Infectious Diseases: preparing for the future

Introduction to the Science Reviews

This document introduces ten reviews of science which have been commissioned within the Foresight project: Infectious Diseases: preparing for the future. It explains why the topics were chosen, and how the reviews have been used in the project.

A short overview of each Science Review accompanies this introduction, and the full reviews are provided on the CD of the complete project reports. All of these documents may also be downloaded from www.foresight.gov.uk.

Selection of the topics for the reviews

The ten Science Reviews explore the scientific and technological foundation on which future advances in the detection, identification and monitoring of infectious diseases may be built. Each addresses an area of basic or applied research relevant to the detection, identification and monitoring of diseases, and assesses current knowledge and the likely direction of this research over the next 20 years. The purpose of each review is not to predict technology for specific future detection, identification and monitoring systems, but to identify general trends in research that will enable new systems to be developed.

The selection of the ten topics followed consultations with around 40 experts and project stakeholders, through workshops and meetings. The attendees considered the potential technological needs for future detection, identification and monitoring systems and, as a result, the following subjects were identified:

- Intelligent sensor networks
- Data mining and fusion
- Non-invasive scanning and screening
- Genomics and bioinformatics
- Biosensors/biomarkers
- Interrogation of natural signals/biomarkers
- Predictive and real-time epidemiological modelling
- Earth observation
- Host genetics and engineering
- Immunological techniques/responses

The ten Science Reviews are provided in full in project reports S3–S12.

Combining the ten areas of science in future detection, identification and monitoring systems

The ten areas of science have an intentional degree of association. Taken together, they span a virtual detection, identification and monitoring process. For example, reviews on genomic, immunological and natural biomarkers may identify kinds of biological information that may be useful in future to indicate the presence and identity of disease agents or of a disease at an early stage of infection.

Alternatively, they may show the susceptibility of populations to a disease. Advances in biosensors and intelligent networks may allow the incorporation of this understanding into devices for disease detection or monitoring, while advances in data mining, earth observation and modelling may allow the output of such devices to indicate new disease outbreaks and project their impact.

From such associations arose a portfolio of technological ideas that were input into a further workshop at which detection, identification and monitoring technology users identified their future needs and aspirations. Matching their needs with possible technologies led to the clustering into four distinct classes of user requirements – within the project, these are called 'user challenges'.

They are:

1 *Advanced data collection, fusion and processing techniques*: these would be at the forefront in spotting the emergence of new diseases, and crucial to tracking the spread of known diseases.

2 *Genomics and post-genomics to rapidly characterise new diseases*: this includes using the host's physiological response, as well as genomic characterisation of the pathogen.

3 *Point-of-care hand-held diagnostic devices – possibly communicating with central data collection systems*: opportunities were seen for the rapid development and introduction of portable genomic sampling devices into all aspects of human, animal and plant disease monitoring systems. The adaptation of such methods to developing-country situations was also foreseen through the development of cheap, 'smart swabs' for rapid diagnosis under rural conditions.

4 *Fast-throughput screening devices at ports and airports*: this includes the non-invasive detection of disease by electromagnetic signals or scanning, or by detecting volatile mixtures associated with diseases. To achieve this, biosensors might use future knowledge of, or actual living components of, animal chemo-sensory systems.

UC1: Data mining and data fusion

- Epidemiological modelling
- Earth observation
- Intelligent sensor networks
- Data mining and data fusion

UC2: Genomics and post-genomics to characterise new diseases

- Biomarkers
- Host genetics
- Immunological responses
- Genomics
- Interrogation of natural signals

UC3: Hand-held diagnostic devices

- Biosensors
- Host genetics
- Immunological responses
- Genomics
- Interrogation of natural signals

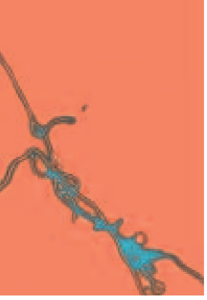
UC4: Fast-throughput screening at ports and airports

- Biosensors
- Non-invasive scanning and screening
- Interrogation of natural signals/biomarkers

Figure 1: The four user challenges, and examples of Science Reviews that have informed their analysis

The detailed consideration of these user challenges was a central part of the project, and Figure 1 shows the principle Science Reviews that informed each of the four. (An overview of the analysis of the user challenges may be found in project report D1, and a more detailed account in D2.)

The development of the Science Reviews also identified important issues relating to social acceptability, and the adoption of new technology within local systems of culture and governance. Such issues were investigated in separate studies (D4.1–D4.3, D5 and D7) and were used to inform the analysis of the user challenges.



Foresight project: Infectious Diseases: preparing for the future

Science Review Summary: Intelligent sensor networks (S3)

Smart engineering

Intelligent sensors are innovative devices for capturing reliable information that can deliver early warning of infection outbreaks, support decision making and help provide rapid and co-ordinated responses to potential threats. They sit at the front end of a pipeline of data capture, information processing, real-time monitoring and information management. Advanced new techniques such as ‘lab on a chip’ promise to give these sensors powerful capabilities in terms of detection, while miniaturisation of hardware brings lower power consumption, robustness and affordability. Properly configured and deployed, they can revolutionise our capacity to cope with the vagaries and unexpected eventualities of disease outbreak and spread.

