FORESIGHT

Infectious Diseases: preparing for the future

A Vision of Future Detection, Identification and Monitoring Systems

OFFICE OF SCIENCE AND INNOVATION

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A Vision of Future Detection, Identification and Monitoring Systems

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This report is intended for:

A wide range of professionals, researchers and people in industry and business whose work relates to infectious diseases in humans, animals and plants. The report takes an international perspective, and will therefore be of interest to governments and non-governmental organisations across the world. Finally, it will be of general interest to anyone with an interest in infectious diseases and their control.

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The Foresight programme is run by the UK Office of Science and Innovation under the direction of the Chief Scientific Adviser to HM Government. Foresight creates challenging visions of the future to ensure effective strategies now.

Executive summary

The aim of the Foresight project: Infectious Diseases: preparing for the future, is to produce a vision of future systems for the detection, identification and monitoring (DIM) of infectious diseases, and to assess how they might transform our capabilities in managing the future threat. Diseases in humans, animals and plants are considered equally.

This report looks ahead 10–25 years and postulates future DIM systems, based on developments in diverse areas of science. The future use of these DIM systems is then illustrated through a series of case examples. Finally, the analysis is drawn together to identify the key issues and choices that will affect their development and effective implementation.

The contribution of future DIM systems to managing infectious diseases

DIM systems in 10–20 years could have capabilities that are a step-change beyond those of today. And when they are integrated into wider systems for disease management, the benefits could be considerable.

In one case example, a self-diagnostic device for sexually transmitted diseases in 2015 saves the National Health Service around £135 million per year for the treatment of infections of chlamydia and gonorrhoea alone. Also, the early detection and treatment helps to reduce the spread of disease and reduce the risk of complications due to otherwise untreated infections – both of which would create further cost savings. For a hypothetical outbreak of foot-and-mouth disease (FMD) in 2015, DIM devices enable early targeted interventions, and virtually eliminate the need for mass culling, reduce the costs of controlling the epidemic from £5 billion to £50 million, and reduce other losses (tourism, rural trade etc.) from £3 billion to £0.35 million.

Note: such examples are only intended to be illustrative – to stimulate thinking on the issues surrounding the DIM systems, and to provide no more than a broad indication of possible benefits.

Key choices for policy makers and disease-management professionals

Governance: different forms of regulation will be desirable to deliver some future DIM systems effectively. The key questions are what regulations will be needed and whether they can be enforced. Important issues include: access, ownership and confidentiality of healthcare and other personal data; regulation of hand-held diagnostic devices, including access by the public, implications for healthcare professionals, waste disposal, and standards for quality and validation; the possible screening for disease at transport nodes such as ports and airports, and its implications for civil liberties and data confidentiality; and promoting the better sharing of biological samples and their associated information.

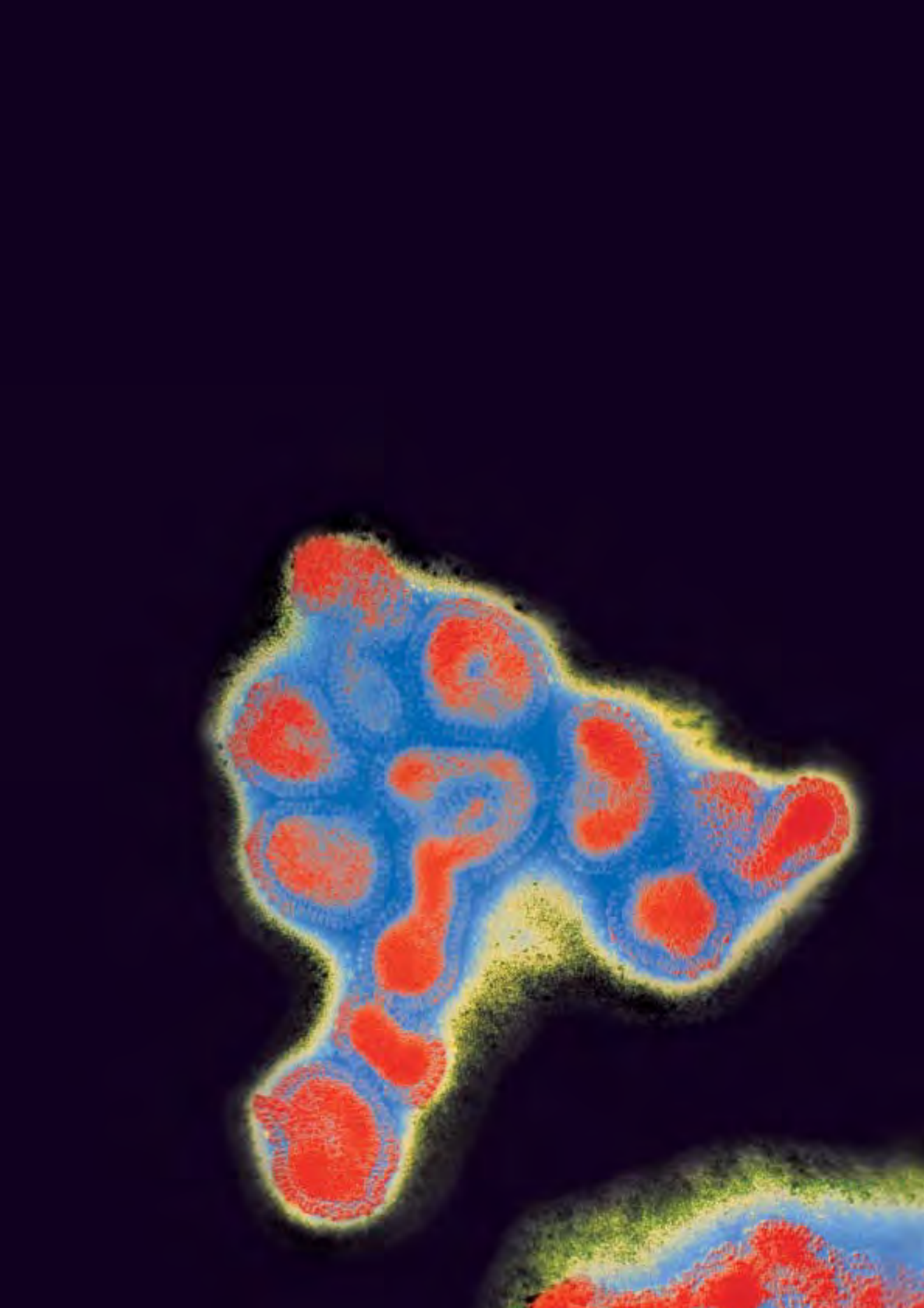
Exploiting exogenous developments: much of the technology on which the future DIM systems will be based is already being developed for purposes unrelated to the management of infectious diseases. The issue is how best to promote access, and how best to exploit it. For example, it would be very beneficial for the purposes of managing infectious diseases, to promote better access to data from sources currently unrelated to disease management – such as remote monitoring and mobile phone tracking data. Also, there is considerable DIM technology being developed for counterterrorism purposes. This issue here is how to promote better access, while protecting personal and security interests.

Maximising the public good: obtaining the best public value from future DIM systems will require consideration of areas such as: promoting interoperability and open access of DIM systems; promoting better access to intellectual property; maximising the benefits from the growing commercial interests of mass electronic manufacturers; how to stimulate diagnostics for diseases that are unlikely to be of interest to industry, such as SARS, and diseases of the developing world; and the need to integrate future DIM systems effectively within wider systems' architectures for disease control.

Africa: the key finding by the African experts in the project is that Africans should take the lead in developing a new Vision and Strategy for the management of diseases across the continent. Key concerns included: the availability of follow-up treatment – the usefulness of DIM systems would be limited without this; the present lack of capacity in Africa for DIM; the concern that the development of DIM systems may not adequately take account of Africa's needs; and the need for smart partnerships between experts from Africa and the developed world.

Science, technology and social science: research areas that are unlikely to be fully realised by exogenous developments, and which are key enablers for future DIM systems include: the integration of social sciences in the development and implementation of DIM systems; interdisciplinary research on health systems; new data processing tools; the design of surveillance systems; biomarker research; robust portable molecular diagnostic devices; understanding animal host response; and the integration of nucleic-acid-based and immune-response-based methods.

Engagement with the public: the public will need to weigh the benefits of the future DIM systems against their possible social 'costs' (e.g. increased monitoring of the population and increased use of personal data). In any case, it will be important to ensure public engagement with the design of many of the potential future DIM systems if they are to be effectively deployed.



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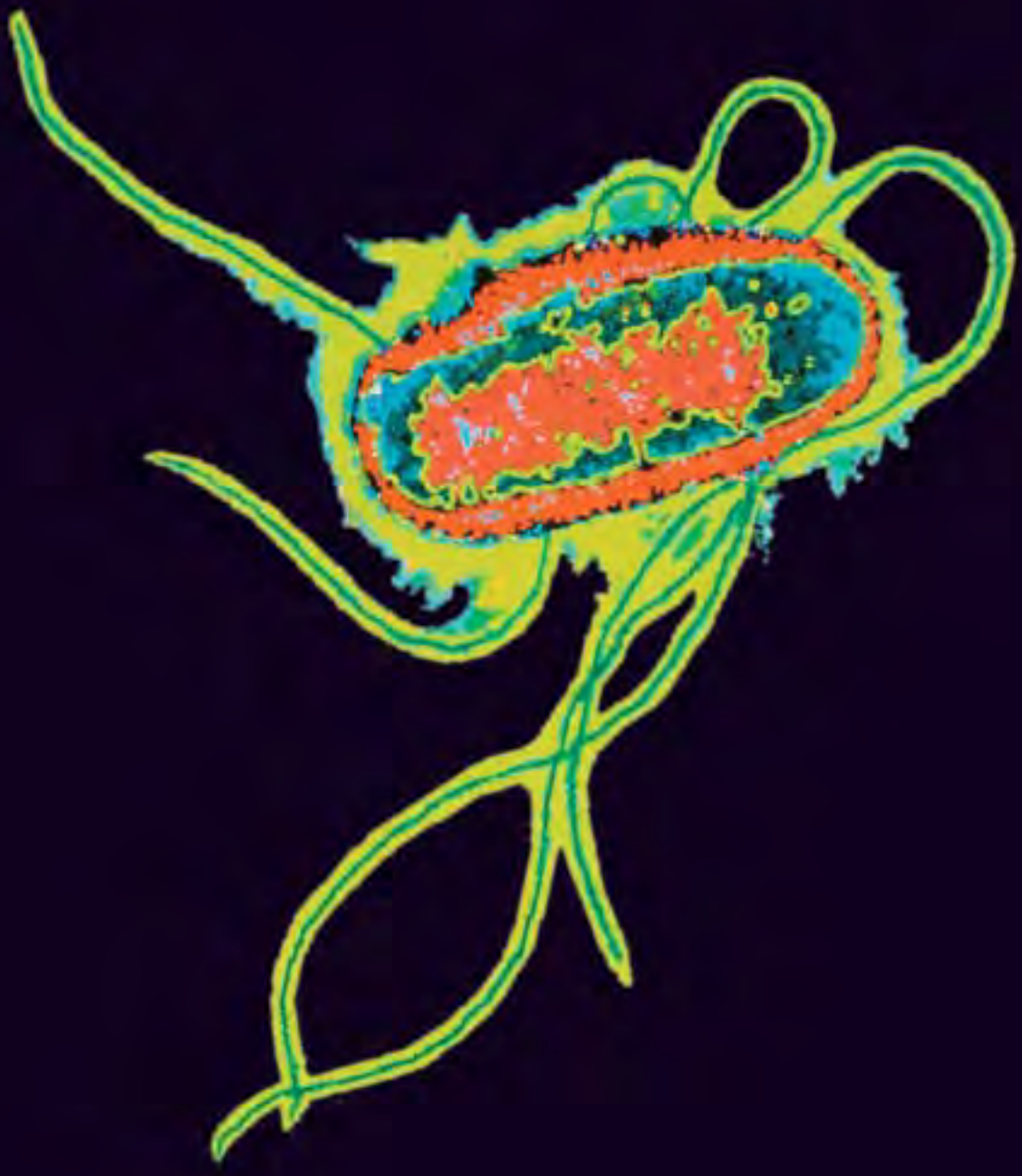


1 Introduction

Chapter 1 introduces this report, which covers the assessment of future systems for the detection, identification and monitoring (DIM) of infectious diseases.

It explains the technical approach to the work, in particular: how the future DIM systems was divided into four categories (User Challenges) for analysis; and the analysis that was performed for each. It also explains how the work differs from other studies.

1 Introduction

By their very nature, outbreaks of infectious disease can spread rapidly, causing enormous losses to health and livelihood. However we decide to control these outbreaks, the best strategy is to stop their spread at an early stage, or prevent them altogether. To do this, we rely on very early **detection** of the appearance of disease or disease-causing agents. Rapid and accurate **identification** of these agents is essential if we are to stop outbreaks with the correct control measure, for instance, antimicrobials or vaccines. This is particularly true for entirely new diseases, where we find ourselves in a race to develop new controls as the disease spreads. In an outbreak situation, **monitoring** of a known problem will involve the same systems of detection and identification and is important, as it informs us where to focus effort.

New control methods will improve our capacity to suppress diseases, particularly where, like vaccination, they protect entire populations from known pathogens. However, the threat of new disease emergence will continue, and hence the need for early DIM to prevent disease spread and future epidemics. In this study, we do not consider in detail the development of future disease control methods, but we do explore how the evolving situation will affect the need for future DIM systems.

The analysis looks 10–25 years into the future to consider infectious diseases in humans, animals and plants. Its primary aim is to produce a vision of new systems for disease DIM – and to assess how they might transform our capabilities in managing the future threat. In particular, this report details the work that identified possible future DIM systems, and which tested them against future disease risks (an outline of the various parts of the project is provided in Appendix C).

This chapter outlines the technical approach to the work and, in particular, explains how future DIM systems were divided into four broad categories for analysis – the ‘User Challenges’. Chapter 2 then reviews the future disease risks that have been identified in the project (reports T1 and T2 – see Appendix D for a list of all project reports), and draws out implications for DIM systems. It also considers, in general terms, the contribution that the User Challenges would make to the management of those risks.

The potential use of the future DIM systems is next explored by using case examples of important future disease threats (Chapter 3). These exemplars have been defined in the project’s risk work, and are used to consider the potential costs and benefits of future DIM systems, and also to highlight the barriers and enablers to their realisation. The exemplars are entirely hypothetical and are intended to be illustrative rather than exhaustive.

Finally, Chapter 4 draws together the comprehensive analysis that has been conducted on the four User Challenges (project reports D2, D2.1–D2.4). In so doing, it considers the key issues associated with their development and effective deployment of the future systems. It also sets out strategic choices facing policy makers, disease management professionals and technology developers.

1a Classifying DIM systems into User Challenges

There are innumerable DIM systems that can be envisaged for the future – each using different technologies, targeting different disease threats, and playing different roles within broader strategies for the management of diseases. In order to identify the most important and promising of these, the following process was used. Following extensive scientific consultation, a cluster of ten science areas relevant to potential future DIM systems were identified, and expert reviews were commissioned on likely future advances in each science area. A workshop comprising the authors of these studies drew out particular technological opportunities for DIM. The final results of this science analysis may be found in project report S1. Parallel to this activity, an analysis of future infectious disease threats and their drivers provided a vision of the challenges that future DIM systems would need to address. The final results of this risk analysis can be found in report T1.

These two summaries on ‘future science for DIM’ (S1) and ’future disease risks for DIM’ (T1) were brought to a workshop of potential DIM users, who were representatives of national and international institutions responsible for plant, animal and human disease prevention and control. Through structured sessions, these users identified the specific DIM tools and technologies most needed to address anticipated future risks. This output was then integrated across plant, animal and human systems to generate a set of common ‘User Challenges’ that best represented the kind of technology and systems needed for DIM in the future. These four User Challenges (UCs) can be summarised as follows:

- **UC1:** novel information technology for the capture, analysis and modelling of data for the early detection of infectious disease events (detailed analysis of this User Challenge may be found in report D2.1)
- **UC2:** early detection and characterisation of new or newly resistant/virulent pathogens using genomics and post genomics (D2.2)
- **UC3:** taking technology for the identification and characterisation of infectious diseases to individuals by designing smart swabs or hand-held or portable devices that analyse fluids (D2.3)
- **UC4:** high-throughput screening for infectious diseases of people, animals and plants using surrogate, non-invasive markers (e.g. electromagnetic radiation, volatile organic compounds), for example, in airports, sea/road containers and livestock markets (D2.4).

1b How the analysis of the User Challenges was conducted and who was involved

The analysis of each of the four User Challenges was conducted by a multidisciplinary team of experts, led by a technical expert, and under the direction of a senior stakeholder – a 'User Challenge Champion'. The Champions and teams are listed in Appendix B, together with the many other individuals who were involved in performing or reviewing this part of the project.

The detailed analysis of each User Challenge (D2, D2.1–D2.4) considered the following aspects, and drew on various workshops and studies within the project:

- key capabilities of the future DIM systems
- the role of the future DIM systems within the wider context of other (non-DIM) technologies for managing future diseases – this drew on reviews of future control of human, animal and plant diseases (D3.1–D3.3)
- barriers and enablers affecting the development and effective implementation of the DIM systems. This analysis drew on studies that considered culture and governance and their effect on DIM systems (D4.1–D4.3); historical perspectives (D5); and also considerations of public perceptions of risk in the UK and Africa (D7)
- the costs and benefits of the DIM systems and their robustness to uncertainty – these were explored both in the detailed reports on the User Challenges (D2.1–D2.4) and through case examples
- the perspective of developing countries
- consideration of how to realise the greatest public good from the DIM systems.

How the Foresight project differs from other studies

The technical approach in the project involved a unique combination of factors. It considered:

- diseases in humans, animals and plants
- the situation both in developed and developing countries
- a long-term perspective – 10–25 years[1]
- social as well as natural sciences.

Addressing diseases in humans, animals and plants: this important aspect of the project responds to several factors:

- Diseases in animal and plants are linked with human health and human infectious diseases. For example, animal infections can jump species to humans: the majority of new infectious human diseases that have become evident in the past 25 years are caused by pathogens arising from domesticated or wild animals (zoonoses). Also, in the developing world, diseases in plants and animals impact on human disease through factors such as starvation, prejudicing economic development and displacing populations.
- Diseases of humans, animals and plants alike are affected by shared, global drivers such as travel, climate change and trade. Trade and commerce particularly link animal and plant diseases and their future impact.
- More generally, there is a convergence of science and technologies that can be used in new DIM systems to manage infectious diseases across these three systems. These include genomics, information and communications technology, and electronics.

Geographical focus: it was outside the scope of the project to consider every region of the world in detail. Therefore two were chosen for comparison – sub-Saharan Africa, as an example of a developing region; and the UK as a developed country.[2] Nevertheless, it is expected that the results will have broad applicability to other parts of the world.

Time horizons: Ten years (from 2005) was chosen as the near horizon, as the aim was to look beyond today's problems and to take a strategic and longer-term view. Twenty-five years was selected as a far horizon, since any visions of future science and DIM systems become very speculative beyond that. (Note: the project found a large overlap between the problems of tomorrow and those of today – so some aspects of the application of the new DIM systems are nevertheless relevant to today's challenges.)
The overall project findings focus on the steps we need to start to take today, in order to be in the best possible position in the future.

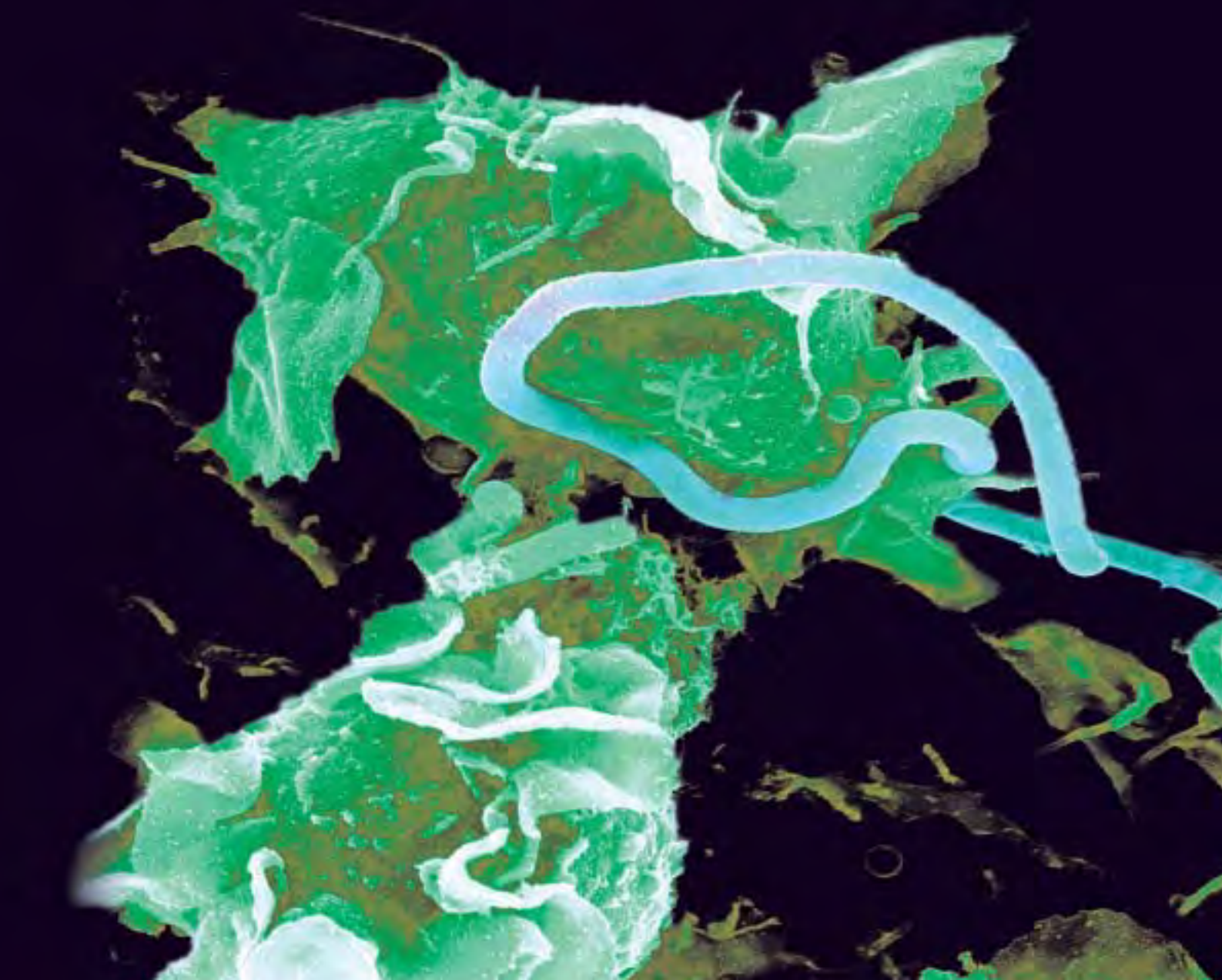
[1] In the consideration of climate change, a 75-year horizon was taken, in view of the long-term nature of this driver.

[2] China was also considered in the context of future human and zoonotic diseases – see reports T1 and T13.

2 Matching future DIM systems to future threats

2a The potential capabilities and role of the User Challenges

2b Future threats and their implications for the User Challenges



2 Matching future DIM systems to future threats

This chapter considers each of the four User Challenges, and outlines their possible capabilities in managing the risks of infectious diseases.

It then reviews the key future threats identified by the project, and draws out strategic requirements for the User Challenges. It also lists eight categories of disease that are considered to be important in the future, and which were identified by the risk analysis. These have been used to illustrate the potential of future DIM systems (Chapter 3).

2 Matching future DIM systems to future threats

2a The potential capabilities and role of the User Challenges

The following provides an overview of the four User Challenges that were introduced in Chapter 1. It outlines the capabilities they could provide in the future, based on science developments that have been identified elsewhere in the project (reports S1, S3–S12). Each starts with a 'grand challenge', which is essentially an ultimate goal for the User Challenge over the next 25 years.

Detailed roadmaps are also provided for each User Challenge in Appendix A. These roadmaps form a succinct timeline for the development of component technologies; their integration into new DIM systems; and the issues affecting their development and deployment. An overview roadmap covering all four of the User Challenges is also provided in Appendix A.

UC1: Novel information technology for the early detection of infectious disease events

Grand challenge: the use of modern information and communication technology systems to gather and interpret timely and relevant data and deliver it to those managing an outbreak

The early detection of disease outbreaks is vital in order to provide the maximum time to determine their nature, and to implement the most appropriate control measures. Outbreaks of new and emerging diseases, in particular, would first present themselves as clusters of mortality or morbidity reports with unusual clinical and/or epidemiological characteristics. Advances in information technology and modelling will offer new possibilities for organising and analysing a wide range of disease-related data, and so detect unusual patterns. This will be especially important in regions where routine disease surveillance is poor.

Information systems could be particularly important in disease surveillance, where extensive, regular sampling is made. Technological advances will allow the possibility of data being collected electronically from hand-held devices (see UC3) and linked to a central information system. This would enable the disease burden to be established and monitored, and could address both the spread of infection in the population and the spread of disease-resistant organisms. Data capture through diverse remote sensors and their central analysis could also become possible – this will be important for the surveillance of diseases in inaccessible natural ecosystems, e.g. monitoring wildlife populations for zoonotic diseases, or forests for exotic plant diseases.

Improvements in modelling that use a dramatic increase in data capture, will permit evaluation of different scenarios for disease development or management. Information technology will enable the rapid transfer of diagnoses into epidemiological models for real-time, spatially sensitive, prediction of disease spread.

Finally, it is possible that increasing use will be made of data that has been collected for non-clinical purposes. For example, information from mobile phones or future transport tracking systems could provide valuable information on the movement of people for modelling the spread of diseases, or indeed for backtracking to where disease outbreaks have originated. Issues of data ownership and confidentiality will be important in such cases.

UC2: Early detection and characterisation of new or newly resistant/virulent pathogens

Grand challenge: to develop a laboratory-based system using genomic and post-genomic methods to detect and characterise, rapidly and cost-effectively, all new and newly resistant virulent pathogens

It will be important to quickly analyse and characterise the infectious diseases that have been detected in UC1, or which have been detected by other means. In future, diagnostic laboratories equipped with genomic and post-genomic technologies may be able to rapidly identify pathogens in samples by referring to reference libraries of known pathogen nucleotide sequences. Similar technologies could be used to detect and characterise novel strains which are resistant to antimicrobials. For entirely new diseases, a novel pathology could be linked to a unique immune signature or nucleic acid profile. Also, as we understand the disease process better, we will be able to identify biomarkers which we can target for measurement.

These technologies will have a particular role in rapidly assessing the altered virulence and transmissibility of known diseases that have undergone genetic change. They might, for example, be able to identifying a mutation of avian influenza capable of effective human-to-human transmission. Technological advances are expected to reduce costs and increase sharing of bioinformation. This will make it easier for these laboratory facilities to be established in more countries, thereby reducing the time for identification.

