence on the environment. The

goal of most pathogenesis research, of course, is to use our understanding of the ecology of host–microbe interactions and their role in pathogenesis to develop predictive models for disease progression and transmission. Unfortunately, our current understanding is rudimentary at best, and we are just now beginning to tease out the intricacies of the co-evolution of pathogens with their hosts and environment and the role that these host-microbe interactions play in emergence of disease.

Human-induced evolution can be extraordinarily rapid and pervasive. The natural history of myxoma virus in American rabbits and its introduction into European rabbits as a means for controlling the rabbit populations in Australia provides an interesting example of the co-evolution of a virus and its animal host [27]. It also provides a glimpse into understanding the emergence of infectious disease. Shortly after European rabbits were first brought to the Americas in 1895, they were found to succumb to a deadly and extremely infectious disease, which nearly half a century later was found to be caused by a vector-borne myxoma virus acquired through contact with the native, more resistant host, the common wild rabbit of South America. European rabbits were first introduced into Australia in 1859 for hunting, but by the 1880s they had become a major pest. To help in controlling the rabbit population, rabbits infected with this deadly virus were introduced in 1950 and the favorable weather conditions for mosquitoes that year helped to rapidly spread the disease, killing millions of rabbits. But, evolution and the power of natural selection then came into play. The myxoma virus that was first introduced killed over 99.9% of infected rabbits, yet a few rabbits survived the exposure. Within a year, new strains of the virus appeared that killed only 90% of infected rabbits, and in subsequent years even more attenuated viral strains appeared. Under such strong

selective pressure, the rabbits, too, evolved to gain increased resistance such that the original, highly lethal virus would no longer kill more than 30% of the rabbit offspring. Clearly, genetic changes in both the viral and rabbit populations quickly altered the outcome of the disease in terms of severity and persistence. Today, only 50% of infected rabbits succumb during a myxomatosis epidemic.

One of the most devastating recently emerged diseases, whose initial and continuing spread can be attributed to human behavior, is that of HIV/AIDS. HIV is thought to have originated in nonhuman primates [28], but has become established in humans and is now transmitted human-to-human through unprotected sexual practices, reuse of needles, and at first (although no longer) through contaminated blood supplies [29, 30]. AIDS was first noticed in the early 1980s as unusual occurrences of a rare cancer, Kaposi's sarcoma, in young homosexual men. The social stigma associated with the disease gradually shifted with the realization that other populations were also at risk, including heterosexual and bisexual women, drug addicts, hemophiliacs, blood transfusion recipients, and babies born to HIV-positive mothers. The annual death toll rose linearly from 1987 with over 13,000 deaths to a height of nearly 42,000 in 1995, before a noticeable decline was observed with the introduction in 1996 of a cocktail of three anti-HIV drugs. By 1997 the annual death toll was down to 15,500 and has since declined to around the 12,000 mark [31]. However, although the death rate has declined, the number of cases reported annually in the U.S. still hovers around 40,000 [4, 32].

Host-microbe co-evolution over time appears to be in effect for HIV/AIDS. There are now a considerable number of HIV-positive individuals who have survived for many years without acquiring AIDS. A large part of this is due to advances in anti-HIV

TABLE 6

Rapid Evolution of Antibiotic Resistance in Staphylococcal Bacteria

Year	Event
1943	Penicillin made commercially available
1947	First penicillin resistance reported
1960s	Switch to methicillin
1980s	Methicillin resistance reported
1990s	Methicillin resistance up to 35%
1990s	Switch to vancomycin
1996	Vancomycin resistance reported
2000	Linezolid approved by FDA
2002	Linezolid resistance reported

medications and improved healthcare. However, even before the increased availability of HIV medications, there were a significant number of individuals engaging in high-risk behavior that appeared to be resistant to acquiring HIV. By examining these "survivors," scientists found a genetic mutation (allele) in a surface receptor, called CCR-5, which prevents the HIV virus from entering host cells [33]. These individuals having the mutant receptor allele are mostly of European decent. In some parts of Europe, up to 20% of the population carry at least one copy of the mutant receptor allele, while populations in the rest of the world do not carry the same allele [34]. It is believed that this allele might have arisen through selective pressure from previous exposure of the population to another plague (perhaps bubonic plague, although this is not certain).

But, importantly, the strong selective pressure that the new antiviral medications have placed on HIV has led to an accelerated deadly arms race. Current antivirals, at an annual cost of over $10,000 per person, are targeted mainly against the viral outer coat proteins gp120 and gp41, the processing protease, and the reverse transcriptase. Although these viral protein targets are less variable than others in the viral genome, HIV has a high mutation rate and the strong selective pressure has caused the virus to rapidly evolve in response [29]. The ever-evolving HIV makes developing new drugs a constant, and costly, challenge [35].

