VIEWPOINT

Emerging Infectious Diseases: Public Health Issues for the 21st Century

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Infectious diseases are the third leading cause of death in the United States and the leading cause worldwide. As the new millennium approaches, the public health community must replenish capacity depleted during years of inadequate funding while simultaneously incorporating new technologies and planning for the longer term. Among the challenges facing the public health community is the need for coordinated, global, multisectoral approaches to preventing and controlling complex infectious disease problems.

After World War II, there was widespread optimism in the United States that good sanitation, vaccines, and antimicrobial agents would conquer infectious diseases. However, public health successes of the 1960s and 1970s were followed in the 1980s and early 1990s by ominous developments, such as the recognition of the extent of the HIV/AIDS epidemic and the resurgence of diseases such as tuberculosis.

Part of this backslide occurred because of decreased funding for and subsequent erosion of the public health infrastructure (*1*, *2*). Starting in 1992, a series of reports called for prompt U.S. government action against emerging infectious diseases (EIDs) (*3*–*5*). As a result of awareness created by these documents and other influences [for example, concern about the threat of bioterrorism (*6*)], Congress appropriated funds to improve the public health infrastructure to address EID threats, including funding for improving food safety and preparing for bioterrorism. The public health community is using these funds to strengthen the critical functions of detecting, controlling, and preventing infectious diseases. Maximizing the benefits from these resources will require balancing the need to replenish basic capacity depleted during years of inadequate funding (*1*) with the need to incorporate new technologies and plan for the longer term.

Detection of EIDs

Rapid detection of EIDs is essential to minimize illness, disability, death, and economic losses. Public health surveillance—the ongoing, systematic collection, analysis, interpretation, and dissemination of health data—is the cornerstone of problem detection and response. The usefulness of augmenting routine surveillance with new technologies—such as molecular tools and rapid communications methods—has been demonstrated many times. For example, the National Molecular Subtyping Network for Foodborne Disease Surveillance (*7*) (also known as PulseNet; Fig. 1) has contributed to the identification of several multistate outbreaks with relatively few affected persons in any given place (*8*). When intensive laboratory study of an illness with characteristics that suggest an infectious origin fails to identify a causative agent, creative approaches, such as searching for host mRNA response profiles that are agent- or class-specific (*9*), may help solve the puzzle.

Although laboratory testing has been the basis for identifying many new diseases, clinicians are often the first to recognize a new disease problem. Networks of medical specialists in emergency medicine, infectious diseases, and travel medicine have been formed recently to enhance collaboration about EIDs (*10*). Physicians in these networks systematically collect data about difficult infectious disease problems, as well as use the Internet and other means to rapidly circulate queries about diagnosis and management of uncommon or poorly understood infectious illnesses. These capacities could be potentially useful during an influenza pandemic or certain bioterrorist events.

Control of EIDs

Systems for detecting infectious disease problems must be tightly linked to systems for controlling them. In addition to ensuring adequate capacity for routine public health control functions, we must ensure surge capacity—ways of rapidly increasing laboratory, epidemiologic, and other staff and facilities to test specimens, conduct epidemiologic investigations, and oth-

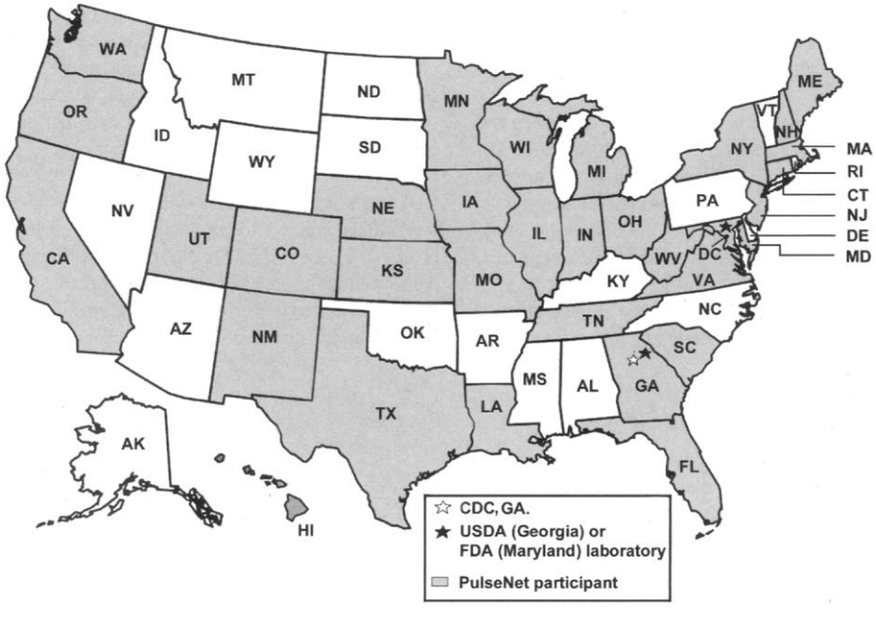

Fig. 1. National Molecular Subtyping Network for Foodborne Disease Surveillance (PulseNet) (*7*). PulseNet is a molecular subtyping network conducted by the Centers for Disease Control and Prevention (CDC), state health departments, the U.S. Department of Agriculture (USDA), the Food and Drug Administration (FDA), and the Association of Public Health Laboratories. Participating clinical and public health laboratories electronically submit pulsed field gel electrophoresis (PFGE) images from clinical specimens to a database, and within minutes the CDC-based computer returns information on specimens with similar PFGE patterns. USDA and FDA laboratories submit PFGE images on isolates from food items to the system.

