

European Academies



Science Advisory Council

Infectious diseases – importance of co-ordinated activity in Europe

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Foreword

Major advances have been achieved during the last century in infectious diseases research and treatment. Significant increase in the understanding of pathobiology for a broad range of micro-organisms has been aided recently by progress in microbial genome sequencing. The efforts of scientists in academia, industry and public health have led to the development and effective introduction into health services of a wide range of diagnostic procedures, therapeutic agents and vaccines. For example, 50 years ago the success of the Salk Polio Vaccine was first established.

However, an earlier optimism that most infectious diseases had been conquered is now seen to have been misplaced and European populations remain vulnerable. There are newly-emerging as well as long-standing challenges to confront: for example, the threat of new influenza variants, particularly avian flu, novel microbes such as SARS, resurgent infections such as TB, growing antimicrobial resistance and the continuing threat from bioterrorism.

This report describes key issues facing Europe in terms of the opportunities for improved disease surveillance and public health infrastructure, the basic research agenda, support for the pharmaceutical and vaccine industry sectors, the needs of developing countries and newer EU Member States, scientific responsibility and public engagement. While some of the issues discussed in the report may be perceived as matters primarily for attention at the Member State level, there is also a considerable role and responsibility for the European Community, for example in understanding the demographics of disease patterns, in co-ordinating surveillance efforts and systems, in supporting research

priorities, in reducing the barriers to innovation, and in helping to ensure that Member States contribute to strategic efforts at the global level. It is no longer possible to manage epidemics solely at a local level and Europe has been at the forefront of infectious diseases research and development. Our messages are directed to policy makers and opinion leaders in the European Commission, Parliament and Member States, acknowledging that many initiatives are already in progress.

EASAC – the European Academies Science Advisory Council – is a means for the science academies of the EU to work together to provide expert, independent advice at the European level about the scientific aspects of public policy issues. The present report, undertaken at EASAC's own initiative and expense, was prepared by a Working Group chaired by Professor Volker ter Meulen of the Leopoldina Academy and reviewed and approved for publication by the Council of EASAC. On behalf of EASAC, I should like to express my thanks to Professor Volker ter Meulen and his colleagues for providing a clear and stimulating account of some very important topics for Europe.

We in EASAC recognise that it is necessary to prioritise future work to attempt to address and resolve this broad front of scientific and policy issues for infectious diseases. The report is intended to serve as an introduction to identify some of the cross-cutting priorities in the public and private sectors. EASAC is now initiating follow-up work in areas discussed in this report and we aim to develop evidence-based, tractable recommendations for academia-industry collaboration and the support of EU innovation in the development of new products and services.

Professor David Spearman
Chairman, EASAC

1 Key points

- (i) EASAC – the European Academies Science Advisory Council – is a means for the science academies of the EU to work together to provide expert, independent, advice about the scientific aspects of public policy issues. This publication, undertaken at EASAC's own initiative, represents the outcome of expert discussion among a group of scientists brought together by the Leopoldina Academy as a contribution to what we regard as a very important policy area.
- (ii) The threat of infectious disease is growing for both industrialised and developing countries. The response to SARS showed that good scientific and public health co-ordination can be achieved globally. It is now important to identify the issues for the EU in developing a longer-term science-based strategy in infectious disease and to act on the priority issues.
- (iii) A co-ordinated Europe-wide programme of research, training and preparation is needed to track and counter biological threats, not only to humans but also to animals. There are significant opportunities in developing dual use technology and preparedness (biodefence-natural infections) and an urgent need to find ways to accelerate the pace of R&D in response to the new challenges and to build new partnerships across academia-industry-health authorities.
- (iv) This report highlights the priorities for EU action – arguing the case for increased investment and coherence to support better responsiveness in infectious disease – and strongly recommends action on:
 - Disease surveillance and control systems – for rapid identification and rapid responsiveness;
 - Public health infrastructure – Europe-wide co-ordination of national structures and building national structures where not yet present;
 - Development of applications – innovation goals for vaccines, diagnostics and therapeutics, requiring an active and viable industry R&D capability;
 - Research and training – improving the capability that supports all the other priority actions, training a greater number of skilled basic and clinical scientists and co-ordinating the human and veterinary science agendas.

- (v) EASAC regards the present report as an introduction to a broad range of key issues for the EU. We will continue to work to stimulate discussion and resolution of these issues – with public policy makers and industry as well as our member academies of science. Building on the present work, we will now initiate specific projects in priority areas, beginning with vaccines. We will consult widely to collect evidence on the current status across the EU and to identify the opportunities and challenges for innovation and health policy. This future work will also focus on the importance of academia-industry initiatives for the development of new products and the issues to be faced in ensuring an innovative and competitive healthcare industry in the EU.

2 The global challenge

Infectious diseases represent a major health problem in both developed and developing countries. Worldwide, infectious diseases account for about one-third of all deaths (46% of deaths in developing countries). Challenges remain in countering micro-organisms even where antibiotics and vaccines are available. There is growing incidence of antibacterial and antiviral resistance and vaccination strategies may fail because of high costs for developing countries, public resistance in some EU countries and antigenic variation of micro-organisms, especially viruses.