Other pathogens have been around for quite some time, but have recently acquired new properties making them increasingly more deadly. During the 1990s, *Staphylococcus aureus* emerged as one of the most common causes of hospital-acquired infections in the US. Drug-resistant infections increase the risk of death, as well as the cost and duration of hospital stays. Over a relatively short period of time *S. aureus* acquired genes that increased the bacterium's resistance to antibiotics [36]. A timeline of the emergence of these new strains of *S. aureus* clearly demonstrates the evolution of a pathogen that is under strong selective pressure to survive (Table 6). Once acquired, antibiotic genes can be spread from one microorganism to another through a process known as horizontal gene transfer, which involves uptake or transfer of DNA encoding those resistance genes within or between different bacterial species. Importantly, the antimicrobial resistance is maintained even after the selective pressure is removed. This exchange of genetic information is believed to contribute to the alarming rise in multidrug resistant

bacteria [37]. Rapid development of antimicrobial resistance is forcing clinical and pharmaceutical researchers to devise alternative, innovative approaches to respond to this threat [38]. Hospitals are thought to be a major source of multidrug resistant bacteria, but agricultural practices involving usage of antibiotics as prophylactics and growth promoters in feed and crops have also played a role in its emergence [39]. Eye-opening evidence for just how prevalent genetic exchange occurs in natural environments is provided by the example of the substantial increase in antibiotic resistance among both community and clinical isolates of bacteria in the gut [40].

Tuberculosis (TB) is the leading cause of death in the world, and after a century of decline in the U.S., TB is once again on the rise, and alarmingly multiple drug-resistant strains have emerged. This increase in cases worldwide is attributable to a number of complex factors, including changes in the social structure and socioeconomic upheaval, the HIV epidemic, and a failure in some countries to improve public treatment programs. Multidrug resistance in TB is a growing international health concern, because it has dramatically increased the difficulty in controlling the spread of TB and because of the high mortality rate associated with co-infection with HIV [41]. Co-infection of multidrug-resistant TB with HIV fuels the transmission of TB by accelerating the progression of latent TB into active disease because of the damage that HIV causes to the host immune system, which normally controls TB infection. Individuals that test positive for both TB and HIV often die with 1–6 months. A major epidemic of TB-HIV infections has spread across the former Soviet Union due to socio-economic changes in the country that have led to overcrowded housing, and in particular overcrowded prisons [42]. Unfortunately, the pharmaceutical industry has largely abandoned TB drug development due to perceived nonprofitable consumer market—at risk populations are also the poorest [43].

ANTHROPOGENIC AND ENVIRONMENTAL DRIVING FORCES IMPACTING BIOSECURITY

The spread of any disease that is transmitted from human to human is greatly facilitated under crowded conditions, which allow for efficient exposure to a higher initial inoculum of the infectious agent. Sporting events, concerts, and other gatherings of large numbers of people in a confined area can promote human-to-human transmission, as well as exposure to new populations. Legionnaire's disease, caused by the bacterium *Legionella pneumophila*, was first recognized in 1976 when it struck a group of American Legion conference attendees in Philadelphia [44]. This bacterial pathogen normally lives in fresh water as a parasite of amoeba, but unfortunately for us it can also live and thrive inside one type of our immune cells called a macrophage. The disease is acquired through aerosol exposure from contaminated water in ventilation systems, such as the air conditioning units in a hotel, or through aspiration during nasogastric tube feedings diluted with contaminated potable water in hospital or nursing-home settings [45].

Since the first widely publicized incident on the Holland-America Cruise Line in 2002, there have been numerous reports of cruise ship passengers succumbing to acute gastroenteritis caused by the Norwalk virus [46]. A cruise, where hundreds of passengers and crew mingle in close contact, can provide optimum conditions for a virus to spread through food, water, and direct contact. Cruise ships are now required to report all gastrointestinal illnesses to the CDC before entering a U.S. port, especially if 2% or more of the passengers or crew are ill. What has been most economically troubling for the cruise line industry is the recalcitrant nature of the virus to decontamination efforts [47].

Overcrowding often leads to poor sanitation, resulting in accumulation of refuse, sewage, and vermin that thrive under such unsanitary conditions. Natural disasters, civil disturbances, and war have caused large population displacements, with millions of people (and their animals) worldwide today living in refugee camps, which are overcrowded with poor sanitation and often without adequate food or clean water. These crowded camps provide ideal conditions for brewing and transmitting new infectious agents in malnourished or immunocompromised populations of humans and animals. The Norwalk virus reared its ugly head once again during the Katrina crisis in 2005 [48]. Of the estimated 24,000 evacuees sheltered temporarily at facilities in Reliant Park, a sports and convention complex in Houston, Texas, 1,169 persons reported symptoms of acute gastroenteritis during a 2-week period at the beginning of September. Medical personnel, police, and volunteers having direct contact with patients also reported symptoms, suggesting secondary transmission. Although the local public health officials and the CDC implemented extensive infection-control measures, including publicizing the need for enhanced hygiene techniques, the outbreak continued for an additional week before declining.

