

3.7 Infectious Diseases

We can no longer be complacent that we can control infectious diseases, despite hopes that this would be achieved in the 1970s following the introduction of antibiotics and vaccines. A wake-up call to a neglected problem has been provided by 35 newly discovered infectious diseases during the past 25 years, including HIV, vCJD, Ebola, SARS, West Nile, and more than 190 documented human infections with potentially pandemic influenza viruses. This is the first time in history that so many new infectious diseases have emerged in such a short period of time, and it is common opinion that novel infectious diseases will be emerging with increased frequency during the 21st century. A growing global population, overcrowded cities, increased travel, intensive food production, sexual practices, poverty, global warming, and breakdown of public health measures are some of the reasons behind the emergence of new infectious diseases and their rapid spread across the globe. The SARS epidemic is a perfect example of how geographical distances are no longer a barrier, and a disease born in any part of the globe can become a global threat in a matter of hours. A snapshot of the global infectious diseases situation is given in Figure 26 below.

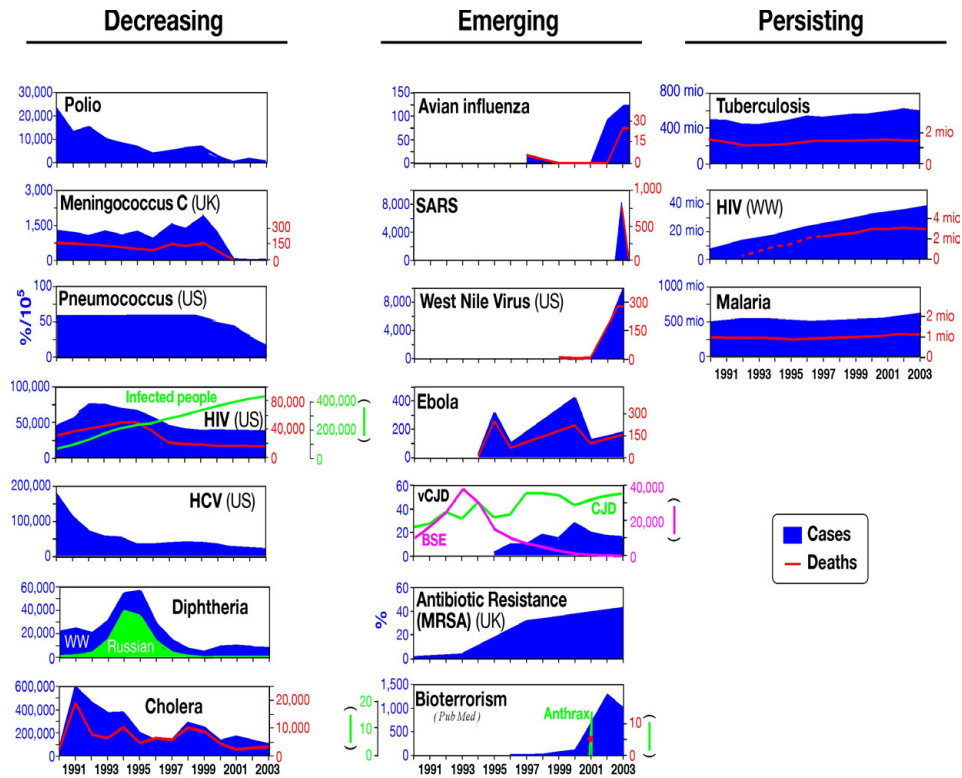


Figure 26 : Global Infectious Diseases Prevalence⁴³

As Figure 26 shows, while progress in controlling many infectious diseases is being made in several countries (left panel), an equivalent number of previously unknown diseases are arising (central panel). Among these, we should take note of the avian influenza, antibiotic resistant bacteria and the bioterrorism threat. Finally, the three major killers—HIV, malaria and tuberculosis—are shown in the panel on the right. Indeed, the population of the developing world faces an enormous burden from infectious and parasitic diseases such as malaria, tuberculosis, visceral leishmaniasis and so on. Over the past few decades, drug development for these diseases has been largely neglected, leaving these countries with serious drug resistance and having to use old and, often, highly toxic drugs. The new funding and philosophical environment has the potential to transform this, and Europe has been at the forefront of the initiatives to develop new medicines for tropical infectious diseases.

⁴³ Rappuoli (2004), From Pasteur to genomics: progress and challenges in infectious diseases. *Nature Medicine* 10:1177-1185.

