Government
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Blackett Review on wide-area biological detection

Government Office for Science

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Foreword

By the Government Chief Scientific Adviser (2008-2013)

This report sets out the conclusions of the Blackett Review looking at the issue of Biodetection. Blackett Reviews, which I started a few years ago, use both Government and non-Government scientists to address problems that require scientific input of the highest level.

We live in a world in which the UK is subject to threats and hazards from within and outside of the UK. One of the responsibilities of government is to address these threats using the best scientific thinking and technologies available to do so.

A terrorist attack using biological agents is one of the highest impact risks within the National Security Strategy (NSS) and CONTEST (the Governments Counter-Terrorism Strategy). Government is therefore committed to accelerating scientific methods to detect biological threats at the earliest opportunity, in order to mount a rapid response and to minimise loss of life.

This Blackett Review on wide area biological detection was commissioned by me at the request of the Home Office and MOD. The review uses internationally regarded experts from inside and outside Government to provide leading edge thinking on the best ways to rapidly detect a biological release. The report identifies a number of recommendations for further strengthening the UK's capability and explores routes for development over the short and medium term.

Professor Sir John Beddington

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Professor Philip Bond	University of Oxford
Professor Jason Crain	University of Edinburgh
Professor Derrick Crook	University of Oxford
Mr Andrew Eland	Google UK
Professor Paul Elliott	Imperial College London
Professor Jeff Errington	University of Newcastle
Professor John Fazakerley	Director, The Pirbright Institute
Dr Paul Gascoigne	Smiths Detection
Professor Vernon Gibson	Chief Scientific Adviser, MoD
Professor Roy Goodacre	University of Manchester
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Professor Nick Jennings	Chief Scientific Advisor for National Security
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1. Executive summary

In Autumn 2012, at the request of Home Office (HO) and supported by the Ministry of Defence, the GCSA convened a Blackett Review to address the question *"Which technologies or capabilities could enable rapid, wide-area detection of a broad spectrum of biological agents in the next 15 years?"*

As well as exploring the implications of rapid advances in the biological sciences over recent years, the review considered the contribution of broader scientific developments on the UK's ability to detect biological hazards.

This report summarises the findings from the review. Specifically it highlights a number of technologies and capabilities that could enhance government's ability to detect and respond to an aerosolised biological attack in the next 15 years. Although advanced technologies will play a critical role in enhancing the UK's capability, the review concluded that the integration[1] of existing information sources and systems could significantly enhance the timeliness and effectiveness of a response in the short term. The review question was based on analysis over a 15 year timescale; however the panel concluded that there were significant opportunities in the short to medium term that justified focused consideration during the meetings.

Whilst the review focused on the detection of a deliberate release of a biological agent, the Blackett panel concluded that the ability to rapidly detect unusual health signals would have significant benefits for public health, taking advantage of the opportunities afforded by near-universal coverage of the National Health Service. Such signals could give valuable early warning of influenza and other epidemics at an earlier stage than possible with current reporting systems. Many of these health benefits are achievable within the short term, but require decisive and co-ordinated government support.

An effective response requires cross-government action. The ability to detect, report and respond to a biological attack or infectious disease outbreak will draw on the resources of several government departments. The successful delivery of a future wide-area biodetection system is critically dependent upon collaboration between the key departments and agencies, industry and academia. In addition, a number of areas of fundamental research are crucial to achieving the required levels of performance for an effective wide-area biodetection capability.

It was not possible to cover the threat aspect of biodetection in detail during these meetings. Panel discussions therefore focused on the opportunities for Government to harness technologies and capabilities, shaped by the above question.

[1] Information framework integrating signals from array of sensors, intelligence, public health/syndromic surveillance, veterinary, social networks/search engine queries and additional sources of information.

The following technical areas were specifically identified for action by the panel:

- Physical Processes
- Sequencing

} **Sensors**

- Alternative Information Sources and Statistics
- Systems Integration

} **Information and Systems Integration**

A number of specific recommendations are made within each of the technical areas above and are captured within the relevant sections of this report. In addition, overarching recommendations are captured below.

Clearly this work was not performed in isolation and supports the work that the Home Office, Ministry of Defence, Department of Health, Cabinet Office and others are doing to address many of the issues discussed in this report.

1.1 Recommendations

Short term impact[2]:

1. Government should assess the feasibility of developing an automated biodetection reporting system. Such a system should integrate data from deployed sensors, public health, veterinary, intelligence and alternative information sources[3], with clear reporting lines, in order to improve the timeliness and effectiveness of a response to a biological attack or infectious disease outbreak.

2. The Government should work with Industry to understand the commercial and market drivers for biodetection and to assess the viability of solutions in a global competitive market.

3. The Government should work collaboratively across departments and agencies and in partnership with Industry, to assess the broader benefits of wide area biodetection systems for public, veterinary and plant health.

4. The Government should support systems engineering studies[4] to develop costed options for a network of wide-area biodetection capabilities within a 5 and 10 year timeframe. Studies should be informed by the findings from table-top exercises.

[2] Benefit realised within 5 years
[3] E.g. Social networks, search engine queries and other alternative signals from the internet.
[4] Systems engineering is an interdisciplinary field of engineering focusing on how complex engineering projects should be designed and managed over their life cycles.

Medium term impact[5]:

1. Government Departments[6] should work collaboratively with other UK research funders, including UK Research Councils and the Technology Strategy Board, and with international partners to develop the underlying knowledge base and infrastructure for wide-area biodetection:

Fundamental research:

- Characterisation of the aerosol microbiome in representative urban environments[7]
- Techniques for sample capture, concentration and preparation
- Statistical design of urban air sampling and sensing regimes[8]
- Enhanced metagenomics and bioinformatics for high confidence wide-area biodetection
- Techniques for high throughput sequencing

Translational[9] research:

- Microinstrumentation for highly portable sensor networks
- Development of high throughput air sampling methodologies and equipment for wide-area biodetection.
- Systems engineering studies[10] to optimise and cost system solutions
- Evaluation of the performance of dispersion models within priority biodetection scenarios
- Application of statistical and data analytics methods for the identification, integration and reporting of biodetection signals from vast datasets in real-time
- Identify and evaluate the most effective sources of alternative data /information in predicting, detecting and tracking the course of a biological attack

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[5] Benefit realised within 10 years
[6] Government departments with an interest in biodetection include HO, MOD, DH, DEFRA, CPNI and BIS
[7] A microbiome is the totality of microbes, their genetic elements (genomes), and environmental interactions in a particular environment.
[8] To enhance probability of detection and reduce false alarm rates
[9] Translational research is scientific research that facilitates the translation of findings from basic science to practical applications that enhance human health and well-being.
[10] To develop a 'multi-layered staircase approach' based on increasing information density and statistical certainty to establish the presence, characteristics, identity and confirmation of use of biological agents.

2. Introduction

A terrorist attack using biological agents[11] is one of the highest impact risks within the National Security Strategy (NSS) and CONTEST (the Governments Counter-Terrorism Strategy). Such events could have a significant effect on human and animal health and on the economy.

The early detection of a deliberate biological release is a critical component of a response to a biological attack, to enable timely responses, to restore normality and to minimise loss of life.

2.1 Technical challenges and aspiration

If a biological warfare agent is released within an urban environment, there is a "window of opportunity" in which protective measures and treatment can minimise loss of life. A relatively small release of infectious agent could travel rapidly and affect a large area. Thus, to be effective and preserve life, a wide area biodetection capability should trigger an alert in real-time and initiate measures as quickly as possible.

