

Emerging Infectious Diseases in 2012: 20 Years after the Institute of Medicine Report

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ABSTRACT Twenty years ago (1992), a landmark Institute of Medicine report entitled “Emerging Infections: Microbial Threats to Health in the United States” underscored the important but often underappreciated concept of emerging infectious diseases (EIDs). A review of the progress made and setbacks experienced over the past 2 decades suggests that even though many new diseases have emerged, such as SARS (severe acute respiratory syndrome) and the 2009 pandemic influenza, significant advances have occurred in EID control, prevention, and treatment. Among many elements of the increase in the capacity to control EIDs are genomics-associated advances in microbial detection and treatment, improved disease surveillance, and greater awareness of EIDs and the complicated variables that underlie emergence. In looking back over the past 20 years, it is apparent that we are in a time of great change in which both the challenge of EIDs and our responses to them are being transformed. Recent advances support guarded optimism that further breakthroughs lie ahead.

Twenty years ago (1992), a landmark Institute of Medicine (IOM) report entitled “Emerging Infections: Microbial Threats to Health in the United States” underscored the important but often underappreciated concept of emerging infectious diseases (EIDs) (1). Although the IOM report was influential in thrusting the issue of EIDs squarely into scientific and public discourse, the awareness that diseases periodically emerge and re-emerge actually goes back millennia (2, 3). For example, ancient Greek, Roman, and Persian writers documented the emergence of many new epidemics. During and after the 14th-century “Black Death” pandemic of bubonic/pneumonic plague, European city officials quarantined arriving ships to prevent its importation and set up quarantine stations to isolate and care for patients. In 1685, the scientist Robert Boyle presciently observed that “there are ever new forms of epidemic diseases appearing. . . among [them] the emergent variety of exotick and hurtful. . .” (4, 5).

By the mid-19th century, the discovery of microbes as causative agents of infectious diseases led to the development of preventive countermeasures such as passive immunotherapy, vaccines, and drugs against infective agents (6). These advances spurred optimistic predictions that infections would soon be conquered (7), and physicians and public health workers began to lose sight of the possibility of the emergence of new and previously unrecognized infectious diseases. To a large extent, it was the shock of the recognition of HIV/AIDS in the early 1980s, followed by the IOM report of 1992, that rekindled awareness of, and interest in, EIDs. Two decades after the IOM report, it is appropriate to ask what has been learned about EIDs, where have we succeeded or failed in our efforts to fight them, and what challenges remain.

THE PERPETUAL THREAT OF EMERGING AND RE-EMERGING INFECTIOUS DISEASES

As predicted in 1992 (1), previously unrecognized infectious diseases have continued to emerge, including variable Creutzfeldt-Jakob disease/bovine spongiform encephalopathy (vCJD/BSE), severe acute respiratory syndrome (SARS), and 2009 pandemic H1N1 influenza, and others have reemerged, e.g., disease caused by multiple-drug-resistant *Staphylococcus aureus* (MRSA), multiple-drug-resistant and extensively drug-resistant (MDR and XDR) tuberculosis, cholera, and dengue.

The recent EID with the greatest global impact has been HIV/AIDS. Over the past 3 decades, humankind has witnessed the unexpected emergence of, and then the relentless devastation resulting from, one of history’s deadliest pandemics (8). At the same time, modern research tools have helped us to understand how, where, and when HIV emerged; to understand its pathogenesis and natural history; and to develop life-saving treatment and prevention modalities that have put the control of the HIV/AIDS pandemic within reach. Surely, future generations will look back on the era of HIV/AIDS as one of the most remarkable periods in the history of human disease, in which civilization was challenged by a devastating pandemic EID and aggressively addressed it from a scientific and global health standpoint, leading to the real possibility of effective control in a relatively timely manner.

GREATER AWARENESS OF EIDS IS ITSELF AN IMPORTANT COUNTERMEASURE

The term EID and the concepts of newly emerging and reemerging infectious diseases have recently become much more widely appreciated. The 1992 IOM report led to rapid and heightened awareness of this issue in the scientific, public health, medical, and lay communities. For example, both the United States Centers for Disease Control and Prevention (CDC) and the National Institute of Allergy and Infectious Diseases of the National Institutes of Health released EID research and response plans (9, 10). In 1995, the CDC established an EID-oriented scientific journal, *Emerging Infectious Diseases*. Now in its 18th year, the journal has published nearly 10,000 articles and has become standard reading for many in the disciplines of microbiology, clinical infectious diseases, public health, and allied medical fields. Other microbiology and general medical journals emphasizing EIDs have been established, e.g., *PLoS Pathogens*, or expanded their coverage of EIDs, e.g., the

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Journal of Infectious Diseases and *Vaccine*, while *mBio* and other journals published by the American Society for Microbiology (ASM) have remained leaders in publishing important EID-related research.

