SCIENCE AND HEALTH POLICY

The Changing Burden of Infectious Disease in Europe

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Infectious diseases continue to pose major public health challenges in developed, as well as developing, countries. The European Academies Science Advisory Council aims to integrate multidisciplinary analyses to define priorities for European surveillance of new, growing, or potential threats from antimicrobial resistance, vector-borne disease, and pandemic influenza. There is a concomitant need to apply such knowledge toward the development of improved health care and robust policies. We discuss how translational medicine can bridge these global issues by helping to mobilize resources between academia, industry, health care services, and policy-makers.

THE EUROPEAN BURDEN

Communicable diseases currently contribute about 10% of the total disease burden in Europe (*1*), and human and animal populations are increasingly threatened by emerging or reemerging infections. In a previous Commentary in *Science Translational Medicine* (*2*), we described some of the opportunities and challenges for research and innovation policy in this broad therapeutic area. The European Academies Science Advisory Council (EASAC; www.easac.eu)—an organization created to provide expert, independent scientific advice to those who make policy in the institutions of the European Union (EU) (*2*)—has continued to analyze health and innovation policy issues. EASAC published a report recently (*3*) that brings together and updates emerging themes from 6 years of study (2005 to 2011). In the present Commentary, we draw on this resource (*3*) to discuss some of the latest changes in the infectious disease burden in Europe, including the transmission of new and reemerging pathogens and the dramatic increase in antimicrobial resistance. We further discuss the implications for translational medicine in this context.

DISEASE SURVEILLANCE DATA: COLLECTION, CURATION, APPLICATION

Sound scientific data are essential for establishing effective public health services and for informing health policy. One consistent theme in the evidence gathered by EASAC is the need to improve standardization of methods for collection, quality control, and interpretation of disease and antimicrobial resistance data. Some European countries do not have the modern molecular techniques necessary for thorough disease surveillance or for acting on the data to control disease effectively (*4*). Recent improvements in European coordination led by the European Centre for Disease Prevention and Control (ECDC; www.ecdc.europa.eu) have helped to form active infectious disease surveillance networks; however, much more can be done to modernize public health practices, including capitalizing on modern microbial genome sequencing technologies to map disease outbreaks—in other words, combining genomics with social science research (*5*).

A rapidly developing, if somewhat controversial, research area with implications for infectious disease diagnosis and control is the use of human genome-wide association studies (GWAS). Host susceptibility to meningococcal disease has been analyzed in European population cohorts using GWAS (*6*) to provide evidence for genetic variation in the innate immune system governing susceptibility to infection. Further work will be required to explore mechanisms of complement activation associated with this variation in the region that correspond to the regulator complement factor H. In addition to host susceptibility, there will be an increasing interest in using GWAS to study general host determinants of infection; however, it is likely that interpretation of such results will be complicated by pathogen genetic variation, particularly if the contribution of host genes is rather limited. We suggest that linkage of GWAS with other research approaches, such as systems biology (which integrates various data sets), will be needed to detect previously overlooked connections between pathogenesis and host response. In the future, it will be crucial for researchers to include a large number of well-phenotyped samples to ensure statistical power to detect meaningful clinical associations.

There are additional opportunities to modernize disease surveillance on the basis of early warning systems—for example, by integrating epidemiological and environmental data. Syndromic surveillance (in other words, collecting health-related data that precede diagnosis) might signal disease outbreak sufficiently early to warrant further investigation. Mining of data from other origins—in particular, social media—may also be valuable for syndromic surveillance and early outbreak detection.

There is also a need to improve clinical assessment, which could be furthered by developing a closer linkage between health services and information technology systems. There are several challenges in establishing data infrastructure and procedures to store, manage, and analyze data sets reliably and securely (*2*). In contrast with some other research disciplines, such as the -omics, data sharing is not yet the norm within the public health community. This lack of data sharing needs to change, or it could limit both academic research progress and its subsequent translation to health benefits (*7*). Last, it is equally important for research-funding bodies and other policymakers to consider how new data on gene–infectious disease associations, if generalizable, can be used to improve diagnostics and therapeutics, as well as the stratification of patient cohorts for clinical trials.

It is important that serious threats from infection are identified in order to inform priorities in data collection and provide goals for translational medicine research. Drawing on the EASAC analysis (*3*), we highlight here some top priorities in the EU, including antimicrobial resistance, vector-borne diseases, and preparedness for future influenza and other viral pandemics.