The capability also needs to link all of the command elements. Given the implications of an incident, Government response will be directed at the highest level; accordingly the indication of an event will require a very high level of associated confidence.

Technical challenges include, but are not limited to the ability to:

- detect 'true' events in near real-time
- minimise 'false alarms'

This requires an understanding of variations in the biological background in representative environments and statistical analysis to inform the location and density of sampling sites in urban locations.

The significant costs associated with developing and deploying early warning systems for biological agents also presents a challenge. In order to provide a high confidence alert of a biological agent release to decision-makers, detection systems must meet stringent performance characteristics, the costs of which can prove prohibitively expensive for industry or government alone to develop and exploit.

Experience to date in deploying wide-area biodetection systems in the US (see box 1) can inform the development of future biological detection systems for use in urban environments.

[11] Viruses, bacteria and toxins

Box 1: US experience of wide area biodetection systems

In January 2003 the US deployed a bio surveillance system ("BioWatch") to provide persistent surveillance of a mass release of biological agents in more than 30 cities. The system cost the US approximately $1 million in initial equipment costs per city, followed by operational costs of $1 million per city per year[12]. If the planned transition to Generation 3 is successful, the estimated annualised direct cost for acquisition and operation over 10 years is $200 million[13]. It has been reported in the media that as of 2012, the system had generated a large number of false alarms, with more than 50 such cases documented between 2003 and 2008. State and local health officials have never ordered evacuations or distributed emergency medicines in response to a positive reading from the system[14].

A review of the BioWatch programme by the National Research Council in the US recommended that the current system be replaced with a new biodetection system capable of more frequent, more rapid, and more comprehensive automated analysis and reporting of results. The review encouraged testing of any future concept in realistic environments to establish its effectiveness. It also advocates collaboration with public health systems to improve its usefulness[15].

An aspiration for government is to develop and deploy an affordable persistent wide area biological detection capability able to rapidly detect, identify and locate a deliberate release of aerosolised biological material(s) over a wide area. No single technology or approach will currently achieve all of these goals.

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[12] "Nationwide Monitoring System Planned For Detecting Bioterror Attack," *The Associated Press*, January 22, 2003.

[13] BioWatch and Public Health Surveillance: Evaluating Systems for the Early Detection of Biological Threats: http://www.nap.edu/catalog/12688.html

[14] http://www.latimes.com/news/nationworld/nation/la-na-biowatch-20120708,0,5093512.story?track=lat-pick

[15] http://iom.edu/~/media/Files/Report%20Files/2009/BioWatch-Public-Health-Surveillance/Biowatch%202010%20Report%20Brief.pdf

2.2 Review format

This Blackett review was convened to take a fresh look at the technical challenges for biodetection and consider how rapid developments in biological science[16] and beyond may enable a step change in the UK's wide-area biological detection capability.

The review specifically asked:

"Which technologies could enable rapid, wide area detection of a broad spectrum of biological agents in the next 15 years?"

The first meeting of the panel consisted of a morning of background presentations and demonstrations by experts within government followed by an afternoon discussion session, chaired by the GCSA. There were two follow-up meetings, each about six weeks apart, to identify and discuss key issues and potential solutions that Government should take forward.

A summary of the panel discussions, key findings and specific recommendations are described below. The recommendations result from meetings of sub-groups in four key areas, highlighted by the panel as having significant potential for impact:

- Physical processes
- Sequencing
- Alternative Information Sources and Statistics
- Systems Integration

Specific recommendations are highlighted in bold at the end of each section.

[16] http://www.upmc-biosecurity.org/website/resources/publications/2012/pdf/2012-06-08-industrialization_bio_natl_security.pdf

3. Sensing system

3.1 System design

The release of a biological agent leads to two main specific events:

- The physical presence of the agent in the environment
- Changes in the health status of exposed individuals, livestock or other biological targets, leading to the identification of associated symptoms by clinicians

Sensing systems are concerned with the identification of the physical presence of the agent in the environment. The aim of a wide-area biodetection sensing system is to gather as much information as possible to provide accurate and confident reporting of the presence of a biological threat agent in the environment, with the secondary benefit of potentially narrowing the extent of the hazard as quickly as possible.

There are considerable challenges associated with using physical methods for the rapid detection and definitive identification of biological agents in the natural and built environment. These derive both from the complex nature of the biological threat itself and from the natural background which is a complex, fluctuating mix of organic and inorganic matter[17].

A multi-faceted series of actions with defined timelines are therefore required in response to a natural or deliberate exposure to biological agents. The event timeline comprises the following steps.

1. persistent (24/7) real-time environmental monitoring,
2. preliminary characterisation of the agent,
3. area delineation and confirmation of the identity of the agent.

This review recommends that a decentralised and networked array of sensors is required to trigger rapid and reliable alarms and to define the nature of the event (origin, agent type and direction of travel) and the geographical perimeter of exposure. Ideally, such detectors should have dual use applicability to drive economies of scale and efficiency to include treatment (public health), warning (national security), prosecution (law enforcement) and intent (intelligence).

To achieve this goal a multi-layered 'staircase approach' to wide-area detection is proposed. Here technologies are viewed not singly but as grouped into a system such that each step descended on the staircase results in an increase in both the quantity of information and the statistical certainty associated with the detection event.

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[17] Stetzenbach, L.D., Buttner, M.P. & Cruz, P. (2004) Detection and enumeration of airborne biocontaminants. Curr. Opin. Biotech. 15, 170-174.

Such detectors would act as a layered system, enabling initial alarms and precursors to trigger a more sophisticated, forensic-level identification and verification of use at the genomic, proteomic or molecular level. The detector technologies can be separated into four categories, as described in Figure 2:

1. Spectroscopic techniques
2. Morphologic generic techniques
3. Physico-chemical sensors
4. Sequencing technique

Box 2: Mass spectrometry

Mass spectrometry (MS) is regarded as powerful method for the identification of proteins associated with toxins, bacteria or viruses. It is also the most comprehensive and versatile tool in large-scale proteomics[18] capable of providing advanced protein/peptide profiling to separate, characterise and quantify analytes from complex biological samples[19].

Currently, MS techniques are routinely used for rapid classification of bacteria, especially by the use of MS-based proteomics methods[20]. Efficient protocols have been developed for bacterial protein extraction and mass analysis that have shown for example identification of Bacillus spores. Discrimination between gram-positive and gram-negative whole bacteria was also obtained with less than 2 minutes analysis time[21,22,23].

Viruses are also distinguished through coat proteins using proteomics[24] approaches[25]. Following the first mass spectrometric analysis of intact virus capsids[26], prospective developments in the next 10 – 15 years include the capability to determine viral size and concentration simultaneously. Full size distributions are anticipated with subnanometer precision from individual capsid proteins to intact viral particles[27]. Development of this approach, and its combination with other mass spectrometry methods for the identity of proteins, could provide the most rapid and precise characterisation of viruses.