Europe has recently suffered health challenges and economic setbacks caused by infectious diseases. The bovine spongiform encephalopathy epidemic has shown how devastating infectious diseases can be for the European economy. The present risk of an influenza pandemic, which may cause hundreds of thousands, or even millions, of deaths in Europe, is another example of a likely emergency that we will need to face in the near future. Finally, it should be remembered that more than 15% of all cancers are directly caused by known infectious agents, and that others are likely to be caused by infectious agents that are as yet unknown. Preventing these infectious diseases will avoid millions of cases of cancer. Given the global nature of the infectious diseases problem, Europe does not have the option of sitting still, but must take a leadership role and drive the global agenda for the control of infectious diseases. Securing a world free of infectious diseases is the only way to protect European citizens from the challenge of infections.

Infectious diseases can be controlled in several ways: anti-infective therapy (antibacterial and antiviral agents) and vaccines, with diagnostics critical to both. Additionally, there are certain diseases for which immunotherapy and biopharmaceuticals, such as monoclonal antibodies or immunoglobulin play a critical role.

Vaccines. It is generally agreed that, when available, vaccines are the most effective way to control infectious diseases and to address the problem of multi-drug resistance. In fact, no resistance has ever been reported to vaccines, although in some cases the ecological niche left empty by very successful vaccines like pneumococcus and hepatitis B may be filled, in part, by other serotypes that the vaccine does not cover. Vaccines, a neglected field for several decades, have now gained in popularity thanks to new technologies that make safer products possible.

Antivirals. The past decade has seen a huge increase in the number of antiviral drugs. The driving force for this boom was pressure to contain the HIV pandemic, combined with an increased understanding of the molecular mechanisms of viral life-cycles. This enabled new targets for therapeutic intervention to be identified. There are a number of validated targets for novel antiviral compounds. These include the viral enzymes necessary for the replication of the viral genome, such as the retroviral reverse transcriptases; DNA- and RNA-dependent polymerases and helicases; the proteases necessary for the cleavage of viral polyproteins; and the influenza neuraminidase that is required for the release of the virus from the cell. The availability of validated target enzymes used for high-throughput screening of natural and combinatorial libraries is complemented by an ability to co-crystallise target proteins and their inhibitors, allowing structure-based drug design to be used for the generation and optimisation of more and better leads. Recently, the understanding of the molecular mechanisms of viral entry into host cells has allowed the development of a new class of antiviral compounds, the fusion inhibitors, one of which (enfuvirtide) is already in use for the treatment of AIDS.

Antibacterials. The golden era of antibiotics, which started after the Second World War and contributed to the conquest of many of the infectious diseases, is now over. The widespread use and abuse of antibiotics has created the emerging problem of antibiotic resistance. The new technologies that have thus far been instrumental in the discovery of antivirals, vaccines and diagnostics have been a total failure in the development of new antibiotics against resistant bacteria, despite substantial investment by the pharmaceutical industry. The continuous failures experienced in the field during the past decade have put off many large pharma companies, and during the past decade they have moved away from the field.

Diagnostics. The diagnosis of infectious diseases is essential for prevention, for therapy and for drug development, and it is needed for all applications. However, many infectious diseases are still diagnosed using slow and ineffective methods, if at all.

In conclusion, vaccines, antivirals, antibiotics and diagnostics are all important in the field of infectious diseases. Taking into consideration the fact that vaccines are dealt with elsewhere in the European agenda, the field that is clearly lagging behind and where the science is a real bottleneck is the one of antibiotics and antibiotic resistance, and the availability of appropriate diagnostic tools in the clinic. For this reason, a meeting of experts was convened to identify the bottlenecks in the development of novel antibacterial drugs, and how industry and academia can work together to move the field forward. The following pages report the output of this meeting.

3.7.1 Summary

Until recently, R&D efforts provided new medicines in time to treat bacteria that had become resistant to older antibiotics. That is no longer the case. The potential crisis at hand is the result of the low research success rate, the increasing prevalence of resistant bacteria, and the marked decrease in industry R&D, as well as government inaction. The problems being experienced in antibacterial drug discovery require a co-ordinated and multi-disciplinary response. An expert group representing key stakeholders, such as the pharmaceutical industry, academic institutions, patient representatives, regulators and representatives of

the European Commission identified and prioritised the following pre-clinical and clinical research bottlenecks.

3.7.1.1 Chemistry

Until recently, it was commonly believed that the low success rate in developing new antibiotics derived from the absence of novel targets. However, it was a great disappointment to find that the advent of genomics did not contribute at all to the discovery of novel antibiotics, in spite of the availability of hundreds of novel targets. This has been an eye-opener for the field, which suddenly realised that the problem was not in the targets but in the unique chemical properties required for molecules that need to cross a complex environment such as the bacterial wall, a problem that so far has been solved mostly by complex natural products.