The present, introductory, report represents the outcome from the deliberations of an expert group (Appendix A) brought together by the Leopoldina Academy to assess the issues for infectious diseases that face policy makers in the EU preparatory to identifying priorities for further work by EASAC that would draw on evidence from all the relevant constituencies – including industry and public health.

There have been demands worldwide to fortify public health systems in consequence of increasing problems in infectious disease caused by a range of novel and resurgent microbes, particularly SARS but also, for example, TB, AIDS, legionnaire disease, Ebola, West Nile encephalitis, nosocomial opportunistic infections, novel strains of influenza, together with concerns about food microbiological safety and the impact of increasing international travel and world trade in agriculture, as well as the threat from bioterrorism. Infectious diseases of animals (livestock), e.g. avian influenza, monkeypox virus, foot and mouth disease, whether transmissible to man (zoonotic) or not, and plants have also recently created problems for policy-makers and represent other potential targets in bioterrorism.

The increasing concern about the impact of communicable diseases has led to some encouraging action in global initiatives, for example the Global Fund to Fight AIDS, Tuberculosis and Malaria and the development of the Global Public Health Intelligence Network (GPHIN). But, there is further need to strengthen and broaden national and international efforts for the surveillance, detection, diagnosis and combating of infectious disease affecting man, animals and plants at the EU level. There are numerous scientific issues that must be considered by policy-makers relating to early warning systems, national and European security, contingency planning, disease control, and there are new multidisciplinary challenges for the research agenda. These issues are generally as relevant to the natural epidemics as to the threat from bioterrorism but new impetus has been imparted by recent initiatives in biodefence.

Potential for bioterrorism (deliberate use of fungal, bacterial or viral micro-organisms). Some of the diseases (e.g. plague, smallpox) have been well characterised microbiologically for many years and their damaging potential for mortality and morbidity, and for inducing terror, are well appreciated. Smallpox, for example, possesses key features to be an effective weapon (stability, transmissibility, pathogenicity, decreasing population immunity); other pathogens (e.g. West Nile, Ebola viruses) may lack necessary features (stability, transmissibility); polio may represent a future threat when widespread susceptibility increases following global eradication; influenza might be relatively easily modified to become highly pathogenic. In addition to the potential for relatively simple genetic modification of existing agents (e.g. large DNA viruses might be engineered to carry toxins as well as other deleterious genes; bacteria might be altered to be resistant to antibiotics or toxin genes altered so that they are not detected by standard PCR procedures), it is at least conceivable that entirely novel pathogens can be constructed from genomic sequences. It is also conceivable that future agents might be targeted to population cohorts according to genetic susceptibility and, perhaps, ethnic differences.

Comparing international responsiveness. European Commissioner Byrne launched the EU Public Health Action Programme in 2003 with a key priority to focus on encouraging rapid reaction to health threats: reinforcing the European Network on Communicable Diseases and the EU rapid alert system for possible bioterrorist attacks.

This Programme launch built on significant recent progress in public health, whose major initiatives have included:

- Decision 1786/2002/EC adopting a programme of community action in the field of public health

- Decision 2009/98/EC on the early warning and response system for the prevention and control of communicable diseases
- Decision 2119/98/EC laying down case definitions for reporting communicable diseases to the community network
- Directive 2003/99 on the monitoring of zoonoses and zoonotic agents and Regulation 2160/2003 on the control of salmonella and other specified food-borne zoonotic agents
- Strong co-operation with WHO Euro, WHO Geneva; various twinning projects between older Member States and the East European countries; EU funded disease specific surveillance networks; expert committees on SARS, international health regulations, influenza pandemic, bioterrorism
- Inception of the European Centre for Disease Control.

While some of the European networks have been heavily focused on research rather than public health objectives, it is to be expected that the increasing role of the European CDC will lead to a better focus on public health surveillance. The recent Report from the Netherlands Presidency Conference "European Response to Public Health Risks from Emerging Zoonotic Diseases" (September, 2004) draws attention to the need for better integration of public health and animal health policies with respect to disease surveillance, early warning, response and control.

The global epidemic of SARS illustrated some of the public health issues for countries; the relatively low incidence of SARS in EU Member States might be taken as evidence of good preparedness – but also good fortune – and it is now important to ensure that Member States share best practice and that the EU develops a science-based strategy to underpin longer-term needs.

The European Community has been relatively slow in agreeing tangible co-operative actions in response to the threat of bioterrorism. The Commission has now implemented a "preparatory action" with a budget of €65 million to lay the foundation for a European security research programme (including protection against biological attacks) that is scheduled for launch in 2006 and will follow a cautious approach. By contrast, the US has mounted a vigorous policy response to bioterrorism, led by BioShield (see later) but also encompassing public sector biodefence research (linked with natural infectious disease research), public health preparedness, control on the transfer of materials (domestic and export) and control of biological information. The NIH-NIAID Research Plan, focusing on co-ordination and validation of research tools, covers

the supply of animal models, standardised reagents and microarray panels, and support for translational research. US biosecurity research is also regulated by new public policies, such as those engendered by the Patriot Act and the Biopreparedness Act. Many, if not all, of the public health issues identified for biodefence are also relevant to improving public health responsiveness for natural infections – local provision of funding for education and response capacity; enhanced surveillance; use of informatics; simulation of disease threats; improving laboratory diagnostic networks; recognising the need for differing levels of microbial identification across the continuum medical diagnosis-epidemiology-forensics (characterising a specific strain).