Foresight asked a leading expert in the field of intelligent sensor networks, David de Roure, from the University of Southampton, to explore the potential of this technology in disease identification, detection, monitoring and control.

Intelligent sensing

Sensors are devices that capture information about the natural world. They can, for example, monitor, in a non-intrusive manner, features of natural wildlife or air pollution in cities. *Smart* sensors go one step further. They don’t just gather and transmit data but can learn, adapt, self-configure, interpret, fuse and validate incoming information. To do this, they have some inbuilt processing capability.

Most importantly, intelligent sensor networks have communication between sensors. The Floodnet system, for example, with its array of sensors for measuring the water levels of a river in Essex, has an adaptive sampling approach: if one sensor fails, the others automatically collaborate to adjust their sampling rates in line with prevailing data collection priorities.

In the context of the detection and identification of infectious diseases, an intelligent sensor network would offer real-time monitoring of data that could be of relevance to infectious diseases and feed these into an interconnected computer system that would process, mine and manage these inputs. Collection devices may be hand-held and portable, such as a mobile phone or personal digital assistant (PDA) equipped with a sensor, or a laboratory-scale instrument. They may even be incorporated into ‘smart buildings’.

So much functionality may be built into devices that they can detect corrupt data, self-test and respond to changing conditions.

Communications

Many kinds of transmission methods are possible. There can be wireless links between mobile and static devices using Bluetooth or ZigBee for shorter ranges and 3G for a wider infrastructure. Passive techniques, too, are possible whereby information is collected from a device using induction loops, as with medical implants and radio frequency identification (RFID) tags.

Data transmission is costly in terms of energy consumption, but current research on energy-conserving techniques is well advanced.

Information can be stored and forwarded, like email, or live, as with a phone call. Networks are increasingly able to make intelligent decisions about routing content to appropriate receiving points.

State of play

Currently, novel sensor technologies are being integrated with legacy systems in hybrid, heterogeneous networks. In the future, smaller, faster, cheaper devices with enhanced functionality will take over from older, less responsive equipment.

At the same time, engineers and others will be addressing the important issues of analysis, security, confidentiality and authenticity of the vast amounts of data being gathered and interpreted.

Some of the future improvements now envisaged include:

- smaller-scale, lower-cost devices, with many more being deployed, improving overall reliability
- interoperability, generating a wide range of information and using and reusing it for both anticipated and unanticipated tasks
- increasingly, tomorrow's sensors will have autonomy, being able to self-configure and calibrate, reconfigure their activities and adapt to changing needs
- security, dependability, trust and reliable information provenance must all be an integral part of any system
- systems on a chip will come from advances in silicon technology whereby entire systems will be fabricated on a single chip – a step forward from traditional application-specific printed circuits; self-powered microsystems – where traditional batteries are not always appropriate – are also coming on stream
- user-friendliness and ease of maintenance are key to making intelligent sensor networks acceptable to potential users.

Provided the obvious hurdles of robustness in harsh environments and affordability for developing countries are overcome, intelligent sensor networks should become a key weapon in detecting, monitoring and controlling infections in the future.

This Research Brief is based on the Research Review written by Professor David de Roure, IT Innovation Centre, Southampton, for the Foresight project: Infectious Diseases: preparing for the future. Editor: Peter Evans.

The full version of this review is at www.foresight.gov.uk

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Science Review Summary: Data mining and fusion (S4)

Revealing information riches

Data – the raw material from which information and knowledge are drawn – is central to effective disease detection, identification and control. It can come from a variety of sources, including biosensors, satellite observation, Web content and hospital records. It can range from the broad scale – such as the remote tracking of crop infections – down to the detailed function of infected cells and their genes.

To make sense of this mountain of input, we need sophisticated tools for mining data from heterogeneous and distributed sources and fusing it all into meaningful information that we can use for decision- and policy-making.

Foresight asked Colin Upstill and his team at the University of Southampton IT Innovation Centre to review the state of the art in data mining and fusion techniques and to consider their implications for the detection and identification of infectious diseases.

Data and disease

There is a considerable volume of research under way on sophisticated data mining and fusion tools. This involves both information and communication technologies as well as advanced theoretical approaches to collecting and making sense of data from multiple, heterogeneous sources.

E-science, pervasive and Grid computing, the Semantic Web, autonomic systems and adaptive, self-organising infrastructures are just a handful of the exciting new technologies being studied.

The detection and identification of infectious diseases in plants, humans and animals will need, if it is to be effective, to draw on such developments. One example is the local data generated by sensors designed to collect vital indicators of infections and their pathogens. A feedback system needs to be put in place so that the sensor data network will be able, in real time, to be modified and adapted to changing conditions, or indeed to adapt itself automatically.

What and how

Exactly what data to collect, how to combine more than one source and then analyse it meaningfully are also key issues that pose real challenges for the new technology.

Data not directly connected with infectious disease, such as weather reports and travel records, may be extremely useful. Rapidly spreading, 'disruptive' technologies, such as Blogs and Wikis, along with new collaborative means for personal communication will also be important sources.

To combine data, we need to handle incompatibilities, ranging from simple mismatches such as different date representations to more subtle matters of semantics and interpretation.

Experience from other domains can point the way. Lessons can be learned, for example, from systems using data fusion to help environmental scientists keep track of water quality, and from methods for mining and viewing massive amounts of data in order to detect money laundering or telephone fraud.