Internet resources devoted to EIDs also have flourished. For example, ProMED was launched in 1994 as a grass roots effort by the Federation of American Scientists and has been continued by the International Society for Infectious Diseases. Today, ProMED's 60,000-plus subscribers from 185 countries can read—openly, online, and in real time—about virtually all important EIDs occurring anywhere in the world. This creates immediate awareness of epidemics not only for scientists but also for the public and the media. ProMED has made it extremely difficult for cautious governments to suppress outbreak information and has greatly enhanced the capacity of public health systems to control infectious disease outbreaks (11).

CDC has expanded the MMWR (*Morbidity and Mortality Weekly Report*), which is now abstracted in medical journals such as the *Journal of the American Medical Association*, so that every week practitioners around the world can get the latest information about EIDs. Such heightened EID awareness has been transformational and catalytic. It has become clear that the five or six EIDs emerging annually (on average) over the past 8 decades have disproportionately emerged from perturbed ecological niches, especially those in tropical areas with vector-borne zoonotic diseases (12, 13).

GENOMICS/PROTEOMICS FACILITATE DIAGNOSIS, PREVENTION, AND TREATMENT OF EIDS

Since 1992, high-throughput genetics techniques have led to the sequencing of thousands of microorganisms, their vectors, and many of their hosts. Genomics and proteomics have helped in the discovery of new infectious diseases and in acquiring a better understanding of the pathogenesis of existing ones; have substantially improved surveillance, diagnosis, and drug and vaccine design; and promise to help elucidate host susceptibility factors and host responses to treatment of infections. For example, by 2003, the genomes of the human species, the mosquito *Anopheles gambiae*, and the malaria parasite *Plasmodium falciparum* all had been sequenced, representing the first time that all the major actors in the drama of an important emerging/reemerging infectious disease had been characterized at the molecular genetic level (12, 14). These breakthroughs are important additions to our continuing efforts to control malaria, which have had recent successes but still require new countermeasures. These genomic data are contributing to vaccine and drug development and are elucidating the pathogenesis of and human resistance and susceptibility to malaria (14).

SCIENTIFIC ADVANCES HAVE REDEFINED THE CONCEPT OF EIDS

Genomics techniques, like PCR and high-throughput deep and whole-genome sequencing, that now greatly facilitate the discovery of EIDs (e.g., the etiologic agents of hantavirus pulmonary syndrome and Kaposi sarcoma) also reveal previously unimagined genomic diversity among microbes. This diversity includes complex and evolving viral quasispecies and microbes that have undergone considerable interbacterial horizontal gene transfer, creating new phenotypic properties of virulence and drug resistance.

Given these and other advances in science and technology, it is now possible to perceive, as Dawkins argued decades ago (15), that the evolution and natural selection of human diseases are not simply a struggle between microbes and hosts. Rather, it is fought out at a more basic level of gene-to-gene competition, pitting the genomes of microbes against those of their hosts (many of whose genomes contain genetic evidence of past microbial encounters). Dawkins contended that the visible evidence of genomic survival is an organism's expressed phenotype, its "survival machine," which is akin to a simple virus being protected by its external protein coat; however, Dawkins proposed that we should think of natural selection as operating at the level of the gene, not the organism it encodes.

This picture becomes more complex when we consider the human microbiome. Specifically, our gut flora represents a complex "external" organ system comprising at least three different "enterotypes" that have coevolved with us over millennia and appear to affect our health, including by preventing and modifying infection (16, 17). Indeed, fecal transplantation is now a novel treatment for *Clostridium difficile* colitis (a potentially fatal EID) (18). Infants who start life with or develop "reduced" flora (e.g., via pre- or postnatal antibiotics) may be at increased risk of IDs and EIDs. Variations in the microbiome may also affect the occurrence of certain chronic diseases, allergies, and malnutrition (19). In this newer view, humans are not just static victims of virulent microbes but hubs of gene flow in which pathogens not only "seek" to survive environmental barriers and natural and acquired immunity but also compete with other microbes on the playing field that we think of as "us."

Additional conceptual advances in EIDs include the realization that many chronic diseases have a direct or indirect infectious basis, e.g., cervical, hepatic, and gastric cancers; gastroduodenal ulcers; hemolytic-uremic syndrome; and possibly some types of tics and obsessive-compulsive disorders (6, 12). We also have become aware of the critical role of microbial coinfections in the pathogenesis of certain infectious diseases (e.g., HIV and numerous opportunistic infections; influenza and measles in association with secondary bacterial pneumonias) and of nutrition, e.g., the link between vitamin A and measles (20, 21).

The "one-health" concept, which emphasizes understanding and studying the unity of human and animal infectious diseases (22), reflects growing awareness that the majority of human EIDs, probably more than 60 per cent (11), are of animal origin (zoonotic), a realization that has implications not only for disease surveillance but also for understanding pathogenesis and controlling disease. For example, HIV/AIDS, influenza, Lyme disease, tuberculosis, measles, plague, smallpox, and possibly even leprosy are directly or primarily of animal origin. Viral host switching, in some cases associated with rapid and complicated microbial co-mutations (23), has become an important research topic (23, 24) for both newer EIDs, such as SARS, and reemerging ones, such as influenza. The processes by which animal-adapted microorganisms leave their hosts and adapt to new species, such as humans, are largely unknown and represent an important challenge in the study of EIDs.