Habitat destruction (e.g. deforestation, slash-burn practices) and urban expansion can uncover natural reservoirs and expose humans and domestic animals to new disease-causing microbes. Each year 100–200 zoonotic cases of the pneumonic disease tularemia, caused by the bacterium *Francisella tularenesis*, are reported in the US, primarily in Arkansas, Missouri, and Oklahoma [49]. Transmission usually occurs through arthropod bites, especially ticks or deerflies, but it can also occur through inhalation of contaminated aerosols. In the late 1930s,

rabbits from Arkansas and Missouri were introduced to Cape Cod and Martha's Vineyard, and cases of tularemia in Massachusetts were reported shortly thereafter. Martha's Vineyard experienced two larger outbreaks in 1978 and 2000, which were linked to outdoor activities of mowing lawns and cutting brush [50]. The humans were presumably infected by inhalation of microbe-contaminated animal remains mechanically aerosolized by the cutting action of the mowers or brush cutters.

Pollution and exposure to waste water or sewage can also lead to the emergence of new diseases. Coral black-band disease is a globally distributed disease that has been causing the degradation of coral reef ecosystems. First reported in the 1970s, the disease is observed as a pathogenic microbial consortium (mat) that migrates from the top to bottom of healthy coral, leaving behind dead exposed skeleton that disrupts the ecological and geological structures of coral reefs (see Figure 1) [51]. A factor that appears to be contributing to the development and spread of coral black band disease is the pollution of seawater from industrial, municipal, and other terrestrial waste sites near the coral reefs [52].
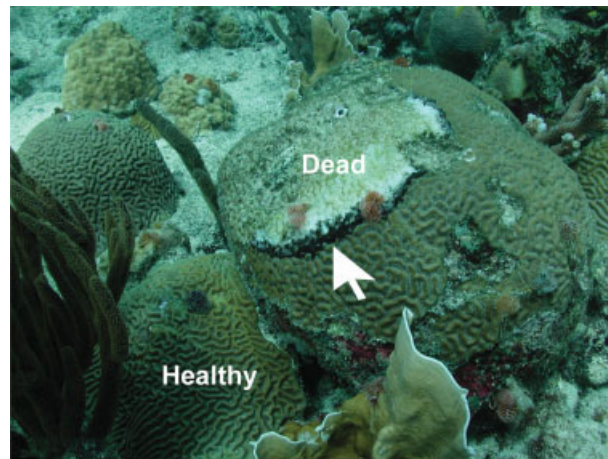
Modern technologies have led to greater efficiency in production, marketing, and commerce of goods around the world. Rapid transport of imported material and tourism related travel facilitate the spread of infectious diseases around the globe and are clearly contributing to the increased prevalence and severity of the diseases. Exotic souvenirs, including wild animals and their associated microbes, have been imported illegally into the U.S. from various parts of the world. An outbreak of monkeypox in 2003 among residents of Wisconsin, northern Illinois, and northwestern Indiana was the result of infection from prairie dogs bought at a pet shop in Texas that became infected after contact

FIGURE 1

Pollution and coral black band disease. Black band disease is one of the most widespread and destructive of infectious diseases accelerating global destructioin of coral reef ecosystems. The diagnostic symptom is the development of a narrow (0.1- to 0.7-cm wide) ring-shaped black or red microbial mat that migrates from the top to bottom, killing healthy coral at rates up to 1 cm per day. Shown is an underwater photograph of coral black band disease in *Diploria strigosa* on the leeward reef tract of Curacao, Netherlands Antilles. A factor thought to contribute to the spread of disease is the daily dumping of sewage and other pollutants directly onto the reef from the harbor of St. Annabaai. The arrow points to the migrating black band. [Photograph courtesy of Dr. Bruce Fouke, University of Illinois at Urbana-Champaign.]

with various exotic African rodents shipped from Ghana and then distributed by other pet shop outlets in the Midwest [53–56]. Rare zoonotic cases of monkeypox in humans had been reported previously only in remote villages of Central and Western Africa near tropical rainforests where there is close contact with infected animals [57, 58]. Recent studies suggest that exposure to monkeypox in these areas has increased due to encroachment of humans into animal habitats. The CDC and FDA subsequently embargoed all African rodents into the U.S. and banned the distribution or sale of African rodents and prairie dogs in the U.S. [59].

Trade routes and human practices have contributed to the spread of numerous diseases throughout history, but the speed with which they are

spreading today have demanded the need for ever more rapid response and containment measures to be in place. An interesting example is that of cholera, caused by the cholera toxin-producing bacterium *Vibrio cholerae*. In Asia, cholera has been endemic for hundreds, maybe thousands of years, and cholera-like disease has been described in a number of ancient texts. The first well-documented epidemic in Europe occurred in 1871. Since 1871, seven major cholera pandemics have occurred [60]. The first six were caused by the classical O1 biotype, whereas the seventh, which began in 1961 and persists today, is caused by the El Tor O1 biotype. In 1991, El Tor reemerged in Peru after a hiatus of over 100 years, and rapidly spread throughout Central and South America over the following

couple of years, with more than 1.5 million cases and over 10,000 deaths [61]. The spread of El Tor in these countries could be traced along the major north-south coastal trucking route and is attributed to poor sanitation in these areas. The most recent cholera outbreaks have occurred in developing countries, such as Angola, where civil strife has hindered water treatment and sanitation efforts [62, 63].