UC3: Hand-held devices

Grand challenge: the development of a robust, cost-effective, mobile, individual/near-target device that can rapidly either directly, or through interface with a system, detect, identify and characterise appropriate infectious diseases

Hand-held devices for rapid identification of known diseases have the potential to become a mainstay technology of disease diagnostics. If they tested for multiple pathogens, they could detect if more than one disease were present, even if the symptoms of one were masked by those of the other. Electronic hand-held devices or ‘smart swabs’ could also have particular value where diagnosis of pre-symptomatic or asymptomatic infections can lead to more rapid, successful and cost-effective treatment. They would have a value, for instance, in testing for

sexually transmitted diseases, where infections are often without symptoms and individuals are often reluctant to attend medical facilities to be tested.

Tests that can distinguish rapidly between viral and bacterial infections in the community would provide a basis for the more appropriate use of antimicrobials for common respiratory and other infections. Diagnostics that detect drug-resistant pathogens will enable more prudent antimicrobial drug use. A simple, cost-effective, robust and reliable hand-held diagnostic test could also be of considerable value in the diagnosis of key human diseases in developing countries, although the issue of cost should not be underestimated.

In animal systems, in particular, portable devices could: allow pen-side testing for notifiable diseases; reduce delays in diagnosis; help to avoid the difficult task of sending samples across the world for analysis; and greatly reduce the difficulty and cost of disease eradication campaigns.

As hand-held devices become a standard diagnostic tool, tests for newly characterised diseases or newly resistant diseases could be rapidly incorporated into devices for the surveillance of disease incidence and spread.

UC4 High-throughput screening

Grand challenge: to develop a system rapidly, cost-effectively and acceptably to detect and identify all known and unknown infectious diseases in high-throughput environments (e.g. airports, ports, train stations etc.)

Increasing international trade, transport and travel will raise future risks of infectious disease introductions. However, ports of entry will provide opportunities for detecting and preventing new disease introductions.

Hand-held devices will become essential for testing individual humans, animals or plants for disease. However, the sheer volume of traffic will require systems using technologies that are non-invasive and high-throughput, often as a first step before individual testing. Such devices would analyse pathogens (e.g. by sampling pathogen spores from airspaces), dusts, or signals – such as volatile organic chemicals and electromagnetic profiles which indicate the presence of disease in individuals or populations. Detecting pre-symptomatic disease will be particularly important.

For animal and plant diseases, improved devices will make screening more extensive and interception more effective. Devices could be deployed in containers in transit, for instance, to detect the appearance of plant diseases during the course of a single shipment. Prevention of transboundary animal diseases would benefit particularly from deployment of these devices at national points of entry. Testing of animal and plant products and detecting illegal imports will be an important application.

For human diseases, high-throughput screening could also play a role in detecting the introduction of acute respiratory diseases, such as an influenza virus. This could give authorities a 'head start' in preparing for a disease outbreak, or in identifying and blocking a pathway of disease movement.

2b Future threats and their implications for the User Challenges

The project reports *Future Threats* (T1) and *Risk Analysis* (T2) look ahead 10–25 years, and consider the future threats of infectious diseases in humans, animals and plants. Some key findings are set out below, and their implications for the four User Challenges provided in italics:

- There is a vast diversity of infectious diseases. Many of these will continue to be important, some will increase in importance, and new diseases will continue to emerge. Some of these new diseases could have substantial impact – as HIV, BSE and cassava mosaic disease have in the past. *We need monitoring and data analysis systems that can rapidly spot new or unusual disease occurrences. We need improved methods to rapidly analyse and characterise any new pathogens detected. And we need new diagnostic systems that are generic – i.e. that can detect a wide spectrum of pathogens.*
- Around 75% of emerging and re-emerging human diseases are also present in animals. *This underlines the need to integrate the DIM of diseases in both the human and animal (domestic and wild) populations. In many cases, surveillance of diseases in animal populations has an important role in protecting public health.*
- Increasingly, people are eating more exotic animal food (bushmeat), keeping more exotic wild animals as pets, and travelling to exotic locations. All of these will tend to bring new populations of animals and humans together and promote the emergence of diseases from the wild animal reservoir. *This implies the need to be able to detect and rapidly characterise exotic and possibly unknown diseases in wild animals, though recognising that this is particularly difficult in developing countries. The size of this task suggests the need for strategies for targeting monitoring resources.*
- Increasing drug resistance is likely to be of importance in many pathogens. *We need diagnostic devices that can distinguish resistant strains so that appropriate drugs can be immediately prescribed. Also, we need a device that can distinguish between bacterial, viral and no infection – helping to avoid the overuse of antibiotics and the build-up of antibiotic resistance.*
- Some of the major threats will arise from combinations of diseases – for example, TB was thought to be under control 20 years ago, but it is now becoming an increasing problem, driven by the HIV epidemic and the emergence of drug resistance. *It would be helpful if some diagnostic devices could target important combinations of diseases, although it is recognised that*

such devices could be technically complex. Such multi-target devices could also be of potential benefit in developing countries if they could be made sufficiently cheaply. This is because it can be onerous for people to visit healthcare practitioners – therefore being able to screen for a range of diseases could maximise the outcome of such visits.

- As travel, trade and migration increase in the future, the opportunities for the spread of diseases will also increase. *This implies the need for rapid on-the-spot capabilities to detect and characterise diseases emerging in an area – without the need to wait several days while samples are shipped across the world for analysis.*
- It is expected that there will continue to be important diseases in the future that can be asymptomatic for substantial periods – for example, sexually transmitted infections such as chlamydia, HIV and gonorrhea. *It is therefore important that future DIM systems are capable of picking up asymptomatic infections, and that they are deployed in a way that can access sections of the population that would otherwise remain untested.*
- Plant diseases will continue to be characterised by the extreme variety of hosts and the extreme variety of pathogens. *This suggests the need for generic broad-spectrum diagnostic tests.*
- Diseases will emerge from anywhere in the world – new epidemics will be best detected early and controlled at source. This implies the need for good monitoring in developing as well as developed countries. However, monitoring and diagnosis in developing countries can be a problem due to a lack of resources, unavailability of refrigeration and power, and a lack of skilled workers to perform and interpret diagnostic tests. *This implies the need for: innovative solutions that do not necessarily rely on local capacity; cheaper and simpler DIM systems; and systems that are more robust (e.g. which do not require refrigeration). It also underlines the importance of building capacity for disease surveillance in developing countries.*
- Infectious disease outbreaks in humans will continue to affect travel, especially international travel. Diseases in livestock and crops will continue to be important impediments to trade for developing countries. The importation of livestock diseases will also be very costly for developed countries wishing to maintain disease-free status for export purposes and for developing countries, which already have substantial disease burdens to manage. *This implies the need for devices that can screen ever larger numbers of people and animals and ever larger volumes of animal and plant products faster and cheaper.*

The project identified eight broad categories of diseases that are considered likely to be important in the future, and for which DIM systems could play an important role (see project report T1 for a detailed discussion of each of these eight categories). The eight categories are set out in Table 2.1 and from these were

drawn exemplar diseases (also Table 2.1) which are used in Chapter 3 to illustrate the potential of future DIM systems.

Table 2.1: The eight categories of disease used to test the efficacy of the future DIM systems (left-hand column). Specific diseases used as illustrative exemplars (Chapter 3) are shown on the right.

Disease categories	Exemplar diseases
Novel pathogens: new species and new variants	Avian and pandemic influenzas
Zoonoses	
Acute respiratory infections	SARS
Pathogens acquiring resistance	HIV/AIDS and tuberculosis – including drug-resistant strains
HIV/AIDS, tuberculosis and malaria	
Epidemic plant diseases	Broad range of plant diseases (the specific device considered here is also capable of diagnosing diseases in fish, animals and humans)
Sexually transmitted infections	Chlamydia (including *Lymphogranuloma venereum* (LGV)), syphilis, gonorrhoea and genital herpes
Transboundary animal diseases	FMD
	Bluetongue

Table 2.2 shows the extent to which each the four User Challenge systems could contribute to the management of each of the eight disease threats. The following points are worth noting:

- Hand-held devices (UC3) have considerable potential across the entire spectrum of human, animal and plant diseases.
- Rapid identification of new and resistant diseases will depend on DIM systems that detect unusual patterns of disease (UC1), linked to systems that characterise new disease agents (UC2).
- Managing diseases that move rapidly around the world (e.g. through agricultural trade or as rapidly spreading acute respiratory infections of humans), will benefit particularly from DIM systems that analyse data on disease patterns and movement (UC1) or which detect diseases at transport nodes (UC4).

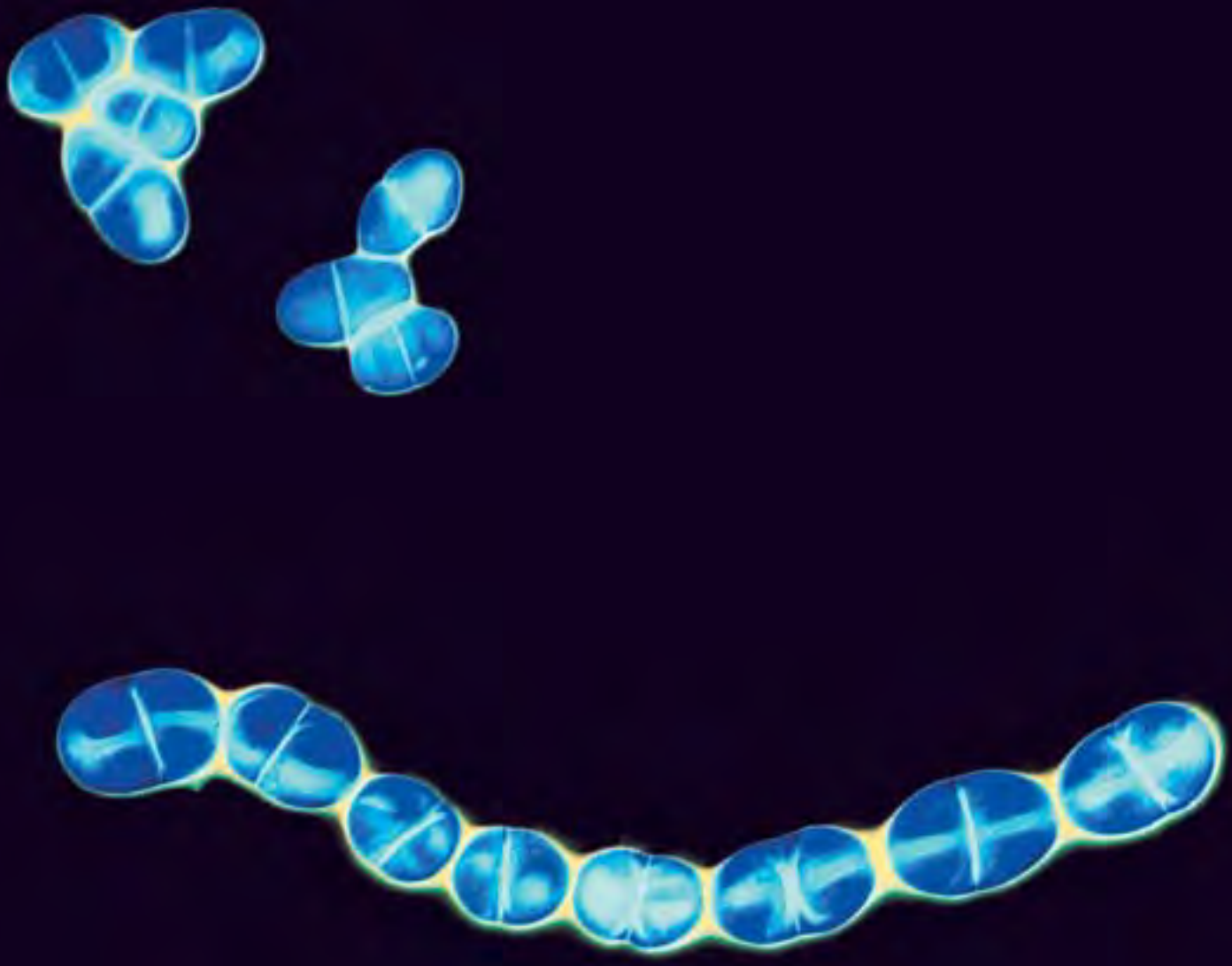
Table 2.2: Comparison of disease threats with DIM technologies. Potential contribution ranges from moderate (*) to high (***). Note: the award of three stars is sometimes made because of the high degree of relevance of the User Challenge, and sometimes because the User Challenge is the only option.

Categories of disease threat	Potential contribution to managing future risk			
	UC1	UC2	UC3	UC4
Novel pathogens	***	***	**	**
Pathogens acquiring resistance	***	**	***	*
Zoonoses	**	**	***	***
HIV/AIDS, tuberculosis, malaria	**	*	***	*
Epidemic plant diseases	***	*	***	***
Acute respiratory infections	***	**	***	***
Sexually transmitted infections	**	*	***	*
Transboundary animal diseases	***	**	***	***

KEY * ** ***

Increasing potential →

3 How DIM could make a difference – science fact or science fiction?



3 How DIM could make a difference – science fact or science fiction?

This chapter presents case examples of how future DIM systems could contribute to the management of important diseases and combinations of diseases 10–20 years from now. The aim is to expose the potential benefits, but also illustrate some of the key issues they raise.

These case examples are intended to be illustrative rather than exhaustive. As such, they complement the detailed analysis of the four User Challenges (see reports D2.1–D2.4).

A word of warning: these case examples are entirely hypothetical, and are conditional on many future developments relating to technology and systems of governance. **They are intended to stimulate thought and should not be regarded as predictions.**

3a Avian and pandemic influenzas in 2025

A new avian influenza emerges in 2025

It is 2025. In a rural community in an Asian country, local farmers experience a sudden high mortality in their chicken flocks. They call the local veterinary services. A local veterinarian visits the farm and, using a hand-held device, tests cloacal samples. Her recorder uses a microarray system and is set to identify the entire range of livestock viral infections. The recorder – which is wirelessly connected to the national surveillance lab and global reference databases – confirms that a form of avian influenza (AI) is responsible, but indicates that the viral sequence differs significantly from any other recorded in Genbank. The recorder transmits an alert signal along with its analysis of the new strain to the regional veterinary office. Within minutes, the vet receives a call on her mobile phone from her regional office that authorises a local cull and establishes a protection and surveillance zone around the village. She takes samples for full genomic and proteomic analysis testing and sends these by courier to the laboratory.

At the national laboratory, more detailed bioinformatics analysis of the recorder data suggests the new strain may have high human virulence and the potential for human-to-human transmission. This initial conclusion is then backed by automated full genome–proteome analysis of the sample sent to the lab. Health authorities are informed, and appropriate antiviral treatment is delivered to the village, coupled with mass screening of the population for infection. The national laboratory contacts the reporting vet and others in the district to visit farms and flocks and to take samples from flocks. Details of the new strain are deposited in global databases and transmitted to the global AI monitoring centre. From this point, hand-held recorders anywhere in the world are able to identify the new strain. This point is reached within 24 hours of the call to the local vet. Within weeks, the extent of spread and evolutionary history of the new strain has been elucidated.

A human influenza pandemic, the same year

A hospital in a tropical city admits a middle-aged woman who has travelled from a semi-rural area on the outskirts of the city. She has a severe respiratory illness and reports that other members of her family are also ill. As part of initial diagnostics, doctors test a nasal swab using one of the compact automated pathogen identification diagnostic units in the hospital. Within an hour, the unit reports that the sample contains a novel influenza strain (in addition to multiple bacterial pathogens). The unit has compared the sequence of the virus with Genbank data and has identified a novel avian strain identified two weeks earlier as the most closely related strain. However, the new human strain has accumulated four additional point mutations thought to be linked to transmissibility.

The hospital authorities issue a novel pathogen outbreak alert, and control teams visit the woman's family. Interviews with neighbourhood residents indicate that a large number of people in the area have experienced moderate but non-life-threatening respiratory illness in the past three weeks. Testing confirms at least 80 individuals have been infected with the novel strain. Data is transferred to the global influenza surveillance centre and a pandemic alert is issued. Seventy-two hours have passed since the index case was admitted to hospital.

Real-time epidemic modelling at the global influenza surveillance centre suggests a low probability that the outbreak will be contained due to the numbers infected, the often mild symptoms and the proximity of the outbreak to a major urban area. Nevertheless, antiviral prophylaxis is initiated in the affected area in an attempt to slow spread, flights from the affected city are suspended and the population is urged to avoid all non-essential travel. Nevertheless, spread is rapid, with cases occurring in most major cities in the country within three weeks and in most European countries within five weeks.

Cell-based production of a live attenuated pandemic vaccine is initiated at some 20 manufacturing facilities worldwide within one week of the initial case being identified. Regulatory pre-approval and rapid safety and efficacy testing enable the first doses to be given to vulnerable groups within three weeks. The scaleable nature of the manufacturing technology enables production to be ramped to 100 million courses per week with one month, and 300 million courses per week a month later. Round the world, children and the old are prioritised for vaccination – the former to reduce transmission and the latter to minimise mortality.

In the UK, progress of the pandemic is tracked using real-time surveillance data from all GPs and hospitals. Often this clinical surveillance is backed by real-time pathogen diagnostics. There is a race between the production and delivery of vaccine and the spread of the virus, but use of school closure and widespread prophylaxis using stockpiled antivirals slows the spread sufficiently to enable 70% of the population to be vaccinated before they are infected. Of the 30% who are infected, use of antiviral prophylaxis and treatment reduce morbidity and mortality substantially – to levels barely worse than a normal influenza season. Overall, mortality is 10-fold lower than for previous influenza pandemics.

How might we get from here to there?

These two episodes illustrate future routine application of technologies identified in the four User Challenges of this project. To get to this point, however, much more than new technology development is required. Here, for each User Challenge, we elaborate on the roadmaps that would take our present knowledge to these future uses. In doing so, possible improvements in performance and capability are outlined.

UC1: In 2025, international and national disease centres now operate information networks with access to all national human, animal and plant disease data, including output of a growing number of real-time remote sensors. They use machine learning algorithms to search these data sources for patterns of disease emergence, distribution and movement. New data-mining methods have been important to this development, but most important has been agreement at a high governmental level to share this information.

Methods for the real-time epidemic analysis and prediction have developed significantly in the two decades leading up to 2025. All major national governments and international agencies have global simulation models which are linked in real time to disease surveillance data centres, and to real-time data feeds from global transport systems. Additional data on control measures being implemented in different regions are entered manually. Advances in computational capacity and more efficient simulation algorithms mean these models are run thousands of times per hour to fit them to the emerging epidemic and get the most reliable short- and medium-term projections of spread. The predictive power of these models is still less than perfect due to the fundamental stochasticity of epidemic spread, but has improved dramatically since 2005. Fundamental to this improvement has been the incorporation of a more realistic description of the natural history of disease in infected individuals, and how this varies between people. Data on the natural history of disease has been revolutionised in the preceding 10 years by the availability of reliable hand-held diagnostic devices.

UC2: Greater monitoring of diseases worldwide means that, in 2025, new diseases and variants of existing diseases are reported more frequently. One of the benefits of the widespread deployment of hand-held devices for disease diagnosis has become the detection of diseases similar to, but not matching, existing forms recognised by the devices. In the past, identification of these diseases meant despatch to a few specialised laboratories, often overseas. In 2005, reluctance of airlines to carry samples or to subscribe to safety procedures extended long transit times, while the tests themselves to identify the strain of influenza would take over 24 hours. Hence, precise identification of a bird influenza strain could take almost a week. Now, national laboratories have been established with the equipment necessary to sequence genomes, so identification is never more than a day away. Bioinformatic capacity, and in particular the capacity to interpret genome change with respect to virulence and host range, is networked internationally to these centres. In Africa, where national capacity is still limited, regional centres of excellence perform this task.

UC3: Hand-held devices for the detection of avian influenza and other diseases were in prototype stage as early as 2006. Their high-profile press coverage created the false impression that widespread use of this technology was imminent. In fact, years of effort were still required to turn prototypes into affordable, widely used products. Development of these devices required considerable public funding. While medical uses of hand-held devices facilitated

product development, specific applications to disease diagnosis were too narrow to attract commercial investment. Public funding bridged the gap and also ensured that interoperable systems were developed, which was particularly important to developing countries.

As a result of this effort, by 2015, hand-held devices have become ubiquitous for use in medical diagnosis and monitoring, as well as in agricultural biosecurity. These initially use inserted microarray ‘cassettes’, but by 2025, the devices are undertaking full genome sequencing for all viral pathogens. They store a local copy of key viral pathogen sequences for genetic matching, but can also interrogate global comprehensive sequence databases wirelessly. The devices are able to report specific variation in diseases, such as resistance to drugs or antigenic variation.

For all of these technologies, international organisations played a critical role in their development, creating dialogue and funding initiatives on technology development, responsibility, harmonisation and interoperability and capacity-building in the developing world.

3b Managing the risk of SARS in 2015

The early 2000s

Severe acute respiratory syndrome (SARS) emerged in late 2002 and went on to cause over 8,400 probable cases (10–15% of whom died) in 32 countries by the end of July 2003. The causative agent, SARS coronavirus, a virus belonging to a family of viruses more usually associated with the common cold, was rapidly identified and diagnostic tests developed. No specific antiviral treatment or vaccine had yet been developed against SARS and the outbreak in 2003 was controlled by rapid identification and isolation of clinical cases, follow-up of contacts, and infection control. Screening for SARS in international travellers was applied in some countries but was not assessed to have been an effective control measure.

SARS was believed to have emerged from an animal reservoir and passed to humans, probably in association with wild animal markets in southern China. Following the declaration, in July 2003, that the global transmission of SARS had been halted, four further small and rapidly contained outbreaks of SARS occurred over the next 12 months. Three of the outbreaks were related to biosecurity breaches in laboratories and the fourth to a presumed, but unidentified, animal source.

Measures to reduce the likelihood of future re-emergence of SARS in the human population were taken and include the closure of such markets and tightening of laboratory procedures. If SARS did re-emerge, earlier recognition and the application of well-established control measures made substantial international spread unlikely.

Nevertheless, the fact that the animal reservoir(s) for SARS were not known at the time and the possibility of future laboratory releases, combined with the fact that some human cases are especially efficient at spreading infection (‘super spreaders’), meant that the re-emergence of SARS and spread in the human population could occur, and vigilance needed to be maintained. It was not possible to precisely quantify this risk, but the likelihood of an outbreak on a scale greater than the four incidents that have occurred since July 2003 was considered to be small.

2015: new DIM systems offer new tools for managing outbreaks

In 2015, confirmation of the re-emergence of SARS is still based on the result of clinical and public health vigilance combined with highly specific laboratory diagnosis. The scope for innovative detection systems is still limited at this stage, other than in the development of methodologies for highly specific reference laboratory diagnostics in general.

However, when an outbreak emerges in 2015, new DIM systems are now available to manage the situation. In particular, there are now rapid and reliable

tests to diagnose SARS infection. The test is based on the detection of nucleic acid or viral antigens in saliva and is used in three broad groups of people:

1 People presenting for medical attention with an illness compatible with SARS. A rapid and simply applied test in these circumstances is used by health workers for patients in the community and on initial presentation to hospital. It enables immediate prioritisation for the purpose of isolation, treatment and contact follow-up.

2 Contacts of SARS cases. The saliva test enables the identification within a few days of exposure of infected contacts and enables their early isolation and treatment.

3 International travellers. The saliva test is used for passengers with a febrile illness. It enables early isolation and treatment of cases, and identification of contacts for follow-up.

Operational considerations

The consequence of a diagnosis of SARS, for both the patients themselves and those in the community around them, is substantial. So the test had to be highly specific as, in most circumstances, the great majority of people who might be tested would not have SARS and even small numbers of false-positive cases would be very disruptive. Conversely, the consequence of failing to diagnose a true case of SARS, which would result in the possibility of further spread of infection due to failure to isolate the patient, would be very damaging to the control strategy and disruptive to the health service. Thus, the new test needed to be both highly specific and highly sensitive – manufacturers had found this difficult to achieve in a simple and rapid test.

It was considered unlikely that screening of all international travellers would be an effective control measure as some who had been exposed but who were at a very early stage of infection would be unlikely to be detectable by even the most sensitive test. However, a strategy based on the early identification of cases and follow-up with early diagnosis of their contacts was seen as possibly obviating the need to screen all passengers. Testing could then be reserved for passengers complaining of illness or noticed to be visibly ill by airline staff. At this stage, the saliva test could be employed to provide a rapid diagnosis.

Importantly, SARS was not seen to be a health problem for most of the time and the development of such a diagnostic test was therefore an unattractive proposition for commercial development. It therefore had to be developed under funding from public health sources.

Costs and benefits

Rather than attempt to assess the benefits of the new DIM systems for a future hypothetical outbreak of SARS, the following assesses the benefits using the

2002/2003 outbreak as an exemplar. In doing so, the calculations evaluate the savings that would have resulted in this outbreak had the future DIM systems been available and in use.

In 2002/2003, SARS resulted in substantial disruption to the economies of the areas affected. An impact of US$40 billion was estimated on the economy of the Asia–Pacific region, although economic activity in the region was observed to have recovered rapidly. Much of the impact was seen in travel and tourism. Flights in the Asia–Pacific region were reduced by 45% during the SARS outbreak compared with the same period the previous year. A 1% reduction was estimated in the annual US$200 billion economy of Toronto as a result of the SARS outbreak. US$763 million was separately estimated to have been the cost to the Toronto healthcare system. This corresponds to an approximate cost to the Canadian economy of US$46 million for each of the 43 deaths from SARS in Canada, or US$18 million per death in healthcare costs.

The availability of a reliable saliva test for the groups of individuals outlined would have considerably increased the likelihood that SARS was brought under control in any locality, involved fewer patients and reduced the risk of onward spread of infection to others. In the event of a re-emergence of SARS, industrialised countries were concerned about the possibility of imported cases leading to outbreaks similar to that seen in Canada in 2003. The availability of a test with the characteristics outlined might be expected to at least halve the costs of direct healthcare as a result of rapid containment. In Canada, this would have corresponded to US$380 million.

3c Integrated dual detection of HIV and active tuberculosis in 2015

The situation in 2006

In 2006, HIV and tuberculosis (TB) are major causes of infectious disease mortality in adults in the developing world. The impact of HIV on the resurgence of TB has been devastating. An estimated 13 million people are co-infected with both organisms and about 10% of TB cases worldwide are attributable to HIV. The greatest impact of these infections is in sub-Saharan Africa where, on average, TB notifications have trebled since the mid-1980s. The problem of TB and HIV is extending to other parts of the world, including Russia and eastern Europe.

One-third of the world population is estimated to be infected with tuberculosis. But in most infected people with competent immune systems the infection is contained (latent infection) and only about 5–10% of infected individuals develop TB disease during their lifetime. However, in people with a compromised immune system, such as those with HIV, the risk of developing TB disease as a result of reactivation of a latent infection increases to 5–15% annually, rising with increasing immune deficiency. As the HIV epidemic matures and an increasing number of infected individuals become immune-compromised, notifications of TB will continue to increase. TB notifications mirror increases in HIV prevalence, and in Africa, where HIV is the main underlying cause of TB, this is sufficient to cause a global increase of about 1% per year.

