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Infectious diseases and the future: policies for Europe

A non-technical summary of an EASAC report, *European Public Health and Innovation Policy for Infectious Disease: The View from EASAC*

Foreword

The European Academies Science Advisory Council (EASAC) is formed by the national science academies of the Member States of the European Union (EU). As such it offers European science a collective voice, enabling member academies to collaborate in providing advice to European policy-makers.

In his foreword to the full EASAC report on which this lay summary is based, Professor Volker ter Meulen (chairman of the Council's Biosciences Steering Panel) writes, "Infectious disease continues to represent a major public health challenge for the EU". Over the past six years, he adds, EASAC itself has responded to this challenge with a series of studies of issues that public policy-makers need to take into account. The report brings together some of the findings of these previous analyses, reinforces their conclusions and updates their recommendations.

It is important, Professor ter Meulen continues, for the EU to be more ambitious in tackling a range of issues. These include disease surveillance, private sector innovation leading to the creation of health and wealth, and the recognition that health issues are often relevant to strategic decisions in other policy areas. "During the six years of our work in this area, EASAC has consistently emphasised the importance of partnership – between academia, industry, health services, the charitable sector, government – and we continue to urge new models of collaboration, accompanied by new efforts to communicate about the issues to society-at-large."

In presenting this non-technical account of the full report's principal content and conclusions, EASAC is aiming to make a direct contribution to the last of these objectives.

Introduction

"It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body."

Nobel Lecture by Sir Alexander Fleming, discoverer of penicillin, 11 December 1945

"The spread of superbugs. What can be done about the rising risk of antibiotic resistance?"

Headline from the *Economist* magazine, 31 March 2011

"Most antibiotics are useless against EHEC"

Headline from *Die Welt* during the enterohaemorrhagic *E. coli* bacteria outbreak in Germany, 30 May 2011

The 20th century saw a series of social, scientific and medical developments that freed the people of Europe from the ravages of infectious disease to an extent that would have been unimaginable to their great-grandparents. By the end of the 1950s it had begun to appear that a combination of public health measures, vaccination and antibiotics would soon render most infectious illnesses a distant memory. Young doctors who were thinking of a career in this specialty were sometimes warned to reconsider; there might soon be little need for their services, they were told.

Over the next two decades it became increasingly clear that these declarations of impending victory over infection were premature. In spite of Europe's success in the control of a variety of diseases such as diphtheria, tetanus and hepatitis B, and the advent of vaccination programmes against meningitis and human papilloma virus (the cause of cervical cancer), communicable illness still accounts for some 10% of the total burden of disease across the continent.

The optimists of half a century ago, looking ahead to the near future, had failed to foresee or take sufficient account of several important factors. These include the emergence of new infectious micro-organisms, especially those transmitted to humans from animals; the advent of influenza virus variants; the resurgence of hitherto declining infections such as tuberculosis (TB); the effects of increasing migration and other travel, and of globalisation; and the genuine, if so far unrealised, threat of bioterrorism. Above all – and in spite of early warnings from Alexander Fleming, the man who discovered the first antibiotic – they had failed to grasp the implications of antibiotic resistance, now a major health and economic burden for the EU. Recent data suggest that resistance is increasing, and that up to 400 000 patients annually suffer from infections caused by

Credit: AMI Images/Science Photo Library

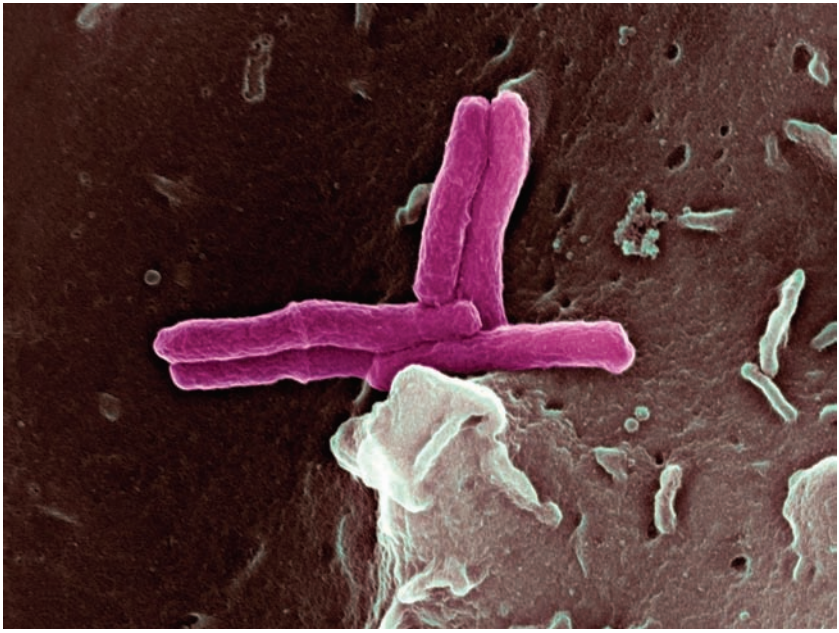
E. coli bacteria, coloured scanning electron micrograph (SEM).