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[18] Proteomics is a term in the study of genetics which refers to all the proteins expressed by a genome; proteomics involves the identification of proteins in the body and the determination of their role in physiological and pathophysiological functions.
[19] J.R. Yates, C.I. Ruse, A. Nakorchevsky, Proteomics by Mass Spectrometry: Approaches, Advances, and Applications, Annual Review of Biomedical Engineering, Vol. 11: 49-7, 2009)
[20] Discrimination and Phylogenomic Classification of Bacillus anthracis-cereus-thuringiensis Strains Based on LC-MS/MS Analysis of Whole Cell Protein Digests, J.P. Dworzanski, D.N. Dickinson, S.V. Deshpande, A.P.Snyder and B.A. Eckenrode, Anal. Chem. 2010, 82, 145–155
[21] Freiwald, A.; Sauer, S. Nat. Protoc. 2009, 4, 732–742.
[22] Teramoto, K.; Sato, H.; Sun, L.; Torimura, M.; Tao, H.; Yoshikawa, H.; Hotta,Y.; Hosoda, A.; Tamura, H. Anal. Chem. 2007, 79, 8712–8719.
[23] Meetani, M. A., Shin, Y. S., Zhang, S., Mayer, R. & Basile, F. Desorption electrospray ionization mass spectrometry of intact bacteria. J Mass Spectrom 42, 1186-1193,(2007).
[24] A. Bensimon, A.J.R. Heck and R. Aebersold, Mass Spectrometry–Based Proteomics and Network Biology, Annual Review of Biochemistry, Vol. 81: 379-405, 2012.
[25] Maxwell, K. L. & Frappier, L. Viral proteomics. Microbiol Mol Biol Rev 71, 398-411,(2007).
[26] Tito, M. A., Tars, K., Valegard, K., Hajdu, J. & Robinson, C. V. Electrospray time-of-flight mass spectrometry of the intact MS2 virus capsid. J Am Chem Soc 122, 3550-3551,(2000).
[27] Pease, L. F., 3rd. Physical analysis of virus particles using electrospray differential mobility analysis. Trends Biotechnol 30, 216-224,(2012).

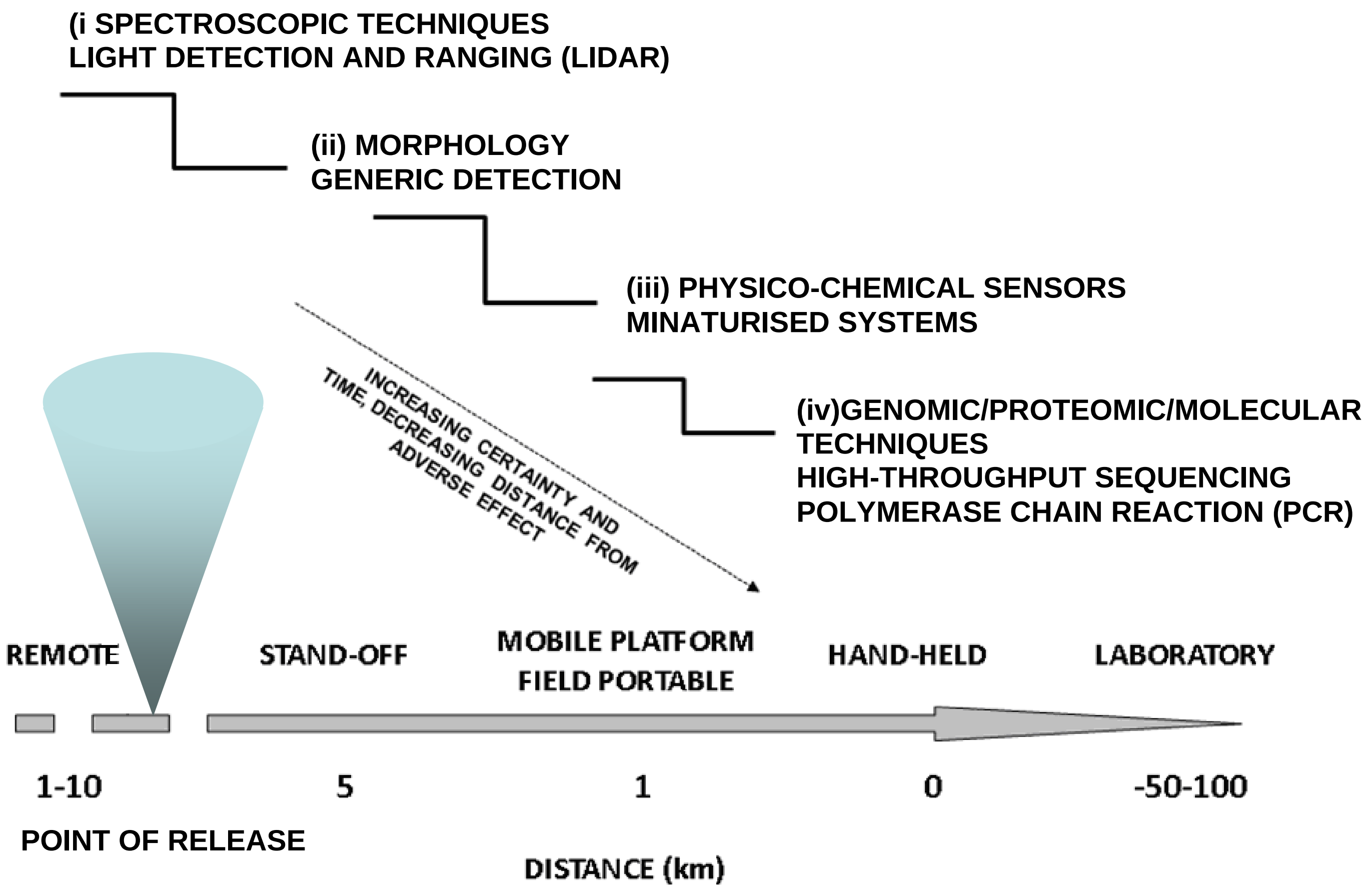

Figure 2 – The proposed staircase system capable of analysing the origin, direction of travel, geographical distribution and nature of emerging threats

Detectors could function remotely at some distance from the target (spectroscopic detectors) to provide wide-area surveillance and/or be deployed as part of an array to provide generic feature analysis (generic detectors). Further elements could provide preliminary identification (physico-chemical detectors) and ultimately confirm the identity of an agent (PCR, high throughput sequencing).

The methods with the least specific information content are the fastest (physical and spectroscopic methods, <1second), chemical methods are intermediate (physico-chemical, minute to hours), whilst the most discerning and information-rich biological methods are the slowest (minutes to days).

