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Norman Noah

UNDERSTANDING PUBLIC HEALTH

Controlling Communicable Disease

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SERIES EDITORS: NICK BLACK & ROSALIND RAINE

Controlling Communicable Disease

Optimism that communicable diseases are no longer a threat is clearly misplaced. New diseases, such as HIV, have appeared and some chronic conditions, such as gastric ulcers, have been shown to be caused by infectious agents. This book is about controlling such diseases, a task that is impossible without surveillance, knowledge of basic microbiology and multi-disciplinary public health teams.

The book examines the challenges facing different countries regarding:

- Surveillance
- Outbreak investigation
- Vaccines
- Specific infections including hepatitis, TB, influenza and gastroenteritis

Norman Noah is Emeritus Professor of Public Health at the London School of Hygiene & Tropical Medicine.

There is an increasing global awareness of the inevitable limits of individual health care and of the need to complement such services with effective public health strategies. *Understanding Public Health* is an innovative series of twenty books, published by Open University Press in collaboration with the London School of Hygiene & Tropical Medicine. It provides self-directed learning covering the major issues in public health affecting low, middle and high income countries.

The series is aimed at those studying public health, either by distance learning or more traditional methods, as well as public health practitioners and policy makers.

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UNDERSTANDING PUBLIC HEALTH

Controlling Communicable Disease

Understanding Public Health

Series editors: Nick Black and Rosalind Raine, London School of Hygiene & Tropical Medicine

Throughout the world, recognition of the importance of public health to sustainable, safe and healthy societies is growing. The achievements of public health in nineteenth-century Europe were for much of the twentieth century overshadowed by advances in personal care, in particular in hospital care. Now, with the dawning of a new century, there is increasing understanding of the inevitable limits of individual health care and of the need to complement such services with effective public health strategies. Major improvements in people's health will come from controlling communicable diseases, eradicating environmental hazards, improving people's diets and enhancing the availability and quality of effective health care. To achieve this, every country needs a cadre of knowledgeable public health practitioners with social, political and organizational skills to lead and bring about changes at international, national and local levels.

This is one of a series of 20 books that provides a foundation for those wishing to join in and contribute to the twenty-first-century regeneration of public health, helping to put the concerns and perspectives of public health at the heart of policy-making and service provision. While each book stands alone, together they provide a comprehensive account of the three main aims of public health: protecting the public from environmental hazards, improving the health of the public and ensuring high quality health services are available to all. Some of the books focus on methods, others on key topics. They have been written by staff at the London School of Hygiene & Tropical Medicine with considerable experience of teaching public health to students from low, middle and high income countries. Much of the material has been developed and tested with postgraduate students both in face-to-face teaching and through distance learning.

The books are designed for self-directed learning. Each chapter has explicit learning objectives, key terms are highlighted and the text contains many activities to enable the reader to test their own understanding of the ideas and material covered. Written in a clear and accessible style, the series will be essential reading for students taking postgraduate courses in public health and will also be of interest to public health practitioners and policy-makers.

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Overview of the book

Introduction

The optimism during the third quarter of the last century of many clinicians, epidemiologists and others that infectious diseases were no longer a threat has proved to be dramatically wrong. Much of the optimism was certainly misplaced, especially in assuming that antibiotics would cause infectious diseases to disappear. They haven't, and probably never will if antibiotics are to be our only weapon.

Many changes have taken place. Several 'new' diseases have emerged. Few of them are really 'new' and many have been shown to have been causing infections long before they were discovered. HIV/AIDS, Lyme disease, campylobacter, norovirus and legionnaires' disease are just some examples. Other organisms have shown resistance to antibiotics and even to some antivirals.

This book is about controlling communicable disease. Its two main themes are how this is virtually impossible without surveillance, and how knowledge of basic microbiology is crucial to applying epidemiology to investigation and control.

There are three further and recurrent themes in this book. First is the importance of applying a basic knowledge of microbiology to epidemiology. Without understanding the basic biology of an organism, how can we understand how it spreads and causes disease, or indeed how to control it? The second theme is that facts are surely important, but it's often how you interpret the facts that matters. The newspaper article in Chapter 13 is a good illustration of how we can get the facts right but the assumptions wrong. The third theme is that communicable disease control is not the province of the infectious disease epidemiologist alone, nor of any single professional. We need the expertise of the microbiologist, environmental health officer, veterinarian, sociologist, manager, statistician, biologist, biochemist, immunologist and even the politician for success.

Part of the discovery of new infections is due to surveillance. The importance of surveillance has been increasingly recognized recently. This has meant that surveillance systems in many high, middle and even low income countries have become much more sophisticated than they were, and have uncovered many infections whose impact on populations was not realized. Outbreak investigation and a rational approach to vaccine use, two more themes of this book, depend greatly on effective surveillance.

Why study the control of communicable disease?

There has been an undoubted resurgence of infectious disease in the last 30 or so years. Changes in social attitudes have had a significant effect on many infections,

not just with AIDS and sexually transmitted infections (STIs). Travel has increased substantially. Foods are manufactured in vast quantities and distributed widely, both nationally and internationally. The resurgence of West Nile virus, dengue and other arboviruses suggest that global ecological or climate changes may also be playing a part. A new pandemic of influenza seems to be on the horizon. Complacency in both the health care professions and the public induced by effective treatment with antibiotics and prevention by vaccines has not helped. As diseases disappear due to effective vaccination people forget how dangerous the diseases were, and worry about minute or non-existent risks from the very vaccines that have helped to ensure that they are alive today. Smallpox has gone, but despite having an even more effective vaccine than smallpox vaccine ever was, polio is proving to be more stubborn. The need for a practical approach to controlling infection is great. Vaccines and sanitation have made many improvements but organisms have ways of fighting back. Hence the need to study the principles of communicable disease control.

Structure of the book

This book is based on a study unit run jointly with Health Protection Agency at the London School of Hygiene and Tropical Medicine on 'Communicable Disease Control in Developed and Middle Income countries'. It has however been written afresh to make it appropriate for distance learning, for those who are non-medical, for those from low income countries (although tropical infections are not covered here) and to make it less orientated to high income countries.

The book is in four sections, and has 19 chapters. Although the sections are fairly discrete, each is important to the others. Three sections deal with the three basics of communicable disease control: surveillance, outbreak investigation and vaccines. The fourth section covers some important infections which serve as practical illustrations of the principles outlined in the first three sections.

Each chapter includes, where appropriate:

- an overview;
- a list of learning objectives;
- a list of key terms;
- a range of activities;
- feedback on the activities;
- a summary.

Surveillance

Control is not possible without information, and information is not possible without data, so I have devoted a large part of the book to surveillance. The first of four chapters describes the principles of surveillance, and although fairly theoretical, the activities cover many practical examples. The second is more practical and covers implementation. Although some fairly sophisticated surveillance systems are described, it must be remembered that even basic systems can produce useful data for action, and I hope those of you in countries with less well-developed

infrastructures will find inspiration in learning about what is possible. The third chapter documents the usefulness of trans-national surveillance, which has proved to be very useful, and is surely the way forward for the world. Examples of world-wide efforts to control infectious disease are smallpox, polio, malaria, guinea-worm and influenza. The last chapter in this section consists of a set of exercises giving you some practice, and I hope some enjoyment, in analysing and interpreting surveillance data.

Outbreaks

Outbreak investigation is obviously integral to communicable disease control, and the ability to investigate, manage and control an outbreak is an integral part of the infectious disease epidemiologist's work. The first chapter in this section runs through the principles of outbreak investigation, using a mainly epidemiological approach. Managing the investigation however is equally important, and the second chapter deals with the nuts and bolts of this. The third chapter reverts to epidemiology, and takes you through the thought processes that you should use, like detectives do, to unravel the mysteries of an outbreak. Its theme is to sift through what is known about an infection, keep in mind what is likely to be useful to the epidemiologist, use it to work out what happened in the outbreak, and then control it.

Vaccines

The third section covers the main aspects of vaccines as they concern the epidemiologist. It reviews the essential role of epidemiology in the implementation and use of vaccines. There is a logical sequence to the chapters in this section, as indeed there is to each of the first three sections. First, we need to assess the need for a vaccine (Chapter 8), then evaluate it (Chapter 9), decide how to implement it and what is the best strategy (Chapter 10) and then assess it for efficacy and effectiveness (Chapter 11). Once the vaccine programme is in place, all is not over, because surveillance must continue to ensure it is effective and efficient (Chapter 12). The last chapter in this section is a fun, but serious, exercise discussing a newspaper article on vaccines.

Topical themes

The final section covers some topical infections which illustrate many of the principles covered in the first three sections as well as providing some background to the diseases themselves. The diseases chosen include those spread by blood, by the respiratory route, by the gastrointestinal tract, sexually and in hospitals – the four most important modes of transmission, and one important setting for infection. Each chapter covers important clinical, epidemiological and microbiological features of each group of infections, their diagnosis, surveillance, and prevention and control. Various other topical infections are covered in some detail elsewhere in the book.

As the emphasis is on the practical, the book is not comprehensive in the sense that

every important infection is covered. On the other hand I hope I have covered most of the important methods of control available to us outside the field of tropical diseases. Economic appraisal, risk theory and risk assessment are covered elsewhere in this series. Mathematical modelling is also not covered systematically – the student is referred to more specialized texts for that – but I have nevertheless provided examples where relevant.

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I would like to thank the staff of the HPA (Centre for Infections) for their support in this project and for allowing me to use some of their material. I have run the study unit with, successively, Dr James Stuart, Dr Lorna Willocks and Dr Barry Evans, with all of whom I have had useful discussions. I would also sincerely like to thank Dr John Watson, Dr Carol Joseph, Dr Mary Ramsay, Dr Koye Balogun, Dr Pam Sonnenberg, and Dr Punam Mangtani at LSHTM, for their valuable feedback. I also thank Deirdre Byrne (series manager) for help and support in preparing this book.

I am especially indebted to Dr Barry Evans for writing the chapter on AIDS and STIs.

This book is dedicated to my wife, Veronica.

SECTION 1

Surveillance

1 General principles of surveillance

Overview

Surveillance is the backbone of any disease control programme, even if the disease is not of infectious origin. This chapter provides the theoretical background for setting up a surveillance system. It covers the purposes and elements of surveillance, and its scope.

Learning objectives

After studying this chapter you will be better able to:

- **explain the theoretical basis for setting up a surveillance system**
- **describe the purposes of a surveillance system**
- **define the different types of surveillance**
- **explain the broad scope of what can be put under surveillance**

Key terms

Methicillin resistant staphylococcus aureus (MRSA) Another increasing and important public health problem, not only in hospitals but also in the community.

Prions Proteins which can enter cells and convert intracellular proteins into replica prions, causing infection. Human-to-human transmission occurs through blood transfusion, growth hormone injections, tissue transplants, food.

Reye syndrome Rare serious condition affecting infants and young children, causing brain and liver disease; associated with use of aspirin.

vCJD (Variant Creutzfeldt Jakob disease) A fatal brain disease caused by prions, spread from cows with a brain infection.

Definition of surveillance

Two dictionary definitions of surveillance follow:

- *Chambers Dictionary*: vigilant supervision; spy-like watching; superintendence.
- *Oxford English Dictionary*: supervision; watch or guard; especially over a suspected person.

Activity 1.1

Can you make up a definition of surveillance of disease?

Feedback

Here is a definition from John Last (1995): 'Ongoing scrutiny, generally using methods distinguished by their practicability, uniformity and frequently their rapidity, rather than by complete accuracy. Its main purpose is to detect changes in trend or distribution in order to initiate investigative or control measures'. Your definition should have contained elements of the following, most but not all of them taken from the Last definition:

- ongoing collection of data
- practicality
- uniformity
- rapidity
- usefulness
- timely information for action

There are concepts important to surveillance in this definition. 'Ongoing' distinguishes surveillance from a survey, which is more finite. Practicality, uniformity and rapidity are self-explanatory. Definitions of what to report are helpful in ensuring uniformity, but this term also includes regularity. The emphasis on rapidity over accuracy is another important feature of infectious disease surveillance, but this does not mean that striving for accuracy is unimportant.

The Last definition does not emphasize sufficiently timely feedback for action. This is crucial for useful surveillance, especially of infectious diseases. In emergency situations in particular, such as with new infections or disasters such as the 2004 tsunami in South-East Asia, systematic collection of data is worthless without a timely response.

There are other definitions of surveillance which you may prefer. It doesn't matter provided it covers the important elements above.

Activity 1.2

In what way does a survey differ from surveillance? How does surveillance differ from monitoring?

Feedback

Surveillance can also be distinguished from a survey because it usually makes use of already available data. The reports (e.g a laboratory diagnosis) are generally obtained for clinical or other reasons, not just for surveillance. Thus surveillance is efficient because there is nothing extra to pay for in getting the information, only for having to send it to the surveillance centre. In a survey someone has to take steps to obtain information about a subject primarily for the objectives of the study, by using a questionnaire.

The term 'monitoring' should apply when an intervention has been put into place, and the result of the intervention has to be measured. Thus the effect of mass vaccination on a disease is monitored through surveillance of disease and surveillance of vaccine. Similarly the effects of hand-washing on nosocomial infection rates can be monitored in a hospital or ward.

Purposes of surveillance

Activity 1.3

Spend a few minutes thinking about the objectives of conducting surveillance. Write down as many points as you can.

Feedback

You should have written down at least some of the points included in Table 1.1. For the efficient running of any public health programme, surveillance is essential – indeed it has been called the backbone of public health. The basic purpose of surveillance is to

Table 1.1 Purposes of surveillance

Impact of disease
• extent and limits
• vulnerable groups
• natural history
• severity
• complications
Detection of changes
• early warning
• forecasting
• outbreak detection
Monitoring effectiveness of preventive and control measures
Highlighting priorities
Basis for costing studies
Aetiological clues

Source: Noah (2002)

establish background information about a disease – or other factor, see below – in a population. This means not only incidence, but also the age, sex, geographical and seasonal distributions – *i.e.* time, place and person. Without this, it would be impossible to detect changes meaningfully and take action. Generally some public health action should be available for each disease under surveillance, although sometimes conducting surveillance on a new, emerging or severe infection may be necessary.

'Measure of incidence' may be a safer term to use than 'incidence' because surveillance rarely measures incidence – active or enhanced surveillance and a known and stable base population are usually necessary for this to be possible (see below). Nevertheless if reporting is consistent, changes in numbers reported may be indicative of changes in incidence. However, care must always be taken in interpreting changes in reporting numbers as changes in incidence.

The factors likely to affect changes in the numbers of cases reported in a laboratory surveillance system are:

- true change in incidence, including seasonal patterns;
- a new laboratory diagnostic method making the diagnosis easier or less expensive;
- increasing interest in the disease;
- someone making special efforts to increase numbers diagnosed (e.g. with an interest in the condition or writing a thesis);
- change in personnel (whether less or more motivated);
- economic effects, like a laboratory no longer being able to afford some tests;
- other spurious reasons, such as a laboratory or reporting centre failing to report.

In making the basic analyses by time, place and person, perhaps the most important purpose can be fulfilled – to detect change. Change may be natural or induced. Natural variations can be seasonal or secular. They can be useful for early warning or forecasting, or may signify some important change in the susceptibility of the population to that disease. Changes can be induced by some 'accident', such as an outbreak or a new disease, or purposeful, as with a vaccination or other public health intervention.

Subtle changes may occur without it being apparent in the numbers reported, just as undercurrents may not disturb the surface of water.

Activity 1.4

1. Figure 1.1 gives the numbers of notifications of infective hepatitis. What do you observe?

2. Look at Figure 1.2 and comment on what you observe.

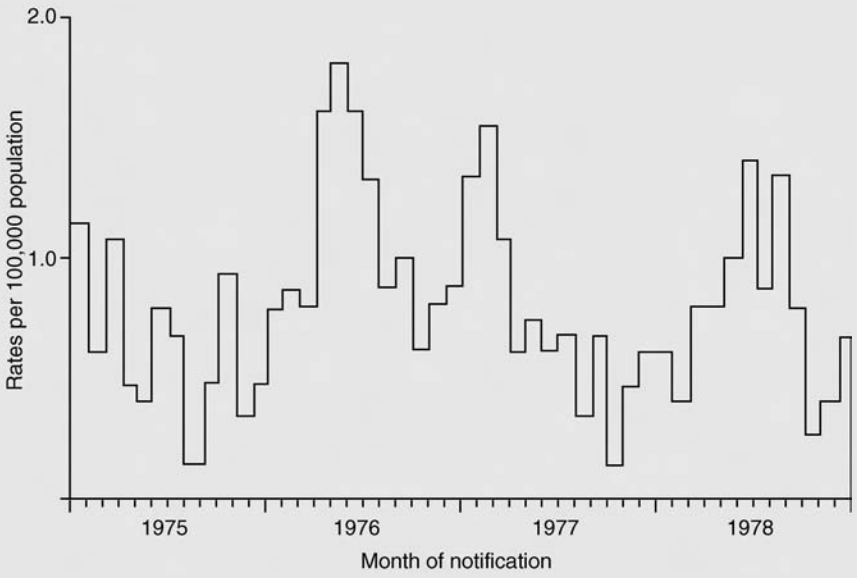

Figure 1.1 Rates of notification of infective jaundice in district A, 1975–8
Source: Adapted from Limentani *et al.* (1979)

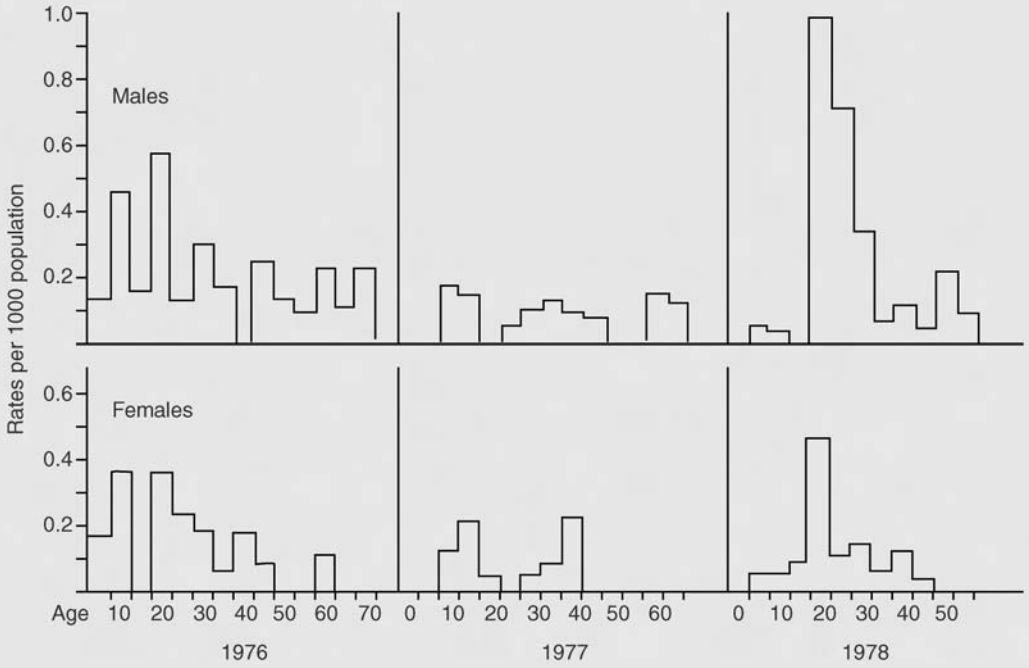

Figure 1.2 Rates of notification of infective jaundice in district A, 1976–8, by age and sex
Source: Limentani *et al.* (1979)

Feedback

1 There seems to have been an increase in notified rates in 1976, and low rates in 1975. In 1976 and 1978 there were summer peaks, in 1977 a winter peak. Was there possibly an outbreak in 1976? This seems to be the only feature of interest in this figure.

2 The age and sex distributions in the three years of higher incidence show quite clearly that an outbreak of jaundice affected young men aged 15–29 in 1978. Nearly all of them had in fact contracted hepatitis B from one tattooist. Figure 1.3 shows how the tattooed cases had been hidden by other cases and causes of jaundice. Because infective jaundice was being notified rather than a specific form of hepatitis, comparing four years of notifications would not have uncovered the outbreak – in Figure 1.1, 1978 was unremarkable. However, the age and sex analyses instantly revealed that something unusual was happening.

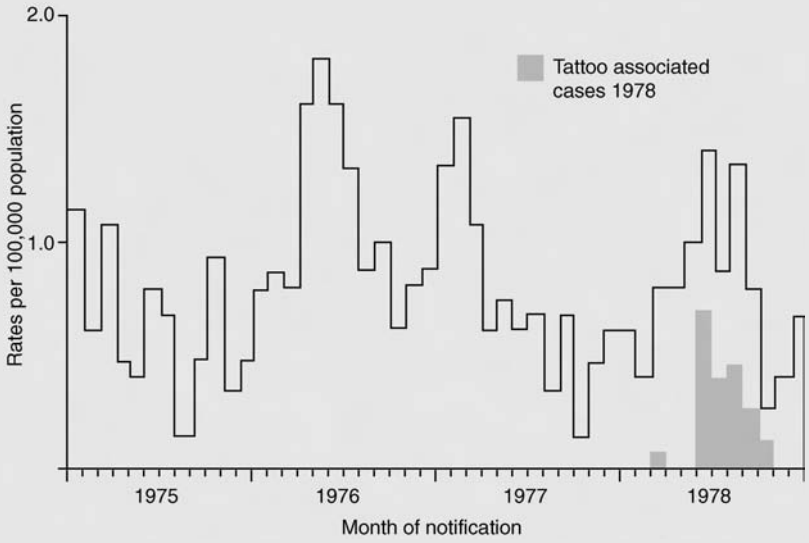

Figure 1.3 Rates of notification of infective jaundice in district A, 1975–8

Source: Limentani *et al.* (1979)

If surveillance data cover a large area, changes may occur within a district or smaller area, and may not be detectable unless data are analysed by place. The invaluable part played by surveillance in the early detection of outbreaks will be discussed further in Chapter 5.

Surveillance can also detect groups of people who may be especially vulnerable to a disease. Fairly sophisticated surveillance systems may be needed for this, but vulnerable age groups or geographical areas can sometimes be detected with even basic systems. It is not possible to monitor successfully the success or otherwise of any public health interventions without surveillance.

Activity 1.5

Can you think of some examples of public health *interventions* for which surveillance is essential? For each example list what you would need to put under surveillance.

Feedback

Some public health interventions for which surveillance is essential include:

- the effects of mass vaccination on the infection
- the effects of the introduction of sanitation and clean water supplies on diarrhoeal disease
- controlling an epidemic of salmonella by withdrawing a contaminated food
- monitoring the effect on legionnaires' disease of a law requiring regular maintenance of wet cooling towers

For a mass vaccination programme, surveillance of the numbers of cases of disease and uptake of vaccine is essential. More sophisticated surveillance systems should include changes in the age distribution of the disease, side-effects of the vaccine, immunity levels of the population and enhanced surveillance of cases (see below) as they become fewer. These are discussed in the chapters on vaccines.

For sanitation, numbers of cases of diarrhoea in the areas in which sanitation has been introduced could be compared with areas without sanitation or the period before sanitation. In more advanced systems, laboratory reports should be included.

If an outbreak of salmonella has been caused by a widely-distributed foodstuff, the numbers of cases after the cause has been withdrawn or otherwise treated should be monitored. The number of outbreaks can also be part of surveillance. The mass immunization in the UK of chickens against salmonella infection led to a dramatic fall in the numbers of *Salmonella enteritidis* PT4 infection. This had a 'double effect' in reducing not only food poisoning from chickens but also from hens' eggs.

The reported incidence of legionnaires' disease and the source of cases can be compared before and after the law was introduced.

Sentinel surveillance

Sentinel surveillance is essentially a type of 'sample surveillance'. Reporting sources are situated at various sites covering an area (which may be very large, such as a country), and may provide complete reporting within the population covered by each reporting source.

Activity 1.6

Can you think of some situations in which sentinel surveillance would be the best option? Why or when would you use sentinel surveillance rather than any other type of surveillance?

Feedback

General practice (primary health care) systems are the ideal base for using sentinel surveillance. If the GPs know the age and sex distribution of their patients, incidence and prevalence data can be calculated. However, because the sentinel practices are by definition widely distributed, the diseases under surveillance have to be fairly common, with little if any geographical variation, so that if there are large areas under- or not represented, it will not matter.

Common illnesses such as chickenpox, herpes zoster or gastroenteritis are ideal for sentinel surveillance. Indeed one would prefer to use sentinel surveillance rather than notification for such conditions: first because it would be wasteful to use a large unwieldy system for common diseases, and second because the compliance and accuracy associated with a sentinel surveillance system is usually considerably better than with a countrywide system. In a sentinel system the reporting personnel tend to be more motivated and likely to make more accurate diagnoses. Each source of information is usually a volunteer, or chosen at random but with agreement. Laboratories and hospitals can also be used as part of a sentinel surveillance system, either as part of a GP-based one or on their own. The same principles apply – use for common diseases with little geographical variation.

Active surveillance and enhanced surveillance

Most surveillance is passive, in the sense of reporting being automatic and there being no real control over the regularity and consistency of the reporting sources. Notification systems generally are an example of this. The surveillance centre is, in effect, accepting some incompleteness in the data. Negative reporting is not required in passive surveillance.

Sometimes, however, more complete reporting is required. The global eradication of smallpox is the best-known example of this: *'each local health unit was "coerced, persuaded, and cajoled" to report cases of smallpox each week, intensive further case finding was undertaken when a case was notified, and sources of information other than medical – teachers, schoolchildren, civil and so on – were used'* (Henderson 1976). Completeness was crucial to smallpox eradication.

In infections for which the goal is eradication or elimination, the closer one gets to the target, the greater the demand for completeness and accuracy of reporting. When measles was common in England and Wales, notifications were adequate. Even at around 500,000 cases a year pre-immunization, they were probably

incomplete but accurate enough for the purpose, *i.e.* the system could cope with a few misdiagnoses. Even when mass immunization was first introduced, in 1968, and the number notified began to fall (see also Chapter 3), notifications were sufficient. When, however, the immunization campaign was stepped up in the late 1980s to achieve elimination, and cases began to be reported in hundreds rather than thousands, completeness and accuracy achieved greater importance and the diagnosis in each case had to be confirmed. Only in this way could the success of the elimination targets be assessed.

Examples of where completeness of reporting is important include:

- less common but important conditions, especially those for which a vaccine is available: more active surveillance required, e.g. meningococcal infections;
- conditions for which public health measures such as quarantine/isolation, chemoprophylaxis, vaccination or immunoglobulin are necessary: completeness/accuracy important, e.g. meningococcal infection (chemoprophylaxis, vaccination) and viral haemorrhagic fever (quarantine/isolation) are examples;
- highly contagious infections for which contact tracing is required: completeness essential, e.g. diphtheria, smallpox, SARS;
- very rare diseases which are not necessarily preventable, but for which more information is required: active surveillance indicated, e.g. see BPSU below;
- serious infections such as botulism, rabies; some new diseases, such as variant CJD: completeness and accuracy essential; although some of these infections, which include rabies and vCJD, are rarely transmissible from human to human, this usually occurs under somewhat artificial conditions (blood transfusion/tissue transplantation), and the risk of human infection is not the primary reason for placing them under surveillance.

Active surveillance requires negative reporting of reporting sources – if a reporting source has no cases they must send in a negative return. Sometimes telephone follow-up is done by the surveillance centre. An example is the surveillance run by the British Paediatric Surveillance Unit (BPSU) in London. They initially started surveillance for Reye syndrome, a rare but serious condition affecting children. Many other conditions have now undergone surveillance through the BPSU, interestingly each for only a limited period. Several other similar systems, modelled on the BPSU, now exist in other countries, and an international network of Paediatric Surveillance Units was formed in 1998 (Lynn *et al*. 1999).

'Enhanced surveillance' is a term coined in England and Wales for a particular type of surveillance in which certain regions or areas are selected to perform active surveillance. It is suitable for infections which are fairly common, such as meningococcal infection. Before the vaccine against group C meningococci was introduced on a mass scale, it became important to assess the real incidence of the infection. Thus all laboratories, hospitals and family doctors were alerted in the areas concerned to report cases, ensuring completeness as far as possible. Steps were taken to eliminate duplicate reporting.

Scope of surveillance

Disease should be considered as a dynamic process which includes the ecology of the pathogen, host, reservoir, vectors and the environment. This is an important concept at all levels of disease control, from the clinical doctor treating the patient at the bedside to the public health practitioner attempting to prevent disease at a population level. Similarly we now broaden the concept of surveillance from the surveillance of disease to surveillance of factors that can *affect* disease. Examples of surveillance at each level are shown in Tables 1.2, 1.3 and 1.4.

Surveillance of morbidity is the surveillance of disease, but can be at various levels (e.g. general practice or hospital). Most notification systems depend on GPs but there are also some specific GP-based systems based on non-notifiable but important diseases. Hospital-based systems clearly measure disease at a more serious level.

Table 1.2 Surveillance of disease

- Disease
  - Mortality
  - Morbidity
  - Outbreaks: disease and environment
  - Laboratory
- Drug utilization
  - Therapeutic
  - Diagnostic
  - Prophylactic
- Vaccine
  - Utilization and efficacy
  - Side-effects

Source: Noah (2002)

Table 1.3 Factors relating to determinants of disease

- Biological functions
  - Growth
  - Development
  - Nutritional status
- Biological changes in agents
  - Influenza
  - Antibiotic resistance
- Reservoirs of infection
  - rabies
  - malaria
  - brucellosis
- Vectors of infection
- Environmental and occupational
  - Pollution
  - Natural phenomena
- Social disease determinants/lifestyle

Source: Noah (2002)

Table 1.4 Factors relating to susceptibility to infection

- Antibody studies
- Skin testing
- HLA/blood groups
- Enzyme deficiencies
- Pharmacogenetic

Source: Noah (2002)

Death certification is the usual source of data on mortality, but reporting of deaths as part of a surveillance system can be particularly useful because case fatality rates may be calculable, as when deaths are routinely reported through a laboratory surveillance system.

Activity 1.7

If several different sources of information are available for a given infection, is it wasteful to use more than one of them?

Feedback

Not necessarily. Because a disease has many different facets, different types of information can be helpful. Food poisoning is notifiable, and most of the information comes from family doctors. However, laboratory reports provide vitally important detail on whether the cause is salmonella, norovirus, staphylococcal etc. Notifications of meningococcal disease or bacterial meningitis provide early warning of an infection, but hospital and laboratory data give detail on the type of infection and are more likely to be complete.

It should be noted that laboratory surveillance offers primarily a qualitative aspect to surveillance of disease. By this is meant that, with the biases inherent in laboratory reporting, incidence rates for a particular infection cannot often be calculated. Nevertheless, laboratories provide essential detail about clinical diagnoses for which the details provided may be insufficient – further examples include hepatitis or influenza.

Death certification gives yet another perspective on the *severity* of the disease. Surveillance of infection at different levels is discussed in more detail later in this chapter.

For economic or other reasons it may not always be feasible to report individual cases of infection. If so, setting up a system for reporting outbreaks or suspected outbreaks may be considered. These can then be investigated and controlled. Outbreak surveillance is valuable in its own right. It can produce information on the number and size of outbreaks, the importance of an organism in causing outbreaks

and on the type of outbreak – for example, types of catering (restaurants, caterers etc.) most likely to need training and education in food handling techniques. Outbreaks can be reported on suspicion by family doctors, public health professionals, the media and even members of the public, and then further investigated for confirmation and control.

Surveillance of drug utilization also has potential. For this to be useful, only drugs that are fairly specific for certain conditions, such as pentamidine which used to be the main treatment for *Pneomocystis carinii* pneumonia, can be monitored, and high-quality statistical information systems must be present to monitor their use. Surveillance of vaccine usage is discussed in more detail later. The use of some vaccines, such as influenza vaccines, to monitor their uptake is still fairly underdeveloped.

Biological changes in agents

With the ability of micro-organisms to change and adapt, surveillance for detecting biological changes in agents is clearly of vital importance in the fight against disease. Such changes in micro-organisms occur frequently. Many of these appear to be 'natural' – for example, the subtypes and variants of influenza A virus (change); others, notably the development of antibiotic resistance, are in response to man's efforts to treat infections (adapt). Examples include:

Influenza A virus changes periodically – major changes are called shifts and the 'new' virus is a subtype. Minor changes are drifts and the changed virus a variant.

Serotypes of meningococci show considerable variation from time to time. Whether these are 'natural' or in response to human susceptibility is not clear. Antibiotic resistance which has developed in some meningococci is certainly adaptation.

Strains of *Staphylococcus aureus* have developed resistance to methicillin (MRSA), making treatment of these infections much more difficult.

Enteric bacteria have likewise developed resistance to antibiotics, notably *Escherichia coli* to vancomycin, and *Salmonella typhi* to chloramphenicol.

Multidrug resistance to *Mycobacterium tuberculosis* has made its treatment, and both treatment and prophylaxis of malaria, much more complex.

Reservoirs of infection

Humans can act as reservoirs of infection. Typhoid, malaria, measles, whooping cough, rubella, mumps, smallpox and hepatitis A (as well as hepatitis B and C) are examples of this, even though some of these organisms can also infect other primates.

Cows, sheep, goats and pigs are the main reservoirs for brucellosis in man, and many biting mammals (but not rodents) for rabies. Influenza affects many animals and birds, and the mixing of strains is thought to be the main source of new

subtypes affecting man. Other examples you may have thought of include psittacosis (birds and sheep), leptospirosis (pigs, dogs, rats, cattle, raccoons and others), Lyme disease (ticks, rodents and deer), lassa fever (multimammate rats), various tick-borne infections (both ticks and animals), plague (wild rodents mainly), Q fever (domestic and farm animals, birds and ticks) and salmonellas excluding typhoid (animals, reptiles and birds).

Examples of infections for which the environment is the main reservoir include Legionellas, *Clostridium tetani and C. botulinum*, Listeria (probably some animals as well) and meliodosis Most of these dwell in soil and water. Some, such as tetanus, come from the intestines of horses and other animals, and are excreted into the soil.

Surveillance of animal and bird reservoirs is useful for assessing risks to humans. For eradication, surveillance of infection in animals is probably essential (e.g. detection and treatment, usually by culling, of cattle in brucellosis). Tuberculosis eradication schemes (*M.bovis*) rely on efficient surveillance. Surveillance of influenza A subtypes in birds and animals in many countries of the Far East is now well developed.

Other types of surveillance (see Table 1.3) may have an indirect bearing on infection (e.g. lifestyle and social trends on the incidence and characteristics of STIs, and pollution on respiratory infection). For some useful information on surveillance of non-communicable disease risk factors see 'useful websites' below.

Susceptibility to infection

Factors relating to susceptibility to infection were listed in Table 1.4.

Most of these are potential rather than existing examples of surveillance of factors related to susceptibility, and are included here to show some future possibilities. As long ago as 1971 Raska argued for the use of serum banks and immunological surveys in surveillance. Antibody surveys – serosurveillance – are now well developed, and can assess susceptibility of populations to infection and the need for vaccination (Morgan-Capner *et al.* 1988). In England and Wales, small samples of the population are regularly tested for antibodies to the latest circulating influenza variants and to new variants. In this way the probable response to an existing influenza vaccine – or the need for a new strain to incorporate into the vaccine – can be evaluated. Susceptibility to infection can also be measured by skin testing, as used with diphtheria (Schick test) and tuberculosis (tuberculin), though these are rarely if ever used for surveillance.

Multidisciplinary surveillance

From the above, it should be clear how wide is the scope for surveillance and how, often, many facets of one disease need to be placed under surveillance. Coordinating with veterinarians is essential for diseases such as salmonella, brucellosis, leptospirosis, tuberculosis, influenza and many others. With the arbovirus diseases,

malaria and many other tropical infections, the surveillance of human disease in isolation is usually inadequate – animals, insects and the environment are vital loops in the chain of transmission. Microbiologists working with animals, birds, and insects as well as those with information on the environment (rivers and lakes in particular) may be vital partners in the team.

Summary

Surveillance is fundamental to public health. In this chapter you have learnt about different types of surveillance and the broad scope of the type of information – not relating just to disease, but also to the determinants of disease – that can be placed under surveillance.

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Useful websites

Health Protection Agency (HPA). The HPA in England and Wales plays a central role in the surveillance and control of infectious diseases: http://www.hpa.org.uk/.

The HPA Centre for Infections websites are particularly useful for up-to-date surveillance reports: http://www.hpa.org.uk/infections/default.htm and http://www.hpa.org.uk/cfi/about/epidem_surveil.htm.

The weekly *Communicable Disease Report* is freely available at http://www.hpa.org.uk/cdr/index.html

Eurosurveillance is freely available weekly and monthly: http://www.eurosurveillance.org/index-02.asp.

British Paediatric Surveillance Unit (BPSU), London: http://bpsu.inopsu.com/.

World Health Organization (WHO) websites – for general epidemiology and publications: http://www.who.int/topics/epidemiology/en/. For surveillance of epidemiological risk factors: http://www.who.int/mediacentre/factsheets/fs273/en/.

For epidemiological surveillance: http://www.who.int/topics/epidemiologic_surveillance/en/. For surveillance of risk factors: http://www.who.int/mediacentre/factsheets/fs273/en/

CDC website: http://www.cdc.gov/doc.do/id/0900f3ec8022729e.

2 Implementing a surveillance system

Overview

In this chapter you will look at more practical aspects of surveillance including the elements and features of surveillance, its uses and how to interpret the data.

Learning objectives

After studying this chapter you will be better able to:

- **understand how to collect and analyse surveillance data**
- **understand how to interpret data**
- **appreciate the importance of timely feedback for action**
- **evaluate a surveillance system**

Key term

Secular (temporal) trends Changes over a long period of time, generally years or decades.

Pre-implementation: objectives

Before implementing a surveillance system an evaluation must be carried out of the importance of each infection to the country, and the feasibility of collecting data on it. Cost considerations are clearly important. One would also expect that collecting data on any infection is not just a sterile exercise – some of the purposes of surveillance were covered in Chapter 1. Hence it is essential to develop a set of carefully thought-out objectives for each disease included in a surveillance system, to be used as a set of criteria by which it can then be evaluated. A description of the methods – how the system is going to work – should also be prepared, agreed by and made available to all those in the team – reporters and analysers. Nevertheless, '*Determining the most efficient approach to surveillance for a given health event is an art. There is room for creativity and the opportunity to combine scientific rigour with practical realities*' (Klaucke 1994). Evaluation of surveillance systems is considered further at the end of this chapter.

Factors for consideration in surveillance

Activity 2.1

When setting up a new surveillance system for infectious disease, what do you think might be the important attributes you would strive for?

Feedback

Important features of a successful surveillance system include:

- importance of the diseases under surveillance
- timeliness
- representativeness
- consistency
- completeness
- accuracy

The diseases under surveillance must be *important*, and appreciated to be important, by the reporting centres and those involved in any necessary actions arising out of the results. The infection does not have to have a vaccine for it, or to be treatable, to be important. Surveillance of AIDS/HIV is essential because of its seriousness, and because surveillance can uncover vulnerable groups of people and the main modes of transmission, so that preventive action can be taken, however limited the results may be. For emerging diseases surveillance provides an assessment of the likely impact of each disease and the vulnerable groups affected.

Criteria for priority diseases may vary from country to country but here is a list (adapted from WHO 2005):

- Does the disease have a high impact, in terms of morbidity, mortality (e.g. influenza, AIDS, food poisoning, measles)?
- Does it have a significant epidemic potential (e.g. meningococcal infection, cholera, SARS, AIDS)?
- Is there significant public health action being taken (infections with a national mass vaccination programme such as measles, polio, whooping cough), or that could be taken?

Timeliness is very important because the point of surveillance is to provide early warning and take action. Nevertheless some degree of delay is inevitable. There is always delay between clinical diagnosis and laboratory confirmation. Culturing micro-organisms needs time, as does serological testing, although the use of immunoglobulin M (IgM) and rapid methods of confirming the cause of an infection has made diagnosis more timely. Other factors affecting timeliness include failure of the reporting sources to report punctually.

The need for *completeness*, at least for the more common infections, is often overstated. In the same way as sampling can indicate, often quite accurately, the characteristics of a defined population, so can an incomplete surveillance system provide useful information about an infection. Indeed, it can be a waste of time and

effort insisting on completeness when a smaller number of reporting sites can provide sufficient information for action. For rare diseases however, including those infections which have become uncommon through vaccination or other prevention, completeness is important, and the rarer the disease the greater the need. An active surveillance system may have to be put in place for rare diseases. Some of these aspects were discussed in Chapter 1.

Representativeness is probably the most important single goal of any surveillance system. Nevertheless, it is often difficult to be certain how accurately the data reflect trends. A wide geographical spread of reporting centres is generally reassuring, especially if they cover rural and urban centres as well as a range of populations of varying social class. Multiple sources of data also can be helpful in assessing representativeness: for meningococcal infections for example, notifications, hospital and laboratory data can be compared, in time, place and person.

Accuracy of data provided is also important to ensure the data are representative. The use of definitions helps accuracy. In a notification system this may be difficult to control, but there is some evidence that those who do notify do so accurately. The accuracy of the data provided by the laboratory will depend on its expertise, as well as how closely it complies with reporting guidelines. Accuracy is greatly facilitated by participation in a quality control scheme, and one of the useful spin-offs of a surveillance system is the ease with which such a scheme can be organized within the network.

Consistency in reporting ensures that the surveillance is representative. It can also be helpful in assessing representativeness. Inconsistent reporting means biased reporting: reporting centres may tend not to report at busy periods, or may choose what to and what not to report rather than following agreed stated/statutory guidelines. This should be avoided at all costs: the essence of reporting to a surveillance centre is to make it a routine. Computing and electronic methods of communication have greatly facilitated consistency.

Elements of surveillance

There are four basic steps required in running a surveillance system:

- collection;
- analysis;
- interpretation;
- response.

Although these are the four basic steps for surveillance, they form a logical and systematic approach to any scientific investigation, and indeed to most thought processes in life before one makes a judgement (e.g. in making a diagnosis in a patient, or in a court of law). In surveillance these four steps are inseparable. Miss one and it is no longer surveillance.

First, you have to collect the facts. In surveillance collect the data, in a scientific investigation make the observations, at the bedside, elicit what the patient is complaining about and the physical signs present. Second, analyse the data – in surveillance or scientific investigation put into appropriate tables, at the bedside make further enquiries about the symptoms: time, quality, referral of pain etc. Third,

interpret – facts by themselves are rarely enough. In other words, what does it all mean? The epidemiologist will be looking for biases in the data while deciding what to make of it (and what not), the doctor at the bedside will be trying to fit the symptoms to a diagnosis, while excluding others. Finally, respond – with feedback and/or action. For the epidemiologist, this means writing a report or a publication and taking action; for the doctor, deciding on treatment.

Activity 2.2

Can you work out how a similar process would work in a court of law?

Feedback

The accused gives the facts, these are analysed by the barristers, the judge and jury interpret them, and finally action is taken – guilty and punishment, or not guilty and free.

You now need to examine the same four steps in the scientific epidemiological process – see Figure 2.1. These steps are fairly self-explanatory. The step from statistics to information is where the skill of the epidemiologist lies – you can be drowning in statistics yet thirsting for information. The crucial interface between facts/statistics and interpretation/information is explored in Chapters 4, 7 and 13.

Figure 2.1 Elements of a surveillance system

Source: HPA Centre for Infections

Collection

Activity 2.3

What would you consider to be the essentials of this collection process?

Feedback

Collection should be:

- systematic
- regular
- uniform
- timely

Contributors should know exactly what, and what not, to report. There should be clear guidelines and case definitions. Reporting has to be regular, otherwise it is not surveillance, and all contributors should conform to a uniform set of rules and guidelines. Clearly, reporting should be prompt in infectious disease surveillance.

Some examples of situations in which you need to be clear about what to report are:

- meningococci or pneumococci isolated from asymptomatic carriers;
- positive results from special one-off surveys;
- isolates of organisms which have nothing to do with causing the disease in the patient (e.g. herpes simplex from a cold sore in a patient with pneumonia);
- serological tests: what are acceptable and what are not.

These examples do not necessarily mean that they must not be reported, only that it needs to be made clear to reporters. For example, asymptomatic carriers may need to be reported in gonococcal or chlamydial infections.

The case definition is important, especially if you are striving for consistency and uniformity in reporting. Sometimes it may be advisable to choose a sensitive case definition, especially with common or serious infections. The need for greater specificity arises for rare infections. However, a case could be made for having a sensitive definition for a rare condition, and then investigating further each case reported. In this way completeness is more likely to be achieved, especially if the case definition is complex. Each case must be judged on its merits, and the criteria for reporting may even change with time.

Analysis by time

Time changes can be:

- seasonal;
- secular;
- epidemic;
- random.

It is possible to pick up trends in time by 'eyeballing' a table, but it is nearly always worth using a graph, to make it easier to analyse trends. You will get some practice at reading graphs of time trends in Chapter 3. With modern computerized systems it is possible to programme in automated algorithms which are based on moving averages to account for seasonal changes. These may then be used to detect and flag untoward events, such as outbreaks or increases in incidence.

In surveillance, hours or days are rarely used – weeks, months, quarters and years are common. For seasonal trends, weeks and months (or four-weekly periods) are useful, for secular trends yearly periods. Longer intervals than this are rarely necessary. For detecting outbreaks in sensitive surveillance systems days or weeks may be needed. In some local notification systems it is possible to analyse daily data, which will be useful for detecting outbreaks. It is epidemiologically correct to use the horizontal (x) axis for plotting time periods as it is the independent variable. The vertical (y) axis is the dependent variable and should always be used for numbers or rates.

When analysing temporal data in infectious disease, especially those based on laboratory reports and on short intervals (weekly or even four-weekly), there are inevitable gaps between date of infection, onset of illness, date of specimen, result of laboratory tests and eventual report to the surveillance centre. Moreover dates may vary considerably even with one organism. From one patient a virus can be isolated or identified by a laboratory close to the date of onset. With another patient with the same infection and the same date of onset, isolation of the virus may be unsuccessful and the diagnosis made by a fourfold rise in antibody titre. This means two blood samples, the second one about six weeks later while the patient is convalescing. Thus two infections occurring on the same date are reported some weeks apart.

Analysis by person

As a routine, age and sex are basic characteristics, and of most value in analyses. The outcome, even in simplest terms (survived/died), is useful if available. Don't ask for too much otherwise an unnecessary burden will be placed on the reporting centres. Occupation, social class and ethnic group have to be fully justified if requested. For legionnaires' disease, and some other conditions such as typhoid and viral haemorrhagic fever, a travel history is essential. For certain infections it may be justifiable to ask for more information. Ethnic group and perhaps occupation for tuberculosis in some countries, and food handlers for salmonella reports, are examples. Age grouping is the critical analysis for detecting subtle changes in disease trends. Standard age groups should normally be used.

Activity 2.4

What age groups would you use in surveillance? Are there exceptions?

Feedback

It is important to use standard age groups, but equally important not to be too rigid about them. These are generally 0–4, 5–9, 10–14, 15–24, 25–44 *etc.* as in epidemiological analysis generally. However, depending on the infection concerned, one might expand some groupings and amalgamate others. With conditions affecting mainly young children, such as *Haemophilus influenzae* meningitis which virtually disappears as a cause of meningitis in adults, using a distribution similar to <1 month, 1–11 months, 1–, 2–, 3–, 4–, 5–9 years, 10–14, and >15 years for example may be sensible. With some sexually transmitted infections, one would need to concentrate on the 15–34, or 15–44 age groups.

Analysis by place

Analysis by place is useful as localized changes in incidence may not otherwise be detected. Analysis by place can give clues about changes in vaccination status of the population, outbreaks and susceptible groups of people. In national surveillance programmes, small area changes are not usually detected, whereas they can and should be in more local systems.

Use of denominators in surveillance

Epidemiologists should always strive to use rates rather than numbers. This is not always possible in surveillance, because of the variables in reporting – the catchment area is not often known for example. Nevertheless, provided reporting is consistent over a reasonable length of time, trends using the term 'reported incidence' can be described with some confidence.