bacteria resistant to multiple antibiotics. Besides the overuse of these drugs, which fuels the development of resistance, the current threat has been worsened by increasing medical tourism (travel for elective, often cosmetic, surgery) which facilitates the rapid spread of resistant bacteria from Asia to Europe.

Why should EASAC get involved? And why the public?

Infectious disease knows no frontiers; it cannot be tackled solely at a local or national level. So when EASAC was founded in 2001 to provide science advice to EU policy-makers, infectious disease naturally found a place on the agenda.

Much of the effort required in this area falls firmly within the domain of professionals working in the fields of science, health and policy. But experience has shown that public opinion on certain issues can prove, for good or ill, highly influential. These issues include immunisation strategies, a willingness to prepare for climate change and for health threats from emerging diseases, and the stigmatisation or acceptance of high-risk groups such as migrants with TB – whose access to health services can also be swayed by public attitudes. If too few people are familiar with the facts – scientific and otherwise – policy-makers may find it difficult to formulate plans that are not only rational and appropriate, but also acceptable to the public.



Credit: Science Photo Library

M. tuberculosis bacteria infecting a macrophage white blood cell, coloured SEM.

Drawing on evidence from a broad range of scientific disciplines, and in the light of studies undertaken over the past six years, the new report identifies several key priorities. These are to understand disease patterns, to co-ordinate surveillance efforts, to support fundamental science, to train the next generation of scientists and to reduce barriers to innovation. Although much has already been achieved, EASAC believes that much is still to be done. The remainder of this document identifies and reviews the main challenges.

Knowing the facts

The collection and storage of data about infectious disease – who has acquired which infection and in what numbers – may not be glamorous, but it is the bedrock on which health services and health policy are founded. The consequences of incomplete or inaccurate data are misconceived health policies, and health services that fail to prevent illness or to treat it properly or both. Compiling Europe-wide facts about the prevalence and spread of disease depends on having standardised methods for collecting and interpreting data. Some early EASAC studies revealed weaknesses in the system and, among some of the newer Member States, inadequate resources. Matters improved with the formation of pan-European communicable disease surveillance networks led by the European Centre for Disease Prevention and Control (ECDC) and the

World Health Organization. But attempts to assess the true extent of infections acquired by patients in hospital, to take one fairly recent example, have demonstrated that not all arrangements for collecting information are yet satisfactory.

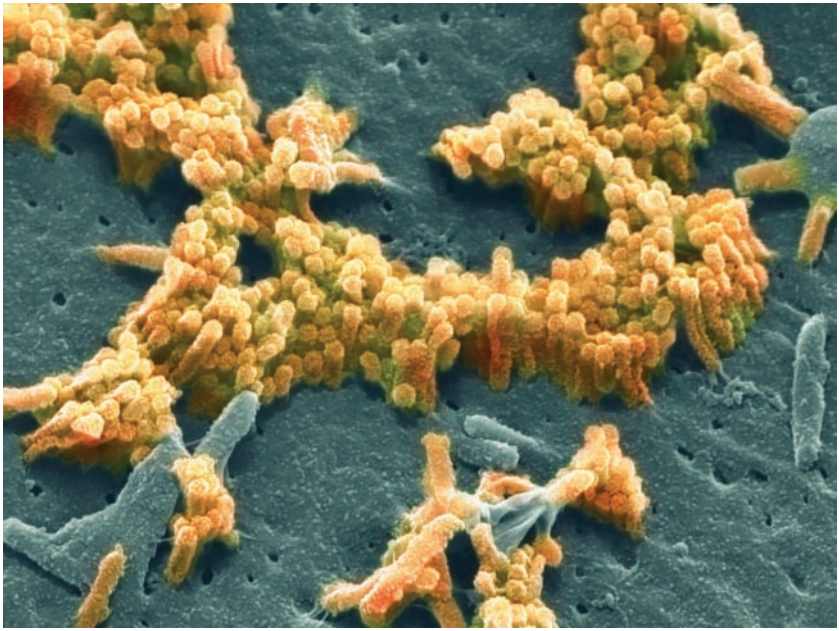
EASAC has in the past stressed the need not only to improve surveillance systems, but also to make them sufficiently flexible to detect novel threats as they arise. The pattern of infectious disease is constantly evolving, and the list of infections routinely monitored needs to be revised accordingly. The same is also true of the ever-changing pattern of antibiotic resistance, and will probably become so of drugs directed against viruses and fungi.

