EUROPEAN POLICY

Translational Medicine Policy Issues in Infectious Disease

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The European Academies Science Advisory Council has published a series of reports on infectious disease policy issues, analyzing priorities for building the science base as part of public health strategy. Among current challenges facing the European Union are the needs to tackle antibiotic resistance, promote vaccine innovation, prepare for the emergence of novel zoonoses, and integrate research approaches to human and animal health. The scientific community must help public policy-makers to address the organization, balance, and sustainability of research funding and infrastructure; encourage the creation of a more supportive regulatory environment for translational medicine; and evaluate new models for public-private partnership to facilitate innovation.

INTRODUCTION

Infectious diseases worldwide account for about one-quarter of all deaths (*1*) (Fig. 1). In developed countries, an earlier optimism that most such diseases had been conquered by improved surveillance and public health measures is now seen to have been misplaced. In Europe as elsewhere, there are newly emerging threats to confront (*2*): new influenza variants; new microbes, especially those transmitted by animals; resurgent infections like tuberculosis (TB); resistance to antimicrobial drugs; and bioterrorism. Increasing migration and other effects of globalization compound these challenges.

Communicable diseases have major economic as well as health effects. In England, for example, the direct economic burden calculated from the cost of primary care, hospital admission, and hospital-acquired infection was estimated as up to $15 billion annually (*3*). The net impact is much greater when other ramifications are included. Emerging zoonoses—infectious diseases that can be transmitted to humans from other animals—can be disruptive on a global scale. For example, the cost of the severe acute respiratory syndrome epidemic (which occurred from 2002 to 2003 and was caused by a virus that probably originated in bats), including the effects on travel, tourism, economic growth, and financial markets, was estimated at $80 billion.

EASAC AND THE EU

In 2001, the national science academies of the European Union (EU) member states formed the European Academies Science Advisory Council (EASAC) to provide expert, independent science advice to those who make policy in the European institutions (Table 1). In a series of reports on infectious diseases (*4*), EASAC identified EU priorities for building the science base as an integral part of public health strategy. In this Commentary, we draw on this accumulating evidence to analyze policy issues that affect multiple countries to improve the translational medicine environment in Europe and indicate where further reform should be sought.

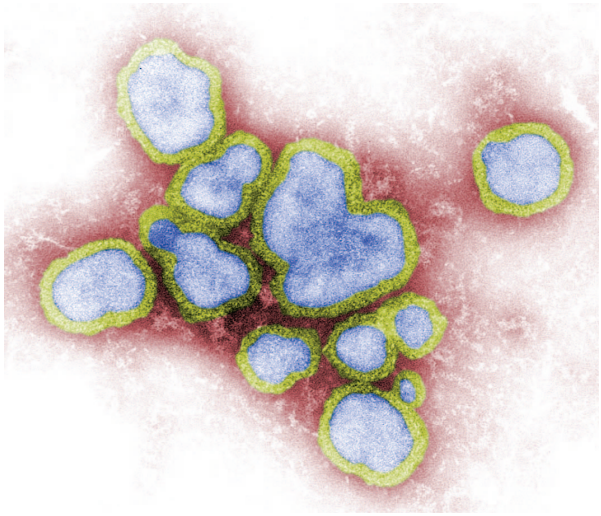

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Fig. 1. Death by infection. Viral and bacterial infections are responsible for a large fraction of deaths worldwide. This digitally colorized negative-stained transmission electron micrograph shows several influenza A virions.

APPRECIATING THE IMPORTANCE OF R&D POLICY

That different policy-making functions must be better coordinated at national and EU levels to capitalize on the scientific evidence base is a pervasive theme in EASAC work. The challenge of antibiotic resistance exemplifies the problem: Historically, policy-makers' use of evidence has been weak and short-sighted, despite resistance accounting for half of the deaths from health care–associated infections in some parts of Europe (*5*). A recent recommendation from the EU Council (*6*), following European Commission proposals (*7*) to contain antibiotic resistance by (i) strengthening surveillance, (ii) standardizing infection-control procedures, and (iii) improving the awareness of the hospital workforce and patients, typifies the short-term efforts to make better use of research evidence that is already available. The scientific and medical communities together with policy-makers must pursue an important translational medicine agenda to measure and contain the transmission of clinically relevant pathogens and aim to implement Europe-wide accreditation programs for hygiene standards, diagnosis, and prescribing.

