

Surveillance of Infectious Disease



Microbes such as bacteria and viruses cause a wide range of infectious diseases. They can be highly adaptable and evolve rapidly to changing environments. This can change their ability to spread and their susceptibility to antimicrobial drugs. Surveillance is key for detecting and responding to novel and re-emerging microbes. This briefing describes current surveillance efforts and examines new technological developments and their likely impacts on UK and international public health.

Background

A recent report by the Chief Medical Officer highlights some of the key factors driving the emergence of novel and re-emerging infectious diseases.¹ These include microbial adaptation, most notably the spread of antimicrobial resistance, urbanisation affecting human-animal interaction, increased travel and the expansion of international trade. A key component for preventing the spread of infection is surveillance, which involves tracking the frequency and distribution of disease to inform control, treatment and prevention efforts. This POSTnote:

- describes the burden of infectious diseases
- outlines current surveillance networks
- examines new approaches to surveillance and their potential impact on public health policy.

The Burden of Infectious Disease

Global health statistics are compiled by the World Health Organisation (WHO). However, these only provide best estimates, since many countries have weak or no surveillance systems. Globally in 2011, approximately 12.5% of all deaths were caused by infectious diseases; respiratory infections, diarrhoeal diseases, HIV/AIDS,

Overview

- Surveillance is important for monitoring infectious disease at the local, national and international levels and to inform prevention and control measures.
- It involves monitoring symptoms reported to doctors and NHS Direct, reports of microbes isolated by laboratories, and information on the spread of antimicrobial resistance.
- Current laboratory-based surveillance is underpinned by traditional methods which can be time consuming and does not always provide information on transmission chains.
- New diagnostic tests and whole genome sequencing, in combination with current methods, have the potential to speed up the diagnosis and accuracy of outbreak investigations and improve public health.
- A major future challenge will be improving linkage, analysis and interpretation of data provided by current and new approaches.

tuberculosis (TB) and malaria were the top five contributors.² Overall UK infectious diseases have declined because of improved hygiene, vaccination and antimicrobial drugs. For example, hospital cases of MRSA and *C. difficile* have declined because of mandatory national surveillance, which includes controlling antibiotic prescribing and improved hygiene measures.

Infectious diseases are still a major health and economic burden. For instance, human infectious diseases in England including costs to the health service, labour market and the individual are estimated at £30 billion per year. In the UK:

- the number of reported diagnoses of gonorrhoea increased 25% from 2010 to 2011³
- in 2012 there were 8,741 cases of TB, which is high compared to most Western European countries⁴
- an estimated 25% of the population is affected by gastrointestinal infection each year, leading to approximately 1 million GP visits and nearly 29 million days lost from school or work
- in 2011, 21% of all days of work were lost because of coughs, cold and flu.⁵

Box 1. UK and International Health Regulations

Notification of specified infectious diseases by healthcare professionals to a 'Proper Officer' of the Local Authority or local Health Protection Unit is a legal requirement in the UK. The list comprises 31 diseases such as TB, measles, meningitis and malaria. In England in 2010, legislation was updated to include notification of any infection that presents a significant risk to human health. A list of diseases to be covered by EU-wide surveillance is provided by the European Commission Network of Communicable Diseases. In 2005, the World Health Assembly adopted a revision of the International Health Regulation. This became the world's first legally binding agreement to address public health emergencies of international concern. 194 countries agreed to implement the regulations.

Current surveillance**National**

Public Health England (PHE) runs many of the surveillance systems in England. It also co-ordinates health protection across the UK in collaboration with its equivalents in Scotland, Wales and Northern Ireland and contributes to European and international surveillance networks. A current focus of surveillance is monitoring the spread of antimicrobial resistance to identify new threats and changing patterns of infection to inform treatment. In the UK, most surveillance data come from mandatory notification of disease by health professionals or laboratories (Box 1).

Diagnosis may be based on clinical judgement or traditional laboratory testing. The latter can involve multi-step processes such as culturing bacteria to determine drug resistance. If a notifiable disease is reported, this may prompt an investigation. This normally involves clinical staff contacting an infected person to give advice and, if appropriate, arrange relevant treatment or trace recent contacts. New approaches such as whole genome sequencing and rapid and decentralised point-of-care diagnostic tests offer the potential to provide more information to outbreak investigations as described opposite. Syndromic surveillance is another relatively new approach to supplement current surveillance. It monitors the trends in anonymous reports of symptoms (rather than a specific diagnosis) to inform public health services (Box 2).

