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viewpoint

Future trends and challenges in pathogenomics

A Foresight study

Sven Pompe, Judith Simon, Peter M. Wiedemann & Christof Tannert

The difficult thing about the future is that it is so hard to predict. After the Second World War, the availability of vaccines and antibiotics and the successes of improved hygiene and public health policies led to such a dramatic fall in mortality that in 1969 the US Surgeon General claimed that "we can close the book on infectious diseases." In hindsight, his prediction of the future was utterly wrong—infectious diseases are back with a vengeance. Nearly 25% of the annual deaths worldwide are directly related to pathogens (Morens *et al*, 2004); multidrug-resistant tuberculosis and HIV/AIDS are on the rise worldwide; and *Staphylococcus* and *Enterococcus* strains in Western hospitals are becoming increasingly resistant to antibiotics. In addition, the rapid spread of new pathogens, such as the SARS (severe acute respiratory syndrome) and West Nile viruses, has shown the frailty of global public health, which is further affected by tourism and trade. Experts in security and public health also worry that publicly available scientific information and advanced genetic technologies could be misused to create weapons for bioterrorism.

To overcome these threats to human health, research on pathogenic microbes and the development of new diagnostics, vaccines and therapeutic strategies remains an important task at the beginning of the twenty-first century. It is in this context that we conducted our Foresight study, 'Future Trends and Challenges in Pathogenomics', as part of the EU-funded ERA-NET project PathoGenoMics, to provide an overview of current and future trends and challenges in the field of genomic research on pathogenic microorganisms. Clearly, a Foresight study is not a crystal ball to peek into the future, but it does allow the identification of important trends in science, as well as perceived gaps in research, and places them in the context of future challenges for public health.

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We pursued a dual approach, conducting both a survey with national and international experts in the field of pathogenomics and an extensive literature research. For the survey, we developed questionnaires and emailed them to 329 experts in research on human-pathogenic microorganisms and related fields. We received 65 replies and 40 completed questionnaires; an overall reply rate of 19.8 % and a return rate of 12.2 %, which are satisfactory (Comley, 1997; Totten, 2002; Sheehan, 2001). For the literature review, we used both academic search engines and direct access to scientific journals. The search was conducted using the following keywords and combinations of terms: pathogenomics, infectious disease, public health, bacteria, fungi, bioweapons, bioterrorism, human pathogen. From the 3,542 resulting hits, we selected 186 review articles, abstracts and press releases, and analysed them for further trends and challenges in research, threats to public health and current bottlenecks in commercial drug and vaccine development.

One clear trend is that, according to Weinstock (2000), the study of pathogenic microorganisms is undergoing major changes, triggered by the availability of whole genome sequences, new screening technologies, proteomics, comparative genomics and bioinformatics. These technologies, in combination with conventional methods of serology and the cultivation of strains, are becoming increasingly important for the classification and evolutionary analysis of microorganisms (Lederberg, 2000). Molecular fingerprinting, single-nucleotide polymorphism analyses and molecular epidemiology allow the study of the molecular processes during infection, including inflammation and host immune responses, and the function of cell-surface proteins and bacterial secretion systems. *In vivo* expression analyses and new bioimaging techniques to measure gene expression and protein transport now enable scientists to investigate the role of

individual genes during infection in real time (Doyle *et al*, 2004). All these technological advances and their application in microbiology contribute to a better understanding of host–microbe interactions and immune responses on the molecular and physiological level.