However, these relatively immediate actions are not enough. In the view of EASAC, policy-makers must also commit to a longer-term agenda to promote science and innovation; inform coherent strategy; and create new tools to detect, monitor, prevent, and treat infections. Translational medicine encompasses opportunities to understand the behavior of both microbial and human populations, but requires better integration of research activities and therapy development to conceive new interventions and use them in new ways—for example, as diagnostic-therapeutic combinations in personalized medicine.

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Table 1. European institutions with responsibility for developing and applying policy associated with translational medicine. Activities at the EU level must also take into account the role of national authorities to support research, deliver public health, and manage the approval and availability of medical products.

Institution	Description
European Commission	Directorates-General for Research, Enterprise, and Public Health have operational roles to support health-related research and its application. The European Commission initiates law-making, develops policies, and manages programs while respecting the principle of subsidiarity (in those domains where the EU does not have exclusive competence to act).
European Agencies	ECDC has roles to identify, assess, and communicate threats from infection. EMEA has responsibility for EU-wide marketing authorization, comprising assessment, supervision, and pharmacovigilance.
European Parliament	Directly elected body of EU that can draft legislation and request the executive to present proposals. Has codecision role in law-making with EU Council.
Council of EU	Composed of ministers from member states and has codecision role with Parliament. Can also set out general guidelines and political priorities for the other institutions. Presidency of the council is held by each member state for 6 months in turn under a rotating system.

OPPORTUNITIES FOR TRANSLATIONAL MEDICINE: THE EXAMPLE OF VACCINES

EASAC reports (*4*) explored two European gaps in translation: from basic science to clinical studies and from clinical research to routine application of new therapies in health practice. Much more effort is needed to link the advances in fundamental science on pathogen characterization with clinical infection research, product discovery, proof-of-principle in early drug development, and clinical scale-up. Merely improving linear progression along the R&D continuum is not enough; capitalizing on feedback from outcomes in human research to inform preclinical understanding, test hypotheses, and steer the selection of novel disease targets must also occur.

This complexity is exemplified in EASAC's analysis of the policy issues for vaccine innovation. Although it is vitally important to make the best use of vaccines already available, there are unmet vaccine development needs in Europe, as elsewhere—for pandemic influenza, established diseases (including TB, human immunodeficiency virus infection, and respiratory syncytial virus infection), other emerging diseases (for example, West Nile virus infection), and antibiotic-resistant pathogens. New opportunities are arriving: The sequencing of bacterial and viral genomes has created the discipline of pathogenomics, facilitating "reverse vaccinology" (*8*). In this approach, scientists search for vaccine targets by studying sequence information, as well as the microorganisms themselves. For example, European vaccine research on mutating virulence genes produced a TB strain potentially conferring greater protection and fewer side effects than the standard bacillus Calmette-Guérin, or BCG, vaccine (*9*). But funding agencies need to realize that advances in genomics necessitate the simultaneous pursuit of an ambitious and diverse research agenda in fundamental science—for example, to understand the innate immune system and the induction of T lymphocyte responses, as well as to characterize pathogen functionality (particularly for growing threats such as the flaviviruses)—before a new disease appears.

In short, vaccine R&D deserves a higher priority. The use of improved research methodologies must be matched by a receptivity at regulatory agencies for new types of information. Preclinical work can suggest biomarkers to serve as correlates of infection and protection to help shorten the duration of vaccine trials. But this process requires iteration across basic and clinical research to screen and validate sensitive and specific markers, as it is often the clinical outcome that informs preclinical routes to efficacy and safety indicators. Microbial challenge studies—in which human volunteers are deliberately infected with microorganisms—provide another very specific example of the value of feedback from human research. Such studies continue to contribute to the understanding of pathogenesis (for example, for malaria) and the immune response and may furnish proof-of-concept for an intervention (*10*, *11*).

POLICY CHALLENGES FOR A BROAD SCIENTIFIC AGENDA

Advances in basic science are beginning to clarify key pathogen population functions such as virulence and quorum sensing (during which cells in a population coordinate their behavior), and provide an information resource for translation into novel diagnostics and therapeutics, as well as vaccines. Basic bioscience will deliver further insight into mechanisms of pathogenicity, interspecies transmission of infection, and host adaptation. These fundamental advances and their applications carry implications for health services and the regulation of innovation. For example, the narrow therapeutic specificity that is the likely consequence of virulence inhibition mandates rapid and precise diagnostic methods to direct therapy.