The success of TB control programmes in Africa will depend on the prevention and treatment of HIV infection. A more inclusive approach to TB control is needed that embraces methods of preventing both HIV and TB and reduces the progression of latent infection to active disease in HIV-infected individuals. Novel diagnostic solutions are seen as essential to achieving this.

In developing countries with a high prevalence of HIV and where most cases of TB occur, the diagnosis of TB is usually based on non-specific clinical signs and symptoms and laboratory findings based on the presence of acid-fast bacilli in a sputum smear. Although smear microscopy is easy and quick, it is relatively insensitive, with up to two-thirds of all cases of TB remaining undiagnosed. For example, smear microscopy does not detect pulmonary TB where there are low levels of bacilli, nor does it detect cases of extra-pulmonary TB. Furthermore, as some acid-fast bacilli are not *Mycobacterium tuberculosis*, a diagnosis of TB cannot be confirmed. Sputum culture on initial samples is required to confirm the diagnosis of TB disease. However, this requires several weeks before the results can be seen, thereby delaying a firm diagnosis, and in most developing countries, culture is only performed in reference laboratories. For all patients, the initial *M. tuberculosis* isolates should be tested for drug resistance to ensure effective treatment, but this is rarely feasible in the developing-country setting.

Rapid tests to diagnose TB that are affordable, reliable and easy to carry out are urgently needed. Large numbers of individuals at risk could then be tested in outreach clinics to identify infected individuals at an early stage to permit prompt and appropriate treatment. If tests for HIV and TB were performed simultaneously on the same sample, the clinical management of both infections could be integrated. Obviously, the availability of antiretroviral therapy for HIV- positive individuals co-infected with TB is an important requirement.

2015: a dual detection system in operation

Integrated HIV–TB control programmes are now fully operational after initial validation studies in different community settings. The test kits have been widely distributed, with the support of international agencies in poorer countries. Those suspected of dual infection and those at risk are tested for HIV and active TB at the same time using a single urine sample and a hand-held diagnostic device. The test measures fragments of DNA (from TB) and RNA (from HIV). TB could be accurately diagnosed from urine around 2007 but HIV was more challenging because of the labile nature of RNA. Nevertheless, by 2012 both HIV and TB could be diagnosed in urine. It took a further two years to transfer the technology to a hand-held device and validate the tests. It is envisaged that in a further 3–5 years, a saliva test may be available. This has been especially problematic as it necessitates the measurement of very low levels of TB antigen in saliva. However, significant improvements in biosensor technology now make this seem a viable option for the future.

The potential benefits of locally based dual-infection testing have been demonstrated. The test is simple to carry out and can be used by appropriately trained staff. The kit, which gives an immediate test result, comprises a disposable cassette plugged into an electronic unit resembling a mobile phone. Information is passed from the device to a local medical centre triggering a clinic appointment for those found to be positive. Diagnosed cases, together with information on resistance, are notified to the local surveillance centre database, which provides routine statistics to the national surveillance centre. This information is integrated into the global statistics required for monitoring international control programmes.

Testing sessions are preceded by group discussions on the nature and prevention of these infections and the importance of early diagnosis and treatment. Following diagnosis of HIV and/or TB, tested individuals are referred immediately to a healthcare centre for counselling, further examination and treatment. Those with active TB are given a nucleic-acid-based saliva test for antimicrobial resistance to ensure that the treatment they receive is optimal.

As HIV infection is the most potent risk factor for converting latent TB into active infection, HIV-infected patients who do not have active TB are tested for latent infection using a T-cell-based assay that requires overnight incubation. Those with

latent infection are regularly monitored for active infection and preventive therapy considered. The T-cell-based assay, which requires laboratory facilities, is still not widely available in some settings, particularly in poorer countries.

Obstacles to realising the benefits of advances in HIV–TB control

In introducing the new tests, operational, professional and social barriers needed to be addressed.

The potential impact of these hand-held devices is greatest in sub-Saharan Africa, where the problem is most acute. However, success here depended not only on the deployment of local testing but also on the availability of human and other resources to provide the necessary infrastructure for the onward referral and management of patients diagnosed with infection. The impact of efficient diagnosis hinged on the general availability of antiretroviral and other antimicrobials for the treatment of infected individuals.

Follow-up of patients on treatment was essential and facilities needed to be in place to cope with the increased caseload, taking into account requirements for confidentiality. Those being tested needed to understand the implications of a positive result and to consent to testing. When they received a positive test result, they needed support and counselling.

Notification of cases of infection and of TB resistance needed to be comprehensive and sustained.

Barriers between professional groups had to be overcome in the initial stages of the implementation of the dual test. Experts in HIV and TB had not worked together before and came from different branches of medicine. They had different knowledge bases and networks and felt that their reputation, position and influence were under threat. This problem was overcome and there is now a new genre of specialist who is expert in both infections and their prevention.

Social barriers were important and critical to the success of the programme. Practical issues such as transportation to clinics and financial needs, family pressures and stigma were all important.

Assessing the benefits

Following the introduction of the dual-testing programme, notifications of both TB and HIV increased dramatically causing worldwide concern. However, the increase reflected the success of the programme and the increasing number of people being tested and diagnosed, together with much-improved case notification. By the end of 2015, the number of notifications began to decline.

The integrated attack on HIV and TB succeeded in reducing mortality and morbidity in those countries where it has been possible to exploit the advantages

of novel dual-testing technology followed by appropriate treatment. The impact was reflected in a decline globally in the prevalence of these infections and reductions in mortality and morbidity.

The integrated treatment and management of these two infections has been cost-effective and improved both prevention and patient care. It has also played a part in the de-stigmatisation of HIV infection.

3d Fighting the *Phytophthora* threat to UK native trees and woodlands with an innovative biosecurity chip in 2015

2003: a problem appears

In 2003, large rhododendron bushes and beech trees in historic woodland gardens in the heart of Cornwall were found to be dying from an unknown cause. Further investigations by Forest Research and the Central Science Laboratory revealed that the problem was caused by a previously unknown fungus-like pathogen. This new plant pathogen has now been named *Phytophthora kernoviae*. It was found during a survey for another exotic pathogen called *P. ramorum*, first found in the UK some years earlier. Although P. ramorum was new to the UK, it had previously been described in the USA, where it is responsible for the disease called sudden oak death. The extent of damage to trees and shrubs and the apparent speed with which symptoms were developing indicated that *P. kernoviae* posed a potentially serious threat to native woodland environments in the UK. By 2006, concern has become focused on the potential threat to the UK's 83,000 hectares of beech 'high forest' and woodlands along with a further 3.4 million individual beech trees outside of woodlands.

Fig 3.1 *Rhododendron dieback* – Phytophthora kernoviae

As *P. kernoviae* is a recently described species, our knowledge of its origins, development and spread remain limited. A number of studies have now been initiated by the Department for Environment, Food and Rural Affairs (Defra) and the Forestry Commission to better understand the biology of the organism, but these will take some years to complete. To date, the disease has only been reported at a limited number of sites in Cornwall, south Wales and Cheshire, and statutory action is taken whenever the pathogen is found. Meanwhile, further new *Phytophthora* species continue to be found outside the UK, including some in the USA, that also infect indigenous tree species. In the absence of any firm knowledge of the threat (if any) that these new findings pose to the UK, it is difficult to know what resource should be dedicated to combating them.

A scenario for plant pathogen detection in 2015

By 2012, rapid advances and the plunging cost of DNA sequencing have permitted the sequencing of the whole genome of thousands of isolates of plant-infecting *Phytophthora* species. International consortia of scientists have also developed re-sequencing 'chips' and other tools to allow the rapid recognition of new species as well as newly emerging and evolving variants (including hybrids and mating types) of existing species. In parallel and by 2015, advances in our knowledge to predict the biology of newly described plant pathogens based only on their DNA sequence permitted predictions of important factors such as which hosts the new agents would infect and how damaging they would be.

Newly emerging species of *Phytophthora* are now rapidly recognised and characterised by national plant health surveillance programmes and the information shared in real time on common international databases. Any new species that appeared to pose a significant new threat to crops or native flora are also rapidly identified and alerts issued to relevant inspection agencies and industry. By this time, inspection agencies are routinely using hand-held devices of the kind envisaged in UC3 and are reacting and targeting inspections of at-risk plant material moving in trade, based on such internationally based intelligence and even remote monitoring devices based at points of entry and in transit as envisaged in UC4. Hand-held and remote monitoring devices are quickly updated with new detection modules to be able to recognise characteristic genomic or other signatures of the newly identified plant pathogen.

Some problems emerge

Implementation of the new technology and surveillance systems was not entirely problem-free and a number of issues emerged that needed addressing. By 2015, harmonisation of international phytosanitary regulations and commitments to free-trade agreements had become much more firmly embedded. Some countries, however, were still accused, on occasion, of using data generated by the international plant disease surveillance networked databases to erect trade barriers not based entirely on risk. In parallel, plant health authorities faced the continuing challenge of updating international legislation to reflect a new emphasis of taking action based on pathogen sequence motifs rather than traditional species concepts. Getting widespread agreement on a fair and equitable balance on who should pay for the plant health surveillance, inspection and control procedures between public and private interests, as well as between importers and exporters, was also a complex task.

Benefits

Plant diseases caused by the 60 or so species of *Phytophthora* appear to be causing rising concern throughout the world. Diseases such as potato late blight, the cause of the Irish potato famine in the 19th century, are well known to the public, whereas others, such as the Western Australian 'jarrah dieback' fungus,

P. cinnamomi, threaten to destabilise entire world heritage natural ecosystems. In the UK, the two new tree- and shrub-infecting *Phytophthora* species pose a still unquantifiable risk to native flora. It is difficult to put a value on such ecosystems, but a number of socio-economic studies have indicated that the British public might place a value of £1–2 billion per annum on our woodlands and trees.

Monitoring imports and taking statutory action on findings of the disease place a further burden on the taxpayer and industry. The improved ability to detect plant pests moving in trade at points of entry will also be significant in the face of expected increased risk posed by climate change and trade globalisation. Defra currently plans to inspect 100% of regulated plant imports from non-EU sources, but finite resources mean that only a small proportion of non-regulated imports are currently inspected. Advanced detection technology could significantly enhance our capability and resilience against future plant health threats. The expected advances in plant disease surveillance and detection described in this study will hopefully contribute to safeguarding our crops and native flora against such risks well into the future.

It is expected that the techniques developed will also make more certain the detection of quarantine pests. The ability to test and confirm the presence of pests at the point of entry will bring with it the lowering of the risk of quarantine pests entering the UK. Timescales between sampling and testing will be virtually reduced to zero compared with today's practices. Costs will be lowered compared to laboratory diagnostics, and costs for inspections would be made lower, thereby benefiting trade.

An innovative biosecurity chip for diseases in humans, animals and plants

This Foresight project has shown that advances in molecular biology will offer unparalleled new opportunities for the rapid detection and characterisation of newly emerging infectious agents of plants, animals and humans in the near future (UC2). In particular, the project predicts that microarray ('lab on a chip') and novel DNA sequencing technologies currently being developed for the development of new medicines will be at the forefront of this revolution.

Realising this potential, the Chief Scientist's Group at Defra has commissioned a new project: 'the Defra biosecurity chip'. This will develop a diagnostic microarray for just such a purpose. This new tool will initially be aimed at the detection and characterisation of quarantine viruses of importance to the department and will be capable of detecting over 600 different viruses in a single test. Importantly, this innovative project will exploit the clear synergies between studies of plant, animal and human infectious disease recognised within this Foresight study. The 'chip' will be able to detect viruses that infect plants, bees and fish as well as livestock and 'zoonotic' viruses that threaten human health. The project will also develop so-called 're-sequencing chips' which will allow the detailed characterisation of high-pathogenicity avian influenza, rabies and FMD viruses and will be capable of detecting newly emerging viruses.

A unique multidisciplinary team comprising the Central Science Laboratory, the Institutes of Animal Health at Compton and Pirbright, the Veterinary Laboratory Agency, the Health Protection Agency, the Centre for Fisheries and Aquaculture Science and the Royal Veterinary College has been assembled to develop this new tool.

A logical extension of this project would be the subsequent development of further diagnostic chips capable of detecting new and emergent bacterial and fungal pathogens of plants, animals and humans including the new *Phytophthora* species that currently threaten our native woodlands.

3e A personal diagnostic device for sexually transmitted infections in 2015

In the years leading up to 2015 in the UK, there had been ever-increasing pressure on clinics for sexually transmitted infections (STIs), making it more difficult for them to meet their targets for seeing patients quickly. The causes included:

- the trend towards high-risk sexual behaviours, evident since around 2000, which had continued
- the emergence of diseases that were novel to the UK – such as LGV in the early 2000s – partly due to people holidaying in increasingly exotic locations and becoming exposed to new diseases
- increases in drug-resistant strains – partly fuelled by the growing use of inappropriate drugs bought over the internet
- too many young women still becoming infected with undiagnosed asymptomatic STIs – particularly chlamydia, exposing them to the risk of infertility and other complications.

An increased demand for testing had also resulted from educational campaigns empowering individuals to take more responsibility for their own sexual health by encouraging those who change their sexual partner to seek screening for STIs. However, around 5 million individuals each year had at least one change of sexual partner – a number far in excess of the capacity of specialist genito-urinary medicine (GUM) clinics and their supporting local networks in community contraception services and primary care.

Advances in diagnostic methods (from 2000 to 2015)

From 2000 to 2015, there had been a rapid expansion in diagnostic methodologies for the detection of STIs. For some years, validated minimally invasive tests utilising urine, oral fluids and material from genital swabs had been available for the detection of antigens and antibodies. Moreover, technological advances, not least in the miniaturisation of rapid nucleic acid detection and quantification methodologies, had allowed a trend from laboratory-based towards point-of-care (POC) tests. POC devices came to deliver high-quality results with improved sensitivity and specificity in a timely manner.

By 2015, conventional laboratory-based culture techniques and classical serology-based tests were rarely used. Even before this, POC devices for detecting an array of STIs in a single test were available for professional use in clinics. Between 2010 and 2015, there was a general trend towards their use outside traditional clinical settings and towards individuals taking more control and responsibility for their sexual health. By 2015, self-testing kits were readily available and could be purchased from pharmacies and supermarkets (see

below). Initially, these tests, especially when self-administered, were used to supplement conventional diagnostic techniques and the results tended to be verified by more conventional assays – but high-quality approved POC tests replaced conventional assays to allow more efficient and cost-effective use of professional time in one-to-one interactions with patients. Poor-quality tests could still be purchased via the internet – a series of programmes was initiated to address this problem.

During the final years of the last decade, accurate testing for multiple pathogenic causes of genital ulceration from lesion swabs became routinely available within specialist services. These provided results within 30 minutes, allowing treatment to be given on the day of presentation. Subsequently, multiplexed tests for all common causes of urethritis, including *Niesseria gonorrhoeae, Chlamydia trachomatis, Mycoplasma genitalium* and other mycoplasmas, trichomoniasis, and herpes simplex virus (HSV), became available on POC devices – these tests utilised urine samples or genital swabs. In the first generation of these devices, the user was directed to a second follow-up test that detected genetic mutations and polymorphisms within the identified pathogen(s) and allowed selection of the most appropriate treatment regime. More recently, identification and antimicrobial susceptibility have been combined in a single device – see below.

Increasingly, it became possible to perform POC tests in peripheral locations and link test results to a central laboratory via the internet for the results to be interpreted and reports to be issued by a consultant microbiologist.

A new lifestyle accessory becomes widely available

In 2015, hand-held diagnostic devices for the detection of STIs were widely available. The devices had two parts: an electronic unit costing around £100, and a disposable test cassette that plugged in and which cost £10 each. The devices resembled a mobile phone, and indeed, were developed and marketed by mobile phone companies. They were cut-down versions of tests that had been used for screening in GUM clinics since 2011.

The devices were marketed as a ‘lifestyle health check-up’ and quickly became very popular. Instead of waiting for an appointment at a GUM clinic, it meant that people could test themselves at home, within an hour, using urine, self-taken genital swabs or other samples as directed by the manufacturer. They still had to go to their doctor or a clinic for treatment, but some clinics gave fast-track appointments to people who had already tested themselves. The commercial success provided impetus for the manufacturers to accelerate development of the next-generation cassettes – these would detect more diseases, and identify drug-resistant strains, e.g. ciprofloxacin-resistant gonorrhoea.

The principle of each test cassette was similar to the multistrip testing of urine that had been used in the latter part of the 20th century, but updated with a wider range of diagnostic tests and using technological advances in testing techniques.

The devices came in two basic types:

- The first detected the presence of antibody to various pathogens in body fluids, and could utilise urine or saliva (for syphilis, HIV, viral hepatitis, HSV-2 antibodies). These tests give a reliable indication of infections acquired by the individual at least six weeks prior to the date of testing.
- The second type contained an array of tests for detecting antigens in relevant secretions. These could be used in self-taken specimens from the urogenital tract, including urine and genital swabs, the rectum, and oropharynx (saliva could be used).

These tests were capable of detecting *Chlamydia trachomatis* D–K strains that caused genital infection and L1–3 strains causing LGV, syphilis, gonorrhoea, *Mycoplasma genitalium*, candidiasis, trichomoniasis, and bacterial vaginosis, and HSV-1 and HSV-2.

A mixed reception by professionals

Despite the popularity of the diagnostic devices, particularly with the younger middle classes, the attitudes of healthcare professionals were mixed. On the positive side, they recognised that the devices could play a valuable role in diagnosing asymptomatic infections in large parts of the population and empowering individuals who would not normally visit a GUM clinic. Moreover, in areas of socio-economic deprivation, where STI prevalence was high, many local health organisations had made these tests available in a variety of healthcare settings, including supermarkets and pharmacies.

However, on the downside, websites immediately sprang up offering drugs matched to test results. Such ‘treatment’ sites proved difficult to control and caused several concerns:

- There was a fear that inappropriate or sub-standard drugs were sometimes sold, possibly promoting drug resistance not only in STIs but also in other microbial agents that caused community-acquired infections.
- The treatment websites severed the link between the patient and professional healthcare workers. This prevented the infections being professionally viewed within the wider context of the patient’s health. It also prevented the encouragement of partner tracing.
- Thirdly, they prevented the central collection of diagnostic data. This could, in principle, be partly avoided by reengineering the device so that diagnostic information was automatically sent to a central database via a telephone link – the developer was well placed to achieve that. However, concerns about data confidentially were causing heated political debate.

There were also concerns that test results would not be subject to validation, interpretation and report by a suitable healthcare professional. Although test sensitivity had been shown in different populations to be 90–95%, the 95% specificity of most test components resulted in a significant proportion of false-positive cases when used in low-prevalence populations. There was also concern that false-positive diagnoses could expose patients to the potential adverse consequences of unnecessary treatment, induce stress, or have potentially serious adverse consequences for the partners of those who had given positive results.

There was also the possibility that individuals who frequently changed sexual partners would be falsely reassured by a negative test result on one occasion, then continue an unhealthy lifestyle that placed themselves and others at ongoing risk of STI acquisition and transmission. So there was a concern that the devices might promote an increase in the lifetime number of sexual partners, and that this could overcome the potential benefits of earlier detection and treatment of STIs. For this reason, the manufacturers were obliged to include information about each STI being tested for, about what infections could not be reliably detected by the test kit, and advice about relevant lifestyle issues.

The disposal of the test cassettes was also a concern – pharmacies were asked to provide bins to promote their safe disposal.

Potential benefits

More timely diagnosis would help to prevent onward transmission and the development of complications. In particular, wider screening would help to identify a larger proportion of the asymptomatic reservoir of infected individuals. In the case of chlamydia, around 9% of sexually active young women were thought to be infected, 70% of whom were asymptomatic (50% in men).

Patients with positive results would be encouraged to seek healthcare for either curative treatment and/or sexual health lifestyle advice – to reduce the risk of onward transmission of latent STIs, and to reduce individual risk of acquiring more serious STIs such as HIV infection.

It would not be unreasonable to assume that over a five-year period the overall prevalence of STIs such as chlamydia, gonorrhoea and of new HIV transmissions would decline by about one-quarter. The immediate health economic benefits from such reductions in hospital admissions for chlamydia and gonorrhoea could amount to around £45 million for outpatient treatment of uncomplicated infections and at least double this amount for treatment of complications – chlamydia is the most common cause of ectopic pregnancy and pelvic inflammatory disease, leading to infertility. However, this would be far outweighed by the cost benefits of reducing HIV transmissions. Each HIV transmission averted is worth £0.5–1 million in lifetime economic benefits (National Sexual Health and HIV Strategy 2001) so the cost saving from reducing 1,000 HIV transmissions per annum would be worth £0.5–1 billion to the economy.

3f Foot-and-mouth disease – smart detectors save national livestock in 2015

A livestock epidemic unfolds

It is 2015 and our Norfolk farmer has diversified his livestock enterprise to respond to the ever-increasing public demand for lean meat. He has replaced his commercial pig unit with an outdoor wild boar herd and built up a fallow deer enterprise alongside his beef herd.

However, in the past week, he had noticed some of the deer were not well. As usual, he obtained a disposable diagnostic test via the internet – selecting one that would test for all endemic ruminant diseases. He did not consider engaging a veterinarian. There were few remaining in his area prepared to undertake large animal work and the internet was a cheaper and faster way to make a diagnosis. It was also a way of obtaining treatment. In this case, the test had shown a positive for infectious bovine rhinotracheitis (IBR) and he was able to obtain IBR vaccine, again via the internet, for controlling the outbreak.

This particular week, he was preparing to take some of his prize deer to the Royal Norfolk Agricultural Show – his only other problem had been that a few wild boars had escaped through the perimeter fencing of the farm. As this had happened before, he knew they were nearly impossible to recapture, particularly with the increasing wild population in the ‘set-aside’ agricultural environment.

Unfortunately, after two days at the Show, three of his deer showed clinical signs of lameness, not eating and general discomfort. He informed the Show officials that this must be IBR and that all animals had been vaccinated. However, the show’s veterinary surgeon was not satisfied. Her clinical examination revealed a further possibility. She used her mobile phone ‘smart detector’, which allowed her to dial in the essential clinical signs, select a relevant disease profile which, in this case, was ‘ruminant vesicular diseases’. The ‘smart detector’ required a smear of saliva on its sensor-pad which, within 30 minutes, could be analysed for the viral RNA and DNA programmed in the selected profile. Within this time, the nucleic acid signature obtained through the ‘smart detector’ had been transmitted to a data base at the Central Veterinary Laboratories, which, by analysis of the signal profile, had returned a positive identification for IBR. It had, however, also provided a positive diagnosis for foot-and-mouth disease virus (FMDV). There was now automatic connection from this central database to the national and international surveillance networks to provide further alerts of FMD diagnosis. This, in turn, triggered an official procedure for control. Rapidly, the orders for statutory movement controls were set in place.

Further problems arose. As the Royal Norfolk Agricultural Show attracted animals from the entire country, many potential 'dangerous contacts' had been created, some of which had already returned home. Furthermore, the wild boar that had escaped from the home farm could now become integrated into the feral wild boar population. Finally, at the FMD World Reference Centre at Pirbright, Surrey, further genomic analysis of virus isolated from swabs and blood from the deer revealed that this was the same exotic FMDV type A strain that had caused widespread and severe disease in small ruminants and pigs in Asia, and recently in the Middle East.

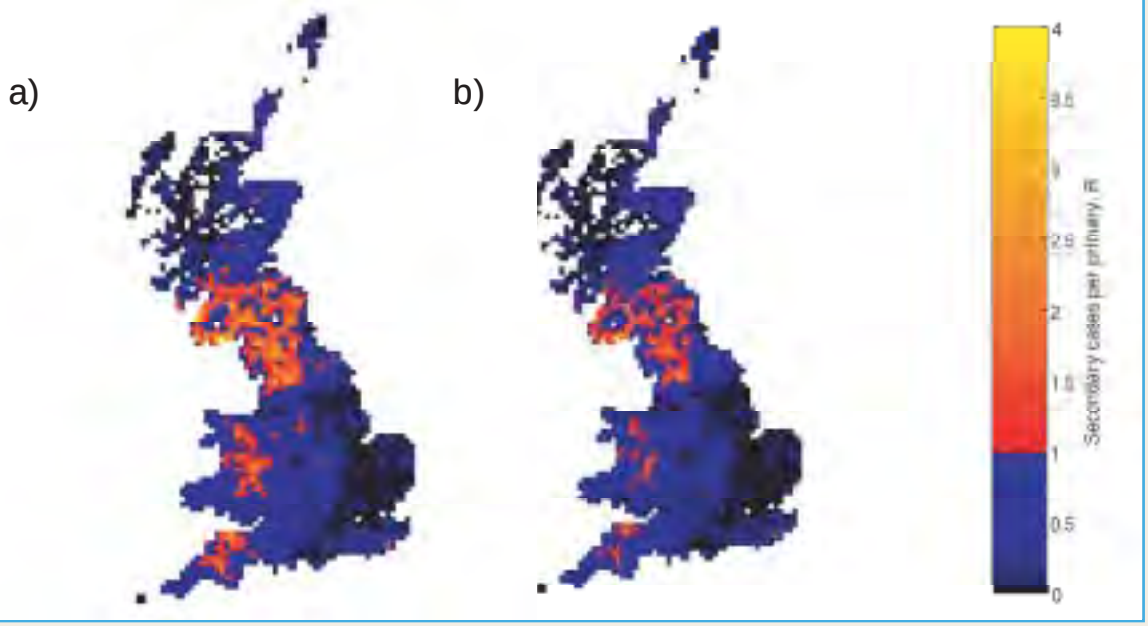
The benefits of DIM in livestock disease control and surveillance

FMDV is the most highly transmissible virus disease of cloven-footed livestock and has now been eradicated from most of the developed world, i.e. Europe, North America and Australasia. In our 2015 scenario, it remains rampant across many countries of Asia, the Middle East and sub-Saharan Africa. In the past two decades, new strains have arisen that have spread epidemically across these continents, often replacing the local viruses. In their wake, there have been considerable animal and production losses. This has damaged the viability of agricultural markets and curtailed their global trading in animal products. Moreover, for the developed countries that now have a greater reliance on sourcing food from these regions, there is considerable concern.

The increasing global trade in animals and food to these developed countries has increased the threat of introducing FMD infection. Its re-emergence in these regions can still be catastrophic, with the potential for wider transmission of the virus through airborne spread and through animal movements. In spite of this, there is still no financial incentive for routine vaccination of the national herd. In fact, it would not be permitted. In 2015, we have an effective molecular-engineered vaccine (a 'marker vaccine') that can only be used in the face of an outbreak. It gives rapid protection but does not interfere with diagnosis.

However, the challenge for control remains in the rapid detection of infection. Modelling studies had shown that a delay of 3–4 days in a correct diagnosis can double the size of the outbreak. The availability of a 'smart detector' permits an examination of all known ruminant viruses, through microchip technology, thereby allowing the rapid detection of single, dual or even multiple infections within a sample.