In England and Wales, the sentinel surveillance system run by the Royal College of General Practitioners is based on spotter practices. Each participating practice has a known number of patients, and their age distribution. Thus data are reported as age-specific rates. As they are GP consultations, they are known as consultation rates and will better measure incidence than notifications or laboratory data. Nevertheless they are consultation rather than incidence rates. As they are based on clinical diagnoses, albeit made by experienced and motivated GPs, they are likely to be more sensitive than specific.

Interpretation

Interpreting raw data after they have been analysed – turning statistics into information – is where the skill of the epidemiologist lies. Notifications and laboratory reports represent only part of the total burden of illness caused by an infection. Consider an infection, say influenza, and a finite population at risk. When influenza causes an outbreak, only a proportion of the population will be infected. Some of those, perhaps a large proportion, will not be ill (asymptomatic) (Figure 2.2) or will have an unperceived illness (Figure 2.3).

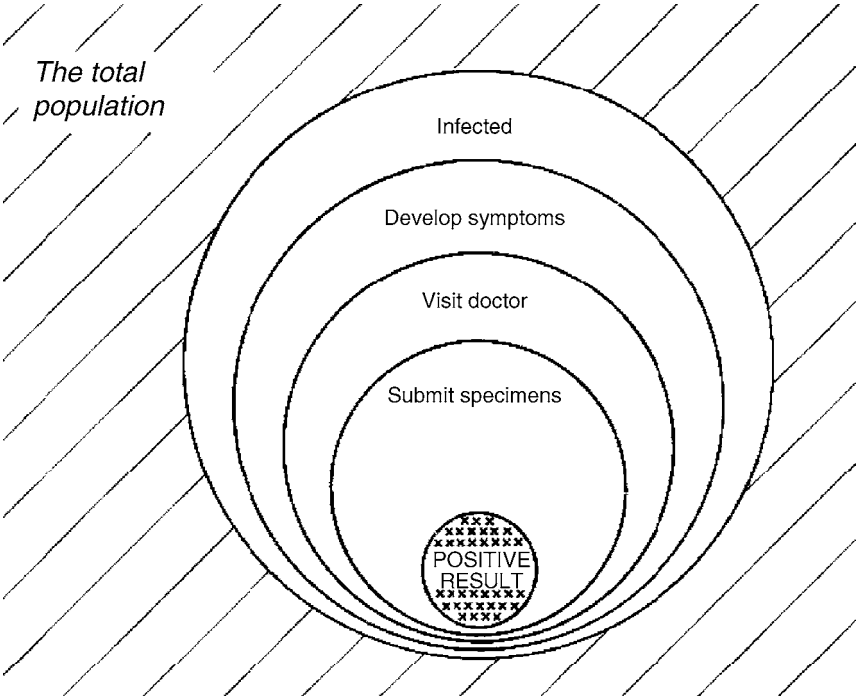

Figure 2.2 Stages in laboratory reporting of an infection
Source: Noah (2002)

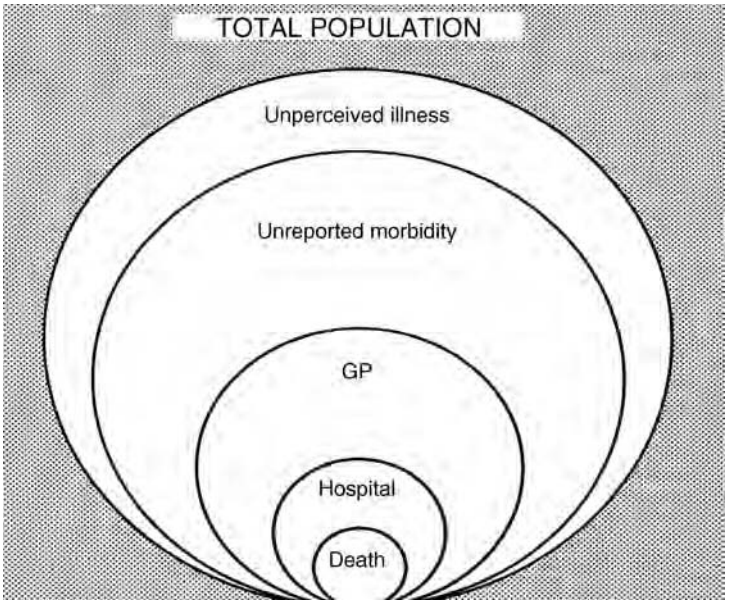

Figure 2.3 Stages of an illness
Source: Noah (2002)

Activity 2.5

How can you detect asymptomatic infections?

Feedback

Carriers can be detected by identifying the organism via: swabbing (throats for meningococci, streptococci, respiratory viruses); testing faeces (polio, other enteroviruses, salmonella); blood (hepatitis B, C, D). Asymptomatic infections can be detected by swabbing, as above, and by serological testing, usually blood but also saliva. Asymptomatic infections are not usually detected in surveillance.

In prevalence studies of carriage, in outbreaks, and in studies of the natural history of an infection, the ratio of symptomatic to asymptomatic infection gives an indication of the infectivity, but not virulence, of an organism. To go back to Figures 2.2 and 2.3, a proportion of people will develop symptoms. This is not always easy to establish, as many people will have mild symptoms – perhaps, with influenza, just feeling out of sorts (malaise) for a day or so. Thus a proportion will not visit a doctor, and will have no real chance of being recognized, much less reported, as a case of influenza. This is *unreported morbidity* (Figure 2.3). Some will visit a doctor, who may not make the diagnosis, or may make the diagnosis in someone who does not have influenza. This can be easily done, as it can be difficult to differentiate influenza-like illness from influenza. If influenza is notifiable, not all doctors will report it. This will account for further unreported morbidity, though this is not the same as asymptomatic infection. Thus for notifications, the notified cases will be incomplete and probably have some inaccuracies (non-cases). You have to be aware of these biases, but should not make too much of them. Incompleteness is a fact of the epidemiologist's life. Moreover, there is evidence that family doctors who notify make fairly accurate diagnoses: age distributions tend to be constant over many years (showing consistency) and changes in vaccination schedules leading to changes in age distributions of infected persons can be detected in notifications.

Doctors are probably more likely to notify severe cases, or perhaps certain age groups more than others – babies and children, or the elderly. In the laboratory model, to take it further, not all specimens will be positive, and indeed all positive results may not be reported. Laboratories may try harder to get a positive result with severe infections, and possibly also with babies, children and young adults. Since influenza tends to affect the elderly more than the young, certainly with fatalities, during epidemics, and probably even at other times, laboratory resources may be diverted away from them to younger age groups. If an influenza outbreak affects residents of an old people's home, only a few patients may be sampled on the assumption that everyone affected has the infection. In the morbidity model (Figure 2.3), the more severe cases are more likely to be admitted to hospital, though patients are sometimes admitted for social reasons. Those who die will have had the most severe illnesses, and the ages of those who die are likely to be substantially different from the background morbidity pattern. Other characteristics

mentioned above, such as timeliness and representativeness, also need to be taken into account.

Thus, understanding the surveillance system, and 'getting a feel for it', is essential to meaningful interpretation of the data it produces. 'Get as much out of it as you can, but no more than it deserves' is a useful rule to follow.

Feedback from surveillance

Providing feedback is the primary objective of any surveillance system, with the aim of effecting change. Ultimately, your surveillance reports should be aimed at those high up in public health or political arenas who are in positions to effect change. Whether politicians would ever read a surveillance bulletin is unlikely, so their close professional advisers, with the ability to understand the implications of the data provided, are perhaps the key target. Nevertheless a wider dissemination of the output of surveillance is important, because changes can be made at a much lower level. Other public health specialists need to know for outbreak control and vaccine strategy. Feedback to the providers of the data is also essential – they can see what viruses, food poisoning organisms etc. are circulating, which in itself will influence what they look for in their own tests, and importantly, the usefulness and significance of their reporting. Surveillance of vaccine uptake data can stimulate poorly performing districts to improve their own uptake, and the role of surveillance in motivating and improving performance should not be underestimated.

Activity 2.6

How often do you think you should provide surveillance reports?

Feedback

This depends on resources available, but also on the periodicity of reporting. If contributors are expected to report weekly, weekly reports are appropriate, especially for infectious disease surveillance. Supplementary monthly reports can be used for detailed reviews. Annual summaries are also helpful. It is useful to have a mechanism for sending *ad hoc* urgent bulletins in suitable situations.

Electronic systems have made it much easier to communicate effectively and rapidly (and indeed cheaply), and full use should be made of their potential. Rapid dissemination of information about outbreaks is now within the reach of most countries with effective surveillance systems.

Surveillance systems must not be static. Regular review of data collected, discarding infections which are no longer of interest, and adding new ones, is recommended.

Content and presentation of reports

Information is important, but this must be built round statistics. Relevant, easily understood tables and figures summarizing the statistics are key factors underlining the commentary. Regular in-depth informed reviews discussing longer-term trends are useful, probably essential. Reports by contributors, of outbreaks for example, should be encouraged.

Organizing a surveillance unit to be able to respond to *ad hoc* enquiries can be built in and is generally appreciated by contributors and others.

Sources of data

- *Death*: most countries have death certification, which is an important source of information. These can however be inaccurate, especially in complex cases. Death certification data are also not usually timely. Note that case fatality rates cannot generally be derived by comparing certified deaths with another source of morbidity such as notification or GP data. This is because death certification has a near 100 per cent coverage, while morbidity data are often incomplete. For example, most deaths from meningococcal infection are accurately diagnosed and certified, whereas notifications, even in countries with well-developed surveillance systems, can be seriously incomplete. Using the ratio of deaths to cases would give an unduly high estimate of case fatality. Trends in this case fatality ratio can however usefully be monitored. Care must be taken in their interpretation. With other types of information system, such as laboratory reporting, information on deaths is valuable, but reporting tends to be of variable quality, and care must be taken in interpreting such data.
- *Hospital admissions*: hospital data reflect a tier of severity below that of deaths. Hospital data are good for infections with a high admission rate, such as meningitis and septicaemia, and less good for others such as food poisoning. Collection of hospital data depends greatly on the quality of the coding and the training of the coders. Hospital data are generally only available some time after the event. This makes it of limited use in infectious disease surveillance, and they are most used as confirmatory evidence of trends.
- *Morbidity systems*: notification and GP-based systems have been discussed above. They tend to be the most useful, well-established and timely of all sources of surveillance data. Laboratory systems have confirmatory and qualitative roles. Thus they can confirm the aetiology of an outbreak – for example, food poisoning or influenza-like illness, as well as provide information for the extra detail necessary in investigation – for example, salmonella serotypes as well as phage types, influenza A or B and subtype/variant. Sometimes isolation of certain organisms may provide clues about the cause of an outbreak. In the UK *Salmonella enteritidis* phage type 4 is associated with egg and chicken consumption.
- *Asymptomatic*: serological surveillance gives some information on asymptomatic as well as symptomatic infections. Generally surveys rather than surveillance are conducted on populations to assess population immunity. Serological surveillance is especially useful in assessing the need for vaccination or the need for a change in vaccination schedules.

In general, it is not necessarily wasteful to have different sources of information. As in Figure 2.3, an infection – indeed any disease – has several facets and an information system that includes as many of these as possible helps to build a picture of a disease. Even within one tier, the morbidity/GP level, running a GP as well as a laboratory surveillance can add different types of information to one condition. Aseptic meningitis, gastroenteritis, hepatitis and influenza-like illness can be given as examples. Nevertheless, as part of evaluation, surveillance centres should always be mindful of wasteful reporting and discontinue any unhelpful sources.

Evaluation of surveillance systems

'The goal is to maximize the system's usefulness and to achieve the simplest, least expensive system that meets the objectives' (Klaucke 1994).

It is helpful to divide the surveillance process into three phases: pre-implementation, implementation and feedback. There are other options. Using these subheadings however, you have the following:

Pre-implementation

- Is there an infrastructure present for meaningful surveillance? Is what is being proposed compatible with the existing infrastructure?
- Is the disease worth placing under surveillance – or do other diseases have higher priority?
- Is there any action you will be able to take with the data? Only information that can be used for public health decision-making should be collected.
- Is it collectable – cost, feasibility, simplicity?

Implementation

- Are the objectives being met?
- Are the case definitions clear, appropriate, consistent and being met?
- Collection/methods: is the system efficient, as simple as possible, cost effective, timely, comprehensive? Are the data accurate and numbers and detail sufficient? Staff inputting data adequately trained?
- For laboratory reporting, are any audits or quality assessment exercises being carried out between laboratories?
- Analysis: being done correctly, using appropriate techniques, properly presented, timely?
- Interpretation: converting statistics to information – how well is it being done? Are the staff trained and understand how to deal with the data?
- How well does the surveillance meet the qualitative and quantitative criteria of timeliness, representativeness, consistency, completeness and accuracy? Is the process flexible?

Feedback

- Timely?
- Understandable?
- Reaching appropriate audience?
- Have any public health actions resulted from the surveillance? Have any outbreaks been uncovered? Has the surveillance produced new information about the infection?

A report with recommendations should be made after each evaluation. Klaucke (1994) has suggested a format for the report as follows:

- public health importance;
- objectives and usefulness;
- system operation;
- quantitative attributes;
- cost of operating the surveillance system;
- conclusions and recommendations.

The pre-implementation phase should always be included in evaluation because priorities may, and do, change. Sometimes more details of an infection may be necessary, but it may be sufficient to require reporters to do this for a finite time – for example, age and sex, ethnic group or occupation for a particular infection for one year only. Evaluation of surveillance systems is considered in greater detail in the references and websites at the end of this chapter.

Surveillance in emergencies

Activity 2.7

1 Can you think of a recent emergency in which surveillance had to be implemented very quickly, with timely information dissemination?
2 What types of surveillance would you introduce?
3 What infectious diseases would you place under surveillance in the event of a disaster similar to a tsunami?

Feedback

1 SARS is a possible answer. However the tsunami of 26 December 2004 in South-East Asia brought into play not only the emergency relief services, but also emergency surveillance of infection by the WHO emergency response and other local and international teams.

2 Both active and passive surveillance are essential, using relief workers, family doctors, hospitals and laboratories. Surveillance in the internally displaced camps is essential.

3 Some of the conditions to consider are:

- cholera

- typhoid
- dysentery
- measles
- malaria
- dengue fever
- Japanese encephalitis
- hepatitis A and E
- tetanus
- wound infections

A useful plan in these situations is to use 'syndromic surveillance' – reporting of symptoms such as watery diarrhoea, bloody diarrhoea, high fever or acute jaundice. Case definitions with algorithms for health care staff to follow in diagnosis and management are recommended. Early surveillance following the tsunami highlighted some unanticipated problems, such as tetanus and wound infections. This meant that health care staff could be primed to look out for these conditions, prevent them where possible, and plan for them by ensuring stocks of tetanus vaccine, immunizing those most at risk and obtaining stocks of appropriate antibiotics for wound infections.

Summary

You have learnt how the implementation of a surveillance system involves a thorough assessment of the need for surveillance, and whether it is practical and cost-efficient to do surveillance. Timeliness, representativeness, consistency, completeness and accuracy must be acceptable for a meaningful surveillance. The steps in a surveillance system should follow the logical order of collection, analysis, interpretation and response or feedback. All surveillance systems should be evaluated regularly and remodelled as necessary.

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WHO (2005) www.who.int/csr/resources/publications/surveillance/WHO_CDS_CSR_ISR_99_2_EN/en/.

Further reading and useful websites

CDC *Framework for Evaluating Public Health Surveillance Systems for Early Detection of Outbreaks*, MMWR 2004; 53(No. RR-5):1–13, www.cdc.gov/mmwr/PDF/rr/rr5305.pdf.

Jajosky RA and Groseclose SL (2004) Evaluation of reporting timeliness of public health surveillance systems for infectious diseases, *BMC Public Health*, 4: 29, electronic version: www.biomedcentral.com/1471–2458/4/29.

RCGP UK: www.rcgp.org.uk/bru/index.asp

Thacker SB, Parrish RG and Trowbridge FL (1988) A method for evaluating systems of epidemiological surveillance, *World Health Statistics Quarterly*, 41: 11–18.

WHO: www.who.int/csr/resources/publications/surveillance/WHO_CDS_CSR_ISR_99_2_EN/en/.

3 International surveillance

Overview

In this chapter you will learn about the usefulness of international surveillance. Legionnaires' disease will be used as a model for this, and so the epidemiology of this disease will be covered here also. Other infections discussed as examples are dealt with elsewhere in this book.

Learning objectives

After studying this chapter you will be better able to:

- **explain the value of participating in international surveillance systems**
- **describe the different ways in which international surveillance can contribute to efficient communicable disease control**
- **explain the problems associated with international surveillance**
- **understand the care needed in interpreting international data**

Key terms

Arbovirus An arthropod-borne virus, i.e. spread by an insect.

Biofilm Slime, a film of biological matter which sticks to surfaces.

Whirlpool spa A warm bath with built-in whirlpools and water jets, often shared by several people. Water is recycled after filtering and disinfection. Also known as jacuzzis, named after Candido Jacuzzi, an Italian-American.

Introduction

Activity 3.1

List some diseases you think would benefit most from international surveillance.

Feedback

Your list could reasonably include:

- legionnaires' disease

- salmonellas
- E. coli O157
- influenza
- cholera
- meningococcal infection
- SARS
- AIDS/HIV
- hepatitis A
- West Nile virus

Not all of these infections are necessarily ideal for international surveillance. Some are for discussion as potential candidates. At the end of this chapter you will be exploring this question in more detail.

Legionnaires' disease (LD)

This is a serious infection which causes pneumonia and has a high fatality rate. It had certainly been around for many years before causing a large outbreak affecting legionnaires attending a convention at a hotel in Philadelphia, USA, in 1976. It has become important in modern times because our complex plumbing and air-conditioning systems are ideal breeding grounds for legionella. It is an illness we have managed to create for ourselves.

Important epidemiological and microbiological features

Legionella are gram-negative bacilli and require special media containing certain nutrients including charcoal and cysteine to grow. Although more than 40 species have been recognized, only about 20 affect humans, of which *L. pneumophila* is by far the most common. Other species tend mainly to infect those who are immunosuppressed. Eighteen serogroups of *L. pneumophila* have so far been identified and most infections are caused by serogroup 1.

L. pneumophila serogroup 1 also cause Pontiac fever, which is benign and does not cause pneumonia or death. Recovery is spontaneous. Outbreaks caused by *L. pneumophila* serogroup 1 can be 'mixed', causing both Pontiac fever and LD. In outbreaks, the attack rate for Pontiac fever is generally considerably higher (about 95 per cent) than for LD (0.1–5 per cent). It is thought that Pontiac fever is a reaction to inhaled antigen rather than actual infection. This would be compatible with the much higher attack rates and shorter incubation period of 12–48 hours.

The incubation period for LD is between two and ten, commonly five or six, days. Transmission between humans, like many other pneumonias, does not occur. Infection is virtually unknown in those aged less than 20. It is commoner in those over 50, and in males (M:F ratio ~2.5:1), smokers, heavy drinkers, those with chronic underlying conditions and the immunosuppressed, including those with transplants. Thus hospital patients are especially vulnerable, both to infection and serious disease. Infection is commoner in late summer and autumn.

Legionellas are 'natural' organisms and are widely distributed in aquatic environments. They require aquatic organisms such as amoebae and protozoa which harbour the bacteria, and algae, flavobacteria and Pseudomonas, which supply essential nutrients for growth. Other water conditions that promote the growth of legionella include stagnation, temperatures between 20° and 50°C (the optimal growth range being 35°–46°C); pH between 5.0 and 8.5 and sediment that tends to promote growth of commensal microflora. Thus they grow well in biofilms. They can survive indefinitely in water hot enough to be inimical to other organisms given such conditions, as well as in tap and distilled water. They can also survive in water at normal levels of chlorination, but can be rendered ineffective by heating water to high temperatures (at least 60°C) or by high chlorine levels or other biocides. Because they are ubiquitous, finding the organisms in a suspected source is not necessarily proof of the source.

The most usual form of transmission to humans is by aerosol. Any fine mist from a suitable watery reservoir which has had a period of stagnation is a risk. The droplets must be small enough to penetrate the lung and large enough to contain at least one organism. The organism can survive in the cysts of amoebae, which can then be inhaled and cause infection.

Exposure risks include hot and cold tap water, showers, whirlpool spas, air-conditioning systems as well as wet cooling towers, humidifiers, fountains, mist-generating devices (e.g. as used in supermarkets on vegetable displays) and respiratory therapy or dental cooling devices. Direct aspiration of contaminated water can also lead to symptomatic infection. Direct exposure to dry soil, such as potting compost, has been reported but is, fortunately, rare. In soil, the particles inhaled were amoebae within which the organism had 'taken refuge'. Rarely, the organisms can infect surgical wounds.

Activity 3.2

In an outbreak, serogroup 1 legionellas were isolated from a suspected water source and confirmed as the cause of infection in those affected. Does this prove that the water source was the cause of the outbreak?

Feedback

In outbreaks, isolating the organism from a suspected source in itself is not adequate. The extent of contamination as well as molecular analysis of water and case strains is needed for definitive evidence.

Activity 3.3

Compile a detailed list of your main aim and objectives in investigating an outbreak of legionnaires disease.

- Aim: to identify a source as quickly as possible so that it can be removed immediately or rendered safe.
- Objectives:
  - identify as many linked cases as possible: detect and treat as many cases as possible, as soon as possible, of this potentially fatal infection; obtain as much epidemiological information as necessary.
  - Use relevant information from all known cases to identify a common source of exposure epidemiologically. This may mean knowing just one street the patients walked through, or one building they stayed in or visited, within the incubation period.
  - Confirm the source microbiologically by taking environmental samples. These may not always be positive as the legionella may be transient or have disappeared by the time the samples were taken.
  - Ensure that appropriate hygiene measures are instituted so that conditions for legionella growth are minimized.
  - Draw up guidelines for the hygienic management of water systems.

Serological course of *L. pneumophila* infection

The mechanism of immunity to *L. pneumophila* infection is not yet clear. Somewhat unusually, the bacteria multiply intracellularly in alveolar macrophages, which normally destroy bacteria. Thus cell-mediated immunity appears to be more important than humoral immunity. However, antibodies do form and probably act by facilitating phagocytosis generally.

Diagnosis

Detection of antigen to *L. pneumophila* serogroup 1 in urine is now highly specific and sensitive, and is the method of choice. Definitive diagnosis is by isolation of the organism from a specimen of sputum or blood culture. Direct visualization of the organism using appropriate stains in respiratory secretions or tissue biopsy is also possible. A fourfold rise in antibody requires four to six weeks for a diagnosis to be confirmed.

Prevention of legionnaires' disease (LD)

It can be prevented by eradicating the organism from the water source. This can be difficult and expensive. Superheating the water to at least 60°C in storage tanks and 50°C at tap outlets is required but may scald users. The organism's relative resistance to chlorination means superchlorination, which in itself causes problems. Effective biocides are available, but water and air-conditioning systems may be closed down and drained while these are used. Regular cleansing, monitoring and maintenance of cooling systems is essential. Tap water is a risk if used in respiratory therapy devices. There are instances of water managers being sued for manslaughter for inadequate maintenance of water systems that caused an outbreak with fatal cases. Good maintenance and operation of whirlpool spas and demonstration baths is also necessary.

Outbreaks

As in all surveillance systems a case definition for LD is necessary. A clinical illness with pneumonia suggestive of LD and supporting laboratory evidence of legionella infection is generally adequate.

Surveillance of legionnaires' disease

Activity 3.4

What would be your reasons for instituting a *national* surveillance of LD?

Feedback

LD is a 'natural' for national surveillance because it is possible to prevent cases continuing in an outbreak and produce and enforce guidelines for hygienic management of plumbing systems nationally.

Other important reasons are: that it is a serious and potentially fatal illness; it can be fairly accurately and easily confirmed by a laboratory from urine rather than sputum; most symptomatic cases are hospitalized thus facilitating diagnosis and epidemiological investigation; and it is not so common as to make surveillance a serious burden. Timeliness is clearly highly important in any surveillance system of LD.

Activity 3.5

What would be the main point of conducting international surveillance of LD?

Feedback

The short answer is to detect travel-associated cases and outbreaks as early as possible. Because hotels are among the buildings most prone to causing LD, infection can occur while on holiday. Symptoms usually develop, or the infection is diagnosed, when back home. With the low attack rates, small numbers of cases may present in several different countries – i.e. one or two in each country. Thus an outbreak would often not be recognized unless information was collated at a central surveillance centre.

In Europe, nearly all countries collaborate in EWGLINET (the European Working Group for Legionella Infections) which includes the European Surveillance Scheme for Travel-Associated Legionnaires' Disease.

The plan below is based on the European model which can be modified for individual networks.

- Early reports by local surveillance unit of all cases of LD to National Surveillance Unit (NSU).
- NSU reports to the (European) Coordinating Centre each confirmed case of LD with a history of travel within two to ten days of onset to another European country or own country within the network.

For single cases (not known to be associated with other cases):

- Coordinating Centre contacts NSU in country of origin with details of case and suspected site of infection (usually a hotel).
- Response required by country of infection which must include contacting the place of accommodation and sending the management a 14-point checklist to ensure legionella risks are minimized.

For clusters (i.e. two or more cases who stayed in the same accommodation within two years of each other):

- As above.
- Cluster alerts and reports sent to all NSUs in the network.
- Report made to WHO and health ministry of country concerned.
- Preventative and control measures are undertaken by EWGLINET collaborator in country of origin. They must respond by arranging a technical site inspection and risk assessment, as well as environmental investigations, sampling and implementation of emergency control measures. They must report back with preliminary and final reports at two and six weeks respectively. Sanctions apply if these procedures are not followed, leading to publication of the hotel name on the EWGLINET website and likely immediate withdrawal of the hotel concerned from lists of tour operators.

A long interval is necessary because LD usually has a low attack rate; some cases may well not be recognized or reported, and so may be missed; contamination of water sources may be intermittent (e.g. seasonal variation); experience has shown that some clusters occur with cases separated by a long interval. Although the prime function of an LD network is to detect widespread outbreaks, advantage can be taken of such a network to improve collaboration in other areas. These include building a dataset for descriptive epidemiology of LD, so as to identify changes in epidemiological features of LD and assess the impact of preventive measures on incidence; introducing a quality assessment (QA) scheme for detection of legionella species in water, legionella urinary antigen, and typing of *L. pneumophila* and other legionella species. Finally, guidelines for control can be formulated collaboratively and implemented widely. These pertain only to Europe but can readily be accessed on the internet.

For transcontinental surveillance you would need a coordinating centre in each continent or other large region to conduct surveillance within that continent and report transcontinental travel-associated cases to an overall central coordinating centre, run perhaps by the WHO.

International surveillance of other diseases

Salmonellas and *E. coli* O157

There is an element of similarity with LD in that one reason for international surveillance of salmonellas/*E. coli* is the early detection of outbreaks caused by a food source in another country. However, the main emphasis is on detecting a widely distributed foodstuff so that it can be recalled and further cases prevented. A variety of contaminated foodstuffs have been identified in this way. Gastroenteritis and food poisoning are reviewed in Chapter 16.

Influenza

The main objective here is the laboratory identification of new strains – both variants and subtypes, but especially subtypes. Indeed, the global surveillance of influenza includes surveillance of new subtypes appearing in avian and animal species as well as in man in an attempt to predict and identify as early as possible any new subtype that can cause a pandemic. Nevertheless, producing a vaccine is almost certainly going to be a race against time as the virus tends to spread globally somewhat faster than our ability to produce enough stocks of a vaccine for it. Influenza is reviewed in Chapter 14.

Cholera

With cholera the emphasis is to chart the spread of new strains and assess their virulence. Laboratory characterization of strains and surveillance of cases are the backbones of cholera surveillance. There were six pandemics of cholera between 1817 and 1923. Between 1923 and 1960 cholera remained mainly confined to the Indian subcontinent. In 1961 a biotype of *Vibrio cholerae*, El Tor, which had caused only sporadic cases and small outbreaks mainly in Indonesia up to then, reappeared in Indonesia and caused a seventh pandemic. This caused some surprise as the WHO had, only in 1958, declared the strain to lack the capacity for international spread. This strain has lasted longer and spread more widely than any other. It was feared that a new cholera strain, O139, which appeared in 1992 in the Indian subcontinent and caused large outbreaks there would cause another pandemic but this has not yet happened. This illustrates some of the difficulties of predicting epidemics, even with well-established international surveillance.

Meningococcal infection

With meningococcal infection, the case for international surveillance may not be as strong but it is still worthwhile. Although a serious infection, its incidence is generally not high enough in most countries for them to prioritize it. The case for international surveillance is for laboratory identification of meningococcal clones as they spread, early warning of local outbreaks as they occur, assessing the burden of infection worldwide, and estimating the need for vaccine usage. New typing and

cloning techniques should make it easier to chart the progress of new strains across the world. Major epidemics of meningococcal infection with group A (also group C) occur in the sub-Saharan region of Africa, and the WHO conducts international surveillance within this region. In other parts of the world the infection can flare up without warning: epidemics in recent years have occurred in Norway, England, Nepal, India, Sao Paulo in Brazil, Auckland in New Zealand and the Philippines. There have been outbreaks during the Hajj when pilgrims have been affected during their visit and have then spread the organism to contacts in other parts of the world on their return home (Aguilera *et al.* 2002). There is an existing scheme for European surveillance. Vaccines are available for groups A, C, W135 and Y, but not for group B, which is the commonest group in most developed and middle-income countries.

SARS

SARS is a severe respiratory disease caused by SARS coronavirus (SARS CoV). The sudden appearance of SARS in November 2002 in China and Hong Kong, its high mortality rate, its contagiousness and its incredibly high rate of spread to other countries made an unassailable case for international surveillance. The concerted efforts of laboratories, epidemiologists and the WHO almost certainly helped in containing the disease by July 2003. Nevertheless surveillance, both in humans and animals, continues, and four small and rapidly contained outbreaks of SARS have been reported since, three of which appear to have been linked to laboratory accidents, and the fourth possibly to an animal source. Clearly, surveillance of SARS needs to continue, even without any reported cases currently. Further details of SARS are in Chapter 14.

AIDS/HIV

The case for international surveillance of HIV infection is also fairly straightforward, though here it is not outbreak detection but burden of disease and assessment of risk factors, as well as the seriousness of the infection and high mortality, that are the important factors – see Chapter 18.

Hepatitis A

Hepatitis A is included for discussion because like LD, a person can be infected in one country from a common or point source, and develop the disease back home. Thus people from several countries affected in one place can return without realizing that an outbreak has occurred. This makes a case for international surveillance. In the event, the disease is probably not serious enough to warrant international surveillance, and such outbreaks, although they undoubtedly occur, are probably insufficiently common to justify the effort. Moreover, most point sources are not ongoing – they are usually a one-off food product, or a food-handler contaminating one dish. Rarely, a contaminated product, such as a frozen soft fruit, may be widely distributed across countries.

West Nile virus

West Nile virus is an arthropod-borne flavivirus spread by mosquitoes, which can cause infection in birds, animals and humans. Symptoms are of a viral fever with a skin rash. Meningoencephalitis is an uncommon but serious complication. After it was first isolated in Uganda in 1937, it rarely caused outbreaks of infection in humans, and those documented were mainly in Africa and the Middle East. Since 1996 however it appears not only to have spread more widely, but also to have become more virulent: it has been causing more outbreaks in horses and humans, and more severe human and avian disease. The 1996 strain (ROM96) first appeared in Romania. Since then further variants have appeared. Isr98, which caused an outbreak in Israel in 1998, is closely related to NY99, which caused an outbreak that led to fatal encephalitis in six elderly people in New York in 1999. Both have caused illness and death in humans and animals. The timing of the outbreaks and the similarity of the strains suggested that the virus was imported from the Middle East to the USA, though whether this was from humans, birds, mosquitoes or an animal host is not known. The virus caused high mortality in crows in New York, prompting an avian surveillance system which showed that the virus was widespread in birds in large areas of the USA. Fortunately, human infection has been less common and much more localized. Several mosquito species were also shown to be infected. Outcomes of surveillance include increased larval control early in the season and health promotion measures to avoid mosquito bites, as well as surveillance of the extent of infection in birds (Petersen 2001).

West Nile virus seems to be a good candidate for international surveillance. At present it seems mainly to be causing human infections in parts of Africa, the Middle East and the USA. However, the infection in birds and animals seems to be more widespread than the distribution of human infection suggests. The virus appears to have undergone a change of some sort that has made it more virulent and its geographical boundaries are spreading. Although there is a surveillance programme in the USA, global surveillance seems to be more informal. West Nile virus surveillance is a good example of multidisciplinary surveillance, which needs to involve human, veterinary and entomological virologists.

International surveillance systems

There is a need for rapid investigation and control of serious outbreaks anywhere in the world, especially in countries that may not have the necessary infrastructure or expertise, and the WHO Global Outbreak Alert & Response Network (GOARN) helps fill this void. The Network is a technical collaboration of existing institutions and networks which pool human and technical resources for the rapid identification and confirmation of, and response to, outbreaks of international importance. The Network provides an operational framework to link this expertise and skill to keep the international community constantly alert to the threat of outbreaks and ready to respond.

Some international surveillance systems include non-infectious disease. The International Network of Paediatric Surveillance Units (INoPSU) is a collaborative organization. Established in 1998, it currently has as partners 14 diverse countries to conduct surveillance of uncommon conditions of childhood. The member units

span the globe from the Netherlands via New Guinea to New Zealand. Their mission is '*the advancement of knowledge about rare and uncommon childhood infections and disorders through the participation of paediatricians in the surveillance on a national and international basis*'. Collectively, INoPSU members conduct surveillance in a population of over 46 million children. More than 8000 clinicians contribute and over 180 conditions have so far been studied.

Summary

You have learned how, with increasing travel and other means of spread of infectious disease, such as mass production and distribution of foodstuffs, the need for international surveillance of certain infectious disease is essential. The examples given above are not comprehensive. The objectives for international surveillance of any disease will vary with the disease. With some, the emergence of new strains that may lead to pandemics needs to be detected as early as possible. With others, a source of infection, such as a foodstuff, has to be identified and dealt with appropriately. Other infections may have already spread rapidly around the world, and justify international surveillance on grounds of severity and high incidence.

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Peterson LR (2001) West Nile Virus: a re-emerging global pathogen, *Emerging Infectious Diseases*, 4: 611–14.

Further reading

Broome C (1998) *Effective global response to emerging infectious diseases*, *Emerging Infectious Diseases*, 4: 358–9.

Chin J (2000) Control of Communicable Diseases Manual. 17th edition. Washington DC: APHA.

Heymann D and Rodier GR (1998) Global surveillance of communicable diseases, *Emerging Infectious Diseases*, 4: 362–5.

Nelson KE (2001) Surveillance, in KE Nelson *et al*. (eds) *Infectious Disease Epidemiology: Theory and Practice*. Frederick, MA: Aspen Publishers.

Useful websites

www.hpa.org.uk

www.who.int/en/

www.cdc.gov

AIDS/HIV
www.hpa.org.uk/infections/topics_az/hiv_and_sti/default.htm

Cholera
www.who.int/topics/cholera/en/

Gastrointestinal
www.hpa.org.uk/hpa/inter/enter-net_menu.htm
www.hpa.org.uk/hpa/inter/enter-net_outbreaks.htm

Goarn (CSR)
www.who.int/csr/outbreaknetwork/en/

Hepatitis A
www.hpa.org.uk/infections/topics_az/hepatitis_a/menu.htm

Influenza
www.hpa.org.uk/infections/topics_az/influenza/flu.htm

Legionella
www.EWGLI.org
www.watersafety.co.uk/
www.cdc.gov/ncidod/dbmd/diseaseinfo/legionellosis_g.htm

Meningococcal
www.hpa.org.uk/infections/topics_az/meningo/gen_info.htm
www.who.int/topics/meningitis/en/

Paediatric surveillance
International Network of Paediatric Surveillance Units (INoPSU):
www.inopsu.com/

SARS
www.hpa.org.uk/infections/topics_az/SARS/menu.htm
www.who.int/csr/sars/en/

4 Some examples of surveillance

Overview

This chapter gives you practice in interpretation of surveillance data. As the skill of the public health practitioner lies in interpreting data, these exercises should be gone through systematically and thought about carefully. You may even disagree with some of the conclusions. That's acceptable if you can justify your disagreement.

Learning objectives

After studying this chapter you will be better able to:

- **describe and analyse secular data about infectious disease**
- **use a systematic process to interpret data**
- **explain the biases in any data and make adjustments accordingly in your interpretation**

Key terms

Acute poliomyelitis A viral infection which causes paralysis of any muscle in the body. Most infections are asymptomatic; risk of paralysis increases with age at first infection. Spread mainly by faecal-oral route. Live (oral) and inactivated (injection) vaccines are available.

Diphtheria A bacterial infection caused by *Corynebacterium diphtheriae*. It may produce a white membrane which can block the upper respiratory tract, or a toxin which can damage the heart, often fatally.

DTP polio vaccine Diphtheria, tetanus and pertussis vaccines given as one injection in three doses at under 1 year of age, together with oral **polio** vaccine.

Measles An extremely infectious viral disease with serious complications. Before the vaccine, infection in childhood was virtually universal.

Rheumatic fever A generalized response to infection with group A streptococci involving joints and heart. Heart valve changes often became permanent. Rheumatic heart disease was a common cause of death until recently.

Scarlet fever An infection caused by a streptococcus. A toxin produced by the streptococcus makes the skin turn red. It had a high mortality in the early part of the twentieth century. It is susceptible to penicillin.

Subacute sclerosing panencephalitis (SSPE) A rare fatal complication of measles, causing a slow deterioration of brain function (panencephalitis). Now rare in countries with effective measles immunization programmes.

Whooping cough A bacterial infection caused by *Bordetella pertussis*. It causes a paroxysmal cough, especially severe in babies.

Introduction

Dramatic changes have been observed in many infectious diseases in the last century. In this chapter, you will learn about some of them and interpret them as best you can. When looking at figures or tables, always describe first, then interpret.

Scarlet fever

Activity 4.1

1 First, describe systematically what you see in Figure 4.1.
2 What further useful information might you ask for before interpreting the graph?

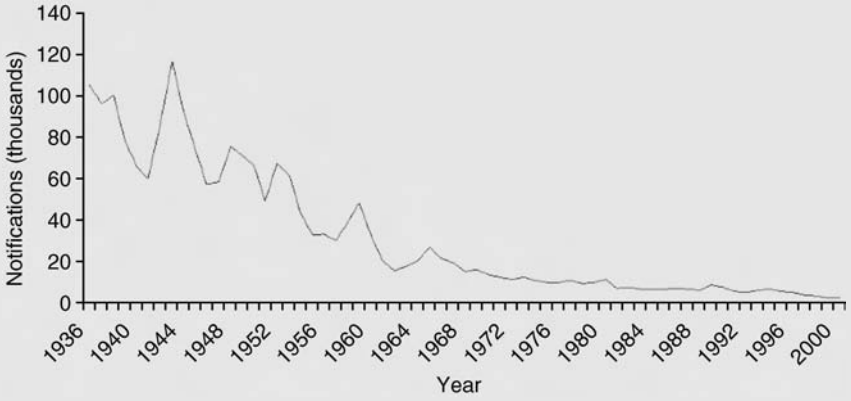

Figure 4.1 Scarlet fever notifications England and Wales, 1936–2000
Source: HPA Centre for Infections

Feedback

1 This graph shows notifications of scarlet fever in England and Wales from 1936 to 2000. There were more than 100,000 notifications of this infection annually when notifications began in 1936. Apart from a small increase from 1941–4, the trend has been generally downwards over about 60 years, reaching very small numbers in 2000.

2 Rates are not provided, so knowing the number of births per year (as this is predominantly a disease of early childhood), would help. The number of certified deaths would also be helpful.

Figure 4.1 shows numbers, not rates. There were about 700,000 births a year in England and Wales during the middle of the century so the notification rate was high – about 15–20 per cent of children were notified. A clinical diagnosis was usually made so there may be some inaccuracies (confusion with other childhood illnesses causing a red rash), also probably some undernotification. The short sharp rise between 1941 and 1944 seems to have coincided with World War II. The disease has now virtually disappeared. No deaths are shown in this figure so it is not possible to judge mortality (in fact mortality was high).

Antibiotics possibly caused the drop in notifications, as they first became available around 1949. However, scarlet fever was diminishing before that, and the fall was too gradual – one would have expected a more dramatic fall if antibiotics had had an effect. Moreover they may have had a high cure rate but were unlikely to have prevented many cases as they are given after the onset of disease. The fall is probably related to improving standards of living of the population, especially children. Another theory is that the streptococcus diminished in virulence but scientific evidence to support this is lacking. Other diseases related to streptococci also fell around the middle of the 1900s (e.g. rheumatic fever, acute glomerulonephritis). In fact, scarlet fever had a high mortality rate in the early twentieth century, with babies and young children dying in epidemic numbers. Antibiotics probably did little to change the incidence but may have improved survival rates. Unfortunately they did not become available until the 1950s but were most needed well before this.

Tuberculosis

Activity 4.2

Describe systematically what you see in Figure 4.2.

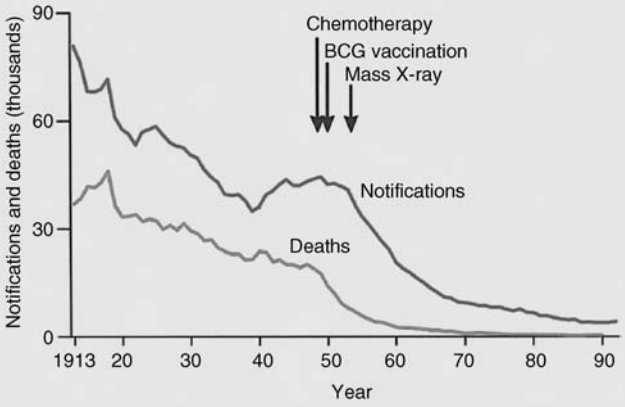

Figure 4.2 Respiratory tuberculosis notifications and deaths, England and Wales, 1913–92

Source: HPA Centre for Infections

Feedback

This is a graph of notifications of tuberculosis and certified deaths from 1913 to 1992. Notification and deaths are on the same scale, in thousands, and the dates of introduction of chemotherapy, BCG and mass X-ray are shown. Both deaths and notifications of tuberculosis appear to have been in decline between 1913 and 1940. Between 1940 and about the mid-1950s there was a slight but sustained increase. From about 1950 three methods of intervention were introduced within five to six years: chemotherapy appeared first, then BCG and finally mass X-ray. Tuberculosis then began to decline again, until 1992. The temporary hiatus in the decline of notifications seems not to have been mirrored by the deaths, apart from a slight increase around 1940 for a year or two only.

Tuberculosis was decreasing in both numbers of cases notified and deaths certified long before the introduction of the three main forms of intervention in the 1950s. The reasons for this are unknown, but are generally attributed to improving standards of living. Accuracy of diagnosis must be considered – if this was constantly improving and becoming more specific, this would account at least in part for the apparent decline. The parallel decline in deaths, assuming that diagnosis at death was more likely to be accurate, possibly indicates that much of the decline was real. The less sustained increase in deaths between 1940 and 1955 could mean either a spurious increase in notifications due to more complete reporting, or better treatment of cases leading to longer survival or recovery. The introduction of the three methods of intervention appears to have accelerated the decline in both notified cases and deaths, leading to low levels in more modern times. In summary, though suggestive, one cannot be certain whether the interventions had a definite effect on the overall decline of tuberculosis in the last century, and indeed, if so, which method was most effective. The decline in notifications appears to have started with the introduction of mass X-ray, and in deaths with chemotherapy, both of which are plausible, although mass X-ray should have increased the number of notifications.

Drugs worked because, unlike many acute infections, tuberculosis tends to become more, not less infectious, as it progresses. Effective treatment can prevent infected persons from infecting others, or otherwise curtail the period of infectiousness. The role of chemotherapy in infection is discussed below.

Tuberculosis only became notifiable in the UK in 1932. Assuming the death certificates were reasonably accurate, Figure 4.3 suggests that the decline in deaths from tuberculosis dated at least from around 1880. In the absence of any known effective medical interventions, improving social circumstances and/or a decrease in the virulence of the bacterium are possible reasons.

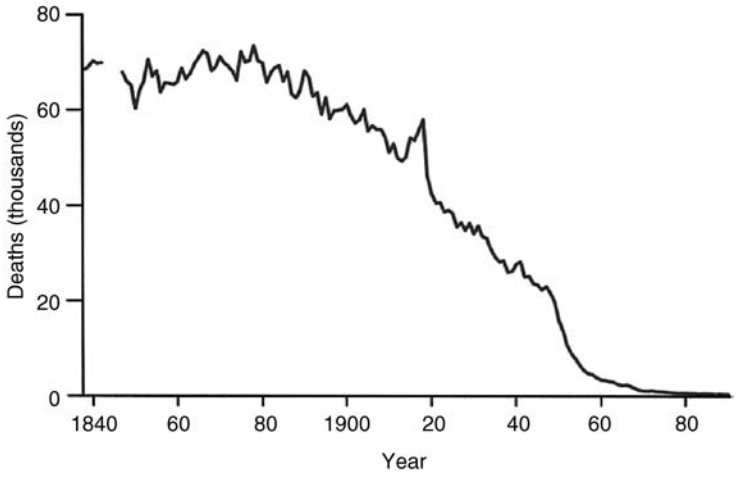

Figure 4.3 Tuberculosis (all forms) annual number of deaths, England and Wales, 1838–1990
Source: HPA Centre for Infections

Poliomyelitis and diphtheria

Activity 4.3

Study Figures 4.4 and 4.5 and describe what you see.

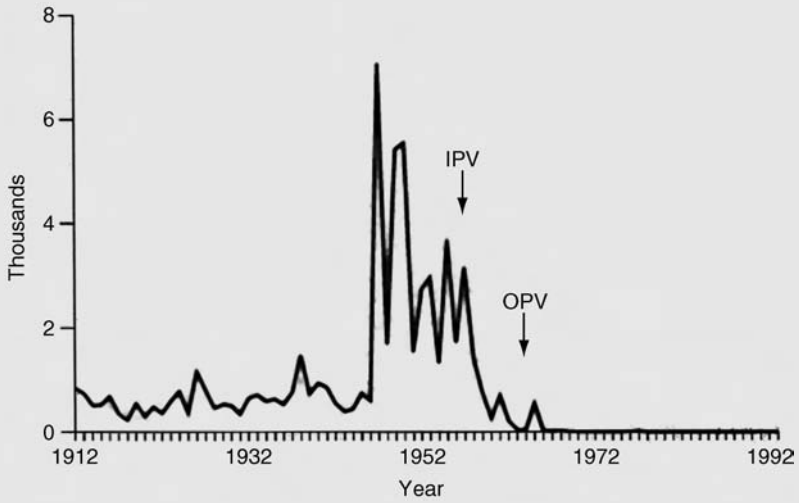

Figure 4.4 Notification of acute poliomyelitis in England and Wales, 1912–92
Source: HPA Centre for Infections

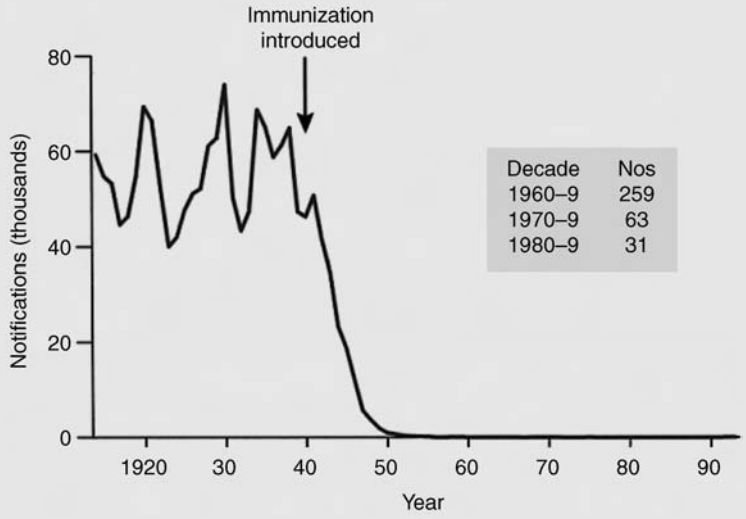

Figure 4.5 Diphtheria notifications, England and Wales, 1914–93
Source: HPA Centre for Infections

Feedback

Figure 4.4 shows notifications in thousands of acute cases of poliomyelitis between 1912 and 1992. There were fewer than 1000 notifications each year until 1946 when a huge increase occurred reaching more than 7000 cases. Cases continued to be notified at a high level until a dramatic fall between 1960 and 1962. By the mid-1960s the disease had virtually disappeared.