ANTIMICROBIAL RESISTANCE

Antibiotic resistance has been exacerbated by the inappropriate use of antibiotics in human and veterinary medicine. Viewed

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as a collective failure of society (*8*), antibiotic resistance has emerged as a stimulus for continued innovation. It is also increasingly clear that antibiotic resistance is a problem shared globally (*9*, *10*), which continues to increase and take on new dimensions. For example, a rise in resistance to several antibiotics was observed when comparing the antimicrobial susceptibility of the Gram-negative bacillus *Bacteroides fragilis* (found in the gastrointestinal flora and commonly involved in anaerobic infections) in Europe with data collected 20 years ago (*11*).

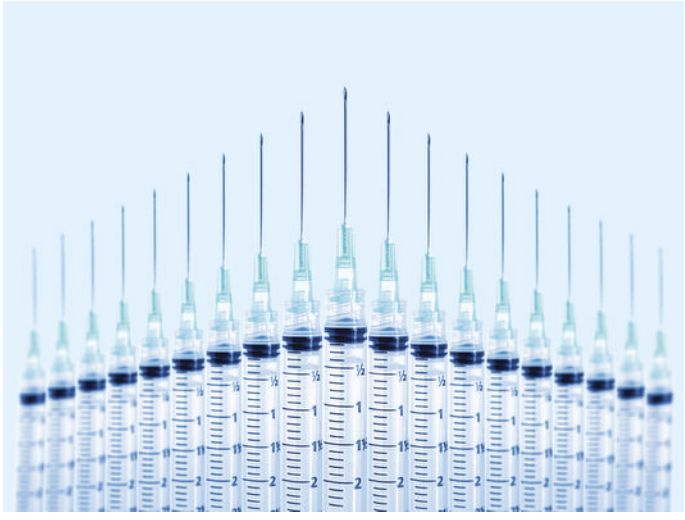

Fig. 1. Public, private, and transatlantic partnerships are essential to reverse the downward trend in the development of new antibiotics and to refill the antibiotic pipeline.

Despite many warnings, the EU remains unprepared to face growing instances of antibiotic resistance (*12*). In particular, this has led to problems with hospital-acquired infections, with respect to both increased incidence and cost (*13*, *14*). The annual health care cost of hospital-acquired infections, which affect ~7% of EU patients, has been estimated at 7 billion euros. There are approximately 37,000 directly attributable deaths annually, half of which might be from multidrug resistance (*3*). Recent data from the United States show 1.7 million cases of hospital-associated infection annually, resulting in up to 100,000 excess deaths (as compared with 13,000 in 1992) and costing the U.S. health care system more than 35 billion U.S. dollars (*14*). Incidence rates in many developing countries are probably even higher than in the EU and the United States (*15*).

In the EU, community-acquired infections are also an issue, although more needs to be done to quantify the socioeconomic impact (*13*). The most recent data from the European Antimicrobial Resistance Surveillance Network and the ECDC (*16*) confirm that resistance to antibiotics is increasing; however, such data probably underestimate the problem. Surveillance in parts of the EU does not involve microbiological confirmation of case findings and is further confounded by the reluctance of some institutions to publicize their data. Microbial genomics has potential to revolutionize epidemiology if widely adopted—for example, clarifying geographical origin and intrahospital spread of *Staphylococcus aureus* (*17*). The escalating threat of drug resistance is also exemplified by recent changes in the EU health burden caused by *Clostridium difficile*, which is coincident with the emergence of hypervirulent strains that are resistant to fluoroquinolone antibiotics (*18*).

We previously described (*2*) some of the major political and technological implications for translational medicine policy arising from the threat of antibiotic resistance. Vaccine innovation is vital to reduce the incidence of antimicrobial resistance, as illustrated by the impact of the pneumococcal conjugate vaccine (*19*). The development of cheaper, faster, and more reliable diagnostics is also crucial because uncertainty in diagnosis is a major reason for the inappropriate use of antibiotics. However, there are often challenges in translating diagnostic assays developed in the academic laboratory and small companies to commercial-scale devices. Markets may also be weak because health budgets are fragmented and it can be difficult to demonstrate that increased spending on diagnostics will be cost-effective. Nonetheless, progress is being made in some areas—for instance, in tuberculosis (TB) diagnostics, where there is potential for novel approaches encompassing signatures from metabolomics, proteomics, and transcriptomics (*20*, *21*).