Fig 3.2 Predicted impact of more rapid diagnosis on risk of foot-and-mouth disease in the UK in 2015. Risk is expressed as reproduction ratio (R) through local spread assuming 7 days to detection of disease on farm (Figure 3.2a) and assuming only 5 days to detection (Figure 3.2b). The proportion of 10km x 10km squares where the average R is above one is 15% and 9% respectively, illustrating the benefit of early detection and control at the farm level for reducing the likelihood of a major epidemic.



Defra's quick response to major threat

Less than an hour after the call to the veterinarian, a provisional diagnosis of FMDV had been made. The veterinary authorities immediately imposed a total ban on livestock movements and closed livestock markets. As it turned out, because the index case had been detected so quickly the movement ban was effective in preventing any 'silent spread' (in marked contrast to the 2001 epidemic where livestock movements spread the disease widely before it was known to be present). Also within the first hour, a specialist team was dispatched to the Norfolk Show Ground and to the deer farm to inspect all animals. Only those animals that were infected or directly in-contact were culled, whereas all others were monitored for a further six weeks to investigate onward transmission.

Samples taken back for laboratory analysis allowed a full genomic analysis and provided sufficient information to identify the strain and relevant 'marker vaccine'. The routine electronic tagging of livestock had allowed the authorities to direct veterinary surveillance to all premises from which Show livestock originated. In the event, only three further farms were subsequently shown to be affected; all were sheep that had been penned close-by the original infected deer at the Show. All three farms and dangerous direct contacts were culled. The real

concern about the possibility of 'silent carriers' in sheep transmitting FMDV nationally, as seen in 2001, was not realised. No vaccination was needed. There is still some concern about the potential for carriage of virus by the feral wild boar but this is being considered in collaboration with the wildlife agencies. Fortunately, the predictions were reassuring; in previous FMD outbreaks, wildlife had played little part in the spread of FMDV. The countryside was not closed to the public apart from the neighbourhood of the four affected farms until their culling, disposal and disinfection had been completed.

Table 3.1: Number of animals culled and costs in 2001 and 2015

Year	No of animals culled (on infected and contact premises)	No of animals culled (for welfare reasons)	Costs Control of epidemic	Costs Environmental Loss of tourism, rural trade etc	Costs Total costs
2001	4 million	2.5 million	£5 billion	£3 billion	£8 billion
2015	3,500	none	£50 million	£35 million	£85 million

It was clear to the authorities that the smart detectors had been a valuable aid to the veterinary teams but it was also clear that the vigilance of the veterinarian at the Show had been the most important 'front line' diagnostic resource. A different scenario might be predicted if there had not been such vigilance and no availability of rapid and effective 'smart detectors'.

Misuse of new technology

By 2015 there has been a growing trend for livestock owners to obtain diagnostic kits directly from the internet. It is considered cheaper than engaging veterinary services and, for some geographical regions, overcomes the lack of local livestock veterinarians. To some degree, this is a circular argument with lack of support for, and from, the professionals. This trend is most apparent with the small 'back-yard' or 'hobby' enterprises. The diagnostic kits are often not standardised and rarely connected to a central data base. As such, they are limited in their range and may mistake single infections for the cause of complex diseases. It has been known for owners to use such diagnostic kits and not declare the diagnosis of diseases of national importance. Although illegal, the use of these kits is increasing and difficult to control.

3g Bluetongue in the UK in 2015 – fighting it with a modern DIM system

The threat of bluetongue in 2015

Bluetongue is a devastating midge-borne viral disease of ruminants that emerged in Europe in the late 1990s. By 2005, at least six strains of the bluetongue virus (BTV) were recorded across 12 countries, having spread over 1,000km further north than previously recorded. As a result, over 1.5 million sheep were killed and substantial losses in livestock trade were incurred (through reductions in meat and wool production as well as restrictions on livestock movements). During this unprecedented spread, north European midge species, for the first time, played a substantial role in transmission, probably because regional warming had increased their population sizes, seasonal activity and ability to replicate BTV.

In 2015, through the continued involvement of these species, outbreaks reached northern Iberia and central France. Given its proximity to these outbreaks and its dense midge and sheep populations (fine-wool and mutton breeds that are particularly susceptible to bluetongue), the UK was forecast to be under considerable threat of an incursion. In late July, prediction became reality and BTV was detected in sentinel cattle herds along the Kent coast and caused clinical outbreaks further inland in sheep in August. The DIM system in place enabled the prediction of the approximate timing and location of this incursion by the wind-borne dispersal of infected midges and the probable patterns of establishment and spread. The speed and efficiency with which control measures, including vaccination and vector control, could subsequently be implemented and directed at high-risk areas led to the successful arrest of this outbreak at an early stage.

DIM systems for vector-borne pathogens

When designing DIM systems for pathogens transmitted between hosts by vectors (usually blood-sucking insects or ticks) one must consider: (1) that such pathogens can spread, irrespective of borders and in the absence of host movements, by the movements of their vectors; (2) that the locations, intensity and timing of BTV transmission are highly influenced by climatic and other habitat factors (e.g. land use) that limit the vectors. This necessitates continental-scale co-ordination of the detection and monitoring of these pathogens and evaluation of the important environmental influences on vectors and transmission from the farmyard/household scale to the continental scale.

Predicting the arrival of bluetongue

By 2015, national BTV surveillance schemes established across Europe are relatively ‘joined up’ – with standardised methodology and rapid and accurate dissemination of data. Disease data are routinely integrated with demographic information for both hosts and vectors in the same geographical framework –

within computer-based geographical information systems (GIS). Adding remotely sensed (RS) data from satellites has greatly enhanced the analytical and predictive power of DIM systems for climate-sensitive diseases such as bluetongue.

BTV has often been transferred between land masses in Europe by wind-borne dispersal of infected midges that can be carried up to several hundred kilometres across the sea in a night. The type of wind events and trajectories that historically favoured these kinds of movements have been quantified and are now monitored, allowing epidemiologists to forecast the entry of BTV into south-east England from across the English Channel. Following confirmation of circulation in sentinel herds set up on both sides of the Channel, rapid strain identification was possible with reverse-transcription polymerase chain reaction (RT-PCR) technology. Extensive sequence databases and breed–strain distribution information built up across Europe were mined to determine the origin of this strain and its likely pathogenicity for UK sheep breeds.

Where in the UK might bluetongue establish and spread?

As BTV moved across Europe in the two decades before 2015, the continental DIM system allowed investigation of the shifting environmental space (or limiting conditions) occupied by BTV transmission areas and by biting-midge vectors. Multi-temporal satellite images at low resolution (1km grid squares) provide a picture of the seasonal conditions of rainfall, humidity, temperature and vegetation cover across Europe that are crucial in driving transmission. Determining the relative roles of these conditions in determining the birth rates and mortality rates of midges has enabled researchers to produce maps that indicate not only how suitable a farm is on average to support a midge population, but also:

- how abundant (and competent) adult midges are likely to be in a given month across the UK
- the relative likelihood of onward transmission of BTV if it is introduced into different areas and livestock populations in the UK.

Furthermore, ground surveys combined with the analysis of high-resolution images (1–30m grid squares) has allowed land use and vector habitats, such as the moist soil/dung breeding sites of biting midges, to be delineated within farmyards. But these regional and farm-scale prediction maps only have use combined with control measures that are rapidly and accurately implemented.

Counting the benefits of the DIM system for bluetongue

In 2015, disease control strategies for bluetongue involve: (1) monitoring the extent of infected populations of vectors and ruminants; (2) containing the spread of BTV by movement restrictions into, out of and through designated protection zones (PZs) and surveillance zones (SZs); (3) the adoption of procedures within farms to reduce populations of midges and reduce exposure of susceptible

animals to midges; (4) the removal of susceptible hosts by vaccination (currently with first-generation inactivated vaccines).

Historically, PZs were circles of 100km radius around affected farms throughout which surveillance and vaccination were uniformly implemented. In SZs, which extended 50km beyond the PZ, only surveillance is carried out (Scenario 1 in Tables 3.2a and 3.2b, Figures 3.3a and 3.3b). Vector control activities would probably be restricted to a 20–50km inner protection zone (IPZ) around the infected holding. During this year's (2015) outbreak in the UK, however, a risk-map-driven approach (Scenario 2) was taken. Here, these activities were restricted to those areas of farmland within the IPZs, PZs and SZs that were predicted to have a medium–high likelihood of containing sufficient midges for the onward transmission of BTV in summer, as indicated in the yellow–red regions in Figure 3.3a. As a result, around half as many livestock holdings were targeted for control activities (Table 3.2a, red areas on Figure 3.3b). Vaccinating half a million fewer ruminants in the PZ resulted in a saving of around £1.5 million (Table 3.2b), while controlling vector numbers and biting activities on only 2,300 as opposed to 3,800 holdings in the IPZ is estimated to have saved over £5 million. Further savings in surveillance effort are not estimated here but will also have been considerable.

Not only were the overall material costs of control activities substantially reduced, but those areas of farmland at highest risk could be targeted first – a strategy epidemiologists believe was instrumental in preventing the spread of BTV beyond the Kent borders. Within farms, adulticides and larvicides could be more accurately directed at larval and adult habitats identified with the aid of high-resolution imagery. These benefits dwarf, by orders of magnitude, the costs of research effort, software, hardware, imagery and co-ordination activities required to maintain the DIM system.

The drawbacks in the 2015 system

- The picture of the environmental space occupied by BTV in Europe must be rapidly updated as new data are collected and made available to the modellers (issues of data ownership notwithstanding). An inadequate picture of how BTV survives and spreads in climatic conditions experienced this far north led to some false predictions of low risk of transmission in a few farms close to the initial outbreak. Fortunately, this did not hamper the rapid eradication of the virus during this incursion.
- The DIM system would be better able to predict the likely direction of spread of BTV overland, once it arrives in the UK, if the rates at which midges move in different wind conditions over different landscapes in Europe were quantified.
- The DIM system currently relies on the supply of satellite data from NASA and the National Oceanic and Atmospheric Administration (NOAA), which has suffered from sensor failures and the cancellation of new missions. The effectiveness of DIM systems in Europe were also conditional on the adoption by the European Space Administration (ESA) and the European Organisation

for the Exploitation of Meteorological Satellites (EUMETSAT), of a more open attitude to data sharing, accessibility and costs, along the lines shown by NASA/NOAA in the 1990s.

- Researchers had some difficulty in communicating the meaning of risk maps to farmers, veterinarians and decision makers. Reciprocal familiarity is essential between the languages and terminologies of farmers, public and animal health scientists and researchers involved in DIM systems.

Table 3.2a: The number of holdings and livestock within the Inner Protection (IPZ), Protection (PZ) and Surveillance Zones (SZ) including all farmland in Scenario 1, and only farmland with medium–high risk of containing sufficient bluetongue vectors for transmission in Scenario 2.

	Scenario 1 – all farmland (red and grey areas – Fig 3.3b)				Scenario 2 – medium-high transmission risk farmland (red areas – Fig. 3.3b)			
	IPZ	PZ	SZ	Total	IPZ	PZ	SZ	Total
Number of holdings	3,828	13,402	14,588	27,990	2,289	7,378	7,936	15,314
Number of sheep	385,568	712,648	283,213	995,861	229,422	401,712	135,193	536,905
Number of bovines	50,941	220,980	247,142	468,122	32,049	121,526	113,670	235,196
Number of goats	513	2,824	2,292	5,116	362	1,541	794	2,335
Total number of ruminants	437,022	936,452	532,647	1,469,099	261,833	524,779	396,609	921,388

Table 3.2b: The costs (£) of vaccination, vector control and isolation of livestock from midges, including all farmland in Scenario 1, and only farmland with medium–high risk of containing sufficient bluetongue vectors for transmission in Scenario 2.

	Scenario 1 (£)	Scenario 2 (£)	Saving of Scenario 2 – the risk-map approach (£)
Costs of vaccination of all ruminants in the PZ @ £3 per capita including vaccine and vet costs	4,407,297	2,764,164	1,643,133
Costs of vector control in the IPZ @ £2,500 for contractor and insecticides per holding	9,570,000	5,722,500	3,847,500
Costs of isolating livestock from midges in the IPZ @ £1,000 per holding for modifying buildings and moving livestock	3,828,000	2,289,000	1,539,000
Costs of maintaining DIM system integrating vector, virus and RS data for two researchers and associated software and hardware @ £100,000–150,000 p.a.	0	150,000	–150,000
Total saving in vaccination and vector control costs of Scenario 2			6,879,633

Fig 3.3a Probability of UK farmland within the protection and surveillance zones supporting sufficient biting-midge vectors for BTV transmission (at a 1km resolution) in summer 2015. Probability is on a colour scale from green (= low probability) to red (= high probability; see inset scale in left-hand panel). Call-out box: close-up of farmland surrounding the first notified outbreak, indicated by the blue star.

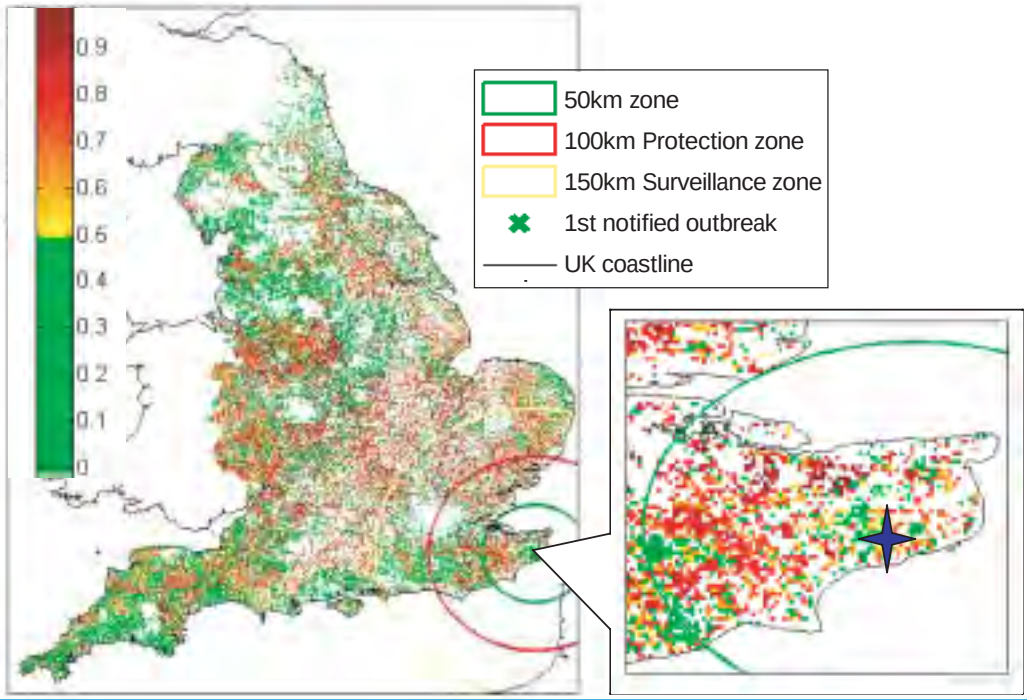
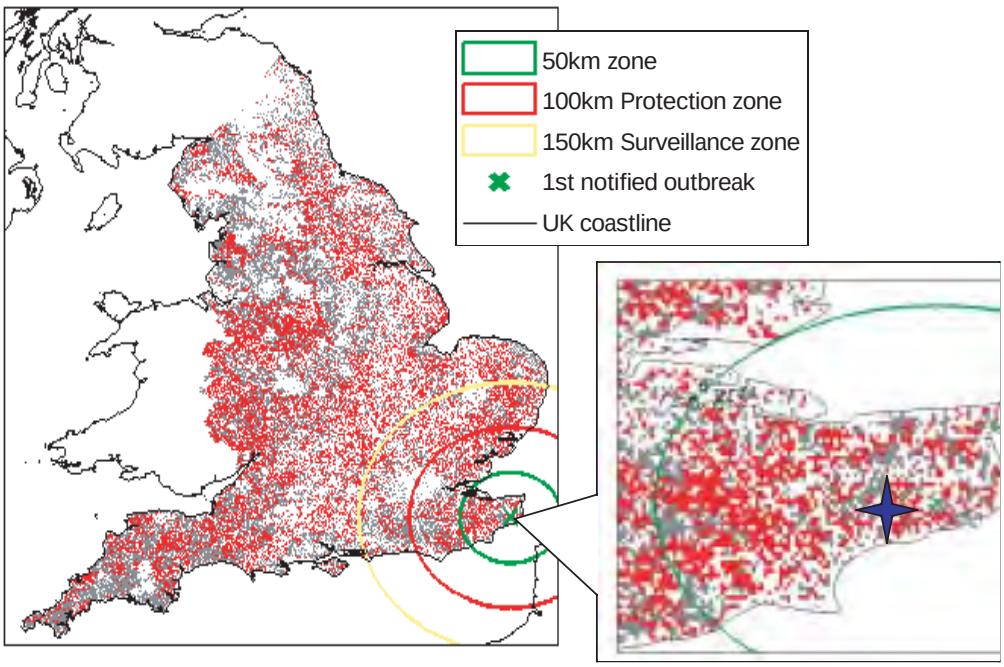


Fig 3.3b UK farmland within the protection and surveillance zones in grey and the proportion supporting sufficient biting-midge vectors for BTV transmission summer 2015 in red (probability >0.5).

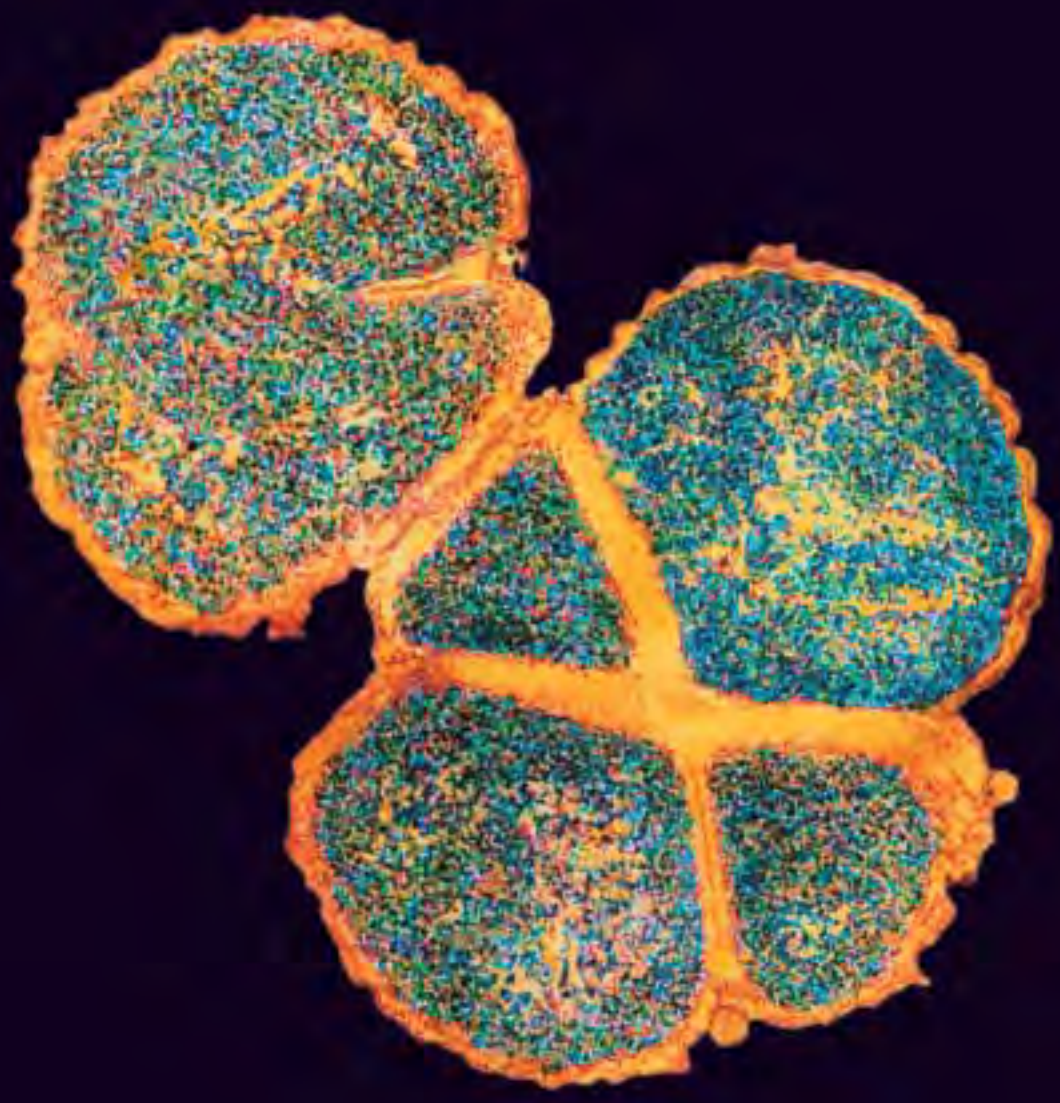


Note: the figures and tables here are based on hypothetical predictions of midge abundance but actual numbers of holdings and ruminants (from Defra annual survey 2002).

4 Key issues and choices

4a Why DIM systems? – their importance within wider strategies for disease control

4b Issues affecting the development and deployment of the User Challenges



4 Key issues and choices

This chapter draws together the detailed analysis of the four User Challenges (reports D2.1–D2.4). In so doing, it identifies the key issues that will affect their effective development and deployment.

It also considers the key choices facing policy makers and people concerned with managing diseases. These choices will, in particular, influence the extent to which the public good will be maximised for the future DIM systems.

4 Key issues and choices

4a Why DIM systems? – their importance within wider strategies for disease control

The case examples in Chapter 3 show that DIM systems in 10–20 years' time could potentially have capabilities that are a step-change beyond those of today. And when these systems are integrated into wider strategies for disease management, the benefits could be considerable:

- ***Influenza in 2025:*** in the hypothetical scenario envisaged, the use of a range of new DIM systems, integrated into an international management strategy reduces UK mortality from a pandemic 10-fold.
- ***SARS:*** a reliable saliva test could have played a crucial role in achieving savings of around US$380 million in direct healthcare costs for the outbreak in Toronto, due to rapid containment. The benefits, if used to contain the spread across the world, could have resulted in savings to non-related sectors such as services and tourism of many billions of US dollars.
- ***The Phytophthora threat to native trees and woodlands:*** it is difficult to put a financial figure on the protection of beech forests and other native flora. However, a number of socio-economic studies have suggested a value of £1–2 billion per year on our woodlands and trees. The biosecurity sensor which is proposed in Chapter 3 could play a central role in protecting this national asset.
- ***Sexually transmitted diseases:*** the immediate health economic benefits for a widely available and cheap self-diagnostic device could be around £135 million per year for the treatment of infections of chlamydia and gonorrhoea alone. However, this would be far outweighed by the cost benefits of consequentially reducing HIV transmissions – each HIV transmission averted is worth £0.5–1 million in lifetime economic benefits. So the cost savings of reducing just 1,000 HIV transmissions would be £0.5–1 billion.
- ***FMD:*** in the scenario outlined, DIM devices could virtually eliminate the need for mass culling of animals (on infected and contact premises), reduce costs of controlling the epidemic from £5 billion to £50 million, and reduce other losses (tourism, rural trade etc) from £3 billion to £35 million.
- ***Bluetongue:*** this disease is advancing on the UK as climate change progresses. In one scenario when it strikes the UK, DIM systems could play a crucial role in achieving savings in vaccination of around £7 million.

The above figures should be regarded as illustrative and not formal predictions – many assumptions and factors are embedded in the various case examples in Chapter 3. However, they do provide a broad appreciation of the savings that could potentially be realised, pending more detailed cost-benefit studies.

However, it is important to recognise that the future DIM systems only provide information, and therefore will only yield benefit when linked to timely and effective disease management measures, and when properly embedded in disease management infrastructure. The examples in Chapter 3 show that the information they provide makes three things possible:

- ***buying time:*** in a potential pandemic of an acute respiratory infection, there is a race between the production and delivery of vaccine and the spread of the virus. The extra time provided by the DIM systems in the pandemic influenza case example was a critical factor in reducing mortality 10-fold.
- ***enabling more effective and more efficient targeting of resources:*** in the FMD case example, the 'smart detector' enabled infected animals to be distinguished from non-infected – so that disease management resources could be tightly focused. This was instrumental in preventing the costly and devastating effects of mass culling.
- ***opening up new possibilities for disease management:*** in the case example covering sexually transmitted diseases, the availability of a cheap self-diagnostic device would enable many people who would not normally visit a GUM clinic to test themselves at home. This could bring testing and diagnosis to a large section of the population who have asymptomatic diseases which, left undiagnosed, could lead to severe health complications and costly treatment.

4b Issues affecting the development and deployment of the User Challenges

While the potential benefits of future DIM systems are considerable, it does not necessarily follow that the market by itself will deliver what disease management stakeholders most want, nor that the resulting systems will be effective:

- Even if a DIM system could yield substantial benefits, industry may not want to fund its development. SARS is a good example: it will not be a health problem for most of the time. So there is little incentive for business to develop a test on the relatively low probability that an epidemic may occur, and in the expectation that it will then sell large quantities of stockpiled items.
- Neither should it be assumed that the DIM systems that emerge from developers will provide the greatest global public good. There may well be greater profit in targeting diseases in companion animals in developed countries, rather than life-threatening diseases in Africa.
- There are many factors that will determine the effectiveness of the DIM systems, and which are affected by decisions of governments and disease management organisations, rather than developers. For example, in the case of international data processing systems (UC1), these may require agreements to be in place for countries to share information freely – and that could be difficult if trade and tourism are at stake.

The implication is that there is a strong role for stakeholders concerned with the management of diseases, in ensuring that: the right systems emerge; public good is maximised; and the new DIM systems are able to be exploited to their full potential when they become available.

The project has analysed many factors affecting the development and deployment of DIM systems for each of the User Challenges (D2.1–D2.4). The reader wishing to focus on a particular User Challenge is referred to these reports (the key points from these are summarised as graphical roadmaps in Appendix A). However, Chapter 3 has shown that the future systems are best viewed together, and as part of integrated systems for disease management. The following therefore draws all these threads together and discusses the key issues and choices facing policy makers and those responsible for the management of diseases.

Governance

Issues of governance have already been touched on in Chapter 2 – where, for example, it was suggested that it was desirable to promote better linkages between the animal and human disease management communities, and to promote better monitoring of the wild animal reservoir. In this chapter, however, the focus is more on issues of governance relating directly to the four User Challenges.

Regulation will certainly be desirable for some of the future DIM systems. The key questions are what regulations are needed, and whether they can be enforced.

- ***Novel information technology for the early detection of infectious disease events (UC1):*** there is a considerable amount of disease data already collected. A major problem is that this information is poorly connected. A key issue is how to better promote access to and linkages between this information so that the greatest good is achieved.

  It is also desirable to promote access to data which is collected for purposes unconnected with infectious diseases (such as weather, mobile phone position information). This raises substantial issues of data ownership and public acceptance for the use of the data.

  Protecting confidentiality and preventing misuse of data needs to be appropriately addressed through agreements at both national and international levels. However, this will be a sensitive issue for the public, who will need to weigh the advantages of better disease protection (through wider access to more forms of data), in the context of concerns relating to confidentiality and misuse. For example, health diagnostic information could potentially affect the ability of an individual to get a mortgage, insurance or employment.