European

PHE participates in all European public health infectious disease networks supported by the European Commission, and EU-funded research networks like the European Centre for Disease Prevention and Control (ECDC). ECDC conducts surveillance through networks such as the European Antimicrobial Resistance Surveillance Network (EARS-Net), the largest publically-funded system in Europe.

International

PHE houses several WHO collaborating centres and laboratories. As part of the Government's 'Health is Global' strategy, PHE is developing projects to assist with implementation of WHO's International Health Regulations in priority countries such as Brazil, Russia, India, China and South Africa. Electronic networks such as ProMED-mail

Box 2. Syndromic Surveillance

Anonymous reports of symptoms such as fever, flu-like symptoms, diarrhoea and vomiting are collated from the following sources in real-time to provide early warnings :

- calls to NHS 111 (previously NHS Direct) in England and Wales
- GP consultations (over 2,900 practices in England)
- emergency departments in England
- GP out-of-hours services and NHS walk in centres across England
- calls to NHS 24 in Scotland.

The main limitation of this approach is a lack of specificity. However, this system has and continues to contribute to surveillance during mass gathering events and seasonal outbreaks. Public Health England is also reviewing the potential benefit of additional data sources such as those provided by Google flu trends. Google monitors flu-related search queries to track flu-like illness in a population. Social media and mobile technology could also play an increasing role in disease surveillance.

The 2012 Olympic and Paralympic Games

The Olympics presented a major potential challenge to public health and surveillance because of the large increase in the number of visitors to the UK. To fill gaps in surveillance, two new syndromic systems were set up. One aimed to monitor emergency department activity and the other aimed to monitor calls to out-of-hours GP services. This combined approach allowed 24-hour monitoring of infectious disease in local residents and visitors.⁶ These additions to surveillance contribute to seasonal monitoring of flu and norovirus. This is important for providing early warnings for healthcare teams so that they can be better prepared for outbreaks and respond rapidly.

provide up-to-date online global news on disease outbreaks. For instance, the first reports of the Severe Acute Respiratory Syndrome (SARS) and more recently, Middle East Respiratory Syndrome Coronavirus (MERS-CoV), were listed on ProMED-mail. ProMED-mail is now used routinely for real-time disease reporting on new outbreaks.

New Approaches to Surveillance
Microbial Whole Genome Sequencing

The whole genome sequence of a microbe can hold valuable information about the type of disease it can cause and antimicrobial resistance, which can be used to identify transmission chains. Whole genome sequencing can also be used to identify microbes against which vaccines can be developed. This approach, in combination with current surveillance, could revolutionise investigation of outbreaks by enabling real-time analysis of microbial DNA isolated from patient samples.

Current platforms are capable of sequencing whole viral and bacterial genomes. They are becoming faster and cheaper; a typical bacterial genome can be sequenced within 48 hours for as little as £40.⁷ The technology is also being miniaturised; one such device currently in development is the size of a USB memory stick (see picture on page 1). Several studies have looked at the potential effect of whole genome sequencing on outbreak investigations (Box 3). Potential challenges to implementing genome sequencing and other new approaches are discussed on page 3.

Box 3. Case Studies for Microbial Whole Genome Sequencing**Detecting Transmission of MRSA on a Special Care Baby Unit**

Whole genome sequencing was used to detect transmission of MRSA on a special care baby unit in Addenbrookes hospital, Cambridge. The rapid availability of this information meant that clinical interventions could be put in place to prevent further transmission and illness, which had not been possible using standard approaches. The same hospital is setting up a real-time sequencing project which will be the first use of whole genome sequencing for direct patient benefit.⁸

Investigating a Novel Virus: MERS-CoV

Coronaviruses can cause a range of illness from the common cold to SARS. In 2012, a novel coronavirus (CoV) emerged associated with a condition known as Middle East Respiratory Syndrome (MERS). Up to November 2013, there have been 157 laboratory confirmed worldwide cases of MERS-CoV, including 69 deaths reported to WHO.² Whole genome sequencing of the virus from confirmed samples across Saudi Arabia recently showed that transmission pathways are complex and are associated with the movement of animals, animal products and infected people.⁹

Speeding Up Diagnosis of TB

Whole genome sequencing has been used retrospectively to show the potential of this approach to speed up the diagnosis of drug resistant TB from weeks to days. In well-resourced countries this has the potential to replace current diagnosis methods and provide information on antimicrobial resistance which could guide treatment and reduce transmission.¹⁰

New Diagnostic Tests

Simple and easy to use devices are being designed for rapid medical diagnosis at the patient's side (point-of-care) or for the patient to use themselves (self-testing). Tests are being developed in the UK to detect drug resistant strains of the microbes that cause malaria and TB, and for the rapid diagnosis of infections such as chlamydia that, if left untreated, may cause infertility. These tests use gene amplification, a process that allows a small amount of DNA from a microbe to be amplified to a detectable level so that a diagnosis can be available within minutes.

