

**Supplement to European Science Foundation Policy Briefing 24:**

**“Research on Infectious Diseases”**

*Full Report of ad hoc Expert Group on basic research in microbiology and infectious diseases, in collaboration with the European Society for Clinical Microbiology and Infectious Diseases (ESCMID).*

**The global situation regarding infectious diseases**

*Introduction*

Infectious diseases are a global concern. Of the annual 12 million deaths attributable to infectious diseases on the planet, 95% occur in the developing world, particularly in the most impoverished areas where individual and general hygiene standards remain very low and prevention policies are non-existent, poorly adapted or insufficiently funded. On the other hand, economic and industrial development also accounts for the emergence of infections, such as food-borne pathogens that take advantage of the increasing industrialisation of the food chain, nosocomial infections in the increasingly complex hospital environment and travel-related infections. In addition, the demographic trend towards an ageing population in Europe enhances the risk of increasing infection as elderly people are prone to invasive medical procedures and are, in general, more susceptible to infectious diseases. For example, in Germany the number of people aged 65 years and over increased from 12 million in 1975 to 14 million in 2000 and will reach 19 million in 2025. In 2025, this age-group will constitute 23% of the total population in Germany, 20% in the United Kingdom, 22% in France and Spain, and 25% in Italy. Further, annually, 30-40 million passengers travel by air, many to regions of the world where infectious diseases are endemic, and there is increasing migration from these regions to industrialised nations, including those in Europe. These factors illustrate that one is living in a world where globalisation of trade and travel poses a renewed threat to our western societies that, in spite of major efforts in public health, remain fragile and at risk of infections that initially emerged abroad. This was the case with HIV that has now infected 40 million people principally in Africa and Asia, with multidrug-resistant tuberculosis and, more recently, with SARS.

Therefore, there is a need for an international agenda to address these problems which will have a major impact on health and economics as the world's population keeps growing (currently 6.2 billion of which 2.8 billion live on an income of less than US\$ 2/day [1.5€/day] and with 200 000 new births/day). New threats are also recognised, such as bioterrorism. These issues have been discussed at the highest level at meetings of the World Health Organization (WHO) and at the global summit in Johannesburg<sup>1</sup>. Two major reports that consider the impact of infectious diseases on global development were subsequently issued. One is the World Health Organization World Health Report 2002 entitled *Reducing Risks, Promoting Healthy Life*<sup>2</sup>, the other is more concerned with the implementation of basic and translational research in biotechnology applied to the prevention and cure of infectious diseases<sup>3</sup> and was issued by the Organization of Economic Cooperation and Development (OECD), following a 2002 meeting entitled *Biotechnology for Infectious Diseases: Addressing the Global Needs*.

In the case of vaccine development, which can be taken as a paradigm of a cost-effective action to prevent infectious diseases, it is apparent from these and other reports that the difficulties in developing vaccines for serious and immediate infectious disease problems such as HIV, tuberculosis, malaria, acute respiratory infections and diarrhoeal diseases are due to scientific and technological limitations as well as economic circumstances and lack of political will. Because of this, industrial research and development in the area of new antibiotics and vaccines is dramatically decreasing. Only five companies account for 90% of the vaccines produced on the planet. Increased funding is needed and long-term action (i.e. sustainability) is required.

European science must play a major role in this fight to curb infectious diseases, particularly through the establishment of a stronger and more coherent surveillance and control system and through a substantially increased investment in research to underpin this endeavour. Only with this investment will Europe be able to manage infectious diseases within its own boundaries. In addition, Europe will also be able to help prevent the emergence and spread of infections prevailing elsewhere on the globe and to pursue its historical tradition of giving assistance to the poorest countries.

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<sup>1</sup> World Summit on Sustainable Development 2002, Johannesburg, South Africa, August 26 - September 4, 2002

<sup>2</sup> [www.who.int/whr/2002/en/](http://www.who.int/whr/2002/en/)

<sup>3</sup> [www.oecd.org/dataoecd/23/23/2508407.pdf](http://www.oecd.org/dataoecd/23/23/2508407.pdf)

### *Morbidity, mortality and the socio-economic impact of infectious diseases*

**Morbidity** arising from infectious diseases is phenomenal and numbers of cases are so great that they lose their impact. This is why figures are usually provided regarding mortality. However, morbidity has a cost and a socio-economic impact that can be calculated in absolute and relative terms as compared to the burden of other diseases such as cancer, metabolic disorders and cardiovascular diseases. Mortality is considered first, followed by Disability Adjusted Life Years (DALY) (see below), an index that is increasingly used to monitor the socio-economic impact of diseases.

With a **mortality** of 11-12 million people every year, infectious diseases account for 26.2% of disease- and trauma-related deaths on the planet<sup>4</sup>. The major killers are acute respiratory infections (3.8 million/y), AIDS (2.8 million/y), diarrhoeal diseases (1.8 million/y), tuberculosis (1.6 million/y) and malaria (1.2 million/y). Noticeably, measles currently cause 760 000 deaths every year in spite of the availability of a cheap, efficacious and well-tolerated vaccine. Even though such scourges are less prevalent in OECD countries, infectious diseases still account for significant mortality. For example, in OECD countries, around 1.5 million people suffer from severe bacterial sepsis each year. Thus, in these highly developed states, every day, 1 400 people lose their lives because of severe sepsis. Another under-recognised cause of preventable mortality is healthcare-associated infection. Based on a conservative estimate of 10% of the European population that is hospitalised every year and considering that 5% of them suffer a nosocomial infection, this represents 1.75 million hospitalised patients with at least one episode of infection. Assuming a conservative 10% attributable mortality rate, this equates to 175 000 deaths from these infections every year. These figures do not take into account the enormous cost of treating these infections and the disabilities that they cause, for which reliable estimates are lacking in Europe. In 2000, the US Centers for Disease Control and Prevention estimated the total costs of nosocomial infections to be \$5 billion in the USA<sup>5</sup>.