The experts involved in UC1 considered that uniform standards for data collection and storage would be highly desirable, although the problems in reaching international agreement would be considerable. An alternative approach was to accept the heterogeneity of the data and develop advanced techniques to process it.

- ***Early detection and characterisation of new or newly resistant/virulent pathogens (UC2):*** since the 9/11 terrorist attacks, the sharing of samples and their associated information has become much more difficult. This will act as an inhibitor to the development, testing and validation of new DIM systems and may also impede their use in the field. It is desirable that ways are found to better promote the sharing of biological samples and their associated information, while protecting security interests (this issue is also relevant to UC3).
- ***Hand-held devices (UC3):*** the aim of regulation for these would be to ensure high-quality systems that are primarily delivered in a professional environment.

  Regulation for validating the quality of systems will be vital – for example, false negatives could allow the early stages of an epidemic to go unnoticed, with vital days being lost. In the case of FMD, a delay of 3–4 days could result in the doubling of the size of the epidemic (see section on validation, below).

  The disposal of biological waste from hand-held devices will be a substantial issue. This could usefully be considered within the development of regulations concerning quality of UC3 systems.

  It may be desirable to regulate against certain diagnostic tests being made available to the public – for example, where it is particularly important to ensure counselling following a positive result. This is already the case for HIV – where the advertising and sale of HIV testing kits directly to the public has been banned since 1992 in the UK. However, the enforceability of such regulations will be increasingly tested as such diagnostic tests become available via the internet.

  If certain diagnostic devices or diagnostic tests were to be made widely available, three substantial issues will arise:

  – It would be more difficult to ensure that the devices met quality standards compared with those intended for professional use – devices sourced through the internet could be difficult or impossible to control.
  – There is a substantial danger that the commercial availability of self-diagnostic devices could disconnect the professionals from both the patient and the diagnostic information – particularly if individuals seek treatments over the internet and do not seek professional advice. The implications for the healthcare and veterinary professions could be considerable, and will need to be given careful consideration in developing policies for self-diagnostic devices and their associated regulations.

– It will be important to promote education and knowledge in home users to ensure that they only buy devices and reagents from reputable sources and that any positive diagnosis is followed up with professional advice.

One might also envisage a situation whereby commercial diagnostic devices incorporate a communications link enabling the immediate purchase of treatment from a particular supplier. This would further sever the link between the patient and the healthcare professional. It would also raise concerns if the supplier of the diagnostic device stood to benefit financially from the subsequent purchase of treatment.

- ***High throughput screening devices – for example, at ports and airports (UC4):*** here regulation is the responsibility of governmental and intergovernmental bodies. A key issue will be how far governments might seek to enforce the testing of people, animals and plants at the point of embarkation, while in transit, or on disembarkation. For human travellers, the detection of disease creates responsibilities for caring for infected travellers.

  Exporters and importers of plants, animals and their products must already comply with standards, and penalties for failure are severe. Improved DIM systems will help to enforce these and may also be adopted by the private sector as part of their own quality control procedures.

  There could also be a demand for fast-throughput devices in other fields – for example, some businesses might seek to use them to test their staff. Or, indeed, they might want to use them to test their customers, fearing they would otherwise be negligent in protecting their employees from a health hazard. Such use would raise regulatory and ethical issues, for example, concerning the rights of the individual not to be tested and the use and ownership of the diagnostic information that is generated.

- ***Validation:*** any diagnostic device/system should be validated in order to show that it is fit for its purpose. Validation, which usually involves clinical trials, can be time-consuming, costly and challenging. Retrospective studies (using sample banks) are used wherever possible, but many of the systems described by the User Challenges will need to be assessed in prospective studies – which are slow.

  Challenges will include:

  – the collection and availability of appropriate samples (this is especially challenging for pre-symptomatic disease). Longitudinal and different samples (i.e. blood, saliva, sweat, urine and vaginal swabs etc.) will need to be collected. The creation of longitudinal sample banks of a range of biological fluids in wild animal populations could be a particular challenge.

– the availability of good clinical data to underpin the sample banks (e.g. whether the animal was sick, the stage of disease reached, whether the biochemical profile was pre-symptomatic at the time of sampling).
– reproducing the conditions in which one wants the diagnostic device/system to function (for example, for some of the mass screening described in UC4, this will need careful thought).

How to best exploit exogenous developments

Fortunately, much of the technology which the future DIM systems will need is already being developed for purposes unrelated to the management of infectious diseases. Examples include genomics, information technology, electronics and miniaturisation. A key issue is how to extract the maximum advantage from these exogenous developments.

In some areas, there is little need for intervention by governments or public bodies. For example, the huge commercial drive towards patient-specific drugs is stimulating rapid advances in genomics, and this is of direct use in several of the User Challenges. However, the following areas have been identified where the maximum advantage is not being realised, and where further effort could usefully be directed:

- ***use of data from sources unrelated to disease management (UC1):*** such data includes remote monitoring, weather and mobile phone tracking data. All such data could be assembled into very large databases for filtering and analysis, with the aim of informing disease management. Possible applications include: linking weather data with epidemiological modelling to predict outbreaks of vector-borne diseases; using anonymous phone-tracking data to improve epidemiological modelling, and to so develop more effective control measures; using remote monitoring data to assist in backtracking the source of disease outbreaks.

  Using such data raises important issues of data access and data confidentiality, both at a national and at an international level (see section on governance, above). However, the benefits of enabling access and use of such data could be considerable. Any future proposals would require significant public engagement.

  Disease management stakeholders could play a key role in bringing the various parties together to identify the barriers for data access, and to work out possible solutions. Such parties could include: phone operators, academics, and organisations involved in disease monitoring and management. One suggestion would be to start by considering the problem at the national level and then to extend the debate to the international stage.

- ***promoting the wider use of DIM technology being developed for counterterrorism purposes:*** this is relevant to all the User Challenges, but particularly UC3 and UC4. Experts involved in the analysis have suggested the need for innovative technology transfer mechanisms to be developed – which protect security interests, but which enable the wider benefits to be realised.

Maximising the public good

The analysis of the four User Challenges considered the key trends and drivers underpinning the development of future DIM systems (see roadmaps in Appendix A). Some of these are global socio-economic factors – such as increasing trade and internationalisation. Many are technological – stemming from commercial developments in fields unconnected with the management of infectious disease. It would therefore be surprising if these factors were to conspire to create systems that maximised the public good without the involvement of disease management stakeholders. Therefore, a key issue is whether to let the market take its course or whether to influence developments for the wider public good.

The analysis of the User Challenges identified a number of areas where public good could be enhanced:

- interoperability and open access: if they can be achieved, these generally work to the benefit of the user/purchaser, and can also benefit developers by opening up markets and allowing small companies to introduce niche products. This could be particularly important in promoting products and systems for the diseases of the developing world.

  Sequencing is going in the right direction, with open access approaches emerging. This will greatly benefit UC2. However UC2 would also benefit from:

  – standards to ensure physical compatibility IT systems
  – compatibility of datasets of genomes and sequence
  – compatibility of databases of sequences that different researchers and firms are identifying
  – compatibility of standards across diseases relating to humans, animals and plants.

  In the case of UC3, diagnostics firms do not generally have a history of developing systems with interoperable components – preferring to lock customers into their range of products. However, it would be advantageous for common standards to be developed, for example, so that reagents from one manufacturer could be used with the micro-fluidic devices from another, or so that a test from one manufacturer could function on the platform of another.

- ***promoting access to intellectual property:*** a key concern spanning all the User Challenges is the need to promote access to technology that a manufacturer may have developed but chooses not to exploit. It would be advantageous if developers could agree to allow licensing of their technology – so that all such advances can be exploited to the full. The question is how to incentivise developers to share their technology.
- ***maximising the benefits from the growing commercial interests of mass electronic manufacturers:*** manufacturers of personal electronics and mobile phones are increasingly becoming involved in the drive for hand-held diagnostic devices. This paradigm shift could add a substantial impetus to the development of personal diagnostic devices. However, it would be advantageous to bring together key players to consider: the devices that might emerge; the diseases they would target; and how their use would be integrated within existing strategies for disease management. Consumer electronics firms, diagnostics companies and healthcare stakeholders should all have an interest in such a forum.
- ***how to stimulate the development of diagnostics for diseases that are not of interest to industry – such as SARS, FMD and diseases of the developing world:*** at the heart of this issue is who would benefit most from a diagnostic test, and who would pay for its development. SARS is a particularly interesting example since the biggest beneficiaries of a test would be airlines, the tourist industry and businesses unconnected with infectious disease. Yet the onus for development would fall on healthcare stakeholders as such a test is unlikely to be an attractive commercial proposition.

  There is no easy answer to this problem. However, the adoption of open systems and common standards would tend to reduce development and implementation costs, and make it easier for niche suppliers to satisfy the need.

- ***the need to integrate future DIM systems effectively within wider systems' architecture for disease control:*** for example, when a new disease outbreak is detected, it may be necessary to immediately switch on commercial vaccine production or other control strategies. This suggests the need to plan for the integration of future DIM systems at the outset. However, this is a considerable challenge, as it would involve governments and public and private stakeholders operating both nationally and internationally.

It is not necessarily governments or public bodies that need to take action in all these cases. There is a strong case for industry – perhaps through trade associations – to take the lead in considering and addressing some of these issues with a view to benefiting themselves from the larger markets and greater customer demand that would be stimulated.

Africa

Detailed consideration of African perspectives of future DIM systems are considered in detail in report A1. These are some of the main conclusions:

- Africa is currently beset with a plethora of infectious diseases, old and new. The African experts involved in the project considered that Africans should take the lead in developing a new Vision and Strategy for the management of diseases across the continent. This would be surveillance-based and supported by regional centres of excellence. The Vision and Strategy would also cover diseases in humans, animals and plants, recognising that these are interlinked in complex ways and that their detection is increasingly dependent on a common technical platform.
- Africa's needs concerning new DIM systems are very different to those of the developing world. Necessary characteristics would be low cost; simplicity in use (bearing in mind the relatively low capacity in Africa); and robustness with regard to the African environment and situation – for example, this means avoiding, where possible, the need for power and refrigeration facilities.
- A substantial issue for Africa is whether subsequent treatment would be available. The DIM systems would yield little benefit to those tested if such treatment was not available. However, the information provided might nevertheless be useful in informing preventative measures for others.
- There was a substantial concern that many of the developments of future DIM systems would be driven by the needs of rich countries and that they could have limited applicability to Africa. The use of open systems and standards could help to mitigate this to some extent. Smart partnerships could also play a role (see below).
- Smart partnerships could usefully be promoted between experts from Africa and developed countries to share information and expertise and to maximise the potential for new DIM systems to be relevant to the continent. These smart partnerships were seen by African experts involved in the project as particularly important in helping to build and maintain capacity.
- The new DIM systems (UC4) could potentially help African countries verify that livestock and agricultural products were disease-free and could therefore promote market access. However, there was a substantial African concern that certain countries use disease as an instrument for imposing and justifying trade barriers. It would be important to address such concerns in the international deployment of the DIM systems.

Science, technology and social science

A consistent message from many of the project experts was that much of the technology needed for future DIM systems is already being driven forward by industry for purposes unconnected with disease management. However, the

experts did identify a number of areas of research that are unlikely to be fully realised by such developments and which are key enablers for future DIM systems. These are listed below and could usefully be considered within research prioritisation exercises:

- ***the integration of social sciences and humanities in the development and implementation of DIM systems:*** this was found to be important for all the User Challenges. However, a key issue for research bodies is whether institutional arrangements can be developed to further incentivise such cross-disciplinary working and to support it on a sustainable basis.
- ***the need for health systems research:*** this would consider how new DIM technologies can be used most effectively and how to promote their use as part of systems for managing human, animal or plant diseases. It would include more detailed study of the needs, expectations, capabilities and sensitivities of the end users and other stakeholders. This would require an interdisciplinary approach and, as such, would benefit from any initiative resulting from the integration of social sciences in the development and implementation of DIM systems (see above).
- ***new data processing tools as enablers for UC1:*** a fundamental requirement for UC1 is the development of techniques to: combine strongly heterogeneous data of uncertain provenance; extract useful information from such huge worldwide and complex systems; and combine that information with epidemiological models to provide quick and accurate response options. Associated with this is the need to obtain agreement for data access and use – taking account of the diverse systems of culture and governance where the data is collected.
- ***design of surveillance systems:*** the science of designing disease surveillance systems to detect unusual disease events or to identify at-risk populations is relatively underdeveloped. Modern computational and modelling approaches could usefully be applied to address this issue.
- ***basic enabling science for UC2:*** this is needed to enable the construction of sequencing databases and to develop the techniques to interpret the data in relation to risk. This is a key enabling technology for UC2.
- ***biomarker research:*** this is a fundamental enabler for DIM systems in respect of all the User Challenges. It is important to consider pathogen and host response, and genetic, RNA and protein markers are all relevant.
- ***robust portable molecular diagnostic devices:*** devices capable of functioning in extreme conditions (e.g. in the absence of clean water and electricity) was a key requirement identified by the UC3 team of experts. This is a difficult and complex challenge as both sequencing and microarray technologies are highly sensitive to fluctuations in temperature.

- ***understanding animal host response:*** this means understanding better the means by which animals distinguish complex chemical and other signals associated with disease that might be exploited for DIM. The aim would be to capture in vivo capabilities, e.g. olfactory recognition of simple volatile molecules, and in vitro capabilities for development as diagnostic tools.
- ***the integration of nucleic-acid-based and immune-response-based methods:*** these could usefully be integrated into disease detection technologies and the synergies between the two exploited. Both approaches already provide powerful diagnostic capabilities, e.g. through DNA microarrays or monoclonal antibodies, but they use different and potentially complementary information which, together, may be even more powerful.
- ***skills training:*** traditional training in science and technology does not deliver the range of skills necessary to tackle the breadth of issues relevant to assessing and managing infectious disease risks. Appropriate training courses, more opportunities for scientists and technologists to broaden their skillset at any stage in their careers, and international exchanges of knowledge and expertise would all help to address this problem.

Finally, for UC4 (fast-throughput screening devices), it was considered that the UK and US had particular strengths. It was therefore suggested that consideration be given to developing UK–US alliances in this area.

Engagement with the public

The public will need to weigh the 'costs' of some future DIM systems (e.g. concerning civil liberties) against the benefits the systems will bring (e.g. reduced risk from disease). Public engagement with these issues will be a precondition for ensuring the effective design of such systems. For example:

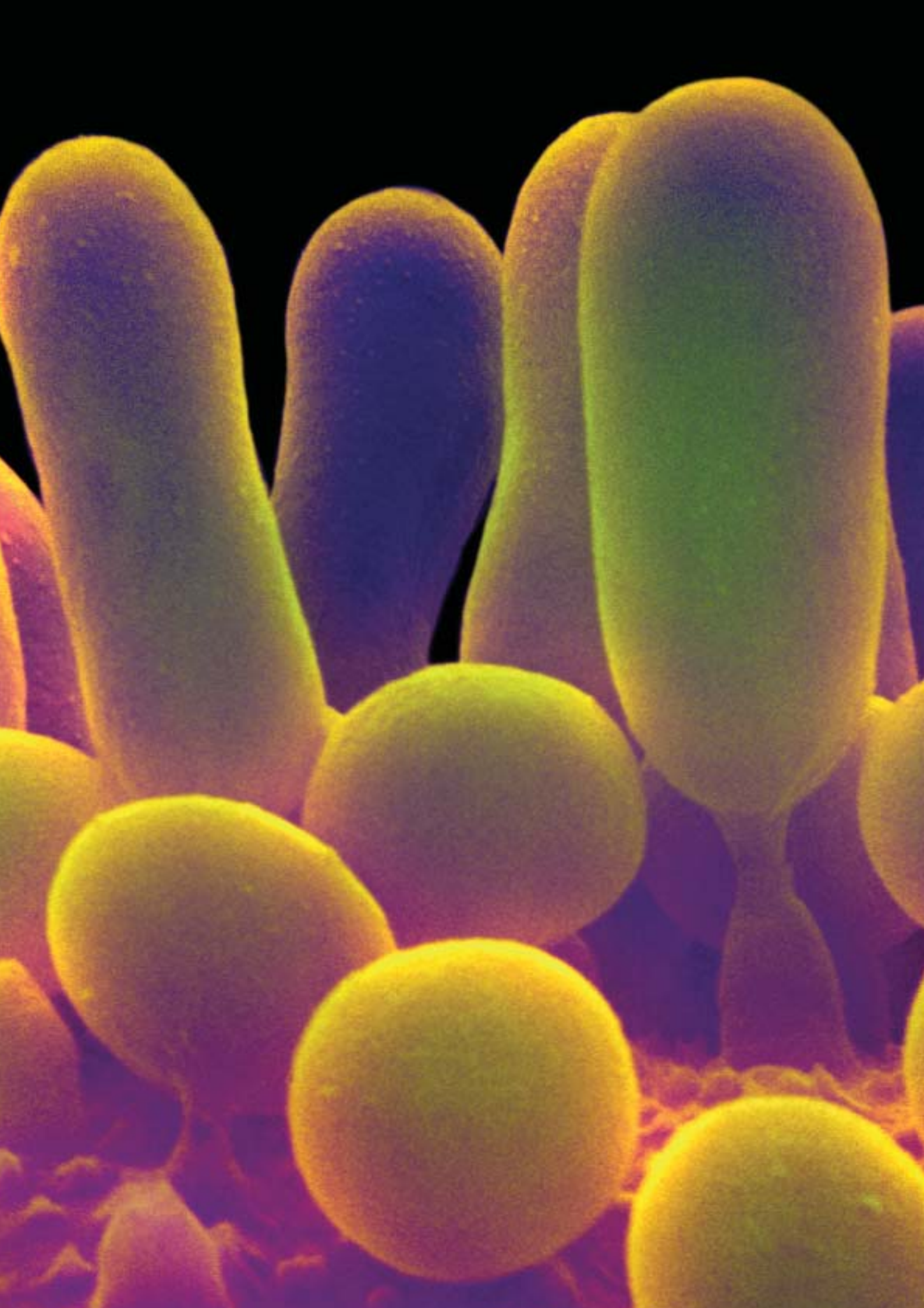
- Where DIM systems use personal data, the public will need to be convinced that its collection and use in monitoring systems is necessary, and that desired confidentiality will be maintained. For example, the use of trusted bodies could usefully be considered as a gateway for particularly sensitive data (to ensure personal information is not passed on).
- Hand-held diagnostic devices (UC3) offer considerable scope for inappropriate use. As they become more widely available, nationally and internationally, it will be essential to engage with potential users to develop systems that support the use of devices and reagents only from reputable sources. It will also be important to ensure that users are supported with professional advice to enable them to use the devices safely and to take the appropriate actions in response to the diagnoses they obtain.
- High-throughput screening, for example at ports and airports, presents particular sensitivities. Any future systems would need to take careful account of the needs and concerns of the wide range of travellers and operators that might be affected.

Implications of this report for counterterrorism

The DIM systems that have been analysed in this report have been considered against the threats identified in project report T1. These generally cover non-deliberate release and do not cover terrorism. Certainly such deliberate releases are important and need to be given careful consideration. However, it was considered that other bodies were better placed to make informed comment on the size and character of the terrorist threat – particularly those with access to classified intelligence.

Nevertheless, it is considered that many of the DIM systems that have been identified and analysed in this project will be broadly useful for counterterrorism. For example, a hand-held diagnostic device would work equally well on a given virus whether it has been maliciously released or not. Moreover, some of the future science and technology identified could open up new and innovative approaches.

However, it is recognised that the detailed design and implementation of the DIM systems might need to be modified to maximise their effectiveness within a counterterrorist context. For example, hand-held devices might need to look for a different set of pathogens compared with 'normal' use, and algorithms to detect a deliberate release (as opposed to non-deliberate) might need to be modified to account for possible differences in the pattern of release/emergence. There is therefore a case for experts concerned with counterterrorism to discuss the detailed findings of this project with key project experts with a view to examining such issues and maximising technology transfer.



Appendix A

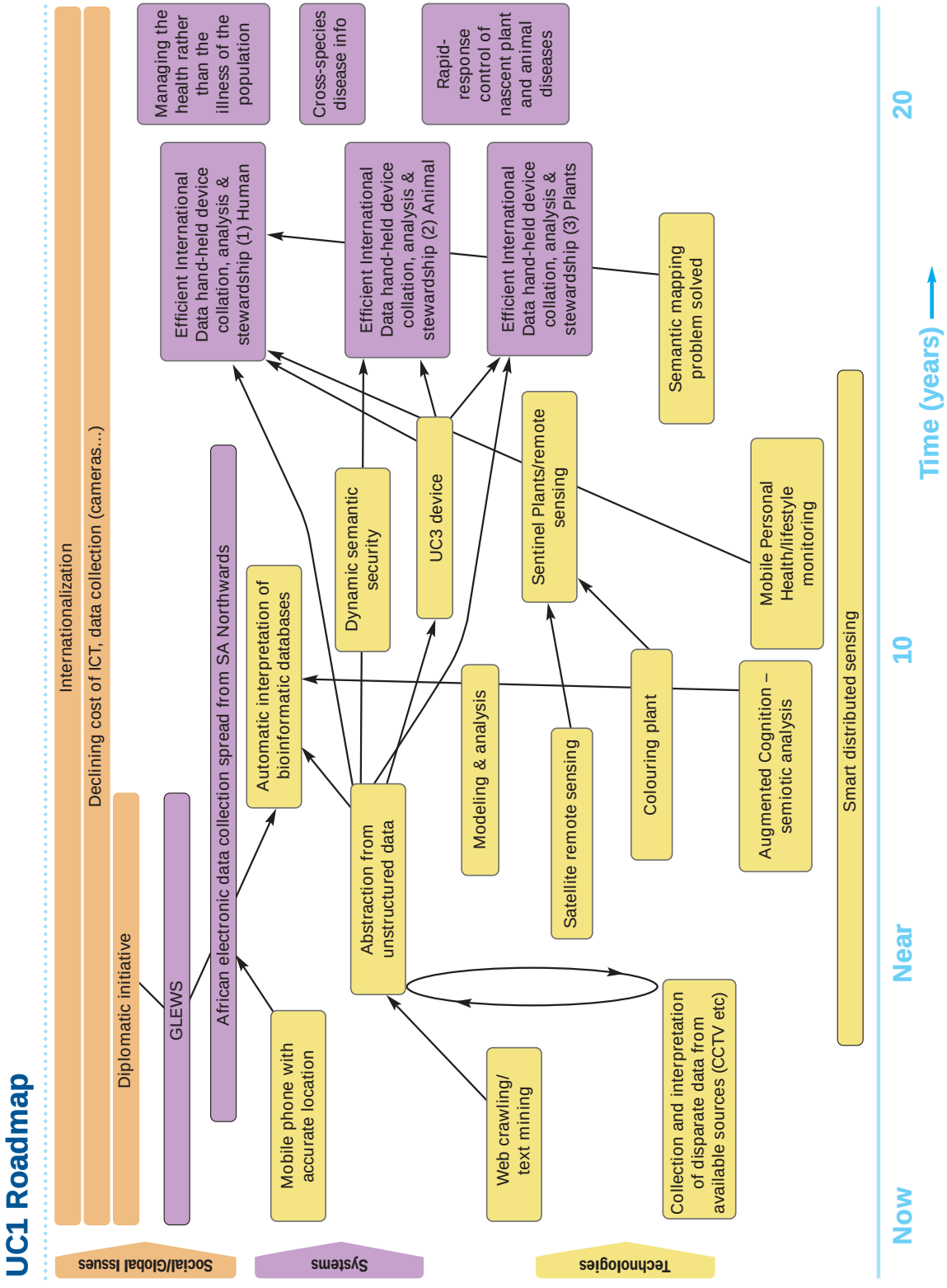
Detailed roadmaps of the User Challenges

Each of the teams that analysed the four User Challenges was tasked with producing a roadmap. These encapsulate in a graphical form:

- the key technological developments that are likely to arise in the future, and the DIM systems which they could enable
- the barriers and enablers to realising the development of the future DIM systems and their effective implementation
- the background trends against which the future is likely to develop.

This appendix provides the four detailed roadmaps, together with a glossary of terms for each. A top-level roadmap covering all four User Challenges is also presented.

Within the project's work on risk, an algorithm was devised that could be adapted and used to provide early input into the implementation of these roadmaps. This algorithm is described in Section 5 of the Risk Analysis report (T2). This algorithm is based on a formal risk analysis that takes account of the scientific and social aspects of the specific threat, along with analysis of the interactions among sources, pathways and drivers that have the potential to enhance or diminish the risk.


UC1 Roadmap
Social/Global Issues
Systems
Technologies
Internationalization
Declining cost of ICT, data collection (cameras…)
Diplomatic initiative
GLEWS
African electronic data collection spread from SA Northwards
Mobile phone with accurate location
Automatic interpretation of bioinformatic databases
Abstraction from unstructured data
Web crawling/ text mining
Collection and interpretation of disparate data from available sources (CCTV etc)
Dynamic semantic security
Modeling & analysis
Satellite remote sensing
UC3 device
Colouring plant
Sentinel Plants/remote sensing
Augmented Cognition – semiotic analysis
Mobile Personal Health/lifestyle monitoring
Smart distributed sensing
Efficient International Data hand-held device collation, analysis & stewardship (1) Human
Efficient International Data hand-held device collation, analysis & stewardship (2) Animal
Efficient International Data hand-held device collation, analysis & stewardship (3) Plants
Semantic mapping problem solved
Managing the health rather than the illness of the population
Cross-species disease info
Rapid-response control of nascent plant and animal diseases
Now
Near
10
20
Time (years)

UC1 roadmap glossary

(Terms that are not defined are deemed to be self-explanatory)

Abstraction from unstructured data

This milestone is concerned with the ability to find patterns or key elements in unstructured data. Structured data are records in databases or cells in spreadsheets. Unstructured data are emails, reports, PowerPoint presentations, voicemail, photographs, web pages, etc."

African electronic data collection spread, from South Africa northwards

Availability and collection of data in Africa will vary by region. There can be little doubt that the South African cell phone system as it currently exists means that in that country and adjacent countries in the region as far north as Zambia and Malawi, data collection will be possible – although following a gradient of reducing availability as one travels northwards. In other regions, use of cell phones may be non-existent or intermittent – with only limited hope for improvement. The Democratic Republic of Congo, southern Sudan and Angola probably fall into this category. In Uganda, Kenya and some other countries coverage is good, while in others, it is restricted mainly to the urban areas, for example, in Nigeria where satellite phones are used for local calls by prosperous individuals.

Augmented cognition – semiotic analysis

Computerised data mining, theme identification and analysis will be an invaluable tool in the process of gathering information from diverse sources of variable dependability. However, this cannot be a purely mechanical process. Human interpretation and monitoring will be essential if these data are to be properly interpreted and given meaning. Without this, there will be serious risks of, at best, mere waste and, at worst, missed significant messages.

Automatic interpretation of bioinformatic databases

As described under 'Augmented cognition – semiotic analysis', the effective interpretation of data will require human input. This milestone represents the point where bioinformatic data can be analysed automatically without continuous human involvement in interpretation. The word 'continuous' is of significance, and quality assurance schemes should be applied to the systems to ensure that high-quality, reliable, information is provided to the user.