Figure 4.5 shows notifications of diphtheria in thousands between 1914 and 1993. Cases were notified at 40,000 to 70,000 per year until in 1940 there was a sharp drop which continued so that, by 1950, the disease had virtually disappeared.

These changes are unlikely to be natural as they occurred over such a short space of time. Some medical intervention must have taken place. For polio, inactivated (Salk) vaccine was introduced in 1957; this was replaced in 1963 by the live attenuated (Sabin) vaccine. A toxoid vaccine was introduced for diphtheria in 1940. Both diphtheria and polio vaccines were used on a mass scale and had an efficacy of over 90 per cent. The uptake rates for DTP Polio during the 1950s through to the early 1980s was around 80 per cent (except for pertussis). Uptake rates increased gradually after this. Even at uptake rates of about 80 per cent these vaccines appear to have been extremely successful and virtually eliminated both infections in England and Wales.

Measles and whooping cough

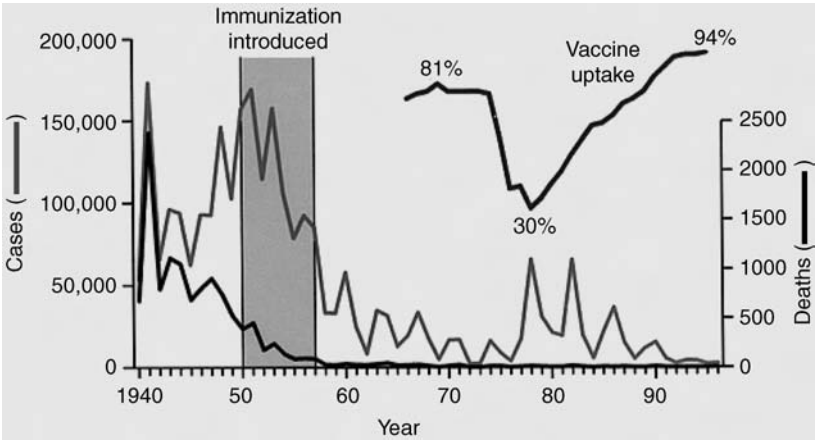

Figure 4.6 Whooping cough notifications: cases and deaths, England and Wales, 1940–96
Source: HPA Centre for Infections

Activity 4.4

Look at Figures 4.6 and 4.7 and describe what you see.

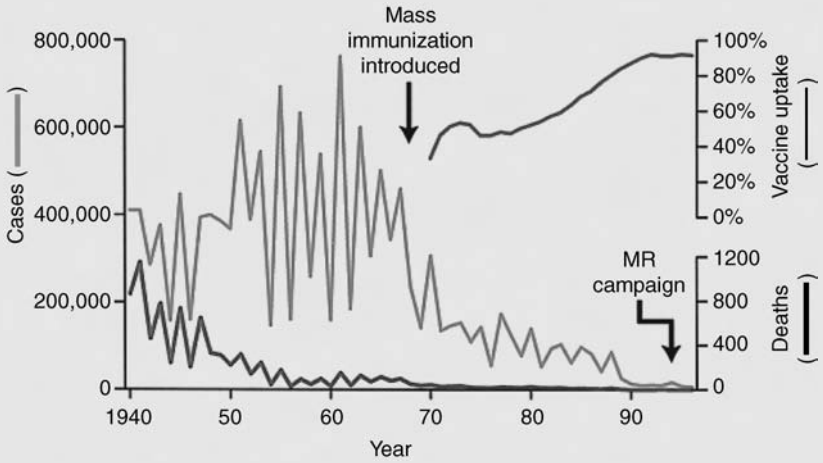

Figure 4.7 Measles notification: cases and deaths, England and Wales, 1940–96
Source: HPA Centre for Infections

Measles vaccine was introduced on a mass scale in 1968. MMR vaccine was introduced in 1988. Efficacy of measles vaccine is around 95 per cent. Whooping cough vaccine took a long time to be generally accepted, hence the length of time shown in the figure. Efficacy of whole cell pertussis vaccine was around 70 per cent.

Feedback

Whooping cough became notifiable in 1940. Between 60,000 and 180,000 cases were notified annually until 1952 when the number began to fall. Mass immunization was introduced gradually from 1950. Notified cases declined gradually from about 1950/1 until 1976 when numbers began to rise again. Two sharp epidemics occurred reaching peaks in 1978 and 1982, followed by two smaller ones in 1986 and 1990, after which cases declined to low numbers. Deaths are shown on a different scale. At first they followed the pattern of notified cases, reaching almost 2500 cases a year, before beginning to fall in the mid- to late 1940s, even while the cases increased. This decline continued and by the end of the 1950s few deaths from whooping cough were being certified. Vaccination rates ran at about 81 per cent from the mid-1960s and early 1970s, fell to 30 per cent in 1978, but slowly recovered to more than 94 per cent by the mid-1990s.

Measles also became notifiable in 1940. About 400,000 cases a year were notified on average, although these fluctuated wildly between fewer than 200,000 to about 800,000 a year. With the exception of a few years in the late 1940s, there was a marked biennial pattern in notified cases. Numbers notified began to fall from 1968, but gradually, and the marked biennial pattern previously noted also became less marked. By 1990 very few cases were being notified, although there appears to have been a slight 'bump' in the late 1990s. Deaths, plotted on a different scale, followed the pattern of measles cases initially, reaching about 1200 cases at the peak, but then began to fall in the mid- to late 1940s, and reached very low levels by the mid-1950s and almost negligible levels by the 1970s. Immunization levels were initially low, below 50 per cent, but began to rise from about the late 1970s and eventually reached more than 90 per cent in 1996.

Both diseases were very common in the 1940s, measles more so even than whooping cough. Given that around 700,000 births occurred in England and Wales annually, about two thirds of all children were notified with measles and about one sixth with whooping cough. The introduction of mass immunization in the 1950s for whooping cough and in 1968 for measles appears to have led to a gradual reduction in the numbers of both these infections. However, this does not appear to have been as dramatic as the effect it had on diphtheria and polio (Figures 4.4, 4.5). A fall in the uptake of whooping cough vaccine in the mid-1970s was associated with a series of epidemics of diminishing size, as the uptake increased again. As the uptake reached >90 per cent, notified cases diminished to low levels. With measles, a small drop in immunization rates seems to have occurred in the mid-1970s, at the same time as whooping cough, but the fall was not sustained. Indeed immunization rates increased gradually and the number of cases fell. After 1988 when MMR vaccine was introduced, the rates fell even further. A small rise in notified cases in the mid-1990s stimulated an immunization campaign, which appears to have been successful.

With both whooping cough and measles, immunization had little detectable effect on the deaths. Indeed the number began to decrease in the late 1940s, well before immunization was introduced. Possibly, the introduction of mass immunization accelerated this decline slightly but there is little doubt that the major fall in deaths from both infections occurred before immunization.

The two factors basic to success of a mass immunization programme are vaccine efficacy (VE) and vaccine uptake (VU). The vaccines for diphtheria and polio were both highly effective (>90 per cent), and the uptake for each high enough for the given efficacy of each vaccine to cause sharp falls in reported incidence. For whooping cough on the other hand, the uptake rate of around 80 per cent (adequate for diphtheria and polio with higher VE rates) for a VE of 70 per cent was not enough for a dramatic, as opposed to a gradual, fall in incidence. Only when the uptake rates increased to >90 per cent in the late 1980s and 1990s, apparently necessary for a VE of only 70 per cent, did the numbers fall to very low levels. With measles, the VE was high (95 per cent) but the uptake poor – barely 50 per cent. With measles the same falls in notified cases as with whooping cough occurred when uptake rates increased. The relationship between VE and VU is explored further in Chapter 10.

What affects survival from infection? Good nutrition, higher standards of living, good primary and secondary health care – and treatment. Vaccines in general prevent people from contracting an infection, not necessarily surviving it. In the late 1940s several changes occurred in England and Wales: standards of living and nutrition improved; the NHS made health care free to all and the population more aware of health; and antibiotics were being introduced. These factors would have improved survival, but not to any extent the number of cases getting the disease. A vaccine was necessary for that (or other preventive method such as sanitation for diarrhoeal diseases).

Activity 4.5

To consolidate this hypothesis further, examine Figures 4.8 and 4.9 and describe what you see.

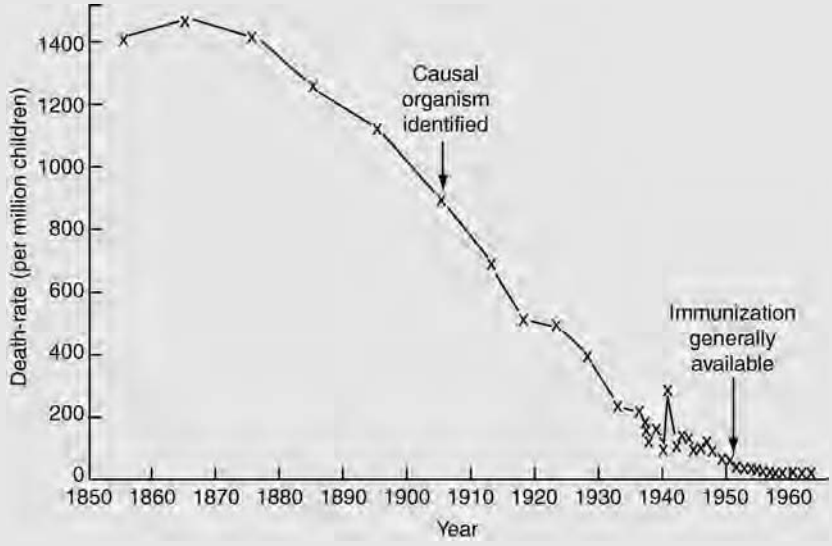

Figure 4.8 Whooping cough death-rates of children under 15: England and Wales, 1850–1960

Source: McKeown (1979)

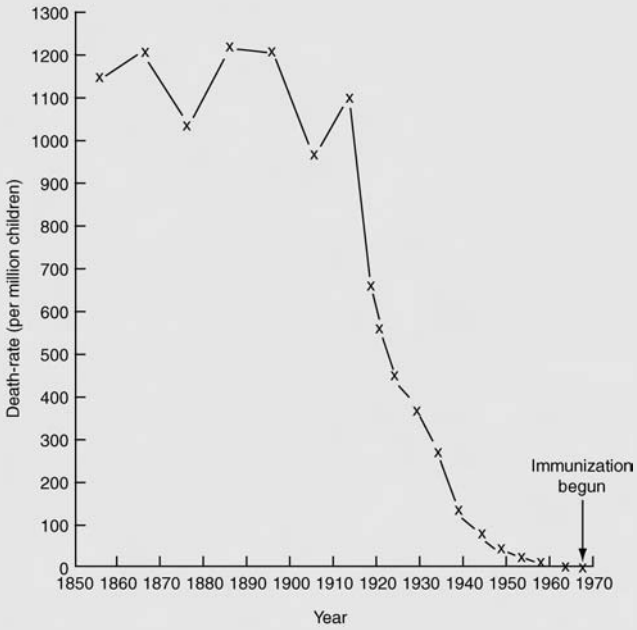

Figure 4.9 Measles: death-rates of children under 15: England and Wales, 1850–1970
Source: McKeown (1979)

Feedback

The number of deaths began falling a long time ago, in the fourth quarter of the nineteenth century for whooping cough and the first quarter of the twentieth for measles. As with tuberculosis we cannot be certain why. Improving standards of living seem likely but we cannot exclude diminishing virulence of the causative organisms.

Activity 4.6

Figures 4.8 and 4.9 were interpreted as showing the apparent worthlessness of vaccines. Do you accept this? How does Figure 4.10 help?

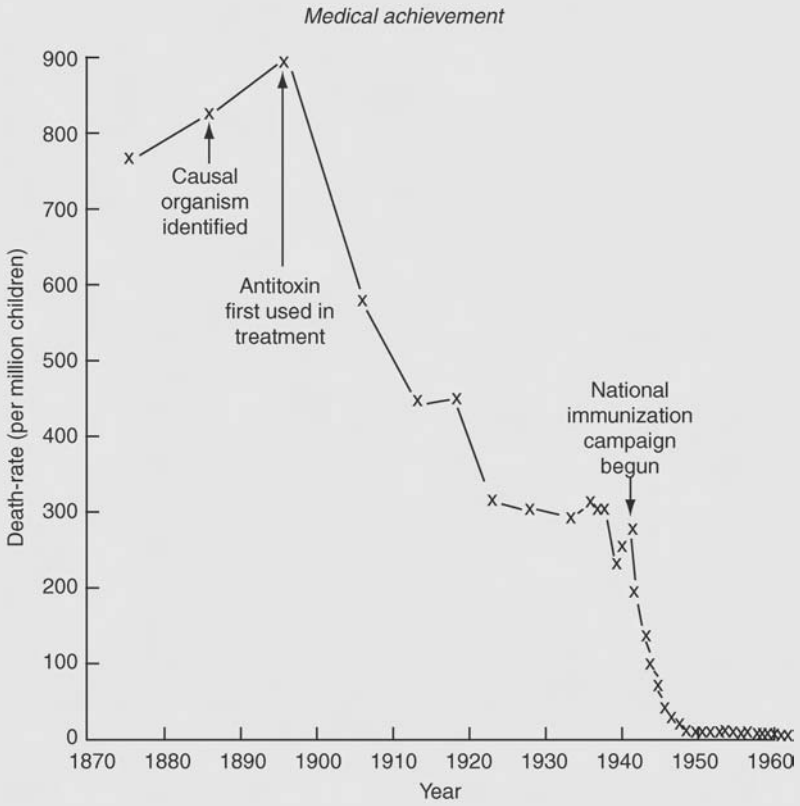

Figure 4.10 Diphtheria: death-rates of children under 15: England and Wales, 1870–1960
Source: McKeown (1979)

Feedback

No, vaccines are not worthless. Vaccines prevent cases – when the number of cases falls, the number of deaths from that disease will normally also fall. If there have not been any improvements in treatment, or if there is better innate resistance, the case fatality rate will not improve. With diphtheria, the vaccine was introduced in 1940, with tetanus. This was considerably earlier than with the others and while the case fatality rate was still high. We have seen already that diphtheria vaccine had a dramatic effect on the infection, and Figure 4.10 confirms that reducing the incidence of the disease also reduced deaths from diphtheria much more quickly than previously. With all these diseases it is highly probable that if a vaccine had been available earlier, both incidence and death rates would have fallen together. Vaccines are thus much more efficient than treatment.

Sexually transmitted infections

Figure 4.11 shows that the incidence of sexually transmitted infections (STIs) increased dramatically at a period of greatly improving treatment with antibiotics. Easily available, non-painful and effective treatment may even induce complacency, as people are less concerned about contracting an infection. Figure 4.12 confirms the steady rise in the number of attendances in genitourinary medicine (GUM) clinics. However, treatment did lower the death rates from syphilis (Figure 4.13), the only infection among the STIs with a significant case fatality rate until AIDS. Note that the disease codes for syphilis changed slightly over the period shown on the graph, making the different rates approximately but not strictly comparable, as shown on the graph.

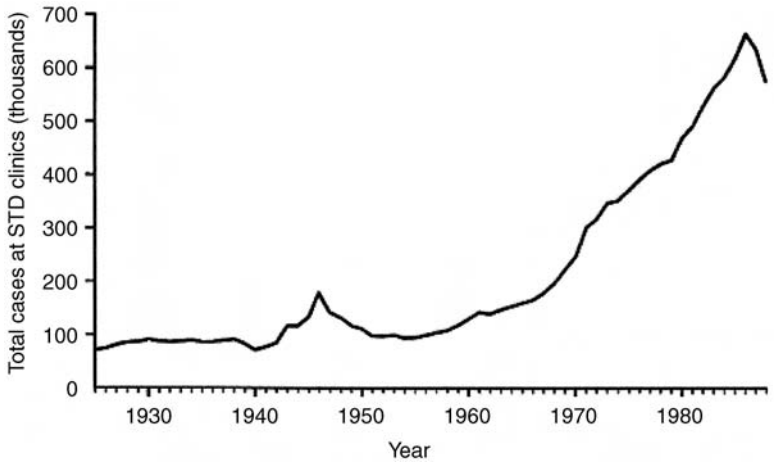

Figure 4.11 Sexually transmitted diseases, England and Wales, 1925–88

Source: Department of Health, prepared by HPA Centre for Infections

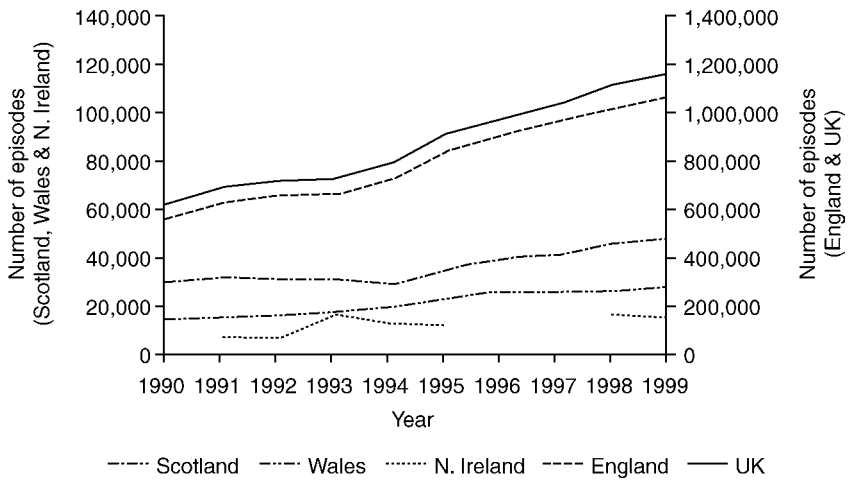

Figure 4.12 Number of new episodes seem in GUM clinics, United Kingdom, 1990–9

Source: HPA (England, Wales and Northern Ireland), DHSS&PS (Northern Ireland) and Scottish ISD(D)5 Collaborative Group (ISD, SCIEH and MSSVD)

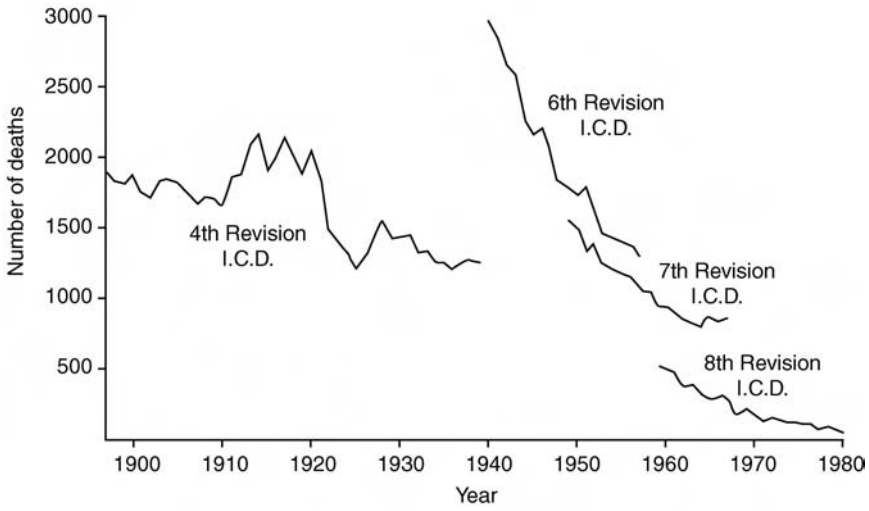

Figure 4.13 Syphilis: Registered deaths, England and Wales, 1897–1981
Source: HPA Centre for Infection

Summary

When attempting to interpret a figure or table, describe what you see first, including any biases that may be present in the data shown, then interpret. Many infectious diseases, especially those of childhood, decreased without any medical intervention, while one, poliomyelitis, increased. Vaccines have on the whole been instrumental in reducing the incidence of many infections. If introduced early enough they will produce an accompanying but indirect fall in mortality. Mortality is more likely to be directly influenced by effective treatment, such as with antibiotics, and improving social circumstances.

Reference

McKeown T (1979) The role of medicine: dream, mirage or nemesis? Oxford: Blackwell.

SECTION 2

Outbreaks

5 Epidemiological investigation of outbreaks

Overview

This section will provide you with a framework on how to investigate an outbreak and cope with its management. Chapters 5 and 6 introduce the principles of outbreak investigation and management respectively. Chapter 7 probes the analytical thought processes used in investigating an outbreak with some practical exercises.

This chapter covers the 'scientific' part of outbreak investigation. It provides a systematic model to follow when investigating an outbreak so that you can go about it purposefully, without disorganization or panic. You will need to know the basic principles of epidemiology, in particular the differences between descriptive and analytical studies, case control and cohort studies, how to choose controls and define cases, and how to calculate incidence and attack rates (and how they differ). By the nature of this type of investigation, a 'quick and dirty' approach is usually needed. The art of epidemiology lies in how to interpret soft data and outbreak investigations generally afford many opportunities for you to acquire this skill.

The ten steps in outbreak investigation form the core of this chapter, although several other important aspects will also be covered.

Learning objectives

After studying this chapter you will be better able to:

- **describe and understand the steps in outbreak investigation**
- **choose the most appropriate study for a given outbreak**
- **analyse and interpret the data you obtain**
- **understand the need for preparing a report**
- **investigate an outbreak**

Epidemiological investigation

Outbreak investigation is one of the most exciting functions of a public health practitioner. If surveillance represents the 'backbone' of communicable disease control, outbreak management is its nerves and muscles. It affords the intellectual satisfaction of 'solving a mystery' as well as testing one's expertise in epidemiology, organization and management, important skills in public health. Management involves managing not only those affected but also other investigators, managers, politicians and the press. In the process of investigation, epidemiological and statistical skills are tested, as well as knowledge of microbiology and the effect of the environment on infectious disease.

Most people go too early for finding out the cause of the outbreak. Much basic systematic work collecting information is needed first. There are ten basic principles of a field investigation (adapted from Gregg 1996 and Ungchusak 2002):

1 Determine if this is an outbreak.
2 Confirm the diagnosis.
3 Define a case, conduct case finding.
4 Collect information on cases.
5 Analyse data epidemiologically: time, place, person, exposure.
6 Interpret: who is at risk of becoming ill? Develop a hypothesis.
7 Test hypothesis with an analytical study, with microbiological and environmental studies as necessary.
8 Draw appropriate conclusions.
9 Prepare a written report.
10 Execute control and prevention measures.

It is important to realize that you may have to do several of these steps at the same time (e.g. step 10 could sometimes be the first step). Think of it as more of a framework than a rigid flow chart. You may need a pilot study on a small number of cases to form a hypothesis. If so, you should normally omit those who took part in your pilot study in your analytical study. In a point source outbreak steps 5, 6 and 7 could merge into one. Note that these 10 steps follow the format of collect, analyse, interpret, act.

Determine the existence of an outbreak

Activity 5.1

In what ways may an outbreak be spurious?

Feedback

- it could be based on an impression; by looking at previous records, especially by season, this can be verified
- overenthusiastic notifying is possible (e.g. a new GP)
- laboratory errors, or a new test, are further possibilities

Always take a short history from whoever called you in, including some background about people affected and the environment and circumstances. Look at data carefully, discuss with health professionals on site. Sometimes after discussion an outbreak does not seem possible, and although instinct may be a useful guide, especially with experienced investigators, a spurious cause must be found to explain the increase in cases. If an outbreak is likely, ask yourself: is it an outbreak that should be investigated?

Confirm the diagnosis

Ensure that appropriate samples and swabs will be, or have been, taken for the laboratory. Do not forget 'appropriate' here includes not just those affected, but also possible sources (such as food and water) and the environment (e.g. kitchen surfaces and utensils). Establish a relationship with the laboratory director/technician at an early stage. Work out a plan with the laboratory for sampling, especially if the outbreak is a large one: what proportion of cases needs to be sampled and who will obtain them? Have a differential diagnosis to work on until the diagnosis is confirmed.

Define a case and conduct case-finding

A case definition requires a balance between sensitivity and specificity. With a sensitive case definition for hepatitis (e.g. anyone with, say, just a loss of appetite, a well-known symptom of hepatitis), you will pick up more cases, but some of them will be non-cases. With a more specific case definition (e.g. laboratory confirmation of HAV immunoglobulin (IgM), which is easy to do and remains positive three to four months after onset of illness) you can be fairly sure that everyone positive will be a case, but you may miss some if the specimens were taken too late or some refused. However, this rule is not as simple as it sounds because in hepatitis A laboratory testing often picks up asymptomatic cases, thus increasing both sensitivity and specificity. With gastroenteritis this rule works better, because affected people tend to excrete the causal organism for a much shorter period, and stools may become negative more quickly. Thus a sensitive case definition may include everyone with say, nausea; a specific one will only accept cases proven by a laboratory. You may have a mixed (more than one) case definition but you must be consistent. You can also have definite, probable, possible cases. Put the limits for dates of onset of cases into the definition as well. You can wait for the questionnaires before making a case definition.

The usual sources of cases are GPs and hospitals, especially accident and emergency departments. Laboratories are another important source. Occasionally you may want to approach local schools, factories, other establishments, local chemists and, more rarely, the press. If the outbreak is localized to a particular group of people, such as a wedding party, it is usually wise to contact everyone who went to the wedding. The more cases you have for your investigation, the more likely you will be to lead a successful epidemiological investigation. You will have a better idea of the extent of the outbreak and its impact.

Collect information on cases

Activity 5.2

What would be your first step in collecting information about the outbreak?

Feedback

Compile a questionnaire. By now it should be clear whether a case-control or cohort study is appropriate. You may already have a hypothesis. Decide to whom you are going to administer the questionnaire and how (post, interview etc.). You may have to do a pilot study first, using a questionnaire which can be modified later.

This list forms a useful framework to use when attempting to compile a questionnaire. However, ask only what is necessary or important to collect. Short focused questionnaires are better than long ones and are much more likely to get a good response.

- *demographic data*: age, sex, address, phone, name of GP, occupation if relevant;
- *details of illness*: clinical features, laboratory tests, date/time of onset;
- *burden of illness*: severity of illness (visited GP, hospital), days ill/off work, costs involved;
- *exposure details*: i) food or other histories, duration or dose of exposure important sometimes (e.g. glasses of water per day in waterborne outbreak); ii) contact data: type of contact with others, frequency, duration (for case-to-case outbreaks);
- *details of secondary cases*: relationship to primary cases, and type of contact.

Analyse data epidemiologically: time, place, person, exposure

The importance of drawing a graph of times of onset cannot be stressed too highly. It provides an essential feel for an outbreak, and by putting important exposures or happenings on the graph, it can give clues. This most important analysis can usually tell you with some certainty whether an outbreak is due to a point or continuing source, or through case-to-case transmission. A graph of incubation periods is not the same, or as essential, but can be helpful. Start with the shortest possible time interval (chosen according to the incubation period) and see what it looks like. You can always group times together later (e.g. change daily to weekly). In a community outbreak do not start from the first case, but earlier.

In community-wide outbreaks, look at place and try and correlate the distribution of cases with a possible causal factor, such as water, food or milk supply, wind direction or vector distribution. Note that place is not always about where you live: where do you work and where have you been are relevant questions in certain situations. In the outbreak of legionnaires' disease caused by the BBC cooling tower in the middle of London, the first two cases were diagnosed several miles away, in Essex, where the patients lived.

The number of outbreaks for which maps are needed is limited. Nevertheless, plotting data by place on a spot map, provided it is relevant, can be helpful. The famous diagrams of Soho round the Broad Street pump drawn by the nineteenth-century epidemiologist John Snow are a good example. A further advantage of a map is in showing the outliers, as in the well-to-do family in Hampstead who sent their coachman down every day to Broad Street for the water. They too contracted cholera, thus convincing John Snow that he was right about the pump.

Place can give clues not only to environmental but also social factors. Thus rates of disease found to vary by place may reflect social class differences rather than local environmental conditions.

The many different possible variables of *person* which can be analysed include age, sex, race, social class and occupation, which can be converted to rates. In outbreaks in which no hypothesis is emerging, analysing various parameters systematically may provide clues. Age is often particularly helpful in these situations.

Exposure is really an extension of person. This may also be part of step 7. Sometimes the type of exposure to analyse is fairly obvious, as in an outbreak of food poisoning. At other times, as in a community outbreak of legionnaires' disease, it may be more difficult. Examples of analysis by exposure are given below and in the chapters that follow in this section.

Interpret: who is at risk of becoming ill? Develop a hypothesis

After these basic analyses, the pattern of the outbreak will be emerging – how and when the outbreak started, its progress, the type of people involved, and whether it's still ongoing, coming to an end or all over. Even if the source of the outbreak is obvious, consider if the outbreak is wider than first realized, and if people outside the initial group are also involved. In formulating a hypothesis consider not just the source of the outbreak, but also how it was transmitted and the likely pathogens. The importance of differentiating as early as possible between an outbreak caused by a point or continuing source, and one that has been spread from case-to-case, is critical as the management of these differ. Indeed, the aims and objectives of the investigation of these two types of outbreak are quite different. Most of what follows is for a point or continuing source outbreak. Management of a case-to-case outbreak is covered in Chapter 6.

Test hypothesis with an analytical study, with microbiological and environmental studies as necessary

Generally, in a point-source outbreak within a closed community, information on exposure can be collected together with time, place, person, using the initial questionnaire. Those not affected act as controls. The type of study possible here is usually a cohort study. In an outbreak of food poisoning following a wedding or party, all guests and catering staff are sent a questionnaire, and food-specific attack rates can be calculated (see below). In effect, the cohorts vary with each food item consumed. However, in some point-source outbreaks, such as an outbreak of legionnaires' disease from a cooling tower affecting people walking in the street below, only a case-control study may be feasible.

In a community outbreak in which there are no real clues as to cause, the investigation may have to be done in two stages: analyse by time, place, person first, formulate a hypothesis, and then test this with an analytical study. This is commonly done in community outbreaks when it is not immediately clear how the outbreak originated. Usually a case-control rather than cohort study is more viable.

Activity 5.3

Why do you think a case-control rather than cohort study is more viable in a community outbreak?

Feedback

This is because if you suspect, say, a food source that has been distributed through a population, it is usually not possible or easy to get two groups together, one who have eaten the suspect food and another who haven't. This is so especially if an answer is required in a hurry, so that the food can be withdrawn. You enquire of cases about their food histories, choose appropriate controls and make the same enquiries of them. Moreover, with a case-control study, one has far more flexibility in looking at various exposures to test. Thus if it is unclear if say, shellfish or ice cream has caused an outbreak in a community, you can test for both (as well as other suspect foods) in a case-control study.

For example, an outbreak of hepatitis A occurs in a city. There may be some clusters within families, but in general cases seem to be sporadic. Moreover they have occurred over about a month. In this type of situation, a pilot study will be needed. From this a clue appears: most of the cases questioned had some cockles (a type of shellfish usually cooked very lightly before consumption), eaten as a snack with drinks in various inns. This becomes your hypothesis but it will be almost impossible to collect a group of people who have eaten cockles (and the number required may be very high if the attack rate is low) and compare the attack rate in this 'cockle-eating cohort' with that in a non-cockle-eating cohort. A case-control study is far more feasible to test the hypothesis. Generally, you should exclude those who have been included in the pilot study, unless there is an insufficient number of cases to test your hypothesis (O'Mahony *et al.* 1983).

Activity 5.4

What problems would you anticipate in choosing controls in a suspected food poisoning outbreak in a community?

Feedback

In this type of situation controls have to be chosen carefully. Food habits vary considerably with age, sex, social class, ethnic group and geographical location. The types of people who consume say, ice cream, infant powdered milk, cockles, oysters, herbal tea, bean sprouts or salami (cured sausage) vary considerably. The need for speed has to be weighed against the need for academic rigour. Generally, in infectious disease outbreaks, choosing an unaffected friend of the same age and living in the same area controls for many other possible variables.

The importance of microbiological studies cannot be stressed too highly. Generally, epidemiological studies alone are not considered as 'proof', however convincing they may be.

In a microbiological study you will have taken steps to ensure that correct samples have been taken. At a later stage, when the epidemiology has narrowed the possibilities, more selective microbiology can be done. In an outbreak of legionnaires' disease, sampling several cooling towers or other sources of aerosols is counterproductive, especially since the organism is often found in such samples. In an outbreak of gastroenteritis on board ship, suspected to be caused by the consumption of food or drink, the variety of foods available will be far too great to send for sampling. Once the epidemiology has made it clearer which of the foods or drinks has caused the outbreak, more selective testing can be done. Sometimes, the rate of contamination may be so low that many samples of the same food are tested before a positive is found. In an outbreak of salmonella affecting mainly infants, the epidemiological studies pointed conclusively to a brand of infant dried milk. To confirm this, several thousand unopened cartons were tested before *one* of them proved to be positive (Rowe *et al.* 1987). Further typing, including using phages or antibiotic sensitivities, may be necessary, especially for common organisms. Molecular techniques to further characterize the strains isolated from cases and the source can prove a causal association beyond doubt. Typing and molecular studies can also prove that cases are linked. With some outbreaks, such as tuberculosis, confirming the strain in the source case may be particularly important. The important relationship between the epidemiologist and the laboratory is examined further later in this chapter.

Finding the source is not always sufficient. Environmental studies must be undertaken in many instances to complete the investigation. There are two types of environmental study, in effect. One is concerned with providing microbiological evidence. Swabs from kitchen surfaces and utensils, samples of foods and sources of foods, and food-handlers, may provide further evidence of causality.

The second type of environmental study is really concerned with 'biological plausibility'. Investigating an outbreak and pinpointing a source can be curiously unsatisfying if, at the end, no one knows what went wrong. What went wrong in the preparation of the food? How did the food become contaminated? Was it in the kitchen or was it already contaminated? If it was already contaminated, how did that happen? How did a public water supply become contaminated? What went wrong in the servicing of cooling towers? These questions are important to institute preventive measures, which is after all the main reason for investigating an outbreak.

Draw appropriate conclusions

At this point review all the findings, both positive and negative, and draw a conclusion. From what is known of the infection, could the outbreak have happened? How sound was the epidemiology in incriminating a particular source? Was there any supporting microbiological evidence? What were the lapses in hygiene that led to the incident? Did the food handlers found to be positive cause the outbreak or

were they also victims (much more likely)? If all the findings add up to a coherent explanation for the outbreak, in other words everything fits, the case can be presumed to be watertight.

Prepare a written report

The reasons for producing a report of the investigation are several and are fully considered in Gregg (1996). They are:

- A document for action: it is often not possible to implement any recommendations for action until a report explaining what happened, how it was investigated and what should be done has appeared.
- A record of performance: this should cover performance not only of the investigation team but also of the resources expended. If you don't write it up no one will remember it happened and that you investigated it.
- A document for potential legal and medical issues.
- Enhancement of the quality of the investigation: as you write new and different thought processes are generated, bringing about a better understanding of the incident.
- An instrument for teaching epidemiology: teaching by example is best. Publishing is also important – examples can be referred to using readily obtainable information, as in this and several other chapters in this book.

The outcome of an investigation should not determine whether it is written up or not. Documenting outbreaks that have not been solved is equally important.

Activity 5.5

What broad headings would you use in a report?

Feedback

These do not have to be followed rigidly, but a general approach as follows is recommended:

- *Introduction*: background of outbreak, the setting, how it came to light.
- *Methods of investigation*: how you went about it. Include your questionnaire as an appendix. Use subheadings such as epidemiological, microbiological, environmental.
- *Results*: give a response rate for your questionnaire. Comment on non-responders. Give results in same order as above.
- *Discussion*: weigh the evidence. How good was the epidemiology? Does the microbiology support it? Do the environmental inspections explain how the outbreak occurred? Does it all hang together?
- *Conclusion and recommendations*: the crux of the report. Make the recommendations practical and relevant to the outbreak described. Do not take a high moral stance or overstate your case.

- *Lessons learnt*: it is a useful exercise to add a section on this at the end of any outbreak report. Even with experienced investigators there will always be lessons to be learnt from which others are also going to benefit. This is especially useful to document if there were some modifications that could have been made in the investigative methods.

Execute control and prevention measures

These measures will depend on the nature of the outbreak, its aetiology and mode of transmission. By reading about the infection beforehand you will know what measures are available or possible. These include:

- withdrawal of the food product, if the outbreak was caused by a widely distributed, manufactured product;
- instituting hygiene measures if the outbreak was spread by case-to-case or poor food-handling;
- treating or quarantining the carrier if one is found to be the cause (e.g. a person with open tuberculosis);
- use of immunoglobulin (rabies, hepatitis A, varicella);
- use of vaccine (hepatitis A, measles, varicella);
- use of antibiotic prophylaxis (meningococcal infection, streptococcal sore throat).

Prevention can be achieved by hygiene education and promotion and changes of policy.

Before you finish there are a few further issues about outbreaks which you need to address.

Why investigate outbreaks?

Particularly with a point source outbreak, it can be argued that it is not possible to curtail the outbreak, and that the source, whether it be a dish of roast chicken or a carrier of hepatitis A (who never carries for longer than a week or two), is no longer a threat.

First, it is possible to curtail many outbreaks. This applies particularly to outbreaks in which there is a continuing source (Rowe *et al.* 1987), or case-to-case transmission. For point source outbreaks, innocent food-handlers and others can often feel guilty, or be made to feel guilty, when they are not responsible. Moreover the fear of the unknown is considerable, and by finding a cause fear and accompanying panic are removed. Furthermore, there is always the opportunity to provide education in hygiene.

Second, sometimes a small outbreak can uncover a widespread problem, as with a contaminated foodstuff that is marketed widely. It can also stimulate effective preventive measures with legal backing. The widespread contamination of hens' eggs with *Salmonella enteritidis* prompted research into a vaccine for chickens, which has

been very effective in controlling this epidemic. It also encouraged a change in food-handling habits, such as the use of pasteurized liquid egg in catering and the avoidance of raw egg consumption.

Third, outbreaks are experiments in the natural history of an infection, and stimulate productive research. Information on dose responses, incubation periods, communicability and severity can be provided. They can also point to important problems. A review of food-borne outbreaks reported over a period of years showed that cross-contamination from raw to cooked food was the single most important food-handling lapse. This was useful in targeting preventive measures.

Fourth, outbreaks are often the first clue in the discovery of a new organism – in recent years, HIV, SARS and legionnaires' disease (and others) were discovered through outbreak investigations.

Finally, outbreaks nearly always fill in gaps in knowledge, whether it be about an organism, the way it spreads, the incubation period or the attack rates. Nevertheless, resources may not be available to investigate every outbreak, and choices may have to be made.

Importance of the laboratory

The importance of working in a partnership with a laboratory cannot be overemphasized. Environmental health departments are also often necessary to the investigating team. As stated earlier, epidemiological evidence may not constitute 'proof'. Nevertheless, epidemiological conviction can be strong. By identifying a cause, or narrowing the possibilities, the epidemiologist eases considerably the work of the microbiologist. On the other hand, not having a microbiological or clinical diagnosis can make the investigation of many outbreaks extremely difficult, if not impossible. The microbiologist also needs the epidemiologist. In a food-borne outbreak the food may no longer be available for testing, or it may not be technically possible in a routine laboratory to detect the organism in the food (e.g. hepatitis A). In the *Salmonella ealing* outbreak (Rowe *et al.* 1987) without the strong epidemiological evidence incriminating the powdered milk, not many laboratories would have persevered with examining several thousand cartons before finding the organism. Epidemiology has limitations also. An epidemiological approach would not work if, in a set meal, everyone at the table ate everything (this rarely happens).

Cohort and case-control studies

When analysing data obtained in a cohort or case-control study, ensure that you tabulate the data appropriately for the type of study. Take food poisoning as an example.

Activity 5.6

In an outbreak of food poisoning, draw the outlines (headings) for two tables, one for a cohort and the other for a case-control study. For the row headings you would list the different food items. What would you put as the headings for the columns?

Feedback

Your tables should look like Tables 5.1 and 5.2.

Table 5.1 Cohort study: food-specific attack rate

	People who ate specified food				*People who did not eat specified food*					
Food item	*Ill*	*Not ill*	*Total*	*Attack rate %*	*Ill*	*Not ill*	*Total*	*Attack rate %*	*Attributable risk*	*Relative risk*

Table 5.2 Case-control study: food preference rate

	Ill (case)				*Not Ill (control)*				*Odds ratio*
Food item	*Ate*	*Did not eat*	*Total*	*% ate*	*Ate*	*Did not eat*	*Total*	*% ate*	

A cohort study is more powerful because it can give you a food-specific attack rate, a relative risk and attributable risk. However, you need to know how many people were exposed and how many were not. The food-specific attack rate for any food item is calculated by dividing the number of people who ate the item and were ill by the total number who ate the item. Looking at the highest food-specific attack rates on their own will not necessarily tell you which is the culprit food – all it does is probably to tell you the most popular ones. If everyone drank water, the food-specific attack rate will be high in this group. But it will also be high in those who did not become ill (unless water caused the outbreak). So to obtain the risk you can attribute to eating the food, the control group – those who did not get ill – have to be considered. Calculate the attack rate in those who did not eat the food. Some people who did not eat the specific food item will become ill (there are nearly always a few). Subtract one from the other. This is, naturally, called the *attributable risk*. By dividing one by the other you obtain the *relative risk*. You can then do the appropriate significance tests (χ^2) and confidence limits.

A case-control study is less powerful because it gives you a food-specific *preference rate*. It tells you that of those who were ill, a number ate the food item, giving you a preference rate for those who were ill. By comparing this rate with that obtained with those who were not ill, the controls (the proportion or percentage of those who were not ill who ate the specific food item), you can find the most likely food. You can then work out the odds ratio as follows:

	Number ill	*Number not ill*
Number who ate food item	a	b
Number who did not eat food item	c	d

Odds ratio = ad/bc

Confounding in outbreak analyses

Imagine an outbreak caused by a meal. Among the dishes served were two or more foods that go together, such as fish and chips, curry and rice, strawberries and ice-cream. If only one of a pair of those items was contaminated, both items of the pair could be significant. This is because both items were eaten together by most people. By using more sophisticated statistical methods it is sometimes possible to incriminate one of those items. However, the statistical tests (notably Cochrane's test) are outside the scope of this book.

Summary

You have seen how investigating an outbreak is a logical process. Following this process will lead in many instances to a successful outcome. A basic knowledge of epidemiology and microbiology is essential. Teamwork is also essential and is discussed further in the next chapter, as experts in other disciplines may have to be consulted.

Investigating an outbreak can test all one's epidemiological skills, often at speed. There is rarely time available to clean data, and the careful interpretation of imperfect data is characteristic of the work of an infectious disease epidemiologist.

References

Gregg MB (1996) Conducting a field investigation, in MB Gregg (ed.) *Field Epidemiology*, pp. 44–59. Oxford University Press, Oxford. This focuses on a point source epidemic and demonstrates a systematic, basic approach.

O'Mahony M, Gooch CD, Smyth DA, Thrussell AJ, Bartlett CLR and Noah ND (1983) Epidemic hepatitis A from cockles, *Lancet*, I: 518–20.

Rowe B *et al*. (1987) Salmonella ealing infections associated with consumption of infant dried milk, *Lancet*, II: 900–3.

Ungchusak K (2002) Principles of outbreak investigation, in R Detels *et al*. (eds) *Oxford Textbook of Public Health*, 4th edn. Oxford University Press, Oxford. An account with a slightly broader classical approach.

Further reading

Goodman RA *et al*. (1990) The epidemiologic field investigation: science and judgment in public health practice, *American Journal of Epidemiology*, 132: 9–15. A thoughtful commentary on outbreak investigation.

Recommended journals that frequently feature papers on outbreaks include *Epidemiology and Infection* and *Emerging Infectious Diseases*. You are also recommended to consult the *HPA Communicable Disease Report* for England and Wales, the *Scottish Weekly Report* and the *Eurosurveillance Weekly and Quarterly*. Promed run a useful website at www.promedmail.org.

6 Management of an outbreak

Overview

In this chapter you will learn about the 'operations' part of investigating an outbreak: planning and management; setting up an incident room; communications; and information systems. There is some overlap between these activities.

Learning objectives

After studying this chapter you will be better able to:

- **explain the importance of planning in an investigation**
- **describe the importance of using the expertise of other professionals**
- **set up the right committees, staffed by the right people**
- **appreciate the value of organizing communications**
- **set up an incident room**

Introduction

Investigating an outbreak is like waging a war. Although the skill of the soldiers is important, the planning and management are crucial. Gathering and sifting information about the enemy, setting up an incident room and a multidisciplinary team with the requisite expertise, plus good communication with the public are essential.

Pre-planning is important. An organization responsible for an outbreak investigation would be wise to draw up an outbreak control plan, identifying the options for lead investigators and supporting staff, identifying in advance suitable premises and equipment for an incident room, and conducting simulation exercises to give practice and iron out problems.

You will use an outbreak of salmonella infection as an example, and at the same time revise some of the steps outlined in Chapter 4.

Activity 6.1

Your local surveillance system or public health laboratory has informed you that 16 cases of *Salmonella heidelberg* infection have occurred in your district of about 100,000 people in two months. What would be your first action?

Feedback

Ascertain if this is likely to be an outbreak. Look through the previous records to see how common *Salmonella heidelberg* is.

The records show that normally only one or two cases are reported a year in this population. The laboratory is not conducting a special survey on salmonellas, and have not changed their diagnostic methods.

To all intents and purposes this is an outbreak, though it would be wise to ensure (tactfully!) that it is not a laboratory error. Clearly you need not take steps to confirm the diagnosis, though further typing studies (molecular or phage type for example) may be necessary if the organism is a common one, and more samples may be needed later from any further cases.

Activity 6.2

Should this outbreak be investigated?

Feedback

An immediate answer could easily be that you do not know until you have investigated it! However, a decision has to be made. Other considerations apply, including what other outbreaks are occurring at this time, the extent of the time and resources available to you, the potential seriousness of the infection and what you can do about it. With a salmonella outbreak of this sort, whether caused by an ongoing (continuing) source of infection or case-to-case transmission, there is certainly potential to prevent further cases. Moreover the infection can be fatal, cases are still occurring (and at a rate far higher than normal for this salmonella), and the numbers may escalate. The outbreak may be due to a widely distributed foodstuff, which will have to be recalled and appropriate action taken with the manufacturer to ensure it does not happen again. There is little to be said for not investigating further.

Outbreak control team (OCT)

Outbreaks are invariably unexpected events and there is a need to act quickly. The purpose of the OCT is to coordinate the investigation and control of the outbreak: 'The team approach enables the integration of a variety of abilities and skills and coordination of the efforts of individuals, hopefully preventing the confusion and even conflict that might arise if they were working in isolation' (Mitchell 1998). In the absence of a higher level outbreak management group (OMG), this is the forum in which policy decisions are taken on further investigation and control measures.

The OCT are like the officers in the front line. They should undertake the following:

- epidemiology: conduct the necessary descriptive and analytical epidemiological studies (collection, analysis and interpretation of data);
- communication: communicate with government, other health departments and the public;
- specimens: organize collection of suitable specimens from humans, animals and the environment; in a salmonella outbreak this might include swabs from kitchen surfaces or ingredients that make up suspect foods, or imported foods distributed nationally;
- prevention: work with OMG in controlling the outbreak, both urgently and long-term;
- reports: producing regular interim reports and a final report.