> There are also many aspects in the medical system itself that pose a threat to public health

According to Hatfull & Jacobs (2000) there has also been much progress in studying the genetics of infection and pathogenesis, as well as the communication between microorganisms. But much more needs to be known; Parsek & Fuqua (2004) highlight the importance of research on surface-associated pathogens, such as biofilms or planktonic cultures, which has so far been neglected. Such knowledge will help researchers to understand the complex interactions between microbes, whereas modelling of stress factors in the environment can elucidate interactions between microbes and host factors. In this context, the identification of virulence factors and secreted effectors that modulate the human immune system, such as exotoxins, small molecules or extracellular enzymes, is another important goal. To meet the increasing problem of antibiotic resistance, basic research should also concentrate on the detection and analysis of mobile pathogenic elements and resistance transfer through genomic islands (Hacker & Carniel, 2001). Another important development is the fusion of cell biology with microbiology, which will be of great importance for studying the *in situ* expression of genes (Roux *et al*, 2004). Denning and colleagues (2003) note recent advances in microscopy, such as multidimensional imaging, laser-scanning microscopy, epifluorescence microscopy and fluorescent light-based imaging, while stressing the importance of microscopy and histopathology. The need for better cooperation between basic and clinical research, particularly when collecting epidemiological data or devising new or more efficient therapies, is also a related concern. Here, nanobiotechnology will also gain importance for analytical approaches in chip technology, as will systems biology for the analysis of experimental data (see sidebar titled 'Important challenges for basic research').

In general, these new technologies are needed to understand more clearly the nature of infection, so as to devise new strategies against infectious organisms. An important goal will be the identification of specific target genes for DNA chips used in clinical diagnostics and for the development of new antibiotics and vaccines. According to Weinstock (2000), the discovery of such target genes will not be a major problem, rather the development of high-throughput methods to test the efficacy of new therapeutics. Furthermore, he forecasts that candidate genes will be identified and will be in commercial use long before scientists are able to understand fully the molecular mechanisms of infection and pathogenesis.

Another important research area, particularly in light of new and re-emerging diseases, concerns the dynamics of microbe populations and the effects of environmental factors on these populations. These include the natural reservoirs of pathogens and their geographical distributions, differentiation between generalists and specialists among human-pathogenic agents, and microbe–environment interactions (Cleaveland *et al*, 2001). According to Woolhouse and colleagues (2001), population biology will explain the evolutionary dynamics of pathogenic specialization and the stress responses of microbes. Woolhouse (2002) also emphasizes the importance of studying routes of pathogen transmission through vectors (such as arthropods) and direct (for example, physical contact) or indirect contact (such as through food). Ultimately, this epidemiological research will contribute to the early identification of novel and re-emerging diseases caused by bacteria, fungi and multi-resistant bacterial strains. In this context, the understanding of immune selection and the impact of vaccination and antibiotic intervention on microbial populations are future challenges for research (Grenfell *et al*, 2004). So far, such studies have mostly used pure bacterial cultures, which of course do not reflect reality. DeLong (2004) therefore stresses the need for microbial population genomics to characterize uncultivatable bacterial and fungal species, and the interactions between various microbial populations.

IMPORTANT CHALLENGES FOR BASIC RESEARCH

Methods
- Automated high-throughput methods (microarray technology)
- Genomics, transcriptomics, metabolomics and proteomics
- Improvement of serology, spectroscopy, chromatography and microscopy
- *In vivo* approaches (animal models, bioimaging, real-time PCR)
- Novel technologies (for example, microfluids, siRNA, multiplex assays)
- Whole-genome sequencing and bioinformatics

Understanding ways of infection
- Comparative and functional genomics
- Factors of virulence and resistance (mobile pathogenic elements)
- Host switching and antigen diversity (genome plasticity)
- Immune response (defensins, inflammation)
- Role of surface proteins

Understanding pathogenesis
- Communication between species (biofilm, intestinal linings)
- Effects of DNA methylation and identification of conserved DNA regions
- Factors and mechanisms of pathogenicity (secretion systems)
- Host–microbe interaction
- In-host competition
- SNP analysis and molecular epidemiology

Diagnostics
- Chronic infections and chronic inflammation
- Development of specific antibodies
- Identification and classification of human-pathogenic bacteria and fungi
- Identification of toxins, small molecules and allergenic compounds
- Specific DNA arrays to identify species in polymicrobial cultures