The US Institute of Medicine Report in 2003, in concentrating on improving international efforts to track and treat emerging and existing infectious diseases, emphasises the importance of (1) accelerated vaccine and antimicrobial drug development and (2) greater co-operation among governments, health authorities, academic groups, companies.

EU needs. It is now important for Europe to build on the previous achievements so as to progress a co-ordinated strategy. In part, this is a matter for the national research communities, for example in bringing together the national professional societies in microbiology through the Federation of European Microbiological Societies, in activities relating to scientific co-ordination as well as development of training facilities. Most importantly, there is also a range of strategic objectives for EU policy makers and for those who seek to influence them:

- Integrating individual country approaches
- Emphasising how science and technology can best inform the broad response to infectious disease as well as the specific research agenda
- Identifying European research strengths and weaknesses, particularly with regard to disease surveillance and counter-measures
- Clarifying what is achievable with regard to microbiology research, diagnosis and prevention, medical practice
- Showing that many of the activities initiated in the scientific response to bioterrorism are also relevant in bringing benefit to public health more generally (capitalising on opportunities in dual-use technologies).

The development of EU policies on the identification and response to infectious diseases requires mapping and analysis of European capabilities in key areas:

- (i) A survey of the existing activities in individual Member States with regard to surveillance,

infrastructure, training, research and its applications so as to identify weaknesses, strengths, duplications or absence of effort in the response to threats;

- (ii) An analysis of the European-level and international research programmes on disease surveillance, detection, diagnosis, prevention and treatment of current and emerging threats from pathogens;
- (iii) Clarification of the issues for veterinary as well as human infectious diseases;
- (iv) An analysis of the number, distribution and quality of European facilities dedicated to disease surveillance and of the standards of staff training and the availability of programmes for dissemination of data on diseases throughout the EU;
- (v) A consideration of mechanisms for the dissemination of accurate and balanced information across the EU in the event of threats to health.

3 What policy problems should be addressed?

Among the strategic areas that raise policy issues and challenges across the natural-biodefence spectrum of infectious diseases are the following:

- 1 *Disease surveillance.* The need for well functioning systems to provide information for priority-setting, planning, implementation and resource allocation for preventative programmes and control measures. Sharing of best practice across the Member States is imperative. The SARS experience showed the importance of laboratory testing to confirm clinical diagnosis – and illustrated current variability in international practice.

One key research issue is to improve the ability to detect unusual/novel signals superimposed on a background of variable “noise” level. Informatics-based approaches will have much to contribute by drawing on advances in interpretation of other multiple, large datasets.

An important policy issue is the need for pan-European co-ordination. For a surveillance system to be effective, it needs both to implement modern molecular technologies at the local level and be linked with global awareness. Europe can do better in both regards. The EU must continue to improve linkage with international surveillance systems (WHO, US-CDC) and establish the integrated European CDC. There is concern that the European CDC, based in Stockholm, appears to be weakly resourced. The solution is not to seek to copy the US

model but rather to create a network of centres to co-ordinate and standardise Member State activities in surveillance, with scientific advisory boards for specific pathogens, based on the existing networks. Improved, co-ordinated surveillance will also facilitate linkage to international surveillance systems such as WHO and should reduce the workload for Member States to contribute to international systems. Moreover, through standardisation of definitions, workflows and IT, the European Centre can result in strengthening the surveillance infrastructure in those Member States that have so far not been able to develop a modern system. For example, recent technical developments in Germany at the Robert Koch Institute – SurvNet (an electronic reporting system collecting data locally for central surveillance), SurvStat (real-time generation of surveillance maps and differentiated epidemiological analysis), SurvAlert (combining analysis methods to generate alerts on possible outbreaks) - provide the opportunity for further development across the EU. Syndromic surveillance systems, based on collecting data on clinical syndromes (as, for example, initiated during the Athens 2004 Olympic Games) should also be further evaluated.

Developing an active role and responsibility for the European CDC also requires good linkage with the established EU bodies, the Communicable Diseases Committee with the Special Pathogens Surveillance Networks and the Health Security Committee with its Rapid Alert System.

There is significant variability in expertise in laboratory pathogen diagnosis across the Member States and there is rarely standardisation of procedures or co-ordinated networks of laboratories. Some European Reference Laboratories are good, but there are major concerns about the quality of microbiology training – in particular in molecular technologies – at the local laboratory level, where the first clinical samples may be received, and about the consistency and efficiency in linking the local laboratories into public health reporting systems. Country-level health authorities need to be strengthened not only to ensure a good surveillance system but also to be the focal point for early intervention.

- 2 *Public health infrastructure – focusing health services response to prioritise counter-measures.* Infrastructure requires both physical and human resources. Generation of a larger trained cohort of people has implications for university training facilities (infrastructure and programmes).