The **impact** of infectious diseases on economic growth is visible, encompassing both the direct cost of medical care and the reduction in years of healthy life expectancy and productivity because of early death and chronic illnesses. This, in return, leads to a reduction to business and infrastructure investment, social cooperation and social stability. Last but not least, the control of infectious diseases is a strong driving force in the acceleration of demographic transition, by modifying the 'quantity-to-quality trade off' paradigm of parents.

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<sup>4</sup> [www.who.int/whr/en/](http://www.who.int/whr/en/)

<sup>5</sup> [www.cdc.gov/mmwr/preview/mmwrhtml/mm4908a1.htm](http://www.cdc.gov/mmwr/preview/mmwrhtml/mm4908a1.htm)

The evaluation of the burden of disease is often based on an index called the Disability Adjusted Life Years or DALY. It corresponds to the following equation:

the annual number of lost life years arising from a given disease  
multiplied by  
a multiple of percapita income.

This provides a rough estimate of the aggregate economic loss. Table 1 shows that infectious diseases represent the highest fraction (almost one half) of the socio-economic burden related to disease.

**Table 1. Global burden of diseases – DALYs (WHO World Health Report 2002<sup>6</sup>)**

Condition	Percentage
<i>Infectious/communicable diseases</i>	30
Respiratory diseases	6.1
HIV	5.8
Diarrhoea	4.1
<i>Non-communicable diseases</i>	46.7
Neuropsychiatry	12.9
Cardiovascular diseases	9.9
Cancer	5.1
Respiratory diseases	3.7
<i>Traumatology</i>	12.2
<i>Perinatal-maternal conditions</i>	11

Although it is difficult to produce accurate figures, some simulations have been produced by WHO and partners regarding the impact, even partially, of controlling mortality and morbidity of the three current priority diseases: tuberculosis, AIDS and malaria. For example, in the case of tuberculosis, the global economic burden amounts to approximately 16 billion US\$ [12 billion €]. This figure is based on the estimate that 8.7 million people are ill (loss of 30% income, 1 billion US\$ [0.75 billion €]), that 2 million people die of tuberculosis each year (15 years' income = 11 billion US\$ [8.3 billion €]) and that expenses for diagnosis and treatment amount to about 4 million US\$ [3 million €]. A 58% reduction in deaths is estimated to cost 0.9 billion US\$ [0.6 billion €]. Based on the fact that in 2010 about 22 million sick people would be cured and about 16 million deaths would be avoided, the economic return would

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<sup>6</sup> [www.who.int/whr/en/](http://www.who.int/whr/en/)

amount to an impressive sum of 6 billion US\$ [4.5 billion €]. Similar calculations can be made for malaria and AIDS.

Such numbers need no further comment. It follows that improvement of personal hygiene through better education – particularly through mothers' literacy, development of sanitation and preventive medicine, and implementation of the currently available vaccines (i.e. enabling every child benefit from the Extended Programme on Immunization, EPI), would undoubtedly and very cost-effectively reduce the global burden of infectious diseases. As shown above, the impact of, even partially, controlling mortality and morbidity of the three current priority diseases (tuberculosis, AIDS and malaria) would save the poorest countries an enormous portion of their GNP that could efficiently be reinvested in development.

The above figures support the cost-effectiveness of interventions leading to significant control of infectious diseases. However, interventions such as vaccines against AIDS, malaria, tuberculosis and diarrhoeal diseases and new drugs against multiresistant HIV, *Mycobacterium tuberculosis* and *Plasmodium falciparum* strains remain to be developed. This will require a massive investment in basic science in order to generate the knowledge required to better understand the pathogens and their interactions with their hosts and vectors. Research, however, should not concentrate on only a limited number of diseases: pathologies such as acute respiratory infections, diarrhoeal diseases, parasitic diseases other than malaria, nosocomial, food-, water-, and air-borne infections represent a major source of mortality and morbidity that justify a broad portfolio of research activity and an even repartition of effort.

The alarming emergence and spread of antibiotic resistance among common pathogenic bacteria threatens the effectiveness of therapy for many infections. Resistance develops under the pressure of antibiotic use, which is considered to be largely excessive and often indiscriminate in both the medical and animal health sectors. This phenomenon stems from selection of adaptive mutations, horizontal transfer of determinants of resistance on mobile genetic elements such as plasmids and transposons and clonal dissemination of multiresistant strains. The spread of multiresistant bacteria such as *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Enterobacteriaceae*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Mycobacterium tuberculosis* is of particular concern. A number of studies have documented the adverse outcomes associated with infection by antibiotic-resistant strains of *M. tuberculosis* or nosocomial pathogens like methicillin-resistant *S.*

*aureus*, in terms of excess morbidity, mortality, cost and duration of treatment and hospital stay. Hotspots for the development and spread of resistance include closed communities exposed to frequent antibiotic use, such as patients admitted to healthcare facilities or children in daycare settings. A striking example is the recent emergence in hospitalised patients of highly multiresistant strains of *S. aureus*, which have acquired vancomycin resistance in addition to methicillin resistance, through plasmid-mediated transfer of a vancomycin-resistant transposon from *Enterococcus faecalis*. Gradual increase of drug resistance in major pathogens causing chronic infection such as HIV and *Helicobacter pylori* is also a major challenge for future management strategies.

There is a paucity of data from well-designed outcome studies as well as great variation in the degree of resistance from country to country and even within countries, making it difficult to generalise the impact of antibiotic resistance on treatment outcomes and on global health and economic burden. Antimicrobial resistance has been identified as a priority by public health agencies worldwide and has prompted the publication of national and international recommendations including the WHO *Global Strategy for Containment of Antibiotic Resistance*<sup>7</sup> and the European Commission *Community Strategy Against Antimicrobial Resistance*<sup>8</sup>, both published in 2001. As the origin of this problem is multifactorial, the containment of antimicrobial drug resistance needs a global strategy based on a better understanding of its determinants and dynamics. It will also require a rigorous validation of intervention strategies and the development of alternative therapies.