The composition of the OCT depends on the circumstances. You do not want a large OCT at any time, and certainly not for a small outbreak. You also need to be flexible in case the outbreak escalates or turns out to be larger than anticipated. Moreover the composition of the OCT will be different if the outbreak is national or international rather than local. For professional expertise, an epidemiologist/public health specialist and a microbiologist are usually included. For a food poisoning outbreak, as in the salmonella example, an environmental health officer would be an important addition. For legionnaires' disease, plumbers or engineers could be considered. Entomologists, veterinary surgeons, clinicians and nurses may be appropriate for other types of outbreak. For outbreaks affecting the community, a press officer should be considered, as well as a representative of the management or government. Sometimes, when a foodstuff or water source is suspected, a representative from the appropriate commercial source is a useful addition to the team. The chairperson needs to be someone of experience with a sound knowledge of epidemiology and microbiology, and the requisite qualities of leadership, political acumen and efficient man management. The members should be sufficiently senior to take, or agree to, policy decisions on behalf of the agency that they are representing.

Activity 6.3

What would be the functions of the epidemiologist?

Feedback

The epidemiologist will,

- ensure a systematic epidemiological investigation of the outbreak is performed (see Chapter 5)
- supervise case-finding
- identify risk factors (by descriptive or analytical means), analyse and interpret the data
- identify interventions
- work with others to implement control measures that prevent further exposure and infection

A support team of field workers, statistical and/or information staff, as well as clerical staff to take and send messages, ensure records are up to date, and for general help, is often essential, as is a secretary to take minutes and ensure efficient communication. You may need to borrow staff from other districts, or ask for assistance from a central epidemiological unit in your country. Communicating with your central unit by telephone may be sufficient. The functions of the support team are to:

- assist with collection of epidemiological data by direct or telephone interviews, assist with case-finding and data entry;
- staff the helpline, including giving clear advice to the public;
- organize samples (food, environmental, clinical specimens) as requested by the OCT, ensuring they are sent to the appropriate laboratory, and that the results are correctly entered and communicated to the OCT;
- conduct other routine tasks such as giving prophylaxis, vaccines or immunoglobulin to contacts.

Outbreak management group (OMG)

For large national or international outbreaks, a higher tier responsible for the OCT, an OMG, may be necessary. They would meet less regularly than the OCT, who would have to report to them.

The purpose of the OMG is to act as a senior responsible group to oversee or direct the OCT, and to ensure teamworking. An OMG is usually only necessary for large complex outbreaks crossing district, regional or international boundaries. For the *Salmonella heidelberg* example used here, confined so far to one district, an OCT in contact with a central national epidemiological unit is probably sufficient. In this event, the responsibilities outlined below could be assigned to the OCT. The OMG should:

- agree a plan of action for the epidemiological and microbiological investigation and control measures;
- commit the appropriate amount of resources to the OCT;
- decide on a communication strategy.

The composition of an OMG will depend on local circumstances. A senior epidemiologist and/or microbiologist experienced in the investigation and management of outbreaks are useful members. A senior manager or health official from the Ministry of Health or equivalent may have a part to play. The epidemiologist is important in the overall planning and in making decisions about analytical studies. The microbiologist has to decide on the number and type of specimens to take, and the tests necessary. If a nationally- or internationally-distributed foodstuff is involved, official action must be taken through the senior manager. If large amounts of vaccine or drug have to be used or authorized, official sanction may be required. The OMG decides, in consultation with the OCT whenever possible, what urgent preventative action should be taken. In an outbreak of legionnaires' disease, for example, several cooling towers in a vicinity may have to be disinfected until the epidemiology has been clarified. In the salmonella outbreak, if a food or shop is suspected, appropriate action to stop further distribution of the food or closure of the shop may be required. The three-tier system is outlined in Figure 6.1.

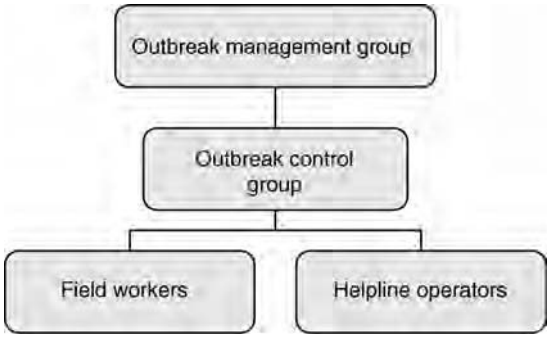

Figure 6.1 Model organizational structure for outbreak management
Source: Mitchell (1998)

Setting up an incident room

An incident room is expensive, so the size, severity and extent of the outbreak are important. If extensive retrospective case-finding still has to be done, and you are relying on members of the public to phone in, or cases are still expected and you need to identify them, and there is considerable press and political interest, an incident room may be essential. For the salmonella outbreak with 16 cases initially confined to one district, an incident room is probably *not* justified, even if the outbreak was found to be somewhat more widely distributed than expected. If the cause was suspected to be milk, water or other similar vehicle distributed nationally, and cases were being reported from a wider area, an incident room may be necessary. The following criteria are a useful guide for when to institute an incident room:

- serious outbreaks: in judging the seriousness of an outbreak, take into account the urgency of the problem, the number of people involved or at risk, the seriousness of the infection, how infectious it is, and how widespread it is – or is likely to be;
- major outbreaks in hospitals;
- high-profile outbreaks, including those likely to worry the public.

Examples of incidents that could justify setting up an incident room include:

- one case of toxigenic diphtheria in contact with several members of the public;
- a case of rabies in a dog known to have been 'friendly' to several members of the public;
- a patient with SARS who stayed in a hotel and used the public rooms and lifts extensively;
- a practising surgeon found to be HIV-positive or a high-risk carrier of hepatitis B;
- legionnaires' disease caused by a cooling tower or air conditioning system in a hospital or other public building;
- an outbreak of hepatitis A or E caused by a public water supply;
- a contaminated foodstuff such as chocolate, salami or powdered milk distributed widely throughout the country;

- an outbreak of norovirus gastroenteritis or MRSA affecting several wards of a hospital over some months.

Activity 6.4

Using the three suggested criteria for justifying an incident room, classify each of the above.

Feedback

You will find that several of the above have two of the three criteria. All of them are either serious or major, and most of them could be, or could become, high profile – such as the surgeon who is a high-risk hepatitis B carrier.

A room must be dedicated solely to this purpose for the duration and must obviously be accessible to all staff expected to work in it. It is helpful to have other rooms available close by for interviews and other uses. Size is important, because if the outbreak turns out to be much larger than anticipated there may be need for expansion. The OCT must be on a health authority site, but separate enough not to be subject to distraction from or to other workers. Accessibility also means that it should be available over longer than normal times, 24 hours a day if appropriate (especially for outbreaks involving several countries). It must be capable of being secured against intruders both while occupied and when not.

Inside, it needs to have telephone and fax lines, with the facilities to increase the number available if necessary; sufficient computer lines not only for access to emails and the internet, but also for collection and analysis of the data. There should be adequate space, including tables, chairs and wall space for an incident board and for messages and other important papers. Toilets and coffee-making facilities must be close by. As it may be difficult to find and organize such a room at short notice, health authorities should identify suitable accommodation for this purpose in advance which can be vacated and equipped quickly in an emergency.

Someone has to be placed in charge. This does not have to be the leader of the OCT – it is probably better not to, and a competent unflappable manager may be a good choice. He or she would be responsible for the daily running of the room, including ensuring adequate furniture, supplies of stationery, working phones, adequate IT backup, a rota system for clerical staff to man the phones, record information/incoming calls, facilitate communication, and everything else from encouraging good relations and teamwork to ensuring supplies of hot and cold drinks, fast food if staff cannot be spared from their desks, to toilet facilities. Computer support, including emergency support such as for a computer system breaking down and backing up the information as it comes in, is essential.

Communications strategy

Activity 6.5

What would be the purpose of a communications strategy, using appropriate information systems? Think of good communications as 'internal' and 'external'.

Feedback

Internally, between the members of the OCT and between the OCT and the OMG. Both teams need to know what is going on and who is doing what. The leaders of each team should ensure this. Electronic communication using emails has made this much easier. Externally, local government, politicians, local GPs and hospital doctors and commercial interests, may have to be kept informed. Not least, the needs of the media and members of the public (both those affected by the outbreak and others) may have to be satisfied. Other bodies, such as schools and the police, may need to be involved. For larger or high-profile outbreaks a professional press/public relations officer (PRO) is generally useful.

The point of setting up an incident room is to ensure good internal and external communication. Dealing with the media and public can be tricky. A balance has to be struck between being too alarmist and underplaying the severity and extent of the outbreak. Conflicting statements must be avoided. The experience of a PRO in drawing up appropriately-worded press statements at appropriate times can be indispensable. Moreover, such a person can remove the burden from those who are better qualified to investigate, and will ensure consistency in the messages emanating from the incident room or investigative teams. The often complex lines of communication necessary for the successful management of an outbreak are summarized in Figure 6.2.

Information systems

Activity 6.6

What are the essential characteristics of any outbreak data and information?

Feedback

The essentials include:

- accuracy
- consistency
- freedom from bias
- confidentiality
- security
- accessibility

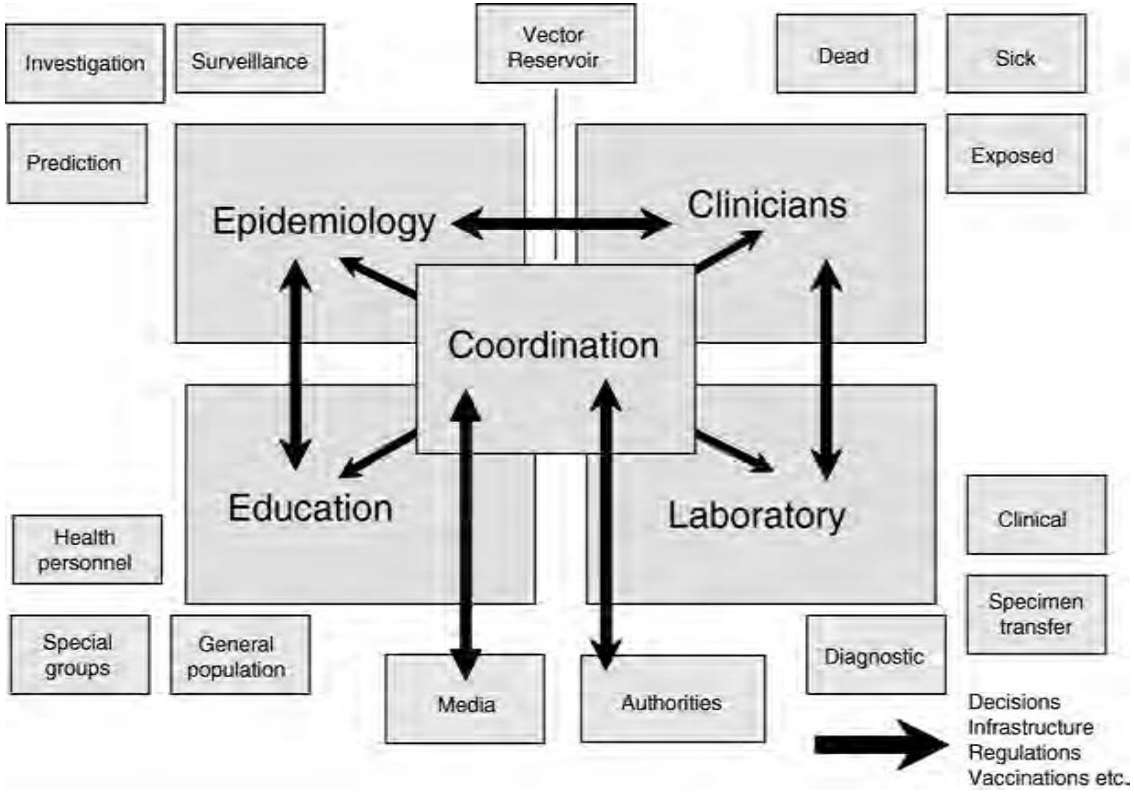

Figure 6.2 Lines of coordination for successful management of an outbreak

Source: Ryan (personal communication)

Chaos can only be avoided by collecting information in a standard form. A questionnaire must be drawn up by the OCT. This can be on paper or computer. It must be applied to all cases and controls without fail. Obtaining contact details of every caller so that you can go back to them for missing or extra information is essential. Training the interviewers, even if it takes only a few minutes in an emergency situation, is critical. The information they collect must not only be accurate but must also be collected so as not to suggest or prompt answers. As with all epidemiological interviews, interviewers must be unbiased. Confidentiality must be respected and authorities should ask all staff to sign a confidentiality document. However, emails, faxes and mobile phones are no longer secure and care has to be taken when using these forms of communication.

The information should be collected in an easily analysable and accessible form. Lists of cases must be updated regularly. A standard web of communication for the flow of information is critical. Adding the results of any microbiological investigations on cases, food or the environment should be simplified – accuracy here is particularly essential. Using computers for running an information system has made life easier for investigators. Desktop computers or laptops can be used and the software should enable running a database, word processing, analysing data, as well as providing a statistical and a graphics package, with facilities for emails and printouts.

All minutes, paper results of laboratory investigations, letters, questionnaires, reports, press statements and other papers relating to the outbreak must be kept safely and securely in a master file. Litigation following an outbreak is becoming common, hence the need not only for the master file, but also for accuracy in recording all information and phone calls.

An outbreak may come to light in a number of ways:

- *Surveillance/notifications*: in a country with a well-organized infrastructure, and a sensitive surveillance system, outbreaks often come to light through routine reporting of data. Thus, for *Salmonella heidelberg*, in this particular district, only two or three infections were reported yearly, so 16 cases in two months was distinctly unusual, and denoted an outbreak unless proved otherwise.
- *Laboratory*: if most of these previously rare salmonellas had been isolated in one laboratory, the outbreak could have been recognized in this way. Laboratories often notice that a particular age group or small geographical area is involved.
- *Media*: sometimes cases are reported in a local or national newspaper. These tend to be clinical, and often a source is mentioned, such as a wedding.
- *Local government*: sometimes a member of the public, usually someone who has been affected and suspects a particular food outlet, will telephone the local government offices.
- *Family doctor*: GPs occasionally telephone their suspicions of an outbreak, if cases happen to present to one practice.

Summary

You have learnt how the investigation of an outbreak requires management as well as scientific skills. Teamwork with other disciplines and clear lines of responsibility are essential. Communication both within the investigative team and outside it

should be organized and consistent. Information collection and analysis should be accurate and unbiased, and should make use, where possible, of computers and appropriate software.

Reference

Mitchell E (1998) Setting up an incident room, in ND Noah and M Mahony (eds) *Communicable Disease: Epidemiology and Control*. John Wiley & Sons, Chichester.

7 Analytical approaches to outbreaks

Overview

In this chapter you will learn the importance of integrating your knowledge of the epidemiology, microbiology and ecology of a disease when investigating and controlling an outbreak. Although it mostly uses hepatitis A as an example, it is not primarily about hepatitis A. Nevertheless you will learn something about this important infection at the same time.

Learning objectives

After studying this chapter you will be better able to:

- **explain how to approach the epidemiological investigation of an outbreak**
- **appreciate the importance of integrating a sound knowledge of basic microbiology and ecology with epidemiology in an investigation**
- **appreciate how a logical approach can help to find the cause of an outbreak**
- **analyse epidemiological exposure tables and graphs of outbreaks**

Key terms

Fomites Inanimate materials which are likely to carry infection.

Hepatitis An inflammation of the liver, caused by a variety of agents, including chemicals and viruses.

Three cases of hepatitis A on a ferry

Consider the following scenario. Three cases of hepatitis A occurred during April and May (1 and 20 April and 20 May) in the crew of a large ferry boat which makes several trips every day. It is now mid-June. The diagnosis was confirmed in all three cases. You can assume that three cases of hepatitis A in this setting is unusual and that this is an outbreak. Although none of them was a food-handler, there is some concern as to whether passengers have been infected.

Activity 7.1

What do you do first?

Feedback

Before investigating any outbreak, it is a good plan to do background reading, including some recently published review papers if possible.

Ten important facts about hepatitis A for an epidemiologist to know when investigating an outbreak of hepatitis A are shown in Table 7.1. A virus does not of course grow on food. It is not yet possible routinely to identify the organism in food so one has to rely heavily on epidemiology to investigate outbreaks.

Table 7.1 Ten important facts about hepatitis A for the Epidemiologist

1	A very small dose is required for infection.
2	Route of spread is virtually always faecal-oral.
3	The incubation period is 15–40 days, median of 28 days.
4	The minimum incubation period (15 days) is shorter than the spread (range, 25 days) of incubation periods.
5	Patients are at their most infectious while asymptomatic (before the illness). By the time jaundice appears they are usually no longer infectious.
6	Asymptomatic infections are common, especially in the young.
7	Asymptomatic cases are infectious.
8	There are no chronic carriers of hepatitis A virus.
9	Second infections are unknown – immunity seems to be permanent.
10	The organism is hardy and can survive on surfaces, in water and at freezing temperatures.

Activity 7.2

1 From the list in Table 7.1, what thoughts do you have on this outbreak? Is this part of a large point source outbreak affecting passengers as well? Is it likely to escalate? Are the passengers at risk, and do you need to contact all passengers who have sailed on this ship in case they have had, or are at risk of having, hepatitis A. If so what date limits would you set?

2 How can you tell almost from this extremely early stage what type of outbreak this is? (Think this through – the answers are there, among the ten important facts.)

Feedback

1 First, its high infectivity (small dose) means that people get it not only from food but by transmission from person to person. This may not always be direct – it can spread from contaminated fomites such as toilet door handles and taps. The high resistance of

the virus will make this even more likely to happen. So, this could be a propagated or case-to-case outbreak.

2 By checking the incubation period: 15–40 days (spread 25 days). The spread of these three dates of onset is across 50 days, so this cannot possibly be a point source outbreak. It must be either a continuing source or case-to-case transmission. It could be a continuing source but this seems unlikely with three single cases spread over almost seven weeks. Case-to-case transmission however seems to fit neatly. There is a gap of 20 days between cases 1 and 2, and 28 days between cases 2 and 3. Both these intervals are well within the range of incubation periods.

Now you know what type of outbreak it is, you have less reason to worry about a food-borne incident affecting a large number of passengers. Instead you have a hygiene problem on board a ship. These can be more difficult to control, especially if case-to-case transmission occurs in a setting in which improving hygiene is going to be difficult – such as a psychogeriatric ward of a hospital or a school for children with special needs. But you can dispel fears of a major outbreak, and concentrate on the ship. You can elicit histories from the three affected crew, inspect the ship, do case-finding (among the crew only), and from the histories and inspection find and deal with the most likely method or methods by which infection was transmitted. The first case may well have been food-borne, though you are unlikely to be able to show this. Unless the three have had some sexual or other direct contact with each other, the most likely outcome is that you will find some serious lapses in hygiene on board ship, with perhaps dirty ill-equipped toilets that crew members, including the affected three, used. Appropriate hygiene measures will need to be instigated.

Activity 7.3

It is still possible that some passengers may have been infected. What should you do about this? Give your reasons.

Feedback

Probably do nothing. First, available evidence is that infection was confined to crew who have their own accommodation (toilets, eating space, lockers, lounges).

Second, case-finding in the absence of any reports of illness among passengers could create panic; moreover the disease is self-limiting, rarely fatal, and there are no permanent carriers.

Third, none of those affected was a food-handler, and even if one was, it is unlikely that much would be gained on the off-chance that a foodstuff was contaminated and served without cooking to a passenger.

In practice, no cases came to light among passengers. The toilet used by the crew was filthy, there was no soap and a damp roller towel was used. Hygiene measures were introduced, with soap and disposable towels. No more cases occurred.

An outbreak of hepatitis A in a small town

The incubation period is critical in several ways. Let us move the scenario from a ship to a small town where an outbreak of hepatitis A has undoubtedly occurred. Assume the diagnosis was confirmed.

Activity 7.4

After case-finding, the pattern of the outbreak by date of onset is shown in Figure 7.1. What are your conclusions about this outbreak?

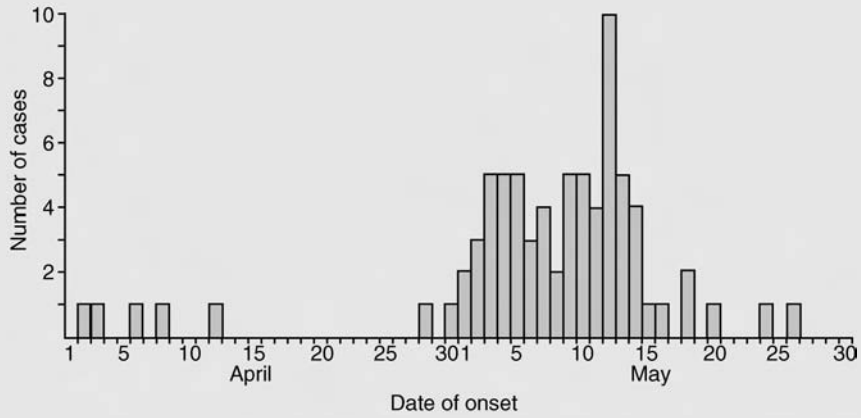

Figure 7.1 Outbreak of hepatitis A in a small town

Source: Schoenbaum and Jezek (1976)

Feedback

First, you should have noted that the dates of onset have been plotted by day. Even for a disease with a long incubation period, it is often better to plot by the shortest time period (i.e. days not weeks). You will get a much better feel for an outbreak of this sort. Second, you should have decided whether this is a point source outbreak or not. If you ignore, for the moment, the first few sporadic cases (those occurring in early April), it looks like a point source.

You can calculate the spread of incubation periods for hepatitis A. 'Spread' is another useful concept to work with. An incubation period of 15–40 days equals a

spread of 25 days. Look at the first case of the main cluster of cases on the graph. This occurred on 28 April. By 25 days later, all but two cases had occurred, and these two were only just outside the 25-day spread. This strongly suggests a point source outbreak.

Note that the spread of 25 days is somewhat longer than the shortest incubation period of 15 days (fact 4 of the ten facts). Why is this important? It means that you can already be getting secondary cases from the earliest cases before the spread period from the point source is over. This is an important point to remember especially when you analyse case-to-case outbreaks. Thus in Figure 7.1, the cases with onset on 24 and 26 May could have been infected by contact with the earliest cases (in fact even those up to 9 May), 15 days earlier. So the cases on 24 and 26 May could be:

- not part of the point source outbreak but secondary cases;
- perhaps slightly wrong in estimating their dates of onset;
- because the point source was acting as a source for more than one day.

It is also important to note that some of the later cases, even though within the 25-day spread period, may have been secondarily infected by some of the earliest cases. However, the most likely hypothesis by far is that all cases from 28 April to 20 May, and probably to 26 May, were exposed to a point source.

Since the lowest incubation period is 15 days, and the first case of the cluster occurred on 28 April, the exposure could not have occurred *after* 13 April. The last case of the cluster is a little more difficult as we cannot be certain when this was. If you take the 20 May case, and go back 40 days, you can say that the exposure could not have occurred *before* 10 April. Thus you have a window of 10–13 April and you see that there was indeed a case notified within that period. (If you take the 26 May case as the last case, and go back 40 days from this, you get to 14 April, which gives 13–14 April as the exposure dates.) In this type of situation the median incubation period is useful because it does not depend so much on the dates of the first or last cases. A median incubation period of 28 days from the middle case, which occurred on 9 May, leads to 11 April. So everything points to 10–13 April. There was no large dinner or gathering involving the town on those dates.

Activity 7.5

A patient with hepatitis A was notified on 12 April. Discreet enquiries revealed that she was a young woman who served hamburgers in a local fast food outlet. What do you do now?

Feedback

The evidence is entirely circumstantial. If your hypothesis that she caused the outbreak turns out to be wrong, there will be problems. Instead analyse the epidemiological evidence and see if the hamburger outlet or other source is implicated. As you have a point source outbreak to work with, this should be possible.

You should first undertake a descriptive study. The investigators found that about two thirds of those affected were children so they focused on the schools. Most cases came from one school. Analysis of the ages of those affected in this school showed that nearly all were in the older age groups who were allowed out for lunch. So the investigators then went out of the school system and analysed the lunch habits of affected adults and children. They found that drinking water or buying from a hamburger shop and a bakery were the most common lunch activities among those affected. However, all this means is that drinking water and visiting these two food shops for lunch were the most popular activities among those affected.

It is time now for an analytical study. Analysis of unaffected controls, matched for age and in the same school and matched unaffected adult controls showed that water and the hamburger shop were equally popular, but not the bakery. Thus the bakery was suspected and the association with the bakery was statistically significant.

Ideally a questionnaire analysing the foods eaten at the bakery should have included controls but in this instance nearly all those affected had eaten two types of bakery product, both of them with a sugar glazing (made from icing sugar and water). The glazing was added after baking (i.e. it was not cooked). The 'glazer' had had an illness with dark urine and pale stools around 10 April but had continued to work throughout. Thus although he was symptomatic he had not been reported as he had not visited his doctor. Not all cases are notified by doctors, so even if he had sought medical care he may not have been shown on the graph. He mixed the glaze by hand and often, in the interests of economy, used leftover glaze on subsequent days. The server in the hamburger shop was innocent and must have acquired her hepatitis elsewhere.

Activity 7.6

What would you now do about the man who was still working in the bakery, and why? You may want to look at the ten important facts about hepatitis A above.

Feedback

You do not sack him or remove him from his job as he is no longer infectious. He cannot be a chronic carrier of hepatitis A because they do not exist. He is now immune and will not spread hepatitis A again. He needs some training in hygiene, but note that it does not necessarily follow that his or any food-handler's hygiene was poor – at least not for an illness in which many million infectious particles are excreted per gram of stool and only a few are enough to infect. Hepatitis A virus is highly infectious and no one has shown that proper washing of hands after defaecation will remove all infectious particles. This does not mean that it must not be done, but some viruses may well remain for some time even after thorough washing.

A village outbreak of hepatitis A

Activity 7.7

Examine Figure 7.2. What type of outbreak is this?

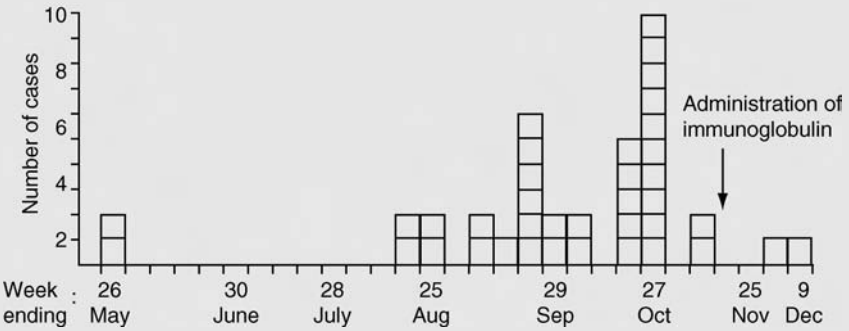

Figure 7.2 Village outbreak of hepatitis A: onset by week of cases

Feedback

This is a case-to-case outbreak because if you look at the spread of cases in the main part of the outbreak, from week ending 18 August to week ending 9 December, the gap is 17 weeks, which is considerably more than the 25 days of one incubation period for hepatitis A. It could be a continuing food source eaten intermittently by a small number of people only but this looks unlikely.

The outbreak took place in a village with about 600 people and a primary school. Cases were mainly in young adults up to about 45 years of age but there were also a few children. The first two cases were in children and occurred in the week ending 26 May. Forty days after this takes you to the week ending 7 July and no cases occurred up to this date, or even (just) up to a further 40-day cycle after this. If you use the median incubation period of 28–30 days, it becomes clear that there were at least two case-free cycles after the two primary cases.

Activity 7.8

How do you explain the long gap between the two cases on week ending 26 May and the outbreak starting on week ending 18 August?

Feedback

There are two possibilities. Maybe there was no connection between the index cases and the rest of the outbreak. More likely however, there was. Look again at Table 7.1, and point 5 in particular. Children are more likely to be asymptomatic but can still be infectious. So it is quite likely that there were some asymptomatic cases during the early part of the summer holiday. The only way to find out would be to do IgM tests on saliva, which would uncover infections that have occurred within the last three months.

Activity 7.9

What would you gain by asking for IgM for hepatitis A on saliva samples from the whole village?

Feedback

Very little – it would be 'over the top'. There are no chronic carriers of hepatitis A and finding one or two people who had asymptomatic infections some time in June and July, and who are no longer infectious, is not useful.

The two index cases in May probably infected others – presumably children who had mild or symptomless infections but then infected others. As there are more than two incubation periods between the primary cases and the rest, this probably happened at least twice. The probability is that several people were infected during this period, which accounted for the outbreak beginning in mid-August. Then case-to-case transmission continued in earnest and in several directions until the administration of immunoglobulin stopped it. (Now you would use hepatitis A vaccine as well.)

As case-to-case transmission is occurring, this is a village with a hygiene problem. There is no point in chasing a food point source, or innocent food-handlers. There is also little point in trying to go back and ascertain who infected whom, especially as infection can be spread by fomites and not always by direct contact. Think of a fishing net below the surface of a body of water, being held horizontally by buoys. You can't see what there is under the surface of the water – these are the asymptomatic or unreported infections. However, some symptomatic cases occur – the buoys – but you still can't see the connections these buoys have beneath the surface. Your management must be on hygiene, supplemented by immunoglobulin and hepatitis A vaccine as appropriate. That this is a case-to-case outbreak should be apparent early by plotting the dates of onset. Your investigation and management must be directed accordingly. This is a similar situation to that described above with the three cases on board ship.

An outbreak of legionnaires' disease

Activity 7.10

Re-read about legionnaires' disease in Chapter 3. Make a list of the facts that you think are important for an epidemiologist. Examine Figure 7.3. What type of outbreak is this and why?

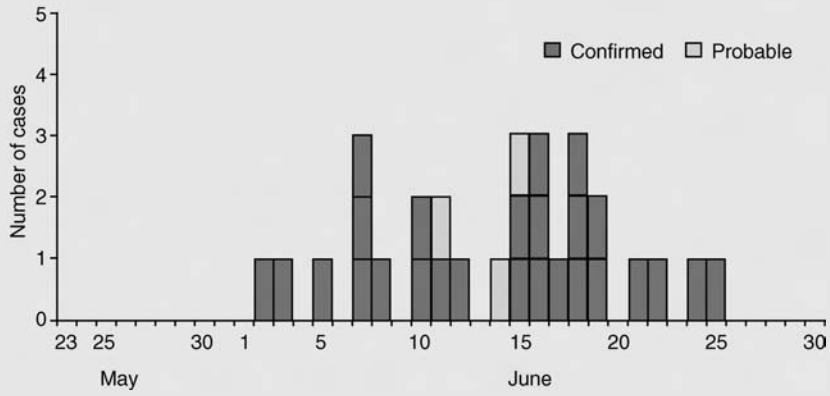

Figure 7.3 Epidemic curve, legionnaires' disease outbreak, Zaragoza, Spain, May–June 2004
Source: Pérez de Ágreda (2004)

Feedback

This is not a case-to-case outbreak caused by the cases that occurred on 2/3 June. Two important facts about legionnaires' disease are the incubation period and the mode of transmission. Legionnaires' disease is not transmissible from person to person so this cannot be a case-to-case outbreak. Since the incubation period is two to ten days, commonly five to six days, it's not ideal for a case-to-case outbreak anyway, as most clusters here are only one day apart. In legionnaires' disease the mode of transmission is usually from one external environmental source such as air-conditioning cooling towers, showers and cold and warm water taps. In fact this is a continuing source outbreak: two cooling towers in a hospital were contaminated and spreading the organism to vulnerable patients over a length of time. The maximum length of time during which the cooling towers could have been transmitting, using maximum and minimum incubation periods of ten and two days was 23 May to 23 June, a period of 31 days.

Activity 7.11

For further practice, here are four graphs of dates of onset for outbreaks. For each, decide whether it is a case-to-case, continuing source or point source outbreak, and why.

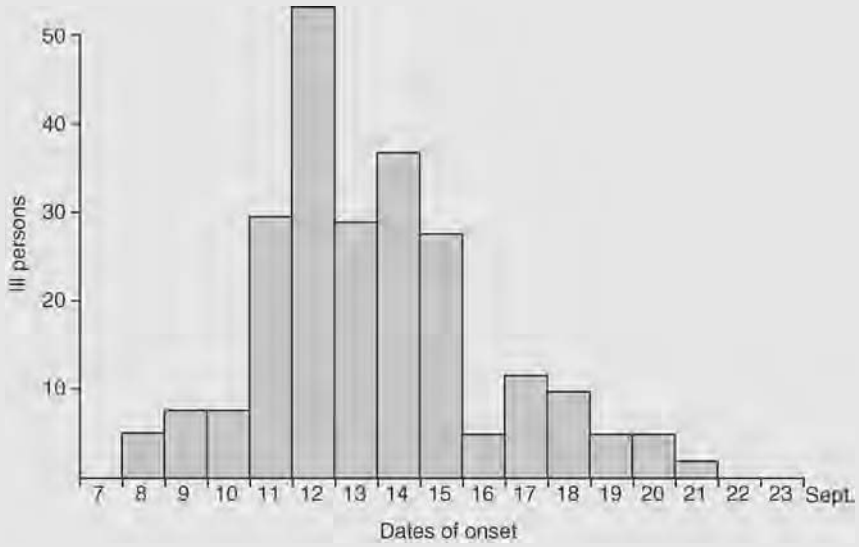

Figure 7.4 Outbreak of gastroenteritis on board ship
Source: O'Mahony *et al.* (1986)

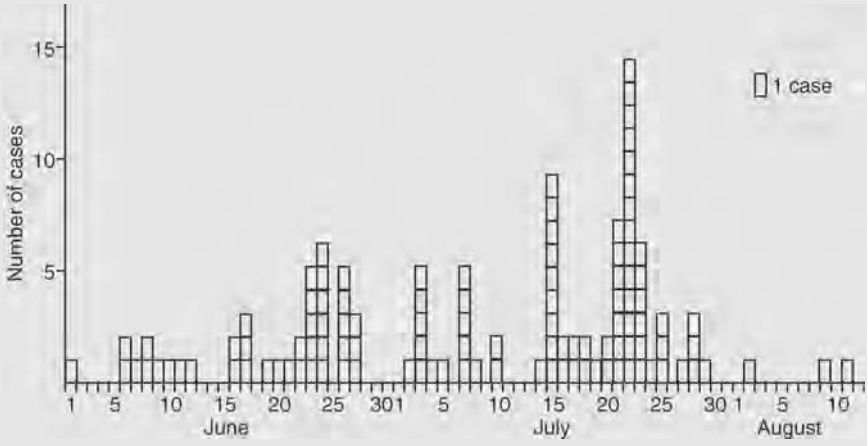

Figure 7.5 Shigellosis outbreak in a village

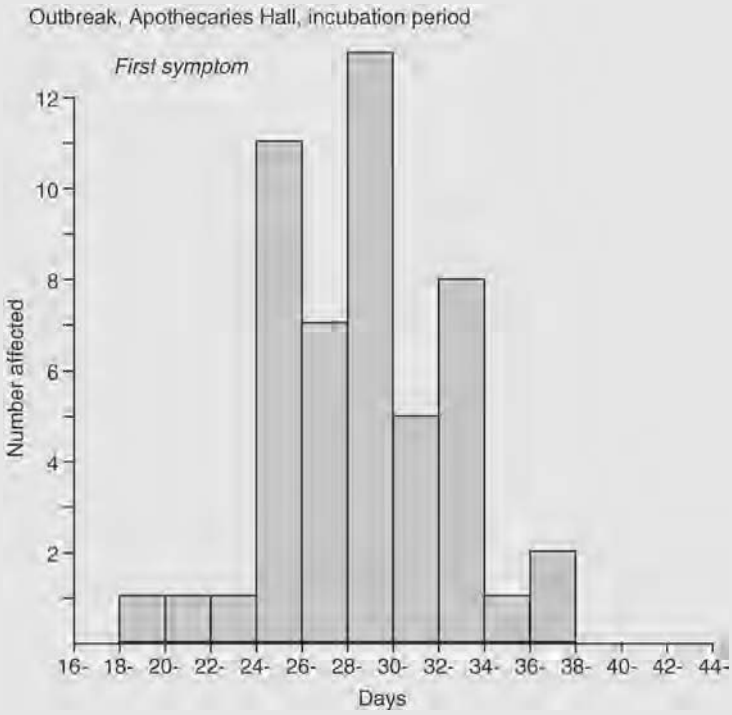

Figure 7.6 Outbreak of hepatitis A – dates of onset

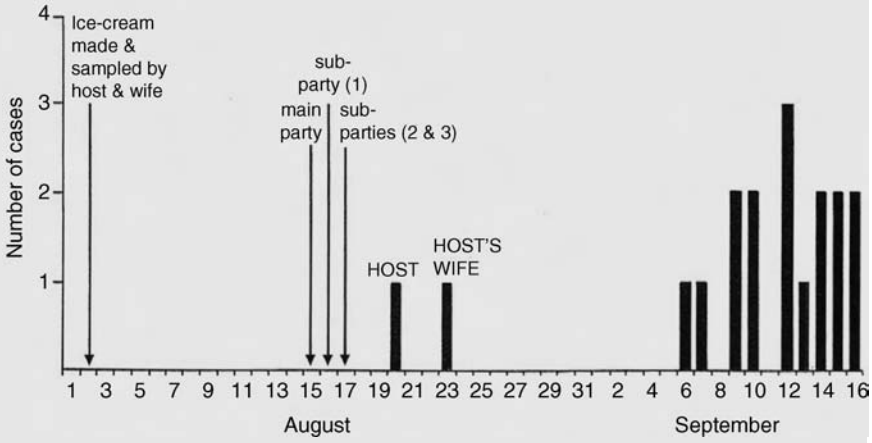

Figure 7.7 Hepatitis A outbreak among friends and family – sequence of events and dates of onset

Feedback

1 The outbreak on board ship looks like a point source, but is in fact a continuing source, with possibly some case-to-case transmission as well. Most causes of gastroenteritis have incubation periods of less than three days, so this couldn't possibly have been a point source outbreak. The reason for suspecting that there was some case-to-case transmission as well is that there was a 'tail' to the outbreak.

2 Again, look up the incubation period first. For shigella it is about one to three days. It is a low-dose organism, and this is a straightforward case-to-case outbreak. Focus on hygiene, though in communities where this type of outbreak occurs, this is not always easy to do.

3 As the incubation period for hepatitis A is 15–40 days this is a classic point source outbreak. You can calculate on which date the median case fell and find that this was exactly on the 28th day. This outbreak followed a dinner for a group of doctors in London. A batch of frozen raspberries puréed with cream and sugar was responsible.

4 This outbreak was caused by some home-made ice-cream which happened to use the same batch of contaminated bought frozen raspberries. When the host and his wife sampled the ice-cream they became infected and developed hepatitis A 18 and 21 days later respectively. The guests were served on 15 August as was some leftover food on 16 and 17 August. The guests who developed hepatitis A did so between 22–24 and 32–34 days later. The raspberries (Figures 7.6 and 7.7) had been picked and contaminated two years earlier and had survived freezing for this time.

Summary

In any outbreak investigation, first try and obtain some background about the infection. Make a list of, or learn, the facts about the infection that are most likely to be useful to the epidemiologist. Analyse each outbreak carefully by time because doing this will give you some vital clues about the type of outbreak and how to manage it. You may sometimes have to revise your initial assessment, so flexibility is important. Determining as early as possible the type of outbreak – point-source, case-to-case or continuity source – is essential as management is different in each of these situations.

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SECTION 3

Vaccines

8 Assessing need for immunization

Overview

This chapter explains the background to immunization and the need for a rational strategy before setting up a vaccination programme. The importance of an epidemiological approach is emphasized.

Learning objectives

After studying this chapter you will be better able to:

- **explain why before implementing a vaccine programme the need for it has to be assessed**
- **assess need**
- **describe the steps in implementing a vaccine programme**
- **monitor the vaccine after it is in place**

Key terms

Operational (technical, productive) efficiency Using only the minimum necessary resources to finance, purchase and deliver a particular activity or set of activities (ie avoiding waste).

Vaccine effectiveness The final outcome of a vaccine programme in controlling a disease, dependent on uptake and efficacy.

Vaccine efficacy (VE) The protective rate of a vaccine – per cent protected by the vaccine if 100 per cent uptake.

Introduction

Together with sanitation, vaccines are the most effective method of disease prevention available today. Epidemiology is essential to the proper implementation and use of vaccines.

Activity 8.1

What are the stages in the implementation of a vaccine strategy?

Feedback

You need first to assess whether a disease is sufficiently important to warrant the use of a vaccine. The efficacy and safety of a vaccine then needs to be assessed, the best strategy determined and the outcome monitored. Put simply:

> How severe is the infection? How good is the vaccine? How do we use it? How well is it doing?

How severe is the infection?

In other words, do we need a vaccine for it? Essential here is surveillance, supplemented by surveys if necessary. Questions to answer are: how common is the disease, what ages and populations are mainly affected, what are the rates of complications, hospitalizations, deaths? Seasonal or secular patterns may influence timing of any mass vaccination strategy or campaign. Geographical distribution may also be relevant in determining strategy. Costing studies are important even at this stage.

How good is the vaccine?

Planned epidemiological cohort studies are needed to establish how effective the vaccine is, the duration of efficacy and what side-effects there are. These are described in greater detail below.

How do we use it?

What is the best strategy – mass or selective vaccination? If selective, who to give it to? If mass, what age groups, how many doses how long apart including the need for booster doses? Do we aim for containment, elimination or eradication? Modelling studies are useful.

How well is it doing?

Surveillance of vaccine usage does not stop with implementation of a strategy. Indeed it could be argued that it becomes even more important. Uptake, efficacy, duration of protection and side-effects need to be monitored continuously. Side-effects not apparent even after properly conducted randomized controlled trials may come to light in the post-implementation phase. Surveillance for revealing such problems is essential, supplemented as necessary by special surveys, case-control or cohort studies.

The logical approach outlined above has rarely been followed in the past, mainly because of the lack of good surveillance systems and the availability of personnel to conduct such detailed surveillance – and perhaps an appreciation of the need for

pre-vaccine assessment and post-implementation surveillance. Many high income countries now have surveillance systems sophisticated enough to work at all these levels.

Surveillance for assessment of vaccine need

Measles

Before mass immunization for measles was introduced into England and Wales in 1968, a study based on notifications (Miller 1964) made the following estimates:

- hospital admission rate 1 per cent;
- respiratory and otitis media complication rate 6–9 per cent;
- neurological complication rate 0.7 per cent.

The main neurological complication was encephalitis which caused death or permanent brain damage.

Activity 8.2

On the basis of these data alone would you consider mass vaccination worthwhile? (You may find it helpful to review the material on measles in Chapter 4.)

Feedback

Before you answer this question, you need a denominator – use the number of cases of measles each year. You may also wish to have the annual number of live births. With about 400,000 notifications of measles each year, varying from 200,000 to 800,000 (see Figure 4.7), especially bearing in mind that notifications would not be complete, and could be only 50–70 per cent, this is a large number of cases. Indeed, as about 700,000 children were born annually at that time, nearly all children would expect to get measles at an early age. Accepting 400,000 for the purposes of this exercise, these data suggest 4000 hospital admissions, 24,000–32,000 respiratory or middle ear infections and 2800 cases of encephalitis, most of them causing severe permanent brain damage and death, every year in England and Wales alone. Estimates of subacute sclerosing panencephalitis (SSPE) were not attempted: generally accepted rates of 1–5 per million would have accounted for a further two or three cases of a highly distressing fatal complication of measles. These estimates would almost double if we assumed that nearly all children get measles early in life. Measles itself is a miserable disease, causing children to lose several days from school, and their parents several days off work to look after them. On this basis, mass immunization against measles is eminently worthwhile.

Interestingly, a further study by Miller (1978), done after mass immunization was introduced, showed that, although the incidence rates had fallen with mass vaccination, the complication rates had changed little. This reinforces the point

made in Chapter 4 that many vaccines will not by themselves usually alter the case-fatality rate, but bringing down the incidence rate will reduce the total mortality as well as the number of serious complications requiring expensive treatment and perhaps lifelong health care.

Haemophilus influenzae meningitis

Consider the following abstract from a paper (Trollfors *et al.* 1983): 'Four hundred and seventy cases of meningitis caused by *Haemophilus influenzae* in children and 30 cases in adults were identified in Sweden between 1981 and 1983. The age specific incidence in the most susceptible age group (0–4 years) was 31/100,000/year (440 cases), which is higher than previously reported from Europe. A further 30 cases were seen in children aged 5–14. The risk of developing *H. influenzae* meningitis before the age of 15 was 1 in 669'.

For most countries, an incidence of 31/100,000/year of invasive *H. influenzae* infections in children aged 0–4 is high, and this seems to be high even for Europe (though it may be due to more complete surveillance in Sweden). The risk for developing the disease before age 15 is also high.

Activity 8.3

It seems to be a significant burden but what else do you need to know?

Feedback

Some information on the severity and cost of the disease.

The abstract continues: 'There were 11 deaths (2%) and five cases of serious neurological sequelae among the children. Only 18 children (4%) had predisposing diseases. All but one of the 294 strains of *H. influenzae* from children that had been serotyped were type b. Infections in adults differed from infections in children. Five of the adults died (17%), 12 had important predisposing diseases, and at least six of the infections were caused by non-typable strains. It is concluded that research into the prevention of invasive *H. influenzae* infections in children should have high priority'.

Before accepting that conclusion it must be weighed against other priorities for that country. Although there were only 11 deaths, there was a 2 per cent case fatality rate and a further five cases had serious neurological sequelae. Although the incidence in adults is low, the case fatality is high. A selective immunization programme is out of the question as few children had identifiable predisposing causes. So universal vaccination in Sweden is probably justified. Moreover the target group for immunization is not widespread among all age groups but concentrated within children under 5.

Activity 8.4

What else, ideally, would you like to know?

Feedback

This assessment of the burden of the disease is probably enough, but further useful information could include number of days spent in hospital for each patient, how many required treatment in an intensive care unit, and possibly how many days off school or work were taken. Long-term follow up is also important. Children who suffered acute neurological complications had poorer school performance and more behaviour difficulties than siblings used as controls (Taylor *et al.* 1990).

The Swedish data are for one small well-off country. In low income countries there are 400,000 estimated cases of *H. influenzae* meningitis, of which 80 per cent are in infants, 30 per cent die and a further 30 per cent recover with substantial impairment (Peltola 2000). These data were estimated about ten years after an effective vaccine became available. One worry about establishing a mass immunization programme is the high fatality rate in adults, even with small numbers involved. If protection from the vaccine is short-lived, the incidence in adults may increase after some years of mass immunization.

Poliomyelitis

Most poliomyelitis infections are asymptomatic, and the milder symptomatic infections include benign meningitis. In low income countries especially, infection in childhood was fairly universal, so that there were enough paralytic cases (even with a low paralysis to infection ratio) to justify mass vaccination. In the more developed world, the sudden rise in notified cases of acute paralytic and fatal polio in the late 1940s/early 1950s (including England and Wales – see Figure 4.4) together with the emotive but still important photographs published in newspapers and magazines of young people in iron lungs or walking with calipers, was enough to convince the authorities of the need for a vaccine to be used on a mass scale as soon as it became available. Cost benefit was probably not even an issue. The world eradication website is www.polioeradication.org.

Activity 8.5

Most studies were retrospective, based on surveillance data and done on populations. If you were given the opportunity to do a cohort study on a population of a large town with its own district general hospital, what information would you collect to be able to estimate the burden of disease?

Feedback

You would probably want to collect:

- incidence – total, as well as age, and sex-specific
- types and rates of complications (from GPs and the hospital)
- time off work
- GP consultation rates: what proportion visit their family doctor, number of visits
- treatment given
- hospital admissions, including A&E: rates, how long in hospital, type of care given
- death rates
- ideally follow-up cases long-term.

Serological studies can also be used in assessing the need for a vaccine. Age-specific immunity rates can indicate the need for immunization and which age groups to vaccinate.