Clinical importance
- Development of new diagnostic and therapeutic agents
- Evaluation of effects of chemotherapeutics (such as antibiotics)
- Creation and extension of databases
- Link between diagnostics and therapy (individualized medicine)
- Rapid, sensitive, cheap and standardized diagnostics
- Validation of diagnostics and molecular methods
- Target identification (new vaccines, antimicrobial targets)

A literature review by Cleaveland and colleagues (2001) identified 1,415 species of organisms known to be pathogenic to humans, including 538 bacteria and rickettsia and 307 fungi, and according to Rappuoli (2004), "dozens of new infectious diseases are expected to emerge in the coming decade." Viruses, particularly RNA viruses, seem to emerge most rapidly. In this context, Lederberg (2000) stresses the need to understand evolutionary strategies of pathogenic microbes that facilitate their re-emergence and the emergence of new, unknown pathogens due to their rapid reproduction and enormous potential for genetic variation. Mutation, genetic variation, recombination and horizontal gene transfer of pathogenic islands are keys to the evolution of pathogens (Hacker & Carniel, 2001), which still have to be understood.

Of course, these trends and developments in basic research have to be put into context with current and future challenges for public health (see sidebar titled 'Challenges for interdisciplinary research on human-pathogenic microorganisms'). These encompass demographic changes in ageing populations, and the effects of globalization, population growth and migration—whose social, ecological and economic factors and their interplay are still poorly understood (Pang & Guindon, 2004). Most experts in our survey identified HIV and the spread of multidrug-resistant tuberculosis in Eastern Europe as major problems for public health—some experts estimate that about one-third of the world is infected with *Mycobacterium tuberculosis* (Fauci *et al*, 2005). Other problems mentioned in the expert survey included malaria, SARS, monkey pox and sexually transmitted, respiratory and diarrhoeal diseases. The greatest challenge is what Chan and colleagues (1999) describe as the substantial differences between developed and developing countries with respect to the burden of infectious diseases. The authors estimate that about 40% of the population of the developing world are infected with at least one pathogenic organism compared with only 2% in the developed world.

In many developing countries, socioeconomic factors, such as poverty, crowding and poor hygiene, represent major risks for the transmission of infectious diseases and accordingly for global public health (Wilson, 1995). Man-made ecological changes, such as deforestation and pollution, and the effects of land use or water storage, also influence the biological diversity and distribution of parasitic and infectious diseases (Guernier *et al*, 2004). Chan and colleagues (1999) estimate that global climatic conditions in particular are the most important determinants for pathogen distribution, but so far few studies of this phenomenon are available. Irrespective of global climatic conditions, simple weather changes influence the emergence of infectious diseases and their vectors (Sutherst, 2004), for example the El Niño phenomenon in the Southern Pacific, or floods that cause outbreaks of malaria or waterborne disease such as cholera (Morens *et al*, 2004). Altekruse and colleagues (1997) therefore identify food-borne and water-borne diseases as major threats to public health. Morens and colleagues (2004) also describe an increase in zoonotic and vector-borne diseases due to environmental factors and recent man-made interventions. This trend is further accelerated by antibiotic overuse in agriculture, which may increase the proliferation of bacterial and fungal diseases.

The rapid spread of SARS in 2003 from China to the rest of the world showed that infectious diseases can no longer be seen as problems of developing countries, now that global trade and tourism enable the rapid distribution of infectious organisms. Mangili & Gendreau (2005) thus predict an increase in airborne, food-borne, vector-borne and zoonotic diseases caused by the increasing ease and affordability of air travel. Cleaveland and colleagues (2001) therefore stress human behaviour as the main factor for the spread of infectious diseases.