One critically important issue is developing the scientific capacity to differentiate rapidly between

those who are infected and those who are not (with reassurance for the latter). In the US anthrax attack, one million people presented themselves to the East Coast health services – 23 persons were infected. An overwhelming number of non-infected but worried individuals challenges the capacity of public health services to respond effectively.

There are also particular public health infrastructure issues for travel facilities, for example preparedness in airports with regard to quarantine procedures, sample handling and transfer of patients. Generally, the mechanisms needed for response to an emergency can be very similar to those involved in the response to routine events. Therefore, if the normal responsiveness is weak, then the likely response to an emergency will also be poor. Even relatively simple procedures can be improved, for example disinfection as a control process by more rigorous application of the current expert guidelines for hospital hygiene.

- 3 *Research agenda.* The starting point for any further analysis of research needs and opportunities is to recognise what the EU has already initiated or is currently negotiating – exemplified by the Framework Programme 6 Networks of Excellence on pathogen genomics, zoonotic infections (MedVetNet, see later) and epizootic infectious diseases (Epizone), potentially stimulating the use of information to develop better prophylactics, diagnostics and therapeutics, as well as supporting training needs.

The European Science Foundation Task Force on Infectious Diseases has recently reported on key issues for the basic research agenda so the present position paper does not cover basic research in detail. However, it is noteworthy that progress in fundamental understanding, for example on genetic flexibility in accounting for pathogenic properties, and the development of new techniques, for example RNA interference, provide new opportunities to develop countermeasures.

The change in a pathogen's ability to cause disease can be associated with either loss or gain of genetic information. "Reductive evolution" is an important feature in the evolution of genomes of pathogens. Comparisons of variola virus (the cause of smallpox) with vaccinia virus showed that several genes that are intact in vaccinia virus and which contribute to vaccinia virus virulence are destroyed by mutation in variola virus. Similarly, a comparison of *M.tuberculosis* and *M.leprae* showed that the latter pathogen has lost very many genes compared to the former. Micro-organisms acquire new gene clusters (virulence genes, pathogenicity islands, fitness genes) by

horizontal transfer, enabling them to colonise and invade new hosts. Changes in the environment, in food production and in animal farming result in the selection of new pathogens or pathotypes of bacteria and viruses. Examples include the emerging pathogens such as SARS, avian influenza, Escherichia coli pathotype EHEC, pneumococci, Campylobacter jejuni, Salmonella enterica of diverse serotypes, Neisseria meningitidis and Legionella pneumophila. Thus, one key area of study that requires urgent support is the ecology of pathogens – molecular and evolutionary aspects.

There is need for improvement in the multinational co-ordination between human public health institutions and those institutions responsible for food safety.

There is also significant need for better understanding of the determinants of disease emergence and persistence and for more flexibility in funding to ensure a fast scientific response in informing on pathogen discovery and host specificity. It is important to do more in co-ordinating animal-human interfaces in research and in surveillance and control of infectious disease – where the impact of international co-operation may be most effective – building joint research funding programmes and policy development (see later).

Furthermore, the research agenda associated with demographic changes in Europe needs to be considered. In particular, the aging population leads to new challenges in infectious disease research. Elderly people show a different commensal bacterial colonisation, and particular infectious diseases, such as urinary tract infections and community acquired respiratory infections are more common in the elderly.

In addition to the funding priorities for specific microbial research areas, it is desirable to advance some underpinning disciplines more broadly and attend to research process issues, including:

- *New opportunities – Quantitative modelling.* It is now possible to do more to develop multidisciplinary approaches to modelling of outbreaks and to surveillance, by bringing together biology and mathematical modelling techniques, although the limitations must also be recognised (from experience with modelling CJD, SARS). For modelled estimates to be meaningful, it is necessary to subject assumptions on parameters to sensitivity analysis to yield a range of scenarios with confidence intervals, and to commit to iteration of the process so that identified gaps in datasets are filled and the

margins of error decline. Generally, there is need to build epidemiology research capacity across the EU.

- *Handling pathogens and the regulation of research.* Individual scientist self-awareness and systems of self-regulation by scientific peers are preferable to mandatory controls. The experience outside the EU with recent SARS cases and anthrax illustrates the concerns about laboratory handling of biological materials and reinforces the importance of enacting international rules and regulations. Recognising the existing excellent legislation on working with pathogenic micro-organisms in many Member States, there should be normalisation of regulations across the EU rather than an emphasis on introducing new regulations. Generally, there is also continuing need for the scientific community to counter inappropriate pressures to constrain animal research and to communicate the importance of building appropriate laboratory containment facilities for safe handling of micro-organisms.

- *Skills and training needs.* Some of the education, training and career development problems in this area are generic for European research. There is a lack of trained researchers both in conventional microbiology and in more speculative research; the erosion of the knowledge base in veterinary research is even worse, although a current EU programme allowing researchers access to high security laboratories provides some support to the knowledge base. The skills deficit is not just an issue for the support of research. There is demand for additional infectious disease specialists, both clinical and scientific, to respond to the threat of infection, now and in the future. The universities should be able to provide technical training to students and young postdocs in infectious diseases – in this context, research training schools such as Graduate Colleges and Postdoc Academies are important. It is also important to train all medical students in the key issues – for example, antibiotic resistance. Furthermore, continuing education for all public health employees should also incorporate field-based and simulated exercises with scenarios based on both biodefence disasters and natural epidemic emergencies.