The technology is developing quickly and could potentially provide more clinical information such as drug resistance, compared to current diagnostic tests. However, these new tests must also provide surveillance data as well as support and advice for patients. One approach being explored is integration with mobile phones to allow data to be collected in real-time as well as providing information to the patient remotely. However, this raises concerns about data protection and security.

Challenges to Improving Surveillance

Implementing new approaches raises a number of challenges. These include limitations of the new tests, data handling and interpretation, quality assurance, issues raised by data sharing and the need for international collaboration.

Test Limitations

For point-of-care and self-testing, concerns include the reliability of diagnosis and specificity in detecting the disease-causing microbe, particularly when dealing with small volumes of specimens. For whole genome sequencing

Box 4. Crowd Sourcing Approach to an *E.coli* Outbreak

An outbreak in Germany in 2011 of *E.coli* O104:H4 caused more than 3,000 cases of human infection. A novel approach to analysing whole genome sequencing data involved open-source data release and crowd sourcing. In this case the *E.coli* O104:H4 genome was sequenced and the data were released into the public domain. Experts on four continents contributed to the data analysis and within a week it was possible to identify the microbe and the genes that caused virulence and antibiotic resistance.¹¹ Had the genome information been posted nearer the start of the outbreak, the approach could have informed clinical practice to control the disease.

one of the major challenges is detecting a novel microbe amid the complex background of other microbial or human DNA found in samples.

Data Handling and Interpretation

Bioinformatics is the application of information technology to biological data. It involves handling complex data from techniques such as whole genome sequencing and helping researchers to interpret it. One approach that has been used to aid interpretation of data is crowd-sourcing (Box 4).¹¹ As genomics, bioinformatics and crowd sourcing start to play a bigger role in clinical practice, software will need to be developed to extract relevant information in an automated and reliable way. Professional skills development for example in bioinformatics-genomics is one of the key areas identified as needing more training by the NHS Modernising Scientific Careers programme.

Quality Assurance

Studies are required to determine whether routine use of whole genome sequencing or new diagnostic tests is cost-effective, robust, accurate, safe and beneficial to public health. Tests that are developed within the NHS and used exclusively 'in-house' are exempt from the requirements of the proposed new European regulations on medical devices and *in vitro* diagnostic medical devices. However, new diagnostic tests sold commercially will have to comply with the regulations.

Data Sharing

PHE holds specific permission to collect public health data for the purpose of controlling infectious diseases as well as monitoring various health programmes such as vaccination. The use of data is limited to these purposes. Data processing is used in a way that protects an individual's privacy. The holding and sharing of personal data is regulated by the Data Protection Act 1998. Under the Act, personal data are any data that allow a living person to be identified. This includes medical records or genome sequence information that may be useful for surveillance purposes. Sharing such data raises the three key issues discussed below.

Informed consent

The Data Protection Act requires individuals to give their consent for personal data to be held or processed. There are different models of consent. The model used by UK Biobank involves participants giving broad consent for their

data to be used for health-related research that is in the public interest. A new draft European Data Protection regulation requires consent to be specific, informed and explicit. Medical research charities have expressed concerns that this will prevent or impair research studies that use personal data. The Confidentiality Advisory Group advises the Health Regulation Authority and the Secretary of State for Health on applications for access to patient information without consent. This protects patients' interests while allowing for the possible use of information for purposes beyond direct patient care.

Confidentiality

A potential benefit of point-of-care and self-testing is that results can be used in a pseudo-anonymous way for surveillance, particularly where the tests are integrated with smart phones. However, it is not currently clear whether such data are covered by the draft European regulation.

Commercialisation and Intellectual Property (IP)

Data from surveillance may also raise IP considerations. For instance, a sample of MERS-CoV that originated in Saudi Arabia was sent to researchers at the Erasmus Medical Centre in Rotterdam. The researchers tested, sequenced and identified the virus, and applied for a patent on the use of the sequence and host receptor data. Some researchers suggest that this has impeded research, although the Erasmus team claims to have freely distributed the virus to other research groups, albeit under the terms of a material transfer agreement that prevents other labs from distributing it more widely.