Trust security and privacy

The more data there is, the more we need to build in mechanisms for ensuring that it is reliable, coming from a trusted source.

Any information technology for disease detection and identification must have inbuilt validity and accuracy checks to ensure that what data is collected can confidently be relied on.

At the same time, there is also a powerful need for privacy and security, especially when data is arriving in an unstructured fashion from a wide variety of sources. Flexible, but highly managed, control systems need to be in place to regulate who can access data and exactly how they should use it.

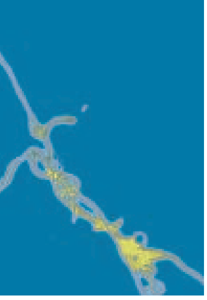
Agile collaboration

Any particular 'detection and identification of infectious diseases' scenario – whether it is the geographical spread of an insect-borne animal disease or the emergence of a new plant pathogen – will draw on the collaborative efforts of a team of data handling experts and analysts. This means creating the appropriate management structures, supported by the right tools and technologies.

In addition, we must also bear in mind that the data that needs to be captured for disease detection – and how this is analysed – will change over time as, for example, an infection spreads. As we move from the initial disease monitoring phase to the outbreak of an epidemic, data mining and fusion methods need to be far more agile than today's relatively static approaches. Everything changes: geographical locations, sensor configurations, data types and volumes. So, too, must the technological framework for capturing and using this kaleidoscope of data, information and knowledge.

This Research Brief is based on the Research Review written by Dr Colin Upstil, Dr Matthew Addis, Dr Freddy Choi, Dr Steve Taylor, and Dr Rowland Watkins, IT Innovation Centre, Southampton, for the Foresight project: Infectious Diseases: preparing for the future. Editor: Peter Evans.

The full version of this review is at www.foresight.gov.uk



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Science Review Summary: Non-invasive scanning and screening (S5)

New ways to monitor infection

It should be possible to borrow, for diagnosing and screening for disease, some of the advanced imaging techniques currently used in a medical setting. Humans, animals, and perhaps plants too, may be the beneficiaries of these non-invasive technologies. Whereas medical screening for, say, breast cancer using X-ray mammography only benefits the individual patient, screening for infectious diseases may help reduce the risks of spread to a whole community.

Foresight asked Peter Wells, of Cardiff University, to consider imaging techniques, present and future, that could be applied to scanning and screening for infectious diseases. He was also asked to consider their economic and safety implications.

Current imaging techniques

Among the various scanning technologies used in medicine, X-ray imaging is today still the most common. It may show internal structures on photographic film or in digital format. In the context of infectious diseases, it can also be used to detect bacterial, parasitic and viral infections in the thorax.

Ultrasound images the body by using reflected or scattered sound waves. To date, it has been used for investigating bacterial infections in the thorax, inflammation and parasitic invasion of the abdomen and joint infections. In the future, one could envisage a hand-held ultrasonic scanner that would be cheap enough to be widely deployed by medical personnel. It could be used in the context of routine examinations for detecting and identifying a number of infections, both in humans and small animals.

Radionuclide scanning (including PET scanning) gives a 2D image of the distribution of a radioactive tracer. Bacterial infections of the thorax and joint infections are currently detectable using this technology.

X-ray computed tomography – the CT scan – extends the diagnostic uses of X-rays and it also provides information on joint and spinal infections.

The MRI scanner offers insights into diseases of the head and neck, thorax, abdomen and the musculoskeletal system, ranging from bacterial, parasitic and viral infections to infective inflammation and prion disease.

One other technology that deserves a mention is thermography. This produces images from the infrared radiation emitted by the bodily structure being examined. At the level of the skin, it can detect fever such as patients experienced during the SARS outbreak, but currently not with sufficient specificity to be of practical value.

Today's scanning technologies used for detecting and identifying infections in humans can also be applied in animals. In plants that generate heat, it would also be possible remotely to detect infection using thermography.

Visions for the future

A number of novel imaging techniques are currently the subject of research. These include optical, optical tomography, microwave, teraHertz, thermo-acoustic, electrical impedance tomography, magnetic field and microscanning. In short, a vast range of the electromagnetic spectrum is now being explored, suggesting that there is potential for extending existing detection and identification technologies or inventing new ones.

However, there are some important considerations surrounding future developments in scanning:

- Where radiation is involved, the benefits derived must outweigh any real or hypothetical costs in terms of safety. The radiation exposure must be the minimum necessary to acquire the required information.
- In a situation in which remote or semi-remote screening was required, the best approach would probably be based on thermography, microwave, or teraHertz imaging.
- There are practical constraints on various forms of imaging. It would be unrealistic to use X-rays, for example, to try to detect tuberculosis in passengers walking through airports.
- The newer techniques are as yet untried and their applicability in disease identification and detection is far from clear.
- There are ethical questions surrounding the unobtrusive screening of individuals without their consent.
- Unskilled personnel need to be trained sufficiently to interpret data from many kinds of imaging systems. We are a long way off replacing human observers with automated systems.

This Research Brief is based on the Research Review written by Professor P.N.T. Wells, University of Cardiff, for the Foresight project: Infectious Diseases: preparing for the future. Editor: Peter Evans.