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erwise respond to difficult and complex public health problems. Additionally, special capacities must be available to address problems that are not part of routine public health—for example, to test for organisms that require Biosafety Level 4 facilities (known lethal organisms potentially transmissible in a laboratory environment for which no known prophylaxis or treatment is available) or to manufacture and distribute vaccines and medications during an influenza pandemic.

Prevention of EIDs

Preventing EIDs requires using proven tools, and developing and evaluating new ones. Vaccines provide excellent examples of proven, cost-effective disease prevention. For instance, in 1993 in the United States, 23 million elderly people failed to receive the pneumococcal vaccine; vaccination would have saved an estimated 78,000 years of healthy life and $194 million (*11*). Other proven prevention tools include screening and treatment of blood and blood products to prevent hepatitis B and HIV transmission (*12*) and administering intrapartum antibiotics to women at high risk for transmitting Group B *Streptococcus* to their newborns (Fig. 2) (*13*).

For some disease problems, such as antimicrobial resistance, effective approaches to prevention and control have been difficult to develop and implement (*14*). Overuse and misuse of antimicrobial agents are major contributors to antimicrobial resistance. Reducing inappropriate prescribing of antimicrobial agents requires intensive, sustained efforts; approaches that have been used with varying success have included physician and patient education, peer review with feedback, computer-assisted decision support, and administrative interventions (*15*). Examples of newer approaches that will place less emphasis on behavior change (*16*) include targeting bacterial virulence (which would not lead to selective pressure for antimicrobial resistance) (*17*) and changing food production practices (*18*), for example, the use of competitive exclusion (selectively establishing indigenous intestinal flora in food animals to reduce colonization with pathogenic or resistant organisms) (*19*). Development of new vaccines that reduce the number of people asymptomatically harboring an organism [for example, the soon-to-be licensed pneumococcal conjugate vaccine for young children (*20*)] may decrease antimicrobial resistance by interrupting transmission of the target organism, with resultant reductions in antibiotics used for treating actual disease or presumptive treatment of other conditions.

Long-term Challenges for the Public Health Response to EIDs

Most of the factors that contribute to disease emergence will continue, if not intensify, in the 21st century (*3*). These include social factors (for example, lack of adequate health care and increases in international travel), demographic factors (for example, the aging of the population in developed countries, urbanization, and population growth), and environmental factors (for example, global climate change, lack of adequate sanitation, and land use practices that result in human contact with previously remote habitats), as well as microbial evolution. The public health community must develop long-term strategies to respond to these challenges.

As we enter the new millennium, new technologies, like biosensors (*21*) and high-density DNA microarrays (*22*), are likely to have profound effects on clinical medicine and public health practice. Biosensors use immobilized antibodies or antigens to detect minute concentrations of their binding partners in biologic fluids. Microarrays consist of arrangements of thousands of sequences of synthetic or cloned DNA sequences able to detect complementary sequences in a sample. These techniques may allow rapid and specific disease diagnosis, so that a clinician can rapidly determine what organism is causing an illness and whether it carries antimicrobial resistance genes.

New understandings of human genetics may lead to immunizations, treatments, and other interventions tailored to an individual's genetic profile (*23*); the public health community must help develop, assess, and use genetic tests (*24*). New informatics tools to link and analyze large, diverse, and distributed databases will facilitate important public health findings but will raise difficult issues related to patient privacy (*25*). The sheer volume of data available for analysis, for example, on human genetic profiles as analyzed on microarrays, will require new methods for studying associations between the characteristics of individuals and their risk for diseases and responsiveness to treatments. A new generation of DNA vaccines and edible vaccines may be safer and more effective than those currently in use (*26*). Such vaccines may be easier to produce, store, and transport than conventional vaccines, greatly simplifying delivery even to remote parts of the world and raising the possibility of global elimination or eradication of many diseases that have been difficult to control.

With increasing international travel and global commerce, prevention and control of EIDs must involve global efforts (*5*, *27*), including ensuring adequate supplies of safe food and drinking water, providing immunizations, improving personal hygiene, and reducing inappropriate antimicrobial use. The recent threat from H5N1 influenza in Hong Kong (*28*) illustrates the importance of international communication and cooperation and the need for a global perspective.