### **The current situation in Europe regarding microbiology and infectious diseases**

There is a growing public awareness of the issue of infectious diseases, with particular interest in emerging/re-emerging infections (AIDS, SARS, and tuberculosis), nosocomial infections and the multiresistance of microorganisms, bioterrorism and the health status of the developing world. There is also a growing awareness by European authorities of a need for action. This has recently translated into the decision of the Commission of the European Communities to establish a **European Centre for Disease Prevention and Control** (ECDC). However, a coherent European policy in the prevention and control of infectious diseases also needs to be backed up by a strong basic research component. Therefore, basic research in microbiology and infectious diseases should be encouraged. Topics to be

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<sup>7</sup> [www.who.int/csr/resources/publications/drugresist/EGlobal\\_Strat.pdf](http://www.who.int/csr/resources/publications/drugresist/EGlobal_Strat.pdf)

<sup>8</sup> [http://europa.eu/int/comm/health/ph/others/antimicrob\\_resist/](http://europa.eu/int/comm/health/ph/others/antimicrob_resist/)

supported and organisational and financial means to foster this support are the aim of this report.

The current situation in Europe is characterised by strengths and weaknesses.

### *Strengths*

The strengths are dominated by a strong tradition of research excellence in this field that has its historical roots in the work of dominant figures such as Louis Pasteur, Robert Koch and Alexander Fleming. Europe also benefits from strong institutions that have a significant research component in microbiology and infectious diseases. In addition, Europe has a large workforce of experts in clinical, environmental and public health microbiology as well as growing medical resources in well-trained infectious disease clinical specialists and communicable diseases epidemiologists. Universities and medical schools offer excellent training programmes in various relevant fields including microbiology, immunology, genetics, molecular biology, biochemistry, ecology and epidemiology. Small, medium and large enterprises in the biotechnology and pharmaceutical industries have numerous research and development facilities that are active in vaccine and drug discovery across the EU.

### *Weaknesses*

The weaknesses are essentially:

- deficient private and public funding;
- lack of vision and long-term commitment of funding programmes;
- fragmentation of research programmes by discipline and by country;
- lack of integration and interaction between basic and applied research;
- important heterogeneity between European countries in terms of levels of scientific and technological development
- missing expertise in some specific areas;
- obstacles to the mobility of scientists and physicians because of discordant national training tracks and qualifications;
- lack of visibility and attractiveness of the research field;
- insufficient development of technical platforms;
- slow implementation of basic discoveries in molecular medicine;

- deficit in translational research, particularly regarding the discovery of new anti-infectious drugs and vaccines.

In 2003, 43 new drugs were certified by the US Food and Drugs Administration (FDA), of which only 4 were anti-infective agents or vaccine (3 anti-viral agents and 1 influenza vaccine). The pharmaceutical industry is reducing its efforts in developing new anti-infectives, notably antibacterial and antiparasitic agents and vaccines, because of the high costs of research and clinical testing as well as regulatory problems. In view of increasing antibiotic resistance, this trend may be considered dramatic and is seen in the USA, Japan and particularly in Europe. In addition, the gap in this area between Europe and North America is likely to widen in view of the fact that the budgets devoted to infectious diseases in the US have recently increased astronomically. For example, the US National Institute of Allergy and Infectious Diseases, in 2003, spent \$1.9 billion [1.4 billion €] on biodefence research, \$1.4 billion [1.06 billion €] on HIV research, and \$0.9 billion [0.6 billion €] on all other infectious diseases. These massive investments also help their citizens to realise the extreme importance of research in the field.

### **State-of-the-art in infectious disease research and gaps to be filled**

#### *Molecular and cellular pathogenesis of infections*

Research on bacteria and bacteriophages gave birth to molecular biology. In return, molecular techniques, such as polymerase chain reaction (PCR), have revolutionised microbiology as well as many related fields like taxonomy and phylogeny, thus not only creating a basis for a better knowledge of the microbial world but also offering innovative tools for diagnostics. Molecular approaches have enabled a better understanding of the actions of anti-infectious agents as well as the resistance mechanisms of microbes to these agents. Accordingly, new drugs are able to be developed, although the number of such drugs is smaller than a justified expectation. The availability of genomes of many bacterial species, including the major human pathogens, symbolises the entry into a new research era. This new dimension in our knowledge of microorganisms has been justly seen as a boost to the development of new means of controlling infectious diseases, particularly through new drugs and vaccines.

Over the last 20 years following the introduction of molecular biology, the area that has undergone the most impressive changes is pathogenesis of infectious diseases. In brief, following a period characterised by the description of the major human pathogens and some of their essential virulence factors, as well as the development of several animal models in which some of the key infections could be reproduced, a first revolution occurred in the late 1970s when the then emerging discipline of **molecular biology** began to be applied to the understanding of infection mechanisms. This opened the way for exploration of the molecular pathogenesis of infections, resulting in a great number of mutants and putative virulence genes that needed to be tested *in vitro* in cell assay systems (animal models not being up to the numbers of assays required). Almost naturally, a second revolution occurred, the creation of an interface between microbiology and cell biology, **cellular microbiology**, leading to a detailed study of the interactions between microbial effectors and their cellular targets and to a deciphering of the signalling processes mediating these interactions. This, again naturally, led to a sub-cellular approach involving the development of methods to identify the cellular targets of microbial effectors, sophisticated imaging technologies to trace microbes in their cellular compartments and to visualise the molecular interactions, and structural studies to unravel the structure-function relationships between effectors and their respective targets. A third revolution is currently ongoing as the study of microbial pathogenesis has gone global because of the explosion of genomics (providing knowledge of the genomes of many major pathogens), and the availability of high-throughput procedures such as transcriptomics and proteomics (offering the potential for studying gene and protein expression of the whole microbial organism as well as its infected eukaryotic target). This mass of information requires a new paradigm of approaches that involves a strong component of infection bio-informatics. However, this emerging science should not overrun the need for strong 'idea/hypothesis-driven research' that characterised the previous successful revolutions. Also, a current trend is aimed at bridging the gap between the cellular scale and the tissue/organ scale of microbial interactions. This requires the development of relevant animal models as well as high-resolution tools that allow observation of these events, live and in real-time. This trend should encompass the integration of new imaging technologies such as magnetic resonance imaging (MRI), PET-SCAN and others. Such a paradigm shift toward an integrative approach represents a unique opportunity to better integrate microbiology, infectious diseases and immunology.