The full version of this review is at www.foresight.gov.uk

Foresight project: Infectious Diseases: preparing for the future

Science Review Summary: Genomics and bioinformatics (S6)

Entering the genome

Enormous strides are being taken in genomics – technologies for accessing and interrogating the whole of a living organism's genetic information. We are acquiring powerful tools for rapidly detecting and identifying the micro-organisms that cause disease and determining the susceptibility of their human, animal and plant hosts.

Not only does this developing technology give us the means to detect and identify known organisms or resistant strains, it will also enable us to identify those novel or unexpected pathogens that can erupt and cause disease.

Foresight asked Julian Parkhill and Nicholas Thomson, from the renowned Sanger Institute in Cambridge, to asses the impact of the genomics revolution on the detection and identification of infectious diseases, including its implications for monitoring and control strategies.

Technologies present and future

Genomics draws on several key technologies. *Sequencing* is the process of determining the precise chemical structure of a given piece of DNA. It is like reading out the letters of the coded message of a gene. The drive to expand and accelerate this technology currently comes from the medical field where there is a need to rapidly and cheaply identify small individual differences for personalised treatments.

But this same technology can also be used for detecting and identifying microbial agents of disease. They, too, have genetic code that acts as a fingerprint of their identity.

Within the next 3–5 years, it will be possible to routinely sequence a whole bacterial genome overnight – a matter of millions of individual elements – on just one machine, as opposed to the tens of machines typically used today. And costs are dropping dramatically all the time. The off-the-shelf $1,000 bacterial genome machine is near at hand, and the human genome equivalent is not far off. These are startling innovations with widespread applications.

Another important tool is the use of *microarrays* to identify known DNA sequences. Current arrays are low density and low accuracy. But new technological approaches coming onto the market, though as yet not widely available, use microengineering to greatly improve performance.

Alongside these developments, there are also novel ways of improving current methods for detecting tiny genetic differences between individual organisms – so-called single nucleotide polymorphisms (SNPs/'Snips'). Also, there are improvements afoot in the established technique of DNA amplification – a form of genetic photocopying called polymerase chain reaction (PCR) – which will make this easier and more accurate to use.

Once acquired, genetic information from an organism's DNA needs to be stored, accessed and analysed using sophisticated mathematical tools. Handling the anticipated large increases in the breadth of and throughout DNA sequences draws on the science of *bioinformatics*. Here again, current tools are being expanded and extended to cope with this growing demand.

Applying the new tools

Disease-causing organisms – pathogens – can be detected and identified using these novel technologies in several ways.

In situ, high-density microarrays enable us to rapidly home in on known pathogens and resistant strains. Novel or unexpected disease agents will yield to very high-throughput sequencing technologies, while an increase in sequence data increases our knowledge of microbial variation and spread. The outcome should be the early detection of genetic changes indicating the emergence of novel infections.

On the bioinformatics front, we need to build up DNA reference collections and services, both for epidemiological and evolutionary purposes. Large-scale microbial genome sequencing will help us identify the evolutionary pathways followed by recently evolved human pathogens.

Drug resistance and the mechanisms by which micro-organisms adapt to their environment will also be increasingly illuminated, ultimately leading to methods for predicting potential outbreak strains.

This Research Brief is based on the Research Review written by Dr Julian Parkhill and Nicholas Thomson, The Sanger Institute, for the Foresight project: Infectious Diseases: preparing for the future. Editor: Peter Evans.

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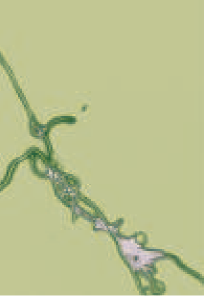

Foresight project: Infectious Diseases: preparing for the future

Science Review Summary: Biosensors and biomarkers (S7)

Supersensitive sensing

Biosensors are, basically, devices for converting information from the living world into an electrical or electronic signal. Our eyes and noses are biosensors. They convert light or scents into electrical information that is interpreted by the brain. What synthetic eyes, ears and noses can we make to eavesdrop on the world of infectious diseases?

We are entering a new era in biosensor technology: ‘smart’ biosensors that not only capture signals but also interrogate, process and, to some extent, interpret them. These portable, low-power, ultra-fast microsystems are futuristic, but they potentially offer us smart, powerful sensing that would be robust in non-ideal conditions, useful as early warning systems and applicable in locations where fully trained operators are not available.

Foresight asked two leading experts in the field of advanced biosensing, Christofer Toumazou and Tony Cass of Imperial College, to report on the development and deployment of biosensors for infectious diseases. Their findings point the way to some futuristic tools for detection and monitoring.

Linking to disease

Diseases often advertise themselves by way of a biological marker. An obvious example in humans and animals is raised temperature. Here, the relevant sensor is a thermometer, which, in a very non-specific way indicates that something is wrong. The microbes that cause diseases and the hosts that they infect also generate biomarkers – often proteins – which act as a more selective indicator of the presence of a particular infection.

Sensors that pick up on some chemical or physical marker could therefore be of great value in detecting and diagnosing disease. In the case of cattle, it is already possible to use a sensor that goes beyond mere temperature and responds to different proteins indicative of different diseases.

The core of such a sensor is a recognition molecule that responds specifically to another molecule characteristic of a particular disease. In the future, sensors may well be able to react to a wide range of molecules on the surfaces of cells – surface antigens – with the specificity of a key to a lock.