The extent of the global cholera burden has been grossly underreported [62], in part due to limited resources, but also due to the detrimental effects such news can have on trade and travel to those regions. In some endemic areas, such as Bangladesh, improved management strategies by the government and WHO, including aggressive rehydration therapy and antibiotics, have shortened the duration of illness and have reduced the fatality rates from natural cholera epidemics, which are largely seasonal in nature. In 1992, a new strain of *Vibrio cholerae*, designated O139 or "Bengal," caused a massive cholera epidemic in South Asia [64]. What was most disturbing about this new strain was its high prevalence in adults, suggesting that prior immunity gained during childhood through exposure to the classical or El Tor O1 strains offered little or no protection against this new O139 strain. Its subsequent spread to other Asian countries lead some to worry that it may cause an eighth cholera pandemic, but luckily so far this has not materialized due to timely mobilization of effective control measures by researchers and healthcare officials. However, an emerging concern is the increased incidence of antibiotic resistant strains of *Vibrio cholerae* in Bangladesh. Nearly all isolates are now resistant to the less expensive antibiotics, tetracycline, trimethoprin-sulfamethoxazole, and erythromycin. Although most are still sensitive to ciprofloxacin, the effective doses needed for treatment are increasing.

Seasonal changes in rainfall and sunlight can trigger periodic or transient emergence of some human pathogens such as cholera. An intriguing observation comes from the study of the annual epidemic profile of endemic cholera in the Bengal region of Bangladesh and India, where nearly all cases occur in a synchronized, explosive outbreak during major transitions of climate in the post-monsoon months of October and November [65]. As the rains decline and sunlight increases there is a burst of algal and zooplankton bloom. It has been proposed that the increased concentrations of these particles (surfaces to which the bacteria adhere) in drinking water sources consequently increase the rates of ingestion [66, 67]. During other times in the year, cholera cases occur only sporadically because the zooplankton sediment and there is less ingestion of bacteria-coated particles. Recently, an additional factor has been credited toward the seasonal cholera epidemics, namely predation of the *V. cholerae* bacteria by bacteriophage (viruses that infect bacteria) due to amplification of the phage in the intestines of humans, followed by release into the environment [68]. Support for this model comes from the inverse correlation of the phage count with the abundance of toxigenic *V. cholerae* in water samples and with the incidence rates of cholera [65, 69].

Climate change can also dramatically alter the spread of arthropod-borne diseases, which are most prevalent in a limited range of temperatures or environments preferred by these vectors. Shifts in warming or cooling trends may extend or narrow the range of such vectors and the diseases they transmit. Drought or flooding can also lead to spread of disease into new populations of animals or humans. The West Nile virus is an example of a recently emerged vector-borne disease that has been introduced to a new geographic area. The virus was first isolated in Uganda in 1937 and has since

been known to cause disease in Africa, West Asia, Europe, and the Middle East [70]. Until 1999 when it caused a deadly outbreak in the New York metropolitan area, it had never been observed in the U.S., but now it has spread to every state, except Alaska and Hawaii, as well as Canada and Mexico. As of March 2007, the cumulative number of human disease cases in the U.S. is 4,256 [71]. The West Nile virus is usually transmitted between birds by mosquitoes, but can be transmitted to humans and other hosts, particularly during favorable seasonal conditions with a hot dry summer followed by a wet fall, as what occurred in the New York area in 1999. Its introduction into the U.S. is thought to have occurred recently since the genetic profiles of the New York virus isolates suggest they came from a single source, which is related to a virus isolated in 1998 in Israel [72]. Although not known for certain, it is possible that an infected bird could have been imported or an infected mosquito or tick may have hitched a ride on an international flight or on a ship carrying old imported tires infested with mosquito larvae.

Large holding and storage facilities for meat, grains, dairy and produce provide new habitats and breeding grounds for insects and vermin such as mice and rats. Humans can be infected with the deadly hantavirus through inhalation of aerosolized virus present in dried rodent urine in grains or feedstuffs. In 1993 the southwestern U.S. experienced a mysterious outbreak of a new deadly respiratory illness in healthy people, which within a couple of months was identified by the CDC as a previously unknown type of hantavirus [73, 74]. Because the researchers knew that other hantaviruses were transmitted by rodents, they began trapping mice and rats in the area around the victims' homes and discovered that the deer mouse was the primary natural reservoir. Further investigation revealed that there

had been earlier unexplained deaths due to this hantavirus, but these cases were sporadic. The reason for the clustered outbreak in the 1993 could be connected to the unusually high numbers of mice in the area during that season [75, 76]. For several years, the region had experienced drought, but in early 1993, heavy snows melting and rainfall helped revive the flora and fauna in the region, such that the deer mice had plenty to eat. The mice increased dramatically in numbers, and consequently increased the likelihood of transmission to humans.