Accordingly, a number of new topics and visions can be identified regarding the future developments in **molecular and cellular pathogenesis of infections**. These comprise:

- Exploiting sufficiently the potential of the new paradigm of approaches in knowledge acquisition and applications in fields such as virology, mycology and parasitology. In these areas a transdisciplinary approach needs to be applied via the integration of microbiology with cell biology, structural biochemistry, genomics and experimental medicine.
- Developing integrative projects encompassing microbiology with other disciplines such as developmental biology and neurosciences. These endeavours may include, for example, modelling the passage of barriers as important as the blood-brain barrier, developing molecular and cellular studies on the implantation, maintenance and homeostatic control of commensal flora (i.e. cutaneous or digestive), and boosting research in mucosal immunology.
- Boosting research on the infected host which is vital in combating infectious diseases and requires an unprecedented effort. Topics may include, for example, the genetic basis of host resistance-susceptibility to infections, innate immunity and how it affects the transition to the adaptive response, and the adaptive response itself. A similar cellular microbiology approach should be applied, with an emphasis on the interaction of the microbes with the cells of the immune system. Model systems need to be developed. Model organisms such as *Drosophila* (fruit fly) have not yet been fully exploited for their potential to unravel new sensing/signalling pathways. Forward genetic approach to decipher the pathways of immune response needs to be further developed in addition to the development of gene-deficient and dedicated transgenic mice. New post-genomic tools such as transcriptomics and proteomics should be exploited to enable a global study of host-cell and tissue responses. This will require significant technical developments with regard to relevant experimental models, treatment of samples, improvement/miniaturisation of molecular techniques, and data management.
- Applying state-of-the-art approaches to the development of new vaccines, based on the emerging in-depth molecular knowledge on both microbes and host. Vaccines against globally important infectious diseases have so far failed, e.g. in the case of tuberculosis, malaria and HIV. It is not yet clear why these efforts have been unsuccessful. It is therefore time to refocus vaccine programmes onto basic research elucidating germ-specific evasion strategies and organ-specific immune factors. This type of research would also encompass the 'natural history of infectious diseases' by placing more emphasis on human patients rather than on animal models. Such studies would require the development of innovative techniques to perform non-

invasive imaging and other necessary procedures in order to gain access to very small tissue samples.

### *Microbial evolution, molecular diagnostics and epidemiology*

Other fields which have progressed spectacularly thanks to the technology revolution in life sciences are the study of microbial evolution, molecular diagnostics and epidemiology of infectious diseases. The comparative analysis of microbial genomes has provided quantum leaps in the understanding of population genetics and genome evolution. The majority of bacterial species pathogenic to humans exhibit some degree of clonal structure which predominates in *Haemophilus influenzae*, *Escherichia coli* and *Salmonella*, whereas other species appear basically panmictic, as shown by *Helicobacter pylori* and *Neisseria gonorrhoeae*. The importance of horizontal gene transfer in bacterial evolution is increasingly recognised, even in clonal organisms, to the extent that the chromosome has been viewed as the 'genetic necropolis of previously mobile genes'. These acquisitions of foreign DNA from related or, less frequently, distant organisms, occur by conjugation, transposition, transduction and transformation. An example of the medical importance of these mechanisms is the recent polyclonal emergence of hypervirulent strains of *S. aureus* that have integrated a resistance island (the type IV staphylococcal chromosomal cassette *mec* conferring methicillin resistance) as well as a pathogenicity island harbouring the locus for the Panton-Valentine leukocidin. These combined traits have given a selective advantage to these methicillin-resistant *S. aureus* (MRSA) clones which spread in the general population, causing severe soft tissue and pulmonary disease, resistant to first-line therapy.

The explosion of technologies for nucleic acid amplification, separation and sequence analysis, combined with computerised analysis systems, has greatly increased the access of clinical and public health microbiology laboratories to sophisticated microbial detection and genotyping methods. Molecular detection and identification of microbial pathogens from clinical specimens has increased the sensitivity and rapidity of diagnosis of infection. The evolution of diagnostic technologies has taken two directions: increased availability of portable, point-of-care testing and specialised sample testing in large, centralised laboratories with high volume automated instruments. This raises the issue of safeguarding and in fact enhancing the role of consultation between physicians and clinical microbiologists to ensure optimal use and interpretation of these tests for management of individual patients and the protection of public health. It also underpins the need to assess the cost-effectiveness of treatment algorithms based on novel diagnostic modalities as compared with

the conventional approach that is largely syndrome-based and frequently associated with inadequate antimicrobial therapy.