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Technological trends

The truly smart biosensor needs not just to recognise a particular disease in human, animal or plant. It should also be able to manipulate incoming data before transmitting it to some central point for further analysis and action.

The essence of local intelligence is smallness of size coupled with availability of adequate power. At Imperial College, London, Chris Toumazou and Tony Cass at the Institute of Biomedical Engineering are envisaging the 'BioSignal Processing Engine' (BSP). This is a nanoscale device – 100 thousand millionths of a metre in size – that uses the minuscule 'leakage' currents from traditional silicon semiconductors to analyse signals.

The BSP would combine real-time chemistry, microminiaturisation and communications technology in one device. It would automatically be able to perform analytical chemistry in a microfluidic 'lab on a chip', for example, on a blood sample, rapidly processing the data from this micro-lab and sending it to some central computer for further action.

Considerable progress has been made on the sensing end of these smart devices. Recently, an electronic 'nose' for sniffing out *Mycobacterium bovis* infections in badgers and cattle was piloted. There has also been a trial of an assay for detecting surface antigens of the bacterium *E. coli*, using antibodies that are specific to each antigen.

What is now needed is an integration of such functions using appropriate, robust technologies along the lines of the BioSignal Processing Engine. The range of applications is truly enormous.

This Research Brief is based on the Research Review written by Professor Christofer Toumazou and Professor Tony Cass, Imperial College, London for the Foresight project: Infectious Diseases: preparing for the future. Editor: Peter Evans.

The full version of this review is at www.foresight.gov.uk

Foresight project: Infectious Diseases: preparing for the future

Science Review Summary: Interrogation of signals and biomarkers (S8)

Borrowing from nature

Infectious diseases of plants, animals and humans are caused by organisms such as bacteria and viruses that might be detected and identified by means of natural signals emitted by the host. Just as a burglar alarm conveys the presence of an intruder, so it is with infected plants and animals. Here, though, the signals are not sound waves, but chemicals.

When, for example, a plant is infected by a pathogen, it sends out volatile chemicals – its ‘stress response’ – that indicate not just the general nature of the stressor but the identity of the infecting organism. Animals and humans also emit volatile chemical signals by way of breath, sweat, urine, faeces and wound sites, which can indicate the development of a specific disease, thereby opening up the prospect of new diagnostic tools in infections.

Insects that feed on plants, animals or humans use volatile, host-derived chemicals to home in on their hosts. This is true for insects that can transmit (‘vector’) major infectious diseases. Furthermore, the hosts are differentially attractive to the insect according to the natural chemicals they emit. So, there is a possibility that we may be able to interfere with that attractiveness to control insect-borne infection.

Foresight asked two leading experts in the relatively novel field of host response signalling, John Pickett and Michael Birkett, from Rothamsted Research in Harpenden, UK, to examine the ways in which biomarkers and natural signals might be interrogated to detect and identify pathogens and to help in the monitoring and prevention of disease spread.

Their findings point the way to some innovative tools for detection and monitoring, including the use of ‘smart plants’ that give early warning of infectious attacks and honeybees that behave as ‘molecular bloodhounds’ in recognising pathogens.

Chemical markers for disease

The early onset of many infectious diseases in plants, animals and humans is accompanied by metabolic changes in the host that lead to the release of volatile chemicals. These can act as biomarkers for disease monitoring and non-invasive early detection and diagnosis.

Many, if not most, plant diseases, especially those caused by viruses, are vectored by insects. These mainly consist of aphids, beetles and weevils, along with many plant-, tree- and leafhopper species. Researchers are also identifying many of the volatile chemicals given off by plants when these vectors start feeding. These signals can act as an indicator for the presence of vector populations at low levels, and therefore possibly the disease.

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Tools for monitoring disease vectors

Pheromones that are used by insect vector populations in crops and other plants have also been identified. The ambition is to devise systems that incorporate these pheromones, which are volatile chemicals, into traps that would be highly specific for target vectors. The trapped vectors could then be screened for pathogen presence using rapid diagnostic techniques. Thus, pheromones would be a foundation for mounting vector-borne disease monitoring and even vector eradication programmes. Where pheromones are not used by the insect, other chemical signals may be applied. These signals, termed ‘semiochemicals’, are emitted by the host plant and are used by the insect vector in host location.

Animal – including human – disease vectors such as mosquitoes, midges, bugs and ticks also use pheromonal or other ‘semiochemical’ cues for host location and aggregation. Again, many of these semiochemicals have been identified for important diseases such as malaria, filariasis, West Nile virus and leishmaniasis, suggesting, as for plants, that novel monitoring and control technologies can be developed for vector-borne animal and human infectious diseases.

Future prospects and technologies

For the remote detection and identification of volatile disease markers, some portable biosensor systems can potentially be deployed to detect infectious diseases, e.g. an ‘electronic nose’ system for detecting the antibiotic resistant superbug MRSA in hospitals. However, this system is currently of limited practical use as it cannot yet distinguish between resistant and susceptible strains. Sophisticated techniques, including the use of high-resolution gas chromatography and mass spectrometry, are required for volatile marker detection. As these markers occur only at minute levels in complex mixtures, there is a need for powerful, portable mass-spectrometry-based detection technologies that could be deployed *in situ*, drawing on advanced miniaturised instrumentation.