Summary

These are examples of the preliminary studies that should theoretically be carried out before embarking on manufacturing a vaccine. In practice, vaccines are often prepared on the grounds of feasibility, and sometimes on the grounds of personal research interests. Nevertheless, with serious infections, in addition to advocacy from public health personnel, there is usually sufficient public and media pressure to stimulate research into formulating vaccines. So the system works, in a fashion, sometimes with success, as with polio vaccine, and sometimes without (so far), as with HIV. In some instances, such as measles, the pressure is not shared by public or media, and public health professionals have to do the background work and then convince the public.

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9 Evaluation of new vaccines

Overview

In this chapter you will learn how vaccines are tested initially and in the field, and what they are tested for. There are three phases in pre-implementation trials of a vaccine, and one post-implementation phase. Some features of randomized controlled vaccine trials are summarized.

Learning objectives

After studying this chapter you will be better able to:

- **describe the different phases of early vaccine assessment**
- **explain what is measured in each phase and why**
- **explain the principles underlying phase 3 trials**

Preclinical and field studies

The characteristics of an ideal vaccine are:

- *efficacy*: 100 per cent efficacy – all persons at all ages gain permanent immunity with just one dose;
- *side-effects*: none;
- *route*: non-painful, preferably given as a sweet;
- *cost*: free;
- *stability*: 100 per cent at all temperatures and never deteriorates.

This has of course never been achieved! Nevertheless various vaccines have not done too badly by these criteria.

Before human trials begin, there has to be theoretical evidence that the components of the vaccine work. The vaccine has to pass stringent tests for sterility and stability. Animal studies give some information on dose response and the ideal routes of administration. These early studies are classified as preclinical. The earliest human trials would need to establish efficacy and safety. Even if the infection is extremely common, it is not usually possible to test for protection against the disease at this stage. Instead efficacy is assessed by testing for seroconversion. Trials of vaccines in humans are generally done in three phases. Success in each phase is necessary before going on to the next one.

Phase 1: the vaccine is given to a small number (<50) of healthy volunteer adults with a low risk of acquiring the disease, to assess safety mainly, though

immunogenicity is also investigated. The vaccine must have been shown to be consistent with the circulating strains of the organism in the world or country. The dose may need to be adjusted. Sequential testing can be done – i.e. testing fewer than ten people in each batch, adjusting the dose each time. Only serious and common side-effects are evaluated in this phase. The information available from a phase 1 study is clearly limited, especially if the eventual target group is babies and very young children. It is not necessary to have a control group.

Phase 2: a larger sample – about 100–200 – of the target group is vaccinated in this phase, preferably with a control group. Although it may not always be possible, the risk of acquiring the disease in this sample should be low. In contrast to phase 1 in which antibody and cellular responses are a subsidiary aim, here they are the main aim, although side-effects are also carefully monitored. As this is a preliminary to a larger phase 3 trial, information on the dose-response relationship is obtained in order to ascertain the most appropriate schedule for the next phase. Some information on contraindications may emerge.

Phase 3: this is an efficacy trial, much larger and aimed at the target population, with appropriate controls, and carried out under strict ethical scientific procedures. Generally speaking this means a randomized controlled trial. Subjects undergoing a phase 3 trial must be at high risk of developing the disease.

The number included in a phase 3 trial must be estimated statistically, taking into account the expected incidence of the disease, the estimated vaccine efficacy (VE) and the precision with which VE is to be measured, as well as the power and significance levels chosen (Begg and Cutts 1994). In phase 3 trials protection against disease becomes the main outcome to be measured, though clearly other important outcomes are side-effects and acceptability.

Activity 9.1

Draw up a table similar to Table 9.1 showing the different characteristics of the four types of trial. Fill in the blank boxes using the information given above.

Table 9.1 Characteristics of vaccine trial phases

Phase	*Number*	*Subjects of trial*	*Type of trial*	*Main outcome measure*	*Subsidiary outcome measure*	*Main aims*	*Subsidiary aims*
Preclinical							
Phase 1							
Phase 2							
Phase 3							

Feedback

You should have arrived at Table 9.2 The borderlines between the phases are not that strict, so your answers may be slightly different.

Table 9.2 Characteristics of vaccine trial phases

Phase	*Number*	*Subjects of trial*	*Type of trial*	*Main outcome measure*	*Subsidiary outcome measure*	*Main aims*	*Subsidiary aims*
Preclinical	Variable	Animal	Case series	Immune response	Side-effects	Immunogenicity and safety	
Phase 1	<50	Human adult volunteers	Case series	Side-effects	Immune response	Immunogenicity and safety	Dose response
Phase 2	100–200	Target population with low* risk	Cases and controls – cohort study	Immune response	Side-effects	Immunogenicity and safety Dose response	
Phase 3	Variable, high	Target population with high risk	Randomized controlled trial	Protection against disease	Side-effects Immune response	Vaccine Efficacy	Immunogenicity Safety Doses/intervals Adjuvants Acceptability Contraindications

* May be high risk

In a controlled phase 3 trial, it is important to randomize whenever possible. Everyone in the study should be volunteers, but they should then be randomized into 'case' and control groups. This is because vaccinating only volunteers may have some distinct biases – such as social class – and there would be no 'blinding'. It is essential that the subjects should be 'blinded' and properly randomized, otherwise estimating side-effects of the vaccine would be particularly difficult, as would clinical diagnosis of infection if that is one of the main outcome measures. It is also desirable to 'blind' the investigators.

Activity 9.2

Why do you think social class would lead to biases in a non-randomized volunteer-based study?

Feedback

Many infections may be more common or more severe in disadvantaged populations – e.g. whooping cough, dysentery and tuberculosis. If volunteers are mainly from higher socioeconomic groupings they may get milder forms of the infection or, by being less exposed, no infection at all. It is important to try and sample a population as closely

matched as possible to the eventual target population. Biased ascertainment of the outcome is also possible.

While the allocation above is individual – i.e. each person is allocated to one or other group by a random process – an alternative that could be suitable for a phase 3 vaccine trial is group allocation. Groups can be different towns, schools, factories etc.

The advantage would be expediency – i.e. the trial would be easier and quicker to do, and the results easier to analyse. The disadvantages are several: difficult to match control groups closely enough to minimize biases, difficult to truly randomize and blind so that neither investigators nor subjects know whether they are case or control group. If the vaccine is effective, the vaccinated and unvaccinated groups are likely to realize this early in the study, leading to biased ascertainment in both groups.

Activity 9.3

There are obvious advantages to a randomized controlled trial in a phase 3 study. Are there any disadvantages?

Feedback

The disadvantages are those of any randomized controlled trial, cohort or longitudinal study of this sort: need for large numbers of patients and high drop-out rates. These are surmountable, and drop-out rates tend not to be high in vaccine trials. It is not as if the two groups have to take a treatment several times a day regularly over a long time, which needs more motivation than having a vaccine, even if more than one dose is necessary. Nevertheless, as with all trials the conditions are artificial – think of it as the equivalent of an *in vitro* experiment in a laboratory. Hence the need for continued monitoring of vaccine performance after licensing and while the vaccine is in use – the parallel of *in vivo* studies. Hence, as is increasingly being recognized now, the work does not stop when a vaccine strategy is implemented.

Two further considerations are ethical approval and adequate training of staff involved in trials. Although it is outside the scope of this book to describe these in detail, the need to get ethical approval for phase 2 and phase 3 trials, and probably for phase 1 as well, is paramount. Staff should be trained to maintain confidentiality, in interviewing, and in the avoidance of blood-borne and other infections.

A classic phase 3 study by Szmuness *et al.* (1980) is summarized below.

We assessed the efficacy of an inactivated hepatitis B vaccine in a placebo-controlled, randomized, double-blind trial in 1083 homosexual men known to be at high risk for hepatitis B virus infection. The vaccine was found to be safe and the incidence of side

effects was low. Within two months, 77% of the vaccinated persons had high levels of antibody against the hepatitis B surface antigen. This rate increased to 96% after the booster dose and remained essentially unchanged for the duration of the trial. For the first 18 months of follow-up, hepatitis B or subclinical infection developed in only 1.4 to 3.4% of the vaccine recipients as compared with 18 to 27% of placebo recipients ($P < 0.0001$). The reduction of incidence in the vaccinees was as high as 92.3%; none of the vaccinees with a detectable immune response to the vaccine had clinical hepatitis B or asymptomatic antigenemia. A significant reduction of incidence was already seen within 75 days after randomization; this observation suggests that the vaccine may be efficacious even when given after exposure.

Summary

Once a vaccine has passed the stringent tests for sterility and stability, and possibly some testing on animals, studies on volunteer humans can begin. Phase 1 trials are on a small number of adult volunteers to test mainly for safety; phase 2 trials are on 100–200 of the target population, testing for immunogenicity and side-effects; phase 3 trials are randomized controlled trials on the target population testing for efficacy and side-effects. Phase 4 of vaccine development is considered in Chapter 12.

References

Begg N and Cutts FT (1994) The role of epidemiology in the development of a vaccination programme, in Cutts FT and Smith PG (eds) *Vaccination and World Health*. John Wiley & Sons, Chichester.

Szmuness W *et al*. (1980) Hepatitis B vaccine: demonstration of efficacy in a controlled clinical trial in a high-risk population in the United States, *New England Journal of Medicine*, 303: 833–41.

10 Delivery of immunization programmes

Overview

A vaccine is not of much use if it is not being delivered to the right people at the right time. This chapter discusses how to use a vaccine – what options are available, what is the best strategy and how to get the vaccine programme across to the target population.

Learning objectives

After studying this chapter you will be better able to:

- **describe the differences between immunization strategies**
- **explain the rationale for implementing them**
- **understand the basis of herd immunity**
- **explain the importance of population immunity**

Deciding on a vaccine strategy

There are various options in deciding on a vaccine strategy. The first decision to make is whether to go for selective or mass vaccination. A selective vaccine policy means giving the vaccine to only certain groups of people or individuals selected because they have a greater risk than the general public. Mass policy does not necessarily mean that the whole population has to be vaccinated. One or more age groups is usually sufficient, but your strategy should be to include everyone in that group, and ultimately to protect the whole population. As with all definitions there are blurred edges, as will be apparent later in this chapter.

Some reasons for choosing a selective rather than a mass vaccine policy are:

- rare diseases;
- disease more common in certain identifiable groups such as travellers, occupations (including laboratory workers) or those specially vulnerable;
- threat of a serious infection being imported or causing an outbreak;
- the cost of the vaccine may also influence choice of strategy.

Selective immunization

The infection has to be rare in the country itself or much more likely to affect a particular occupational or otherwise susceptible group. Examples are typhoid, rabies, hepatitis or tick-borne encephalitis, all uncommon in many developed countries, but (selectively) commoner in other countries.

Let us use rabies vaccine as an example. Although generally fatal once symptoms appear, this infection is not common enough even in endemic countries to warrant mass immunization. Moreover post-exposure prophylaxis is usually effective if given promptly, which is a further important consideration. In most developed countries however, the vaccine is given routinely to certain occupational groups. These could include laboratory workers handling the virus, those who regularly deal with imported animals, such as animal quarantine workers and zoo keepers, and licensed bat handlers. For travellers travelling from a non-endemic country to one in which the infection is common, rabies vaccine may still not be warranted as a routine measure. Under these circumstances further considerations apply. If on a guided tour, for example, a well-heeled tourist staying in five-star hotels needs to be advised not to touch or make friends with dogs and other biting animals, and to get vaccinated immediately if bitten. However, travellers living rough for an extended period of time in remote areas where rabies is endemic and post-exposure prophylaxis unavailable, may need pre-exposure prophylaxis.

Medical students in the UK are required to be screened for and then vaccinated against hepatitis B. There is a list of indications for influenza vaccine. This is because the prospects of containing or eliminating influenza, which varies in its antigenic make-up almost every year, with existing vaccines which in turn are not highly effective nor produce a long standing immunity, are poor at present. Nevertheless the short-term immunity induced by existing vaccines is deemed worthwhile for those at particular risk – not so much of being exposed to influenza but of developing serious complications from it. Influenza is considered in more detail in Chapter 14. Initially the policy in the UK for controlling congenital rubella was to vaccinate females at 10–11 years of age. Sometimes with a start-up campaign, certain groups are vaccinated in addition to a mass vaccination programme starting in childhood. This happened with meningococcal group C vaccine, in which university students were selectively targeted in addition to infants.

Activity 10.1

1 The policy on rubella vaccine mentioned above is not as strange as may appear at first. Assuming for simplicity that rubella vaccine efficacy is 100 per cent, and that 80 per cent of children were naturally infected with rubella by the age of 10, what would be the immunity rate achieved at puberty in females if the UK vaccinated 80 per cent of females at 10–11?

2 Redo the sums using the more generally accepted 97 per cent efficacy for rubella vaccine, and leaving the vaccination acceptance rate at 10–11 years in females at 80 per cent.

Feedback

1 If 80 per cent of children had had natural rubella by the age of 10, 80 per cent would be immune and 20 per cent still susceptible. At this age 80 per cent of all female children would then get vaccinated. Assuming 100 per cent efficacy, this means that of the 20 per cent susceptible, 80 per cent i.e. 0.8 × 20 per cent = 16 per cent of those previously susceptible would become immune. This makes the total immune at puberty 80 per cent + 16 per cent = 96 per cent. Moreover 80 per cent of the population would have had a lifelong natural immunity compared to a vaccine-induced immunity. At that time, the persistence of immunity induced by the vaccine was uncertain. In the event, although the number of congenital rubella cases dwindled, there were still a few cases each year because the small percentage of women still susceptible were being infected during epidemics of natural rubella in female children and males which were allowed to go unchecked. The strategy was then changed to one of elimination, with universal vaccination of children at 12–15 months.

2 Twenty per cent would still be susceptible at 10 years. Sixteen per cent would be vaccinated with a 97 per cent effective vaccine, making 15.5 per cent (16 per cent × 0.97 = 15.5 per cent) immune after vaccination. Add this to the 80 per cent naturally immune and the immunity rate would be slightly lower at 95.5 per cent.

Activity 10.2

What are the advantages and disadvantages of a selective immunization policy?

Feedback

The advantages are that there is less waste, and indeed fewer side-effects in those receiving a vaccine they don't need. Being able to target particular groups may make the process more efficient. The disadvantages are that it is not always possible to target such groups effectively and it is often difficult to find or predict those who are most likely to need a vaccine – travellers for example may not check what vaccines they need or be given inappropriate ones. With selective immunization herd immunity cannot be achieved.

Mass immunization

If an infection is common enough, serious enough and an effective vaccine is available, the essential ingredients are present for a mass immunization programme. However, the strategy depends on the aims of the programme.

The options available when a programme of mass immunization is deemed to be necessary are:

- *containment*: the reduction of morbidity and mortality to levels in a region/country at which the disease is no longer considered to be a public health problem;

- *Elimination*: the disease is no longer being transmitted in the region/country, although the organism may still be present in the country itself or elsewhere;
- *Eradication*: the disappearance of the disease and the organism causing it. Controlled stocks of the organism in laboratories may still be present.

Before discussing these options further, you need to learn about some important concepts related to what you are trying to achieve.

Fortunately not everyone has to be immunized. For diseases that can spread between humans, a high level of herd immunity can be achieved without very high vaccination rates. This means that the incidence of the disease falls more than would have been expected by the vaccination rate. This is also the reason why the rates of a communicable disease in children and adults can diminish when children are immunized, avoiding the need for immunizing the whole population. For diseases that are not transmissible between humans, such as tetanus and legionnaires' disease, herd immunity does not work.

As a result of herd immunity a proportion of children may remain susceptible because they were not immunized and, because of the lowered incidence of the infection, will not have been exposed to it. Indeed the proportion remaining susceptible may be greater than before immunization was introduced. As they reach early adulthood and come together in universities and colleges for example, pockets of susceptibility may allow outbreaks to occur. As most childhood infections are more severe in adults, this can be a serious side-effect of herd immunity.

Common to all these aims, and the main aim of any vaccination programme, is reaching a high rate of immunity to the disease in question in the target population. This is true even in a selective vaccination programme. This can be ensured by a high vaccine uptake rate and vaccine efficacy.

Activity 10.3

If you have a vaccine with 90 per cent efficacy, and vaccinate 100 per cent of the target population, the immunity rate in this population will be 90 per cent. Similarly if you use a vaccine with 100 per cent efficacy and vaccinate 90 per cent of the population, the immunity rate will again be 90 per cent. What would the immunity rate be if both vaccine efficacy and vaccine uptake rates were 90 per cent?

Feedback

This should be easy – 90 per cent efficacy × 90 per cent uptake = 81 per cent immunity rate. Considering just the uptake of a vaccine is not enough. This point was discussed briefly in Activity 4.4. The calculations assume homogenous mixing and absence of exceptional efficient transmitters of infection.

Activity 10.4

Complete the blank cells in Table 10.1.

Table 10.1 Efficacy, uptake and immunity rate

Efficacy	*Uptake*	*Population immunity rate*
95%	95%	
95%	98%	
95%	90%	
98%		95%
95%		96%

Feedback

Table 10.2 Efficacy, uptake and immunity rate

Efficacy	*Uptake*	*Population immunity rate*
95%	95%	**90.25%**
95%	98%	**93.1%**
95%	90%	**85.5%**
98%	**96.9%**	95%
95%	**101%**	96%

Of the two factors, vaccine efficacy cannot be improved, at least until new improved vaccines are introduced. Mathematical models can give some indication of the levels of immunity rate required to achieve eradication or elimination. If this is the case, the uptake rate required can be calculated, as in the last two rows of the table. However, it will be noted that if a population immunity level of say 96 per cent is estimated to eliminate an infection such as measles, and the existing vaccine has an efficacy of 95 per cent, elimination will not be achievable.

The most important characteristic of an infection that defines the level of population immunity is the average infectivity or basic case reproduction number of the infection. This indicates the maximum potential for transmission. The more infectious the disease, the higher efficacy and uptake rates will you need. The reproduction number depends on the duration of infectivity, the dose required for infection and the ease with which it can be transmitted, the immunity rate in the population and the contact rate. Thus if β is the risk of transmission for each contact (which in turn depends on the dose required for infection and the ease with which it can be transmitted), N the average number of such contacts per person (which will clearly vary considerably with season, age, social class, occupation and a host of other factors), and D the duration of infectivity, then:

$$Ro = \beta \times N \times D$$

The net case reproduction number R is a measure of actual transmission in a population with some who are already immune or infected. Thus:

$$R=Ro(1-p)$$

where p is the proportion of population immune. Measles and whooping cough have very high reproduction numbers (17 and 13 respectively), mumps, rubella and polio somewhat less (4–7). If R>1 the infection will continue to occur in the community, and increase, perhaps causing an epidemic. As the epidemic progresses more and more people become immune, and R decreases. When the epidemic has finished, there will be more immune people and R will decrease temporarily but if it is still greater than 1 another epidemic will occur in due course. If R<1 it will die out. If R = 1 the disease will remain stable in the community. By increasing the immunity rate in a population a successful vaccination programme will reduce R. To achieve elimination R must reach <1. Suppose a vaccination programme achieves an immunity rate of p (the last column in Tables 10.1 and 10.2, representing the immunity rate, not the uptake rate; it is however a proportion, not a percentage, so 95 per cent makes p = 0.95). The number of people 'saved' from infection is $p \times Ro$, and the number of people infected will be $Ro - [p \times Ro]$. So we need to ensure that $Ro - (p \times Ro)$ is <1.

If $Ro - (p \times Ro) < 1$
then
$Ro - 1 < (p \times Ro)$
and
$Ro/ Ro - 1/ Ro < p$
or
$p > 1 - 1/ Ro$

Thus for highly infectious diseases like measles, with Ro estimated at 16, p = ~0.94 and 94 per cent is the immunity rate required. For an infection with Ro estimated at say 5, p = 0.8 and immunity rate required is 80 per cent (after Gieseke 2002).

For diseases for which there is no herd immunity, such as tetanus, legionnaires' disease and those with an animal reservoir, different models have to be called into play.

It should now be clear that the aims of an immunization programme must take into account practical issues, such as the optimum uptake achievable with a given vaccine. Eradication within one country or continent is achievable but cannot be permanent. Eradication should be a concerted worldwide effort. An infection that is easily diagnosable clinically, is confined to humans, does not have a long latent period, has low infectivity and does not have a high rate of asymptomatic carriers, coupled with an inexpensive stable vaccine that produces lifelong immunity, are important but not necessarily essential ingredients for eradication. Poliomyelitis has a very high asymptomatic carrier state, but it has been successfully eliminated from much of mainland America, and from many parts of the world, even though it is still causing disease in some countries. The small success rate for worldwide eradication can generally be attributed not only to the absence of the basic theoretical criteria for eradication but also to a lack of the considerable resources needed for such an effort. Even elimination, more feasible with some existing vaccines, may not always be the ideal goal because of the considerable efforts – and hence expense – of trying to prevent the last few cases.

There is no stigma in being satisfied with containment. Bringing the incidence of an infection down so that it is no longer a public health problem may be legitimate if the resources available, the quality of the existing infrastructure, the costs not only of the vaccine but also of the immunization programme, and the importance of the infection relative to other causes of illness and death in the country mean that any extra effort will be wasteful.

Summary

With every vaccine a choice has to be made about the most appropriate strategy for the country. To achieve success in a vaccination programme a high immunity rate must be achieved. This is a product of vaccine efficacy × vaccine uptake. The higher the basic case reproduction number of an infection the higher the immunity rate necessary to achieve the goals of immunization.

Reference

Gieseke J (2002) Mathematical models for epidemics, in *Modern Infectious Disease Epidemiology*, pp. 119–32. Arnold, London.

11 Vaccine efficacy and effectiveness

Overview

This chapter describes what is needed and what happens after a vaccine strategy is put into place. It explains also how a vaccine can have a high efficacy but still be ineffective. It covers some aspects of phase 4 of a vaccination programme.

Learning objectives

After studying this chapter you will be better able to:

- **describe what studies can and should be done after a vaccine programme has been implemented**
- **evaluate the effectiveness of a vaccine implementation programme**
- **explain the importance of continuous monitoring of vaccine efficacy**
- **assess vaccine efficacy after implementation of an immunization programme**

Introduction

The epidemiological work continues – indeed is crucial – even after an immunization programme is implemented. The effectiveness of the vaccine in controlling the disease has to be constantly evaluated. Vaccine efficacy and uptake also need to be continuously monitored. Surveillance or special surveys for side-effects are also important. Methods include surveillance of incidence (notifications, laboratory reports or dedicated surveillance) and serological testing (seroconversion and seroprevalence).

Vaccine effectiveness

Incidence is the simplest and a useful method of assessing effectiveness. A notification system, supplemented by laboratory reporting if possible, may be adequate until the numbers become very small. Within this notification system the ability to detect outbreaks early – of measles for example – and changes in the age distribution would be important. Increases in incidence over the short term may not necessarily be a reason for concern about the effectiveness of the vaccine, especially in the early years of the programme. Sometimes a dramatic fall in incidence will happen (see Figure 4.5). In some instances however, especially when the immunity rate induced by uptake/efficacy of the vaccine is moderate, there can be small but

fairly obvious changes in the reported annual incidences (see Figures 4.6 and 4.7). Small increases in incidence in particular age groups could signify a partial failure of the vaccination process.

It is important to remember that a reduction in incidence following a mass immunization programme is not necessarily causal. Examples of a 'natural' reduction in incidence include scarlet fever (see Figure 4.1) and tuberculosis (see Figures 4.2 and 4.3). A fall in incidence following an intervention can be suspected to be causal, but without a control group is not proof.

Activity 11.1

In an immunization programme what clues would you look for which indicate that the intervention is producing the fall in incidence?

Feedback

Age and sex: if the target population is a particular age (and sometimes sex) group, one should see a reduction in this group initially, or a greater reduction in this compared with other groups. With an infection for which no herd immunity is expected, the reduction will only be in the target group.

Uptake rates: if uptake rates vary by district, as they often do, looking for a correlation between incidences and uptake rates can be useful. However, notification rates may vary by district also!

In Chapter 8, you learnt about the severity of *Haemophilus influenzae* meningitis and the need for vaccine. In Figure 11.1 the number of strains referred to the haemophilus reference laboratories in England and Wales is shown over a five-year period.

The graph shows cases of infection with *H. influenzae* type b and non-capsulate strains by quarter from 1990 to 1994. About 100 cases of the infection were reported (range ~40–~120) quarterly on average until the third quarter of 1992. Then the number fell dramatically, reaching fewer than 20 cases/quarter by mid-1993 and almost no cases thereafter. Cases in those over 5 years of age stayed the same until late in 1994, and the non-capsulate strains seemed also to remain the same. The vaccine was introduced in October 1992 in infants, and there were no laboratory changes during this period.

Activity 11.2

What is the evidence from this graph that the vaccination campaign was successful?

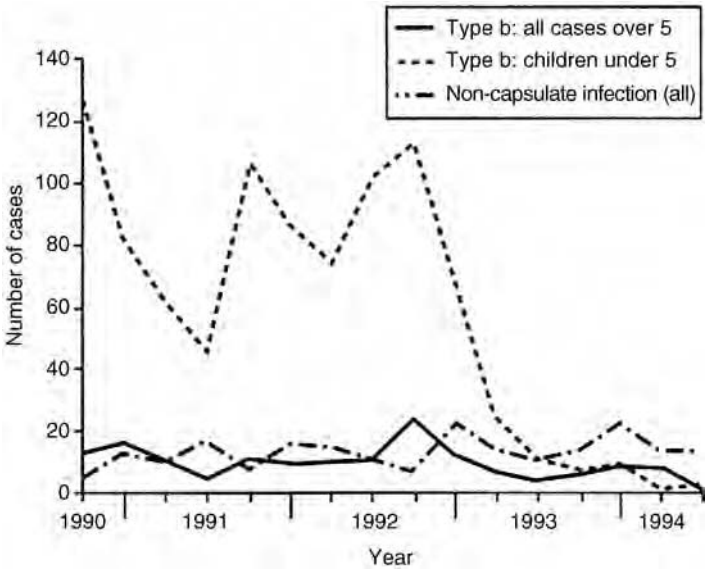

Figure 11.1 Invasive *H. influenzae* type b and non-capsulate infections by quarter
Source: Hargreaves *et al.* (1996)

Feedback

The rapid fall in the number of cases reported by laboratories after the start of the vaccination programme is the most striking finding. However, there are two other pieces of evidence which you should have noted:

Disease caused by non-capsulate strains did not decrease, as one would expect with a vaccine containing b capsular strains only. Indeed they increased slightly from 0.25 to 0.37 per 100,000 cases during this period, an increase that was 'approaching significance', especially in those aged over 65 (you cannot see this from the graph).

The numbers of cases of invasive infection in those over 5 showed no change until towards the end of the period. (You need to see what happened after 1994 to make any observations as to whether this was a sustained decrease or not.) As the vaccine was given only to infants, this again would be consistent with it being effective. These two latter observations provide small but specific evidence of the effectiveness of this vaccine.

When the resources are available, regular surveillance of sera, using for example stored samples taken for other reasons, can provide valuable and specific information on changes in immunity in a population.

In a surveillance study of rubella susceptibility, serological testing of antenatal women was analysed (Noah and Fowle 1988). The results of about 340,000 pregnant women annually, about half the number of antenatal women in the UK, were reported over three years to the study coordinators. Figure 11.2 shows the

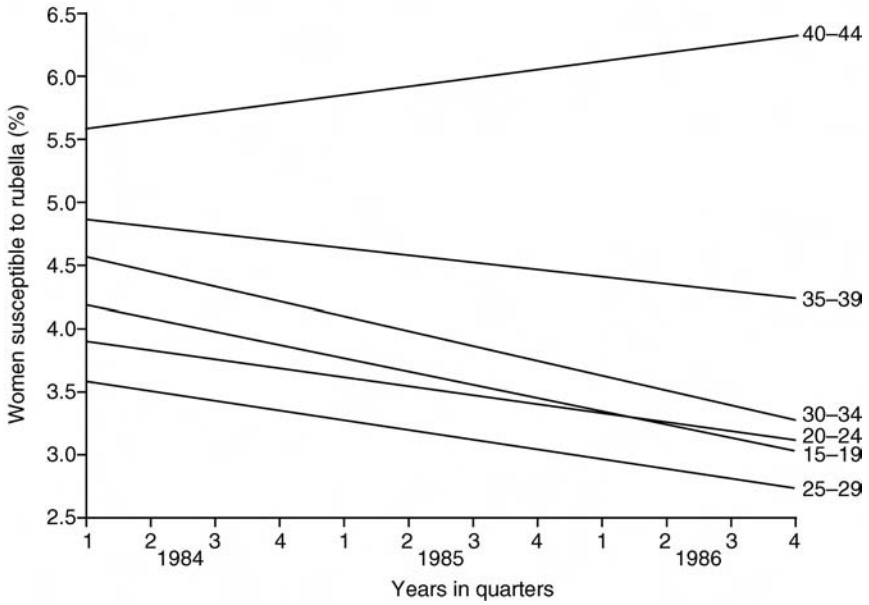

Figure 11.2 Lines of best fit for pregnant women susceptible to rubella by age group, 1984–6
Source: Noah and Fowle (1988)

trends over the three years of the study for susceptibility to rubella in different age groups.

In the UK at this time the rubella vaccine strategy which started in 1970 was a selective one – i.e. to immunize all schoolgirls and women of childbearing age. The Department of Health had just begun a campaign in 1987 to increase uptake of vaccine in this target population.

Activity 11.3

Describe the trends and interpret them.

Feedback

The figure shows the lines of best fit for susceptibility to rubella in pregnant women in five-year age groups from 15–44 years. The data cover three years from 1984–6 in quarters. The figure shows that those aged 25–9 were least susceptible to rubella, and those 35 and above most susceptible, especially the 40–44 group. Susceptibility to rubella decreased gradually by about 1 per cent over these 12 quarterly periods in all age groups except those aged 40–44, in whom it increased by about 0.7 per cent. The rate of fall varied with age group, and was greatest in teenagers: from third to second best over this three-year period.

Before making conclusions from these data, you need to know if there had been a larger than usual outbreak of rubella leading to an increase in natural immunity and what the trend was before 1984. If there had not been an outbreak, the vaccination strategy and/or the campaign would appear to be working. The change in three years in the people within each age group would have been about 60 per cent and the data suggest that the strategy and/or campaign in schoolgirls especially, as well as in younger women of childbearing age, had modest success. The high susceptibility rate in women aged 40–44 is easy to explain: they probably missed routine immunization which started in 1970. The increase in susceptibility in these women is more difficult to explain; possibly those aged 37–9 at the beginning of the study were more susceptible than the others in this age group. If so this would show as an increase as they moved into the older age group, while the vaccine campaign was producing greater immunity in those aged 35–9. That the lowest rates were observed in the 25–9 group can probably be attributed to postnatal immunization of women as well as the general 'catch-up' campaign in women who had not been immunized as schoolgirls.

As this study covered just under half the population of pregnant women in the UK, it seems to be fairly representative. The data do not cover those women who do not attend antenatal clinics. About 340,000 women were analysed every year, but you are not told how many there were in each group. Most of these would be in the 20–4 and 25–9 age groups, and far fewer in the 15–19, 35–9 and 40–4 groups (in fact there were only 11,360 women aged 40–4 in the three years). If each region was well represented in these data, and the pattern of reporting in each quarter fairly consistent, this would be reassuring. In fact, the numbers reported in each region varied from 11, 570 to 227, 985, suggesting some imbalance, although the percentage susceptible in these outlying regions was well within the range of susceptibilities estimated. The pattern of reporting was fairly consistent, although in the first two quarters of the study smaller numbers were reported. The methods of laboratory testing did not change during this period, nor did the criteria for deciding immune/susceptible. The susceptibility rates by region were significantly negatively correlated with the reported immunization rates.

Immunity rates were sufficient to reduce the incidence of congenital rubella to very low levels. However, a selective vaccine strategy meant that the 'normal' epidemics of rubella continued. Thus a small but important number of pregnant women were still being exposed to rubella. In the event, a combined measles mumps and rubella (MMR) vaccine came into use which was given at 13–15 months of age. It also became clear that immunity from rubella vaccine given in infancy lasted into childbearing age.

Vaccine efficacy

Activity 11.4

Doubts about the efficacy of a vaccine may arise after implementation. What factors have been shown to affect vaccine efficacy?

Feedback

Vaccine efficacy is at its highest when vaccine leaves the manufacturer. Factors likely to produce a lower than expected seroconversion rate are:

- wrong age of patient, e.g. measles vaccine at less than one year in developed countries
- wrong site, e.g. buttock for hepatitis B vaccine; subcutaneous instead of intradermal for *Bacillus Calmette-Guerin* (BCG)
- vaccine deterioration – out-of-date vaccine, or not stored as instructed, e.g cold chain broken for a live virus vaccine, or bacterial contamination of a multidose vial
- reconstituted vaccine not made up correctly or used within recommended period
- immunological status of patient
- change in the prevalent organism, e.g. with influenza

Surveillance of incidence may indicate that the vaccine efficacy is waning for some reason, but it is not usually possible to estimate it using incidence. A rising incidence may be detected only or mainly in one age group. This may be attributable to a fall in vaccine efficacy, but is more commonly caused by a build-up of susceptibles.

Immunological testing may be useful in assessing vaccine efficacy. If it can be done systematically, waning immunity may be detected early. It may be attributed to waning of immunity with time, or a decreasing vaccine efficacy. Immunological testing includes skin testing, which is now rarely done as part of a systematic surveillance, or serological testing.

Serological testing can be used to detect antitoxin (diphtheria and tetanus) or antibody (measles and rubella). Seroconversion or seroprevalence studies may be necessary. Seroconversion studies are more common in pre-licensing studies. Seroprevalence studies can be useful for assessing vaccine effectiveness, less so for efficacy. Seroprevalence is used also for assessing the duration of immunity. In seroprevalence studies, the presence of antibody cannot necessarily be attributed to a vaccine, except in infections such as tetanus and diphtheria where natural infection requires such a low dose of toxin that no detectable antibody response is produced, or in countries in which the natural infection is so rare (e.g. polio) that the presence of antibody can only be attributable to the vaccine. Seroconversion on the other hand can be more readily attributed to the vaccine.

An outbreak can sometimes be used to estimate vaccine efficacy. In many ways this can be an ideal setting as vaccine efficacy is being tested under field conditions, rather than the more artificial conditions of a randomized controlled trial. Ideally the immunization histories should be obtained from the entire cohort, or a sample if the cohort is very large, and the attack rates in immunized and unimmunized people analysed, excluding those who have had the disease in the past.

Consider an example. In Texarkana, a city which straddled a state boundary in the USA, one part of the city was in Texas, the other in Arkansas. Arkansas had a measles vaccine policy in place at the time, but not Texas. In an outbreak of measles which affected the entire city, the attack rates were 105.9/1000 in the Texas side of the city, and 4.3/1000 in the Arkansas side.

Table 11.1 Case-control study

	Case	*Control*
Immunized	a	b
Unimmunized	c	d

Vaccine efficacy can be calculated from these data using Table 11.1. The attack rate in the Texan (exposed) side is the absolute attack rate, but one needs to know the rate in the unexposed cohort also. Thus the rate attributable to the lack of vaccine is 105.9 – 4.3 = 101.6/1000. This is the observed attack rate. However, the expected attack rate is 105.9/1000 – this is what it would have been if the children had not been immunized, and assuming they would have had the same risk of being exposed to measles. Hence the vaccine efficacy is 101.6/105.9 = 95.9 per cent.

The formula for vaccine efficacy therefore is:

$$\text{VE} = \frac{\text{AR (unimmunized)} - \text{AR (immunized)}}{\text{AR (unimmunized)}} \times 100$$

or

$$\text{VE} = 1 - \frac{\text{AR (immunized)}}{\text{AR (unimmunized)}} \times 100 = (1 - \text{RR}) \times 100$$

where RR is the relative risk.

Cohort studies can be used to estimate post-licensing vaccine efficacy. At this stage a randomized controlled trial is not usually feasible. The basic information needed is attack rate (unimmunized) and attack rate (immunized); it may be difficult to obtain sufficiently large cohorts if the disease has become uncommon and the immunization rate high. One possibility is to obtain the immunization history of every child notified or reported, and the numbers and percentages of those immunized and unimmunized in the base population, then calculate vaccine efficacy from this using the formula above.

Case-control studies are an uncommon and somewhat limited method of assessing vaccine efficacy. They can be difficult to do (Cornstock 1994) because:

- each case must be representative of all cases in the specified population with respect to the exposure of interest – i.e. the vaccine and the controls should similarly be representative of all non-cases in the same population;
- information about risk factors/exposures in both cases and controls must be similar in quality.

Case-control studies have been used with some success in BCG studies (Smith 1988). The advantages of a case-control approach over a cohort approach in BCG evaluation are:

- when the overall incidence of the disease is low, using existing cases of a disease to evaluate a vaccine given many years earlier is cheaper, quicker and easier;
- with a low attack rate and a long period required for the development or not of tuberculosis, a cohort study can be expensive;
- difficulty in ensuring a double blind or truly randomized approach;
- the large variation in estimates of vaccine efficacy (57 = 100 per cent) using the cohort approach.

Case-control studies have also been used to evaluate poliomyelitis vaccine, as well as others. To calculate the vaccine efficacy from a case-control study, first calculate the odds ratio, which is ad/bc. Then VE = [1 – OR] × 100.

Summary

You have learnt how vaccine efficacy depends on the biological nature of the vaccine itself, while vaccine effectiveness depends on the way it is used. Vaccine effectiveness can and should be monitored after the implementation of a vaccine programme, and this can be done not only by monitoring the incidence of the disease, but also by changes in age groupings, microbiological types where possible and serologically. Vaccine efficacy can be affected by improper storage or administration. It can be monitored by serological testing after vaccination, and also epidemiologically using available data.

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12 Surveillance of vaccination programmes

Overview

This chapter covers monitoring two of the essential parts of post-implementation surveillance – vaccine uptake and side-effects. Together with Chapter 11, it makes up phase 4 of the steps in vaccine implementation described in Chapter 8.

Learning objectives

After studying this chapter you will be better able to:

- **describe the importance of monitoring uptake**
- **investigate the reasons for a low uptake**
- **implement a system for assessing side-effects of a vaccine**

Key term

Vaccine failure When infection occurs despite receiving a full course of an effective vaccine.

Surveillance of vaccine uptake

Constant surveillance of vaccine uptake is necessary, both at local and national levels. It is an ideal example of surveillance for action. The reliability of the data obtained depends on the efficiency of the vaccination programme. Epidemiological studies of vaccines now embrace studies of poor uptake, and are an important addition to the broad range of vaccine research.

Activity 12.1

List some factors likely to affect uptake of a vaccine.

Feedback

Management: efficiency and cost of vaccine implementation. Social perception of the public including politicians, doctors and others concerned with implementation of

vaccines. You may also have in your list various subsidiary factors but most of them will fall under these two headings.

Efficiency is essentially an administrative problem: educating the appropriate health professionals, ensuring that all the target population is called for immunization, recording every successful immunization, recording and following up every unsuccessful immunization, and producing prompt and relevant feedback. A clear line of responsibility all the way up to a person in the Ministry of Health is essential. Immunization coordinators in districts or regions have proved to be useful. Clear guidelines and policies should be available. Health care staff with the knowledge, sympathy and expertise to deal with worried or sceptical parents and answer their questions truthfully and tactfully are also essential. A central or national coordinating or reference unit to answer difficult questions or dilemmas gives the backup that staff in vaccine clinics, and family doctors, need. From 1990, a programme for the rapid evaluation of immunization rates (COVER) was mainly responsible for improving uptake rates in the UK to well over 90 per cent. Districts with poor immunization rates were targeted and support given to improve vaccine uptake. Computerization has made administration, management and monitoring of vaccination programmes much more manageable and efficient. COVER was able to exploit a child health management system.

Being aware of factors that are known to be associated with low immunization rates helps to concentrate efforts on certain groups. Studies have shown the following as being associated with low uptake rates: underprivileged populations; overcrowding; unmarried or single parents; large family size; living in areas of high population density or inner-city areas; unskilled or unskilled parent; belonging to certain cultural or ethnic groups; mobile families; living in areas with poor community health services; large numbers of elderly; single-handed family doctors.

The cost of a vaccine can be a small part of all other costs associated with its implementation. The use of combined vaccines is an important step towards efficiency and cost effectiveness. Public perception has an important effect on vaccine uptake. Politicians have to provide money and the infrastructure to enable a programme to function. They may enable legislation to ensure compliance and even a mechanism of compensation for unforeseeable vaccine damage.

The public can have a preconception of a disease or vaccine, or change their perceptions rapidly, sometimes irrationally. One publication stating that a vaccine has a serious side-effect can do more damage to a vaccine programme than several papers showing that the vaccine definitely does *not* cause that side-effect. The media are clearly important in affecting public perception. Figure 4.6 illustrates the catastrophic effect that this sort of adverse publicity can have: the uptake rate for whooping cough vaccine fell from 81 per cent to 30 per cent following publication of a paper describing an association between the vaccine and brain damage. This was taken up not just by the media: it was backed by one or two prominent medical practitioners, and it is possible that, without this support from members of the health care profession, the media would not have pursued this on their own. As a result, two large and some smaller epidemics followed. An exercise on whooping cough vaccine and the influence of the media is in Chapter 13.

It has been shown that public perception of a vaccine and its importance can be greatly influenced by medical and other health care staff. Health care staff at all levels clearly must be educated and motivated, both in terms of remuneration and support as well as belief in the benefits of the vaccine.

Surveillance of vaccine side-effects

Surveillance of side-effects is useful and important in the post-implementation phase, even though properly conducted and randomized controlled trials may have been completed. Think of a randomized controlled trial as an *in vitro* experiment – i.e. done in the laboratory. Implementation of a mass vaccine programme can be considered a massive ongoing *in vivo* experiment. However, post-implementation surveillance cannot really be considered an experiment – it is an uncontrolled cohort study, unless those who have not been vaccinated are also followed up. This can rarely be achieved and if the uptake rates are very high is probably not feasible if wishing to compare rates of rare side-effects in the vaccinated and unvaccinated. However, a surveillance system for side-effects can be set up similar to one for drugs (in UK there is a yellow card system, where doctors complete and send a card to a central agency).

Activity 12.2

What is the main problem with such a system? Are there any other problems you can think of?

Feedback

The lack of controls is the main problem. Other problems include incompleteness, bias and the difficulties of trying to associate a temporal association with cause. There are no denominators – only numbers (numerators). Side-effects that occur some time after the vaccine – months or years – are probably impossible to detect with this sort of system. This would be so even in a randomized controlled trial, unless follow-up of controls and cases was continued for a long period. If a vaccine is given at the same time as a well-known condition (e.g. convulsions), the association could be strong but spurious.

If part of a large countrywide system, including side-effects from drugs, this type of surveillance can be useful for arousing suspicions of serious and rare side-effects. These would then need to be confirmed by more scientific studies. For rare side-effects, a case-control study may be undertaken. Furthermore, although there are no denominators, time intervals between the vaccine and the alleged side-effect can be analysed. If these time intervals are completely random, a causal association would seem less likely. If the side-effect reported is specific and happens to be a condition found rarely, again the suspicion that the association is causal would be higher than if it were non-specific.

For example, convulsions, although not common, have many causes, including fever in childhood. If convulsions occurred shortly after giving a vaccine, unwarranted suspicion may be aroused. In one of the original studies, on measles vaccine, convulsions occurred in 18 of 9577 children, compared with 5 of 16,327 controls. Further analysis revealed that of the 18 immunized children, 11 developed convulsions six to nine days later, whereas none of the 5 unimmunized children had convulsions during this period. Thus convulsions, a non-specific clinical feature, had a specific incubation period if caused by measles vaccine. The convulsion rate in children after clinical measles was in fact shown to be at least ten times higher. Thus what could have been an unacceptable risk of convulsions from the vaccine was shown to be acceptable.

Brain damage, said to be caused by pertussis vaccine, is a non-specific condition. If a particular clinical condition or particular part of the brain was consistently involved after giving the vaccine, the association may have been real but no more specific diagnosis than 'brain damage' was identified. Some normal children may develop encephalopathy of unknown aetiology in infancy.

A typical asymmetrical lower motor neurone paralysis after a polio vaccine, chickenpox rash after varicella vaccine, or measles after measles vaccine would be highly specific. Caution is necessary to ensure that the vaccinee was not already incubating the infection when the vaccine was given.

Guillain-Barré syndrome (GBS) is a specific condition and is fairly rare. If it follows the administration of a vaccine suspicions of a causal effect may reasonably be aroused. However, if it had been decided to vaccinate more than 200 million people in one country with this vaccine over a few weeks or months, it could be quite difficult to separate background GBS from any induced by the vaccine. In the USA in 1976 it was decided to vaccinate the entire population against a strain of influenza. The campaign had to be stopped when cases of GBS began to be reported in those who had been given the vaccine. There remains uncertainty as to whether there was in fact a causal association. Influenza vaccine has never since been identified as associated with GBS despite many millions of doses (albeit with different strains) having since been given.

Even large randomized controlled trials will not uncover rare side-effects of a vaccine. Case-control studies are required. To investigate the brain damage/pertussis vaccine relationship a very large case-control study was conducted in the UK. Every case of encephalopathy reported to the research centre was contacted and a vaccination history obtained. For each case a control was identified and also contacted. An association between persistent brain damage and pertussis vaccine was identified but the risk was estimated to be 1:310,000 injections, with extremely wide 95 per cent confidence limits of 1:54,000 to 1:5.31 million. This illustrates the difficulty of attempting to prove or disprove alleged rare side-effects of vaccines.

Other aspects of post-implementation surveillance

Activity 12.3

What other components of the post-implementation phase do you think could and perhaps should be placed under surveillance? Chapter 8 may give you some clues.

Feedback

There are four components you may have thought of:

- epidemiological side-effects of vaccines
- vaccine failures
- replacement of types of organism
- carrier rates

Interfering with the immunity of a population on a large scale is interfering with an ecological process, and there will inevitably be some side-effects of this. Most commonly, there may be a change in the age distribution of cases. If the immunization programme achieves lower population immunity than the natural infection, a group of individuals will grow up without having either received the vaccine or responded to it, and without having been exposed to it because of the herd immunity induced by the immunization programme. When these individuals meet as young adults, in colleges or universities, outbreaks (measles, rubella, mumps) may occur. Most childhood infections are more serious in adults.

No vaccine has 100 per cent efficacy and follow-up or surveillance of vaccine failures is a necessary component of post-implementation surveillance. You have learnt about the rationale for and the effectiveness of *Haemophilus influenzae* type b (Hib) vaccine in previous chapters. The vaccine was found to be highly successful in reducing the incidence of the disease by 98 per cent, as shown in Figure 11.2. Surveillance of vaccine failures was carried out. This was an active national surveillance which began from October 1992, the date of implementation, and involved paediatricians, microbiologists and public health physicians throughout the country with the specific aim of assessing the 'clinical and immunological factors associated with vaccine failure'. True vaccine failure was reported in 115 children over six years. It was found that 33 of 105 children had developed a low Hib antibody response even after natural infection, though most then responded to a further booster dose of Hib vaccine. It was also found that 44 per cent of these children who had been vaccinated before the age of 1 had either a clinical risk factor, an immunological risk factor, or both, compared with 67 per cent of those over 1 (Heath *et al.* 2000).

Translating the information given means that an inexplicably poor response to the vaccine was present in 56 per cent of vaccine failures given the vaccine <1 year compared with 33 per cent over 1 year. The better response in the older child suggested the possibility of changing the vaccine strategy. The surveillance provided some guidelines to paediatricians for detecting children who were likely to have a poor antibody response to the vaccine, though somewhat unfortunately most of these babies appeared healthy at the time of vaccination. Premature infants had poorer antibody responses to the Hib conjugate vaccine and could be identified more readily. There was some evidence that an increase in cases of vaccine failure was associated with the use of acellular pertussis (aP) vaccine in the three component vaccine (DTaP-Hib) rather than whole-cell vaccine (wP) (Peltola *et al.* 2005). Although there is controversy as to whether this was causal (it was not apparent in other countries in which the same vaccine was used), it was only

through the surveillance of vaccine failures that the possibility emerged for further investigation. The combination of aP with DTP was known to lower Hib antibodies.