Regarding antibiotic innovation, a recent analysis of the origin of drugs approved by the U.S. Food and Drug Administration for the period from 1970 to 2009 (*22*) showed that U.S. academia has contributed substantially to tackling infectious diseases. This suggests that the public sector has given more priority than the pharmaceutical sector to this therapeutic area. Partnership is essential to develop the next generation of antibiotics and to identify and characterize innovative approaches that are based on new targets and mechanisms (Fig. 1). One recent initiative is the U.S.-EU Transatlantic Task Force on Antimicrobial Resistance, which was established to find ways to encourage research and development as part of an ambitious objective to develop 10 new licensed antibiotics within the next 10 years (*23*). A recent publication of the responses to the EU consultation on this task force (*24*) disclosed consistent support for transatlantic cooperation from across the public and private research sectors with agreed objectives to improve the antibiotic pipeline.

VECTOR-BORNE INFECTIOUS DISEASES

Recent data identify potential new risk areas in Europe for the transmission of mosquito-borne diseases, including West Nile virus, dengue, chikungunya, and malaria (*25*). A colony of the tropical species of mosquito *Aedes aegypti* was recently found in the Netherlands (*26*) and, although the vector is unlikely to survive the winter in northern Europe, this observation implies that there may be similar problems in other countries that might monitor new vector invasions less thoroughly. Scientific evidence is beginning to identify and characterize the impact of climate change on the transmission and distribution of human and animal infections, many of which are carried by mosquitoes or other vectors (*27*). For example, the impact of climate change on the incidence and distribution of tick-borne diseases is becoming apparent (*28*). The spread in Europe has increased since the 1980s, with approximately 85,000 cases of Lyme borreliosis reported annually.

Uncertainties in the current and projected assessments of changes in climate are compounded by gaps in the surveillance data. There is a need for more intensive and multidisciplinary study of the impact of environmental change on pathogens, their vectors, and their hosts (*29*) and on the human behavior that may influence exposure

to pathogens. Many emerging and reemerging diseases are zoonoses; therefore, in addition to integrating international epidemiology (*30*), it is important to build better links between the human and animal disease research agendas, particularly to study how pathogens cross the species barrier and extend their host range (*31*). Results from integrated research may be expected to underpin discovery pipelines for both human and animal health.

THE PANDEMIC THREAT

The H1N1 influenza outbreak of 2009 has been a relatively mild pandemic to date. However, there is a danger of creating a false sense of security; the next emerging infection may be much more of a threat, so there is reason to invest in innovation to reinforce pandemic preparedness. Various lessons can be learned from the pandemic in the 2009–2010 flu season. First, it is essential to improve surveillance, particularly in sentinel animal populations known to pose a risk for humans. Improved human sero-prevalence data are also vital for forecasting trends. Second, there is a need for better virus characterization and analysis of immune responses—for example, to understand why older people have been less likely to contract the pandemic H1N1 strain. Lastly, the public- and private-sector medical and scientific communities must continue to explore potential causality of adverse events (*32*) and to articulate the value of vaccination in credible, consistent, and unified messages in order to counter antivaccination lobbying and build public trust (*33*). New vaccines will be required on account of antigenic drift and the potential for virus reassortment. The threat of pandemics will be magnified if vaccine manufacturers are discouraged from committing to future rapid responsiveness, and this policy issue merits increased attention.

INFECTIOUS DISEASE AS A GLOBAL CHALLENGE

EASAC has recommended (*3*) that the EU help develop laboratories throughout Europe for testing infection and drug sensitivity. Setting up new laboratory infrastructures will require quality control and training programs in new diagnostics. The recent creation of the European Reference Laboratory Network for TB (*34*) will include EU accession countries as well as current member states and could help to catalyze assistance to other neighboring and developing countries. A comparable initiative of great relevance is the United States' activity to develop the first modern TB diagnostic laboratory in North Korea (*35*).

Such commitments are also good examples of "science for diplomacy," placing cooperation in science and health at the heart of foreign policy (*36*). New initiatives in global health governance (*37*) could bring new opportunities in translational medicine. The National Academies of Science in the G8 countries recommended to their heads of state the establishment of partnerships for research and innovation in the developing regions, with the objective to achieve the "Millennium Development Goal," amongst which is a focus on tackling the spread of infectious diseases (*38*). International partnerships remain essential to generate and use knowledge, both to inform policy development and implement innovative health care solutions.

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