In addition to better integration of basic and clinical studies, research funders and practitioners need to attend to two other germane matters. First, they must incorporate findings from the social sciences. For example, it is important to clarify the determinants of antibiotic resistance in different settings and educate health professionals about these factors to improve rational prescribing. Similarly, funders and practitioners must clarify how to communicate with the public about the benefits and risks of vaccines to build public trust about vaccine use. Better socioeconomic assessment of the impact of infections and health care interventions is also needed to raise the political visibility of these issues and inform priority-setting.

Second, funding agencies and researchers must integrate approaches to human and animal health. The importance of coordinating research to foster "one health" is a constant EASAC theme. This task is increasingly necessary: About 75% of new infectious diseases discovered in the last 10 years affecting humans have originated in animals. Research to contain the influenza pandemic required coordinated work on several animal species as well as humans. The current disconnect between the sectors amplifies the fragmentation between basic and applied research and between national and international policies that impedes the translation of discovery into clinical advance. The steps needed to achieve this better integration pose problems for policy-makers because it may be necessary to modify the entire organizational structure of infection research, prevention, and response, perhaps by creating a national institute for infectious disease

(*12*). At both national and European levels, such changes require political will.

NEW WAYS TO BUILD TRANSLATIONAL MEDICINE RESOURCES

New infrastructure. EASAC proposed that one way of integrating across disciplines and across sectors would be to create multidisciplinary infectious disease centers of excellence with areas of expertise designed to span the sciences. For Europe, such centers should be networked to ensure research capacity building in all member states and access to patients. In addition to providing critical mass and interdisciplinarity, these centers could help to remedy European weaknesses that will otherwise hinder the progress of translational medicine.

One current deficit is in the provision of training. By promoting education and career development, new infrastructure can become an important part of initiatives such as the Clinical and Translational Science Network (*13*). But the success of translational medicine does not depend only on integrating different skills and perspectives. EASAC highlighted the problem of declining skills in traditional disciplines, such as microbiology, immunology, and epidemiology, that may compromise the performance of the next generation of researchers. Other disciplines, such as entomology, vector biology, and microbial ecology, have also been neglected yet are newly critical for translational medicine in terms of understanding the increasing incidence and spread of infections that are occurring as a result of climate change and other environmental pressures (*14*, *15*).

European capacity can also be augmented by adding value to preexisting medical microbiology infrastructure. In many European hospitals, microbiology services are poorly connected to research, teaching, and training; microbiology laboratories also tend to merge and be located remotely from hospitals. European funding agency encouragement of collaboration between universities that harbor fundamental research groups and hospital microbiology laboratories would facilitate efforts in pathogen function elucidation, molecular epidemiology, target discovery, improved screening assays, data management, and modeling.

Another current weakness is the lack of integrated database resources. TB research exemplifies the value to be gained by constructing an accessible and comprehensive repository of well-characterized pathogen strain isolates together with their genomic, clinical, and epidemiological data to study relationships between molecular variation and clinical consequences (*16*) and, if also including human samples, to study the interplay between the bacterium and patient (*17*). This knowledge platform could improve drug susceptibility testing, enhance the modeling of future drug-resistance scenarios, and act as a resource for developing new interventions. To be effective, a database must be international, requiring collaboration between centers of excellence with the European Centre for Disease Prevention and Control (ECDC), the U.S. Centers for Disease Control and Prevention, and other resources worldwide. Such coordination presents a challenge for global policymakers for technical, institutional, and, perhaps, ethical reasons (*18*).

New funding models. New funding models should be created to facilitate multidisciplinary, long-term, costly infectious disease research. The current EU system, based on competition between individual research groups and fragmented research prioritization strategies, should be reformed to incorporate the concept of Grand Challenges (*19*), whereby policy-makers identify societal priorities and the research community agrees on specific research goals for coordinated, sustained inquiry.

New regulatory environment. The Clinical Trials Directive was implemented by the European Medicines Agency (EMEA) for the European Commission in 2004 with the objectives of improving research standards, protecting patients, and enhancing the competitiveness of large-scale medical trials. However, the academic and smaller-company research communities are concerned that the directive dramatically increased bureaucracy and costs for researchers without enhancing clinical safety or quality (*20*). The inadvertent consequence of reducing the number of academic researcher-initiated trials in Europe is unfortunate; researchers must inform policymakers on the options for proportionate trial regulation. There are also more general lessons to be learned—the academic community must be more proactive in advising policy-makers earlier in the legislative life cycle, and, in turn, policy-makers should consult more widely if they are to avert unintended consequences of legislation.