Collection and interpretation of disparate data from available sources (CCTV etc.)

Analysing existing data sources for useful tracking or biomedical or behavioural characteristics (face recognition, gait recognition, etc).

Colouring plant

Genetically modified plants that change colour in response to the recognition of volatile organic compounds (VOCs) indicative of disease.

Cross-species disease information

Informatics, modelling and global networks could be used to predict which pathogens, and under what conditions, would be likely make a species jump. ‘Hotspots’ could be monitored by UC2.

Declining cost of ICT, data collection (cameras etc.)

The story of ICT emphasising that it is the steeply declining cost (as well as rising performance) that is the key driver; arguably the key driver for the modern world.

Diplomatic initiative

The clearly necessary but very challenging drive to obtain widespread agreement in pursuit of a collective benefit.

Dynamic semantic security

This milestone represents the ability to provide active and immediate security to databases and systems through the use of semantics. Security policies are semantically aware (based on the meaning of documents or messages) and dynamic (sensitive to the context in which access is requested)

Efficient international data hand-held device collation, analysis and stewardship (1) Human

Efficient international data hand-held device collation, analysis and stewardship (2) Animal

Efficient international data hand-held device collation, analysis and stewardship (3) Plant

These each define an ideal scenario objective.

GLEWS

Global Early Warning System for Transboundary Animal Diseases and Zoonoses. This is a joint initiative between the World Health Organization, the Food and Agriculture Organization and the World Organization for Animal Health (OIE).

Internationalisation

The drive to a connected world, in every sense.

Managing the health rather than the illness of the population

An ideal – the between this and existing techniques is that health is monitored at all times, with 'illness' defined in terms of departure from health rather than necessarily as a known ill condition. This would also enable the mapping of vulnerability among currently 'well' populations.

Mobile personal health/lifestyle monitoring

A developing mobile-phone-based service uses portable monitoring and location information to keep track of the user's health and lifestyle – this is aimed at personal support, initially of diabetics and other special groups but probably ultimately of all users. It will enable 'health'- as opposed to 'illness'-based services that may be vital for UC1.

Mobile phone with accurate location

While mobile phones inherently provide some location information (obviously needed to route incoming calls/data), the next generation will provide much more precise locations, probably via global positioning systems (GPS). This is driven by commercial opportunities but is very helpful for this User Challenge.

Modelling and analysis

Mathematical representations of relationships between variables, when based on well-estimated parameters and validated (i.e. based on fitting available data and, where possible, by making model predictions and then comparing data to the predictions), can provide valuable insights into the behaviour of systems.

Rapid-response control of nascent plant and animal diseases

An ideal scenario in which departures from normal would be picked up very early, enabling response at a more manageable stage.

Satellite remote sensing

As Earth observation becomes more finely tuned, it will be possible to observe individual plants, animals and humans. The data generated could inform UC1 networks and systems. For example, modelling could be used to predict environmental change and identify 'hotspots' for disease outbreaks.

Semantic mapping problem solved

Semantics is the study of meaning (which can be linguistic or non-linguistic). Considering the richness and diversity of different languages and their dialects, coupled with the use of language by varied and changing cultures, this is not trivial. It is necessary not only to recognise words but to appreciate their context. Semantics gives meaning to data. An ontology is the definition of a domain-specific vocabulary. Semantic mapping accounts for the mismatches between different ontologies.

Sentinel plants/remote sensing

A combination of satellite remote sensing and colouring plants. Sentinel plants, genetically modified to change colour in response to volatile organic compounds (VOCs) indicative of disease, could be placed at specific sites to detect pathogens before mainstream crops become diseased.

UC3 device

The hand-held devices described by UC3 fall into two basic categories:

1 simple devices such as urinary dipstick etc.

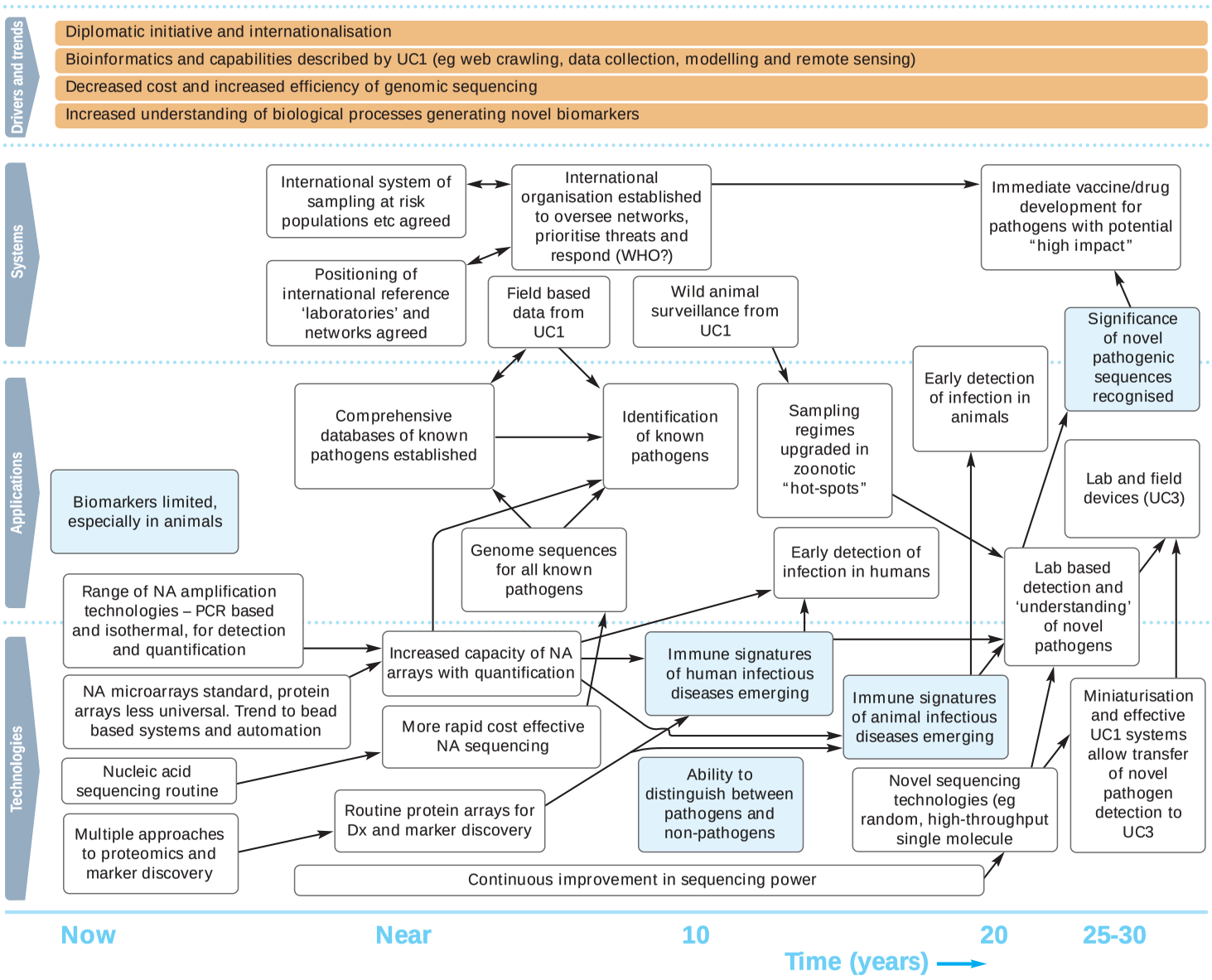
2 sophisticated devices linked to global network(s) – where data can be collected, interpreted, clustered and trended etc.

The second category is represented on the UC1 roadmap.

Web crawling/text mining

Automatically indexing the web and identifying meaningful content in free text. Text mining is a young interdisciplinary field which draws on information retrieval, data mining, machine learning, statistics and computational linguistics.

UC2 Roadmap



Pale blue boxes represent capabilities that require a significant amount of fundamental research in order to be realised. The "Biomarkers limited, especially in animals" box has been highlighted as this is the starting point.

UC2 roadmap glossary

(Terms that are not defined are deemed to be self-explanatory)

Pale-blue boxes represent capabilities that require a significant amount of fundamental research in order to be realised. The 'Biomarkers limited, especially in animals' box has been highlighted as this is the starting point.

Ability to distinguish between pathogens and non-pathogens

This capability represents a significant UC2 milestone. In order to address this, it is necessary to understand what makes an organism pathogenic. Like many of the UC2 capabilities, a significant amount of fundamental research will be required to address this in full.

Bioinformatics and capabilities described by UC1 (e.g. web crawling, data collection, modelling and remote sensing)

Bioinformatics and the global network capabilities described by UC1 will be imperative for the effective advance of UC2. While UC2 can initiate its own sampling regimes, information on potential hotspots from UC1 networks and systems will be critical. Management of the data generated by UC2 will rely on bioinformatics and UC1 databases.

Improvements in bioinformatics and the capabilities described by UC1 will occur independently of UC2 and help to drive UC2 forward.

Comprehensive databases of known pathogens established

Database will be continuously improved and updated as research progresses. Existing databases should be combined and standardised.

Continuous improvement in sequencing power

The efficiency of sequencing nucleic acids will continually improve – speed will increase and cost decrease.

Decreased cost and increased efficiency of genomic sequencing

A capability likely to be funded and driven by research into areas other than infectious disease.

Diplomatic initiative and internationalisation

Diplomatic initiative: the clearly necessary but very challenging drive to obtain widespread agreement in pursuit of a collective benefit.

Internationalisation: the drive to a connected world, in every sense. The global nature of infectious diseases means that their DIM and subsequent control can only be achieved through international agreements and networks.

Early detection of infection in humans

The detection of pre-symptomatic disease may emerge from a comprehensive understanding of the immune signatures of disease.

In addition to detecting pre-symptomatic infections, it may be possible to ascertain an individual's/animal's/population's susceptibility to disease. Fundamental research is required to map single nucleotide polymorphisms (SNPs) and other genetic variations to susceptibility. Other factors, such as malnutrition, which is of particular significance in sub-Saharan Africa, will influence susceptibility and should form part of the bioinformatics algorithms etc.

Field-based data from UC1

Data collected from web crawling and surveillance etc. begins to inform UC2.

Genome sequences for all known pathogens

When one considers plants, animals and humans, this is an aggressive timeline. However, some data are already available and the predicted continuous improvement in sequencing power makes this possible.

Identification of known pathogens

While known pathogens can be identified now, this box represents their rapid analysis and identification within a global reporting structure. At this point in the roadmap, routine sequencing and array technologies will be faster and less expensive. Bioinformatics and the comprehensive databases described above will play a significant role in achieving this goal.

Immediate vaccine/drug development for pathogens with potential high impact

The early detection of novel pathogens will only be worthwhile if their identification results in an appropriate and measured response. This box represents the importance of immediate response to pathogens with potential high impact.

Immune signatures of animal infectious diseases emerging

Immune signatures of human infectious diseases emerging

Infection of an animal or human host with a pathogen results in rapid changes in gene expression and protein synthesis by cells of the host's immune response. An appreciation of the immune signatures of disease will aid the detection of pre-symptomatic infection and our understanding of pathogens and the disease process in general.

Increased capacity of nucleic acid arrays with quantification

The use of nucleic acid microarrays are routine today. However, researchers make a choice to either look at the expression profiles in a qualitative manner, on microarrays, or measure the concentration of a number of defined nucleic acid sequences with, for example, quantitative polymerase chain reaction (PCR). Developments in analytical systems will bring these together. Initially, this capability is likely to be realised in a modular iterative system.

Increased understanding of biological processes generating novel biomarkers

Fundamental research in areas outside infectious diseases, for example, in immunology and oncology, will provide novel candidate biomarkers to UC2.

International organisation established to oversee networks, prioritise threats and respond (WHO?)

The international infrastructure required to oversee the implementation of the UC2 capabilities should be agreed at this point. This system may be an extension of the WHO's responsibilities. As UC2 matures, this and/or other organisation(s) will be paramount in prioritising threats and initiating appropriate responses, e.g. vaccine development.

International system of sampling at risk populations etc agreed

The sampling regimes essential to UC2 will require international agreement. This may be challenging – it will be necessary, for example, to collect biological samples from wild animal populations.

Lab and field devices (UC3)

It is generally accepted that, from a technological perspective, anything that is achievable in a laboratory setting ultimately has the potential, through miniaturisation etc, to be transferred to a hand-held device. Within the timeframe being considered by the Foresight project, it is unlikely that all the UC2 capabilities will be transferred to UC3 devices and systems. However, beyond 25 years, certain capabilities will become more field-based.

Lab-based detection and 'understanding' of novel pathogens

Clearly, lab-based detection of pathogens is achievable today. However, attributing a pathogenic sequence to a particular disease can be time-consuming. This box represents the capability to identify novel pathogens and their significance in a timely manner. As portrayed in the roadmap, this application will emerge from an understanding of the immune signatures of disease (at the nucleic acid and protein level), an ability to distinguish between pathogens and non-pathogens, and improved nucleic acid sequencing power. Comprehensive databases and bioinformatics systems will also play a critical role in reaching this milestone.

Miniaturisation and effective UC1 systems allow transfer of novel pathogen detection to UC3

It is anticipated that the full realisation of this capability will extend beyond 25 years. The emphasis of the UC2 laboratory may change to include the co-ordination and regulation of DIM and the management of effective responses, e.g. vaccine development. Fundamental research into the biological processes of infectious disease will continue.

More rapid cost-effective nucleic acid sequencing

This forms part of the continuous improvement in sequencing power. It has been boxed separately to define a timeframe.

Multiple approaches to proteomics and marker discovery

This is the age of marker discovery. Today's 'bottleneck' is not in identifying candidate biomarkers but in validating them. Bioinformatics, proteomic approaches, nucleic acid microarrays and mass spectroscopy are all used routinely to discover novel biomarkers. In many cases, the relative concentrations of a series of markers will define a disease – this points to the continued need to establish excellent bioinformatics capabilities to analyse and manage complex algorithms.

Novel sequencing technologies (e.g. random, high-throughput single molecule)

Continuous improvement in sequencing power will eventually result in a portfolio of rapid novel technologies. These will improve the efficiency of sequencing. Some may be suitable for UC3 devices, others will be more appropriate for high-throughput laboratory-based systems.

Nucleic acid microarrays standard, protein arrays less universal. Trend to bead-based systems and automation

Microarrays are standard for the detection of DNA and RNA sequences. Protein arrays are technically more challenging but are in existence. As with many technologies, the trend is towards high-throughput screening and automation.

Nucleic acid sequencing routine

A number of technologies and platforms are available for the routine sequencing of nucleic acids.

Positioning of international reference 'laboratories' and networks agreed

The location of UC2 laboratories should be agreed alongside the sampling regimes. There are strong arguments for having a presence in Africa – perhaps a mobile laboratory moving between hotspots.

Discussions with leaders implementing UC1 capabilities should be initiated to ensure that the appropriate information is sourced, managed and delivered to UC2.

Range of nucleic acid amplification technologies – PCR-based and isothermal, for detection and quantification

A wide range of nucleic acid amplification technologies are in routine use for the detection and quantification of nucleic acids. Techniques based on the polymerase chain reaction (PCR) are probably the most widespread. PCR methodology employs temperature cycling but a number of isothermal technologies exist.

Routine protein arrays for Dx and marker discovery

It is anticipated that over the next 5 years some of the difficulties in making multiple protein measurements on single samples will be overcome. Protein arrays for diagnostics will become more routine. This advance in technology will also aid marker discovery.

Sampling regimes upgraded in zoonotic hotspots

Wildlife surveillance from UC1 will inform UC2 of potential hotspots – sampling regimes can be introduced and/or upgraded in these areas.

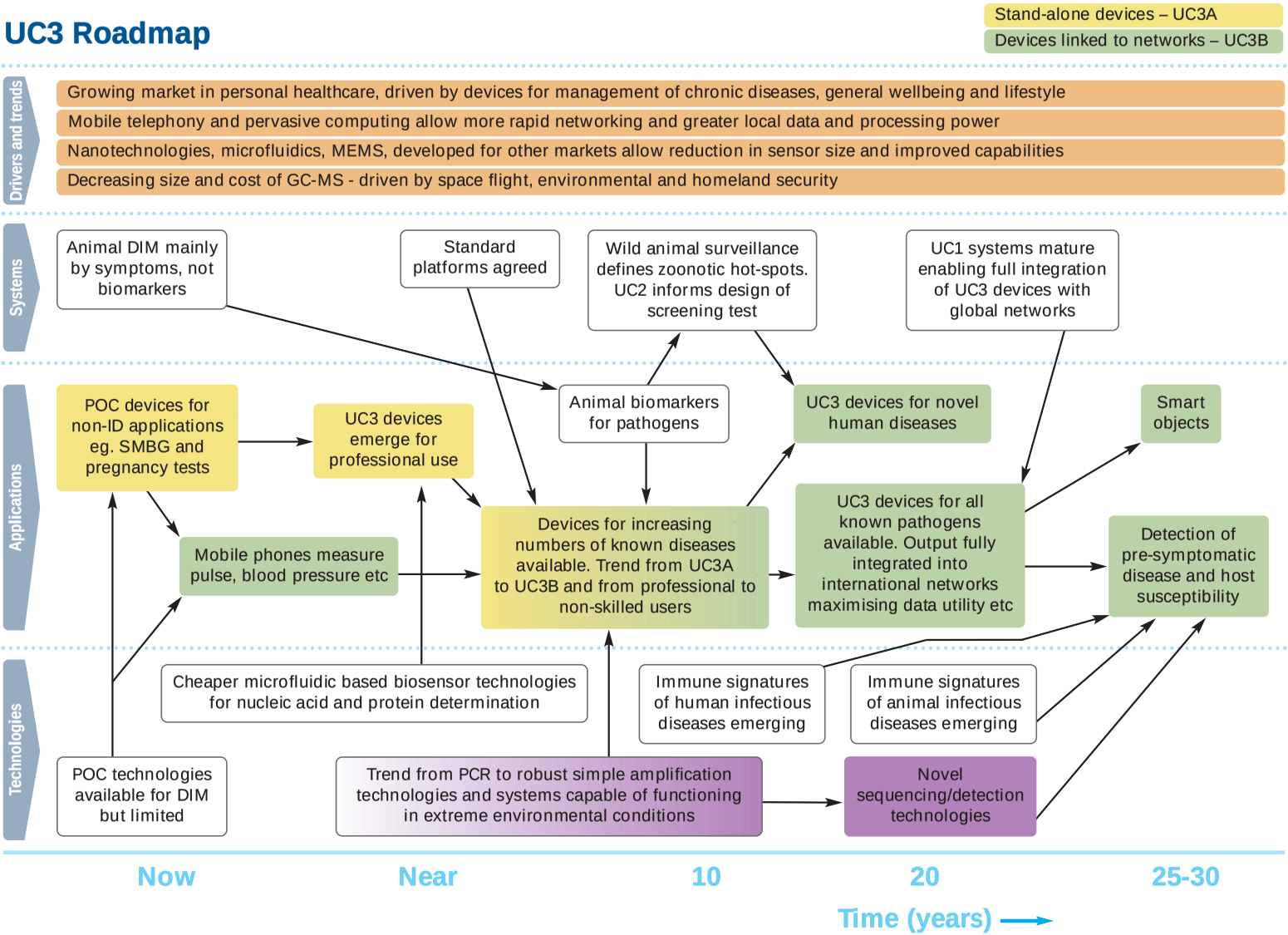
Significance of novel pathogenic sequences recognised

Beyond 25 years, it is anticipated that the full impact of a novel pathogen will be recognised from, for example, its sequence and immune signature. This knowledge will include an understanding of where mutations are most likely to occur and the consequence of these mutations – e.g. mutations may be silent, promote drug resistance or produce a form of the pathogen likely to make a species jump.

Wild animal surveillance from UC1

Wildlife surveillance and data modelling from UC1 will inform UC2 of potential hotspots where pathogens are most likely – because of opportunity and environmental change etc. – to make the species jump from animal to human. In the first instance, UC2 may upgrade its screening regimes in hotspots. Through its databases and knowledge, UC2 experts will advise on the development of a diagnostic for the pathogen in humans, and on the effective rapid transfer of the test to UC3 devices.

UC3 Roadmap


Stand-alone devices – UC3A
Devices linked to networks – UC3B
Drivers and trends
Growing market in personal healthcare, driven by devices for management of chronic diseases, general wellbeing and lifestyle
Mobile telephony and pervasive computing allow more rapid networking and greater local data and processing power
Nanotechnologies, microfluidics, MEMS, developed for other markets allow reduction in sensor size and improved capabilities
Decreasing size and cost of GC-MS - driven by space flight, environmental and homeland security
Systems
Animal DIM mainly by symptoms, not biomarkers
Standard platforms agreed
Wild animal surveillance defines zoonotic hot-spots. UC2 informs design of screening test
UC1 systems mature enabling full integration of UC3 devices with global networks
Applications
POC devices for non-ID applications eg. SMBG and pregnancy tests
UC3 devices emerge for professional use
Animal biomarkers for pathogens
UC3 devices for novel human diseases
Smart objects
Mobile phones measure pulse, blood pressure etc
Devices for increasing numbers of known diseases available. Trend from UC3A to UC3B and from professional to non-skilled users
UC3 devices for all known pathogens available. Output fully integrated into international networks maximising data utility etc
Detection of pre-symptomatic disease and host susceptibility
Technologies
Cheaper microfluidic based biosensor technologies for nucleic acid and protein determination
Immune signatures of human infectious diseases emerging
Immune signatures of animal infectious diseases emerging
POC technologies available for DIM but limited
Trend from PCR to robust simple amplification technologies and systems capable of functioning in extreme environmental conditions
Novel sequencing/detection technologies
Now
Near
10
20
25-30
Time (years)

UC3 roadmap glossary

(Terms that are not defined are deemed to be self-explanatory)

Animal biomarkers for pathogens

The availability of biomarkers for pathogens in animals will undoubtedly aid in the speed and accuracy of diagnosis.

Animal DIM mainly by symptoms, not biomarkers

In general, animal diseases are diagnosed by clinical signs without the use of biochemical markers.

Cheaper microfluidic-based biosensor technologies for nucleic acid and protein determination

This is a self-explanatory capability.

Decreasing size and cost of GC-MS – driven by space flight, environmental and homeland security

GC-MS is the effective combination of gas chromatography and mass spectroscopy for the identification and quantification of molecules in complex mixtures. GC-MS is considered the gold standard for the determination of a wide range of analytes. However, the size, complexity and cost of mass spectrometers have prevented their routine use, except in specialist laboratories.

Field portability, transportability and miniaturisation are areas of increasing interest, driven mainly by planetary exploration, environmental and homeland security.

In situ mass spectrometry is rapidly becoming a reality and developments in manufacturing techniques, in particular micro-electro-mechanical systems (MEMS), have meant that some hand-held mass analysers, for specific applications, already exist.

Detection of pre-symptomatic disease and host susceptibility

These capabilities will only be realised after a significant amount of fundamental research (see UC2). The detection of pre-symptomatic disease may emerge from a comprehensive understanding of the immune signatures of disease. Within the timeframe set by the Foresight programme (i.e. up to around 30 years), it is unlikely that we will see the measurement of immune signatures on hand-held devices. However, they may begin to appear at the end of the roadmap timeframe.

The detection of volatile organic compounds (VOCs) is described in UC4 and reviewed in S2 and could also aid in the detection of pre-symptomatic disease – research in this area is most advanced in plants.

In addition to detecting pre-symptomatic infections, it may be possible to ascertain an individual's/animal's/population's susceptibility to disease. As technologies advance, UC3 devices will have the ability to sequence the host genome and identify single nucleotide polymorphisms (SNPs); further fundamental research is required to map SNPs to susceptibility etc.

Devices for increasing numbers of known diseases available. Trend from UC3A to UC3B and from professional to non-skilled users

This will be a natural progression in around 10 years. After this time, improvements in speed, cost and sensitivity with continue.

Growing market in personal healthcare, driven by devices for management of chronic diseases, general well-being and lifestyle

Point-of-care devices for self-monitoring of blood glucose and pregnancy testing are routine today. The trend towards devices for other conditions and general well-being will proceed independently of infectious disease diagnostics and will drive DIM forward.

Immune signatures of animal infectious diseases emerging

Immune signatures of human infectious diseases emerging

Infection of an animal or human host with a pathogen results in rapid changes in gene expression and protein synthesis by cells of the host's immune response. An appreciation of the immune signatures of disease will aid the detection of pre-symptomatic infection and our understanding of pathogens and the disease process in general.

Mobile phones measure pulse, blood pressure etc.

Mobile phone companies recognise that a technical system consisting of intelligent sensor networks connected to a mobile phone network could provide a wide range of opportunities of relevance to health and healthcare. Mobile phones able to measure pulse and blood pressure are on the horizon; systems that will be able to detect, identify and monitor infectious diseases (UC3B devices) form part of a longer-term vision for companies such as Vodafone.

Mobile telephony and pervasive computing allow more rapid networking and greater local data and processing power

It is envisaged that pervasive computing devices, which range from personal digital assistants to the microchips in cars, appliances and telephones, will give rise to an explosion of interconnected smart devices marketed to make our lives easier and more productive. Mobile telephony and communication technology will continue to advance as part of this network. The development of UC3B devices will undoubtedly benefit from these networks and systems.

Nanotechnologies, microfluidics, MEMS, developed for other markets allow reduction in sensor size and improved capabilities

Micro-electro-mechanical systems (MEMS) is the integration of mechanical elements, sensors, actuators and electronics on a common silicon substrate through microfabrication technology. MEMS promises to revolutionise nearly every product category by bringing together silicon-based microelectronics with micromachining technology, making possible the realisation of complete systems on a chip. Clearly, this kind of system has direct relevance to the development of UC3 devices.

Microfluidic systems and capabilities are also a key component of UC3 devices – these systems vary considerably in their complexity and suitability for UC3.

The impact of nanotechnology on the design and development is discussed under UC3 key future capabilities. Essentially, nanotechnology will offer new sensing formats and materials for improved performance.

Novel sequencing/detection technologies

Continuous improvement in sequencing power will eventually result in a portfolio of rapid novel technologies. Similarly rapid, highly sensitive detection technologies will continue to evolve.

POC devices for non-ID applications e.g. SMBG and pregnancy tests

A number of high-quality devices for self-testing exist today. The market for self-monitoring of blood glucose and pregnancy testing is well established. POC devices for cardiac markers are also in routine use.

POC technologies available for DIM but limited

Hand-held devices of varying quality are available for the detection of infectious diseases (see UC3, Appendix A). The integration of hand-held devices into the effective management of DIM starts from this point. Initial barriers for the implementation of UC3A devices are more related to infrastructure than to technology – this is especially true in developing countries.

Smart objects

These could include blue-sky devices such as smart hiking boots that would automatically sample soil samples, and smart toothbrushes that would alert the user to the presence of an infectious disease.