Lurking in the background is the possible future need to mount a defence against bioterrorism. Success at so doing may depend on experience gained in spotting naturally occurring novel infections. The delay in identifying the recent outbreak in Europe of Chikungunya (a tropical virus that causes fever, headache and joint pain and is spread by mosquito bites) emphasises the need to do better. According to ECDC the outbreak could be repeated in other areas of the EU.

Performing these tasks effectively and efficiently depends not only on standardisation but on networking, ideally between a chain of reference laboratories across the EU and beyond it, each able to communicate with ECDC in real time. Not all EU Member States, to say nothing of Accession States and neighbouring countries, have modern systems in place yet. And not all have adequately trained microbiologists to do the necessary work at local level.

Reliable and comprehensive databases can also play a role in patient care and research. A record of what may appear to be inconsequential molecular-level differences between microbial strains will make it possible to find out if these differences actually have consequences for patients. But this can only work if all laboratories are using consistent, reproducible and comparable diagnostic methods. Comprehensive patient information can also be used to improve drug susceptibility testing, predictions of the likely scale of future drug resistance, and much else. The more that different databases can be integrated and compared, the more use they will be in preparing for new challenges of the kind likely to result from climate change.

Other potential beneficiaries of good data collection are groups of people – migrants, for example – at higher than average risk of disease. It is likely that many cases of infectious disease are missed when migrants first enter the EU. 'Pendulum' migration (in which citizens of the former Soviet Union and other Eastern European countries work abroad, periodically travelling back and forth) carries the risk of spreading drug-resistant TB. More generally, the EU, it should be noted, generates more than 19% of the world's international traffic, and is home to the world's top ten most interconnected cities.



Credit: Science Photo Library

H1N1 'swine flu' virus, coloured SEM.

Just as infectious disease does not recognise geographical frontiers, neither does it always distinguish between humans and animals. Zoonoses are infections that can pass between the two; when they do so, any antibiotic resistance they carry goes with them. Multidrug-resistant bacteria, both harmless and otherwise, are common in farm animals in parts of Europe. The likelihood of success in dealing with such problems will be greater if the public health and veterinary health communities work more closely together on disease surveillance and other issues.

Strengthening science

Short-term objectives such as improved surveillance can only be achieved if policy-makers ensure that the infrastructure and training required to sustain scientific research in the long term, including that science needed to understand disease dynamics, receives the necessary support. Many research programmes, from fundamental science through to the translational work needed to move scientific advances out of the laboratory and into the clinic, depend on a continuing commitment to a properly funded science base. EASAC sees one of its roles as being to identify those areas of long-term research investigation where there are gaps in the evidence base, and where there are opportunities to generate new knowledge. For science to advance, there must be renewed

commitment to research: clarifying and addressing priorities, developing infrastructure and implementing a supportive regulatory framework. Several policy issues are relevant to these objectives.

The first is organisational: the *support of investigator-driven basic research*. Although Europe has a tradition of excellence in infectious disease research, its competitiveness will decline unless consciously nurtured. Public funding is still needed to bridge the gap between basic research that has identified promising targets for new drugs, and proof-of-concept studies to demonstrate its academic or commercial potential.

The search for new molecular targets against which vaccines might be deployed is another example of a research topic in this area that merits public support. Finding such targets requires a considerable investment in fundamental science. The same is true of efforts to develop new antibiotics. This will be aided by studying novel points at which to attack microbes. These might include the means by which they stick to the cells and tissues they are aiming to colonise, and their mechanisms of self-protection. It may even be possible to disrupt the chemical signals used by many bacteria to communicate with one another and which modulate their behaviour according to their numbers.