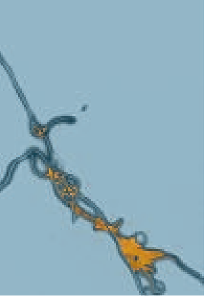
The potential for exploiting volatile chemical markers in detecting and diagnosing infection is, as yet, largely unrealised. It is clear that underpinning scientific research into the detailed nature of these markers before and during disease onset – along with understanding the pheromones and semiochemicals for insect disease vectors – can lead to new and powerful ways of managing infectious diseases in the next 10–15 years.

Exquisitely precise investigations into, for example, the way in which the honeybee’s odour-sensitive cells respond to very low levels of signalling chemicals might lead to our harnessing them as a flying workforce to sniff out volatiles emitted by plants under stress. Another possibility would be to genetically engineer a crop plant to act as a sentinel by changing colour when it is under attack from a pathogen, making control more prompt and focused.

Concurrently, we are developing a wide array of semiochemical (attractant and repellent) tools, based on biologically active chemicals, to trap insect vectors and control infectious disease outbreaks. The potential for deploying these chemicals is enormous.

This Research Brief is based on the Research Review written by Professor John A. Pickett and Dr Michael A. Birkett, Rothamsted Research, for the Foresight project: Infectious Diseases: preparing for the future. Editor: Peter Evans.

The full version of this review is at www.foresight.gov.uk



Foresight project: Infectious Diseases: preparing for the future

Science Review Summary:
Predictive and real-time epidemiological modelling (S9)

Patterns in pathology

Computer models – simulations of how infectious diseases spread through a population – are a powerful tool for aiding the decision maker before, during and after the occurrence of epidemics. These *in silico* representations of the patterns of disease can help to plan for future epidemics, predict their impact and measure the effects of control methods such as vaccination and other technologies.

Models can't tell you whether a particular individual or community will become infected. They can't trace the link between, for example, the arrival in a city of a lone hitchhiker and the subsequent outbreak of a disease. But they do, if well constructed, give policy makers a practical, data-based aid to disease management.

Foresight asked a leading disease modeller, Dr Matt Keeling, University of Warwick, to examine and assess the ways in which computer models might be used effectively in managing diseases in the future.

State-of-the-art models

Epidemiological models for infectious diseases are based on approximations for the transmission of infection between infected and susceptible individuals.

To refine a basic model, and thereby make its predictions more accurate, one needs to build into the computer program elements that take account of several key aspects:

- *Stochasticity* – the fact that there is always a chance or random element in disease spread such that no two epidemics are identical – is a ubiquitous problem. The best models incorporate this chance component by running multiple simulations that give the researcher an indication of the level of confidence that can be placed on any prediction.
- *Heterogeneity* – the biological and behavioural variability between individuals – also needs to be incorporated. No two people are identical. Today's models partition populations, therefore, into segments with similar characteristics. Age structure is one such segment that can sometimes be crucial for diseases such as measles or whooping cough which primarily infect younger children, or diseases such as smallpox, where younger individuals will not have been vaccinated. The number and type of heterogeneities – based on an understanding of risk factors – determines the capacity of a model to account for differences in transmission or susceptibility.

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- *Individual-level accuracy* is another important refinement. All simple models assume constant rates of transmission and recovery. This can be very misleading. Reality is far more complex, and this can have a dramatic impact on the spread of disease and the control measures needed.
- The *spatial structure* of a disease must also be captured in sophisticated models. Large-scale spatial information shows how a national population separates into discrete, local communities – giving insights into the movement of people and possible control strategies. Smaller-scale data can help define the transmission links between individuals – an aid to contact tracing and other local control measures.

Future prospects

Combining these refinements into ever more complex and data-rich models provides a better chance of accurate prediction. This will be invaluable in planning, using plausible scenarios for deciding on control options. Once an epidemic is under way, a sound model can be used to predict its size and duration, again with a view to optimising control policies.

A model is also an excellent way of assessing the potential effectiveness of novel technologies. The development of rapid tests to detect infection earlier could, in theory, help isolate infectious individuals and stop disease spread. However, a model is needed to estimate the potential of such diagnostics and to show they might best be deployed.

To be really useful, however, future models must embody more understanding of human behaviour. Real-time data on movement captured from, say traffic sensors or mobile phone locations could be used, for example, to make predictions about the human response to emerging epidemics. Future models must also take account of the logistics and economics of control measures in order to give policy makers guidance on the desirability of, say, mass vaccination.

As the SARS epidemic shows, due to today's increase in international travel, it may no longer be appropriate to model diseases on a national scale. Tomorrow's models will enable us to think with a global perspective.

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Foresight project: Infectious Diseases: preparing for the future

Science Review Summary: Earth observation (S10)

Taking a long view

Earth observation – the use of satellites and aircraft for observing the Earth, usually for the purposes of environmental management – may be deployed in the context of disease control. It does not promise the direct detection of infectious diseases but rather indirect information on, for example, the die-back of vegetation that may be due to plant infections, the movement of sick animals and future patterns of vector-borne diseases such as malaria.

Observations made from satellites need to be combined with mathematical models to improve our understanding of the processes under scrutiny. Current technological developments in communications and global positioning systems (GPS) also enhance our ability to use Earth observation techniques in a productive manner.