Moreover, host-switching is not just a one-way street from other animals to humans. For example, Ebola virus, a devastating disease for humans, has decimated African gorilla populations; in the United States, suburban expansion associated with deforestation has driven raccoons into the suburbs, increasing rabies trans-

mission to and from them; and a human strain of *Staphylococcus aureus* has adapted to chickens, spread globally, and developed new mutations enhancing avian virulence (25, 26). These examples remind us that ecosystem dynamism in which humans play a critical role is a key variable in EID occurrence and prevention (6, 12).

THE PAST IS PROLOGUE IN THE STUDY OF EIDS

Since 1992, enormous strides have also been made in understanding the history of EIDs, most notably by genetic sequencing of historically preserved microbial DNA and RNA. Perhaps the most significant example is the 1918 pandemic influenza virus, which caused the deadliest single disease event in recorded human history (27). Although that pandemic occurred 15 years before influenza viruses were first identified, recent sequencing efforts from RNA in preserved tissues allowed full reconstruction of the 1918 pandemic viral genome, leading to a remarkable body of ongoing research and a greater understanding of how influenza viruses continue to emerge among humans and other animal species (27, 28).

Of the several thousand microorganisms already sequenced, those of historical importance include smallpox virus strains, the plague bacillus (*Yersinia pestis*) (29), and ancient tuberculosis organisms. Strikingly, paleovirus oncogenes have even been resurrected and studied in infectivity assays to find the original cellular receptors to which they had become adapted millions of years ago (30). Both traditional historical research and study of phylogenetic trees derived from gene sequencing of modern organisms have added significantly to these efforts, leading, for example, to the discovery that the initial jump of what became known as HIV from nonhuman primates to humans probably occurred nearly a century ago with multiple independent host-switching events that ultimately led to the pandemic that was first recognized in 1981 (31). Understanding the history and evolution of emerging microbes allows us to predict more accurately what their potential pandemic impact will be, and to understand how we can best prevent and control them.

GROWING OPTIMISM ABOUT THE CONTROL OF EIDS

It is now becoming accepted that disease eradication has a legitimate place in the armamentarium of responses to EIDs (6). Smallpox, a devastating reemerging disease for millennia, was eradicated in 1980, and the epizootic morbillivirus (measles-related) disease rinderpest was eradicated in 2011 (32, 33). With dracunculiasis and polio disease close to eradication, with measles on the path to eradication, and with significant strides in controlling such diseases as hepatitis B and even malaria and HIV infection being made, it is now possible to realistically consider eradication as an ultimate means of controlling certain EIDs.

Even though antibiotic resistance has accelerated alarmingly, new generations of antibiotics have kept pace (albeit, barely), and vaccines against some of the most important diseases have been developed or improved, such as those against *Haemophilus influenzae* type B, pneumococci, and cancer-causing human papillomavirus strains. The development of antivirals and antiviral combination therapies has led to a historic breakthrough in helping to control HIV/AIDS (12) and major strides in curing chronic hepatitis C virus infection. Future directions in research and drug development likely will include better antibacterial and antiviral combination therapies as well as the development and use of more

narrow-spectrum drugs against infective agents, which are less likely to cause polymicrobial resistance.

In the 20 years since the IOM report on EIDs, remarkable progress has been made in understanding and controlling them. In 1992, HIV infection was considered a death sentence for most patients. In 2012, after the tragedy of more than 35 million AIDS deaths, persons treated early with combination antiretroviral therapy, although not “cured” of their viral infection, can expect to live normal life spans with only a low risk of transmitting infection to others. In 1992, at least a million children died annually of measles. In 2012, fewer than 100,000 are expected to die, and measles eradication based upon an already-available effective vaccine is a realistic near-term goal. In 1992, it was possible to enter villages in many developing countries to monitor poliovirus circulation by conducting childhood “lameness surveys.” In 2012, most lame individuals are adults whose children are largely free of the threat of polio and probably will live to see it eradicated (poliovirus type 2 has already been extinguished).

Despite extraordinary progress during the past 2 decades, infectious diseases still kill 15 million people each year (6), and new and deadly diseases continue to emerge and reemerge. The perpetual nature of the emergence of infectious diseases poses a continuing challenge, which is volatile and ever-changing. This challenge includes a need for constant surveillance and prompt, efficient diagnosis; a need to develop and deploy new vaccines and drugs to combat new diseases; and a need for ongoing research not only in developing countermeasures but also in understanding the basic biology of new organisms and our susceptibilities to them. The future is ever uncertain, because unimagined new diseases surely lie in wait, ready to emerge unexpectedly; however, our ability to detect and identify them, our armamentarium of treatment and prevention options, our capacity to undertake and maintain basic and applied research, and our commitment to eradicating certain EIDs have never been greater. We have made far-reaching advances in the past 20 years since the original IOM report, and scientists are guardedly optimistic that further breakthroughs lie ahead.

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