Intense cross and intraspecies interactions are conducive to transmission of a pathogen from one host to another. The rapidity with which microbes and viruses are able to evolve increases the likelihood of such close host–host contacts to cause the pathogen to "jump" across species barriers. Like BSE, chronic wasting disease (CWD) is a prion-mediated transmissible spongiform encephalopathy of cervids, such as mule deer, white-tailed deer, and Rocky Mountain elk [77]. The potential for CWD to similarly cross the species barrier from cervids to humans is considered unlikely. But, because BSE has been transmitted from cattle to humans (as vCJD), it is feared by some that CWD might also "jump" the species barrier. Although CWD can be transmitted to cattle, sheep, and goats by direct inoculation into the brain [78], studies have not yet demonstrated that domestic livestock are susceptible via oral exposure, the presumed natural route of exposure to BSE [79]. It is feared that homology within critical amino acid sequences of the human and cervid proteins might facilitate cross-species transmission of CWD to humans, as what appears to have occurred for BSE. Thus, understanding how prions overcome resistance to transmission between species is crucial if we are to prevent future epidemics. Although surveillance efforts for CWD in captive and free-ranging cervids are continu-

ing, eradication of CWD from wild populations of cervids is unlikely with currently available management techniques.

IN SEARCH OF BIOSECURITY
The potential emergence of a new disease-causing zoonotic agent that is transmissible between humans is a major concern. Constant exposure and certain behaviors increase the likelihood that a virus will "jump" species. We experienced a frightening example of this with the rapid worldwide spread of the SARS virus. Alarmingly, we are currently at the brink of experiencing another such emergence, which could have devastating consequences on the human population. Already the current spread of avian influenza A virus has resulted in the death from disease or culling of over 300M domestic poultry in Asia, with an estimated $10B in economic losses to the Asian poultry sector (Table 7) [5]. A question on many people's mind today is whether another pandemic flu like the one in 1918 is inevitable [80]. We already know that the circulating influenza H5N1 virus can "jump" from birds to

humans [81], but luckily we have not yet observed significant human-to-human transmission other than a few cases through intimate unprotected contact with a critically ill index patient [82]. Will this fine dividing line be crossed soon? Or, will this threat diminish before it evolves into a more human-specific virus? The truth is that we know very little about the specific factors that trigger a "jump" between species or a transition into a rapidly transmissible virus [83]. We know even less about how to prevent these events from occurring or how to predict when they will occur. The current H5N1 strain, first limited to poultry, quickly spread to migrating birds, but has now emerged in mammals and humans mostly through zoonotic contact. Previously, it was widely accepted that avian viral strains could only readily infect humans after first having undergone genetic shuffling within swine, but now it appears that direct transmission from bird to human can occur [84]. Although its transmission from human-to-human is (luckily) still inefficient, the WHO, the CDC, and other organizations have already mobilized for just such an event [85].

TABLE 7	
Timeline of Influenza A Epidemics—Rapid Evolution of a Deadly Virus	
Human Epidemics	Avian Epidemics
1874 (H3N8)	1959 (H5N1) Scotland, chicken
1890 (H2N2) epidemic	1963 (H7N3) England, turkey
1902 (H3N2)	1966 (H5N9) Canada, turkey
1918 (H1N1) "Spanish" pandemic	1976 (H7N7) Australia, chicken
1933 (H1N1)	1979 (H7N7) Germany, chicken
1947 (H1N1)	1979 (H7N7) England, chicken
1957 (H2N2) "Asian"	1983–1985 (H7N7) Pennsylvania (17M killed)
1968 (H3N2) "Hong Kong"	1997 (H7N7) Hong Kong (1.5M killed)
1976 (H1N1) "Swine" non-epidemic	1999–2000 (H7N1) Italy (2.7M killed)
1977 (H1N1/H3N2) "Russian"	2002 (H7N7) Hong Kong (>1M killed)
	2003 (H7N7) Netherlands (30M killed)
	2004 (H7N3) Canada (17M killed)
	2004-present (H5N1) Asia, pandemic (>300M killed)

Distinguishing a deliberately introduced infectious disease from a naturally occurring or emerging infectious disease is inherently more difficult due to their "dual-use" nature. The good news, though, is that effective medical treatment and prevention strategies for combating a naturally occurring infectious disease will most likely work just as well for one that is deliberately introduced. The exponential advances that have been made in the life sciences, medicine, and biotechnology have not only dramatically enabled our ability to respond to biological threats, but, sadly they have also increased the potential risks of malevolent exploitation and inadvertent misuse. Indeed, a report from the U.S. National Research Council and the Institute of Medicine concluded that the breadth of potential biological threats is far wider than is commonly appreciated and will continue to expand in the future [86]. The NIH invests over $28B annually in medical research. Since 2001, NIH has directed over $10B toward countering bioterrorism alone and currently spends over $3B of its annual budget on infectious diseases with over $1.8B going toward emerging infectious diseases (Table 4) [87].