Standard platforms agreed

Ideally, standard platforms would be open systems and different manufacturers could produce cassettes etc. to slot into the devices. In the commercial world such an open system may not be financially attractive. However, the possibility of encouraging manufacturers to work together should be discussed.

In both the immediate and long-term future, intellectual property will inevitably play a key role in the design and manufacture of UC3 devices – companies should be encouraged to license technologies to ensure that inventions are fully exploited and that progress is not blocked.

Efforts should be made to ensure that developing countries will have access to appropriate technologies – care should be taken not to increase the north–south divide.

Trend from PCR to robust simple amplification technologies and systems capable of functioning in extreme environmental conditions

Polymerase chain reaction (PCR) and other nucleic acid amplification technologies are routine today. A key message from the Foresight project is the need to develop robust and portable molecular diagnostic devices capable of functioning in extreme conditions (e.g. in the absence of clean water and electricity). This is a difficult and complex challenge as both sequencing and microarray technologies are highly sensitive to fluctuations in temperature.

UC1 systems mature, enabling full integration of UC3 devices with global networks

This box represents the maturation of the capabilities described by UC1. These capabilities include the collection, storage, manipulation, modeling and management of data from multiple sources (i.e. effective bioinformatics). At this point, UC1 will be bringing together and making sense of data from satellite remote sensing, web crawling, UC3B devices, UC4 systems and UC2 screening procedures etc.

UC3 devices emerge for professional use

While a number of UC3 devices are already in professional use (e.g. used by clinicians and plant growers), this box represents a greater acceptance and integration of hand-held devices into our healthcare and equivalent management systems for plants and animals. At this early stage, the devices will be UC3A (i.e. not linked into comprehensive networks). In many cases, the barriers to implementing these technologies relate to infrastructure, habit and a fear that professionalism and quality will be lost. Ensuring that devices are deployed in a regulated environment will be paramount to their acceptance by professionals.

UC3 devices for all known pathogens available. Output fully integrated into international networks maximising data utility etc.

This box represents a major milestone in the evolution of UC3 devices.

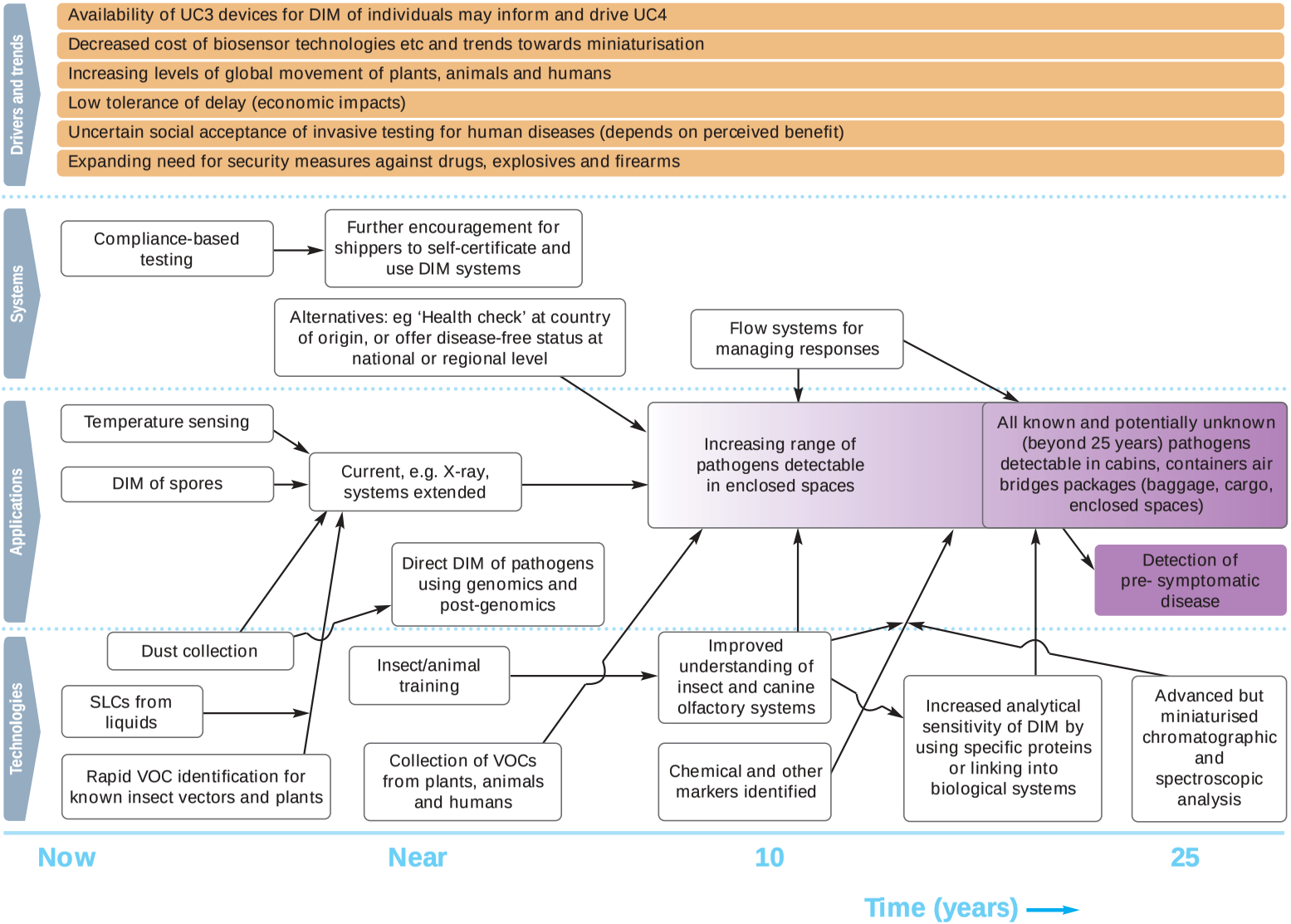
UC3 devices for novel human diseases

These devices will emerge in conjunction with UC1 and UC2 as described under the "Wild animal surveillance" box. Ultimately this capability will evolve to identify novel pathogens without the direct intervention of UC2. For example, one can envisage a UC3 device recognising that a pathogen was present but that it wasn't in any current databases. An interactive UC3B device could instruct the user to insert a separate cassette which could sequence the pathogen etc.

Wild animal surveillance defines zoonotic hotspots. UC2 informs design of screening test

Wildlife surveillance and data modelling from UC1 will inform UC2 of potential hotspots where pathogens are most likely, because of opportunity and environmental change etc., to make the species jump from animal to human. In the first instance, UC2 may upgrade its screening regimes in hotspots. Through its databases and knowledge, UC2 experts will advise on the development of a diagnostic for the pathogen in humans, and on effective rapid transfer of the test to a UC3 device.

UC4 Roadmap


Drivers and trends
Availability of UC3 devices for DIM of individuals may inform and drive UC4
Decreased cost of biosensor technologies etc and trends towards miniaturisation
Increasing levels of global movement of plants, animals and humans
Low tolerance of delay (economic impacts)
Uncertain social acceptance of invasive testing for human diseases (depends on perceived benefit)
Expanding need for security measures against drugs, explosives and firearms
Systems
Compliance-based testing
Further encouragement for shippers to self-certificate and use DIM systems
Alternatives: eg 'Health check' at country of origin, or offer disease-free status at national or regional level
Flow systems for managing responses
Applications
Temperature sensing
DIM of spores
Current, e.g. X-ray, systems extended
Increasing range of pathogens detectable in enclosed spaces
All known and potentially unknown (beyond 25 years) pathogens detectable in cabins, containers air bridges packages (baggage, cargo, enclosed spaces)
Detection of pre- symptomatic disease
Direct DIM of pathogens using genomics and post-genomics
Technologies
Dust collection
SLCs from liquids
Rapid VOC identification for known insect vectors and plants
Insect/animal training
Collection of VOCs from plants, animals and humans
Improved understanding of insect and canine olfactory systems
Chemical and other markers identified
Increased analytical sensitivity of DIM by using specific proteins or linking into biological systems
Advanced but miniaturised chromatographic and spectroscopic analysis
Now
Near
10
25
Time (years)

UC4 roadmap glossary

(Terms that are not defined are deemed to be self-explanatory)

Advanced but miniaturised chromatographic and spectroscopic analysis

This capability is typified by GC-MS – the effective combination of gas chromatography and mass spectroscopy for the identification and quantification of molecules in complex mixtures. GC-MS is considered the gold standard for the determination of a wide range of analytes. However, the size, complexity and cost of mass spectrometers have prevented their routine use, except in specialist laboratories.

Driven mainly by planetary exploration and issues of environmental and homeland security, field portability, transportability and miniaturisation are areas of increasing interest.

In situ mass spectrometry is rapidly becoming a reality and developments in manufacturing techniques, in particular, micro-electro-mechanical systems (MEMS), have meant that some hand-held mass analysers, for specific applications, already exist.

This box represents the utility of these systems to detect biochemical and chemical markers associated with infectious diseases. This will include the detection of volatile organic compounds (VOCs) and small lipophilic compounds (SLCs), as well as more classical protein and nucleic acid markers. In order to realise the potential of GC-MS in a UC4 setting, improvements in sensitivity may be necessary – alongside the requirement for reduced size and cost.

Alternatives: e.g. 'health check' at country of origin, or offer disease-free status at national or regional level

This box relates to the need to establish international agreements relating to the implementation of UC4 systems. It is concerned with alternatives. For example, should there be a health check at the country of origin; should disease-free status apply at a national or regional level?

Availability of UC3 devices for DIM of individuals may inform and drive UC4

The availability of a hand-held follow-up UC3 device may drive UC4 systems forward. In addition, the technologies developed for UC3 may be applicable to UC4 systems.

Chemical and other markers identified

A diverse portfolio of chemical, biochemical and nucleic acid markers will emerge (see UC2) that will be of value in the design and development of UC4 devices and systems. These will include markers directly related to the pathogen and markers associated with the host's response to infection (e.g. VOCs).

Collection of VOCs from plants, animals and humans

It is possible to collect VOCs (volatile organic compounds) from plants, animals and humans now – air from sealed containers of plant shipments is already being sampled and analysed by mass spectrometry.

However, improvements need to be made in the collection of VOCs from live animals and humans (especially in relation to the high-throughput screening described by UC4). It should be noted that this box refers to the collection of VOCs and not to their complete analysis and interpretation.

Compliance-based testing

Today, the screening of plants, animals and humans at ports etc. is essentially compliance-based.

Current, e.g. X-ray, systems extended

Screening of personal possessions and baggage currently involves x-ray and metal detection, but with a growing focus on the non-invasive detection of weapons, explosives and drugs, screening technology is rapidly become more sophisticated and sensitive to a wider range of materials (including organisms).

A much wider 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.

Decreased cost of biosensor technologies etc. and trends towards miniaturisation

A diverse range of biosensor technologies and systems are in development for a wide variety of applications. There is a general trend towards miniaturisation and faster, more robust, sensors, offering increased sensitivity at lower cost.

Detection of pre-symptomatic disease

The detection of volatile organic compounds (VOCs) could also aid the detection of pre-symptomatic disease – research in this area is most advanced in plants.

These capabilities will only be realised after a significant amount of fundamental research (see UC2).

DIM of spores

Techniques already exist for the DIM of spores (in particular, these have been developed for anthrax).

Direct DIM of pathogens using genomics and post-genomics

This relates to the direct detection of pathogens in a UC4 context i.e. on dust particles etc.

Dust collection

Dust sampling is a standard technique and has been used to monitor levels of hazardous materials, such as asbestos, and in forensic investigations.

Our bodies shed 400,000 flakes of skin per minute. Floating skin cells (which make up 80% of dust) are the main means of locomotion for bacteria. Dust is therefore a rich source for the direct and indirect detection of infectious diseases.

Expanding need for security measures against drugs, explosives and firearms

The security services constantly work to improve systems to intercept drugs, explosives and firearms. Some of the technologies being investigated may have relevance to disease detection in organisms, perhaps not so much in the detection of disease per se, but in the detection of organisms themselves in shipments, particularly those moving illegally, where certification will be absent and the risk of disease therefore highest.

In addition, the development of DIM systems at ports or points of concentration of movement may be very relevant to bioterrorism. In this respect, authorities and organisations concerned with security may drive UC4 forward.

Flow systems for managing responses

It is important to build a professional, appropriately regulated, infrastructure to respond to the information and data being generated by the User Challenges. How should positive results be managed at a local and international level?

Further encouragement for shippers to self-certificate and use DIM systems

Animals and plants, and their products, are generally imported under certification that they are disease free. Shippers should be encouraged to self-certificate; perhaps using a hand-held device described by UC3. Through UC1 networks, the result from the UC3 device could be transmitted to a UC4 database.

Improved understanding of insect and canine olfactory systems

Identification of the recognition molecules and biological pathways that give rise to the acute sense of smell demonstrated by dogs and other animals will ultimately provide a range of novel detection molecules and systems.

Increased analytical sensitivity of DIM by using specific proteins or linking into biological systems

This is the exploitation of the improvement in our understanding of the insect and canine olfactory systems described above.

Increasing levels of global movement of plants, animals and humans

Increased levels of global movement (associated with world trade, travel and transport) will undoubtedly drive the need for the rapid and effective detection of infectious diseases. Global movement not only allows existing pathogens to infect more hosts, but may encourage pathogens to mutate and find new hosts in unfamiliar environments etc.

Increasing range of pathogens detectable in enclosed spaces

(leading to)

All known and potentially unknown (beyond 25 years) pathogens detectable in cabins, containers, air bridges, packages (baggage, cargo, enclosed spaces)

This represents realisation of the fundamental goal of UC4.

Insect/animal training

Many animals have an extremely well-developed sense of smell and are able to detect very low levels of substances in complex mixtures. In certain cases, dogs have been shown to recognise substances at concentrations significantly below that achievable by today's mass spectrometers.

While the routine use of insects and animals to detect infectious diseases may not be the way forward, a degree of animal and insect training to explore this possibility is worth while. If an animal is able to distinguish between infected and non-infected plants, animals and humans, it follows that there is a difference in the VOC (volatile organic compounds) milieu that could be exploited by novel systems – such as spectrometers with improved limits of detection.

Low tolerance of delay (economic impacts)

High-throughput systems like ports place a premium on time. For human beings, this relates to the efficiency of transit times and ultimately customer satisfaction. For animals and plants, speed is equally important – delays in transport raise animal welfare issues and lead to spoilage in plant shipments. Low tolerance of delay will drive forward rapid, high-throughput, screening programmes.

Rapid VOC identification for known insect vectors and plants

Techniques for the rapid, small-scale collection and identification of VOCs (volatile organic compounds) from insect disease vectors, along with uninfected and infected plants, have been established.

SLCs from liquids

Techniques for the rapid small-scale collection, isolation and identification of small lipophilic compounds (SLCs) from urine and other liquid samples have been developed.

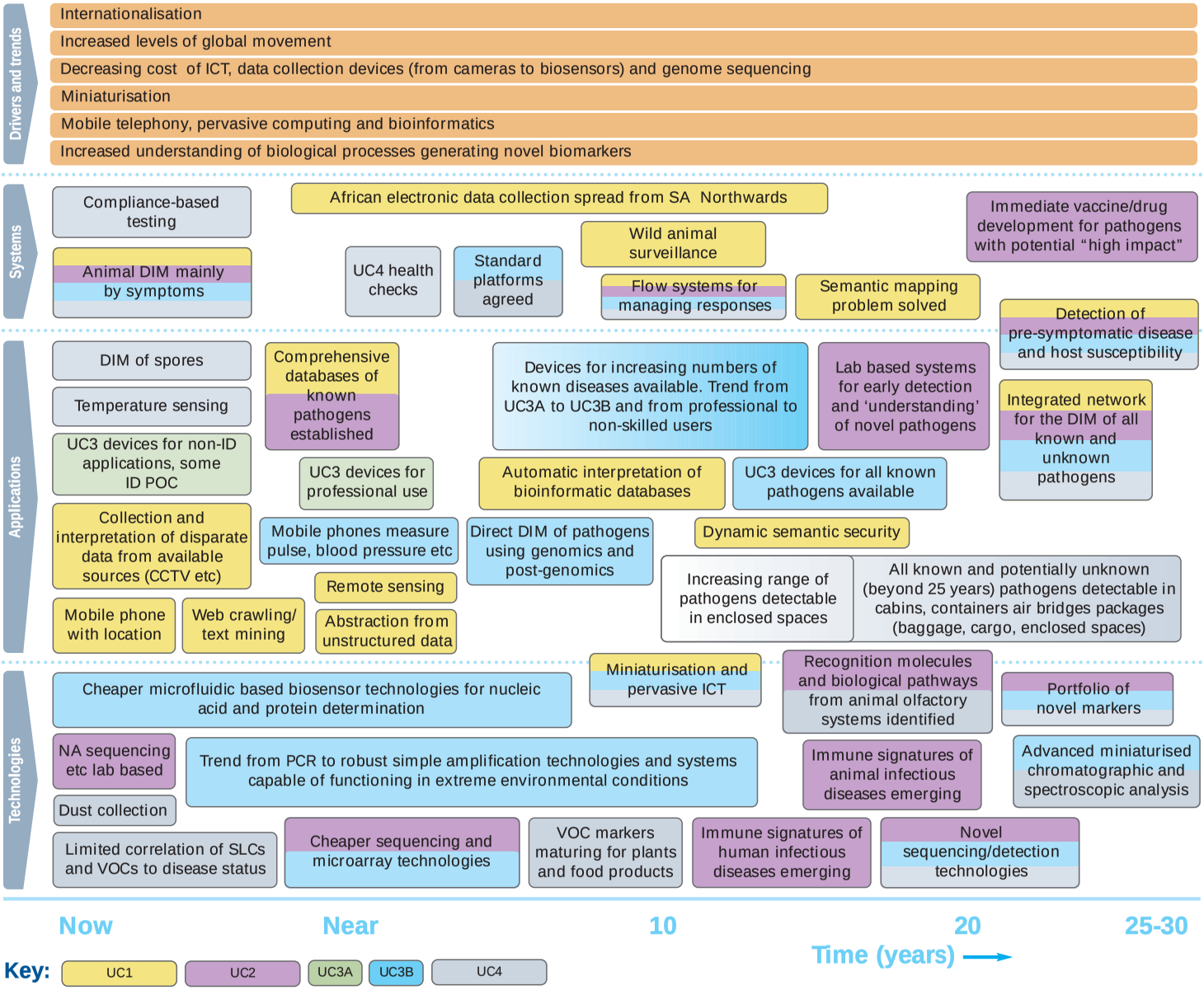
Temperature sensing

Techniques for temperature sensing are well established – thermal imaging was used in the SARS outbreak

Uncertain social acceptance of invasive testing for human diseases (depends on perceived benefit)

Invasive testing of humans (which will be required for initial UC3 devices and UC2 screening procedures) can be difficult to justify for mass screening of essentially healthy individuals. This will drive forward the non-invasive screening techniques described by UC4.

UC Synthesis Roadmap



UC synthesis roadmap glossary

(Terms that are not defined are deemed to be self-explanatory)

Advanced miniaturised chromatographic and spectroscopic analysis – UC3, UC4

This capability is typified by GC-MS, the effective combination of gas chromatography and mass spectroscopy for the identification and quantification of molecules in complex mixtures. GC-MS is considered the gold standard for the determination of a wide range of analytes. However, the size, complexity and cost of mass spectrometers have prevented their routine use, except in specialist laboratories.

Driven mainly by planetary exploration and issues of environmental and homeland security, field portability, transportability and miniaturisation are areas of increasing interest.

In situ mass spectrometry is rapidly becoming a reality and developments in manufacturing techniques, in particular, micro-electro-mechanical systems (MEMS), have meant that some hand-held mass analysers, for specific applications, already exist.

This box represents the utility of these systems to detect biochemical and chemical markers associated with infectious diseases. This will include the detection of volatile organic compounds (VOCs), as described by UC4, as well as more classical protein and nucleic acid markers.

African electronic data collection spread, from South Africa northwards – UC1

Availability and collection of data in Africa will vary by region. There can be little doubt that the South African cell phone system, as it currently exists, means that in that country and adjacent countries, in the region as far north as Zambia and Malawi, data collection will be possible – although following a gradient of reducing availability as one travels northwards. In other regions, use of cell phones may be non-existent or intermittent – with only limited hope for improvement. The Democratic Republic of Congo, Southern Sudan and Angola probably fall into this category. In Uganda, Kenya and some other countries coverage is good, while in others it is restricted mainly to the urban areas, for example, in Nigeria where satellite phones are used for local calls by prosperous individuals.

Animal DIM, mainly by symptom – UC1, UC2, UC3, UC4

In general, clinical signs, without the aid of biochemical tests, are used to diagnose animal diseases. It is a challenge for all the User Challenges to move this forward. In this way, DIM can be more efficient and accurate and may not require the presence of a professional veterinarian – which may be of particular value in developing countries.

Abstraction from unstructured data

This milestone is concerned with the ability to find patterns or key elements in unstructured data. Structured data are records in databases or cells in spreadsheets. Unstructured data are emails, reports, PowerPoint presentations, voicemail, photographs, Web pages, etc.

Automatic interpretation of bioinformatic databases

The effective interpretation of data require human oversight to ensure that appropriate algorithms are generated and significant messages aren't missed. As more data are generated and analysed, we will be able to "educate" bioinformatics programmes to carry out some of the selection processes etc. This milestone represents the point where bioinformatic data can be analysed automatically without continuous human involvement in interpretation. The word continuous is of significance and quality assurance schemes should be applied to the systems – to ensure that high quality, reliable, information is provided to the user.

Cheaper microfluidic-based biosensor technologies for nucleic acid and protein determination – UC3

This is a self-explanatory capability.

Cheaper sequencing and microarray technologies – UC2, UC3

Lab-based systems will benefit UC2 and biomarker discovery programmes. Miniaturisation will be of value to UC3 and possibly UC4.

Collection and interpretation of disparate data from available sources (CCTV etc.)

Analysing existing data sources for useful tracking or biomedical or behavioural characteristics (face recognition, gait recognition, etc).

Compliance-based testing – UC4

Today, the screening of plants, animals and humans at ports etc. is essentially compliance-based.

UC2 will play a major role in identifying markers of disease – these markers can be transferred to UC3 and UC4 devices as appropriate. UC1 will play a critical role in the management of databases and in maximising the utility of data from multiple sources.

Comprehensive databases of known pathogens established – UC1, UC2

Databases will be continuously improved and updated as research progresses. Existing databases should be combined and standardised.

Decreasing cost of ICT, data collection devices (from cameras to biosensors) and genome sequencing

These trends are of significance to all the user challenges. The steeply declining cost of ICT (coupled with rising performance) is the key driver here – it is arguably the key driver for the modern world.

The decreased cost, coupled with increased efficiency, of genome sequencing is of particular relevance to UC2.

Detection of pre-symptomatic disease and host susceptibility – UC1, UC2, UC3B, UC4

These capabilities will only be realised after a significant amount of fundamental research (see UC2). The detection of pre-symptomatic disease may emerge from a comprehensive understanding of the immune signatures of disease. Within the timeframe set by the Foresight project (i.e. up to around 30 years) it is unlikely that we will see the measurement of immune signatures on hand-held devices (UC3). However, they may begin to appear at the end of timeframe.

The detection of VOCs (volatile organic compounds) is described in UC4 and reviewed in S2 and could also aid the detection of pre-symptomatic disease – research in this area is most advanced in plants.

In addition to detecting pre-symptomatic infections, it may be possible to ascertain an individual's/animal's/population's susceptibility to disease. As technologies advance, UC3 devices will have the ability to sequence the host genome and identify single nucleotide polymorphisms (SNPs); further fundamental research is required to map SNPs to susceptibility etc.

Devices for increasing numbers of known diseases available. Trend from UC3A to UC3B and from professional to non-skilled users – UC3

This will be a natural progression in around 10 years. After this time, improvements in speed, cost and sensitivity with continue.

DIM of spores – UC4

Techniques already exist for the DIM of spores (in particular, these have been developed for anthrax).

Direct DIM of pathogens using genomics and post-genomics – UC4

This capability relates to the direct detection of pathogens in a UC4 context i.e. on dust particles etc.

Dust collection – UC4

Dust sampling is a standard technique and has been used to monitor levels of hazardous materials, such as asbestos, and in forensic investigations.

Our bodies shed 400,000 flakes of skin per minute. Floating skin cells (which make up 80% of dust) are the main means of locomotion for bacteria. Dust is therefore a rich source for the direct and indirect detection of infectious diseases.

Dynamic semantic security

This milestone represents the ability to provide active and immediate security to databases and systems through the use of semantics. Security policies are semantically aware (based on the meaning of documents or messages) and dynamic (sensitive to the context in which access is requested).

Flow systems for managing responses – UC1, UC2, UC3, UC4

It is important to build a professional, appropriately regulated, infrastructure to respond to the information and data being generated by the User Challenges. How should positive results be managed at a local and international level?

The early detection of novel pathogens will only be worthwhile if their identification results in an appropriate and measured response, which may include the development of vaccines etc.

Immediate vaccine/drug development for pathogens with potential high impact – UC2

The early detection of novel pathogens will only be worthwhile if their identification results in an appropriate and measured response. This box represents the importance of immediate response to pathogens with potential high impact.

It has been attributed to UC2 as the systems defined by this User Challenge will play a critical role in ensuring an appropriate response to threats.

Immune signatures of animal infectious diseases emerging – UC2

Immune signatures of human infectious diseases emerging – UC2

Infection of an animal or human host with a pathogen results in rapid changes in gene expression and protein synthesis by cells of the host's immune response. An appreciation of the immune signatures of disease will aid the detection of pre-symptomatic infection and our understanding of pathogens and the disease process in general.

Increased levels of global movement

Increased levels of global movement (associated with world trade, travel and transport) will undoubtedly drive the need for the rapid and effective detection of infectious diseases. Global movement not only allows existing pathogens to infect more hosts, but may encourage pathogens to mutate and find new hosts in unfamiliar environments etc.

Increased understanding of biological processes generating novel biomarkers

Fundamental research in areas outside infectious diseases, for example, in immunology and oncology, will provide novel candidate biomarkers. In the first instance, these will be of value to UC2, but a portfolio of biomarkers will be equally important in the development of UC3 and UC4 devices.

Increasing range of pathogens detectable in enclosed spaces

(trending to)

All known and potentially unknown (beyond 25 years) pathogens detectable in cabins, containers, air bridges, packages (baggage, cargo, enclosed spaces) – UC4

This represents the realisation of the fundamental goal of UC4.

Integrated network for the DIM of all known and unknown pathogens – UC1, UC2, UC3B, UC4

This box represents the realisation of the Foresight project's major goal i.e. the effective detection, identification and monitoring of infectious diseases.

Internationalisation

Internationalisation means the drive to a connected world, in every sense. The global nature of infectious diseases means that their DIM and subsequent control can only be achieved through international agreements and networks.

Lab-based systems for early detection and 'understanding' of novel pathogens – UC2

Clearly lab-based detection of pathogens is achievable today. However, attributing a pathogenic sequence to a particular disease can be time-consuming. This box represents the capability to identify novel pathogens and their significance in a timely manner. This application will emerge from an understanding of the immune signatures of disease (at the nucleic acid and protein levels), an ability to distinguish between pathogens and non-pathogens, and improved nucleic acid sequencing power. Comprehensive databases and bioinformatics systems will also play a critical role in realising this milestone.