4 *Diagnostics.* There is a relative lack of diagnostic development capability in the EU and there are key research and innovation policy issues in meeting the needs for:

- *Development of early and specific diagnostics.* It is essential that rapid and sensitive systems be developed for a range of potential biohazards. There is need to develop broad and robust PCR detection systems and antigen detection systems.

Novel pathogens present particular problems, e.g. if modified to evade conventional detection. It is important to build a concerted international effort in diagnostics research and to ensure that the research that is stimulated by the fear of bioterrorism is also used to derive general benefit for public health. It is desirable to explore the potential for developing standard elements in rapid detection tests, e.g. standardised bio-chip technology, pre-approved by Regulatory Authorities, to serve as the basis for customising with a variable region coding for a specific antigen.

- *Partnership.* Progressing a concerted research agenda raises the issue of public-private partnership and new incentives for commercial R&D. The challenge of responding to terrorism or other pandemics should, again, serve as a longer-term stimulus to thinking about novel R&D partnerships.

5 *Vaccines.* There is a range of issues for the established as well as emerging diseases.

- *Influenza.* There are still significant concerns for flu preparedness – associated with insufficient vaccine production; antigenic drift and changing vaccine efficacy; relatively poor understanding of the antiviral drug market (and value of stockpiling strategy) and the risk factors for virus reassortment. There are particular issues for the EU in controlling the spread of the H5N1 virus strain in aquatic bird reservoirs. While prospects for controlling the virus at source (in Asia) involve culling of domestic poultry and vaccination strategies, it is likely that this virus is already endemic in wild migrating birds. Long distance routes of migration pass in relatively close proximity to EU territory (Russia). The EU has introduced several programmes on animal disease surveillance; the most recent (and perhaps the most important) is for flu screening in wild birds (mandatory for all Member States) but there is also need to do more to map migration. The EU must also address those policy issues for agricultural practice where concentrated husbandry of poultry and pigs promotes infection.
- *Commercial production.* There are problems of supply of essential vaccines (for example, childhood vaccines) in major markets (and a similar problem to an extent, for antiviral drugs) because of the perceived lack of profitable return on investment to manufacturers. An additional major disincentive to commercial production of vaccines is fear of expensive litigation if there are adverse reactions to the vaccine. Governments across the EU must find ways to share the costs

of litigation arising from national vaccination programmes (US legislation in 2003 allowed for compensation for the complications of the smallpox vaccination programme to be met from Federal resources).

- *Establishing societal value of vaccines.* Emerging infections may have enormous economic impact even if outbreaks are limited. Current methods for estimating the economic value of vaccines incorporate health care costs and some societal costs (such as benefit of working days saved) but exclude what has been described as the intangible value. For example, the cost of SARS was estimated as \$80 billion when including the wider impact on travel and economic activity. The cost of avian influenza will also be high in terms of the implications for agricultural systems and farmers' income. Better understanding of the societal value of vaccines as preventive medicine is required in order to justify greater rewards to companies in terms of R&D incentives and market pricing.
- *Disease eradication.* The objectives for global eradication of polio, measles, hepatitis B have suffered setbacks. The one current example of eradication – smallpox – has led to some public complacency and opposition to other vaccination programmes, and also raises policy issues associated with emergency planning for a newly susceptible population (in case of bioterrorism or failure of laboratory containment). In assessing its strategy for control of smallpox (for example, timing of any vaccination), the EU, in discussion with WHO, will need to balance multiple issues, including the likelihood for use of smallpox as a weapon, the incidence of adverse effects of the vaccine, and the rapidity with which authorities could move to control an outbreak. After eradication of an infectious agent, the corresponding expertise and essential procedures to diagnose the disease and to identify and characterise the agent should be maintained so as to be readily available in case the infection re-emerges or this risk is conceived. Such preparedness also includes the means for therapy and the production or application of a vaccine.
- *Biodefence.* One strategic issue arises from the concern that military research accounts for a significant proportion of the total, yet military research procedures and needs may differ from civilian (e.g. regarding the acceptability to vulnerable populations groups of vaccines developed for protection on the battlefield). There is a necessary goal for better sharing of information from co-operation between military and civilian R&D but this will be difficult, particularly at the EU level.

• *New vaccine approaches.* Classical vaccination strategies now should be complemented by generic vaccination strategies and immunomodulatory interventions (including both innate and acquired immunity). New products might include multivalent vaccines based on naked DNA constructs and short-term immune stimulants to use as an interim measure before novel vaccines become available.