Considerable attention has been recently focused on developing better preparedness and surveillance (early warning) as strategies for more effective response to biological threats. This depends on having reliable, sensitive and rapid means for recognition of unusual events or unexpectedly high levels of common events. A number of animal and human health laboratory response networks have been established with the goal of maintaining an integrated national and international system for facilitating standardization and movement of information, for expansion of detection and diagnostics measures, for coordinating responses among federal, state, university and commercial clinical laboratories, and for identification of common source outbreaks.

On the international front, the WHO and CDC have increased activities to build capacity for global disease detection and response, with immediate focus on and strengthening of influenza surveillance. The Global Alert and Response Network (GOARN) was established in 2000 by WHO as a partnership of >140 institutions and networks to mobilize human and technical resources for the rapid identification and control of disease outbreaks that are of international importance [88]. The Global Livestock Early Warning System (GLEWS) has been formed by the Food and Agricultural Organization (FAO) of the United Nations and the World Health Organization for Animal Health (OIE) to strengthen epidemiological analysis and prediction of major animal diseases and zoonoses and to improve reporting from a variety of data sources that might impact disease transmission from animals to humans [89]. The recent pandemics have also mobilized strengthening of the International Health Regulations, which were first established by WHO in 1969 to ensure maximum security against international spread of certain diseases (cholera, plague, yellow fever, and smallpox—although smallpox was removed from the list in 1981) with minimum interference of world commerce. In 2005 a revised set of regulations was adopted unanimously at the World Health Assembly to increase the roles and responsibilities of WHO and Member States, including financing, developing, strengthening, maintaining and implementing core surveillance, and response capacities [90].

SLOWING EVOLUTION: STRATEGIES TO ENHANCE BIOSECURITY

Biosecurity requires multipronged, flexible, and interdisciplinary approaches to combat the perpetuation and spread of infectious diseases. In all, simultaneous use of multiple strategies will be necessary for effective infection control and disease management. One such strategy is to use evolutionary engineering (combining predictive evolution and genetic engineering) to design vaccines and drugs based on predictive targets. For example, an innovative approach for control of E. coli O157:H7 contamination of food and water was recently employed to eliminate the source for the organism. By vaccinating the animal reservoir—cattle—the researchers were able to prevent colonization of the cattle with the microbe, reducing the levels of bacteria shed in feces and thereby reducing the risk of human disease [91]. This strategy was shown to significantly decrease the prevalence of E. coli O157:H7 in a clinical trial conducted in a feedlot setting.

Improved sanitation and use of chlorinated drinking water has dramatically reduced the incidence of waterborne disease. Evidence suggests that the cholera epidemic in South and Central America was caused by a complex set of circumstances, including poor sanitation conditions, poor separation of drinking water and waste streams, and inadequate water treatment and distribution systems [61]. Indeed, outside of Peru's capital Lima, chlorination of drinking water supplies at the time of the epidemic was limited at best. Improved water quality and sanitation have since reduced the incidence of cholera in South American countries. Another simple, yet surprisingly effective strategy recently implemented has been the use of filtering water through multilayered cloth filters to remove the plankton and other particles to which the Vibrio bacteria adhere [92].

Over the past 25 years an unprecedented mobilization of resources have been directed at stopping the HIV pandemic, ranging from preventive strategies for persons at high risk for contracting HIV, such as educational counseling, testing, and referral services, to treatment with multiple drug regimens, to management measures

aimed at improving the healthcare of persons living with HIV and preventing further transmission [93]. Although enormous success in prevention of HIV/AIDS in the U.S. has been achieved and we have learned a lot about how to approach rapidly evolving diseases from this experience, a number of prevention and treatment challenges remain. HIV prevalence remains high among homosexual men [94] and racial/ethnic disparities have increased, especially among African-American men and women [95] with prevalence among African-American men reported as high as 46% [96]. New programs are needed to more effectively reach these populations [93].