Indeed, the failure of conventional chemistry to deliver novel antibiotics during the past three decades suggests that a new scientific approach is required, where academia and industry can work together. For example, we need to understand why natural products have been more successful than synthetic chemistry in developing new antibiotics. Absence of chemistry dedicated to molecules that have the properties of antibiotics is a major limitation to the development of new antibiotics. It is recommended that the interest of chemists from academia should be stimulated to find synthetic approaches towards antibiotic-like molecules, while maintaining active programs for novel natural products.

As chemistry is a major bottleneck in the development of new antibiotics, it is probable that much of the necessary work will lie outside the scope of IMI. IMI has deliberately been positioned to address enabling technologies rather than molecules in order to avoid moving into areas of direct competition between the pharma partners, and to avoid any possibility of IMI being seen as a direct subsidy of the industry's core business. It is possible that some applications that will be received in the field of antibiotic chemistry will qualify as enabling technologies and meet the criteria for pre-competitiveness as well as other topics in the SRA. However, the creation of natural product-like libraries, for example, rather than the development of underpinning methodologies, should perhaps be topics that could be funded through other modalities within FP7. Based on the input received at the infectious diseases workshop, the recommendation to develop new knowledge using unconventional chemistry approaches is supported, and basic research should be funded through instruments allowing competition between companies. IMI will ensure that all applications received will be checked for their appropriateness to the IMI vision, and redirected if necessary.

3.7.1.2 Diagnostics

The availability of rapid diagnostics, where results are available within 30 minutes without the need for culturing, would be an improvement with respect to recruitment of subjects into trials of treatment for antibiotic-resistant bacteria.

3.7.1.3 Alternative Approaches

In the long term, alternative strategies, for example molecules that interfere with pathogenesis, virulence or Type III secretion, may provide valuable compounds for dealing with bacterial infections.

3.7.1.4 Burden of Disease

Studies that define the burden of disease for antimicrobial resistance are urgently needed. The lack of quantitative outcome measures related to hospitalisation, morbidity and mortality costs for society is probably closely linked to the problem of lack of development of new drugs.

3.7.1.5 Regulatory

Innovative regulatory approaches can be supported by research into clinical trial design, for example by improvement of statistical methods. The potential use of PK/PD studies as the basis for extrapolation between indications should be investigated.

3.7.1.6 Meetings

As a quick win, international meetings should be organised, with the support of the European Commission, to share experiences of the drug discovery process between industry and academia, especially instances where promising molecules were not taken forward or results were surprisingly disappointing.

3.7.1.7 Diseases of the Developing World

Putting aside the lack of a market, there are two key bottlenecks to the discovery and development of medicines for diseases of the developing world:

- There are several targets, but there is a lack of resources to screen for hits on these targets, and subsequently develop these hits into lead and candidate compounds;
- The lack of capabilities and capacities to conduct clinical trials on investigational medicines in the developing world.

Through the IMI, as a focus for pre-competitive collaborative research, additional funding to address these bottlenecks should be sought from philanthropic sources. This funding could be used, for example, to develop targets and leads utilising pharmaceutical industry know-how and expertise. In addition, activities to educate and train clinical trials investigators in the developing world should be progressed.

3.7.2 Introduction

Therapeutically, antibacterials are unusual compared to most other classes of medicines: natural variation within bacterial populations and the eventual emergence of resistance render these agents less efficacious with continued use. New effective antibacterial agents and therapies will, therefore, be needed on a continuing basis. Unfortunately, this new generation of antibacterials has proved extremely difficult to discover and develop. The pipeline of new antibacterials is drying up as the industry has been leaving the field.

3.7.3 Present Status of the Disease Area

Antibacterial resistance has spread globally at an alarming rate, continues to increase, and presents a tremendous global health challenge. Multi-drug resistance has become commonplace in many disease-causing bacteria. Infections that were once easy to treat are becoming problematic and, in some cases, impossible to treat. In consequence, people are suffering severe illness, hospitalisation times are lengthened and mortality increases as a consequence. There is an acute need for novel antibacterials to combat this growing resistance.

A recent analysis published in *Clinical Infectious Diseases* (CID) found only five new antibiotics in the R&D pipeline out of more than 506 medicines in development. By comparison, pharmaceutical companies were developing 67 new drugs for cancer, 33 for inflammation/pain, 34 for metabolic/endocrine disorders, and 32 for pulmonary disease. The CID analysis found that FDA approvals of new antibiotics have declined by 56% during the past 20 years (1998-2002 versus 1983-1987). Since 1998, only 10 new antibiotics have been approved by FDA – only two of which are truly novel, with a new target of action and no cross-resistance with other antibiotics. A growing number of companies with track records in antibiotic R&D appear to be withdrawing from this market: Sanofi-Aventis, Abbott Laboratories, Bristol-Myers Squibb, Eli Lilly and Co., Procter & Gamble, Roche, and Wyeth.