New time scale in policy development. The clinical and policy-making communities now face an additional collective challenge in accelerating the science advisory processes. The current H1N1 influenza outbreak provides a good example of a situation in which information was generated in real time to inform practical decisions: to identify vulnerable populations, analyze available interventions, and promote public awareness (*21*). This response by the scientific community entailed considerable laboratory, epidemiological, and social science research; the policy challenge is to ensure that the lessons from this episode are embedded in policy-making more broadly and that sufficient resources are made available for researching other threats, some unforeseen.

CONNECTING RESEARCH WITH INNOVATION IN STRENGTHENED PARTNERSHIPS

Antibiotic and vaccine innovation comprise lengthy, expensive, uncertain, and complex processes. EASAC analysis substantiated concerns expressed by many other advisory groups in the United States and EU regarding a declining pharmaceutical pipeline in certain areas of infectious disease R&D, for example, drugs targeting Gram-negative bacteria. If increasing antibiotic resistance portends a return to the pre-antibiotic era, it would be difficult to overestimate the subsequent impact on modern medicine, dependent on the surgery and other intensive hospital care that becomes impossible without effective infection prevention and control.

The nature of the current impediments to innovation for both large pharmaceutical and smaller biotechnology companies has been discussed extensively in the EASAC reports and elsewhere [for example, for antibiotics (*3*, *22*, *23*) and for vaccines (*24*)], and the need for innovative incentives to encourage antibacterial R&D has become a priority for the current presidency of the EU Council. Although there are many issues to face in encouraging innovation—for example, in the regulation of marketing, pricing, and reimbursement to counter industry perceptions of the declining return on investment in this area—some optimism that new approaches to risk-sharing in public-private partnership will help drive R&D is appropriate. The need to stimulate public-private collaboration is a consistent theme in EASAC work.

One recent advance is the Innovative Medicines Initiative, a 2 billion euro partnership between the European Commission and the pharmaceutical industry to sup-

port precompetitive research to tackle R&D bottlenecks in safety, efficacy, training, and knowledge management. It is too soon to judge if the partnerships will succeed, but it is encouraging that the design of the initiative takes account of criteria for success in collaboration, identifiable from the work of EASAC and industry commentators (*25*). The factors deemed critical for success include substantial public funding, international networking, early attention to contentious ownership issues, and the involvement of smaller companies.

Additional advances in shared approaches to safety evaluation will occur. The Serious Adverse Events Consortium recently demonstrated (*26*) a markedly increased risk of liver injury with the antibiotic flucloxacillin in patients carrying at least one copy of the *HLA-B*5701* allele. Subjects and samples were recruited in the United Kingdom in publicly funded research with regulatory agency permission for access to safety records. This model for investigating adverse events merits wider adoption, for example, in vaccine postmarketing surveillance for which EASAC defined a responsibility for EU member states to develop molecular epidemiology networks for research and product monitoring.

Individual companies can also collaborate with academia after the precompetitive research phase. However, as academic researchers often have only a limited understanding of what industry needs in validated drug targets, it is prudent not to overvalue what such research can deliver in the absence of industry advice. Consequently, although there are roles for public research, notably in target assay and validation and in medicinal chemistry for the construction of more diverse chemical libraries [molecular scaffolds (*23*)], to bridge the gap between academia and industry, industry must also teach what is needed for drug discovery research.

BUILDING MOMENTUM IN TRANSLATIONAL SCIENCE AND POLICY

If the current shortcomings in infectious disease research and innovation are to be addressed, public policy-makers need to reconsider the organization and balance of research funding at national and EU levels. This requires better sharing of those skills compartmentalized within the traditionally separate domains of academia, industry, and government (*27*). We conclude by emphasizing two points. First, it is vital not to neglect basic research; without this, translational medicine is impossible. Second, although we focused on the EU, there are opportunities for more coherence in policymaking worldwide. The strategies for translational medicine have implications not only for scientists but for many others, including finance ministries, those concerned with research governance, and the veterinary sector. Such strategies will also affect innovation and competitiveness, public health infrastructure, and global development. The scientific community must continue to stimulate discussion of the policy options.

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