6 *Developing countries.* There is continuing responsibility for the EU to progress R&D for developing-world infectious diseases: the Commission has already taken a lead with the European Clinical Trials Platform and should also be encouraged to continue addressing infections other than malaria, tuberculosis and AIDS through Framework Programme 6 INCO funding. The neglected diseases such as meningitis, childhood diarrhoeal diseases, leishmaniasis, sleeping sickness, Chagas disease, filariasis, schistosomiasis have been progressively marginalised by research programmes in both public and private sectors but have devastating impact globally – there is need for active consideration of what more research can be done within the EU. Furthermore, the impact of global air travel and the potential impact of climate change on the spread of endemic pathogens from developing countries to Europe also have implications for EU disease surveillance and control systems.

The EU also has a responsibility to perform research on infectious diseases prevalent in animals in developing countries – this applies to veterinary indications as well as zoonoses – and recent Framework Programme 6 initiatives (see later) are welcome, if appropriately integrated with the priorities of the World Organisation of Animal Health (formerly, the Office of International Epizootics, Paris) who have a major role to play in this area. Welcome progress can be seen in the recent (May 2004) agreement by the World Organisation of Animal Health and FAO to combine resources to establish a global information network on new viruses jumping the species barrier between animals and man.

7 *Rapid responsiveness.* Perhaps most important, as a general point for diagnostics, vaccines and therapeutics, it is now appreciated that there is much greater need to respond rapidly to new incidents – in determining the R&D agenda, developing necessary skills, creating new funding mechanisms, incentives and processes for consortia formation. The traditional timescales will not suffice. As a benchmark, the US BioShield initiative will fund the accelerated development of next generation medical measures against bioterrorist attacks; the US Government will buy the resulting vaccines and therapies for which there is currently

no market. One general impediment in the EU to rapid responsiveness capability is the public mistrust of genetic modification, that is partly driven by a lack of public understanding of the technology – and the inadequate communication between public and scientists. It is necessary that scientists engage more actively in the debate to explain the benefits of the technology and reject the unfounded allegations of danger. For example, the hepatitis B vaccine was the first genetically engineered vaccine, replacing a vaccine prepared from the blood of those chronically infected by hepatitis B. The biotechnology product represents a significant improvement in being free from the problems that surrounded the blood-derived product – extensive purification and disinfection to remove infectious virus and other blood pathogens, high cost and limited availability.

8 *Antibiotic resistance.* There should be more EU research on the association between antibiotic prescribing and development of resistance (at the individual and group levels). Similarly, there is need for more study of the implications of the policy response reducing inappropriate prescribing on development of resistance (while ensuring that appropriate prescribing and prudent use is not inadvertently reduced). The use of antibiotics in farm animals remains a policy issue — although antibiotics as food supplements are now banned in the EU, large-scale use as prophylactics continues and it is important to establish whether this contributes to antibiotic resistance in man.

New targets must be developed for alternative drugs. Genome research can help to identify new targets; new techniques to isolate and characterise novel natural products and combinatorial chemistry can deliver new potential antimicrobial agents. The occurrence of vancomycin-resistant *Staphylococcus aureus* as well as multiresistant gram-negative bacteria are alarming signs, which should stimulate the scientific community to focus on the development of new targets and new classes of drugs. New incentives for industry development may also be needed.

9 *Communicating balanced information.* It is important for authoritative, science-based bodies to work together to develop a structured, meaningful communication strategy that sets the risks into perspective with attention to public education on epidemic preparedness and on bioterrorism: (a) providing appropriate public reassurance and ensuring that anxieties are not inflamed by media accounts, (b) creating an alert and informed medical workforce. The initiation of Scientific Advisory Panels could help to inform public communication as well as improve the efficacy of policy development. The information

needs to be available in a user friendly but authoritative format and there is a leadership role for the Press and electronic media communication systems in this educational process. Euro-surveillance, the EU website in public health could be expanded in a similar manner to the WHO and CDC sites.

- 10 *Scientific responsibility, ethical codes of conduct and control of information.* It is essential to demonstrate good practice in research conduct to society-at-large in order to engage with the public and build trust. For the policy-maker, implementation of codes of ethics and good research practice is an issue for training, and also for recording and auditing research so as to document research integrity. Such codes are already well established by the professional societies and in the current implementation of the European Clinical Trials Directive.

Now that there is proof of principle (for polio) that viruses can be chemically synthesised, knowing the genome, the concept of disease eradication may need to be re-interpreted and new public dialogue initiated (there are additional issues for national security relating to laboratory containment and bioterrorism). The scientific community must also consider, and communicate with the public, the opportunities and challenges inherent in the construction of novel microbial genomes as a tool in research.

The scientific community must involve itself in discussion of what is dangerous public information and how information might be restricted. Controls will be controversial. For example, removing detail on methodology in a publication to prevent misuse undermines the scientific principle that published results should be repeatable. Self-policing within the scientific community, coupled with responsible editorial judgements (and review of contentious points, for example by institutional biosafety committees) requires international harmonisation.