Molecular genotyping has contributed to unravelling the natural history of endogenous and exogenous infections by identifying the reservoir and the mode of translocation or transmission of bacteria. For example, the source of nosocomial infections has been analysed, such as pneumonia caused by *P. aeruginosa* among critically ill patients. These patients can either develop an endogenous infection arising from *P. aeruginosa* in the gut flora, or become contaminated from the hospital drinking-water system and/or by cross-transmission from other patients. Molecular typing enables accurate testing of transmission hypotheses during outbreaks and provides the evidence base for rational control interventions. In addition, application of molecular typing to multicentre surveillance programmes has enabled tracking of the spread of pathogens across regions or whole continents. For this reason, networks of laboratories are developing standard typing procedures for multicentre surveillance and real-time analysis of a shared bacterial fingerprint database. For example, the PulseNet coordinated at the US Centers for Disease Control and Prevention allows early detection of clusters of food-borne enteric disease across the USA. In Europe, several international networks are pursuing efforts towards coordinated typing and building integrated databases for monitoring epidemic clones of bacterial pathogens such as *M. tuberculosis*, *Salmonella*, *Listeria*, *S. aureus*, and *meningococci*. In the field of viral infections, WHO networks of reference laboratories have demonstrated their value in providing rapid analysis of antigenic composition and sequence data on emerging viruses such as the SARS coronavirus and avian influenza variants. This molecular genotyping approach has become the key to informed interventions for controlling communicable disease from the hospital ward to the pandemic level.

Accordingly, a certain number of new topics and visions can be identified regarding the developments in molecular diagnostics and molecular epidemiology.

These comprise:

- developing integrative projects linking the study of microbial genomic polymorphism to variation in fitness, virulence and resistance allotype, and evolutionary success based on strain ecological and epidemiological distribution.
- providing measures of the molecular clock of various genetic elements associated with the micro-evolution of bacterial clones. This is a prerequisite for the development

of standardised and discriminatory genotyping systems able to monitor the spread of bacterial clones in populations ranging from local to global.

- developing and validating rapid, standardised sequence-based genotyping systems allowing rapid warning of epidemic dissemination of hypervirulent, antigenic variant or drug-resistant microbial and viral pathogens through surveillance networks of clinical and reference microbiology laboratories.
- developing and validating high performance diagnostic assays for bedside and field testing useful in diagnostics, case-screening or surveillance of infections causing a high disease burden and for which test results are likely to impact on the quality of care, containment of resistance or control of disease. Technologies to be explored include immunoassays, nucleic acid amplification tests, nanotechnologies, and biosensors.
- carrying out clinical, epidemiological and health-economic studies for the cost-effectiveness of novel diagnostic and typing tests in the management of patients with infectious diseases and the control of communicable infections.

### *Antimicrobial resistance*

Antimicrobial resistance is among the most challenging problems in microbiology, clinical medicine and public health. In fact, 'antimicrobial resistance' is not just one problem but an overarching term for an array of problems inherent in the evolution of microbes and influenced by antimicrobial use. Basic research provides the fundamental knowledge necessary to develop appropriate responses to antimicrobial-resistance emergence and spread as well as for the development of antimicrobial agents circumventing resistance. Although major scientific accomplishments have contributed to the understanding of the fundamental biological processes of antimicrobial resistance in bacteria, several gaps remain, mainly related to low-level resistance mechanisms, such as over-expression of efflux pumps and its clinical relevance. The detection of resistance genes and of the genetic elements carrying them is necessary for a deeper insight into the transmission of resistance traits, especially in multiresistant isolates. New technologies for comparing microbial population genomics should be introduced to search for resistant determinants and to identify genetic vectors and elements participating in horizontal gene transfer. Epidemiologic research is also needed in well-designed studies that assess the clinical and economic outcomes related to infection by resistant pathogens and the efficacy of control interventions based on improving antimicrobial use and infection control.

New antimicrobial drugs are not being developed rapidly enough to address increasing microbial resistance. Developing each new agent represents a major investment by a pharmaceutical company which consequently may be reluctant to develop drugs, such as antimicrobials targeted to resistant organisms, that are given for short periods to a limited number of patients. On the other hand, when a drug is used widely, allowing recovery of costs and profitability, resistance may develop more rapidly and shorten the useful life of the drug. Because of these economic realities, as well as the scientific limitations and a lag in the perception of a need for new agents, very few novel antimicrobial drugs have reached the market for several years or are likely to become commercially available in the foreseeable future. A major effort in this area is to work with the private sector in exploring and testing innovative ways to address these issues. Approaches to be considered include providing incentives to promote the search for candidate antimicrobial drugs circumventing antimicrobial resistance in both academic and hospital research groups. Pharmaceutical companies are best placed to follow up with pre-clinical phases of drug development (toxicology, pharmacokinetics and pharmacodynamics) and clinical trials.

Accordingly, in the field of antimicrobial resistance research, the following topics should be addressed:

- deciphering the mechanisms of antimicrobial resistance, the ecology and dynamics of transmission of resistant bacteria and resistance genes, the interplay of virulence and resistance, and the external factors (ecological and epidemiological) influencing antibiotic-resistance development and persistence.
- encouraging academic and industry cooperation in antibacterial drug discovery and development of new antimicrobial agents for treating emerging diseases and multiresistant pathogens. The exploitation of novel candidate targets for identification of novel classes of antimicrobial agents should be a priority.
- integrating new molecular tools and mathematical modelling in epidemiological studies to understand the dynamics of emergence and spread of resistant genes and clones in human populations or from animal and environmental reservoirs to humans.
- assessing the economic and health burden attributable to infections resulting from resistant pathogens in hospital and in community. A priority should be given to carrying out well-designed controlled trials of intervention aiming at reduction of

emergence or spread of resistance by modifying antimicrobial treatment and/or infection control strategies.