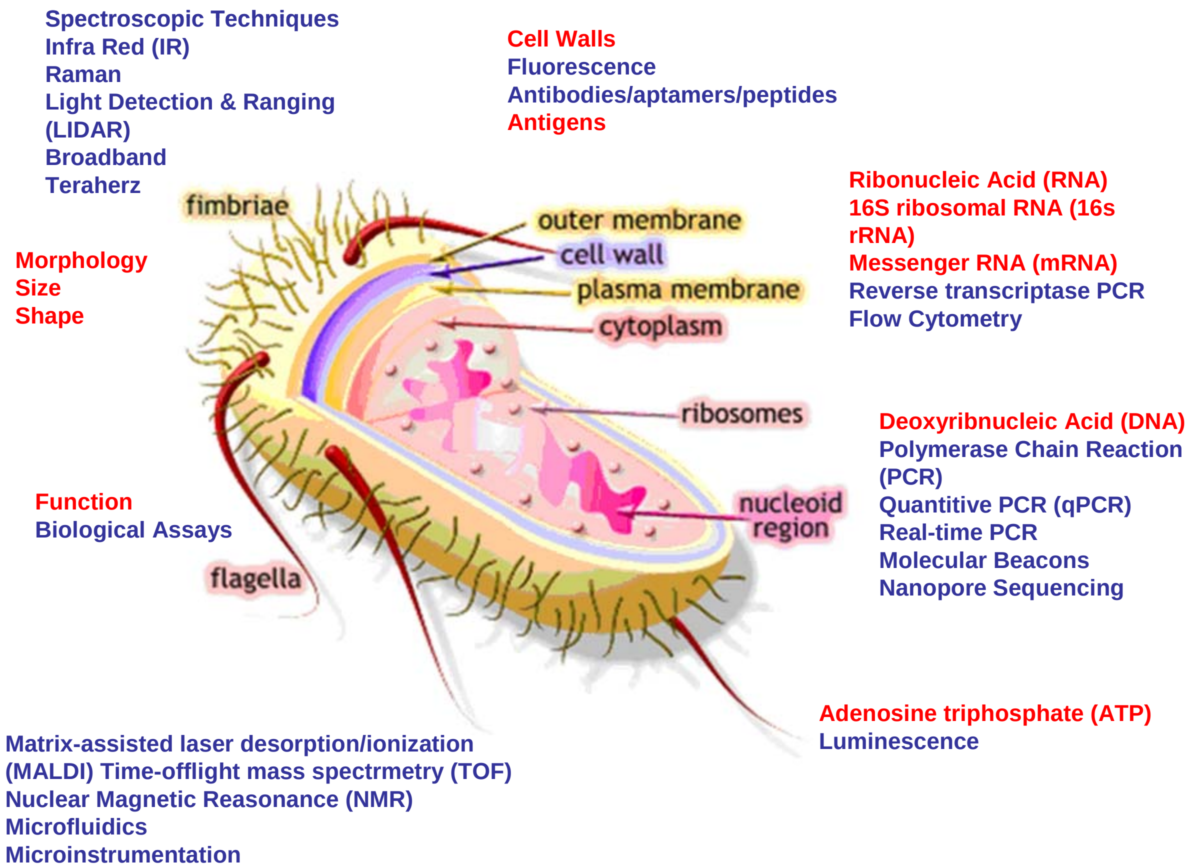

Figure 3 - Illustrative targets and techniques for detection of bacterial organisms

3.2 Sensor technologies

Different types of sensor exist at different levels of readiness for use in a wide area biological detection system. A non exhaustive list of technologies, highlighted by the panel as having significant potential for impact against each task or function outlined above is provided in Table 1 below.

Type of sensor	Task or function	Technology
Generic sensors	Remote wide area detection and trigger	Light detection and ranging (LIDAR), UV laser-induced fluorescence spectroscopy (3D UV-LIF)
Distributed array of point, mobile and handheld sensors	Collection, discrimination and classification	Raman, Fourier transform Infra Red[28,29], TeraHertz spectroscopy
Physico-chemical sensors	Preliminary identification	NMR[30,31,32] MS[33,34,35], Immunoassays and electrochemical, acoustic, optical- based sensor (SPR, SERS)[36,37], PCR[38]
Sequencing technologies[39]	Confirmation	Genomics, Proteomics

Table 1 - Non-exhaustive list of technology options[40]

[28] http://www.rigaku.com/products/raman/firstguard
[29] Globus, T.R., Woolard, D.L., Khromova, T., Crowe, T.W., Bykhovskalia, M., Gelmont, B.L., Hesler, J. & Samuels, A.C. (2003) J Biol Phys 29, 89-100.
[30] NMR: Nuclear Magnetic Resonance: the absorption of electromagnetic radiation by a nucleus having a magnetic moment when in an external magnetic field, used mainly as an analytical technique and in diagnostic body imaging.
[31] Küster, S.K., Danieli, E., Blümich, B. & Casanova, F. (2011) Phys Chem Chem Phys 13, 13172-13176.
[32] Luy, B. (2011) Angewandte Chemie Intl Ed 50, 354-356
[33] MS: Mass spectrometry is an analytical laboratory technique to separate the components of a sample by their molecular weight.
[34] Budzikiewicz, H. (2013) Mass Spectrom Revs 32, 87.
[35] Giebel, R., Worden, C., Rust, C.M., Kleinheinz, G.T., Robbins, M. & Sandrin, T.R. (2010) Adv Appl Microbiol 71, 149-184.
[36] SPR: Surface Plasmon Resonance, SERS: Surface-enhanced Raman spectroscopy. SPR or SERS-based immunoassays are types of platforms where a biochemical test is carried out that measures the presence or concentration of a macromolecule of interest in a solution through the measurement of a binding event between a biological recognition element such as an antibody and the macromolecule or antigen.
[37] Alvarez-Puebla, R.A. & Liz-Marzan, L.M. (2010) Small 6, 604-610.
[38] Polymerase Chain Reaction: a method used to make many copies of specific parts of DNA (DNA is the complex molecule in cells that carries the genetic code).
[39] Sequencing, the process of determining and then reading the genome (Genomics) or proteome (Proteomics) of an organism. Sequencing a genome for example provides a 'bar-code' of incredible precision that can be used to identify a biological threat organism, trace its origins and predict its capacity to cause disease.
[40] Ivnitski, D., Morrison, D. & O'Neil, D.J. (2005) Defense against Bioterror: Detection Technologies, Implementation Strategies and Commercial Opportunities. D. Morrison et al. (eds), 207-220. Springer, The Netherlands.

A significant challenge to exploiting generic physico-chemical characterisation of bioaerosols lies in the development of field portable instrumentation. However, new developments, particularly in miniaturised Time-of-flight mass spectrometry (TOF-MS), Nuclear Magnetic Resonance (NMR) and Raman Spectroscopy are likely to provide a robust, yet enhanced analytical capability suitable for use within a decentralised network of sensors. Developments within this area are promising and should be assessed further for use within a wide area biodetection scenario.

Unmanned vehicles have been used by both military and civilian first responders operating in potentially hostile environments to discern information about their local physical environment in real-time. There are only a limited number of unmanned ground vehicles (UGVs) and unmanned air vehicles (UAVs) that carry chemical sensors and none are equipped with biosensors.

Micro Air Vehicles (MAVs) could be introduced in these settings, with control and guidance operated from a smartphone[41]. Smartphone-guided MAVs equipped with inexpensive micro-engineered physico-chemical sensors thus may provide an opportunity for exploring local air space in cities, towns, buildings and sensitive assets for the detection and localisation of biological and chemical agents.