Monitoring of serotypes after mass immunization is useful. Theoretically, by reducing the risk of infection from particular serotypes or groups of organism by using a vaccine containing those types, other types not included in a vaccine may take over. A small rise in non-b strains of *H. influenzae* is being watched carefully (Peltola *et al*. 2005). Visitors to the Hajj in Mecca received mainly groups A and C meningococcal vaccine, and an outbreak of group W135 disease occurred. Using a group C conjugated meningococcal vaccine in the UK does not appear to have allowed a rise in group B infection however. There is a theoretical risk also with pneumococcal vaccines which contain only a small proportion of available types.

Another factor that may need to be monitored in post-implementation surveillance is what happens to the carrier state. After Hib vaccination, carriage of the organism in children's throats also diminished. This meant that herd immunity was possible, and indeed did occur. On the other hand it also means that there is much less repeated boosting of antibody, with the result that people may become more vulnerable to the infection at a later date. Careful surveillance is necessary to detect any such trend as early as possible.

Summary

You have seen how post-implementation surveillance involves surveillance of vaccine uptake, with early anticipation of problem areas, and surveillance of side-effects, some of which may come to light in this phase even after extensive and well-executed clinical trials. Other components that are now increasingly being included as part of routine and worthwhile post-implementation surveillance are surveillance of 'epidemiological side-effects' of mass immunization, surveillance of vaccine failures, of group, type or serotype changes, and of carrier states. It is only with intensive post-implementation surveillance that fine-tuning of vaccine schedules or vaccine formulation can take place.

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13 Role of the mass media

Overview

This chapter is an exercise arising out of a newspaper article on pertussis and its vaccine. The newspaper is a high-quality paper read mainly by intellectuals and liberals. The authors clearly researched their topic in an effort to provide a balanced view of the controversy that was raging at the time. The article appeared in the *Guardian* newspaper on 30 August 1982.

Learning objectives

After studying this chapter you will be better able to:

- **assess, analyse and dissect persuasive arguments made in the media**
- **appreciate the differences between statistics and information, or facts and meaning**
- **understand media coverage of health issues**

Key terms

FDA Federal Drug Administration, a body in the USA that approves all drugs for sale in the country.

Intussusception A blockage of the intestine which can be fatal. Thought to be caused by some viruses and associated with rotavirus vaccine.

Lyme disease An infection spread by ticks, causing skin rash, cardiac and neurological disease.

Introduction

There has always been an anti-vaccination lobby. Although vaccination is now generally accepted by most societies for its considerable benefits, there is a psychological factor to injecting a foreign protein that will probably always make some people uneasy. Public health issues are frequently in the forefront of our societies, and the media today have a critical influence on people's perceptions of 'health'. Journalists are normally well-motivated to unearth 'the truth', but may not always have the insight or expertise to understand the issues. Nevertheless, many public health issues are often debated in public and it is important for the public health practitioner and epidemiologist to be able to analyse and unravel any misconceptions.

A controversy is raging in the UK about giving measles, mumps and rubella vaccines as a combined MMR vaccine, as to whether it causes autism and/or Crohn's disease. The scientific evidence for its causing these two conditions is weak, while that showing that it doesn't is strong. Nevertheless, the public may not always be able to assess scientific evidence, and some will take the line that there is 'no smoke without fire'. More media coverage may be given to whoever first put forward the evidence that the vaccine is a poison than to those who have proved conclusively that it's nothing of the sort. Consequently uptake rates for the vaccine fall.

A similar controversy about whooping cough vaccine allegedly causing brain damage occurred through most of the 1970s and 1980s.

Whooping cough vaccine was introduced in the 1950s. It is a killed whole-cell vaccine, which is still in use. It was never as effective as tetanus and diphtheria toxoids and acceptance was gradual. By the late 1950s however most local authorities/public health departments in England and Wales were using it to mass immunize infants in their first year of life combined with tetanus and diphtheria as a triple vaccine (DPT). The uptake rate in the early 1970s reached about 82 per cent. The effect of this on the notified incidence of pertussis was shown in Figure 4.6.

In the mid-1970s however some research articles were published which suggested an association between pertussis vaccine and 'brain damage', but the risk (if it existed) was very small (less than five per million doses) and the definition of 'brain damage' somewhat vague. It was nevertheless difficult to prove that pertussis vaccine did not cause brain damage at such low rates. At any rate, 'brain damage' being an emotive phrase, many parents voted with their feet and the uptake of the pertussis component of the vaccine fell to around 30 per cent. The two large outbreaks that occurred subsequently were described in Chapter 4 and Figure 4.6. Although the uptake began to recover, controversy continued to rage into the 1980s and the newspaper article below appeared on Monday 30 August 1982. When it was published the first large outbreak which followed the fall in uptake rates had waned. (Outbreaks of pertussis followed a four-yearly cyclical pattern, and this one lasted from 1977–81.)

In the article by Arabella Melville and Colin Johnson, the people referred to by name are Dr Pollock (misprinted as Tollock in the article) who maintained (together with most vaccine epidemiologists, public health doctors and the Department of Health) that the vaccine was safe; and Professor Gordon Stewart who maintained that it wasn't. He was seen by most parents as their protector against the establishment. (The paragraphs have been numbered to aid the activities that follow.)

When poverty is their ally

1 Like the other infectious diseases of childhood, whooping cough has been in decline for the past 80 years. Its prevalence is cyclic, with peaks just under four years apart. The last of these occurred in 1978.

2 The present notification rate is running at about 1,400 new cases a week, and there have been four deaths this year. Even allowing for the fact that cases are over-reported during upswings in the disease, this represents a major epidemic.

3 The DHSS and the medical profession have reacted with repeated exhortations to parents to have their children vaccinated: the vaccination rate has declined since 1974, to about 50 per cent, mainly because parents are understandably reluctant to expose their children to the risk of vaccine-induced brain damage.
4 These exhortations imply that the epidemic would be less widespread and fewer children would die if parents would comply. The evidence suggests, however, that the course of the illness and the number of deaths caused by it is only partly affected by the rate of vaccination. Five per cent of unvaccinated children are likely to develop whooping cough, but 3 per cent of vaccinated children will also suffer from it. Overall, more than 30 per cent of those who develop whooping cough in England and Wales have been vaccinated against it.
5 Whooping cough can be an unpleasant disease at any age, but it is particularly dangerous for babies in their first year. In fact, most deaths are among infants under three months old – most often death happens at 30 days. The age at which vaccination begins has recently been reduced to three months, but that is still too late to offer protection to those most at risk.
6 Most normal, well-nourished children throw whooping cough off quite quickly, and very few suffer long-term damage. Of more than 800,000 children studied in recent surveys there were 18,000 cases involving 480 admissions to hospital. Not all children from the group admitted to hospital were severely ill, while some came from homes where poor conditions were thought likely to impede recovery. There were two recorded cases of brain disease and three deaths.
7 The incidence of permanent brain damage from the disease – about one in 300,000 cases – is believed to be about the same as the incidence of brain damage caused by vaccination. However, vaccination would not necessarily protect these children, for those who develop encephalopathy with whooping cough are generally children for whom vaccination would be inappropriate.
8 Children catch whooping cough from other children with whom they are in close contact. Even when elder siblings are vaccinated, it does not protect the babies because vaccinated children can still transmit the disease. On the basis of their survey of 21 area health authorities, Dr Tollock and his colleagues at the epidemiological research laboratories at Colindale warned that mild attacks in vaccinated children may contribute significantly to the spread of the disease.
9 Whether vaccination has made any contribution to the reduction of mortality from the disease is doubtful. Following its widespread use since 1957, the benefits have proved elusively small. The Glasgow epidemiologist, Professor Gordon Stewart, found that calculations based on the mortality of whooping cough before 1957 predict accurately the subsequent decline of the illness.
10 As with all infectious disease, of much greater importance were the changes in social conditions that led to declining mortality long before specific vaccines were developed. And the continuing improvement since vaccination began may be attributed to further improvement in standards of living.
11 The present epidemic is likely to worsen when schools open in September. If the general trend of decline of the disease has been reversed, the most probable reason is not the low level of vaccination, but increasing poverty among the most disadvantaged families.
12 Almost all cases requiring hospital treatment come from social classes four and five. What that means in terms of deaths can be seen by comparison with the richer and more egalitarian society of Sweden, where the course of whooping cough is mild, even among infants. In the 1977–1979 epidemic, Swedish doctors notified a similar rate of

cases to their colleagues in England and Wales. However, there were no deaths, whereas we had 27. There has been no such death due to whooping cough in Sweden since 1970, and vaccination ceased in 1979.

13 Comparison of mortality rates between countries, and between social groups within countries, shows a characteristic pattern. Death rates are directly related to income – the association between low income and high mortality is strongest for infants under the age of five.

14 In the Third World, diarrhoea and measles – conditions that usually take a mild course here – are fatal to millions of babies. The differences in diet, social and environmental conditions that produce the contrast between affluent northern countries and the poor South is a more obvious step in the progression that differentiates Sweden from Britain, and their patterns of whooping cough mortality.

15 By emphasising the importance of vaccination, the DHSS deflects attention from the factors that underlie the growing severity of infectious diseases – all are now increasing. Medical intervention can offer little other than hope against social forces. At times of stress in the social fabric, our old enemies the infectious diseases seize their opportunity and emerge once more with poverty as their ally.

Activity 13.1

What is the main message of the article?

Feedback

The main message of the article is that the factors that most influence, maybe even cause, infectious diseases are social, especially poverty. Simple logic then leads to the second main message – that since these social factors are the main causes of infectious disease we should be concentrating on them and not vaccination.

Activity 13.2

Do you think there messages are valid?

Feedback

The authors have a point, but take an invalid stance. Poverty – at least the deprivation that often goes with it – can undoubtedly have an adverse effect on some infectious diseases, including (and probably especially) whooping cough. It is certainly true that most 'cases requiring hospital treatment come from social classes four and five'. As already discussed in Chapter 4, children from lower socioeconomic groups have a higher case fatality rate from pertussis, but there is no convincing evidence that they have a higher incidence rate. Pertussis certainly affects children of *all* socioeconomic groups. Nevertheless, this is not a controversial point. What is more debatable is that

we should be getting rid of poverty rather than vaccinating. Not many would argue about overcoming poverty, but this, even if achievable, will take time, and will never reduce the incidence of whooping cough as much as, or as quickly as, vaccination. There is also a hint of the subversive in the allegation that 'By emphasising the importance of vaccination, the DHSS deflects attention from the factors that underlie the growing severity of infectious diseases' (paragraph 15).

Activity 13.3

How would you, as a public health practitioner, interpret the comment that most 'cases requiring hospital treatment come from social classes four and five' (paragraph 12).

Feedback

First, you would need to know what the base populations are of those who come from social classes four and five. If most of the population was made up of social classes four and five, the statement would not be epidemiologically meaningful. In fact these groups form only a small proportion of the population of England and Wales. So the number of those from social classes four and five admitted for pertussis is indeed disproportionate. Second, however, this still does not necessarily mean that children from social classes four and five are those who are mainly affected by pertussis because many children with pertussis are admitted for social reasons.

Activity 13.4

What do you think of the argument that to prevent disease you should always attempt to remove the cause?

Feedback

By the same argument, you should not be fluoridating water or toothpaste because sugars are the main cause of tooth decay; instead people should stop eating sugar. As cars cause road traffic accidents, you should not emphasize road safety, but get rid of cars. Sanitation is a waste of time as people should not let water become contaminated.

Activity 13.5

Read the fifth paragraph again. There seems to be an unassailable argument here, carefully worded to work up to the fact that whooping cough vaccine is being given too late to offer protection to those most at risk. How much of this paragraph is true? Is the conclusion valid?

Feedback

Most of it is true – except, unfortunately, the conclusion. It is a good illustration of how although facts can be correct, it is the *interpretation* that matters. Take each fact as it comes:

> 'Whooping cough can be unpleasant at any age . . .' This is true.
> 'It is particularly dangerous for babies in their first year . . .' This too is true.
> 'In fact most deaths are among infants under three months old . . .' This again, is true.
> 'Most often death happens at thirty days . . .' An odd sentence here, clearly not true, although the younger the infant, the more likely it is to die. Nevertheless the sentence is irrelevant to the argument.

Up to now it has been a masterly piece of journalism. There is a logical progression of statements leading steadily to a climactic statement: 'The age at which vaccination begins has recently been reduced to three months, but that is still too late to offer protection to those most at risk'. There appears to be the unassailable force of logic – but it's wrong. Herd immunity has not been taken into account. Pertussis is transmissible from person to person, so herd immunity does work if the immunization uptake rates are high enough. In fact, by vaccinating from three months, older children were prevented from bringing whooping cough into homes and infecting younger siblings, and the rates of infection in babies under three months in England and Wales also fell.

Activity 13.6

Read the seventh and eighth paragraphs again. What further observations would you like to make?

Feedback

It was difficult to obtain rates of brain damage following whooping cough vaccine because the definition of brain damage was vague, and because it was so rare. Nevertheless all side-effects of vaccines have to be weighed against the severity and complications of an infection. As uptake of an effective vaccine increases, the incidence of the infection decreases. Eventually the side-effects of the vaccine will become more common than the disease itself – this happened with oral polio vaccine in many developed countries when they achieved high coverage rates and the virtual elimination of polio. There is no doubt that pertussis vaccine is not 100 per cent effective and that cases occurred in the fully vaccinated, who can still transmit the infection. However, this is a fairly rare occurrence, and it is not correct to imply that elder vaccinated siblings as a general rule pass on the infection to babies. Herd immunity had a strong effect on the incidence of whooping cough.

Activity 13.7

Are there any inaccuracies or half-truths in paragraph 9?

Feedback

The first sentence of this paragraph, that whooping cough vaccine has had little effect on mortality, is perfectly true and we examined the reasons for it in Chapter 4. However it is not true then to conclude that 'the benefits have proved elusively small'. As already seen, the incidence rates of the infection fell following the introduction of mass vaccination. The disease is unpleasant and debilitating, can last for some months and causes complications other than death.

Activity 13.8

Return to paragraph 4. The second half of the paragraph makes two statements. The first one compares the percentages of vaccinated and unvaccinated children who develop whooping cough. There is no attribution for these data and it was not possible to find published work supporting them. (If you work out the vaccine efficacy rate from these figures it is 40 per cent and too low for whooping cough.) The second statement is more useful as a discussion point: 'Overall, more than 30 per cent of those who develop whooping cough in England and Wales have been vaccinated against it'. If this statement is true, how does it affect your confidence in pertussis vaccine?

Feedback

The statement is important because most people, including health care professionals, admit that, if true, it would convince them that pertussis vaccine was ineffective. The readership of this article, especially mothers of infants about to be vaccinated, would wonder why they would want to vaccinate their babies and expose them to a risk of brain damage if the vaccine wasn't even effective.

Activity 13.9

What does this statement tell us about vaccine efficacy?

Feedback

This question is best answered with an example. Consider a family doctor with 1000 children in his practice. He wants to vaccinate them against disease X with vaccine X. He vaccinates 90 per cent of them. Most people would accept this as a good result. However, to understand what immunity rate he has achieved we need to know the

efficacy rate of the vaccine. Let us assume the efficacy rate was 90 per cent – a reasonable efficacy rate. So we have 900 children vaccinated, but only 810 of these are immune, giving an immunity rate of 81 per cent. The number of children non-immune is 190. An epidemic of disease X arrives and infects 100 per cent of those who are susceptible (non-immune). This is unlikely in real life but the attack rate is not relevant provided the risks of infection are the same in all children.

Activity 13.10

Overall, what percentage of those who develop disease X have been vaccinated against it? This is equivalent to the statement made and statistic quoted in the newspaper article.

Feedback

190 develop disease X. Of these 90 have been vaccinated, and 100 not. The percentage of those who have already been vaccinated is 90/190 = 47 per cent. This apparently high percentage is in spite of a high uptake and a high efficacy vaccine. The family doctor decides to increase his coverage and achieves 100 per cent uptake rate. This would be a significant achievement. Vaccine efficacy remains the same. This means that no children are unimmunized, but 100 are non-immune. With, again, 100 per cent attack rate, all 100 children will get the disease.

Activity 13.11

What does this statistic – the percentage of those with a disease who have already been vaccinated against it – mean?

Feedback

To help understand what it means another example is given below. This is not newspaper journalism, but a letter to a medical journal from a family doctor who is concerned about his apparently high failure rate for measles vaccine.

Study the letter reproduced below.

Measles vaccine

Sir,

In this area where I am working as a trainee there has been a recent outbreak of measles affecting patients of both local practices. There were 32 cases notified of indisputable

measles, of which 15 had been vaccinated previously. The Schwarz strain live attenuated vaccine is used locally and has been given intramuscularly to at least 90 per cent of the 584 children born between 1972 and 1981 on the lists of local doctors.

It was with alarm that this apparently high failure rate was noted. The *Current Medicine* series states that a single dose confers a high degree of protection in most recipients. It is recognized that vaccinated children may develop modified or atypical measles, and indeed one local child was catarrhal, with Koplik spots but no cutaneous exanthema, however, it was not easy explaining the failure of protection to worried mothers.

These figures show only about a 3 per cent failure for the vaccine in immunized children, while 30 per cent of those not immunized contracted measles. However, extrapolated nationally they would represent a large number of children who may catch measles despite vaccination, unless our local experience is a chance observation. Scrutiny of the community health returns may show if this is so. Can other GPs send in their experience?

A.D.T. Robinson

Activity 13.12

What is the efficacy rate for measles vaccine in this family doctor's practice? Is it really 15 cases out of 32, as the doctor thinks? (he refers to it as 'this apparently high failure rate').

Feedback

An apparent 'failure rate' of 15 cases out of 32 would suggest an efficacy for the vaccine of 15/32 = 47 per cent. But we have seen from the newspaper example that it is not correct to estimate vaccine efficacy from this type of calculation.

If there were 32 cases of measles, of which 15 were vaccinated, 17 would have been unvaccinated. However, there are no denominators here for each group of children – only the numerators. Assuming an overall vaccine uptake rate of 90 per cent, the doctor gives enough information to calculate his denominators (see Table 13.1).

Table 13.1 Attack rates of measles in a family doctor population

	Base population	*Vaccinated*	*Unvaccinated*	*Apparent failure rate*
Measles	32	15	17 (32–15)	47% (15/32)
Base population	584	526 (90% uptake)	58 (584–526)	
Attack rates	5.5%	2.9%	29.3%	

You can now see that 15 out of 526 vaccinated children acquired measles compared with 17 out of 58 unvaccinated children. So there is no high failure rate. Vaccine efficacy can be worked out easily using the formula:

$$VE = \frac{AR\ (unvacc) - AR\ (vacc)}{AR\ (unvacc)} = \frac{29.3 - 2.9}{29.3} = 90 \text{ per cent}$$

29.3

Where VE = vaccine efficacy, and AR is attack rate

You can see that using the ratio of 15 to 32 in Table 13.1 is meaningless and that what you really need is to compare the attack rates. Denominators must never be forgotten. Likewise the phrase: 'Overall, more than 30 per cent of those who develop whooping cough in England and Wales have been vaccinated against it' is also meaningless. Statistics don't tell lies – it's how you interpret them.

A highly effective vaccine is of no use unless it achieves a high uptake in the target population. Maintaining a high uptake rate can be affected by a variety of factors. Sometimes serious side-effects (or those perceived as serious by the public) only emerge after the field trial stage and when the vaccine strategy has been implemented on a mass scale. Sometimes a vaccine is blamed for side-effects even though proof – or even good evidence – may be lacking, and this also affects public acceptance of the vaccine.

Summary

You have learnt about the controversy over pertussis vaccine in the 1970s and 1980s and some of the apparent evidence against it, as published in a reputable newspaper. The media are instrumental in influencing public perception, and being able to analyse some of the arguments used to influence the public was the purpose of this chapter.

References

Melville A and Johnson C (1982) When poverty is their ally. Guardian, 30 August 1982.

Robinson ADT (1982) Measles vaccine (letter) *Journal of Royal College of General Practitioners* 32: 578.

SECTION 4

Topical themes and infections

14 Influenza and other respiratory viruses

Overview

Respiratory infections are one of the most important causes of morbidity and mortality in the world. Viral infections are a major cause of respiratory infection. In this chapter you will learn about the complex influenza A virus, influenza B virus and some other respiratory viruses, including SARS.

Learning objectives

After studying this chapter you will be better able to:

- **understand the difference between variants and subtypes of influenza A virus, and how these affect its epidemiology**
- **collect, analyse and interpret surveillance data on influenza**
- **explain its effect on morbidity and mortality**
- **describe when to use vaccine, and what it can and cannot do**
- **describe the epidemiology of SARS, respiratory syncytial virus, the parainfluenza viruses and some other respiratory viruses**

Key terms

Epidemic A large outbreak usually affecting an extensive area or several countries.

Excess mortality The number of deaths in excess of that which occurs in a non-epidemic or baseline year.

Pandemic A worldwide epidemic.

Clinical, epidemiological and microbiological features of influenza

Until the advent of HIV/AIDS, influenza was referred to as 'the last great plague'. Influenza virus has caused pandemics in waves for some centuries. In 1918 it killed more young people than World War I. Since then two further pandemics have caused considerable morbidity and mortality.

The name 'influenza' is derived from the Italian for 'influence', when it was thought to be caused by the conjunction of heavenly bodies. They found it difficult to explain otherwise (as we still do) how it could suddenly affect a large number of people spread across a country.

Influenza is characterized by the acute onset of upper and lower respiratory tract infection accompanied by fever, malaise and severe aches and pains. A dry persistent cough is also fairly characteristic. It may be difficult to distinguish from other respiratory tract infections but when it arrives, usually suddenly as an epidemic or pandemic, it is unmistakable. Children may have gastrointestinal symptoms, especially with influenza B infection. Pneumonia is a serious complication of influenza A infection. The most common causes of pneumonia in influenza are pneumococci, staphylococci and influenza A virus itself. Mortality may be high especially with staphylococcal and influenzal pneumonia. People most vulnerable to influenza are the elderly and those with debilitating chronic diseases such as respiratory, cardiac or renal failure, and the immunosuppressed. Some pandemics select particular age groups, as the pandemic of 1918 did the young. Asymptomatic infections occur.

There are three main influenza virus types, A, B and C. Type C causes mild sporadic cases and rare local outbreaks and will not be considered further. Type B causes more severe outbreaks, mainly affecting schoolchildren. Types B and C infect man only. Type A is the important virus, and is responsible for the major pandemics of influenza. It infects man as well as a large variety of animals and birds.

Transmission is by the respiratory route. With all respiratory viruses, including the common cold, contaminated hands may also spread infection – nose to hands, hand to another hand or fomite, fomite to another person's hand, other hand to nose. It is difficult however to explain the sudden arrival, sometimes almost on one day, of a major influenza outbreak affecting sometimes a whole country or countries. People with the infection are at their most contagious one to three days before the onset of symptoms to about nine days after onset. The incubation period is one to three days.

Some knowledge of the influenza virus itself is essential to understanding its epidemiology. The virus itself is an RNA virus. Virus type is determined by two internal proteins, nucleoprotein and matrix protein. These are stable proteins. On the surface of the virus however are two glycoproteins, haemagglutinin (H) and neuraminidase (N), which together characterize the virus 'subtype' and are responsible for antigenic variation. Different types are numbered. Major changes that produce antigens so different from previous prevalent types that there is little or no cross reactivity are known as 'shifts' and the changed virus a 'subtype' (e.g. H1N1 changing to H2N2). Less substantial variations of the influenza A glycoproteins H and N that occur within a subtype are called 'drifts' and the changed virus a 'variant'. Variants are named by the type of virus, followed by the place in which the virus was first isolated, the culture number, year of isolation and subtype, for example, A/Singapore/6/86(H1N1). As the differences between shifts and drifts, and subtypes and variants, can be confusing it may be helpful to think of the different subtypes as colours, and the variants as subtle shadings of colour. Thus one could imagine A/H1N1 as say, red, and all subsequent variants (minor changes) of this subtype as shades of red. A major change (shift) to H2N2 could be thought of as blue, and all variants of the new subtype as shades of blue.

Generally a shift is followed by a pandemic with major morbidity, and drifts have less serious consequences. Nevertheless some variants cause more morbidity than others. Drifts occur almost yearly while shifts are more infrequent. The H1N1 subtype circulated between 1918 and 1956, and then disappeared when H2N2

appeared in 1957. In 1967 the H3N2 subtype replaced the H2N2 subtype. In 1977 the H1N1 subtype reappeared. Since 1977 throughout the world both H1N1 and H3N2 have been circulating independently – sometimes only one causes infection, sometimes both and sometimes neither. Recently new subtypes (H5N1, H7N7) have been emerging. Influenza remains unpredictable. Influenza B virus has variants only and no shifts.

Diagnosis of influenza

Diagnosis can be made by culture of virus from throat or nose (as nasal washings) or other respiratory secretions during the acute phase of the illness. For more rapid methods, viral antigens can be detected in nasopharyngeal cells using immunofluorescence and more recently polymerase chain reaction (PCR) of a nose and throat swab. A fourfold rise in antibody in paired serum samples taken early in the illness and during convalescence is diagnostic but the diagnosis is retrospective.

Epidemiology and surveillance of influenza

Activity 14.1

1 What would be the aims of surveillance for influenza?

2 What information would you use if you wished to conduct surveillance of influenza in your country? What source would you use for each item of information?

Feedback

1 The main aim is to provide timely information on morbidity and mortality associated with influenza. This means that, with an effective early warning system, plans can be put into place to alert GPs, hospitals and other health care personnel. Information on the components of the vaccine for the following year can also be provided. Its impact on the population can also be measured.

2 The information you would use includes

- mortality from death certificates
- morbidity from hospitals, GPs, other sources
- laboratory from local virological and national reference laboratories
- serological studies

Mortality

For all of these you need age and sex (essential), geographical location and time of onset of illness. Outcome (died/survived) is also useful. For deaths, cause of death and type of pneumonia, where available, are also helpful.

Mortality data are obtained from death certificates. Influenza is an important cause of death, especially during pandemics caused by a new subtype. However, as already stated, variants can cause considerable mortality during interpandemic periods. During epidemics 80–90 per cent of deaths from influenza are in adults >65, especially those with chronic illnesses. It must not be forgotten that babies and children are also vulnerable, and that all ages can be affected.

Activity 14.2

What causes of death would you analyse in trying to assess mortality from influenza?

Feedback

You would look at deaths from influenza; but deaths from pneumonia, bronchitis, all respiratory disease, coronary heart disease and even total mortality (all causes) also increase during influenza epidemics. As previously stated, this is known as 'excess mortality' and is used for influenza.

After every epidemic, excess mortality is calculated. This provides an estimate – and probably the best measure – of the severity of each epidemic.

The average excess mortality estimated in England and Wales, with a population of around 55 million, is about 12,000 per annum. Table 14.1 shows the considerable variation in excess deaths in the last 14 winters in England and Wales, ranging from zero to 27,590 cases (average 10,124), and the apparent randomness of the numbers in each year. Deaths directly attributed to influenza were fewer than half of these. Bear in mind that these data do not cover a new subtype/pandemic year – viruses circulating were A/H3N2, A/H1N1, which had been circulating since 1967

Table 14.1 Influenza excess mortality in England and Wales*

Season	*Estimate of excess (numbers)*
1989/90	27 590
1990/91	7 170
1991/92	4 938
1992/93	1 113
1993/94	13 131
1994/95	1 549
1995/96	15 215
1996/97	21 292
1997/98	0
1998/99	17 558
1999/00	21 290
2000/01	402
2001/02	5 870
2002/03	4 616

* Unpublished HPA data using a form of time series modelling
Source: HPA Centre for Infection

and 1977 respectively, and influenza B. During pandemics global mortality can be considerable: estimates for the great pandemic of 1918/19 (the 'Spanish flu', H1N1) were 50–100 million, for 1957/8 (the 'Asian flu' H2N2) 1 million, and for the 'Hong Kong flu' (H3N2) of 1968 which caused two consecutive pandemics, the second one larger than the first, 700,000.

Figure 14.1 shows deaths from all causes for three consecutive winters. In the first of these years there was a sharp rise in the total number of deaths from a baseline of about 10,000 to over 20,000 in one week, in the following year very little change, increasing only to about 12,000, and in the third year a moderate increase to about 15,000 deaths. The period of excess mortality also was greatest in the first year, and smallest in the second year. The time patterns follow those shown in Table 14.1. However, it can be seen that deaths from all causes in Figure 14.1 are considerably higher in total than those attributed to influenza alone (Table 14.1) but yet the patterns of mortality are the same.

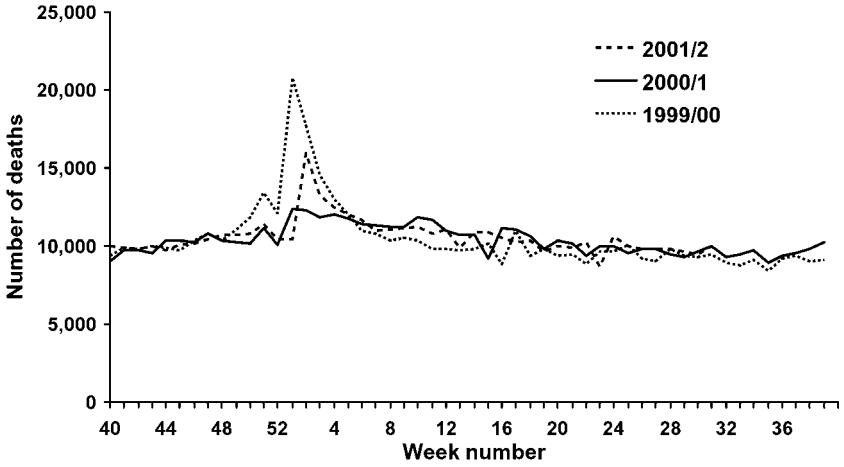

Figure 14.1 Deaths due to all causes notified to ONS by week of notification
Source: Office for National Statistics/HPA Centre for Infection

Morbidity

Morbidity data are obtained from hospitals, GPs and other sources. Influenza is not a notifiable disease in most countries.

Activity 14.3

Why might influenza not be a notifiable disease?

Feedback

Various reasons include:

- difficulty in making a clinical diagnosis – indeed many illnesses are called 'influenza-like'
- during epidemics and pandemics it could overwhelm the surveillance systems
- there is little urgent action, such as tracing contacts or giving vaccine, necessary when a single case or local outbreak occurs
- possibly because morbidity can be measured by other methods which have a higher specificity

Morbidity is usually assessed by sentinel GP practices and via hospital data, special surveys and some 'indirect' methods which will be explained later. Those sources discussed in Chapter 1 will be touched on only briefly here. Hospital data are less useful for influenza surveillance because of lack of timeliness. Obtaining information from sentinel family doctor practices avoids some of the pitfalls of notification, in particular overloading central surveillance systems during high epidemic periods. Accuracy of diagnosis may still be a problem, but GPs in sentinel practices tend to be fairly experienced. Some GP-based sentinel systems distinguish between influenza and 'influenza-like' illness.

A significant advantage of a GP sentinel surveillance system is that, if the age and sex distributions, and perhaps other demographic details of the base population of each GP sentinel practice are known, age- and sex-specific rates of infection (actually consultation rates) can be obtained. Thus epidemics are classified arbitrarily into baseline (< $30/10^5$), normal winter ($30–199/10^5$) and epidemic ($200+/10^5$) (Goddard *et al.* 2003). In Figure 14.2, GP consultation rates for three different epidemics of influenza are shown. The largest epidemic was in 1969/70, soon after the

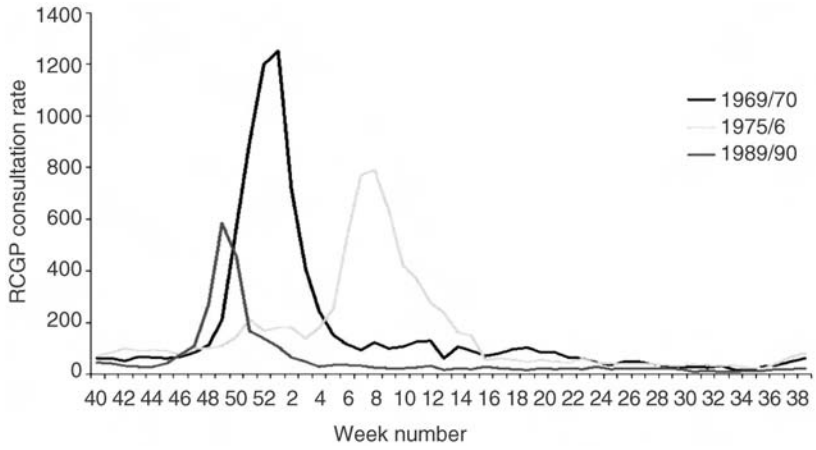

Figure 14.2 RCGP consultation rates for influenza, England and Wales

Prior to 1994 activity was recorded as 'epidemic influenza' and 'influenza-like illness'. Data for 1969/70 and 1975/76 represents a total of these data for comparison with recent years

Source: RCGP Research Unit, Birmingham, England

new H3N2 subtype of influenza A arrived, and the smallest one more recently, in 1989/90. All reached the epidemic threshold of >400/10[5]. Note also that the timing of each epidemic varied from early December to early January and late March.

The rarity of epidemic and even 'above average' rates of influenza in recent years is shown in Figure 14.3. Note that these rates include 'influenza-like' illness. However, influenza is unpredictable and the emergence of a new subtype may herald more frequent epidemics.

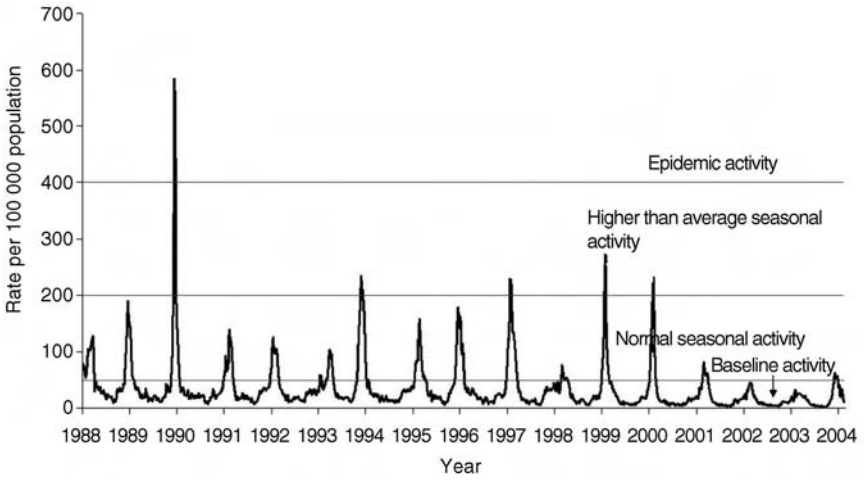

Figure 14.3 RCGP weekly consultation rate for influenza and influenza-like illness

Epidemic activity is now reclassified as >200/100 000

Source: RCGP Research Unit, Birmingham, England

In the USA, valuable use has been made of defined populations, usually communities belonging to a prepaid health care group, to study the impact of influenza.

The 'other and indirect sources' of data for assessing influenza are many and some ingenious methods have been employed. Some of these, though necessarily crude, have the advantage of being timely. They are based on the fact of influenza being one of the last great plagues. Influenza, by causing considerable and sudden illness, can cause mass absenteeism which can be measured in schools and factories and via calls to the NHS advisory service, NHS Direct, calls to ambulance stations etc.

Activity 14.4

What are the uses of the laboratory in identifying influenza?

Feedback

Laboratory sources include local virological and national reference laboratories. Laboratory information is essential for influenza surveillance, not only for confirming the diagnosis, but also to identify the types (A or B), subtypes of A and variants of A and B so that vaccines can be formulated for the following year. The only way to identify a new subtype, which may herald a major pandemic, is by laboratory surveillance.

Moreover, by testing birds and animals, circulation of subtypes can be monitored, as has happened with the avian subtypes in South-East Asia and elsewhere. Indeed, different subtypes seem to be causing different illnesses – H5N1 appears to have a high mortality in humans and is transmitted mainly from poultry. H7N7 on the other hand is more benign and conjunctivitis appears to be the main clinical feature. Emergence of new subtypes is discussed in more detail below.

In addition, the WHO supports a network of laboratories or collaborating centres which characterize the strains isolated. Characterization and surveillance of strains isolated from birds and animals are also undertaken. These networks of national and international surveillance are essential if we are ever to control influenza. The importance of working with veterinary laboratories in global influenza surveillance, as with many other infections, cannot be overemphasized.

Activity 14.5

How do you think serological studies can help in influenza surveillance?

Feedback

Serological studies can help in various ways. First, they can be used to assess the clinical susceptibility, and hence the usefulness, of a vaccine containing a new variant. This is done by testing a representative sample of human sera obtained recently. Second, the likely impact of a new variant can be assessed. Third, serological studies can also be useful in unravelling the history of influenza. By testing different birth cohorts it is possible to tell what subtypes they have been exposed to in the past, and what subtypes have caused pandemics and when.

Prevention of influenza

Trying to plan for influenza, one of the most unpredictable of all infections, is difficult, even with an efficient surveillance system. The virus changes almost every year. The start of the season can vary by four or five months. The impact of the infection varies each year – see Table 14.1 – and also cannot be predicted. Even the age distributions vary. Furthermore, the vaccine is of limited value.

The formulation of influenza vaccine is determined each year by the WHO. It

contains the current variants of the A/H3N2, A/H1N1 and B viruses. Killed virus vaccines are generally used. The vaccine has to be stored at 2–8°C, protected from light and brought to room temperature before inoculation. Under ideal conditions, it has a protection rate of about 70 per cent if it contains antigens close to the currently circulating strains.

Because of the drifts of influenza virus, influenza vaccines are usually one step behind. They provide some immunity if the drift is not too great, but efficacy at best is low. The people for whom they are mainly indicated, which may vary by country, are those who do not respond as well as healthy people. As the indications for vaccination are selective, uptake tends to be poor. Confidence in the vaccine is destroyed when immunized people develop influenza-like illnesses, as they will because the vaccine will not protect them against these, and when no influenza epidemic materializes. The vaccine protects only for a year, so has to be repeated annually. The influenza season may arrive too quickly after the vaccine has been given, or months later when immunity, especially in those for whom the vaccine is most indicated, may be waning. The vaccine should also be given to those working and living in homes and institutions, including hospitals, where many vulnerable or elderly people reside to protect them in an outbreak. Mass vaccination except for those indicated above is not normally recommended in inter-pandemic periods.

Existing vaccines will not protect against a new subtype, when an epidemic is likely to be most severe, because there may be little early warning, because of the time needed to develop new vaccines against the new subtype, and because of the very large number of doses likely to be required. Work is however ongoing to try and develop a pandemic vaccine using reverse genetics and cell culture as opposed to the embryonated hens' eggs method.

Antiviral drugs – M2 and neuraminidase inhibitors – are moderately effective antiviral agents which can be given to those at risk, to those at risk who cannot have the vaccine and to health care workers in an emergency to prevent disruption in a major epidemic. They should be given within 48 hours of onset of symptoms if used for treatment. For prophylaxis they can only be used short-term, such as for contacts. Other methods of control, such as isolation of patients, are not usually effective.

Other respiratory viruses

Avian and other new recent subtypes of influenza A

Although avian influenza viruses are widespread and common, they tend not to cause high mortality in birds, and also do not generally infect humans. In 1997 a subtype of influenza virus A, H5N1, appeared in chickens in Hong Kong, spread to humans and caused six deaths among 18 people known to be infected. In 1999 human cases of A/H9N2 infection appeared in Hong Kong. In 1995 and again more recently, A/H7N7 human cases occurred in the Netherlands and British Columbia, Canada. Although fortunately fairly mild and characterized by conjunctivitis as one of the symptoms, at least one person died. Some antigenic reassortment to H1N2 (from H3N2 and H1N1) was noted in 2001. Outbreaks of A/H7 in poultry

have been noted in Pakistan and the USA, leading to a ban by some countries on importing poultry from the USA.

Since December 2003 extensive outbreaks of A/H5N1 have been noted in the Far East, causing unusually high mortality. Because of the rare ability of this strain to spread to humans, millions of ducks and chickens from infected flocks have been slaughtered. Although there has been only a small number of reported human cases of A/H5N1 influenza in South-East Asia (31), mainly children and young adults, the case fatality rate has been high (22/31, 71 per cent). Case-to-case spread, although documented within a family, appears to be unusual and most human cases have had direct contact with infected poultry. This virus has already been shown to infect pigs. Domestic ducks can excrete large numbers of influenza viruses without becoming ill and may act as a 'silent reservoir' (Stohr 2005). Influenza virus H5N1 has been isolated from duck meat imported from China to Japan and intended for human consumption. In 2006, other birds are known to be infected with H5N1 and have been found in Africa and Europe.

Whether this recent activity is a warning sign of a new pandemic, with the age distribution of human cases and high CFR for A/H5N1 suggestive of the epidemic of 1918, is not yet clear. It is unlikely to be the result of more intensive global surveillance. A pandemic is probably overdue, as the two circulating A subtypes have been around for many years, A/H1N1 for most of the last century. Moreover two of the three subtypes causing major pandemics in the twentieth century, the Asian and Hong Kong subtypes, have been shown to be a reassortment of avian with human viruses.

Severe acute respiratory syndrome (SARS)

On 11 February 2003 China declared that they had an outbreak of pneumonia involving 300 cases with five deaths in Guangdong province. By 12 March cases had occurred in Hanoi and Hong Kong, and three days later cases had been reported from Singapore, Taiwan, Indonesia, Thailand and Philippines, as well as in Canada. The WHO issued a global alert and declared severe acute respiratory syndrome (SARS) a worldwide health threat. Guidance about travel to South-East Asia was also issued. The virus was shown to be a coronavirus.

The clinical features were of an influenza-like illness, with a high fever, cough and shortness of breath, leading in some to pneumonia and acute respiratory distress syndrome. The overall case fatality rate (CFR) was 15 per cent, though higher in older persons and those with chronic illnesses. Children seemed to be relatively unaffected. HCWs were at high risk. Infection was spread by close contact (droplet and direct contact with body fluids), and the incubation period was two to ten days (mean five days). The explosiveness of local outbreaks and the extremely rapid spread to other countries around the world was of concern.

As no vaccine or treatment was available, the only practical response was intensive surveillance and case and contact management, with full laboratory support. Other methods included information, education, travel advice to the general public, contingency planning, collaboration with government and other agencies and international collaboration. With hindsight the fact that infectiousness was greatest when people were ill and not before allowed control of the epidemic with these

basic public health control measures. In the UK a task force was set up to implement this strategy. With similar methods of control in other countries with cases, overseen by the WHO, global control was successful. Since then there have been a few sporadic cases and two laboratory-acquired infections only. The coronavirus was shown to infect civet cats (possibly the reservoir), bats and other animals.

The economic and political impact of this incident was considerable. The successful control of this unique episode of an acute explosive outbreak of a new human virus causing a serious illness showed the importance of local and global scientific collaboration, and of the role of the WHO in control.

Others

Many other viruses, not all of them 'respiratory' (such as the enteroviruses), cause respiratory infections. These include the rhinoviruses, the commonest cause of the common cold, and the adenoviruses. Although rhinoviruses will not be considered further here, in terms of the considerable morbidity caused by the common cold, they are a significant public health problem.

Respiratory syncytial virus infection is the major cause of lower respiratory tract infection in infants throughout the world. It is a common infection. Infants under 1 characteristically develop bronchiolitis and also pneumonia. The age distribution shows a peak at about two to three months, declining thereafter. Younger children are also affected, and evidence is accumulating that it causes considerable morbidity in elderly and high-risk adults (Falsey *et al.* 2005). The infection causes some mortality, especially but not exclusively in poorer areas of the world. Premature infants and those with pre-existing conditions such as congenital heart disease and immunosuppression are particularly vulnerable. The winter seasonal pattern is characteristic and striking (see Figure 14.4).

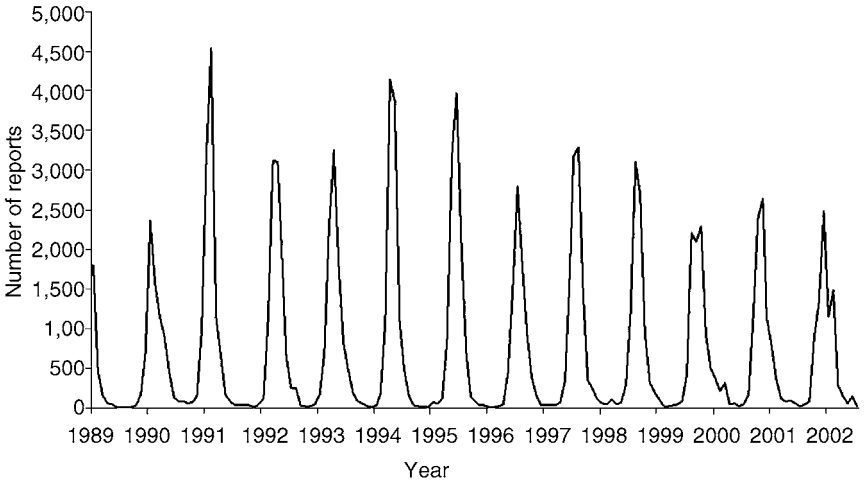

Figure 14.4 Laboratory reports to CDSC of infections due to respiratory syncytial virus, England and Wales, 1989–2002 (four-weekly)

Source: HPA Centre for Infection

Parainfluenza viruses (numbered types 1–4, type 4 is rare) are also common respiratory infections of children with the peak age slightly older than for respiratory syncytial virus. The characteristic clinical feature is croup, though like all these respiratory viruses they also cause pneumonia, bronchiolitis etc. They also exhibit a strong seasonal pattern, with type 3 appearing every late summer/autumn, and types 1 and 2 every second winter. Parainfluenza types 1 and 2 occur in early winter, usually before the year's end in the northern hemisphere, while respiratory syncytial virus usually peaks after the turn of the year, in January or February.

Summary

In this chapter you have learnt about one of the most important causes of morbidity and mortality in the world – respiratory viruses. You have seen how variants and subtypes of influenza A represent challenges in controlling the spread of this infection, in particular the limited potential of vaccination.

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Goddard NL *et al.* (2003) Appropriateness of thresholds currently used to describe influenza activity in England, *Communicable Disease and Public Health*, 6(3): 238–45.

Stohr K (2005) Avian influenza and pandemics – research needs and opportunities, *New England Journal of Medicine*, 352: 405–7.

Useful websites

Influenza pandemic plans

WHO: www.who.int/csr/disease/influenza/nationalpandemic/en/
The WHO sites give access to the plans made by several countries.

UK Department of Health: hpa.org.uk/infections/topics_az/influenza/pdfs/HPAPandemicplan.pdf
HPA: www.dh.gov.uk/assetRoot/04/10/44/37/04104437.pdf

Influenza on the internet – some useful sites

Health Protection Agency, England: www.hpa.org.uk

European Influenza Surveillance Scheme: www.eiss.org

World Health Organization influenza page: www.who.int/emc/diseases/flu/index.html

Centers for Disease Control, USA – Influenza Home page: www.cdc.gov/ncidod/diseases/flu/fluvirus.htm

15 Tuberculosis

Overview

In this chapter you will learn about the epidemiology and microbiology of this ancient but persistent infection, how best to conduct surveillance for it, any special requirements for investigation of outbreaks, and how to control it. Because tuberculosis is different from some other more acute infections that you have studied, some of the features of surveillance discussed in the first three chapters have to be modified.

Learning objectives

After studying this chapter you will be better able to:

- **explain the basic biology and epidemiology of this organism and infection**
- **describe how tuberculosis (TB) is transmitted**
- **explain the importance of social factors in its prevalence**
- **set up a surveillance system for it**
- **manage outbreaks**
- **control the burden of disease in the community**

Key terms

BCG vaccination Insertion of Bacille Calmette-Guerin, a modified attenuated tubercle bacillus, intradermally to stimulate immunity. Efficacy is limited.

Cervical lymphadenitis Enlarged lymph glands in the neck, usually caused by various conditions including TB.