## European strategies and policies on infectious disease research

### *Basic considerations*

Several issues need to be considered as they underline the actions to be supported:

- Infectious diseases are unpredictable. A sense of a need for readiness is clearly apparent with regard to the urgency of public health measures, including rapid reaction for prevention (cf. the efficiency of the quick and courageous measures that were taken to avoid the spread of avian influenza from Hong Kong in 1997 or the spread of SARS in 2003). A similar sense of urgency regarding the basic knowledge of pathogen biology, microbial immune evasion and host immune responses does not exist, even though it may represent the best guarantee of preparedness for the next alert.
- Basic research in microbiology and infectious diseases represents excellent paradigms of integrated approaches to study complex biological processes. This is actually a unique opportunity to work at the interface of two 'interacting genomes'. Microbiology and infectious diseases thus provide excellent opportunities for training young scientists, physicians, engineers and technicians to apply a transdisciplinary and integrated approach.
- Strong, creative, cutting-edge basic research is the only guarantee of generating the original breakthroughs that will lead to innovation in diagnostics, treatment and vaccine prevention. In the absence of strong European encouragement, the discipline will lose its attractiveness and impact, thus causing a massive brain-drain and consequent loss of talented young scientists who will focus their attention on other more visible disciplines such as neurosciences, cell and developmental biology and to more hospitable research environments such as North America.
- As the European Centre for Disease Prevention and Control comes into being, it should be able to benefit from a broad, competitive network of European laboratories able to supply a large spectrum of basic expertise in order to provide timely and relevant support in case of an emerging problem that threatens the populations and requires immediate application of expert knowledge and techniques.
- In addition, there should be more support for the development of standardised state-of-the-art operation procedures for primary and reference microbiology laboratories, allowing the provision of reliable and comparable diagnostic and surveillance

information on both common and emerging infectious diseases. The European Society for Clinical Microbiology and Infectious Diseases (ESCMID) has published a position paper<sup>9</sup> that recommends developing laboratory facilities at the ECDC to support communicable disease surveillance. Furthermore, establishing European reference laboratories and integrating them with centres of excellence in infectious diseases research (e.g. European Institute for Infectious Diseases) would boost the European research capacity and help to develop a sense of collective responsibility among biomedical scientists and healthcare professionals.

### *Issues to be addressed*

Based on these preliminary remarks, the critical issues to be addressed and analysed are:

- To identify the gaps in basic knowledge in microbiology and infectious diseases, and to pinpoint interfaces between disciplines that should be created or strengthened in order to foster innovative research and encourage the current trends that are expected to move the field forward. One priority is better integration of microbiology and immunology, although other disciplines are also concerned, such as cell and developmental biology, structural biochemistry, bioinformatics, epidemiology and neurosciences. Another priority is integration of ecology of microbial pathogens, evolutionary genetics and comparative genomics of pathogens, their vectors and human populations, and epidemiology of infection.
- To reveal essential technical investments, particularly for the development of technological platforms, required to support research efforts. This is true, not only for genomic and post-genomic technologies, but also for cell and whole-animal imaging technologies, physiology and experimental medicine, molecular histopathology, mouse genetics, transgenesis and gene invalidation, standard operating practices for animal models mimicking human infectious diseases, and development of new organ culture and animal models.
- To bring coherence in research programmes through networking at the European level, addressing the particular need for technology transfer to new EU Members States and accession countries. Networking, whenever possible, should be extended to infectious diseases researchers working in the developing world.
- To aim at achieving a critical mass on topics on which research efforts are insufficient or dispersed and at fostering the emergence of new ambitious programmes on cutting-edge

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<sup>9</sup> [www.escmid.org](http://www.escmid.org), News and current issues

topics. In this regard, the feasibility of establishing a new research institute for infectious diseases at the European level, associated with the ECDC, should be considered, in order to provide both the investment for a widely accessible technology platform and the necessary daily interaction between epidemiologists and laboratory scientists. A priority area of multidisciplinary research for this European institute for infectious diseases is integrated molecular epidemiology and evolutionary genomics of microbial pathogens, interfaced with communicable diseases surveillance and alert services.

- To improve the visibility of microbiology and infectious diseases as a discipline and to emphasise its great potential, particularly for young scientists when they need to make strategic choices for their career. In parallel, the issue of visibility is also essential for big pharmaceutical and biotech companies, national and European authorities and leaders, as well as for European citizens in general. More specifically, the aim is to increase the weight of the topic vis-à-vis key organisations such as the European Union (particularly in the context of the ongoing reflection on the format of the upcoming 7th Technological Research Outline Programme, PCRDT), European Molecular Biology Organisation (EMBO), and the future European Research Council.
  - To encourage international exchange of scientists, particularly at doctoral and postdoctoral levels. This issue of mobility is of foremost importance in developing the European scientific area.
  - To attract the best students, postdoctoral fellows and physicians to undertake research in microbiology and infectious diseases by offering appropriate funding and by advertising training and research grant opportunities.
- To support the development of anti-infective drugs and the involvement of biotech companies in areas corresponding to neglected diseases, including diagnostics, innovative vaccine and therapeutic agents such as biological response modifiers.

### **Recommendations of programmes to be supported**

These considerations directly translate into seven major programmes to be supported in the framework of microbiology and infectious diseases.

#### *1. Basic microbiology in the broadest sense*

Basic research in bacteriology, virology, mycology and parasitology must be supported in areas such as:

- comparative genomics;
- replication and gene transcription;
- translation and regulation;
- microbial division;
- biogenesis of cell components, particularly the components of the cell surface and of the cell wall in bacteria
- metabolism;
- sensing of the environment;
- secretion processes;
- basic and comparative microbial physiology;
- development of genetic systems to study pathogens;
- understanding the basic genetic and molecular mechanisms of microbial resistance to antimicrobial agents;
- identification of new targets for development of novel drugs;
- identification of new antigens for potential use as vaccines.