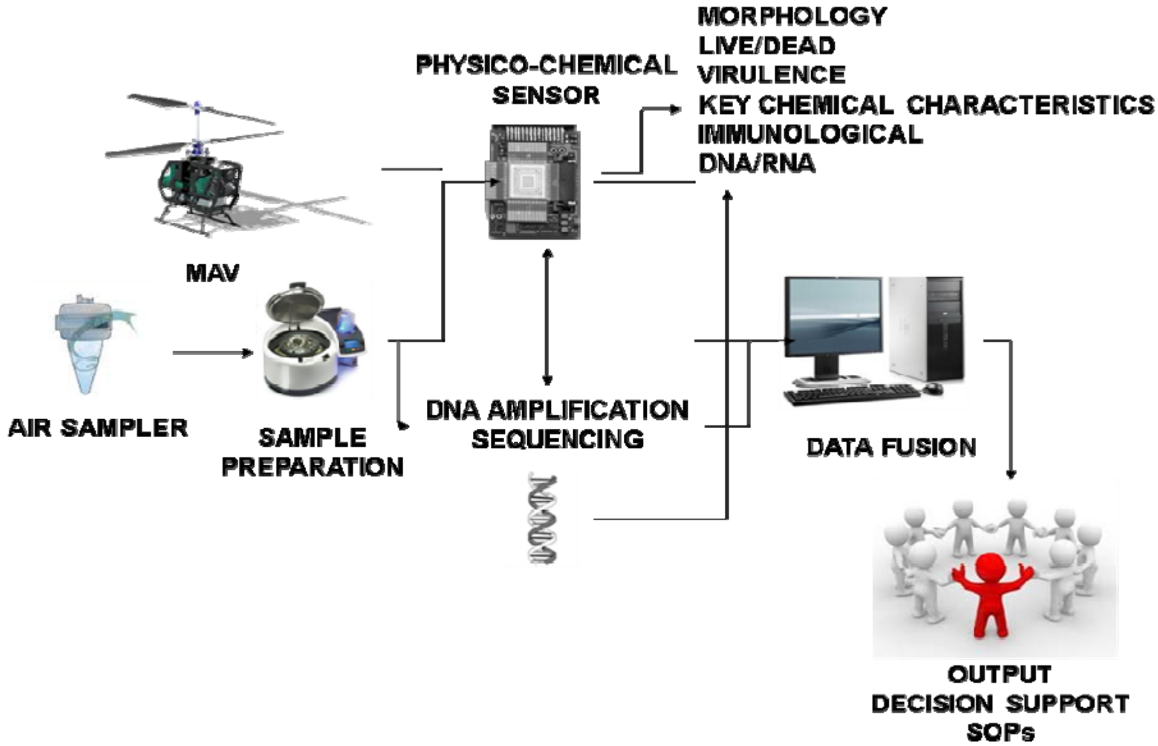

Figure 4 – An integrated systems approach incorporating sample collection, preparation and analysis

[41] Cummings, M.L., Jackson, K., Quimby, P. & Pitman, D. (2012) *Int J Micro Air Vehicles 4, 165-177*

In order to achieve high confidence detection over a wide area and against a variable background, the sensing system will require effective and efficient aerosol sampling, sample pre-processing (collection, purification, concentration and amplification of the pathogen, or components of the pathogen) and delivery methodologies.

The implementation of a fully integrated system of hardware[42], wetware[43] and associated software[44] and infoware[45] would ensure decisions are taken at each level of certainty.

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[42] The collectors, machined parts, sensors, (opto) electronics, power supplies, microprocesors, communications network
[43] The biological sample, reagents, consumables, biochemical and sequencing systems
[44] Communication and control software required to implement the functions in figure 5
[45] The information collected from each module, sensor or device and the fusion of numerous data streams into a reliable, quality, quantitative format that is unambiguously and effectively communicated to the end user

3.3 Sequencing

Sequencing, the process of determining and then reading the genome of an organism, offers significant applicability for wide area biodetection in the short to medium term.

Sequencing a genome for example provides a 'bar-code' of very high precision that can be used to identify a biological threat organism, trace its origins and predict its capacity to cause disease. Within the last five years, there has been a step change in the speed, cost-effectiveness and ease with which DNA sequences can be determined, thanks to a clutch of new technologies which fall under the umbrella term of high-throughput sequencing. Technological innovations, together with strong commercial competition, have resulted in year on year improvements that outpace the often cited Moore's law, which describes exponential improvements in the performance of computers. The increasing speed of analysis, coupled with the high level of precision means genome sequencing is seen as being at the heart of any future wide area detection system.

In the context of a system, sequencing would be used to analyse samples derived direct from environmental sources and not simply the genome of a single organism.

Box 3: Metagenomics

The application of high throughput sequencing to DNA extracted from complex microbial communities or environments is known as metagenomics. Metagenomics delivers genome-scale sequence data from multiple organisms en masse, without prior culture in the laboratory. Where multiple genomes are present there is an increase in the complexity of both sequencing and the consequent analysis of that genomic information. However, the application of sequencing technological and informatics approaches to these 'meta' genome samples has received substantial interest in a range of contexts from environmental to clinical microbiology.

Whilst lagging slightly, the study of airborne biological material is a rapidly developing discipline with clear implications for wide-area detection. Consequently there is now ample evidence in the scientific literature as to the utility of sequencing for the characterisation of the microbial content of airborne environments.[46,47,48]

[46] Bowers, R. M., Lauber, C. L., Wiedinmyer, C., Hamady, M., Hallar, A. G., Fall, R, Knight, R. & Fierer, N. (2009). Characterization of Airborne Microbial Communities at a High-Elevation Site and Their Potential To Act as Atmospheric Ice Nuclei. Appl Environ Microbiol 75, 5121-5130.
[47] Bowers, R. M., McLetchie, S., Knight, R. & Fierer, N. (2011). Spatial variability in airborne bacterial communities across land-use types and their relationship to the bacterial communities of potential source environments. ISME J 5, 601-612.
[48] Tringe, S. G., Zhang, T., Liu, X. et al., (2008). The Airborne Metagenome in an Indoor Urban Environment. PLoS ONE 3, e1862.

The success of this approach depends on continued technical innovations that will deliver faster, cheaper and simpler sequencing capabilities. Coupled with this are the technical challenges associated with increasing the output of genomic sequence data and the accuracy of that information. Based on the experience of the last five years it is reasonable to expect the market to deliver this.

A number of challenges will need to be addressed in order to demonstrate the feasibility of sequencing for wide-area biodetection. These can be divided into four areas:

1. Air Sampling - The availability of accurate, user-friendly platforms for the sampling of large volumes of air in real-time is essential to enable sequencing in a staircase approach.

2. Sample Preparation - The process of acquiring those components to be analysed from the sample of interest. The removal of non-microbial genomic material (e.g. human or plant DNA) such that it doesn't mask the presence of a biological threat organism leading to a non-detection event is a key challenge.

3. Bioinformatics - This refers to the process of computer-based analysis of sequence data. As yet, there is no flexible, well-validated bioinformatics system for detecting specific biological threat organisms from a collection of sequences. Any bioinformatics system must also be capable of accurately determining the number of biological threat organisms present in the sample. This reflects the need to use the information to distinguish between naturally occurring background levels and those seen in a deliberate release.

4. Systems Integration - Finally it will be necessary to bring together all of these components from air-sampling to bioinformatics systems into a single integrated platform.

Real-time high throughput sequencing of environmental sources coupled with real-time bioinformatics analysis is proposed as a novel approach to the detection and characterisation of infectious agents in a wide-area scenario. Analytical workflows will proceed or run in parallel to the sequencing pipeline to deliver 'enhanced metagenomics'. The synergies of the proposed approach with healthcare and environmental applications are likely to provide economies of scale that will enable the development of commercially viable systems.

3.4 Sensing system recommendations

1. Government should adopt a staircase approach to wide-area biodetection, to increase the information density and statistical certainty associated with a biological attack.

2. Government should undertake an in-depth review of UK sampling and sensing capabilities for wide-area biodetection, in partnership with UK industry, to identify the commercial and market drivers and explore dual-use technologies[49] which may be adapted for biodetection purposes.

3. Government should increase research and development on aerosol sampling, sample capture and sample preparation to enhance the performance of sensing systems in detecting an aerosolised biological attack or an infectious disease outbreak.

4. Government should support research to characterise the biological background in representative scenarios to inform sensor system design and to reduce the likelihood of false alarms in deployed systems.