Ghôn focus The initial lesion in the lung.

Miliary Disseminated tuberculosis.

Primary complex of Ranke The primary lung lesion with enlarged lymph nodes at hilum of lung (hilar lymphadenopathy).

Silicosis A widespread disease of the lung caused by inhaled silica particles.

Tuberculin test/PPD A standard solution for testing previous exposure to TB prepared from tubercle bacilli, injected intradermally into the forearm.

Tuberculomas A tuberculous abscess, a large solid lesion with necrotic centre.

Introduction

TB has been proven to have occurred in antiquity and is to this day a worldwide problem and burden in developed, middle-income and developing countries. It is a bacterial infection caused by MTB complex (*Mycobacterium tuberculosis*, *M. bovis*, *M. africanum*). *M. tuberculosis* is of most importance to humans. *M. bovis* mainly affects cattle, but goats, sheep, pigs and deer as well as other mammals, including badgers, can be infected. *M. africanum* is a species intermediate between *M. tuberculosis* and *M. bovis*. Other members of the *Mycobacteriaceae* family cause leprosy (*M. leprae*); skin infections from fish (*M. marinum*); Buruli ulcer (*M. ulcerans*); cervical lymphadenitis (*M. scrofulaceum*); and various other TB-like infections which are uncommon and affect immunocompromised persons (e.g *M. avium complex and M. kansasii*). Only TB will be considered in this chapter.

Important epidemiological and microbiological features

TB is usually transmitted by the respiratory route. Droplets of infected cough-spray about 5μm in diameter lodge in the periphery of the lung. This may cause a small localized infection, called a primary or Ghôn focus. If regional lymph nodes then become infected, the whole is known as a primary complex. In about 90 to 95 per cent of cases, the primary complex heals and leaves a scar which may calcify. More rarely the primary infection may disseminate, leading to miliary TB or meningitis (both more likely in children) within five years. Infections of other organs may also occur. Local rupture of any part of the primary complex may lead to pulmonary, pleuritic or pericardial TB.

The primary complex may contain viable bacilli which remain latent and cause no problem for the rest of the person's life. The Ghôn focus/primary complex may reactivate in some and cause disease, usually within two years. This is post-primary TB and usually affects the upper parts of the lungs. Reinfection may also occur.

M. tuberculosis can also be transmitted by inoculation through the skin, causing a characteristic skin lesion (lupus vulgaris). *M. bovis* is transmitted by swallowing and similarly may form a primary focus in the intestinal wall with spread to abdominal lymph glands or the peritoneum, or even to other organs, with subsequent reactivation many years later. Occasionally it may lodge in the pharynx and cause cervical lymphadenitis.

Activity 15.1

From your existing knowledge or impressions of TB, write down what you think are the most important trigger factors for post-primary TB.

Feedback

Some of these, such as AIDS/HIV infection, poverty and malnutrition you would probably know from general knowledge. Here is a fairly comprehensive list adapted from Roberts and Buikstra (2003).

- immunosuppression, natural (including AIDS) or iatrogenic
- age and sex
- poor nutrition
- poverty
- low socioeconomic status
- overcrowding
- occupation
- ethnicity
- travel/migration
- gastrectomy
- pregnancy
- exposure to animals

Several of these need clarification. Poverty, poor nutrition and overcrowding tend to occur together. Occupational exposure can be because of low socioeconomic status (such as migrant farm workers), increased exposure (HCWs) or occupations which specifically predispose to TB (miners). These are generally people exposed to particulate matter, leading for example to silicosis. Gastrectomy leads to removal of the acid barrier in the stomach. Exposure to animals such as cattle may be a risk for *M. bovis*. The very young and old are more prone to TB, and the very young to disseminated primary TB such as miliary or meningeal.

Post-primary tuberculosis in the lung forms tuberculomas which may be closed, calcify and become non-infectious or, by breaking down into a bronchus, form a cavity which releases large numbers of bacilli into sputum. This is known as open TB and can be highly infectious. Almost any other organ can be affected by post-primary TB.

Untreated, post-primary TB, whether due either to reactivation or reinfection, leads to death in 33 per cent of cases, recovery in 33 per cent and chronic infection in 33 per cent.

Risk of transmission depends, among other factors, on closeness and duration of contact. People with bacilli detectable on a smear are far more infectious than those whose bacilli can only be detected on culture. Generally about 5000 bacilli/ml are needed for a smear to be positive. Those with advanced pulmonary disease and/or a cough are more infectious. Nevertheless, some persons with open TB appear to be less infectious than others, and require prolonged intimate contact to spread disease.

Susceptibility to TB varies considerably between populations and people. Both genetic and ethnic factors play a part. Antibodies play no protective role in immunity, which is entirely cell-mediated by T lymphocytes. The HIV epidemic has had a considerable impact on TB worldwide. As T-cell function is affected in HIV-infected

individuals, they have a high risk of TB, and may develop primary, reinfection or endogenous reactivation. Moreover the tuberculin skin test may be negative and the chest X-ray normal.

Diagnosis

Mycobacteria are slender, slightly curved and rod-shaped. They are acid fast and can resist acids, alkalis and dehydration. Tubercle bacilli grow slowly in the laboratory and require special enriched media. Doubling times are 18 to 24 hours, so culture results are not available for four to six weeks. If >5000 bacilli/ml are present in sputum, acid-fast bacilli can be visualized by light microscopy and a presumptive diagnosis made – smear-positive TB. Culture is necessary to prove the organism is TB and not one of the other mycobacteria. In other cases of open disease the bacilli cannot be visualized and have to be grown on special media which may take several weeks. Genotyping of strains is now possible for outbreaks.

The tuberculin test using purified protein derivative (PPD) is often used to help in diagnosis. The size of the subsequent reaction provides some indication of whether the person has never been infected, or has the disease. Readings have to be interpreted with caution and must take into account the patient's history and medical condition, symptoms, X-ray findings and previous history of BCG.

General epidemiology

The global burden of TB is considerable. The WHO estimates are shown in Table 15.1.

Table 15.1 Estimated TB incidence and mortality, 2002

	Number of cases (thousands)		*Cases per 100,000 population*		*Deaths from TB (including TB deaths in people infected with HIV)*	
WHO region	*All forms (%)*	*Smear-positive*	*All forms*	*Smear-positive*	*Number (thousands)*	*Per 100,000 population*
Africa	2354 (26)	1000	350	149	556	83
The Americas	370 (4)	165	43	19	53	6
Eastern Mediterranean	622 (7)	279	124	55	143	28
Europe	472 (5)	211	54	24	73	8
South-East Asia	2890 (33)	1294	182	81	625	39
Western Pacific	2090 (24)	939	122	55	373	22
Global	**8797 (100)**	**3887**	**141**	**63**	**1823**	**29**

Source: Information Resource Centre HIV, Tuberculosis and Malaria

Activity 15.2

Summarize what the data in Table 15.1 show.

Feedback

Table 15.1 shows the estimated numbers in thousands, incidence and rates for TB and deaths in six WHO regions for 2002. There were almost 9 million cases in 2002 (estimate) and more than 1.8 million deaths. The highest numbers were in South-East Asia but Africa had by far the highest rate, almost double that of Asia. Two regions, the Americas and Europe, had comparatively low rates, but still fairly substantial at 43 and 54/100,000 per year. There was a wide disparity in the rates by region, that of the lowest, the Americas, being barely an eighth of Africa, the highest. The smear positive rates as a proportion of all cases varied remarkably little, from 42.4 to 44.9 per cent. The case fatality rates (CFRs) (number of deaths divided by number of cases) showed high rates of >20 per cent in Africa (23.6), South-East Asia (21.6) and the Eastern Mediterranean (23.0), and lower rates in the Western Pacific (17.9), Europe (15.9) and the Americas (14.3). In a mainly chronic disease like TB, CFRs have to be interpreted with caution. New cases will have been freshly diagnosed, and with modern drugs and health care would be expected to have a better prognosis. HIV infections may have influenced some of the incidence and death rates, and we presume the rates have not been standardized for age.

In addition (not shown in table): 10 per cent of TB cases in those aged 15–49 are associated with HIV infection. The risk of developing TB disease in an infected person without HIV infection is 10–20 per cent over a lifetime, compared with 10 per cent per annum in those with HIV. Of the >1.8 million deaths attributable to TB in 2002 worldwide, 13 per cent (a quarter of a million people) had HIV infection. Within these regions there were considerable variations in rates. In Europe for example, incidence rates reached >50/100,000 in the former USSR and Albania, 20–49/100,000 in Eastern Europe, Portugal and Turkey, and below this elsewhere. In some well-developed countries, TB has had a resurgence.

Activity 15.3

What do you think has caused a resurgence of TB even in some high and middle income countries? Assume this is true increase.

Feedback

- displacement (refugees) and migration
- HIV infection
- poverty (associated with poor housing, homelessness and living rough, poor nutrition, overcrowding)
- political will and priorities, and conflict, leading to disruptions to health infrastructure and poorly-managed TB programmes
- TB drug resistance, especially multidrug resistance

You will already have noted how TB in the UK (and probably in most high and middle income countries) decreased in incidence before any medical interventions (see Figures 4.2 and 4.3). This was attributed to an increasing standard of living. The importance of socioeconomic factors in TB is substantial: in the small but significant resurgence of the disease in the 1990s, TB in England and Wales increased by 35 per cent in the poorest 10 per cent of the population, 13 per cent in the next 20 per cent and not at all in the remaining 70 per cent (Bhatti *et al.* 1995).

Drug resistance is a serious problem in tuberculosis. Strains resistant to at least one drug are well-recognized. Multidrug resistant TB (MDR-TB) is defined as resistance to at least isoniazid and rifampicin, the two most powerful anti-TB drugs. Drug resistance in TB occurs with erratic or incomplete treatment. This can happen if patients feel better and stop their drugs, or take them intermittently. This is fairly common with TB as treatment regimens are for several months rather than days. Sometimes doctors and health workers prescribe the wrong treatment regimens. Occasionally the drug supply is unreliable, or the health care system unsupportive. Rates of MDR-TB are high in some countries, especially in the former Soviet Union.

From a public health perspective, poorly supervised or incomplete treatment of TB is worse than no treatment at all because patients with MDR strains can pass them on to others. While single drug-resistant TB is generally treatable, it requires extensive chemotherapy for up to two years. This can be often prohibitively expensive – perhaps more than 100 times more than treatment of drug-susceptible TB, and is also more toxic to patients (WHO 2005).

Surveillance

The aim of a surveillance programme is to reduce the burden of morbidity and mortality from TB. Unlike many infectious diseases which can be highly infectious when asymptomatic, with TB patients with symptoms spread infection. Thus early treatment is vitally important to protect not only the patient but others. Hence cases need to be notified and treated, and their contacts traced if appropriate. With TB completeness in surveillance is desirable.

Activity 15.4

Why is completeness especially important in surveillance of TB?

Feedback

Completeness is important in TB because investigation of contacts and other local measures may prevent further cases, or uncover source cases. Completeness also ensures accuracy in estimating the size of the burden and the characteristics of the population at risk so that control measures can be targeted, and the success or otherwise of any control measures assessed.

On a population basis, knowing the basic epidemiology (incidence, trends, risk groups and factors, drug resistance and outcome) is necessary. Outbreaks have to be detected. In more sophisticated systems evaluation of treatment programmes and of control and prevention bring additional benefits to inform policy.

Useful sources of data include:

- A notification system is a basic necessity. A two-tier system, with telephone notification of smear-positive cases and suspected outbreaks, and postal/electronic reporting of other cases is a reasonable model to follow. Involving chest physicians directly is advisable.
- Enhanced surveillance is recommended for an infection such as TB for which completeness is desirable. In a country with very large numbers of cases each year, this may be difficult.
- Laboratory backup is essential to ensure accurate diagnosis and to distinguish between high-risk (sputum, smear positive) and lower risk (culture positive, smear negative) cases. It is also essential to monitor drug resistance.
- Death certification, available in most countries, is an important further source of information.

In addition:

- Linkage of laboratory and notification systems requires additional resources but is extremely worthwhile, to build a composite picture of the burden of TB.
- Further linkage with HIV infection should be attempted where possible.
- Resources may not be available to do enhanced surveillance, so periodical surveys (e.g. every five years or so), are worth consideration. Detailed information on each case can be collected. This can be expensive, and if the sample size too small, not representative.
- Other special surveys include using particular communities or children.

Data collected in England and Wales are summarized in Table 15.2. All data are collected by the Communicable Disease Surveillance Centre except death certifications which are collected by the Office of National Statistics.

The flow of information is illustrated in Figure 15.1.

Table 15.2 Main elements of TB surveillance in England & Wales, 2005

- Routine systems
  - Notifications
  - Enhanced surveillance (1999)
  - Treatment outcome monitoring (2002)
  - Laboratory reports (1994)
  - Mortality
  - Linkage e.g. TB and HIV
- Specific surveys (some examples)
  - London case load profiling
  - Paediatric survey

Source: HPA Centre for Infection. Year indicates year of implementation

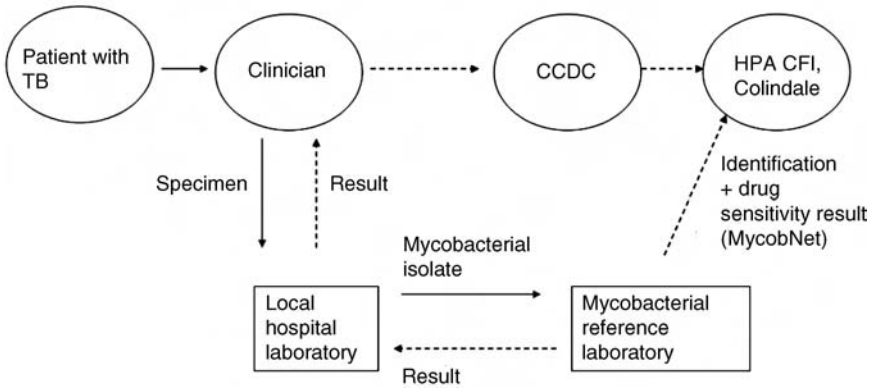

Figure 15.1 Main elements of TB surveillance in England & Wales, 2005

Source: HPA Centre for Infection
CCDC: consultant in communicable disease control (similar to district medical officer of health)
CFI: Centre For Infection
HPA: Health Protection Agency

Activity 15.5

With the background to TB given above, what desirable information would you want to collect on each case?

Feedback

- age and sex
- type of TB (pulmonary, miliary etc.)
- infectivity (smear/culture positive, non-infectious)
- details of organism
- drug resistance
- basic clinical details, previous TB
- any relevant occupational, social and ethnic information
- outcome

The outcome will usually be months or years later, hence the importance of a linkage system. Social and ethnic information may be difficult to collect as a routine.

Enhanced surveillance

In England and Wales enhanced surveillance, as well as specific surveillance of outcomes, linkage with HIV cases and drug resistance are part of the TB surveillance programme. Some data from the enhanced surveillance programme are shown in Figures 15.2–15.6.

In England and Wales information is collected in selected localities using a range of sources as outlined above. Standard case definitions are used and a minimum

dataset obtained. Information flows from local/district to regions to the national surveillance centre. There is some flexibility in the data collection system and steps are taken to ensure strict patient confidentiality.

Activity 15.6

Describe and then interpret the data in Figures 15.2–15.6. Do this with each figure before moving to the next one – in this way you should find a story gradually unfolding.

Feedback

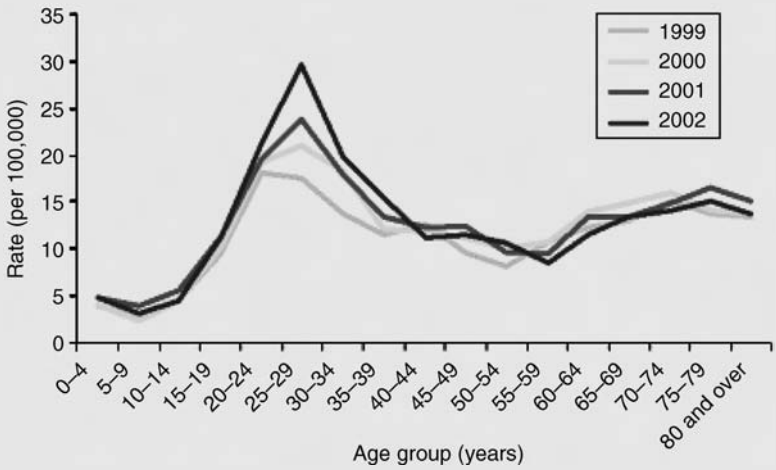

Figure 15.2 TB rates by age group, England & Wales, 1999–2002

Sources: Enhanced Tuberculosis Surveillance, Office for National Statistics mid-year population estimates

Figure 15.2 shows the rate of TB increases from about $2/10^5$ at 5–9 years of age to $30/10^5$ in those aged 25–29 and then drops to about $10–15/10^5$. There is a slight increase with increasing age in older adults. The incidence, as shown in the figure, is slightly higher in children aged 0–4 than in older children. The question arises: why is there an increased rate in young adults, and a trough before another increase in older people?
In Figure 15.3 the rates are much lower for people born in the UK. There is as before a small peak of about $4/10^5$ in those aged 0–4, a trough of $2/10^5$ at 5–9 and then a second larger peak in young adults aged 20–29 reaching about $6/10^5$. In older people the rate increases again with age to reach $10/10^5$. This is only a little lower than the rate in these age groups for all people (Figure 15.2). This suggests that most TB in older people is in the indigenous population (an older chronic group), and most TB in the young in those born abroad, and possibly their children.

Figure 15.4 confirms this observation – note the very high rates, reaching 160/105, the greater fall between 0–4 and 5–9 years, and also the absence of an increase in older

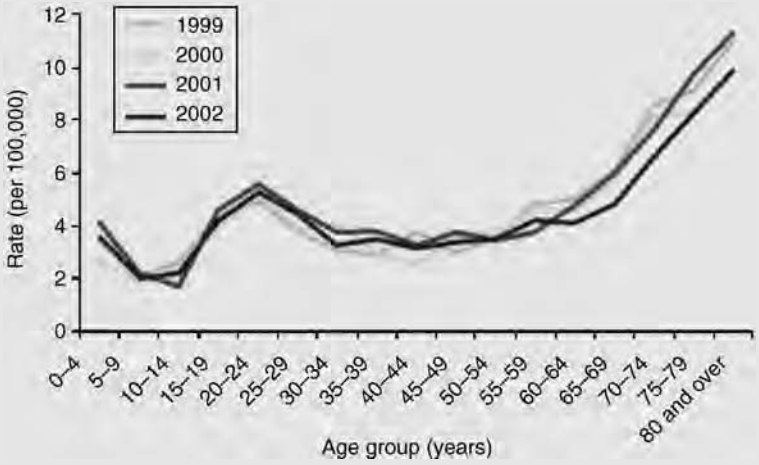

Figure 15.3 TB rates in people born in the UK by age group, England & Wales, 1999–2002

Sources: Enhanced Tuberculosis Surveillance, Labour Force Survey population estimates

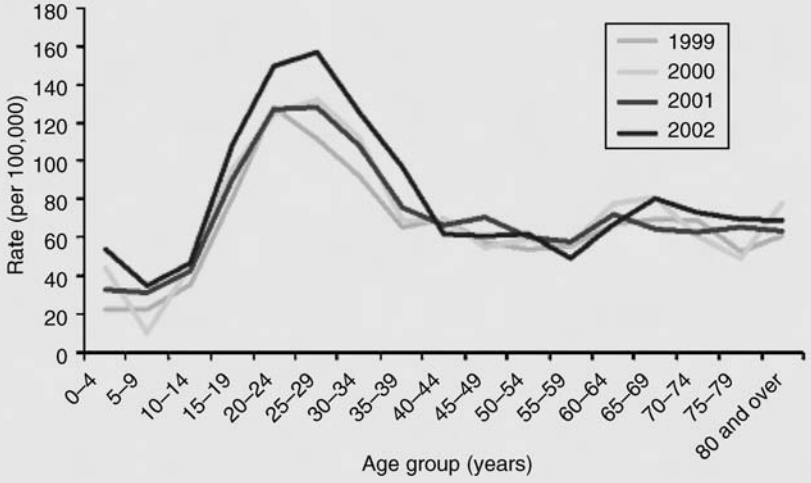

Figure 15.4 TB rates in people born abroad by age group, England & Wales, 1999–2002

Sources: Enhanced Tuberculosis Surveillance, Labour Force Survey population estimates

adults. Figure 15.5 shows the proportion of cases increasing slightly with time in black African groups and Figure 15.6 the marked difference in rates in all ethnic groups in those born abroad and those born in England and Wales.

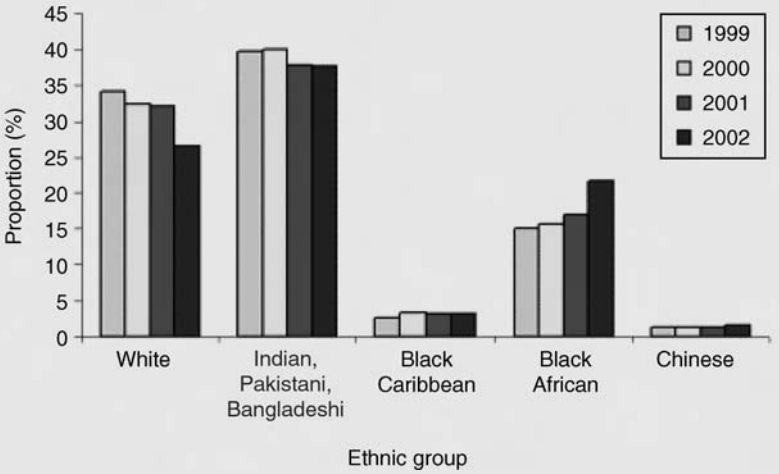

Figure 15.5 TB case reports by ethnic group (%), England & Wales, 1999–2002

Source: Enhanced Tuberculosis Surveillance

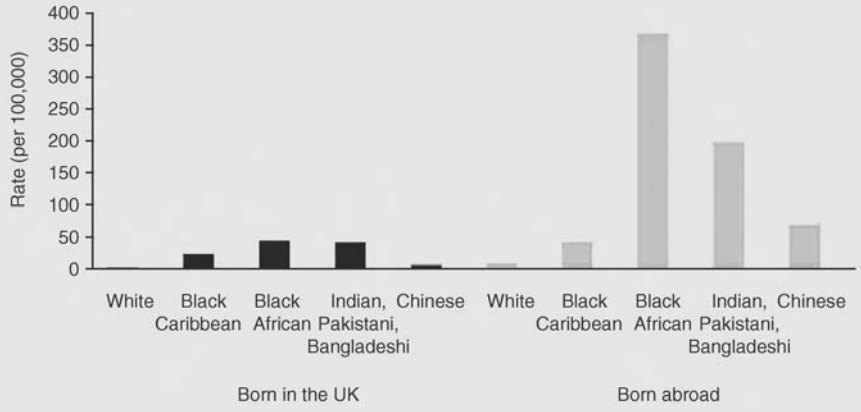

Figure 15.6 TB rates by place of birth and ethnic group, England, Wales & Northern Ireland, 2002

Source: Enhanced Tuberculosis Surveillance, Labour Force Survey population estimates

Outbreaks

The principles of outbreak investigation for TB are the same as for any outbreak (see Chapters 5 and 6). There are however some special considerations in a TB outbreak, because of the long incubation period and the chronic carrier status of the source case. In case-to-case transmission, finding the primary case is important because, unlike most other case-to-case outbreaks, the TB pattern is different. With most case-to-case outbreaks, transmission is by a chain pattern – case A, the primary case,

to B (and maybe a few others), case B to C (or more) and so on. In TB outbreaks, as well as in some blood-borne viral and bacterial infections, case A transmits infection to cases B, C, D or more. The chain pattern is much less common, or much less commonly detected. If case A is the source case, and has smear positive TB, contact tracing must begin. A good plan is to divide contacts into two or three rings round the primary case. The innermost ring would consist of very close contacts (such as family), the two outer rings medium-close contacts (e.g. work colleagues) and remote contacts. If patients are medically or politically vulnerable, for example in a hospital ward, the definition of a close contact may need to be widened. The close contacts need urgent investigation, and if some are found to be infected, the ring is widened, and if some of these again are found to be infected, the ring widened still further. Sometimes investigating the source of the primary/index case may be worthwhile – if a source is found the case is no longer a primary case, but remains the index case.

Very occasionally, a food source may be implicated. *M. bovis* particularly, but also *M. tuberculosis* can contaminate unpasteurized milk or milk products such as cheese. Most developed countries have eradicated *M. bovis* from cattle, but unpasteurized dairy products can be imported.

Prevention and control

Activity 15.7

Given what you have learned so far, make a list of the methods available to prevent and control TB.

Feedback

The four mainstays of TB prevention and control are:

- BCG
- surveillance for case-finding and action on cases
- outbreak investigation
- chemotherapy of cases with disease

Other methods include:

- chemoprophylaxis of infection (without disease)
- improving social conditions

A control programme relevant to the country itself, which can be implemented within available resources, is needed. The key elements are surveillance to detect cases early, contact tracing, effective chemotherapy and ensuring compliance of patients.

Although included as a 'mainstay', BCG has a limited effect on TB prevention. In some countries it is not used at all. BCG is a vaccine made from a modified strain of *M. bovis*. It is a live vaccine and has to be given intradermally (for infants a special

formulation is available to be given percutaneously). The tuberculin skin test should be done first and be negative. No one knows how BCG works, or which component of it works. Its main benefit appears to be in preventing the breakdown of the primary complex from causing miliary and meningitic TB. Moreover its effectiveness seems to vary with different populations. BCG should also be considered for tuberculin-negative HCWs who have been in contact with, or likely to be in contact with, TB cases; staff working in certain types of care homes and prisons; and veterinarians in contact with susceptible animals. Chemoprophylaxis, not BCG, should be considered for HIV positive people in contact with open TB.

Surveillance and action on cases is an important method of controlling TB. Primary cases may have infected several close contacts before the diagnosis is established. Nevertheless if secondary infections can be detected early, they can be treated before they themselves become infectious. Contacts who are tuberculin negative immediately after contact should be retested six weeks later. If still negative they should be given BCG, if positive they can be assumed to have contracted TB and should be considered for chemotherapy. This system is effective at least in preventing the further spread of TB but does depend on good organization of health services and contact tracing. A written strategy and protocol for dealing with newly diagnosed infectious cases is essential.

Activity 15.8

Is the long incubation period of TB an advantage or a disadvantage in outbreak investigation?

Feedback

The long incubation period of TB is helpful in that there is time to detect and treat early cases. Its disadvantage is that prolonged follow-up of contacts is necessary.

TB is one of the infectious diseases in which chemotherapy can prevent further cases. However, compliance tends to be poor, partly because of the long period needed for cure and partly because of the nature of many persons affected by TB. Poor compliance is serious, because it encourages drug resistance and may not prevent new infections. Various strategies for patient compliance have been tried. Directly observed therapy (DOT) has been fairly successful and the WHO website cited at the end of the chapter provides more detail than can be included here. The DOT strategy for TB control consists of five key elements:

- government commitment to sustained TB control;
- detection of TB cases through sputum smear microscopy in people with symptoms;
- regular and uninterrupted supply of high-quality anti-TB drugs;
- six to eight months of regularly supervised treatment (including direct observation of drug-taking for at least the first two months);
- reporting systems to monitor treatment progress and programme performance.

Sputum smear testing is repeated at the end of treatment, and after two months in some countries to check progress. The recording and reporting system ensures that the patient's progress can be followed throughout treatment. It also allows assessment of the proportion of patients who are successfully treated, giving an indication of the quality of the programme. Since its introduction in 1991, more than 13 million patients have received treatment under the DOT strategy, and 95 per cent have been cured.

In children especially, chemoprophylaxis is sometimes given to prevent their getting TB. Chemoprophylaxis is also increasingly being considered for HIV-positive patients. Isoniazid is the drug most commonly used. The use of chemoprophylaxis must always be considered very carefully and discussed with a specialist.

Improving social conditions is an ideal, but is difficult to achieve over the short term. There are many other benefits to improving social well-being.

Summary

You have seen how TB is almost unique among infectious diseases in its protean manifestations, its ability to reactivate, the many different methods that have to be used to control it, and the difficulty and length of successful treatment. Its incidence in most high-income countries decreased over at least a century without any real medical intervention. Its resurgence in some countries may be associated with HIV infection, poverty and homelessness, movements of peoples between countries, multidrug resistance and other unknown factors. As with many other infections, intensive surveillance is the cornerstone of successful control. Adequate clinical and laboratory backup are essential.

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Bhatti N *et al.* (1995) Increasing incidence of tuberculosis in England and Wales: a study of the likely causes, *British Medical Journal*, 310: 967–9.

Roberts CA and Buikstra JE (2003) *The Bioarchaeology of Tuberculosis*. University Press of Florida, Gainesville, FL.

WHO (2005) *Tuberculosis*, www.who.int/gtb/tbestimates/xls.

Useful website

WHO factsheets on TB: www.who.int/mediacentre/factsheets/fs104.

16 Gastrointestinal infections and food poisoning

Overview

In this chapter you will learn about gastrointestinal infections and food poisoning (FP). As with most infectious disease, understanding the underlying microbiology is the key to understanding these infections, and how to prevent them. Bacterial and viral causes of FP and gastroenteritis (GE) will be considered, as will those toxins which are mediated by a bacterium. Some non-infectious causes of acute gastroenteritis are included as it is important to think of them when investigating an outbreak. Hepatitis A is not normally considered with food poisoning as it is more commonly transmitted by direct contact. Hepatitis A as a result of food is nevertheless important and is considered in Chapters 6 and 17.

Learning objectives

After studying this chapter you will be better able to:

- **describe the common causes of GE and FP, including some non-infectious causes**
- **understand the basic microbiology of these conditions**
- **follow a rational approach to investigating an outbreak of GE or FP**
- **manage an outbreak of GE or FP**
- **understand the principles of food hygiene**

Key terms

Acute hypotension Sudden loss of blood pressure.

Anaerobic organisms Those that require absence of oxygen for growth.

Emetic Producing vomit.

Guillain-Barré syndrome A complication of campylobacter and other infections which presents as a symmetrical paralysis of limbs and sometimes respiratory muscles.

Motor end plate Where nerve meets muscle and releases a chemical, acetylcholine, causing the muscle to contract. Important in botulism.

Nosocomial infection Infection acquired in hospital.

Phage (bacteriophage) A virus which parasitizes a bacterium, and reproduces within it. Can be used for typing (e.g. salmonella) and determining virulent strains.

Septicaemia 'Blood poisoning' – a more than transient invasion of the blood with a bacterium.

Tenesmus A continual feeling of wanting to defaecate without necessarily being able to.

Toxoplasma gondii A protozoon not considered as a cause of food poisoning although it can infect beef. Can be hazardous to the foetus if consumed by pregnant women.

Features of gastroenteritis (GE) and food poisoning (FP)

GE is a clinical term and implies acute diarrhoea and/or vomiting caused by a micro-organism or toxin (chemical or organic) acting directly on the gastrointestinal tract (GI tract). It is brought about by an inflammation of the bowel. Thus travel sickness, which causes vomiting, is not GE, nor are chronic conditions such as Crohn's disease and ulcerative colitis, neither of which is acute or self-limiting. Thus, a definition of GE is 'an acute inflammation of the intestinal tract which induces one or more of the following: vomiting, diarrhoea and colicky abdominal intestinal pain'.

With diarrhoea, the consistency of the stool is more important than its frequency. One definition is of a liquid stool, the definition of a liquid being a substance that takes the shape of the container into which it is deposited. Most definitions for epidemiological studies include a frequency of three or more loose stools a day. However, some viruses such as norovirus often produce only one or two loose stools a day with nausea and vomiting being more prominent symptoms. As usual with case definitions there is a fine line between choosing one that is too specific or too sensitive.

FP is an acute illness that follows the ingestion of food. The illness is usually, but not always, gastrointestinal – botulism and listeriosis both cause food poisoning without significant GE. The incubation period is fairly short, generally less than a week. Typhoid, brucellosis and hepatitis A are not considered as FP, although they can all follow ingestion of food or water. Typhoid is however considered briefly below.

GE is preventable, yet it is a significant cause of morbidity and mortality, both in the developed and (mainly) in the developing world. In some countries it is still the leading cause of death in infants. In more developed countries, morbidity in terms of hospitalization and time off work, and some accompanying mortality, make it a significant problem also. In England and Wales, GE costs the country almost £750,000,000 (1994/5 prices) a year.

In the descriptions that follow, for simplicity, GE and FP will be considered together, rather than separating those organisms that cause GE from those that cause FP, especially as some organisms that primarily cause GE have been known to cause FP also. In practical terms it is useful to separate them into short, medium and long incubation period infections, although the divisions are slightly arbitrary and there may be some overlap. This classification is helpful when investigating FP outbreaks.

Short incubation period infections (less than eight hours)

When the incubation period is short, clearly most organisms will not have had time to grow or move far down the gastrointestinal tract. Thus the most likely symptom is vomiting, and the most likely agent a preformed toxin. The main causes of short incubation period GE are shown in Table 16.1. Of these *Staphylococcus aureus* and *Bacillus cereus* are the most important.

Table 16.1 Common causes of short incubation period GE

Cause	*Incubation period (range)*
Staphylococcus aureus	2–4 h (30 min–8 h)
Bacillus cereus [emetic type]	1–6 h
Bacillus subtilis	15 min–3 h
Scombrotoxin	10–60 min
Heavy metals	5 min–2 h
Raw red kidney beans	1–3 h

Source: adapted from Noah (1992)

Staphylococcus aureus

Staphylococcus aureus is one of the few FP organisms that almost invariably comes from a food-handler, who will either have an infection, such as a wound, boil or abscess, or will be carrying the organism asymptomatically in the nose, throat or elsewhere on the surface of the body. The organism is transferred to a food after cooking, grows given the right conditions, and forms a toxin. Only certain types of staphylococci produce enterotoxin. Although the staphylococci themselves do not survive boiling, the toxin is heat-resistant, so reheating will not destroy it. Nor will freezing. Staphylococci seem to prefer slightly salty or sugary foods. Thus hams and desserts, including ice-cream, which have had a long period at room temperature after cooking or preparation, are common vehicles of staphylococcal food poisoning, though any moist protein-rich food is vulnerable.

The time to onset and the severity of symptoms are dependent on the amount of toxin ingested. Vomiting is often dramatic; nausea, abdominal colic and diarrhoea can occur. Very rarely there is acute hypotension, which may be fatal. More commonly, the illness is over in a day or two.

Many people carry staphylococci without knowing it. The organism can also infect a cut or boil. To confirm the diagnosis the type found in the food and/or the patient should be the same as that in the food-handler. The suspected food usually contains $>10^6$ organisms/gm and enterotoxin can be identified also, and typed. Reheating may have destroyed the staphylococci but not the toxin. Enterotoxin can also be detected in vomitus of the patient.

Bacillus cereus (emetic type)

Bacillus cereus, unlike *Staphylococcus aureus*, is a 'natural' organism found in some foods, especially rice. It is normally harmless, but given the right conditions of

moisture and warmth, it will grow and produce toxin. Unlike staphylococci, it is not destroyed by boiling as it forms spores. Thus if rice is boiled and left to cool slowly the spores become vegetative and produce an emetic toxin. This most commonly happens when a large bulk of rice is cooked, left to cool in a warm atmosphere such as a kitchen for many hours, and then served without reheating or with brief reheating. *Bacillus cereus* FP used to be common in restaurants serving Chinese fried rice, but with good education and hygiene it is now rare.

Activity 16.1

How would you prepare rice to avoid FP?

Feedback

Cook in small quantities. If boiled in bulk, eat immediately. If it has to be stored, divide into small portions, cool rapidly and store in a refrigerator.

As with staphylococcal FP, diagnosis cannot be made solely by identifying the organism in a suspect food as it may be normally present. Finding toxin in sufficient concentrations in the food is good evidence, as is the finding of the organism (and the same serotype) in high concentrations (10^6–10^8/g, minimum 10^5) in the cooked food, as well as in the stools and/or vomit of cases, and a food-handler.

Bacillus subtilis

Bacillus subtilis is another organism found in a variety of natural foods and causes a similar set of symptoms as *B. cereus*. Meat pies, sausage rolls, curries with accompanying rice dishes, and even bread, crumpets and pizzas have been implicated. *B. licheniformis* and *B. anthracis* are not causes of short incubation period FP but are other members of the same genus. *B. licheniformis* causes diarrhoea and the incubation period is about eight hours. *B. anthracis* FP is caused by the consumption of insufficiently cooked infected meat, usually carcasses of animals that have died of anthrax. The incubation period is from two days to many weeks. Symptoms are lower gastrointestinal – diarrhoea and abdominal colic – though vomiting can also occur.

Other causes

The other causes shown in Table 16.1, are not all infectious but must be included in the differential diagnosis. Do not assume that every type of GE is of microbiological origin. The heavy metals induce vomiting very quickly, and should be easy to identify in the food or vomitus.

Scombrotoxin is formed as a result of enzymes and bacteria in the flesh of 'scom-

broid' fish (tuna, mackerel, herring) if the storage conditions are inadequate. A histamine-like substance is produced which, if above 1000ppm (100mg/100g fish), induces hot flushing, red skin, palpitations and a burning mouth soon after ingestion. The toxin is heat and canning stable.

Paralytic shellfish poisoning can result from eating shellfish harvested in waters with an overgrowth of algal blooms (red tide). The saxitoxin of dinoflagellate plankton may cause paralysis, pins and needles in the limbs, and difficulty in swallowing and breathing. It can be fatal.

Raw red kidney beans are highly toxic, as they contain kidney bean lectin, a phytohaemagglutinin similar to ricin. Cooking these beans even at 80°C is not only insufficient but also concentrates the toxin, making it worse. Just four to five beans can cause symptoms of severe nausea, vomiting (both within a few minutes) and diarrhoea somewhat later. White kidney beans contain smaller amounts of the toxin.

Medium incubation period infections (8–48 hours)

Activity 16.2

If the short incubation period infections are caused by preformed toxins, and are characterized by vomiting as a predominant symptom, what would you expect for the medium and long incubation period infections?

Feedback

Diarrhoea is more prominent. Symptoms are induced either by a direct effect of the organism on the lower intestine, or a toxin being formed in the intestine by the micro-organism.

The commonest causes of medium incubation period GE are shown in Table 16.2.

Table 16.2 Causes of medium incubation period GE

Cause	*Incubation period (range)*
Salmonellas	12–36 h (6–72 h)
Clostridium perfringens	8–24 h
Clostridium botulinum	12–36 h (6 h–10 days)
Shigellas	24–48 h
Escherichia coli	12–72 h
Bacillus cereus [diarrhoeic type]	8–16 h
Norovirus	24–48 h (10–50 h)
Aquatic organisms	
Vibrio parahaemolyticus	12–24 h (4–72 h)
Vibrio cholerae	1–3 days (12 h–5 days)
Aeromonas sp	18–24 h
Plesiomonas shigelloides	~24 h

Source: adapted from Noah (1992)

Salmonellas

Salmonellas are an extensive species of organisms that are probably the most common known causes of FP in developed and middle-income countries, though not the most common causes of GE. They infect animals and birds as well as man. Fortunately, a high dose (about 10^7 organisms) is normally required to cause symptoms, otherwise it would be even commoner. This means that foods usually have to stand at warm temperatures for some time before a high enough dose is reached for symptoms to occur. Having said that, salmonellas can nevertheless cause nosocomial and institutional infections not related to food, as the dose required for vulnerable elderly, hospitalized or immunosuppressed patients in close proximity to each other is lower. Smaller doses of salmonellas can cause symptoms if the contaminated food has a high fat content – for example, cheese and chocolate.

The illness can be severe, with fever, diarrhoea and abdominal pain the predominant symptoms; vomiting is less common. Infection outside the gastrointestinal tract includes septicaemia, meningitis, arthritis and multiple abscesses. *S. typhi* and *S. paratyphi* cause a more serious febrile illness (enteric fever); a smaller dose is required than for most salmonellas.

Contamination of food by salmonellas occurs in three main ways. First, infection of animals and poultry may result from their feeds or other sources. Chickens and turkeys for example can become infected through contaminated processed bulk foods. Infection of the oviducts of chickens may lead to contaminated eggs, as has happened recently through much of the developed world with *S. enteritidis*. Second, almost any foodstuff can be directly contaminated by faeces-containing material (e.g. water, sewage or direct faecal contact). Pollution can occur from birds, animals or humans. Salmonellas do not form spores, but can survive on dried foods without multiplication for long periods. Slow drying of foods contaminated by salmonellas makes them more resistant. Examples include mung beans, black pepper, dried herbs and spices, chocolate, spent yeast (a flavouring vehicle in packet potato crisps), infant dried milk and salamis. Washing raw salad vegetables in polluted water has also caused outbreaks. Third, cross-contamination may occur from one food to another in the kitchen. A 'food-handler carrier' is a very rare source of salmonella FP. Nearly always it is poor food-handling of a contaminated food that causes FP, not direct contamination of food by a carrier. Salmonellas can be isolated from food, stool, or other local site of infection, such as blood or cerebro-spinal fluid (CSF). For more common strains further typing using phages is available.

Clostridium perfringens

Other members of this genus include those that produce tetanus and botulinus toxin, two of the most toxic substances known to man. The clostridia are anaerobic spore-forming organisms. *Clostridium perfringens* is found in the gut of animals and poultry, and can contaminate carcasses during evisceration. Spores are not destroyed by heating. If meat is cooked in bulk, as in a stew or meat pie, or inadequately reheated, the spores of *Clostridium perfringens* germinate during

cooling and multiply to large numbers if the dish is left for a long period in the warmth. After ingestion the toxin is formed from multiplying bacteria in the intestine, leading to colic and diarrhoea, sometimes associated with nausea. Both toxin and vegetative cells appear to be necessary to produce symptoms. Death is uncommon, but can occur in the debilitated. *C. perfringens* type A causes this milder type of FP; type C causes a much more severe GE in some parts of the world (enteritis necroticans, or 'pig bel').

Finding the organism in stool or food is not enough; finding high numbers ($>10^5$ organisms/gm in food, $>10^6$ organisms/gm in stool) is necessary. Typing and demonstration of enterotoxin are also available as methods of diagnosis.

Clostridium botulinum

The toxins of *C. botulinum* affect the nervous system, more specifically the motor end plate, thus preventing the release of acetylcholine and paralysing the muscle. They are the most toxic substances known. Types A, B and E affect man. Type E is from fish. The toxins are formed when *C. botulinum*, which is common in soil, is allowed to grow in food under anaerobic and other conditions suited to its growth. Low pH and high salt content inhibit its growth, so that pickling is generally safe. Symptoms include nausea, vomiting or diarrhoea, followed by symmetrical paralysis of the cranial nerves leading to double or blurred vision and difficulty in swallowing and speaking. Recovery is prolonged and life support may be necessary. The fatality rate is high. Canned and fermented foods which have been inadequately processed can cause botulism. Commercial canning generally reaches high enough temperatures to kill spores.

Wound botulism can also occur. Sometimes babies have a milder form of generalized botulism which is attributed to spores ingested in foods, such as honey, colonizing the intestine and forming toxin.

The toxin can be detected in food but the amount necessary for symptoms is, as a rule, too small to be detected in serum.

Activity 16.3

Botulinus toxin is preformed in food, but the incubation period is longer than for other preformed toxins. Why do you think this might be so?

Feedback

The toxin does not act primarily on the intestine, and has to be absorbed into the bloodstream and then transmitted to the nerve/muscle junctions before symptoms of paralysis appear.

Shigellas

Shigellas are a common cause of GE worldwide, and an important cause of death from GE, especially in children in developing countries. In developed and most middle-income countries, *Shigella sonnei* is the commonest serogroup and causes the mildest form of the disease. In developing and some middle-income countries, *Shigella flexneri* is the commonest. *Shigella boydii* and *Shigella dysenteriae* cause illness mainly in developing countries. *S. dysenteriae* can cause serious illness with a high mortality rate. Shigellas invade the distal part of the small intestine and the colon, and cause acute watery, mucoid or bloody diarrhoea with tenesmus a characteristic symptom. Fever and intestinal colic are frequent accompaniments.

Activity 16.4

Only 10–100 organisms can cause symptoms. Given this fact, what type of outbreak do you think would be most likely, and which age groups most likely to be affected?

Feedback

Case-to-case transmission is the commonest form of spread, starting from a symptomatic or asymptomatic carrier. Overcrowded institutions with poor facilities are particularly vulnerable to prolonged outbreaks; they include refugee camps, psychiatric hospitals, children's institutions and prisons. Children are most likely to be affected.

An example of this type of outbreak is shown in Figure 7.5. Affected patients may excrete the organisms for some weeks. Kindergarten and primary school children are mainly affected, except in food or waterborne outbreaks. Waterborne disease causing more explosive outbreaks can occur. As the organism, unlike salmonellas, does not grow well on food, FP is uncommon though outbreaks caused by lettuce have recently been reported. Food-handlers may also occasionally cause outbreaks. Flies may also transmit infection to food. Diagnosis is made by isolation of the organism from stool and serogrouping and typing of strains.

Escherichia coli

Escherichia coli cause infections in almost any part of the body, including blood (septicaemia) and the urinary tract. They are part of the normal flora of the gut of humans as well as of many mammals, including cattle, sheep and goats. Certain pathogenic strains cause diarrhoea using a wide range of mechanisms. They are classified according to these mechanisms into the following main groups: enteropathogenic (EPEC), enterohaemorrhagic (EHEC), enteroinvasive (EIEC) and enterotoxigenic (ETEC). New groups including diffusely adherent (DAEC) and enteroaggregative (EAEC) are rare and will not be considered further. Some EHEC strains (STEC) produce a shiga-like toxin (verocytotoxin), which includes *E.coli* O157:H7.

The EPEC group of *E. coli* causes disease and outbreaks in infants under 1 year of age. It is more common in summer. Outbreaks are infrequent in developed countries, more common in developing and some middle-income countries. Diarrhoea can be prolonged, and in low socioeconomic groups death is not uncommon. Food-borne outbreaks are rare.

The EIEC group causes a more severe dysentery-like syndrome, though watery diarrhoea is also common. Like the EPEC strains, they cause illness more frequently in less well developed countries. Occasional food-borne outbreaks occur.

The ETEC group of *E. coli* is a common cause of travellers' diarrhoea. It is also a major cause of GE in children and others in developing countries. By the time they reach middle childhood these children will be immune, but not those tourists who visit! These *E. coli* produce enterotoxins, one of which is similar to cholera toxin.

Activity 16.5

What type of diarrhoea would you expect ETEC strains to cause?

Feedback

As it produces a toxin similar to that produced by cholera, a profuse watery diarrhoea is the characteristic symptom. Full blown 'rice water' stools and acute dehydration leading to collapse are, however, rare. Nevertheless some cases of travellers' diarrhoea require admission to hospital and rehydration, as do many infected children in developing countries. Although in a few instances ETEC travellers' diarrhoea has been associated with certain foods, the associations are rarely strong, and most cases are not known to be food-borne.

EHEC form another important group of pathogenic *E. coli*. Although the incubation period is long (see Table 16.3), it will be considered with the other *E. coli* groups here. *E.coli* O157:H7 is a member of the group that produces shiga toxins 1 and 2. There are other less common pathogenic serotypes. Production of toxins is dependent on phages that some of these bacteria carry. Normally *E. coli* O157:H7 produces diarrhoea ranging from mild to severe and bloody. However, in about 2–3 per cent of cases it causes the serious complication of hemaolytic uraemic syndrome which causes haemolysis, thrombocytopaenic purpura and renal failure, and has a high case fatality.