Future Developments

Strengthening UK Surveillance

In 2013, the UK Health Department published its Five Year Antimicrobial Resistance strategy that recommended improving surveillance data on bacterial resistance, the spread of bacterial infections, prescribed drug use (especially outside of primary care) and clinical outcomes. It also prioritised better sharing of surveillance data collected within the UK at the local, regional and national levels.

Strengthening International Surveillance

The sharing of surveillance data has increased through international agencies such as WHO, ECDC, the US Centres for Disease Control and Prevention, and regional disease surveillance networks and initiatives. However, surveillance still remains patchy in many regions of South East Asia, Africa and South America where healthcare infrastructure is lacking. Implementation of the WHO International Health Regulations has lagged; more than 100 countries were unable to meet the June 2012 deadline for implementing the required surveillance standards.

Global flu surveillance is an example that highlights the importance and benefits of international collaboration. Global data collected by WHO allows seasonal flu vaccines to be reformulated each year and provides information on

Box 5. Global Flu Surveillance Networks

Flu is caused by a highly infectious virus that causes respiratory infection with a spectrum of outcomes from minor symptoms to death. There are three types (A, B C). Only type A and B cause human infections of any concern and it is type A that is responsible for most cases of flu. Pandemic flu occurs when a new virus emerges that is able to spread in the worldwide population. Unlike seasonal flu that generally occurs each winter in the UK, pandemic flu can occur at any time in the year. Seasonal flu vaccines must be reformulated each year because the virus can change rapidly via slight modifications to its surface (H and N) proteins. Larger changes to these proteins, for example human flu viruses acquiring new H or N subunits from species such as birds or pigs, can create new flu strains such as the H5N1 avian flu that threatened to cause a flu pandemic in 1997. The H protein allows the virus into the cell and the N protein allows it to escape. These proteins are the targets for antiviral drugs, vaccines and the body's own immune system.¹²

WHO's Global Influenza Surveillance and Response system links real-time data on circulating flu from across 111 member states. Data are made publicly available through online databases such as FluNET and fluD. The surveillance information provided freely from across the globe allows WHO to recommend formulations for seasonal flu vaccines worldwide, estimate burden of infection and provide information for seasonal and pandemic influenza management.

PHE surveillance data also comes from hospitals, GP reports, laboratory confirmation, mortality reports and calls to NHS 111. Collated data are used to inform policy on prevention and treatment for both seasonal (e.g. formulation of flu vaccines) and pandemic flu (e.g. deployment of antiviral drugs such as Tamiflu and Relenza).¹²

the persistent threat posed by potential new pandemic flu outbreaks (Box 5).

Research and Development

The US Food and Drug Administration identified a need for better reference data for surveillance. It is funding a project to sequence 100,000 pathogen genomes, with an initial focus on microbes that cause food-borne disease. The UK Department of Health's 100k Human Genome Project may also include sequencing of microbes with initial targets likely to be TB, HIV and Hepatitis C. In 2011, the Technology Strategy Board and the MRC provided £180 million to support academic and commercial activities to tackle health care priorities; including £20 million to develop point-of-care tests. The Department of Health and Wellcome Trust's 2012 Health Innovation Challenge Fund provided £13.8 million for the roll-out of diagnostic molecular microbiology.

Endnotes

- 1 Davies, SC. Annual Report of the Chief Medical Officer, Volume two, 2011, Infections and the rise of antimicrobial resistance, DH, 2013
- 2 www.who.int/healthinfo/global_burden_disease/en/index.html
- 3 Gonococcal Resistance to Antimicrobial Surveillance Programme. Action Plan for England and Wales: informing the Public Health Response, HPA, 2013
- 4 Tuberculosis in the UK: Annual report on tuberculosis surveillance in the UK 2013, PHE, 2013
- 5 Sickness Absence in the labour market 2011, Office for National Statistics, 2012
- 6 Elliot AJ et al. J. Public Health, 127, 777-781, 2013
- 7 Koser CU et al. PLOS pathogens, 8: e1002824, 2012
- 8 Harris SR et al. The Lancet, 12, 130-136, 2013
- 9 Cotten M et al. The Lancet online, 20 September 2013
- 10 Koser CU et al. N Engl J Med, 369, 290-292, 2013
- 11 Holger R et al. N Engl J Med, 365, 718-724, 2011
- 12 www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/Influenza/