Foresight asked leading experts in the field of Earth observation, Robert Gurney and Matt Sapiano, from the University of Reading, to examine ways in which this technology may be used and developed for the purposes of disease identification, detection and monitoring.

Observations and disease

Earth observation instruments currently provide information on many variables. Surface temperatures along with atmospheric humidity and rainfall patterns are used in weather prediction, as is wind velocity inferred from pressure measurements.

Soil moisture, surface water and run-off will soon be mapped. Satellites, including Landsat, also collect data on land cover, altitude and sea surface height.

Many diseases need certain temperature, vegetation and moisture conditions in order to flourish. Already Earth observation, coupled with computer modelling, is being used to predict these, and new developments promise even greater relevance for anticipating disease outbreaks.

Specifically, Earth observation data can help to forecast the precursor conditions necessary for disease transmission by vectors, as in malaria and other mosquito-borne infections, water-borne and air-borne diseases. The aim here is to develop an early warning system based on seasonal forecasting models. Given that many diseases are likely to be affected by climate change, there is also a role for satellite data of vegetation amount and other precursor conditions, in identification and monitoring in areas that are currently disease-free.

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Current satellite-based methods for detecting and mapping areas of vegetation die-back will be improved by techniques such as hyperspectral imaging and lidar altimetry. Lidar could in the future be deployed to examine plants, including marine organisms, using fluorescence or colour change, and potentially to sense ‘sentinel’ plants that react to disease by changing colour or fluorescence. At present, direct Earth observation from space of human and animal diseases is not possible. However, satellites could, with GPS technology, gather information from sensors placed in or on animals to measure their health and transmit relevant data, including their position, back to central sites.

Earth observation should play a growing role in monitoring the transport of infections. Wind and water flow, both of rivers and seas, can already be estimated or measured.

Already, space-based mapping is used in managing the spread of infectious diseases. It was applied, for example, in Darfur in the Sudan during the recent crisis. Again, new methods such as lidar altimetry sharpen up our information, but we need to think hard about novel technologies such as GRID computing in order to deliver that information in a timely fashion, thus making it far more useful.

Management issues

By combining advanced Earth observation methods with well-designed computer models, it will become increasingly possible to use satellite information to predict and prevent infectious diseases. Just as, today, famine or crop failure can influence grain prices, so, too, could prior warning of infection have economic consequences. Some of these will be positive, such as giving advance warnings of droughts or monitoring migration. Some will be negative, for example, by allowing the manipulation of markets if data were only available selectively. Therefore, there are clearly social, political and ethical questions to be debated as the new technologies are rolled out.

This Research Brief is based on the Research Review written by Professor R.J. Gurney and M.R.P. Sapiano, University of Reading. for the Foresight project: Infectious Diseases: preparing for the future. Editor: Peter Evans.

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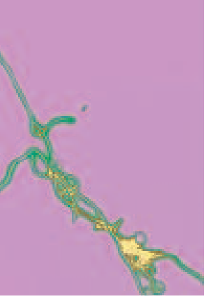

Foresight project: Infectious Diseases: preparing for the future

Science Review Summary: Host genetics and engineering (S11)

DNA route to susceptibility

In any herd of goats, cattle or sheep, some animals will naturally succumb to a disease; others will show resistance or tolerance. The difference lies to some extent in their genetic make-up.

Understanding better the genetic predisposition of animals to disease-causing organisms and how this may be used in improving disease management strategies was the remit of Alan Archibald and Stephen Bishop, both from the Division of Genetics and Genomics at the Roslin Institute in the UK. Foresight asked these leading researchers to explore these issues, along with possible new technologies for helping breeders to combat a wide variety of infectious diseases in their animals.

Host genetics

There is abundant evidence of genetic variation underlying the ability of host animals to control the extent of infection or tolerate its presence. This has been observed for almost every disease that has been studied, and it certainly applies to many of the infections that are notifiable to the Office Internationale des Épizooties (OIE).

There is, for example, genetic variation among birds as regards their ability to cope with the contagious and fatal viral infection, Newcastle disease. Resistance to tuberculosis is another case of genetically determined variation, as are the different responses of cattle and sheep to the fatal, degenerative spongiform encephalopathies, BSE and scrapie.

Already, host genetic variation is recognised and exploited in disease control. Livestock are selectively bred for their disease resistance, often based on detailed knowledge of the specific genes that seem to confer the capacity to cope with infection. Even where the infectious agent is not as yet defined, as in the transmissible encephalopathies, it is still possible to pinpoint genes that may drive susceptibility.

With modern DNA technology, then, it has become possible to breed specifically for desirable disease-related traits or to eliminate gene variants that are undesirable.

Engineering the host genome

There is a modern alternative to traditional selective or cross-breeding in the shape of gene transfer technology. Here, by bringing together recombinant DNA methods with advances in reproductive technology and medicine, the ambition is to introduce single new genes into livestock or to modify existing genes without any unwanted genetic baggage.

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There are several ways of doing this. One is DNA microinjection, whereby transgenic animals are produced by directly injecting multiple copies of a desired gene into single egg cells. Another is sperm-mediated gene transfer, in which animals are produced by *in vitro* fertilisation using sperm that has been incubated with the desired DNA. Yet a further approach is to use viruses as carriers of the wanted gene into a host, without, of course, also conferring infection.