The potential concern about open publication was re-emphasised recently by the Stockholm Peace Research Institute (Yearbook 2004, <http://editors.sipri.se/pubs/yb04/pr04.html>) who note that free access to sequence data from the human genome and pathogenic micro-organism genomes is a great scientific resource but could pose significant threat if misused (for example, to target specific human biological systems, particular ethnic groups). But hiding information will not prevent bioterrorism and many benefits have accrued from open publication (for example, on sequencing of polio virus). There is no evidence that published information has been misused and the view from the research community is well

summarised by the Society for General Microbiology (www.sgm.ac.uk/pubs/policy.cfm). These issues have also been extensively discussed recently by the OECD International Futures Programme, particularly in terms of the importance of creating an inventory of processes for responsible stewardship in the biosciences.

- 11 *New EU Member States.* Problems of research funding, prioritisation and infectious disease control are particularly acute for some new Member States (and for the next Accession countries). It is also important that the EU should focus on infectious diseases for countries that share borders with the EU and this may be a particular concern for some of the new Member States. The process of transition to membership of the EU has not generally increased funding for research; structural reorganisation and consolidation of laboratories and institutions is resulting in a decline in the number of academic researchers and government laboratory experts on infectious disease control. These weaknesses have implications, of course, for Europe as a whole as well as the individual countries and must be addressed by concerted EU strategy as well as by the application of specific pre-existing policy measures such as the use of Structural Funds in support of research and innovation in the new Member States.

4 What research networks are already being supported by the Commission?

Reference has been made in the previous sections to some of the Commission research initiatives. The present report cannot provide a comprehensive list of Commission funded activities, and any such list would need to be augmented by mapping of what research is also being undertaken at the Member State level. The following examples, recently announced by DG Research, are mentioned to illustrate the significant amount of activity that is beginning to be undertaken in one key area – animal infectious diseases. But it must be emphasised that support for networks (a framework for administration and communication) may not actually provide a significant amount of support for new research. Infectious disease research is under-supported in Framework Programme 6.

- MED-VET-NET, a Network of Excellence under Framework Programme 6 thematic priority on Food quality and safety – combining medical and veterinary expertise on zoonoses and working towards centralised surveillance systems (www.medvetnet.org). There are also preliminary Framework Programme 6 discussions on the establishment of a Network of Excellence on epizootic diseases, to be co-ordinated by the Lelystad Institute (a partner in MED-VET-NET) and

steered by a joint committee including the Fredrich Loeffler Institute, Germany and the Institute of Animal Health, Pirbright, UK.

- EADGENE, also a Network of Excellence under the thematic priority on Food quality and safety – to study the genomics of host-pathogen interactions in major farm species including farmed fish.
- European Technology Platform on Global Livestock Development Partnership – to facilitate and accelerate development and deployment of new vaccines and diagnostic tests against tropical livestock diseases that currently threaten the competitiveness of European agriculture (for example, African Swine Fever).

It is also beyond the scope of the present report to map equivalent activities outside the EU but it is noteworthy that the US National Academies of Science have now initiated a national study to evaluate the current state and future needs of veterinary science research. Recognising that recent support for animal-related research has been rather limited, the NAS emphasises that veterinary research has potential to significantly impact many fields, including animal health, human medicine, food safety, and bioterrorism.

As mentioned previously, there is now both a Network of Excellence (Europathogenomic, bringing together leading European groups regarding genome research of pathogenic bacteria) and an ERA-Net initiative in pathogen genomics. While the ERA-Net programme focuses on human bacterial and fungal micro-organisms, there are equivalent issues to study for viruses and parasites and for veterinary pathogens. The outline of the ERA-Net proposed research agenda on pathogen genomics (Appendix B) illustrates the priorities and there is a continuing need for the research community to identify the broader opportunities for pathogen genomics research and training for funding at the EU level.

Among other important Framework Programme 6-funded projects noted during the expert group discussion are:

- TB-VAC: design and testing of vaccine candidates against TB; identification, development and clinical studies, safe to use in poor health infrastructure settings. The new vaccines are based on protein antigens, non-protein antigens, improved BCG, live attenuated mycobacteria and new delivery systems. The Integrated Project will lead from the laboratory to the initiation of phase I clinical trials in Europe and Africa.
- MUVAPRED: mucosal vaccines for poverty related diseases (AIDS, TB), which will induce local immunity

able to neutralise pathogens at their port of entry and systemic immunity to prevent systemic spread of the infection. The Integrated Project will also investigate possibilities for the development of mucosal vaccines against malaria.

- ANTHRAX EURONET: a Co-ordination Action to strengthen networking to accelerate and enhance the development of anti-anthrax products. Exchange of information and performance of pilot tests will help to standardise methods and best practices that ensure safe production of anthrax vaccines and therapeutics as well as set priorities and response plans.

5 Next steps

In summary, EASAC emphasises the importance of increased investment and coherence to support better preparedness and responsiveness in infectious disease, in particular with regard to:

- Disease surveillance and control systems – for rapid identification and rapid responsiveness;
- Public health infrastructure – Europe-wide co-ordination of national structures and building national structures where not yet present;
- Development of applications – innovation goals for vaccines, diagnostics and therapeutics;
- Research and training – improving the capability that supports all the other priority actions, training a greater number of skilled basic and clinical scientists and co-ordinating the human and veterinary science agendas.