The public health community also needs to work more actively with other sectors (such as agriculture, economic development, and health care) with important roles and interests in reducing infectious diseases. In recent years, the decisions to slaughter cows potentially infected with bovine spongiform encephalitis in Britain and to slaughter poultry to stop influenza H5N1 infection in Hong Kong, and proposals to modify regulations governing the use of antimicrobial agents in food production in the United States and elsewhere are examples of multisector responses to EID threats. Even greater collaboration will be necessary to deal with poverty, a particularly recalcitrant contributor to and consequence of infectious diseases. For example, malaria has its greatest impact among the poor nations of sub-Saharan Africa, where annually it kills at least 430,000 to 680,000 children (*29*) and costs 1% of the 1995 gross national product in sub-Saharan Africa (*30*).

Infectious diseases are currently the third leading cause of death in the United States (*31*) and the leading cause worldwide (*27*). The potential threats to public health from problems such as antimicrobial resistance and new infectious agents will continue. We must make a long-term commitment now to ensure the capacity to address current EID problems as well as those in the future.

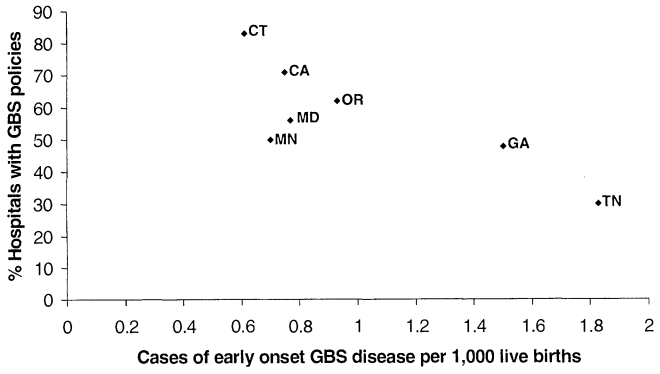

Fig. 2. Association between hospital policies and rates of Group B streptococcal (GBS) disease, 1996. As much as 41 to 78% of GBS disease in the first week of life can be prevented by appropriate use of antibiotics. According to 1996 data from sites with intensive surveillance for invasive GBS disease in seven states, geographic areas in which a higher proportion of hospitals had GBS perinatal disease prevention policies had lower incidences of early-onset GBS disease ($R^2 = 0.62$, $P = 0.03$) (*13*).

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REVIEW

Phylogenetic Perspectives in Innate Immunity

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The concept of innate immunity refers to the first-line host defense that serves to limit infection in the early hours after exposure to microorganisms. Recent data have highlighted similarities between pathogen recognition, signaling pathways, and effector mechanisms of innate immunity in *Drosophila* and mammals, pointing to a common ancestry of these defenses. In addition to its role in the early phase of defense, innate immunity in mammals appears to play a key role in stimulating the subsequent, clonal response of adaptive immunity.

It has long been appreciated that the antimicrobial host defense relies both on innate and adaptive components. Overwhelmingly, however, studies on immunity during the last few decades have concentrated on the adaptive response and its hallmarks, that is, the generation of a large repertoire of antigen-recognition receptors and immunological memory. Only quite recently has innate immunity gained renewed interest, particularly as it became apparent that it is an evolutionary, ancient defense mechanism (*1, 2*).

In this review we will first discuss innate immunity in *Drosophila* where the power of genetics combined with molecular and biochemical approaches has allowed a dissection of pathways required for host defense. With the guidance of paradigms set in *Drosophila*, we will examine the role of innate immunity in mosquitoes and discuss its relevance in reducing transmission of medically important parasites. We will then define the essential characteristics of mammalian innate immunity, namely, its ability to distinguish species self from infectious nonself, and we will illustrate the links between innate and adaptive immunity. A central theme of this review is the marked conservation of innate defenses between insects and mammals, which points to a common ancestry of these systems.

Prototypical Innate Immune Responses in *Drosophila*

Drosophila is particularly resistant to microbial infections. Three mechanisms contribute to this resistance: (i) phagocytosis of invading microorganisms by blood cells, (ii) proteolytic cascades leading to localized blood clotting, melanin formation, and opsonization, and (iii) transient synthesis of potent antimicrobial peptides. These reactions all take place within a short period after septic injury. Whereas information on the involvement of blood cells and of proteolytic cascades in *Drosophila* immunity is still fragmentary, much has been learned in recent years about the structure and regulated expression of the inducible antimicrobial peptides, and we will restrict our analysis here to this facet of the host defense (*3*). The peptides are primarily produced in the fat body (the functional equivalent of the mammalian liver) and are secreted into the blood. In addition to this systemic response, *Drosophila* also produces antimicrobial peptides locally, in barrier epithelia (*4*).

Since the discovery of inducible antimicrobial peptides in the moth *Hyalophora cecropia* by Boman and associates in 1981 (*5*), 400 peptides have been reported to participate in innate immunity, not only in insects but in all multicellular organisms that were investigated, including humans and plants. Paramount among these peptides are the defensins, a group of compact (3- to 5-kD) protease-resistant molecules with three or four disulfide bridges. Defensins have wide spectra of activity directed against various bacteria, fungi, and enveloped viruses (*6, 7*). Four defensin families have been reported in eukaryotes: α-defensins and β-defensins in mammals, insect defensins, and

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