5. Government should support scoping studies to assess the utility of enhanced metagenomics for Biodetection, as well as support longer-term developments in the area of sequencing for wide-area detection:

    a. Development of a modular Biodetection system, exploiting enhanced metagenomics techniques, to satisfy the requirements across government via a Joint Research Initiative on Tools for Enhanced Metagenomics. The initiative would catalyse research and development interactions between diverse sectors (academia, industry, government, health services).

    b. Specific components necessary for wide-area biodetection (e.g. for selected agents) should be developed via a Joint Research Initiative on Tools for Select Agents Genomics. This initiative could include a select group of participants, including Universities, Industry, Home Office and Dstl/MOD.

    c. Feasibility studies to assess the utility of sequencing to provide base-line data on airborne environments.

6. Government should support research to model the location and density of sampling sites in the UK, in parallel with the development of adequate urban dispersion models to delineate the source.

[49] To drive economies of scale and efficiency to include treatment (public health), warning (national security), prosecution (law enforcement) and intent (intelligence)

4. Information and system integration

For an effective response, a wide area biodetection capability needs to be able to trigger an alert, with high confidence, and initiate protective/treatment measures within 24 hours or less of an event to minimise the overall impact on casualties.

A key consideration in development is the sensitivity and specificity of the system: the ability to detect 'true' events, to minimise 'false alarms' and hence maximise the positive predictive value[50].

4.1 Alternative Information Sources (AIS)

Changes in the health status of the population and the corresponding change in behaviour of exposed individuals provide a useful source of information to detect and track the spread of an infection following a biological attack detection[51]. Public health surveillance systems developed by the Health Protection Agency (HPA) currently use data from clinicians to monitor infectious disease in the general public. Alternative information sources (AIS) here[52], can be defined as background signals from the internet that correlate with the release of a biological agent. In isolation these datasets are likely to provide noisy signals and their precision is not considered sufficient to invoke response measures. However when integrated, weighed up in real time and fused with public health and sensor data sources they could provide an early indication of a biological threat. This in turn could prompt further information gathering by the system, enhancing overall sensitivity and specificity. This requires a systems design approach to signal integration and reporting. Identifying high precision alternative information signals from vast datasets will require focused and collaborative research between industry and academia.

Novel statistical and data analytics techniques will be required to identify, analyse and report alternative information signals from vast datasets. Alternative information signals would also be fused with sensor and public health data, so that trained medical personnel and decision-makers can interpret the available information and plan appropriate response measures. In addition, inferential statistics and learning algorithms will be required to determine if and when to trigger an alert, based on past experience, and to forecast the progress of an outbreak as new data is integrated in near-real-time. This will be vital for managing responses and determining the wider socio-economic impacts of an attack or infectious disease outbreak. The development of statistical techniques and learning algorithms will

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[50] The probability that an alarm represents a 'true' event

[51] Infodemiology can be defined as the science of distribution and determinants of information in an electronic medium, specifically the Internet, or in a population, with the ultimate aim to inform public health and public policy; Eysenbach, G *(J Med Internet Res 2009;11(1):e11)*

[52] Alternative information sources could include: hospital A&E consultations, hospital admissions (Hospital Episode Statistics – HES), mortality data (by specific cause), General Practice (GP) case reports, GP out-of-hours consultations and NHS Direct (to become NHS 111 in 2013), results from clinical sample testing, levels of school or work attendance, volume of pharmacy sales, incidence of livestock illness, social media postings indicating illness and search engine query trends. Some of these data sources (e.g. GP consultations from ‘spotter’ practices, NHS Direct) are already used for surveillance of, for example, flu trends. These are not, however, currently analysed in real-time. Some data sources are not available at national scale, othes such as A&E data, have not routinely been used for surveillance.

require focused and collaborative research between industry, academia and government departments and agencies.

4.1.1 Privacy and data confidentiality

Many of the potentially valuable AIS signals, for example consumer purchases or search engine statistics, are held by private organisations. Unlocking their potential will require the creation of a technical framework in which these signals can be aggregated, together with policies to incentivise release. While the need for real-time signals complicates the design of such a framework, these issues are believed to be tractable.

4.2 Public health surveillance

A critical component of any biodetection capability is public health surveillance for the early detection of prodromal[53] or unusual symptoms and the identification of diseases due to biological agents. For example, the occurrence of severe pneumonia in young people, clustering in time and space, may be an early indicator of unusual exposure to an infectious agent. The UK is fortunate in that it has well developed disease surveillance systems that take advantage of the unified healthcare data and systems available through the National Health Service. In England, the Health Protection Agency (HPA) - to become part of Public Health England from April 2013 - is responsible for health surveillance.

The current HPA syndromic surveillance system analyses data from NHS Direct and national GP networks in a batch process. The system has recently been trialled to incorporate and report data from A&E departments and General Practice (GP) out of hours services[54]. Currently, reporting is based on the analysis of summary data, rather than the full data at individual level, limiting its usage. Incorporating and analysing the full data set, in real time rather than batch mode, is likely to improve the signal. In addition, the reporting of unusual symptoms is not systematic and relies on personal contacts between individuals in the HPA, other areas of government and clinicians. Nonetheless, this system provides the basis for real time syndromic/disease reporting that could be automated and extended to improve biodetection capability as part of an integrated systems approach.

For such data to be useful for real-time surveillance, it should be coded as part of the clinical consultation, as already happens in General Practice. Although this would require a 'culture shift', specifically in hospitals where coding is usually undertaken by coding clerks[55], this is entirely feasible and with appropriate systems and training, may prove to be cheaper than current practice. The advantage of direct clinician coding is that the data then becomes instantly available for syndromic and disease surveillance, provided that the necessary data systems are in place to retrieve and analyse those data.

[53] An early symptom indicating the onset of an attack or a disease.
[54] Severi et al., Euro Surveill 2012, 17(31)
[55] Dixon et al 1998

Web-based clinical information systems, incorporating data mining software, are being developed to support diagnosis and treatment.

