MEETING OF THE STATES PARTIES TO THE CONVENTION ON THE PROHIBITION OF THE DEVELOPMENT, PRODUCTION AND STOCKPILING OF BACTERIOLOGICAL (BIOLOGICAL) AND TOXIN WEAPONS AND ON THEIR DESTRUCTION

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Tools and Technologies for the Surveillance, Detection and Diagnosis of Infectious Diseases and Intoxinations

Submitted by the United Kingdom

Introduction

1. The 2004 BTWC Meeting of Experts will discuss strengthening and broadening national and international institutional efforts and existing mechanisms for the surveillance, detection, diagnosis and combating of infectious diseases affecting humans, animals and plants. There are numerous tools and technologies that may be applied in addressing the individual aspects of this topic. This paper will focus on brief examples of some key and emerging technologies that have the potential to make a significant improvement to surveillance, detection and diagnostic systems.

2. Surveillance, detection and diagnostic systems may all be involved at different phases of a disease outbreak and their performance may affect the decision-making process and the outcome of the response. In a natural outbreak, a symptom surveillance alert may allow earlier intervention with medical countermeasures than waiting for laboratory detection and clinical diagnosis, thus reducing the number of casualties. In addition, in the event of a deliberate or accidental release of an infectious agent or toxin, detection at or near the point of release could allow even earlier intervention and greater prevention of casualties.

Surveillance

3. Effective surveillance systems must be continuous, real-time and should generate alerts to provide the earliest indications of illness. Traditional health surveillance systems rely on disease reporting mechanisms and may therefore be dependent on clinical diagnosis and laboratory tests, which inevitably take time. In the UK human health area, communicable disease surveillance involves the collection of data from a range of sources including laboratory and clinician reports.

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However, medical practitioners are also required by law to report notifiable diseases on the basis of symptoms alone.

4. The UK Veterinary Surveillance Strategy includes objectives to increase the value derived from surveillance information and activities. This involves improving the collection of relevant data in a structured way such that it can be analysed to provide an informative output. Information from a variety of sources must be translated into knowledge by analysing it in association with related data from other sources. Essential to the achievement of these objectives is the availability of a reliable data-handling tool. To this end, Defra[1] has developed an integrated information management system known as RADAR (Rapid Analysis and Detection of Animal-related Risks). Its main component will be a large data warehouse that draws together validated information from various animal health operational systems in the UK in a format that supports data analysis for surveillance purposes. It is designed to be flexible enough to access new data sources as they arise and will have a user-friendly, dedicated web portal which will be accessible to stakeholders in the UK and abroad. Such a system has the potential to improve on current mechanisms by providing the means by which threats can be identified, analysed and tested more rapidly and efficiently.

5. Some more recently developed surveillance systems are focused on signs and symptoms of illness rather than on confirmed disease diagnoses. These are generally referred to as symptoms or syndromic surveillance systems. Such systems involve the continuous collection, analysis, interpretation and application of real-time or near real-time indicators of diseases and outbreaks to allow earlier recognition and response than would be possible with traditional systems. A specific UK example of such a system is discussed in the UK paper "Real-Time Symptom Surveillance".

6. New systems and methodologies that may play a role in disease surveillance continue to be developed. The UK Meteorological Office is developing predictive models to help assess the impact of the weather on health[2] and support more effective healthcare planning and delivery. Trials and pilot schemes have been used to assess the viability of using real-time National Health Service (NHS) data, infectious disease data and weather forecasts to predict workloads for a selection of NHS services. Such data would also be useful as an input to surveillance systems, for example in establishing baseline predictions with seasonal variations that may allow the recognition of unusual outbreaks. Also in the field of modelling, there are active programmes in the Department of Health, Health Protection Agency and several academic groups. Targetting includes endemic diseases such as TB, HIV and healthcare associated infections, as well as possible future infections of exotic diseases.

7. The UK plant health area uses Geographic Information Systems (GIS), for example, by utilisation of climatic mapping to identify areas of the country that would be favourable for the establishment of certain plant pests and to identify the location of individual crops at risk in outbreak situations. In symptoms surveillance systems, GIS can also be applied to monitoring and temporal-spatial analyses of data.

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1 Department for Environment Food and Rural Affairs
2 "Forecasting the Nation's Health": details at http://www.metoffice.com/health

Detection and diagnosis

8. In the context of this paper, detection means the recognition of disease-causing agents in clinical, environmental or other relevant samples. Diagnosis is the determination of the nature of a disease, which may be based on a number of factors including the recognition of relevant signs and symptoms, or the detection of a disease-causing agent or a specific immune response to such an agent. Therefore some of the tools and technologies relevant for detection and for diagnosis will have a similar basis.

9. There are many analytical technologies that are used routinely in the detection of microorganisms and toxins and in diagnostics. Such techniques require a number of performance characteristics, such as high sensitivity and specificity, speed and simplicity of operation, and the ability to analyse complex samples. Portability and the ability to differentiate microbial strains or toxins may be useful in some situations. Furthermore, analytical techniques have to be well controlled and fully validated for use in this context. Relevant technologies may include: classical microbiological techniques, such as culture, microscopy and biochemical tests; immunological assays, such as ELISA[3] or dipstick tests; genetic assays utilising the polymerase chain reaction (PCR); and physicochemical techniques such as mass spectrometry. Some of these technologies are discussed further in the UK paper "Investigations into alleged uses of BW – Some considerations drawn from experience in the United Kingdom for sample handling and biological analysis".