There are also many aspects in the medical system itself that pose a threat to public health. The most important problem is the lack of hygiene in hospitals and the resulting increase of so-called nosocomial, or hospital-acquired, diseases (Burke, 2003). New technologies, such as transplantation medicine, immunosuppressive therapies and prosthetic devices, have also raised the prevalence of chronic or polymicrobial infections (Donlan & Costerton, 2002). Their increasing number (Brogden *et al*, 2005), and the deaths caused by mycoses (McNeil *et al*, 2001), should be taken very seriously. Further problems in the public-health system itself include a decreasing number of effective antibiotics, insufficient guidelines and surveillance methods for antibiotic resistance, and a general decrease in research on anti-infectives (Denning *et al*, 2003). Lederberg (2000) criticizes especially the misuse of antibiotics and the popularity of antibacterial products, which further contribute to the spread of multi-drug antimicrobial resistance (Goossens *et al*, 2005), particularly among *Mycobacterium tuberculosis* and *Staphylococcus aureus*. Methicillin-resistant *S. aureus*, vancomycin-resistant *Enterococci* and drug-resistant Gram-negative bacteria such as *Klebsiella* and *Enterobacter* spp. have already become major problems in many hospital settings (Levy, 2001; Kipp *et al*, 2004), which has led Cars & Nordberg (2004) to speculate about the possibility of a post-antibiotic era.

CHALLENGES FOR INTERDISCIPLINARY RESEARCH ON HUMAN-PATHOGENIC MICROORGANISMS

Epidemiology
- Commensal bacterial flora and opportunistic infections
- Lifestyle of humans
- Routes of transmission
- Spread of pathogens
- Transmission bottlenecks
- Vector analysis

Ecology and environment
- Ecological niches and natural reservoirs
- Geographical distribution
- Host range
- Microbe–environment interaction

Evolution and taxonomy
- Identification and classification of clinical species
- Intra-host evolution
- Phylogenetic derivation

Population dynamics and selection pressure
- Cultivation-independent genome analyses
- Dynamics of antibiotic resistance
- Immune selection
- Impact of vaccination and antibiotic intervention
- Interaction between clonal communities
- Understanding mechanisms of generalists and specialists
- Understanding microbial diversity

Finally, the potential misuse of scientific information and genetic engineering for bioterrorism and biowarfare is worrying public health and security experts (May & Silverman, 2003). It remains to be seen whether freely available information on genetics and genomic research is sufficient for the development of biological weapons (Rappert, 2003). The World Health Organization (Geneva, Switzerland; WHO, 2004) accordingly addresses the need for action plans to counteract potential bioterrorist attacks; indeed, Woodall (2005) criticizes that there is no such international body to investigate the sudden emergence of infectious diseases.

Predominantly, what is needed to prevent re-emerging infectious diseases from turning into an epidemic or pandemic is a global surveillance network and vaccination strategy (Mabey *et al*, 2004), especially for childhood immunization (Breiman, 2001). Both developed and developing countries must therefore increase their participation rates in vaccination programmes by improving health education and public policy. In addition to these general measures, Cangelosi and colleagues (2005) recommend more effective monitoring of pathogens in the environment, which would allow researchers to understand their incidence and persistence. Regarding novel infectious diseases, Guillemot and colleagues (2001) address the identification of natural sources and zoonotic reservoirs as the basis of preventing or controlling such outbreaks. According to Enserink (2004), better coordination between labs and public health organizations by global alert networks such as the Global Outbreak Alert and Response Network (GOARN) would lead to earlier identification of novel pathogens.

Education, sanitation and water supply in developing countries must be improved to counteract the increasing internationalization of health risks brought about by infectious disease (Pang & Guindon, 2004). The US National Institute of Allergy and Infectious Diseases (Bethesda, MD, USA; NIAID, 1999) stresses the need for food safety, animal-control programmes and clean water and sewers, because many gastrointestinal pathogens are transmitted through water. Moreover, it is essential to develop comparative risk-assessment strategies to set national and global health priorities (Murray *et al*, 2003). Forecasting systems, computer-modelling techniques and disease epidemiology are other measures to assess the impact of disease outbreaks (Hampton, 2004).