More recently, there have been experiments with several novel techniques including: using embryonic stem cells; transferring the cellular nucleus – the process that lead to Dolly the sheep; and so-called gene targeting. The trend is towards higher success rates and better precision in getting the new genes to the place where they are needed.

As well as introducing new genes into farm animals, it is also possible to modify existing DNA to make the host animal more resistant to, or tolerant of, infection. And it is possible to knock out those existing genes that determine susceptibility. The gene encoding the prion protein responsible for BSE and scrapie is an obvious candidate here.

Control, detection and identification

Genetically modifying an animal host's genome is a powerful weapon for controlling infection. One could envisage engineering an animal's genes in such a way, for example, that they dampen the ability of incoming viruses to take hold and spread within the body. What a difference that might make to fighting avian influenza – currently the major livestock disease threat in China, with global implications.

For these technologies to be practicable, however, more research is needed to make them as cost-effective as other control measures. We can expect such improvements over the next 10–25 years. At the same time, we need to consider possible public views about the notion of genetically modified farm animals. This means engaging in discussions about the benefits of reducing the risks of infection, including those diseases that pass from animals to humans: the zoonoses.

Research into host genetics, along with new techniques for engineering the animal host genome, are obviously more useful in control than in the detection and identification of infectious diseases.

However, there is one way in which this work could be used – in producing 'sentinel' animals. Just like the canaries that were used to detect toxic gases in coalmines, these would be individuals with a deliberately engineered, susceptible genetic make-up. They would indicate quickly and reliably the presence of a particular disease. There are logistical, ethical and other problems surrounding the use of sentinels, but they do represent a possible, novel control measure. They could also be of use in helping detect diseases in crop plants where specially introduced genes could 'report' on a crop's disease status. Imaginative, tangential thinking is needed to explore the use of sentinels more widely.

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Foresight project: Infectious Diseases: preparing for the future

Science Review Summary: Immune signatures for detecting and identifying infectious diseases (S12)

Defensive weapons

The immune system is our body's inbuilt defence against infection. It may also, in the future, become a powerful ally in developing high-technology methods for disease detection and identification.

When a virus, bacterium or parasite infects a human or animal, it leaves behind a unique 'immune signature'. We expect to be able to exploit these pathogen-specific traces for detecting micro-organisms or establishing the vaccination status of the infected host.

Foresight asked two experts in immunology from the UK's National Institute for Medical Research, Anne O'Garra and Victor Tybulewicz, to explore ways in which modern immunological techniques might be used for improving the detection and identification of diseases.

Immune signatures: a key weapon

When a host – human or animal – is infected by a disease-causing organism, it automatically mounts a response designed to eliminate the invader. If successful, this immune reaction isolates and eradicates the pathogen; if not, longer-term infection sets in.

The key defensive cells in the blood are the white cells or leucocytes. Detailed analysis of leucocytes from patients with immune-based diseases such as arthritis shows that these cells carry a unique configuration in their RNA expression indicating both the specific type of disease and, sometimes, its severity.

Data is now emerging that host immune cells also carry genetic signatures resulting from the specific microbes responsible for infection. These are, as it were, their RNA fingerprints at the scene of the crime. Patients with acute infections from common human pathogens, including influenza A virus, *Staphylococcus* bacteria and *E. coli*, have distinct patterns of host gene activity in their leucocytes that show which microbe is responsible.

From these observations, we can expect the establishment of large databases of genetic information that will enable us to identify the immune signatures of a wide variety of diseases caused by many different pathogens responsible for acute or chronic infection. This will not only help in identifying the causal agents

– be they virus or bacterium – but also to determine the imprint of an infection or the vaccination status of a host once the pathogen has been eliminated.

Power of the new technologies

There are now a number of advanced techniques for determining these immune signatures, either at the gene level or the protein level, some requiring very small amounts of blood. One protein array technology, for example, enables over 20 inflammatory proteins indicating infection called cytokines and chemokines to be identified from just 50 microlitres of blood: a very small droplet. Microarray technology of host RNA immune signatures can use as little as 1–3 ml of blood and has an even wider power of analysis.

There are several further advantages of using circulating leucocytes. They enable pathogens to be detected and identified in tissues that are relatively inaccessible, and when the micro-organism has already been eliminated from the body. They also help spot a totally novel organism for which no test yet exists.

In the future, even more sophisticated tools will come on stream, such as flow cytometric analysis of characteristic proteins – markers – on the surface of immune cells. This will show exactly how the immune system has changed to meet a microbial challenge and whether it has been suppressed or damaged in any way.

Concurrently, advanced techniques such as RNA microarray analysis and quantitative polymerase chain reaction (PCR) technology will enable us to determine host genetic signatures for specific infectious diseases.

Taken together, these new techniques potentially represent a key methodology for detecting and identifying infectious diseases within a matter of hours. We have some way to go yet in reducing costs, in miniaturising devices and in using bioinformatics data in such a way that they flow freely between the field and the laboratory. But these are hurdles we can overcome.

This Research Brief is based on the Research Review written by Dr Anne O'Garra and Dr Victor Tybulewicz, National Institute for Medical Research, for the Foresight project: Infectious Diseases: preparing for the future. Editor: Peter Evans.

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