In seeking to provide an evidence-based case for action, we stress the need to do more to map systematically the current status across the EU with regard to research, surveillance, standardisation of procedures and public health infrastructure, in order to identify and quantify deficits and clarify recommendations for concerted effort.

EASAC is now initiating a specific project on vaccines – innovation and human health, which may be followed by a report on antibacterial resistance, where we will also collate evidence and perspectives from industry and public health experts so as to generate tractable recommendations that have potential to make a significant impact in these important areas for Europe. There are major challenges for Europe to face in supporting and building industry sectors for R&D of vaccines, diagnostics and therapeutics and there are major opportunities for European industry-academia initiatives for novel products.

Appendix A: Expert Consultation

This paper was prepared by consultation with a group of experts brought together under the auspices of the Leopoldina Academy:

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Philippe Sansonetti, Institute Pasteur, Paris, France

Geoffrey Smith, Department of Virology, Imperial College London, UK

Secretariat – Robin Fears, European Academies Science Advisory Council, UK

The outcome of these discussions was reviewed and approved by EASAC Council.

Appendix B: Proposed agenda for ERA-Net PathoGenoMics

A The microbes

- 1 Microbial ecology and populations
- 2 Metabolism and signalling
- 3 Evolution of microbial virulence and antibiotic resistance
- 4 Biofilm formation
- 5 Genome plasticity and gene pools
- 6 Antigenic diversity

B Host-microbe interactions

- 1 In vivo pathogenesis of infections caused by bacterial and fungal microorganisms with the capacity of affecting human health
- 2 Mechanisms underlying breakage of epithelial and endothelial barriers: (a) receptors and cell surface structures of the host cell, (b) bacterial cell surface structures, (c) cell-cell communication
- 3 Metabolic interactions and adaptations of host cells and bacteria
- 4 Evasion of the host immune defence
- 5 Commensalism and nosocomial infections
- 6 Secondary pathologies (e.g. cancer and autoimmune disease) induced in the host

C Development and improvement of tools

- 1 Development of new bioassays for the identification of novel targets for therapy and vaccination
- 2 Novel diagnostic approaches
- 3 Metagenomics of microbial communities
- 4 New in vitro screening techniques
- 5 Bioluminescence and other imaging techniques to follow infections in vivo
- 6 Microarrays and proteomics of infected tissues
- 7 Animal models by transgene techniques
- 8 Establishment of strain and tissue collections
- 9 Databases and data analysis techniques

Appendix C: Source documents

In addition to the material and websites cited directly in the text, Working Group discussion was informed by presentations at the international symposium "Threat of Infection" (Würzburg, Germany, July 2004; co-organised by the Leopoldina Academy, Academie des Sciences, Paris and the Research Center for Infectious diseases, University of Würzburg) and also drew on the following sources:

Editorial, *Antibiotics, resistance and clinical outcomes*, *British Medical Journal* 2004 328, 1270-1271

European Commission, *Communication from the Commission to the Council and the European Parliament, On Co-operation in the European Union on Preparedness and Response to Biological and Chemical Agent Attacks (Health Security)*, COM (2003) 320 final

European Commission, *Public Health, Network of Surveillance and Control of Communicable Diseases*, http://europa.eu.int/comm/health/ph/others/network/index_en.htm

European Federation of Pharmaceutical Industries and Associations, *EFPIA Response to DG SANCO Reflections on Future EU Health Strategy*, 2004 www.efpia.org

European Medicines Evaluation Agency, *Guidance Document on Use of Medicinal Products for Treatment and Biological Agents that might be used as Weapons of Bioterrorism*, EMEA/CPMP/4048/01 www.emea.eu.int/hums/human/bioterror/bioterror.htm

European Molecular Biology Organisation, *Infectious Diseases: Challenges, Threats and Responsibilities*, *EMBO Reports* 2003 4, S1-S64

European Science Foundation, *Infectious Diseases: A Paradigm for Integrated Research in Europe*, 2004

Goosens, H., Ferach, M., Vander Stichele, R. and Elseviers, M. for the ESAC Project Group, *Outpatient antibiotic use in Europe and association with resistance: a cross-national database study*, *Lancet* 2005 365, 579-587

House of Lords Select Committee on Science and Technology, *Fighting Infection*, 2003 UK HL Paper 138

Institute of Medicine, *Accelerating the Research, Development and Acquisition of Medical Countermeasures against Biological Warfare Agents: Interim Report*, 2003

Institute of Medicine, *Learning from SARS: Preparing for the Next Disease Outbreak*, 2004

Morens, D.M., Folkers, G. K. and Fauci, A.S. *The challenge of emerging and re-emerging infectious diseases*, *Nature* 2004 430, 242-249

Nature Medicine Supplement, Emerging Infectious Diseases, 2004 10, S69-S140

Nature Reviews Microbiology, Focus on Antimicrobial Strategies, 2004 www.nature.com/nrmicro/focus/antimicrobialstrategies/index_mf.html

OECD, *Biotechnology and Sustainability: The fight against Infectious Disease*, 2003 www.oecd.org/sti/biotechnology

Turnridge, J. and Christiansen, K. *Antibiotic use and resistance – proving the obvious*, *Lancet* 2005 365, 548-549