From the perspective of basic research, the identification of factors leading to chronic and secondary diseases and the evolution of antibiotic resistance are most fundamental challenges (Cassell & Mekalanos, 2001). On a more practical level, rapid, sensitive and robust diagnostic tools are needed in addition to improved disease-management strategies and infrastructures as part of an early response strategy to tackle infectious diseases. This does not, however, replace the imperative to develop new antibiotics and make better use of existing ones. According to Bonhoeffer and colleagues (1997), the alternation of different antibiotics, the evaluation of single and multiple antibiotic therapies and the rational use of antibiotics in general are necessary to reduce bacterial resistance.

Education, sanitation and water supply in developing countries must be improved to counteract the increasing internationalization of health risks brought about by infectious disease

Although the development of new antibiotics and vaccines remains an important public-health imperative, pharmaceutical companies have little interest in this research area. The European Federation of Pharmaceutical Industries and Associations (EFPIA; Brussels, Belgium) notes that the European industry has been undergoing radical changes during the past decade, triggered by the increasing costs for R&D and marketing (EFPIA, 2003). This has led to a rising number of company mergers and takeovers and a greater focus on drugs to treat chronic and abundant diseases in mainly affluent populations. Because the development of new antibiotics and vaccines is a long and costly process and will ultimately find only a limited market (Williams & Heymann, 1998), research in this area is not very attractive for many pharmaceutical companies. Spellberg and colleagues (2004) stress that out of 506 drugs that were in late-stage clinical testing in 2004, only six were new antibacterials. Similarly, there is only a small number of biotech companies that develop vaccines or antifungal drugs (Bröker, 2003; Bonn, 1997).

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Nevertheless, there are promising and commercially attractive areas of research on anti-infectives and vaccines. Sheridan (2005), for instance, describes innovative approaches that use recombinant DNA techniques to develop new vaccines. Combination vaccines to prevent complex syndromes might be useful, along with new methods of vaccine application and antibody preparation, which are often faster and cheaper than vaccine development itself (Breiman, 2001; Casadevall *et al*, 2004). Bröker (2003) also forecasts a rising market for products on the basis of reverse vaccinology, genetic vaccination and recombinant antigens, and for conjugate and therapeutic vaccines. According to EFPIA (2003), outsourcing such projects by subcontracting to smaller companies, especially in the area of pre-clinical research or toxicological analysis, could render antibiotic and vaccine development sufficiently beneficial for both the pharmaceutical and biotech industries. Finally, Cockerill & Smith (2004) expect a greater market for genomic-based diagnostics and screening technologies.

However, an important step towards a better fit between industry's interests and public health needs would be more cooperation between public-health authorities, clinicians, affected communities and pharmaceutical companies. Hence, governmental support such as the reduction of administrative barriers (EFPIA, 2004), public–private partnerships as advocated by organizations such as the WHO (Ridley, 2003), partnerships with small and medium biotech companies, and new business models to encourage the development of

new drugs (Nathan, 2004), will be needed to meet the threat of infectious diseases.

We are nowhere near being able to "close the book on infectious diseases." Viruses, parasites and bacteria still claim millions of lives each year in the developing world and even affluent nations have no reason to remain complacent. The effects of globalization, namely trade and travel, as well as domestic problems, such as the increase in antibiotic resistance, mean that infectious diseases will remain a major problem for the developed world as well. Nevertheless, the recent developments in microbiology, and the use of new technologies provided through genomics, proteomics and bioinformatics, hold great promise for understanding microbial evolution and the nature of infectious processes. This knowledge will certainly pave the way for new therapeutic drugs, vaccines and treatments. At the same time, public-health authorities and the pharmaceutical and biotech industries must find new ways to encourage the development of new therapeutics. First and foremost, however, the problem itself requires a greater awareness beyond scientists and public-health experts—it is ultimately up to society and politicians to support much needed measures, such as global surveillance and more research and development, to counter the threat posed by infectious diseases.

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Sven Pompe (top left), Judith Simon and Peter M. Wiedemann (bottom left) are at the Research Center Jülich, Germany.
Christof Tannert is at the Max Delbrück Center for Molecular Medicine in Berlin, Germany.
E-mail: pompe@mdc-berlin.de

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