10. The development of 'near-application' tests allows assays to be performed on samples at the point of collection, giving rapid results that avoid the delays encountered by transporting samples to laboratories for analysis. These tools are generally based on antibody recognition using dipsticks or lateral flow devices, or on PCR using portable thermocyclers with simplified sample preparation and rapid read-out within 30 minutes. They are applicable across the human, animal and plant health sectors. In the human health sector, they are often referred to as near-patient tests. Further improvement in the human health sector can be achieved by the development of 'point-of-care' tests, for example in doctors' surgeries, clinics or hospitals where rapid diagnosis is followed by immediate treatment thus allowing faster intervention in the disease process.

11. Rapid diagnostics is an advancing field, with research into systems that have the potential to allow even earlier recognition and intervention. For example, tools that detect non-specific reactions to infection, such as the early stimulation of the body's inflammatory response will allow earlier indication of disease. Non-invasive diagnostic systems also have the potential to speed up diagnostic procedures. One example is the development of devices for the rapid identification of volatile organic compounds (VOCs) and other gases exhaled in the breath. Human and animal breath contains hundreds of trace VOCs some of which are characteristic markers for disease. Breath analysis is already used to assist in the diagnosis of disease, for example, for gastric ulcers where the amount of carbon dioxide produced by certain bacteria in the gut is monitored in the breath. This is generally a laboratory-based technique, and may not be as widely used as it could be due to cost, robustness, size and speed of the instrumentation. However the recent development of new instrumentation to allow fast, low cost, easy to use and highly sensitive analysis increases the

3 Enzyme Linked ImmunoSorbent Assay

potential of this technology to be used by clinicians to provide an immediate and accurate analysis of a target compound in breath samples. Similar technologies are also being considered in the plant health sector, where detection of specific volatile chemicals may be indicative of particular plant diseases.

12. The detection and diagnosis of emerging pathogens, including potentially genetically modified organisms, has created a significant challenge. Advances in this field have been based mainly on genetic analyses to detect and characterise unknown nucleic acids. Real-time PCR can be used to amplify and detect target DNA in fully automated systems integrating the steps of sample preparation, amplification and detection in minutes. Microarray technologies allow the simultaneous analysis of hundreds or thousands of samples leading to high throughput and rapid results. DNA sequencing may also be used in this context, for example to detect specific sequences that are related to known pathogens. Due to the potentially vast amounts of information generated and required in these processes, the tools of bioinformatics[4] are of increasing importance.

13. The desire for more rapid and accurate analysis has led to the development of robotic equipment that can perform high throughput immunological or genetic tests to enable large numbers of samples to be tested in a relatively short time without cross-contamination, even when using highly sensitive assays such as PCR. Such equipment may be widely used in human, animal and plant health detection and diagnostic systems, with the potential to greatly improve the speed and capacity of systems, which would be of particular benefit in dealing with relatively large disease outbreaks. Nanotechnology also has the potential to increase the speed and throughput of detection assays, for example by the development of nanosensors small enough to allow tests for thousands of different pathogens to be packed onto a single microchip.

14. The use of portable infra red detectors is under consideration in the animal health sector to identify animals with hypothermia or hyperthermia. This equipment measures infra red emissions and converts these into a photographic image based on temperature gradients. This could be used as a tool to rapidly screen large collections of animals to select individuals relevant for further analysis. In a wider context, this technology also has the potential to be used for satellite detection to indicate herds affected by disease.

15. As already mentioned, analytical techniques for use in the detection and diagnosis of infectious diseases and intoxinations must be well controlled and fully validated. For example, in the UK human health area, a continuing process is followed to evaluate newly available diagnostic laboratory tests. The aim is to determine the actual relevance of a test to disease diagnosis, and thus its potential for meaningful use in clinical practice. Before a test can be accepted for routine diagnostic use it must demonstrate repeatability, reproducibility, accuracy, precision, sensitivity and specificity. A suitable panel of samples, including a reference standard must be available to test these attributes. The evaluation must be carried out 'blind' and validated on a second set of samples. It is necessary to identify the circumstances under which the test is useful, e.g. for patient treatment,

4 Bioinformatics is the application of computer technology to the management of biological information and involves the collection, storage, classification, integration and retrieval of information in accessible databases.

for retrospective diagnosis to provide surveillance data, or feedback to aid clinical diagnosis of disease.

16. Once a test has been accepted for diagnostic use, ensuring consistent performance from day to day and from laboratory to laboratory is crucial. External quality assurance schemes are used in the UK to assess, maintain and improve health related diagnostic capabilities in laboratories using 'blind' test specimens, including microorganisms, related antigens or nucleic acids.

Conclusion

17. Many of the key emerging tools and technologies that have the potential to improve the surveillance, detection and diagnosis of infectious diseases and intoxinations are based on underpinning analytical techniques such as those utilising antibodies and gene probes. However, relevant technologies based on other concepts are also emerging. The aspiration for increasingly more rapid, accurate, portable and versatile processes continues to lead to the development of new instrumentation, reagents and techniques to enhance the performance of current technologies and make possible new technologies. This paper outlines just some of the emerging tools and technologies, with examples drawn from across the spectrum of human, animal and plant health. There will clearly be many more examples, now and in the future, of technologies with the potential to assist in the process of strengthening and broadening mechanisms for controlling infectious diseases affecting humans, animals and plants.