To maintain and develop this platform of basic knowledge it is vital to sustain and ideally improve proper conditions to generate new diagnostic tools, to allow the growth of fastidious microorganisms or develop growth models for pathogens that do not replicate well using existing methods, and to develop innovative microbicidal drugs. The study of microbial toxins (biophysical and biochemical properties, mechanisms of action, receptor identification, binding, uptake, translocation and trafficking) should be expanded.

## *2. Molecular and cellular mechanisms of microbial host-cell and tissue interactions*

This area of research has flourished over the last 20 years, bringing the understanding of infection mechanisms to an extraordinary level by molecular resolution that allows the identification of microbial effectors and their host-cell targets and the deciphering of the signals that derive from these interactions at the pathogen-host interface. Although this approach has not yet fully realised its potential, particularly outside the field of bacterial infection, it should enable the design of very innovative anti-infectious strategies. Nevertheless, in this very area, there is an urgent need for basic research to investigate

microbial evasion at the cellular level, including development of novel methodologies for identifying and studying microbial proteins that contribute to persistence and virulence, and to dissect the innate and adaptive immune pathways targeted by microbial-evasion effectors.

### *3. Pathogens, their environments and their vectors*

Although a lot has been achieved regarding the understanding of the mechanisms of infection by pathogens, it has not yet been fully realised that pathogenic microbes have a life outside their natural or accidental human target. This other 'environmental life' may comprise animal or protozoan reservoirs as well as the existence in biofilm communities, or vectors (e.g. insects and ticks) able to achieve transmission of these pathogens. A vivid example of the complexity of this environmental life is *Legionella pneumophila* surviving in protozoan cysts in water-distribution or cooling towers of highly complex environments such as hospitals, exacerbating their virulence in the vegetative forms of these protozoan organisms and taking advantage of this to become highly infective to human pulmonary alveolar macrophages on aerosol formation. Similarly, the life of microorganisms in arthropod vectors or in highly regulated biofilm structures needs to be modelled in order to make these situations as amenable as pathogenesis itself to molecular and cellular studies. As the genomes of model insects such as *Drosophila* and vector arthropods such as *Anopheles gambiae* are now known, better understanding of the environmental life of pathogens is also a guarantee of innovation of control tools in the future. Further topics include studies of pathogenic microbes in natural settings in their hosts and vectors (with regard to development of virulence, persistence traits and host switching), characterisation of population immunity, studies of the distribution and determinants of microbial pathogens in human populations, studies and modelling of vehicles, and mechanisms of transmission of pathogens in human populations in endemic areas.

### *4. Host immune responses to pathogens and genetic basis of human susceptibility to specific pathogens*

In addition to the 'mechanical' aspects of interactions between microbes and their host and tissue targets that define the process of infection, the host innate and adaptive immunological responses should also be considered, because the quality and intensity of such responses largely dictate the nature and severity of symptoms and lesions. The combination of both infection and immune responses defines infectious disease. The recent spectacular progress in the field of innate immunity essentially stems from an unprecedented fusion between microbiology, immunology and developmental biology in model organisms

such as *Drosophila* and the mouse. Tomorrow's vaccines, along with adjuvant development, will undoubtedly benefit from these efforts. Furthermore, it has recently become clear that the susceptibility to some infections is governed by a monogenic trait. In addition to cataloguing a maximum number of these situations, it is also essential to decipher the multigenic nature of the susceptibility to major human pathogens. Other areas include:

- basic studies in microbial pathogenesis;
- mechanisms of mucosal immunity to pathogens;
- mechanisms of immunopathology and immune evasion at the level of the host (animal models);
- identification and characterisation of immunoregulatory pathways in target populations, such as the very young, the elderly and the immunocompromised;
- development of novel vaccine strategies including new adjuvants, and vaccine formulations for optimal delivery;
- identification and characterisation of innate immune pathways as targets for immunotherapy;
- comparative analysis of microbial evasion;
- immune response patterns in co-infections;
- use and development of new animal models, including primate models, for functional genomics (i.e. validating the function of molecules discovered by transcriptomic and proteomic approaches during natural evolution of disease processes);
- validation of new vaccines and adjuvants.

##### *5. Integrated molecular epidemiology and evolutionary genomics of microbial pathogens*

Beyond the in-depth study of prototypic strains, cells and experimental hosts, the complexity of infectious disease processes and their rapidly changing epidemiology in response to ecological and societal changes require a population-based approach to determine the mechanisms of host-pathogen co-evolution. These studies include:

- characterisation and analysis of risk factors related to acquired immunity and innate immunity genetic polymorphism in human populations;
- analysis of microbial genome plasticity and evolutionary mechanisms;
- population genetic structure and diversity of vectors and microbial pathogens;

- distribution of allotype variants of microbial pathogens in human populations and epidemiologic reservoirs;
- epidemiologic studies and mathematical modelling of vehicles and mechanisms of transmission of pathogens;
- validation of the predictive value of these models for epidemiologic impact of therapeutic and control interventions such as immunisation;
- determination of optimal sequence-based typing techniques,
- bio-informatic data processing and standardised criteria/nomenclature for biologically meaningful identification of microbial strains applicable to multicentre disease surveillance and outbreak investigations.

#### *6. Determinants of antimicrobial resistance and assessment of containment strategies*

To overcome the threat resulting from increasing antimicrobial resistance, research programmes should focus on:

- integrated study of mechanisms of resistance;
- dynamics of transmission of resistant bacteria and resistance genes;
- interplay of virulence and resistance and the ecological, societal and epidemiological influences on antibiotic resistance;
- translation of research findings into the development of new antimicrobial drugs for the treatment of infections caused by multiresistant bacteria;
- sharing of antimicrobial resistance data and novel therapeutics between the research community and industry;
- development of novel diagnostic tests for major infectious diseases and clinical-economic evaluations of their impact on patient management and containment of resistance;
- well-designed epidemiological studies and surveillance programmes to determine the adverse outcomes associated with resistance and to evaluate the impact of novel therapeutic and infection control interventions.