One approach toward improved treatment and reduction of drug resistance is the use of multidrug overkill (triple drug therapy). Administration of just a single drug often leads to the development of resistance to that drug, but strong multidrug doses decrease the likelihood of multidrug resistance. For example, recent studies have shown that triple drug combination antiviral therapy in treating HIV-infected persons offer superior viral suppression over other drug regimens [97]. When two or more drugs are used simultaneously, each helps prevent the emergence of resistance to the other drug. Effective regimens for the treatment of TB must contain four different drugs to which the organisms are susceptible. To illustrate how this might be so effective, consider that mutation rates in the TB-causing bacterium lead to a frequency of resistance to isonazid of 1 in 10^8, to streptomycin of 1 to 10^8, to ethambutol of 1 to 10^7, and to rifampicin of 1 to 10^9. Bacterial mutants resistant to any single drug are naturally present in any large bacterial population. An inactive TB granuloma contains 10^2–10^4 bacteria, whereas an active TB lesion contains 10^7–10^9 bacteria. This means that the chance of gaining resistance to any one of the drugs is relatively high in an active lesion, but the chance of gaining

resistance to multiple drugs is considerably less [98].

The course of the four-drug treatment for TB usually lasts from 6 to 9 months. When adherence with the regimen is assured, the four-drug regimen is highly effective; however, a problem with TB treatment is that the drugs used are often counter-indicated, cause unpleasant side effects, and must be administered in series over a long period of time rather than simultaneously, which leads to problems with patient compliance [43]. Nearly half of individuals with TB do not complete their treatments. Reduction of noncompliance can be achieved by direct observation of the patient to ensure full dosage. In developed countries, such as the U.S., this is relatively easy to achieve with the use of healthcare workers and family members. However, in developing countries, there are many obstacles to adhering to treatment regimens, and alternative strategies to improve compliance are needed. In addition to direct observation of treatment, other tactics include sending reminder cards or phone calls, monetary incentives, health education and counseling, and making access to clinic facilities easier [99].

Another strategy for reducing the prevalence of antimicrobial resistance is to remove the overall selection pressure by minimizing exposure to the drug, and especially withholding the most effective drugs, i.e. the "drugs of last resort," until absolutely needed. This is becoming more and more difficult to accomplish with the accelerated rate of spread of antibiotic resistance through the overuse and over-prescription of antibiotics [37, 39, 100]. Indeed, many researchers were dismayed at the large distribution of ciprofloxacin (Cipro™) to treat over 60,000 people after the anthrax attack in 2001 and warned that this widespread use could lead to resistance in other bacteria [101]. The strain of *Bacillus anthracis* strain used in the attack was equally sensitive to other less expensive and

more commonly used drugs. Ciprofloxacin is considered a "drug of last resort" because of its broad-spectrum and efficacy against many pathogenic bacteria, particularly those (such as *Staphylococcus*) that are already resistant to other drugs. Prescreening for sensitivity is another approach that allows for use of narrow-range rather than broad-spectrum antimicrobials, which further reduces the likelihood of resistance developing and spreading to other pathogens.

FILLING IN THE BIOSECURITY GAPS

Management and implementation of effective preventive or containment measures in the event of natural or man-made biological threats will require increased infrastructure and diagnostic and surveillance capabilities. For example, the tremendous scale-up in food production, from the vast herds of cattle to the huge confined feedlots to the slaughterhouses to the many hundreds of distributors and supermarkets, has undoubtedly contributed to the emergence and prevalence of food-borne diseases such as that caused by *E. coli* O157:H7. The complexity of the modern food preparation and distribution process makes epidemiological tracking of the sources of contamination difficult, although there have been noticeable advances.

In response to the need for improved agriculture and food biosecurity, Congress passed the *National Agriculture and Food Defense Act of 2007*, which will require enormous effort and financial commitment on the part of the government and agricultural and food industries. The logistics involved are daunting, particularly in coordinating efforts among many different agencies. One example is the Food-borne Diseases Active Surveillance Network (FoodNet), which is a collaborative project of the CDC, the USDA, and the FDA to monitor and

TABLE 8

CARVER + Shock Assessment Method for Food Safety

Criticality–measure of public health or economic impacts of an attack to achieve terror goals
Accessibility–ability to physically access and egress from the target
Recuperability–ability of system to recover from an attack
Vulnerability–ease in accomplishing the attack
Effect–amount of actual direct economic loss from an attack as measured by loss in production
Recognizability–ease of identifying the target
Shock–the combined physical, health, economic and psychological effects of an attack

The CARVER+Shock method rates each of seven attributes on a scale of 1–10 for identification of vulnerable sites in food processing and distribution system that might be targets for attack or points of contamination.

study the epidemiology of food-borne diseases [102]. In response to the growing need for better food surveillance, the FDA implemented the hazard analysis and critical control point (HACCP) program for prevention of food-borne diseases, which involves monitoring food distribution at critical control points where contamination is most likely to occur [103, 104]. In 2005 the Food Safety and Inspection Service (FSIS) of the USDA established the Food Emergency Response Network (FERN), which will work with the FDA and its HACCP program to integrate a laboratory network across the U.S. that can quickly respond to food-related emergencies [105]. The FSIS, as part of its task of protecting public health through food safety and defense, recently implemented a new assessment method, called CARVER+Shock [106], for identifying the most vulnerable target sites within a food processing system (Table 8).