3.7.4 Bottlenecks

In comparison with other therapeutic areas, animal models are quite predictive of clinical outcome in antibiotic R&D. This causes a high attrition rate in pre-clinical research, indicating that the major bottleneck is to bring valuable compounds into clinical trials. Therefore, five key priority areas have been identified by our expert group where there is a need for improvements, and possibilities for productive and successful partnerships.

3.7.4.1 Chemistry

Chemistry is usually not a bottleneck. Traditionally, it deals with molecules and scaffolds, which are of proprietary nature and therefore usually they are not part of the pre-competitive research agenda. In the case of antibiotics, however, it is clear that conventional chemistry approaches have not led to adequate success. In order to make progress, the science of chemistry for antibiotics has to be readdressed. It is a widely recognised fact that for antibiotics to penetrate the bacterial membrane, different chemical properties – often expressed in complex structures – are required in comparison to other drugs. Antibacterials are often derived from natural compounds, which are usually more complex than traditional small molecules and have been naturally selected to interact with bacteria. Furthermore, therapeutic doses of antibacterials are higher than in other indications. For hospital indications, intravenous formulation is essential, and consequently sufficiently high aqueous solubility is a must. Therefore, natural product-like libraries have to be available for successful screening efforts. Such libraries require the concerted effort of

natural product research and synthetic chemistry. In addition, they should be also available to academic institutions to use these molecules in their screening procedures.

3.7.4.2 Diagnostics

The recruitment of patients with antibiotic resistant bacteria is a great limit in performing clinical trials. Rapid diagnostics, taking about half an hour, without a need for culturing would improve the performance of clinical trials.

3.7.4.3 Alternative Approaches

In the long run, alternative approaches to treat infections may offer a valuable tool to cope with the emergence of antibiotic resistance. There is a need for new strategies, which include not just drugs but perhaps biologicals such as phages, enzymes and monoclonals to control bacterial infections. In addition, molecules that interfere with processes relevant to infection could lead to valuable therapies in certain diseases. The basic science for these processes has made substantial progress, while translational research to bring these discoveries to the clinic has been lagging behind. Multi-disciplinary research approaches are necessary to study combinations of different treatment strategies.

One of the recurrent themes of IMI is to close the gap between basic science and early clinical testing. IMI could, therefore, be one of the instruments to progress research in this area.

3.7.4.4 Burden of Disease

Studies that define the burden of disease for antimicrobial resistance are urgently needed. The lack of quantitative outcomes measures related to hospitalisation, morbidity and mortality costs for society is probably closely linked to the problem of the lack of development of new drugs.

3.7.4.5 Regulatory Approaches

Regulatory research into clinical trial design is a prerequisite for innovative regulatory approaches. Both the design of confirmatory clinical trials and the potential use of PK/PD data should be subject to research to optimise costly aspects of drug development. Since current regulation and guidelines from the EU give opportunity for less than comprehensive drug development in areas of medical need, the investigations proposed in this section could provide strategic directions.

3.7.4.6 Meetings

One major bottleneck is the fact that industry and academia do not talk as much as they should, and therefore have totally different ideas of what is needed. With the support of the European Commission, meetings should be organised where results and experiences are exchanged between industry and academia.

Beside these key priority areas, bottlenecks common to all other disease areas were identified:

- Because of the withdrawal of industry from the infectious disease area, a loss of knowledge has taken place. As a consequence, a systematic documentation and knowledge management process is necessary, and should be co-ordinated with the Knowledge Management pillar of IMI;
- Support for professional education and training is needed, and should be co-ordinated with the Education & Training pillar of IMI;
- Research is needed into predictive *in vitro* toxicology and safety tests;
- A harmonisation between EMEA and FDA would reduce requests for additional data. In the case of resistant bacteria, the lack of harmonisation could be an advantage for Europe, because EMEA accepts that the proof of efficacy against susceptible strains may be extrapolated to resistant strains if it is shown that the new mode of action covers the resistant strains;
- The acceptance of limited toxicology and surrogate clinical end-points by the regulatory authorities should facilitate non-clinical and clinical drug development. In acute bacterial infections, the use of surrogate markers is a challenge.

3.7.5 Resources

The total cost of these recommendations (€10 mn) are yearly estimates, and will be subject to further analysis as appropriate.

Activities	Cost per year (€mn)
Diagnostics	2
Alternative approaches	5
Burden of disease	2
Meetings	1
Total Infectious Diseases (€mn per year)	10

3.7.6 List of Contributors

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