Limited correlation of SLCs and VOCs to disease status – UC4

Small lipophilic compounds and volatile organic compounds can be collected and identified. However, there are limited data on the correlation of the production of these compounds and disease status – especially in humans and animals.

Miniaturisation

This is a self-explanatory term and is of particular relevance to the development of UC3 and UC4 devices and systems.

Miniaturisation and pervasive ICT – UC1, UC3, UC4

Miniaturisation is of particular importance to the development of the hand-held devices described by UC3, but also to UC4. These devices need to function within the communication networks described by UC1.

Mobile phone with location – UC1

While mobile phones inherently provide some location information (required to route incoming calls/data), the next generation will provide much more precise locations, probably via global positioning systems (GPS). This is driven by commercial opportunities but is of particular relevance to UC1 and will also play a role in maximising the data from UC3B devices.

Mobile phones measure pulse, blood pressure etc – UC3B (ie directly associated with UC1)

Mobile phone companies recognise that a technical system consisting of intelligent sensor networks connected to a mobile phone network could provide a wide range of opportunities of relevance to health and healthcare. Mobile phones able to measure pulse and blood pressure are on the horizon; systems that will be able to detect, identify and monitor infectious diseases (UC3B devices) form part of a longer-term vision for companies such as Vodafone.

Mobile telephony, pervasive computing and bioinformatics

It is envisaged that pervasive computing devices, which range from personal digital assistants to the microchips in cars, appliances and telephones, will give rise to an explosion of interconnected smart devices marketed to make our lives easier and more productive. Mobile telephony and communication technology will continue to advance as part of this network. The capabilities described by UC1 include such networks – their realisation will undoubtedly drive forward the development of UC3 and UC4 devices.

Bioinformatics and the global network capabilities will be imperative for the effective advance of all the user challenges.

Novel sequencing/detection technologies – UC2, UC3, UC4

Continuous improvement in sequencing power will eventually result in a portfolio of rapid novel technologies. Similarly rapid, highly sensitive detection technologies will continue to evolve.

Some of the technologies will be suitable for UC2 high-throughput screening systems; others may lend themselves to miniaturisation and be of value in the design and development of UC3 and UC4 devices.

Nucleic acid sequencing etc. lab-based – UC2

This is a self-explanatory capability.

Portfolio of novel markers – UC2, UC3, UC4

The portfolio will include markers directly related to the pathogen and markers associated with the host's response to infection (including immune signatures and volatile organic compounds (VOCs)).

In addition to novel biomarkers, the portfolio could include novel binding components, such as those that may emerge from a study of animal olfactory systems.

Recognition molecules and biological pathways from animal olfactory systems identified – UC2, UC4

Many animals have an extremely well-developed sense of smell and are able to detect very low levels of substances in complex mixtures. In certain cases, dogs have been shown to recognise substances at concentrations significantly below that achievable by today's mass spectrometers.

An understanding of the pathways and recognition molecules involved in producing this acute sense of smell may provide a range of novel detection

molecules and systems. This milestone emerged from discussions centred around the detection of volatile organic compounds (VOCs) in UC4; but the novel systems could also benefit UC3.

UC2 may oversee the fundamental research required to elucidate the biological pathways etc.

Remote sensing – UC1

This box refers to satellite remote sensing. As Earth observation becomes more finely tuned, it will be possible to observe individual humans, animals and plants. The data generated could inform UC1 networks and systems. For example, modelling could be used to predict environmental change and identify hotspots for disease outbreaks – which could be closely monitored by UC2.

Semantic mapping problem solved

Semantics is the study of meaning (which can be linguistic or non-linguistic). Considering the richness and diversity of different languages and their dialects, coupled with the use of language by varied and changing cultures, this is not trivial. It is necessary not only to recognise words but to appreciate their context. Semantics gives meaning to data. An ontology is the definition of a domain-specific vocabulary. Semantic mapping accounts for the mis-matches between different ontologies.

Standard platforms agreed UC3, UC4

Ideally, standard platforms would be open systems and different manufacturers could produce cassettes etc. to slot into the devices/systems. In the commercial world, such an open system may not be financially attractive. However, the possibility of encouraging manufacturers to work together should be discussed.

In both the immediate and long-term future, intellectual property will inevitably play a key role in the design and manufacture of UC3 and UC4 devices – companies should be encouraged to license technologies to ensure that inventions are fully exploited and that progress is not blocked.

Efforts should be made to ensure that developing countries will have access to appropriate technologies – care should be taken not to increase the north–south divide.

Temperature sensing – UC4

Techniques for temperature sensing are well established – thermal imaging was used in the SARS outbreak.

Trend from PCR to robust simple amplification technologies and systems capable of functioning in extreme environmental conditions – UC3

The polymerase chain reaction and other nucleic acid amplification technologies are routine today. A key message from the Foresight project is the need to develop robust portable molecular diagnostic devices capable of functioning in extreme conditions (e.g. in the absence of clean water and electricity). This is a difficult and complex challenge as both sequencing and microarray technologies are highly sensitive to fluctuations in temperature.

VOC markers maturing for plants and food products – UC4

At this point, it is envisaged that it will be possible to interpret the volatile organic compounds (VOC) profile from plants and food products. Humans and live animals will pose a greater challenge.

UC3 devices for all known pathogens available – UC3B

This represents a major milestone in the evolution of UC3 devices. At this stage, the devices will be linked into UC1 networks and data management systems etc.

UC3 devices for non-ID applications, some ID POC – UC3

A number of high-quality devices for self-testing exist today. The market for self-monitoring of blood glucose and pregnancy testing is well established. Point-of-care (POC) devices for cardiac markers are also in routine use.

Hand-held devices of varying quality are available for the detection of infectious diseases. The integration of hand-held devices into the effective management of DIM starts from this point. Initial barriers for the implementation of UC3A devices are more related to infrastructure than to technology – this is especially true in developing countries.

UC3 devices for professional use – UC3A

While a number of UC3 devices are already in professional use (e.g. used by clinicians and plant growers), this box represents a greater acceptance and integration of hand-held devices into our healthcare and equivalent management systems for plants and animals. At this early stage, the devices will be UC3A (i.e. not linked into comprehensive networks). In many cases, the barriers to implementing these technologies relate to infrastructure, habit and a fear that professionalism and quality will be lost. Ensuring that devices are deployed in a regulated environment will be paramount to their acceptance by professionals.

UC4 health checks – UC4

This box relates to the need to establish international agreements relating to the implementation of UC4 systems .It is concerned with alternatives. For example, should there be a health check at the country of origin; should disease-free status apply at a national or regional level?

Web crawling/text mining

Automatically indexing the Web and identifying meaningful content in free text. Text mining is a young interdisciplinary field which draws on information retrieval, data mining, machine learning, statistics and computational linguistics.

Wild animal surveillance – UC1

Wildlife surveillance and data modelling from UC1 will inform UC2 of potential hotspots where pathogens are most likely, because of opportunity and environmental change etc., to make the species jump from animal to human. In the first instance, UC2 may upgrade its screening regimes in hotspots. Through its databases and knowledge, UC2 experts will advise on the development of a diagnostic for the pathogen in humans, and on effective rapid transfer of the test to UC3 and UC4 devices and systems as appropriate.

Appendix B

Experts involved in the work

The authors and the UK Office of Science and Innovation would like to thank the many experts and stakeholder organisations who have contributed to the project's User Challenge work. In particular, the support and expert advice of the four User Challenge champions was most appreciated:

- Professor Roy Anderson, Chief Scientific Adviser, Ministry of Defence (UC1);
- Dr Debby Reynolds, Chief Veterinary Officer, Department for Environment, Food and Rural Affairs (UC2);
- Sir Liam Donaldson, Chief Medical Officer, Department of Health (UC3); and
- Ms Angela Singh, Head of Science Unit, Home Office (UC4).

Those involved in the work are listed below – the authors of this report are shown in bold.

Experts who were involved in the work		
Dr Matthew Addis	IT Innovation Centre	University of Southampton
Professor Roy Anderson	Chief Scientific Adviser	Ministry of Defence
Professor Alan L Archibald	Head of Division of Genomics and Bioinformatics	Roslin Institute
Dr Catherine Arnold	Applied and Functional Genomics Unit	Health Protection Agency
Dr Richard Ashcroft	Reader in Biomedical Ethics	Imperial College London
Dr Richard Baines	Department of Agriculture	Royal Agricultural College
Dr Ian Barker	**Head of Immunological and Molecular Methods**	**Central Science Laboratory**
Professor Tony Barnett	ESRC Professional Research Fellow, DESTIN	London School of Economics
Professor Christopher Bartlett	Visiting Professor of Infectious Disease Epidemiology	Centre for Infectious Disease Epidemiology, University College London and London School of Hygiene and Tropical Medicine
Professor Norman Begg	Medical Director	Glaxo Smithkline
Dr Andy Bell	Chief Scientist CBRN	Home Office
Mr Richard Berridge	EU Policy adviser	Department for Environment, Food and Rural Affairs
Dr Dave Birch	Director	Consult Hyperion
Dr Michael Birkett	Senior Research Scientist	Rothamsted Research
Professor Stephen Bishop	Division of Genetics and Genomics	Roslin Institute
Dr Mpoko Bokanga	Executive Director	African Agricultural Technology Foundation, Kenya
Professor Peter Borriello	Centre Director	Health Protection Agency

Experts who were involved in the work *(continued)*		
Dr David Brown	Director, Virus Reference Department	Health Protection Agency
Professor Joe Brownlie	**Professor of Veterinary Pathology and Director of ECTP**	**Royal Veterinary College**
Mr Tony Bryant	Senior Manager, Project Scanner Team	HM Revenue and Customs
Ms Siobhan Carey	Chief Statistician	Department for International Development
Dr Rachel Carson	General Manager	Inscentinel Ltd.
Professor Tony Cass	Deputy Director	Institute of Biomedical Engineering, Imperial College, London
Dr Mariann Chriel	Epidemiologist	Danish Institute for Food and Veterinary Research
Dr Freddy Choi	IT Innovation Centre	University of Southampton
Dr Richard Coker		London and London School of Hygiene and Tropical Medicine
Dr Denis Coulombier	Head, Preparedness and Response Unit	European Centre for Disease Prevention and Control
Dr Nick Coulson	Head International Animal Health Division	Department for Environment, Food and Rural Affairs
Dr Edward Coyle	Director	British Medical Association Board of Science
Dr Chris Danks	Plant Health Group	Central Science Laboratory
Ms Ann Davison	Consultant to Defra on Consumer Engagement project	Department for Environment, Food and Rural Affairs
Professor Dave de Roure	Professor of Computer Science	University of Southampton
Dr Chris Desmond	Development Studies Institute (DESTIN)	London School of Economics
Sir Liam Donaldson	Chief Medical Officer	Department of Health
Professor Christl Donnelly	Professor of Statistical Epidemiology	Imperial College London
Dr Nigel Dowdall	Director Health Services	British Airways
Dr Alan Doyle	Science Programme Manager	Wellcome Trust
Dr Mel Duffield		Defence Science and Technology Laboratory
Professor Neil Ferguson	Department of Infectious Diseases and Epidemiology	Imperial College London
Professor Paul Fine	Professor of Epidemiology	London School of Hygiene and Tropical Medicine
Mr Christopher Furk	Principal Plant Health and Seeds Inspector	Department for Environment, Food and Rural Affairs
Dr Linda Galloway		formerly, TPU Home Office
Dr Paul Wenzel Geissler	Senior Lecturer in Social Anthropology	London School of Hygiene and Tropical Medicine
Dr Elizabeth S George	Deputy Portfolio Director, Biological Countermeasures Portfolio	Department of Homeland Security, US
Professor Noel Gill	Consultant Epidemiologist	Health Protection Agency

Experts who were involved in the work *(continued)*		
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Professor Rod Griffiths	President	Faculty of Public Health
Dr Peter Grimley	Head of Import Policy, International Animal Health Division	Department for Environment, Food and Rural Affairs
Professor Robert Gurney	Director, Environmental Systems Science Centre	University of Reading
Dr Hans Hagen	Senior Manager	Wellcome Trust
Dr David Harper	Director – Health Protection, International Health and Scientific Development	Department of Health
Mr Steven Hart	Security Development Manager	British Airports Authority
Dr Jeremy Hawker	Deputy Director, Local and Regional Services Division	Health Protection Agency
Mr Gerard Hetherington	Division Head – Health Protection	Department of Health
Dr Judith Hilton	Head, Microbiological Safety Division	Food Standards Agency
Mr Tony Howard	Deputy Director, Intellectual Property and Innovation Directorate	Patent Office
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Dr Matthew Keeling	Department of Biological Sciences	Warwick University
Ilona Kickbusch, PhD		Kickbusch Health Consult, Switzerland
Dr Donald King	Senior Research Scientist,	Institute for Animal Health
Dr Ian Lawston	Chief Scientist, Detection Department	Defence Science and Technology Laboratory
Professor Jillian Lenne		Independent Consultant
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Dr Gordon Logan	Managing Director	Labformatics Ltd.
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Dr John McGiven		Veterinary Laboratories Agency
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Dr Geraint Morgan	Planetary and Space Sciences Research Institute	The Open University
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Dr Kenneth Ombongi	Department of History	University of Nairobi, Kenya

Experts who were involved in the work *(continued)*		
Dr William Otim-Nape	Consultant and Former Acting Director General	National Agricultural Research Organisation, Uganda
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Dr Martin Pearce	Scientific Leader	Defence Science and Technology Laboratory Porton Down
Professor Catherine Peckham	**Professor of Paediatric Epidemiology**	**Institute of Child Health, University College London**
Dr Ed Peeler	Veterinary Epidemiologist	Centre for Environment, Fisheries and Aqua Culture Science
Dr Rosanna Peeling	Manager, Diagnostic Research and Development	World Health Organisation
Dr Ferdinand Peer	Senior Manager Application Field Mobile Health	Vodafone
Dr Elaine Perkins	Deputy Team Leader, Biosensors	Defence Science and Technology Laboratory
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Dr Noah Phiri	Plant Pathologist	CABI African Regional Centre
Professor John Pickett	**Head, Biological Chemistry Division**	**Rothamsted Research**
Dr Beth Purse	TALA Research Group, Department of Zoology	Oxford University
Mr Andy Price	Security Technical and Process Manager	British Airports Authority
Ms M Megan Quinlan	Regulatory Specialist	Interconnect Consulting
Dr Debby Reynolds	Chief Veterinary Officer, Director General Animal Health and Welfare	Department for Environment, Food and Rural Affairs
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Ms Pamela Rogers	Team Leader – Prohibitions & Restrictions	HM Revenue and Customs
Dr Cathy Roth	Team Co-ordinator	World Health Organization
Ms Ros Rouse	Associate Director	Economic and Social Research Council
Mr Owen Rowland	Head of Counter Terrorism and Science and Technology Policy	Home Office
Dr Amal Rushdy	Consultant Epidemiologist	Health Protection Agency
Dr Mark Rweyemamu	Consultant	Tanzania
Dr David Salisbury	Head of Immunisation	Department of Health
Dr Roland Salmon	Director, Communicable Disease Surveillance Centre	National Public Health Service for Wales
Dr Matt Sapiano	Earth Systems Science Interdisciplinary Center	University of Maryland, US
Ms Barbara Saunders	Consumer Consultant	Foodaware
Dr Harald Schmidt	Assistant Director	Nuffield Centre for Bioethics

Experts who were involved in the work *(continued)*		
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Ms Angela Singh	Head of Science Unit	Home Office
Dr Nicola Spence	Head of Plant Health Group	Central Science Laboratory
Mr Jonathan Suk	Research Fellow	Economic and Social Research Council, Innogen Centre
Dr Robert Sullivan	Research and Technology Strategy Division	Department for Transport
Professor Will Stewart		**Independent Consultant**
Mr Simon Strickland	Civil Contingency Secretariat	Cabinet Office
Dr James Stuart	Regional Director	Health Protection Agency
Professor Joyce Tait	Director	Economic and Social Research Council, Innogen Centre
Ernest T Takafuji, M.D.	Director, Office of Biodefense Research	National Institute of Allergies and Infectious Diseases, US
Dr Steve Taylor	IT Innovation Centre	University of Southampton
Dr Paul Thomas	Technical Leader	Defence Science and Technology Laboratory
Dr Gavin Thomson	Consultant	formerly, FAO/AU-IBAR
Dr Nicholas Thomson	Project Manager	The Wellcome Trust Sanger Institute
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Dr Victor Tybulewicz	Head of Division of Immune Cell Biology	National Institute for Medical Research
Dr Stewart Tyson	Head of Profession	Department for International Development
Dr Colin Upstill	IT Innovation Centre	University of Southampton
Dr Nicholas Veck	Director, European Projects	Infoterra Ltd.
Professor Jeff Waage	**Director, Centre for Environmental Policy**	**Imperial College, London**
Professor Lester Wadhams	Head of Chemical Ecology Group	Rothamsted Research
Dr Philip Wakeley	Senior Scientific Officer	Veterinary Laboratories Agency
Dr Vincent Wallace	Technical Group Leader, Medical Applications	TeraView Ltd
Dr Xiaoming Wang	Research Group Leader	Institute of Crop Sciences, Chinese Academy of Agricultural Sciences
Mr Rowland Watkins	IT Innovation Centre	University of Southampton
Dr John M Watson	Consultant Epidemiologist and Head Respiratory Diseases Department	Health Protection Agency
Professor Julius Weinberg	Pro-Vice Chancellor	City University, London
Professor Peter Wells	Distinguished Research Professor	Cardiff University

Experts who were involved in the work *(continued)*		
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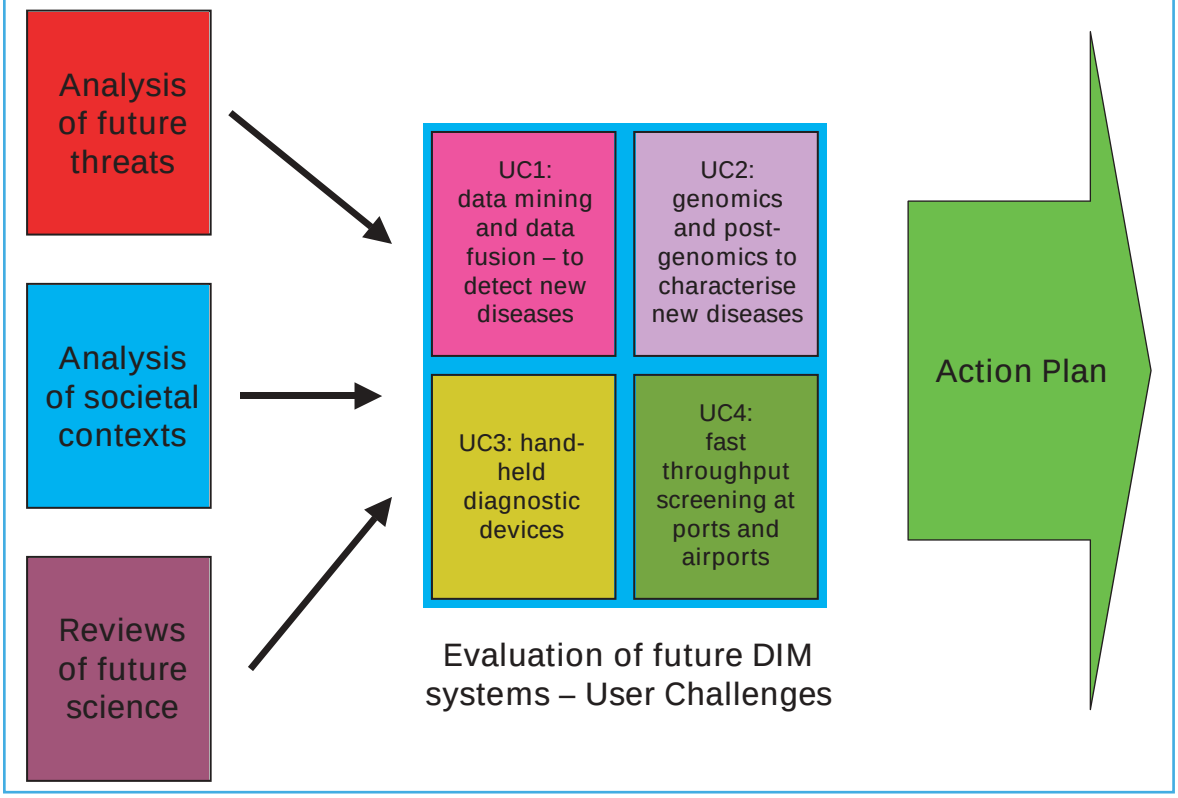
Dr Penny Wilson	**Consultant to the Life Science, Biotechnology and Healthcare Industries**	
Dr Simon Wood	Senior Consultant	Labformatics Ltd
Dr Abigail Woods	Centre for the History of Science, Technology and Medicine	Imperial College London
Dr Marion Wooldridge	Head, Centre for Epidemiology and Risk Analysis	Veterinary Laboratories Agency
Professor Mark Woolhouse	**Director, Centre for Infectious Diseases**	**University of Edinburgh**
Professor Michael Worboys	Centre for the History of Science, Technology and Medicine and Wellcome Unit	University of Manchester
Dr Feng Zhang	Project Coordinator	CABI China Office
Dr Nianzu Zhang		National Exotic Animal Disease Diagnostic Laboratory, Yunnan, China

Appendix C

Overview of the work of the project

The key parts of the project are set out in Figure C1 and are described below. Relevant project reports and supporting papers are indicated in brackets (these are also listed in a chart in Appendix D):

Fig C.1 The principal parts of the project



Analysis of future threats: a starting point was to generate a vision for the future threats of infectious diseases, and the factors driving them. This defines the challenge for future DIM systems. These threats are summarised and analysed in reports T1 (*Future Threats*) and T2 (*Risk Analysis*). The work that these draw on involved:

- new research on the nature of emerging diseases (T15, T16), reviews of the impact of climate change (T7.1–T7.4), and the effect on ecosystems (T11)
- case studies of illustrative disease threats (T5.1–T5.12)
- workshops and reviews of important drivers of risk – including travel and migration (T10), and the bushmeat trade (T12)
- reviews of disease modelling work (T8.1–T8.11)
- surveys, one-to-one interviews and international workshops held in the UK and Entebbe, Uganda, and China (T3, A4, T13).

Analysis of societal contexts: the effectiveness of future DIM systems will depend greatly on their sensitive development and deployment in different systems of culture and governance. These issues were explored through:

- studies comparing the effect of culture and governance on the deployment of DIM systems in Africa, the UK and China (D4.1–D4.3)
- analysis of the control strategies for future diseases (D3.1–D3.3) – this was performed so that future DIM systems could be viewed within this wider context
- a study of historical perspectives (D5)
- a comparison of public perceptions of risk in Africa and the UK (D7)

Reviews of future science: reviews of the state of the art of ten areas of science were commissioned (S3–S12). An overview of each is provided in S1. These reviews were used to inform the capabilities of future DIM systems. The topics for review were:

Table C1: Topics of the state-of-the-art science reviews

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

Evaluation of future DIM systems – User Challenges: four classes of future DIM systems were identified for analysis by four teams of experts. The analysis (D1, D2) drew on all of the above work and informed the action plan which has been produced in consultation with key stakeholders (P1).

Action plan: all of the above has led to the development of a detailed action plan by key stakeholders around the world (P1).

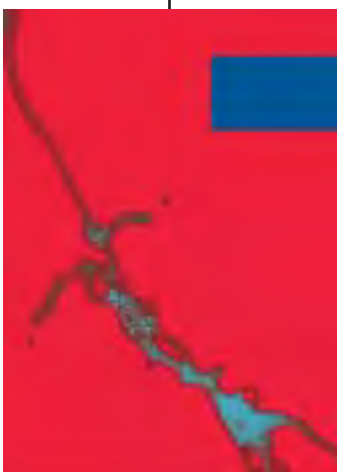
Finally, a substantial part of the project concerned the future threat of diseases in Africa, and the possible contribution of future DIM systems to managing that. All of the Africa-related strands of the project are drawn together in report A1.

Appendix D

Structure of the project reports and supporting papers

E1: Executive Summary

S1: Science Review Summaries



T1: Future Threats

Detailed reviews of science:

S3: Intelligent sensor networks
S4: Data mining and data fusion
S5: Non-invasive screening and scanning
S6: Genomics and bioinformatics
S7: Biosensors and biomarkers
S8: Interrogation of natural signals
S9: Predictive and real-time epidemiology
S10: Earth observation
S11: Host genetics and engineering
S12: Immunological techniques

Risk analysis:

T2: Risk analysis
T3: Expert survey of the UK and Africa

Disease case studies:

T5.1: MRSA
T5.2: HIV/AIDS
T5.3: Influenza in humans
T5.5: Food-borne pathogens
T5.6: Fish diseases
T5.7: Potato late blight
T5.8: Malaria
T5.9: Rinderpest
T5.10: Plant viruses in sub-Saharan Africa (SSA)
T5.11: Sudden oak death
T5.12: West Nile virus

Climate change:

T7.1: Overview
T7.2: Plant diseases
T7.3: Animal diseases
T7.4: Human diseases

Modelling reviews:

T8.1 Overview
T8.2: Malaria in SSA
T8.3: Bluetongue in Europe
T8.4: TB control in SSA
T8.5: Global traffic
T8.6: Foot-and-mouth disease (FMD)
T8.7: Paediatric HIV/AIDS
T8.8: Tsetse in SSA
T8.10: Malaria UK
T8.11: Eco-costs of potato ring rot

NOTE: Report numbers are not sequential.
Some report numbers were originally reserved for reports which were subsequently not commissioned.

A1: Africa

D1: Vision of Future Detection, Identification and Monitoring Systems

P1: Action Plan

Further reviews and research:

T9: Review of initiatives
T10: Travel and migration and their impacts on diseases
T11: Effects of diseases on ecosystems
T12: Wildlife trade
T13: China – human and zoonotic diseases
T15: Plant pathogen database analysis
T16: Human pathogen database analysis

Africa papers:

A3.1 Paper for the Commission for Africa (CfA)
A3.2 CfA paper appendices
A4: Report of a pan-African workshop
A5: Report of a pan-African workshop (French)

User Challenge work:

D2: Introduction to the User Challenge work
D2.1: UC1 – Data mining and data fusion
D2.2: UC2 – Genomics and post-genomics for characterising new pathogens
D2.3: UC3 – Hand-held diagnostic devices
D2.4: UC4 – Fast-throughput screening devices

Future control of diseases:

D3.1: Plant diseases
D3.2: Animal diseases
D3.3: Human diseases

Culture and governance:

D4.1: Plants
D4.2: Animals
D4.3: Humans

D5: Historical perspectives
D7: Public perceptions of risk

Details of all the reports and papers produced by the Foresight project: Infectious Diseases: preparing for the future can be obtained from the Foresight website (www.foresight.gov.uk). Any queries may also be directed through this website. The reports and outputs of the project should not be taken to represent the policies of any governments or organisations involved in the work.

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