In considering the gaps in the U.S. agriculture and food defense capabilities, the main question that must be addressed is: Exactly what level of security do the people of the USA want the agricultural industry to achieve, and our government to enforce, in terms of food safety and biosecurity? It is clear that we (as a nation and international community) are not happy with the current security status of our food and agricultural supplies. The outbreaks and ensuing deaths, economic losses and drop in consumer confidence resulting from contaminated spinach by *E. coli* O157:H7 [11], mentioned above, amply demonstrate this point. But, if we take this episode as an example, one must question exactly what could have been done to prevent or further mitigate this outbreak than was already done. By all accounts, the surveillance, detection, evaluation, containment, and recovery measures were remarkably fast, accurate, and as good as one could possibly hope, considering the circumstances— far better than in previous incidents of a similar nature, thanks to improved measures newly in place. This was considered an accidental outbreak, but what if it had been a deliberate attack? Undoubtedly, the response would have been little different. Yet, what happened is still deemed by most as unacceptable. So, how could this be improved?

Most current measures are aimed at further improvements to detect or contain a future incident by increasing surveillance at the front-end, increasing diagnostics or enhancing epidemiological monitoring capabilities once an incident has occurred. But, just how much of an improvement would that be? Clearly, what the public wants is a near certainty that such an event as occurred with the spinach will not happen again. Part of the difficulty in adequately addressing this need is that current efforts are focused on too broad and vast a target (there are just too many steps in the food processing, where things can go wrong and something could slip through the cracks). Instead, the focus for ensuring near complete biosecurity should be at the very end of the food processing chain, namely at the packaging and delivery stage.

While all the proposed surveillance, detection, evaluation, containment and recovery measure will significantly reduce the possibility of future contamination, and thus should be done to the extent possible, they will not ensure the desired near-complete protection from an incident (which is what the consumer is demanding). So, how can this be achieved? Many scientists see food irradiation as one viable solution. Food irradiation of already processed and packaged food through promising new technology can eliminate disease-causing microbes from foods. The effects of ionizing radiation on food and on animals and people eating the irradiated food have been extensively studied and deemed safe [107–109], and indeed this technology has been implemented already for certain foodstuffs. Yet, bringing this technology into use for most foods has been challenging, primarily due to misconceptions and fear about its safety on the part of the public and policymakers. Closing this gap will require a ramping up of public engagement by the scientific community. Somehow scientists must better communicate with the public and policymakers, convincing them of the benefit

of this technology and at the same time alleviating their fears of its use.

CHALLENGES IN PURSUIT OF BIOSECURITY

To achieve global health biosecurity it is critical that the communication and educational barriers between non-scientists and scientists are overcome and that efforts by public healthcare, scientific and security policy communities are better integrated. Enhanced coordination between multiple agencies is essential for implementing and maintaining global disease surveillance systems, public healthcare, and diagnostic and basic research laboratories. Thus far, many redundancies in effort remain and interagency cooperation is still fragmentary. International cooperation has improved with regard to regulatory and containment (import/export) policies, particularly in the area of travel restrictions during pandemics, but cooperation is still a bit shaky in other areas where commerce and political issues are concerned. And, much work remains in the areas of regulation of agricultural, societal and medical practices, pollution control, and prevention of habitat destruction. Strengthening national and international capacities to prevent and control disease epidemics will require continued promotion of international cooperation and technical partnerships with institutions and networks around the globe to mobilize resources for control of disease outbreaks.

Regulation and oversight of research and use of potentially dangerous bioagents ("select agents" or high-risk or high-impact bioagents) is well underway, but there remain disparities between that conducted in the U.S. and that done elsewhere in the world. Biosafety and biosecurity of pathogens in laboratories and healthcare settings will require enhanced education for better preparedness and increased confidence of the public and policy makers in science. Many scientists feel that policymakers have not fully understood the difference between biosafety and biosecurity and have consequently imposed a number of mandates and regulations that equate enhanced need for security with enhanced danger, i.e. greater biosafety risk. Balancing biomedical and biotechnological advancement with biosecurity will always be at odds due to the ambiguous definition of what constitutes a potential biosecurity threat, but improved education will help with making those decisions.

Although warning and prevention are preferable to coping with the consequences of an attack, an emphasis must also be placed on improving public healthcare and basic research and education. It is critical that we develop a homeland and global biosecurity strategy that is applicable to both intentional and unintentional disease outbreaks. The best defense against any microbial threat is a robust public healthcare system in regard to its science understanding, capacity, and practice. There has been considerable advancement in the area of prevention, with improved surveillance and detection, and with new drugs becoming available at a remarkably rapid pace, but we are still only at the tip of the iceberg in our understanding of pathogen evolution, post-exposure treatment and control, prediction of epidemic versus pandemic spread, rates of transmission, impact of climate change, and preparation for handling a biothreat agent of unknown origin, whether it be from natural, accidental, or deliberate exposure.

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