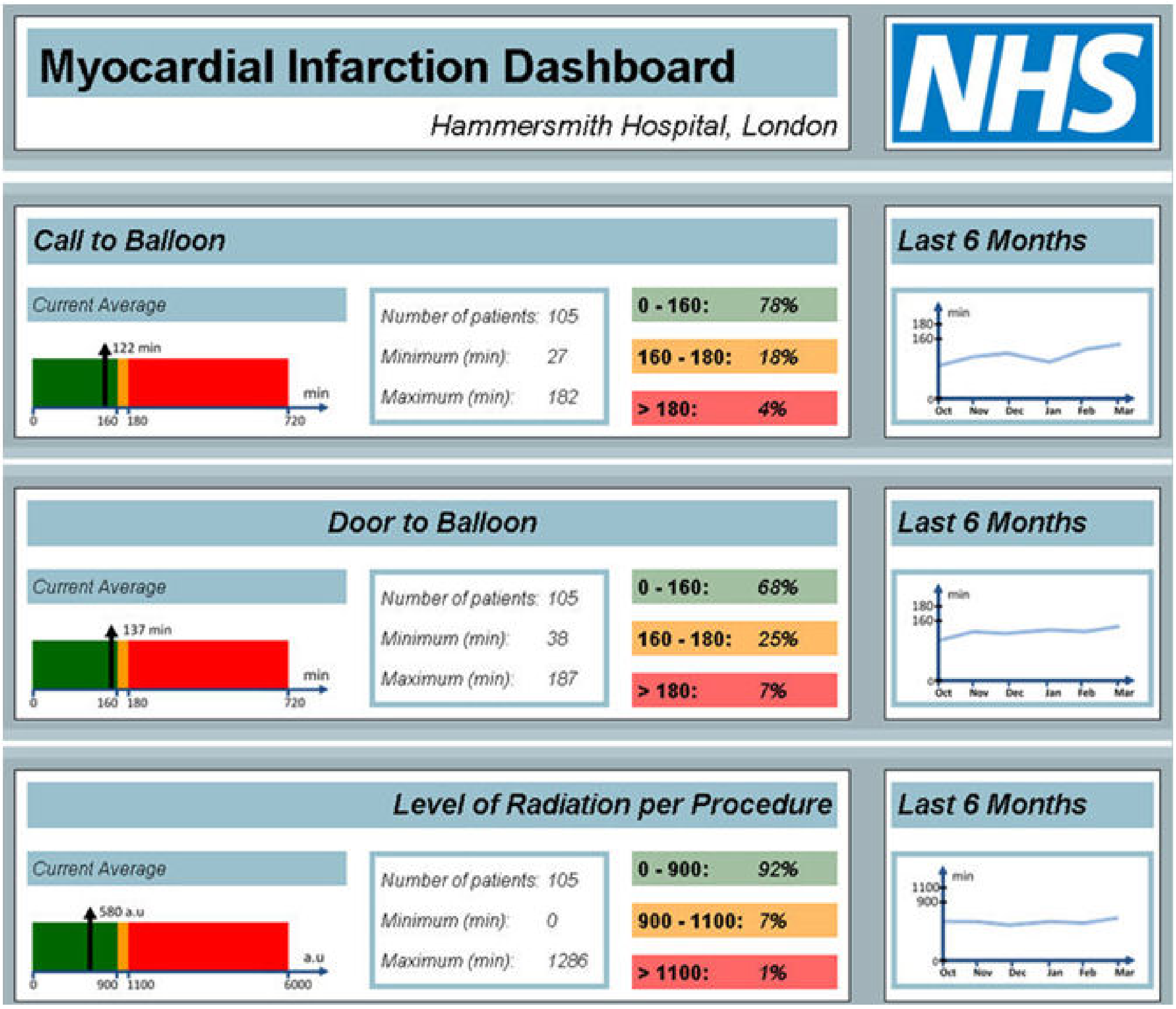

Figure 5 – Example of a real-time management dashboard[56]

Such systems can be programmed to analyse clinical databases and report information relating to public health surveillance. The appearance of unusual syndromic patterns, or the presence of pathogenic agents, could trigger the system so that an alert is reported to clinicians or management via the dashboard.

Access to the location history of individuals exposed to a biological agent is critical to estimating the location of the source of the release. Currently, epidemiologists often rely on interviewing individuals, which carries a high latency at a critical point in the response timeline and may be impossible if the individual is incapacitated.

Mobile phone operators, in addition to other organisations, are able to provide location history for many individuals. Access to location data could enhance source term estimation and determine which individuals to notify following a release. While research suggests that

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[56] The example represents how clinical software could be applied to monitor public health data/trends.

the analysis of aggregate statistical data is possible in a privacy-aware manner, no such results exist for location data. Therefore, the benefits of developing a capability to locate the source of a release, which is based upon access and analysis of mobile phone data, must be weighed carefully against privacy concerns.

Many of the most valuable signals, particularly those regarding public health from the NHS, are held by government. Many of the barriers to working with these signals are organisational. It is currently possible for multiple patients with the same unusual symptoms to be treated in different hospitals, and a link between the cases never to be made. Removing barriers to the exchange of health data presents a clear opportunity for short term improvements to current public health surveillance systems.

4.2.1 Public health benefits

Developing and instituting a system of syndromic and health surveillance for the rapid detection of unusual health signals in real-time or near real-time would deliver broader benefits for public health. Detecting the occurrence of unusual symptoms, or anomalous levels of hospital admission and mortality, may indicate new and emerging infections or environmental hazards, especially if circumscribed in space and time. Earlier detection could allow earlier preventive measures (e.g. vaccination) or treatments to be administered, and the detection of possible hazards that might otherwise have gone unnoticed. In the event of an incident, the data could provide a rapid assessment of the scale of the problem, allowing a proper and proportionate response.

4.3 Modelling

Dispersion modeling is required to interpret monitoring data and predict the full extent of the consequent hazard. However, dispersion in an urban environment is particularly complex. There is significant intrinsic uncertainty associated with dispersion models, which will require a trade-off between the rapidity of response, the sampling errors in concentration data and the uncertainty that these imply. It is probable that a suite of dispersion tools, of which there are several candidates, will be required to support early detection of a biological attack. These should be reviewed for their applicability.

The greater the uncertainty within the system, a function of the amount of information available, the more extensive the potential hazard area in the modelling output. By incorporating additional sources of information that can be correlated with an event, the modelling output can be improved, and the extent of the potential hazard area can be reduced. This is clearly important in determining the source and geographical extent of any response. Running algorithms in parallel could enable output in less than 30 minutes, but this would require investment in a dedicated system.

4.4 Systems integration

A systems approach to biodetection is essential to the successful development of a wide-area biodetection capability. An effective system must integrate and analyse data and information from a variety of disparate sources to establish the presence, characteristics, identity and confirmation of use of biological agents, to trigger a response at a pre-defined threshold. To be effective, the system needs a clear reporting structure and chain of command, integrated seamlessly with a co-ordinated, cross-government response plan.

At the technology hardware level, sensors may need to be combined into a network. Once the structure of such a system has been determined, statistical methods can be used to optimise both the design of the network and help determine triggering thresholds. Since reducing the time to detection is paramount, data will need to be collected from sensors in as close to real-time as possible. The resulting computational and data transfer needs are unlikely to prove problematic, as the scales involved are relatively small by current standards. However, robust statistical methods will be essential to ensure that uncertainties are captured and communicated throughout the surveillance process.

There may be opportunities to work between government, industry and academia to develop and refine Bayesian knowledge based systems to integrate signals from different areas, and issue 'alerts' based on all available data and informed by past experience. Such a system should run and output relevant calculations for different stakeholders or decision-makers. The system should be flexible so that it can adapt as methods to identify agents and infected individuals evolve and new sources of information/signal processing techniques emerge.

Box 4: Key Components of an integrated biodetection system

The key components of an integrated system include:

Sensors. The sensing capability will need to operate persistently, provide near-real time detection and minimise the risk of false alarms, without compromising sensitivity. A network of fixed and mobile sensors, configured in a 'staircase approach', is likely to provide a robust capability.

Modelling. As well as use of modelling to optimise sampling/sensor placement, if an alert is sounded, modelling of the available sensor data is required to delineate the source. Incorporation of additional sources of information will reduce uncertainty in the modelling output.

Health and syndromic surveillance. The process of disease/syndromic surveillance brings together information from NHS Direct and national GP networks in a batch process. The output is based on summary data, rather than the full data at individual level, currently limiting usage. Incorporating and analysing the full data set is likely to improve the signal.

Intelligence gathering. Intelligence is a vital source of information within an integrated system. Methods will need to be developed to ensure that information can be shared at an appropriate level to ensure decisions concerning a potential event take full account of intelligence.

Alternative data sources. AIS may be used to strengthen an integrated biodetection signal or provide a valuable prompt for further analysis. Currently use of such data is in its infancy and research on its use has mainly been carried out by industry. Sharing data with government agencies for the purpose of biodetection involves privacy and data confidentiality issues that will need to be resolved.

Computing and data analysis. Although an integrated systems approach operating in real-time or near real-time will make significant computational demands, these are considered tractable, but will require investments in hardware and software applications.

In summary, information and system integration is a critical enabler for improved biodetection in the short to medium term. Signal integration needs to be facilitated at the earliest opportunity and outputs coordinated, so that information can be reported in a coherent and systematic way at the highest level of knowledge in government.