The second policy imperative is the *integration of human and veterinary research*. This, together with a greater integration of surveillance, will allow a more rational use of resources for tracking disease, developing novel products for both human and animal health, and understanding how microbes cross the species barrier. Reports that West Nile virus has been found in several EU countries including Greece, Romania and Hungary illustrate this need for integration. So does the identification in the Netherlands of a small colony of *Aedes aegypti*, a tropical species of mosquito and a vector (a carrier of infectious agents, a transmitting organism), elsewhere in the world, of yellow fever and dengue.

It is not only microbes that we need to investigate: equally important is a better understanding of our own actions. So the third imperative is *research on human behaviour*. Better ways must be found of encouraging doctors to be more rational in their antibiotic prescribing habits, and hospital staff to be more rigorous about hygiene, particularly hand hygiene. We need to understand how to prepare ourselves for the threats posed by new infections that may result from environmental change. EASAC advocates the integration of data from the social as well as the biological sciences to anticipate trends, test ideas and inform the policy debate.

The fourth policy objective is to *boost clinical and translational research*, a sector in which the EU public sector lacks sufficient capacity. The identification of new 'biomarkers' – proxy indicators of infection and protection – would help. Clinical trials of vaccines, for example, have to be large, lengthy and expensive if they are

Credit: Power and Syred/Science Photo Library

Common sheep tick, a carrier of infectious agents (coloured SEM).

to measure their effects in preventing disease. One way of making them shorter and so more feasible is to find suitable biomarkers that can be observed and measured without having to wait and find out if individuals at apparent risk of developing a clinical illness actually do so.

One organisational hurdle to clinical research in Europe is the negative effect of the EU's Clinical Trial Directive. Introduced to simplify and harmonise the administration of clinical trials in the EU by establishing clear and transparent procedures, critics claim that its requirements have proved excessively demanding and costly. It takes little account of the level of risk to which patients are subjected, and has slowed the implementation of proposed trials. In developing future regulations the EU must consult the scientific community earlier and more widely.

The fifth policy objective must be to *train more researchers* in basic and clinical microbiology, and also reverse the erosion of the knowledge base in veterinary research. The study of insects and of health-determining factors in populations in the interest of public health should no longer be viewed as skills necessary only for those intending to work in developing countries.

The final objective should be to *develop new forms of research infrastructure and funding*. The links between universities and hospital-based microbiology services need to be rebuilt to reconnect all aspects of disease management from

the laboratory to the bedside. Also beneficial would be the creation of centres of excellence in infectious disease: centres spanning epidemiology, field studies, social science, mathematical modelling, genomics, bioinformatics and perhaps even drug discovery. Also needed are new ways of funding research. One such is the 'grand challenge' concept: a project intended to tackle some major societal need. Grand challenges must have feasible goals and their research findings must stand a good chance of being implemented. EASAC recommends that the European Commission consider the broad area of public health and infectious disease, with a particular focus on translational medicine, as a grand challenge.

Creating health and wealth

Accounting for some 17% of total European business research and development (R&D) investment, pharmaceuticals is one of the leading technology-based industries in Europe. But there are fears for its future. Spending on R&D has been declining, and there are signs that the focus of the pharmaceutical market is moving to China and other emerging economies in Asia. Fewer drugs for infectious disease are being developed, particularly those caused by the so-called 'Gram-negative' group of bacteria. If increasing drug resistance should ever return us to a 'pre-antibiotic' condition, the impact on medicine would be difficult to overstate. To prevent such a calamity, policy-makers need to consider how best to encourage industry to innovate. The regulation of marketing, pricing and reimbursement is among several issues that will have to be faced if the industry's confidence is to be maintained. New approaches to risk-sharing in the public–private partnerships advocated by EASAC may help to drive forward R&D, and EASAC would like to see more of these partnerships.

EASAC also has a 'shopping list' of goals it would like European industry to pursue. These include the development of *diagnostics*: new, cheap, rapid and reliable methods to diagnose common viral and bacterial pathogens. Uncertainty in diagnosis fuels the inappropriate use of antibiotics and the growth of resistance. Poor diagnosis can lead to wrong treatments being prescribed, and wastes finite resources. One obstacle to the development of new diagnostic methods is the inadequate translation to a commercial scale of research conducted in academia and smaller companies. EASAC welcomes the advent of the Innovative Medicines Initiative's project for the development of rapid point-of-care microbiological diagnostic tests.