## *7. Encouragement for translational and clinical research*

Medicine as a whole has undergone a true metamorphosis during the second half of the twentieth century. So has medical research in infectious diseases. Thanks to the introduction of molecular techniques, today's clinical microbiologists are able to rapidly diagnose a single microbe from a minute amount of clinical specimen. In order to exploit fully the potential of state-of-the-art technology applied to infectious diseases, meticulous techniques in the pre-analytical stage are crucial but to date this has been a neglected area of research. Similarly, the advantages of rapid and advanced techniques for clinical practice in the field have not been investigated adequately. Moreover, although it is clear that rapid and precise microbiological results are extremely useful for selection and streamlining of antimicrobial therapy, currently the impacts of traditional microbiology reports on daily clinical treatment decisions are not optimal. What is more, in the light of increasing antimicrobial resistance, research on prescribing habits and antibiotic stewardship is another area that needs more research investment. From the same perspective, research on the failure and occasional successes of implementation of hospital hygiene is needed. Therefore, translational research, which has already exerted an impact on the daily practice of clinicians in general and is vital for the continuous development of new applications in clinical medicine, is urgently needed in this area.

Increasing antimicrobial resistance, both in hospitals and in community, is one of the dominant problems in the infectious diseases arena currently. At the same time, the pharmaceutical industry has dramatically reduced its commitment to antibacterial research and development, a problem already regarded as most serious by both American (i.e. the FDA and the Infectious Diseases Society of America, IDSA<sup>10</sup>) and European (the EC and ESCMID) authorities and societies. Moreover, new bacterial molecular targets are desperately needed for developing new molecules. In a 2003 European Conference on the Role of Research in Combating Antibiotic Resistance organised by the EC and ESCMID<sup>11</sup>, several research areas were recognised as being essential for efficient combat against microbial resistance.

Among the disciplines to be strongly encouraged are:

- bacterial physiology;
- clonal selection and spreading mechanisms;

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<sup>10</sup> [http://www.idsociety.org/Template.cfm?Section=Antimicrobial\\_Resistance](http://www.idsociety.org/Template.cfm?Section=Antimicrobial_Resistance)

<sup>11</sup> [http://www.escmid.org/sites/index\\_f.asp?par=3.3](http://www.escmid.org/sites/index_f.asp?par=3.3)

- microbial genomics and bioinformatics;
- mechanisms of reversibility of resistance;
- development of rapid laboratory diagnostic tests and identification of resistance genes in hospital and community;
- implementation of improved studies linking resistance to interventions and outcomes.

Any progress on these topics must involve immediate translation of basic research into clinical practice.

### **Recommendations on possible components of an initiative to address the above priorities**

#### *Training component for graduate students*

In the framework of the new Master of Biology, a programme entitled Basic Research in Microbiology and Infectious Diseases could be established, based on a network of outstanding laboratories and institutions in this field. Young graduate students could be offered, for their first year, a rotating programme (e.g. three 3-month training sessions in three different European laboratories) among this predefined network of excellence. Then, based on the hands-on experience in research laboratories, they could select the best possible European laboratory to carry out their PhD thesis. A similar external training opportunity (e.g. three 2-month training sessions in different European laboratories) could be offered to freshly graduated physicians in the framework of postgraduate specialist training in infectious diseases or clinical microbiology. This early encouragement to mobility may be essential for building the future European scientific space.

#### *Training component for postdoctoral scientists*

A great effort should be made to attract the best possible PhD students trained in molecular genetics, cell biology, structural biochemistry, immunology, developmental biology, genomics, and other relevant disciplines to move to a laboratory working on the interactions between microbes and host. This could be done under the auspices of a special European postdoctoral programme established under the coordination of the European network, in collaboration with national ministries, the EC and EMBO. EMBO members could serve as referees to evaluate these applications. In more applied medical and operational areas of

research, the current postgraduate curricula throughout Europe leading to a PhD have obvious gaps (e.g. pharmaco-epidemiology, epidemiologic evaluation of outcomes and disease control interventions). ESCMID could contribute to building a specific programme to train young researchers and help them to develop these skills and knowledge base.

#### *Funding of transdisciplinary research programmes*

Funding of transdisciplinary research programmes should be aimed at developing cutting-edge projects, particularly in areas corresponding to the gaps in knowledge defined above and in areas requiring new or reinforced interaction (e.g. microbiology and immunology, and epidemiology and microbial evolutionary genomics). In order to support this endeavour, a limited number of Young Investigator' groups could be created, with cutting-edge projects. The feasibility of establishing a European centre for infectious diseases to initiate research programmes in integrated molecular epidemiology and evolutionary genomics of microbial pathogens, in close coordination with the ECDC, should be explored.

#### *Organisation of training courses and workshops*

Training courses and workshops would be devoted to supporting the initiative by presenting cutting-edge concepts and technologies in basic and applied research in infectious diseases (e.g. molecular imaging, immunogenetics, post-genomic approaches, innate immunity, development of relevant animal models, comparative genomics, novel molecular technologies for diagnostics and typing, and drug design). These courses would also be an opportunity to support the development of a truly integrative concept encompassing basic disciplines and their possible applications in diagnostics, drug discovery and vaccine development, i.e. to foster the development of a truly integrated concept of molecular medicine in the field of microbiology and infectious diseases.

#### *Organisation of networks and common data banks*

Well operated networks and data banks are important research infrastructures in infectious disease research. Therefore, organisation of networks and common data banks is central for rationalisation of the exploitation of genomic data and organisation of post-genomic approaches in the field.

In the long term, the hope is that these actions will contribute to reversing the current brain-drain of young European investigators to North-America by improving their visibility in the excellence of European laboratories and attractiveness of the topics they address.