A review of the strengths, weaknesses, opportunities and threats in developing integrated systems for wide-area biodetection is provided in Table 2. The analysis highlights the broad market drivers (public health, animal and plant surveillance) that may result from the proposed approach.

Strengths	**Opportunities**
• Integrated biodetection systems will improve capability and reporting across government and speed up response times. • Real-time health surveillance as part of an integrated biodetection system will lead to improvements in the availability and quality of health data and have knock-on benefits for public health and personalised healthcare. • Government requirement for real-time monitoring via networks of biosensors will speed up commercial developments in this area.	• Development of rapid diagnostics will provide commercial opportunities beyond biodetection. • Miniaturisation of sensors e.g., MS/NMR, offer a commercial opportunity that would enable arrays of low cost mobile sensors to be developed. • Public-private partnerships across government, industry and academia will be boosted to develop robust real-time systems for data monitoring, data analysis and reporting. • There will be opportunities to enhance and add value to existing monitoring systems
Weaknesses	**Threats**
• The density of the sampling is key for wide-area biodetection. There is currently little understanding in this area. • More understanding is needed of 'natural' background variation to be expected in biological sampling, and hence the ability to differentiate signal from noise may limit the utility of the approach. • More robust and precise models of plume dispersion need to be developed to allow rapid delineation of the extent and source of any release.	• Systematic integrated biodetection approaches with sufficient coverage to provide a meaningful response may be unaffordable. • Experience from the BioWatch programme in the USA indicates that integration, communication and coordination across government departments and agencies can be an important limiting factor. • The dissolution of a single national NHS Direct system (in favour of NHS 111) may reduce the availability of the data and utility for biodetection.

Table 2 – SWOT analysis for development of an integrated systems approach to biodetection

4.5 Information and systems integration recommendations

1. Government should assess the feasibility of developing an automated reporting system which integrates data from deployed sensors, public health, veterinary, intelligence and AIS, with clear reporting lines, in order to improve the timeliness and effectiveness of a response.

    a. Government should support the development of novel statistical and data analytics approaches to determine if and when to trigger an alert within an automatic reporting system and to forecast the progress of an outbreak as new data is integrated in near-real-time.

    b. Government should support research to determine the effectiveness of alternative data sources for Biodetection purposes.

2. Government should investigate policy incentives to encourage non-government organisations to contribute signals derived from their privately-owned data to the wider detection system.

3. Government should review potential dispersion models, methods and systems and evaluate their performance within priority scenarios.

5. Conclusions

An attack with a biological warfare agent could have a profound effect on an unprotected population with potentially many thousands affected in heavily populated areas[57]. A wide-area biodetection capability is a key element of the response to a biological attack, to enable timely responses, to restore normality and to minimise loss of life.

This review recommends an integrated systems approach to biodetection, incorporating signals from a dedicated array of orthogonal sensors fused with signals from public health, veterinary, intelligence and alternative information sources (correlated with a biological attack). A staircase approach, based on increasing information density and statistical certainty, will ensure decisions are taken at each level of certainty within the system.

Such a system would maximise the opportunity to confirm the presence of a biological agent sufficiently early and with sufficient certainty to mount an effective government response and ultimately save lives.

5.1 Sensors

A number of sensor developments, including in field-portable instrumentation and high throughput sequencing are highlighted as having significant potential to provide a step-change in the UK's current biodetection capability. It is recommended that further work is supported, in collaboration with industry, to assess the utility of these approaches within a wide-area biodetection context and to identify commercial drivers and viability.

A key challenge is the ability to sample the air efficiently and assess its diverse composition in representative environments. It is recommended that further resource is directed at developing urban air sampling, sample capture and sample preparation methodologies and technologies to improve the overall sensitivity and selectivity of any future sensing system. In addition, statistical methods should be developed to optimise the design of a physical sensor network to detect biological agents and in particular the location and density of the sensors themselves.

5.2 Information and system integration

Information integration is a critical enabler for wide area biodetection and should be facilitated at the earliest opportunity. Transitioning current public health surveillance to a real-time, automated system will speed up response times in the near term and the development of an information framework will allow further sources of information, including from sensors and alternative data sources, to be integrated in the short to medium term. Uncertainty in the system will reduce as additional sources of information are fused with sensor data within the overall system.

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[57] E.g. Emergency response to an anthrax attack, L.M.Wein *et. al*. 4346–4351 , PNAS,_ April 1, 2003,_ vol. 100, no. 7.

Novel statistical and data analytics techniques should be developed to assess the feasibility of integrating disparate biodetection signals[58] within an overarching information framework to ‘trigger’ a government response at a pre-defined threshold. The system should adapt as methods to identify agents and infected individuals evolve and new sources of information/signal processing techniques emerge.

5.3 Implications for public health

Developing and instituting a system of syndromic and health surveillance for the rapid detection of unusual health signals in real or near real time (<24 hours) would have wider benefits for health, taking advantage of the opportunities afforded by near-universal coverage of the National Health Service. Implementing such a system might be achieved using existing data, with improvements such as clinician coding of hospital data, and with real time data access and analysis. Such improvements are potentially feasible on a short time-scale and could potentially be implemented at modest cost (with future costs savings), as much of the necessary data and infrastructure are in place.

As well as the implications for biodetection, such signals could give valuable early warning of influenza and other epidemics, at an earlier stage than possible with current reporting systems.

5.4 National and international collaboration

An effective response to a biological attack requires cross-government action. The ability to detect, report and respond to a biological attack or infectious disease outbreak will draw on the resources of several government departments. The successful development of any future wide-area biodetection system is therefore critically dependent upon collaboration between the key departments and agencies[59], industry and academia.

Collaboration will enable the development of configurable platforms, to deliver broad economic and health benefits to the UK (human, animal or plant health).

Given the above, it is recommended that a mechanism is established to co-ordinate biodetection research across government, including reviewing progress against the recommendations set out in this report.

Because of the far reaching consequences of the release of a biological agent, its impact would transcend national borders; it is therefore also crucial that any UK response is justifiable to our international partners and takes into account their respective strategies to mitigate against such events.

The recent US National Strategy for biosurveillance calls for integration of information sources across health, animal, plant and alternative data sources to enhance national biosurveillance capabilities. The strategy aligns with the findings and recommendations from this Blackett review. The UK should therefore build on our already strong links with our US partners, to ensure complementary approaches for biosurveillance are developed and to build national and international resilience to biological threats.

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[58] That vary in spatial and temporal resolution and which may vary in quality, completeness and confidence
[59] Including Department of Health, MOD, HO, CPNI, DEFRA, DfT

Annex

Annex 1 - The Blackett Review process

The Government Chief Scientific Advisor (GCSA), Sir John Beddington, has established a process for government to engage with academia and industry to answer specific scientific and/or technical questions primarily in the security domain. These Blackett Reviews provide fresh, multi-disciplinary thinking in a specific area. In each review, a small panel of 10-12 experts is tasked with answering a well defined question or set of questions of relevance to a challenging technical problem.

In the summer of 2012 the GCSA convened a group to address the question "*Which technologies will enable rapid, wide area surveillance of a broad spectrum of biological agents in the next 15 years?"* The panel considered how Government could best identify, assess and communicate the potential findings of this report.

The panel met three times over a nine month period and provided an independent scientific review of the current risk management approach of a number of departments, primarily the Home Office and Ministry of Defence. It is written by the Government Office for Science for the GCSA and is based on the discussions at the meetings and additional information provided by panel members.

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