A greater mutual understanding by academia and industry of their respective capabilities and limitations would also offer encouragement in the field of *therapeutics*: specifically in the development of new drugs. Policy-makers must find more ways to encourage the private sector to invest in innovation by, for example, creating new incentives and simplifying existing regulations without compromising product quality and safety. Developing the next generation of antibiotics is a political as well as a scientific issue.

With a growing number of strains becoming resistant to the commonly used drugs, TB remains a particular problem. In spite of the current increasing reliance on more complicated, expensive and less well-tolerated treatment schedules, TB is still not receiving the attention it deserves. Some recent resurgence of activity in TB drug development is promising, but the scale of the challenge should not be underestimated. Here, too, EASAC sees merit in novel forms of public–private partnership to exploit new research findings.

There is also a need to develop *vaccines* for new influenza strains, for established diseases such as TB and human immunodeficiency virus (HIV), and for emerging diseases such as West Nile virus. Innovative thinking is required to develop public health strategies that maximise the benefits of vaccination. H1N1 influenza poses a particular threat – ironically because the 2009 pandemic turned out to be relatively mild. This lucky escape could breed a false sense of security. In the meantime lessons have been learned about the need for increased attention to signs of the emergence of new infections, of the importance of characterising new strains and of comparing the experiences of Member States in vaccination rates (which varied greatly across the continent).

Small and medium-sized enterprises have long played a major role in innovative biotechnology. EASAC believes they can make a potentially valuable contribution in the fight against infectious disease, and their increased participation in the field should be encouraged.

The EU's role in public health

The current economic downturn may exacerbate the challenges posed by infectious disease. Public health is a relatively recent policy area for the EU; EASAC believes that health must be taken into account when other policies – on migration and climate change, for example – are being developed. The scientific community has a responsibility to help policy-makers understand the wider relevance of health.

The balance of responsibilities between the EU and its Member States is always a delicate one, but EASAC can envisage a greater EU-level role for disease surveillance and subsequent action. It recommends more discussion between the Commission, the Parliament, Member States and scientists to re-assess the extent of decision-making allowed to EU agencies. Health issues also need to be seen as a key part of the EU's regional strategies.

Europe's priorities should not be considered in isolation; microbes can move rapidly between continents, and policy must reflect this. The EU could, for example, help to develop research and diagnostic laboratory services in developing countries. The European Commission has put forward a vision on global health that identifies a major role for research. But it makes no mention

Credit: H. Raguet/Eurelios/Science Photo Library

Colonies of tuberculosis-causing bacteria in a Petri dish during research.

of disease surveillance and says little about innovation or priority-setting. In EASAC's view these, too, are essential elements of a global strategy.

Europe's goals

As part of its effort to bring more coherence to health policy across Europe, the Commission's strategy for the period 2008–2013 identifies communicable disease as a priority. EASAC supports this focus, and the appreciation that new technologies can play a major role in dealing with it. But future policy development must emphasise the need for more co-operation and greater flexibility in identifying and monitoring threats, in tackling them through smarter diagnostics, better therapies and new vaccines, and through implementing health policies that offer the promise of better control and containment. Antimicrobial resistance and vector-borne disease are particular threats that must be tackled.

Health is a vital interest of the peoples of Europe. The task is urgent.

EASAC – the European Academies Science Advisory Council – is formed by the national science academies of the EU Member States to enable them to collaborate with each other in giving advice to European policy-makers. It thus provides a means for the collective voice of European science to be heard.

Through EASAC, the academies work together to provide independent, expert, evidence-based advice about the scientific aspects of public policy to those who make or influence policy within the European institutions. Drawing on the memberships and networks of the academies, EASAC accesses the best of European science in carrying out its work. Its views are vigorously independent of commercial or political bias, and it is open and transparent in its processes. EASAC aims to deliver advice that is comprehensible, relevant and timely.

The EASAC Council has 27 individual members and is supported by a professional secretariat based at the Leopoldina, the German Academy of Sciences, in Halle (Saale). EASAC also has an office in Brussels, at the Royal Belgian Academies for Science and the Arts.

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