E. coli O157:H7 and other STEC are the only group of *E. coli* that are commonly spread by food. *E. coli* O157:H7 is a commensal in the intestines of cattle in particular, deer and probably other mammals. Contamination can occur directly to carcass and meat. Beef products are a well-known cause of *E. coli* O157:H7 infections. By mincing or grinding meat for hamburgers, the organism can spread throughout the food and cause infection. Good hygiene practice can diminish the prominence of minced beef as a cause of *E. coli* O157:H7 infection. Cross-contamination to raw vegetables and other foods can occur from raw beef products or *via* the faeces of

animals or contaminated water. Salads and green vegetables eaten raw have been incriminated, as has unpasteurized milk and milk products. Milk labelled as pasteurized but where the pasteurization process has failed is another important cause of outbreaks. Direct contact with cattle, as with children visiting farms, is another risk factor, as is swimming in contaminated water. Humans can, less commonly, infect other humans.

To diagnose, the organism is commonly isolated from stools, so an *E. coli* infection must be suspected and specific tests requested. Different strains of *E. coli* are given numbers depending on their antigens, and depending primarily on the O antigen (somatic cell wall antigen) assigned to one of the six groups. Virulence and enterotoxin can also be tested for.

Activity 16.6

Another cause of FP is *Bacillus cereus* (diarrhoeic type). It forms an enterotoxin in the intestine. What other organism, already discussed, does *B. cereus* resemble?

Feedback

Clostridium perfringens food poisoning, which is however much more common. The symptoms are indistinguishable, and the incubation periods also similar. This type of *B. cereus* can be caused by a wide variety of foods, including meat, vegetables and dairy products.

Norovirus

Norovirus has recently been recognized as a common – perhaps *the* most common – cause of GE in the world. It is the most frequently identified cause of non-bacterial GE in the UK. This follows its identification and the introduction of a diagnostic test. The name (now classified as a calicivirus) encompasses norwalk-like virus, small round-structured virus, and various other filterable agents recognized for some years to cause GE. These gastrointestinal syndromes have been known by various names including 'winter vomiting disease' and 'gastric flu'. There is a strong winter seasonal pattern. Symptoms are those of mild to moderate GE, with vomiting and nausea slightly more prominent than diarrhoea. These symptoms are characteristically accompanied by mild fever, aches and pains and malaise. Vomitus as well as faeces has been shown to be infectious. Evidence is accumulating that vomit releases infectious virus particles into the air and that these can cause infection, either through aerosol or by settling on objects and furniture and then transferring to another person.

In many ways the epidemiology of norovirus is similar to that of hepatitis A (see Chapters 7 and 17). Below are the important facts about hepatitis A you learnt about in Chapter 7. Similarities with and differences from norovirus are added in italics.

1 A very small dose is required for infection. *True*.
2 Route of spread is virtually always faecal-oral. *True*.
3 The incubation period is 15–40 days, median of 28 days. *Different* – see *Table 16.2*.
4 Patients are at their most infectious while asymptomatic. *True*.
5 By the time jaundice/symptoms appear they are usually no longer infectious. *Untrue – possibly less infectious, but infectiousness continues for about 48 hours after diarrhoea stops*.
6 Asymptomatic infections are common, especially in the young. Asymptomatic cases are still infectious. *Untrue*.
7 There are no chronic carriers of hepatitis A virus. *True*.
8 Second infections are unknown – immunity seems to be permanent. *Untrue*.
9 The organism is hardy and can survive on surfaces, in water and freezing. *True, norovirus is probably even hardier*.

In addition, humans are the only known reservoir for both. The diagnosis can be performed by identification in stool by electron microscopy either directly or by binding to antibody, and by reverse transcription polymerase chain reaction (RT–PCR). There are preliminary reports that it can now be isolated.

Activity 16.7

What types of outbreak would you expect norovirus to cause?

Feedback

Exactly the same as hepatitis A: point source, continuing source and case-to-case. Just as hepatitis A can be transmitted by a carrier food-handler to a food, so can norovirus. It can also infect shellfish harvested from faecally-polluted waters, and frozen or other foods distributed widely, causing point source or continuing source outbreaks.

Case-to-case transmission has become much more common with norovirus than hepatitis A. Many large ongoing outbreaks have occurred in hospitals and other institutions, cruise ships and hotels, some of which have had to be closed down for disinfection (not always with success). Health care-associated infections are a particular burden (see Chapter 19).

Activity 16.8

Case-to-case spread now accounts for about 80 per cent of known outbreaks of GE in England and Wales.

Can you think of some possible reasons why case-to-case transmission of norovirus is so much more common and protracted than for hepatitis A?

Feedback

Possible reasons are:

- norovirus is even more infectious than hepatitis A (one to ten particles probably enough)
- norovirus is even more stable in the environment than hepatitis A
- it is more resistant to disinfection
- the potential for spread is much greater because vomit is infectious, and vomiting, especially in children, can be projectile
- there is considerable antigenic diversity among the noroviruses, and immunity is probably type-specific and possibly only temporary, so more people are susceptible to it than hepatitis A

Aquatic organisms

Vibrio parahaemolyticus, *Vibrio cholerae*, *Aeromonas sp* and *Plesiomonas shigelloides* are aquatic organisms that can thrive in brackish water. The vibrio organisms are not found in deep seas, only in shallow coastal waters. Deep-sea fish do not harbour these organisms, but can become contaminated when brought ashore. Cooking destroys these organisms. A pandemic clone of *Vibrio parahaemolyticus* is thought to account for an upsurge of infection in the Far East and the US. The incidence of this infection is particularly high in Japan, whose inhabitants eat a lot of fish, often served raw. Severe bloody or mucoid diarrhoea may occur, with fever and vomiting less common. Another member of this genus, *Vibrio vulnificus* is a more common cause of FP than *V. parahaemolyticus* in the USA; it can also cause septicaemia if in contact with a wound.

Vibrio cholerae has been described in Chapter 3. *Aeromonas sp* has now been accepted to cause FP through contaminated fish or shellfish. There are still some doubts about *Plesiomonas shigelloides*. The diagnosis is made by culture of the organism from faeces or food. For *V. parahaemolyticus*, only the Kanagawa-positive strains cause GE.

Long incubation period infections (longer than 48 hours)

Table 16.3 lists the main causes of GE in this group.

Campylobacters

Campylobacters are the most common known bacterial cause of GE in most of the developed world. Infection is not commonly attributed to a food and in most cases the cause is unknown. Outbreaks are infrequent for such a common infection. Campylobacters tend to cause a severe GE – diarrhoea with blood and mucus, abdominal colic and fever. Vomiting is unusual. Serious complications include

Table 16.3 Causes of long incubation period GE

Cause	*Incubation period (range)*
Campylobacters	3–5 days
E.coli O157:H7	3–5 days
Listeria monocytogenes	Up to 3 weeks (diarrhoea <1 day)
Yersinia enterocolitica	24–36 h to 5 days
Giardia lamblia	7–10 days (3 days–4 wks)
Cryptosporidiosis	4–12 days
Rotavirus	1–7 days
Entamoeba histolytica	2–4 weeks (or many months)
Cyclospora cayetanensis	~ 1 week

Source: adapted from Noah (1992)

septicaemia and Guillain-Barré syndrome. The two main types causing GE are *C. jejuni* and *C. coli*, with *C. jejuni* commoner.

Campylobacter *spp* are found in the intestines of many animals and birds, including cattle, horses, household pets and chickens. Milk and milk from bottles whose tops have been pecked by birds have caused outbreaks, as has water contaminated by animals or birds. Barbecued meats and undercooked poultry have caused infections. Other risk factors include travel to foreign countries; handling and cooking of food, especially raw meat; contact with animals and pets (especially those with diarrhoea) including visiting an animal farm; swimming; and sailing. Flies are thought to spread infection. In most cases no source of infection has been found. Diagnosis is performed by isolation using special media. There are two typing schemes.

Listeria monocytogenes

This bacterium is a strange organism that breaks many rules. It is a cause of FP but primarily causes meningitis, septicaemia or endocarditis, multiple abscesses, or abortion in pregnant women. These serious manifestations occur after about three weeks, but GE if it occurs does so within about one day. The bacterium grows even at normal refrigeration temperatures, though slowly. It does not form spores but is very resistant to the environment and may survive the short-term/high-temperature method used by some pasteurization processes. It takes advantage of people at their most vulnerable: during the foetal and neonatal periods, pregnant women, the elderly and the immunocompromised. Fortunately this unpleasant infection is rare, as the fatality rate for meningitis or septicaemia is high – about one in three. Foods implicated include paté and delicatessen meats, soft cheese, raw milk and hot dogs. The organism is found in farms and animals and in the environment around farms – silage, fodder, mud, water. Farm and wild animals can be infected and act as reservoirs. Diagnosis is made by isolation from the site of infection (blood, CSF etc.). Serovars 1/2a, 1/2b and 4b are the most common in human infections.

Yersinia enterocolitica and *Y. pseudotuberculosis*

Infections with *Y. enterocolitica* are unusual, though reported in Scandinavia and other northern countries more frequently than in other developed countries. They have some similarities with listeria in that they are zoonoses, may survive pasteurization (especially the high-temperature/short-time milk treatment), and can reproduce at refrigeration temperatures. Fortunately the symptoms are milder than with listeriosis – fever with watery, sometimes bloody, diarrhoea, mostly in the 0–4 age group, but can occur at any age. More serious disease is rare. Foodstuffs implicated include raw milk, other dairy products, undercooked pork and pork sausages, and tofu. *Y. pseudotuberculosis* is similar to *Y. enterocolitica* though it is more commonly associated with mesenteric adenitis. It has been put forward as an aetiological agent of Crohn's disease. Pigs are thought to be the main reservoir for *Y. enterocolitica*. Diagnosis is made by isolation from stool and requires special media. Pathogenic strains cannot be distinguished with certainty in the laboratory.

Giardia lamblia

Giardiasis is found worldwide. Incidence is highest in children, though all ages may be affected. *G. lamblia* is a protozoon which infects typically the duodenum and jejunum. Thus it can interfere with absorption of food and the diarrhoea typically includes fatty offensive stools, abdominal colic, bloating and weight loss. Patients may feel tired and debilitated. Diarrhoea may become chronic. However, symptoms range from severe to mild and asymptomatic. Asymptomatic infections are common. The trophozoites of *G. lamblia* multiply in the upper part of the small intestine, but form cysts as they migrate downwards, and are excreted as cysts, which then infect others. Cyst excretion occurs with recovery, so is more likely to be found in formed stool, including those with asymptomatic infections. Thus, paradoxically, patients are at their most infectious when newly-recovered or asymptomatic. Cysts become trophozoites in the stomach of the recipient. Reinfection and repeated infections occur. Breast milk may protect against infection. Some infections may be acquired from animals.

Infections are common where there is poor sanitation and low socioeconomic status. The cysts of *G. lamblia* are resistant to chlorination, so drinking or swimming in chlorinated but unfiltered water is a risk. Boiling water destroys the cysts. Young children who are not yet fully toilet trained have been known to have an 'accident' in a pool and cause an outbreak. Infection acquired directly from an excreter is common. Transmission by food also occurs and sexual transmission has been documented.

Cysts can be demonstrated (either directly or using immunological methods) in formed stool, or trophozoites in diarrhoeic stool. The presence of cysts does not clinch the diagnosis, as asymptomatic infection is common. Cyst excretion may vary, so three specimens taken at 48-hour intervals are required. Duodenal specimens, obtained by aspiration or thread, may have to be examined in difficult cases.

Cryptosporidium parvum

This is another intestinal protozoon which is widespread in vertebrates. It has become important because of the chronic, serious and potentially fatal diarrhoea it causes in people with AIDS and others who are immunocompromised, and because of the massive outbreaks of GE caused by contamination of water supplies. Oocysts containing sporozoites are excreted in stools of affected and asymptomatic persons and animals. These are ingested by the new host, leading to a new life cycle in the host's small intestine. In people with normal immune systems, the course can be variable and fluctuating, with recurrent bouts of profuse watery diarrhoea and intestinal colic. Recovery may take time but is usually spontaneous except in immunocompromised patients when the infection may be life-threatening. Infection rates are highest in children, and generally in developing countries. Like *Giardia*, the organism is resistant to chlorine so filtration of water supplies is necessary. Outbreaks have occurred following drinking, swimming or other contact with unfiltered water. In one extensive outbreak, contamination of city water supplies was caused by water run-off from manured fields following heavy rains. Other risk factors for infection include close family or other contacts of cases or carriers; men who have sex with men; and people in contact with animals.

Diagnosis is most often made by the demonstration of oocysts of cryptosporidium in the stool of affected patients. Immunological methods are available also. Oocysts can also be detected in water and other environmental samples.

Rotavirus

Rotaviruses, part of the family of reoviruses, is probably the most important cause of diarrhoea in children under 5, especially infants (but not neonates), throughout the world. Infection is uncommon in older children and adults; indeed antibody is generally acquired by 3 years of age. The clinical features are not distinguishable from other diarrhoeal infections. Dehydration can be a problem, especially in developing countries, and immunosuppressed children are particularly vulnerable. The virus is responsible for large numbers of deaths each year mainly in developing countries. People are at their most infectious while symptomatic. Transmission through fomites may occur and airborne transmission has been postulated. The fomite route is important because the virus can survive for a long time on inanimate objects, such as children's toys. It is also fairly resistant to disinfectants. The seasonal pattern of rotavirus infection shows a strong winter January/February peak in temperate zones, and has been remarkably consistent since surveillance began. In tropical countries there is little seasonal variation. For such a common infection outbreaks, including food-borne outbreaks, are surprisingly rare. Nosocomial and day nursery outbreaks have however been recorded. Rotaviruses infections are common in animals but the infecting agents do not normally infect man.

The case for infant mass immunization against rotavirus is probably unassailable. An effective rotavirus vaccine was introduced in 1998 but caused intussusception in some of the infants to whom it was given. It was withdrawn in 1999.

Most infections in humans throughout the world are caused by group A, which is

the predominant group in animals also. Group B has caused epidemics in adults in China. As routine methods for growing the virus are not available, diagnosis is made by identifying the virus in stools by electron microscopy, or using immunological methods. Serological rises in antibody can also be demonstrated.

Cyclospora cayetanensis

This recently described coccidian protozoon causes watery, profuse diarrhoea. In the immunocompromised symptoms can persist for long periods, and even in a healthy person can last for up to six weeks. It is an uncommon but well recognized cause of travellers' diarrhoea. The main risk factors are drinking, swimming and other contact with contaminated water. An extensive food-borne outbreak in the USA was traced to imported frozen raspberries, and others to lettuce and fresh herbs.

Streptococcal pharyngitis

Although clearly not GE, streptococcal sore throat with fever can be food-borne. A food-handler with a group A streptococcus in their throat contaminates a food which is then allowed to rest at room temperature or in the warmth for a considerable period. Cheese, milk, eggs and meat have caused outbreaks. The incubation period is 24–48 hours. The source can be confirmed by isolating the streptococci from the throat of the food-handler as well as from those affected. Strains should be typed as many people carry streptococci in their throats, and there should be supportive epidemiological evidence.

Preventing gastroenteritis and food-poisoning

Although there are many causes of FP, there are fortunately some general rules to prevent most of them.

Activity 16.9

From the descriptions given above, can you identify ways to avoid FP? Go through the text carefully before compiling your list.

Feedback

From the information given above, you should have the following points:

1 Cook food thoroughly, especially meat that has been ground or minced.

2 Do not leave moist cooked foods in a warm environment for any length of time – always refrigerate.

3 Avoid cross-contamination of raw to cooked food.

4 Reheat pre-cooked food thoroughly and consume immediately.

5 Be especially careful about cooling if preparing foods in bulk.

6 Avoid eating certain raw foods unless sure they are 'clean'.

7 Wash hands before preparing salads and other foods to be eaten without further preparation.

8 Defrost frozen food thoroughly before cooking.

Although optimum temperatures for reproduction of the various FP bacteria vary slightly, in general they reproduce best at temperatures close to that of the human body – *i.e.* at 37°C with a range of 28–47°C. They double every 15–20 minutes at optimum temperatures. Reproduction virtually stops at >63°C and <4°C. They are killed off above 63°C, but the rate at which they die depends on time and temperature. Spores are not destroyed by boiling, though they are by canning, and some toxins (staphylococcal in particular) can survive boiling for about 30 minutes.

Activity 16.10

Given that in most FP the organism is already in the food, which of the precautions noted above would you want to take?

Feedback

Points (1) and (3) are especially important, points (2) and (5) also relevant.

Meat especially has to be cooked thoroughly if organisms may have penetrated below the surface. This applies to poultry, hamburgers and other minced meat products, meat pies etc. This is also important for boned and rolled meat. Be especially careful if a piece of meat is >3kg. Large frozen items containing meat or poultry should be defrosted thoroughly before cooking. Otherwise the outside will cook but the inside may remain raw.

Cross-contamination is a common fault. Contaminated food (e.g. a chicken) may be cooked thoroughly so that all the salmonellas are destroyed. If it is then placed in the same container in which it has been stored raw, or on a meat board which has been used for raw chicken, or jointed with a knife used for raw meat, organisms from these are transferred to the cooked chicken, which is re-contaminated. If given the time to grow, FP could result. Use separate chopping boards for raw and cooked meat, or wash boards in soap and hot water and leave to dry.

After cooking, do not leave the warm food out of a refrigerator for longer than one and a half hours. If the food is cooked in bulk (e.g. rice), it may take longer than this for the inside to cool, and the dish must be divided into smaller portions if it is not

going to be used shortly. Similarly with casseroles, stews and pies, spores of *C. perfringens* will not be destroyed by cooking and will germinate during the cooling process to high numbers if kept in a warm environment. Reheating must be for long enough and to a high enough temperature (*i.e.* preferably boiling) to penetrate through the bulk of the food. Reheating (as for leftovers) is only allowed once. Dry ingredients, such as herbs and black pepper, may be contaminated with salmonellas, *E. coli* or other organisms. Add these ingredients early to raw food and then cook thoroughly, or add just before consumption.

Eating certain raw foods can be particularly hazardous. Raw milk can contain a variety of undesirable organisms, including salmonellas, *E. coli*, campylobacter and streptococci (as well as *M. bovis* and brucella). Raw eggs may be a little safer now if they come from vaccinated flocks, but unless their origin is known to be safe, eggs are best cooked. Several raw shelled eggs should not be added together in a container and then stored in a warm atmosphere – just one contaminated egg can contaminate all the others. Cook them immediately. Raw shellfish, especially those that filter feed, can also be hazardous unless known to be harvested in sewage-free waters. Cleansing them in ultraviolet treated water will not cleanse them of noroviruses or other viruses, including hepatitis A. Raw minced meat should also be avoided. Steaks whose surfaces have been well seared can be eaten rare as *E. coli* do not in general penetrate the meat, but there may still be a small risk from other organisms, such as toxoplasma.

In the kitchen, surfaces, utensils, pots and dishes used for raw meats should be kept separate from those used for cooked meat or other ready-to-eat foods. Fruit and vegetables eaten raw are in the ready-to-eat category. Washing facilities should be nearby. Temperatures of refrigerators should be checked regularly and kept at 0–4°C. Frequent opening of the refrigerator will raise the temperature inside significantly. Raw meats should be kept on lower shelves and cooked foods or foods that will not require cooking on the higher shelves.

Activity 16.11

Given that food-handlers can be carriers, which of the precautions noted in the Feedback to Activity 16.9 would you want to take?

Feedback

Point 7 is especially important here.

Boils and sores should be covered with a waterproof plaster to prevent staphylococcal food poisoning. Hands should be washed in soap and hot water, and dried on a disposable towel, after going to toilet and after handling raw meat and poultry. Food-handlers with diarrhoea should preferably be put on non-food handling duties or handle only raw foods that are going to be cooked.

Activity 16.12

Work out the likely cause of each of the following outbreaks, what the problem was in the preparation of the food and what should have been done to avoid an outbreak.

Each hypothesis is subject of course to microbiological and epidemiological confirmation.

1 To make a hollandaise sauce, a caterer cracked 100 eggs into a large container and went home. Next morning, he beat the eggs, added butter and other necessary ingredients, cooked the eggs lightly and then placed in a *bain marie* to keep warm. He served the sauce with poached salmon. Outbreak occurred 12–36 hrs after the meal.
2 A man buys several chicken pieces from a supermarket, and roasts them thoroughly. He has to take them to a picnic and replaces them in the containers in which he bought them to save on the washing up afterwards. He covers them in foil. The boot of his car is full, so he puts them on the back seat. As he is early and it is a hot day he stops at a pub for a few beers. The picnic is a success but several people fall ill with diarrhoea and fever the next day.
3 The occupational health doctor of a large firm asks for advice. Employees at her firm developed acute vomiting one to three hours after eating in the canteen. No one had diarrhoea. It was an 'Indian food day' and they served curry for those who wanted Indian food and roast chicken for those who didn't. Should she close the kitchen immediately?
4 After a meal at a restaurant at various times during one day several customers develop vomiting, severe nausea, some loose stools and malaise 48–72 hours later. You do a case-control study which suggests a salad was at fault. The chef at the restaurant had to go home after preparing the salad, as he had developed nausea and diarrhoea, and felt ill.
5 Three cases of a rare salmonella infection occur in a psychogeriatric ward of a hospital on various days over one week. Only patients were affected. The ward has a small kitchen where snacks are prepared and sometimes visitors bringing food for patients microwave their offerings (no cooking allowed, only heating in the microwave). Normal meals are served from the main hospital kitchen. What would be your initial thoughts as to the most likely source of infection?
6 At the end of November in a country in Europe many children in a primary boarding school (a private school for children aged 5–13) develop acute nausea and vomiting. Many suddenly threw up in classrooms and dormitories. Many had diarrhoea as well, some only one or two loose stools. The overall attack rate approached 20 per cent. Only three of the younger ones had to be admitted to the school infirmary, mainly because they were mildly dehydrated. All recovered within a few days. Cases continued to occur over three weeks and the school is now about to close for Christmas. A new cook joined the staff recently. What would be your thoughts on the origins of this outbreak? You are also being asked if the school should reopen after the Christmas holidays.

Feedback

1 Probable salmonella from eggs. The shelled eggs were left unrefrigerated in one bowl overnight and just one infected egg would have contaminated all the others. The eggs were left warm after light cooking for a long period the next day. Prevention: if the sauce had to be made with lightly-cooked egg, it should have been prepared an hour or

so before serving it. Alternatively the eggs could have been shelled the night before and stored in the refrigerator until ready to prepare before the meal, but this is a second-best option.

2 Probable salmonella in the chicken, cross-contaminated from the containers which contained raw chicken. Salmonella multiplied in the chicken when left in the car in the hot sun. Prevention: use clean fresh containers for the cooked chicken, keep the chicken in a coolbox with ice packs in the car while driving, in the boot while not driving (and do not stop for a drink!).

3 Probable *B. cereus*. You ask if rice was served with the curry. It was. No one told you because they did not think rice can cause FP. When was it cooked? The night before. Was it refrigerated? No. Prevention: educate chef not to cook rice the night before and then leave it unrefrigerated. Exclude staphylococcal FP or other toxin as a cause.

4 Probable norovirus, passed by the chef to the salad. Chef prepared the salad with his hands. He had had a slightly loose stool that morning but had felt well enough to work until his illness began in earnest later in the day. Prevention: difficult. He should have used gloves or not handled food to be eaten raw. He did wash his hands after toilet but was in a hurry.

5 With three cases over a week, this is almost certainly case-to-case transmission of salmonella. This may have been introduced in a food by a visitor, but this was more than a week ago and trying to establish the origin is a waste of time. Staff hygiene practices should be reviewed. Surfaces must be disinfected in the ward, kitchen and bathrooms.

6 This is far more likely to be winter vomiting disease caused by a norovirus than food poisoning. The new cook is unlikely to have had anything to do with it. Vomiting caused by FP is usually a point source and not transmissible from person to person. Exclude shigella. The school needs to be thoroughly disinfected, especially the washrooms and toilets, but also the classrooms, dormitories and refectory during the Christmas break.

Summary

You have learnt how an understanding of the underlying microbiology of gastro-intestinal infections is essential to understanding these conditions and how to prevent them. You have also learnt about some non-infectious causes that need to be considered when investigating an outbreak of suspected FP.

Reference

Noah ND (1992) Food poisoning, in AS Truswell (ed.) *ABC of nutrition*. BMJ Press, London.

Further reading

Chin JE (2000) *Control of Communicable Diseases Manual*, 17th edn. APHA, Washington.

17 Hepatitis viruses A, B, C, D, E

Overview

In this chapter you will learn about the epidemiology, virology and impact of these serious, debilitating infections. Hepatitis A and E are transmitted faecal-orally, yet have differences. You have already come across hepatitis A in Chapter 7. Hepatitis B and C are similar in that both are blood-borne and associated with chronic liver disease, yet have many differences. Hepatitis D is an unusual defective virus that is associated with hepatitis B. It is less common and discussed only briefly. Rarer forms of hepatitis (F and G) are not considered here.

Learning objectives

After studying this chapter you will be better able to:

- **describe the epidemiological features of each of these infections**
- **understand how they are transmitted**
- **describe the extent of the considerable morbidity they have produced in the world**
- **explain what methods are available to control them**

Key terms

Hepatitis (viral) Hepatitis is an infection and inflammation of the liver caused by a number of viruses, named alphabetically from A to G.

Horizontal transmission Case-to-case, usually in childhood.

Vertical transmission Mother to foetus.

Introduction

It was realized years ago that there were two main types of hepatitis. One was spread by the oro-faecal route and the other by blood or multiple injections using one needle. The oro-faecal form was known as 'infective hepatitis', the blood-borne as 'serum hepatitis'. The two basic forms still exist, but each now includes several viruses.

Viral hepatitis is common and is responsible for considerable morbidity. The acute illnesses last up to six months, and with the B and C viruses there is a high risk of

chronic lifetime hepatitis. Death can occur either during the acute phase, or as a result of chronic B, C or D infection. Hepatitis viruses A and E (HAV, HEV) are spread by the faecal-oral route. Viruses B–D (HBV, HCV, HDV) are blood-borne. HAV and HEV can also be transmitted by blood but this is rare because they have short blood phases during the course of human infection. These five viruses are not related to each other.

The clinical course of all these forms of hepatitis varies from asymptomatic through mild or moderate to death. Liver function tests (LFTs) also may vary from normal to showing mild to severe damage. Elevation of liver enzymes (alanine/aspartate aminotransferases) is a sensitive indicator of acute liver damage. All these features are non-specific and indicate only that the patient has hepatitis.

Hepatitis A

HAV is a small unenveloped single-stranded RNA virus that is spread faecal-orally. Fortunately, only one of the two serotypes is known to infect humans. HAV is known to infect only humans and primates. It is highly infectious and stable. It can remain infectious for up to four weeks at room temperature, and probably indefinitely if frozen. This means it can readily be transmitted by touch – either direct, or through objects such as door handles and bathroom taps. It is destroyed, though not very easily, by heat – about one minute at 85–95°C is needed. It can survive acid conditions up to about ph1, which accounts for its ability to infect after ingestion. The incubation period is 15–40 days. Patients are infectious from a few days before onset to just after jaundice appears. Persons with asymptomatic or mild infections also shed infectious virus in their stools. The number of infectious viruses in stools is very high – up to 10^8 per gm. Blood can be infectious for a short period – about 10–14 days – before the onset of jaundice or other symptoms, so blood spread is possible but rare. With improving sanitation and hygiene, infection is less common than previously in developed and middle-income countries. Accordingly, a large group of susceptible people in the younger and middle age groups is accumulating. Attack rates in outbreaks may be large.

Serological course of hepatitis A infection

After ingestion of the virus, there is a short period of viraemia a few days before the onset of illness. Blood will be infectious during the period of viraemia. Large amounts of HAV are excreted in the stool a week or more before onset, and this diminishes as signs of liver involvement, and then jaundice, appear. HAV excretion decreases as antibodies develop. First IgM appears, and rises rapidly before falling off, remaining detectable for three to six months. IgG takes time to develop, but provides permanent immunity.

Diagnosis of hepatitis A

The specific diagnosis of acute hepatitis A is made by the demonstration of HAV IgM in blood, saliva or urine. IgM is detectable a few days after the illness begins

and persists for about four to six months. Although the virus can be isolated from stool, this is not a routine diagnostic procedure. Moreover, as the virus cannot routinely be demonstrated in a food responsible for an outbreak, epidemiology is an essential tool in investigating an outbreak of hepatitis A.

Activity 17.1

Knowing about the disease status of cases and contacts in hepatitis A is important. Given the information above, write down the status of people with the following results of testing.

1 A child of 5 is off colour, has mild fever, dark urine and slightly raised liver enzymes.
2 A child of 5, in contact with a friend with HAV infection, has not been affected. His mother develops hepatitis A eight weeks after the friend. Her son's liver function tests were normal. His HAV IgM is raised.
3 A man of 50 had dinner with several others. Many of those who had the meal developed hepatitis A 18–35 days later. He however remained well. On testing eight weeks after the meal, the man had no HAV IgM, only HAV IgG was present.
4 Another man of 30 at the same dinner was ill and was shown to have HAV IgM present at eight weeks.
5 A woman of 40, also at the dinner, did not become ill. Neither HAV IgM nor IgG were present on testing eight weeks later.
6 A third person, aged 45 was also at the dinner but did not develop symptoms. She went abroad and could not be tested until six months later. IgG but no IgM was present. A sample of her blood was found which had been taken six months before the dinner for other reasons – no IgG or IgM was detected in this sample.
7 Another woman developed a febrile illness with slight yellowing of the skin and darkened urine, five weeks after the dinner. She refused to have any blood or saliva tests.
8 The 5-year-old son of case five developed jaundice eight weeks after the dinner. HAV IgM was present.
9 A man of 18 went to the dinner, developed mild fever and malaise four weeks later, but no yellowing of the skin, or change in colour of urine or stool. No tests were performed.

Feedback

1 Hepatitis, non-specific.

2 Asymptomatic hepatitis A infection in the son, secondary to the friend. Became infectious about four weeks later and infected his mother.

3 Immune due to previous infection. Not a case.

4 Infected at the dinner – definite case.

5 Non-immune, but escaped being infected at the dinner. She may not have eaten the contaminated food, eaten a part of it that was not contaminated, or eaten it but just did not become infected (100 per cent attack rate even in susceptibles is rare).

6 Probable case: developed immunity to hepatitis A some time between about three and six months before the dinner and three to four months after (this is because IgG develops about three months after contracting hepatitis A).

7 Unconfirmed probable case.

8 Secondary case from his mother (in absence of any other known contact). Strengthens evidence that case six was infected at the dinner.

9 Possible case.

Epidemiology of hepatitis A

The characteristics of HAV that explain much of its epidemiology were listed in Table 7.1. As the rate of symptomatic infection and severity increases with age, children are more likely to have asymptomatic infections, and to be more susceptible, than adults. Furthermore, as HAV spreads readily from case to case if hygiene is poor, and hygiene tends to be poor in children, it is easy to envisage a situation in a community in which most HAV infection is being spread by asymptomatic children to other children, but also to the occasional (susceptible) adult. As adults are more likely to develop symptoms, they are the only cases being seen whereas a lot of infection is continuing below the surface. This scenario is dealt with in more detail in Chapter 7.

In a society where sanitation and hygiene are good, many children will grow into adults without contracting HAV. So a large population of susceptible adults will be developing. The introduction of HAV into this community could trigger an explosive outbreak if it was spread say by a food, or a continuing smouldering outbreak spreading case-to-case through the community (Pebody *et al.* 1998). This may account for the periodical cycles of infection occurring over many years that are seen in some high and middle income countries.

Poor hygiene and a small infective dose also explain the protracted outbreaks sometimes seen in closed communities where hygiene may be difficult to maintain, such as psychogeriatric units, nursing homes/hospital wards for the elderly, day-care centres, nurseries and homes for those with developmental problems. Other communities which appear to be susceptible to case-to-case transmission are men who sleep with men and intravenous drug users.

Point source or continuing outbreaks have been spread by food or water. Sewage-contaminated water can infect directly, or indirectly through raw or undercooked shellfish harvested from polluted water. A food-handler in the late stages of incubating the infection or with early symptoms will be excreting 10–100 million viruses/gm of stool and, with the small dose required for infection, can easily contaminate any food handled. Numerous outbreaks, including those caused by salads and even acidic liquids such as orange juice, have been caused in this manner. Some foods such as soft fruit could have been contaminated some years before, frozen, and then eaten raw, causing an outbreak. Blood transfusion may cause sporadic cases, and pooled blood products have been known to cause outbreaks.

The basic epidemiology also explains the high immunity and low case rates found in low income countries, and the low immunity and high case rates in high and middle income countries. However, there are many exceptions – countries in some parts of southern Europe may be closer to the low income country pattern, presumably related to more recent introduction of good sanitation and hygiene. Within each country, lower socioeconomic status is commonly associated with higher childhood disease case rates and higher adult immunity rates.

Surveillance of hepatitis A

Activity 17.2

What would be the objectives of running a surveillance system for hepatitis A in your country? What sources of data would you use?

Feedback

The main objective would be to detect outbreaks, though trends and natural variations in incidence will also be under scrutiny. Changes in age distribution and geographical location should also be monitored. The seasonal pattern shows a summer increase in most temperate climates. Any change in the normal seasonal pattern could be an indication of an outbreak. Occasionally foods contaminated with hepatitis A can be widely distributed and cause large outbreaks. Generally sentinel surveillance is not likely to be very helpful as detecting outbreaks is an important objective of surveillance for hepatitis A.

You would use a notification system based on hospital and primary care sources, supplemented by laboratory reports as well if possible. In interpreting notification data you need to be careful about the diagnosis of hepatitis A. Laboratory reports provide specificity but less sensitivity, though as IgM can be measured in salivary samples, more cases are likely to be successfully diagnosed and reported. Hospital data will be more specific than sensitive, but tend not to be timely. Serological surveillance based on regular sampling can be used to help build a more detailed picture of the epidemiology of hepatitis A by monitoring trends in the age-specific immunity to the infection.

Prevention of hepatitis A

Hygiene is clearly important, and not just for HAV infection. For hepatitis A, this means washing hands with soap and water after going to the toilet, and drying them on disposable towels or with an air dryer. Food-handlers in particular need to be careful if they have been in close contact with someone with hepatitis A – at least one food-borne outbreak was attributed to a food-handler who had been nursing a sick spouse at home.

Immunoglobulin is obtained from the blood of people with antibody to hepatitis A. This provides protection more quickly than does the vaccine. It is expensive and provides passive immunity only for a limited period of time, up to five months at a

dose of 500mg. Nevertheless it can be useful for short-term travellers and for close contacts of cases (especially when hygiene is poor), as well as for controlling outbreaks.

Travellers going away for three months or more, or frequently to hepatitis A endemic countries, should have HAV vaccine. One dose provides short-term immunity. A booster dose 6–12 months after the first dose will protect for at least ten years. Children need half the adult dose. Other indications for HAV vaccine include certain occupations, patients with chronic liver disease who cannot afford more liver damage, haemophiliacs who receive numerous injections of blood products, and the control of outbreaks in defined populations.

Activity 17.3

List the groups of people in your country who, by virtue of being exposed more frequently to HAV, you feel should qualify for prophylactic vaccination.

Feedback

People singled out for special consideration could include the following:

- frequent or long-term travellers to endemic countries
- staff and residents of schools for people with developmental problems, psycho-geriatric wards and other institutions in which hygiene is likely to be poor
- staff working in day-care centres
- those working with raw sewage, but not necessarily all sanitation workers
- laboratory workers handling the virus, probably also staff working directly with patients in an infectious disease hospital
- other groups with prolonged history of ongoing hepatitis A infection, such as homosexual men
- injection drug users

Note that this list, which has been adapted from recommendations in the UK, is advisory rather than statutory. You may have included in your list other groups at risk relevant to your own country.

Hepatitis B

Hepatitis B virus was discovered in 1963 to be the main cause of the blood/serum form of hepatitis. Hepatitis B-free blood continued to cause hepatitis however, so the term non-A non-B hepatitis was used for this.

Hepatitis B virus is one of the most infectious organisms known to humans. Patients with circulating hepatitis B are highly infectious – 1ml of blood may contain enough infectious particles to infect many thousands of people. It can be transmitted by skin puncture and also across mucous membranes. The virus is stable at room temperatures, and can for example survive for more than two months on workbench surfaces. Freezing will protect it for even longer. It is destroyed by boiling for one minute. The incubation period is two to six months.

The structure of this virus is essential to understanding the epidemiology of the infection. Hepatitis B virus is a DNA, a hepadnavirus, which includes several animal and bird hepatitis viruses. The main antigens are:

- HBsAg or surface antigen. This is the protein that binds neutralizing antibodies. The surface antigen can be shed in large numbers into the serum and other tissues of the body or remain bound to the virus itself. Antibody to HBsAg protects against hepatitis B infection.
- HBeAg **or e** antigen is a nucleocapsid protein that denotes active viral replication.
- HBcAg **or c**, or core, antigen is another nucleocapsid protein. Core antigen is not detectable in blood.

Unlike hepatitis A, chronic infection leading to prolonged carrier states occurs with hepatitis B. A carrier is defined as a person who has carried HBsAg for more than six months. Risk factors for the chronic carrier state are: asymptomatic acute infections, infections in the perinatal period and the immunocompromised. 'High risk carriers' have circulating HBeAg or HBV DNA in their blood. Sometimes the e antigen disappears but the continuing presence of HBV DNA signifies high infectivity. Those with circulating HBsAg only are less infectious and are 'low risk'. Carriers are a danger not only to others but also to themselves, as they may develop chronic liver disease and liver cancer.

Serological course of hepatitis B

The clinical and serological course of acute HBV infection is shown in Figure 17.1.

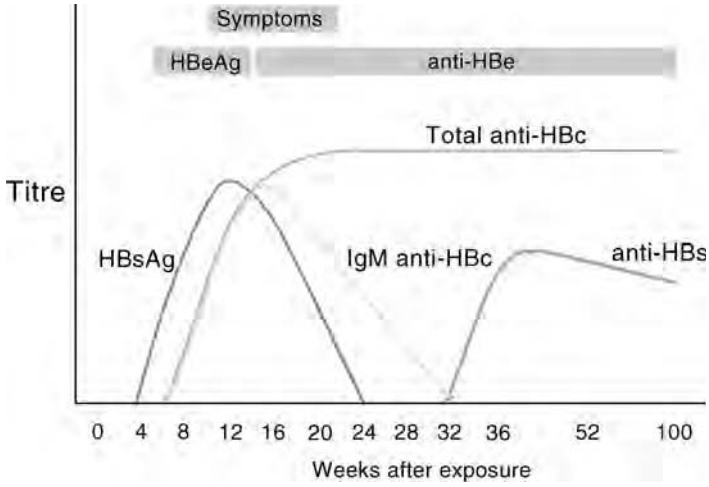

Figure 17.1 Acute hepatitis B virus infection with recovery: typical serological course
Source: Centers for Disease Control, USA

Activity 17.4

Describe briefly what Figure 17.1 tells you about the basic immunology of hepatitis B.

Feedback

About four weeks after exposure HBsAg is detectable in the blood, well before symptoms begin. This is followed about a week later by HBeAg, at which point the patient becomes highly infectious. IgM and IgG antibodies to HBcAg begin to form at around this time. Illness begins any time between eight weeks and six months. The patient becomes much less infectious when the HBeAg antigen disappears, and eventually non-infectious when the HBsAg antigen disappears at about 24 weeks. Antibody to the hepatitis B surface antigen (anti-HBs) is formed after natural infection and protects for life. Anti-HBc is found in those with acute, chronic and naturally recovered infections.

When the carrier state develops, the serological course is somewhat different (see Figure 17.2). With chronic infections, HBsAg appears somewhat earlier in the serum, and persists for the lifetime of the patient. HBeAg also persists in the serum for years (usually a lifetime), compared with only about eight weeks in acute cases. In some cases however HBeAg disappears and anti-HBe appears, usually after many years. In chronic carriers the HBsAg persists and no anti-HBs is produced.

To summarize, the important characteristic feature of chronic carriers seems to be HBsAg persistence without anti-HBs ever forming. When associated with chronic HBeAg carriage it signifies a highly infectious carrier. Although the hepatitis B vaccine is discussed later, the confirmation of successful vaccination is the demonstration of anti-HBs without anti-HBc in the blood of the recipient. The significance of the various antigens and antibodies in hepatitis B is complex and is summarized in Table 17.1.

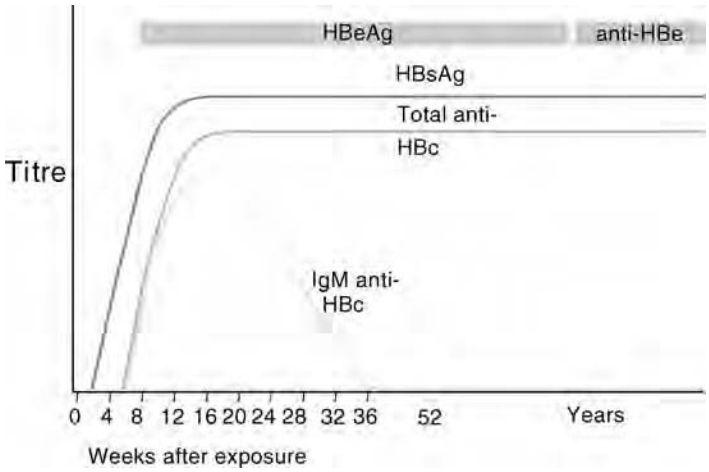

Figure 17.2 Progression to chronic hepatitis B virus infection: typical serological course
Source: Centers for Disease Control, USA

Table 17.1 Hepatits B: diagnosis and significance of markers

	Detection of					
Status	*Anti-HBc*	*Anti-HBc IgM*	*HBsAg*	*Anti-HBs*	*HBeAg*	*Anti-HBe*
Acute	+	+	+	–	+/–	+/–
Carrier (low infectivity)	+	–	+	–	–	+
Carrier (high infectivity)	+	–	+	–	+	–
Recovery (immunity)	+	–	–	+	–	+/–
Immunity (after vaccination)	–	–	–	+	–	–

Epidemiology of hepatitis B

The estimated burden of chronic HBV infection in the world is high: the WHO estimates 350–400 million carriers. They act as the reservoir for hepatitis B in the world. In the European region alone the WHO estimate about 1 million new infections, 90,000 chronic carriers and 20,000 deaths per year.

The epidemiology and carriage of hepatitis B vary considerably in different parts of the world. Prevalence rates of HBsAg (carriage) of 8 per cent or more are considered high, and less than 2 per cent low. In most of South-East Asia, including China and Indonesia, both overpopulated, rates of vertical transmission are high and the carriage rates are very high – well over 8 per cent. In sub-Saharan Africa, the far north of America, parts of South America, the Middle East (Saudi Arabia) and Greenland, horizontal transmission is as common as vertical, and the rates, although also over 8 per cent, are not as high as in parts of the Far East. Less than 2 per cent is classified as low: this includes most of developed Europe, North and Central America and Australasia, as well as parts of South America.

Even within these areas the prevalence of chronic HBV infection varies. In most of north-west Europe the prevalence is <0.1 per cent, whereas in areas bordering the Mediterranean, rates are 1–5 per cent, in Eastern Europe 2–7 per cent and in the Central Asian republics approaching the high rate of 8 per cent.

Activity 17.5

From what you now know about the epidemiology of HBV, what do you think are the main modes of transmission? What biological information would you use in answering this question?

Feedback

The main modes of transmission are:

- parenteral exposure to infected blood or other body fluids
- sexual contact with an infected person
- mother to child transmission (perinatal)
- other horizontal person-to-person contact

Parenteral exposure includes transmission through sharing intravenous drugs, blood transfusion, injections with unsterile needles and non-medical skin piercing (tattooing, acupuncture, ear piercing, body piercing). The infectious dose is so small that visible blood or skin punctures are not requirements for transmission. Moreover, sharing of razors, toothbrushes and towels has been documented as transmitting infection. People who have frequent unprotected sex, men who have sex with men, and others with many partners are at risk. Vertical (perinatal) transmission is important, first because in countries with high prevalence rates risk is high, and second because infections acquired during the neonatal period are more likely to become chronic. Forms of horizontal transmission include children playing together, presumably being infected through open sores and wounds.

Crucial biological information:

- HBV blood-borne
- highly infectious
- transmitted through skin and mucous membranes

Activity 17.6

Prevalence rates of HBV are shown for a country in North Africa in Table 17.2. What does this tell you about transmission rates in that country?

Table 17.2 Prevalence of hepatitis B markers in blood of children in central Tunisia by age

Age group (years)	*Prevalence of hepatitis B markers (%)*
1–3	7
4–6	16
7–9	21
10–12	24

Source: Said *et al.* (1985)

Feedback

The table shows markers of HBV infection, not carriage rates. Carrier rates are probably moderate, possibly even low. If the data are representative, by 1–3 years of age 7 per cent of children have been exposed to HBV. We are not told the prevalence in infants, though the data suggest it will be fairly low. The rate rises throughout early childhood, and the rate of increase slows with increasing age. This suggests high rates of horizontal transmission in early childhood.

Surveillance of hepatitis B

Surveillance of hepatitis B is important especially as a vaccine and other methods of control are available.

Activity 17.7

What would be the objectives of surveillance for hepatitis B in your country? Name your sources of data.

Feedback

The objectives would be to:

- estimate the incidence of acute hepatitis B over time
- estimate the prevalence of chronic hepatitis B (carriage)
- build an estimate of the burden of hepatitis B
- identify outbreaks and the main modes of transmission
- identify any changes in the epidemiology of the infection (e.g. changes in age or geographical distribution)
- choose and monitor control strategies

The sources of data will depend on the facilities available, but the following should be considered:

- notifications
- laboratory reports
- hospital episodes
- death certificates
- special surveillance programmes

The epidemiology of hepatitis B varies from country to country. In England and Wales, about 25 per cent of cases are caused by intravenous drug use, 15 per cent by sex between men and women and 10 per cent by sex between men. About 45 per cent have an unknown cause.

Activity 17.8

Why is there a large proportion of 'unknowns' with hepatitis B in most countries?

Feedback

- the incubation period for hepatitis B is two to six months, so the infection could have occurred a long time before

- the disease is highly infectious – only a minute/invisible amount of serum or blood can infect, and this could have been unnoticed by the patient
- most of the routes of transmission can cause stigma: history of drug usage and/or sexual risks may be withheld
- risk information is often not reported by the clinician

Prevention of hepatitis B

Preventive measures for hepatitis B are now explored.

Screening

Activity 17.9

1 If you were to screen routinely for hepatitis B in your country, which populations would you choose? Use information already provided above.

2 What would be the objectives of screening?

Feedback

1 In order of importance, these would be:

- blood donors
- women in the antenatal period
- health care workers
- those intending to train for health care work (e.g. medical and nursing students)
- certain professions (e.g. tattooists and body piercers)

The priorities in your country may differ.

2 Blood donors clearly are screened to avoid infecting recipients, and women in the antenatal period to prevent neonatal transmission. The others are to protect themselves not only from infecting others but also from being infected by their patients or clients.

Immunization

Hepatitis B vaccine contains HBsAg as the antigen, obtained from yeast cells using recombinant DNA technology. Three doses are given intramuscularly at 0, 1 and 6 months. Children 0–12 years are given a half dose. Some vaccines can also be given intradermally. One further booster dose may be given after a further five years to those who are at high risk, though there is evidence that immunity lasts for at least 15 years in a high percentage of people. About 95 per cent of those given the vaccine develop an antibody (anti-HBS) to HBsAg. Levels of >10miu/ml are generally considered protective, <10miu/ml non-protective. Those who are immuno-

suppressed or over 40 are less likely to respond. The vaccine is not contraindicated in immunosuppressed people, including HIV-positive people. Poor responders need a booster dose and non-responders may need another primary course. Injections must not be given into the buttock. Protection may not be complete until six months after the last dose. In high-risk cases antibody titres should be checked six to eight weeks after the last dose. Babies of carrier mothers are considered below.

Alternatively, passive immunization can be used. Specific hepatitis B immunoglobulin (HBIG) is available and should be used in conjunction with vaccine for post-exposure prophylaxis and for neonates born of HBeAg-positive mothers. As HBIG induces only passive immunity, it protects for a limited period, but more quickly than does the vaccine provided it is given as soon as possible after the risk event, and no later than seven days later. It should be given with HB vaccine, as it does not reduce its efficacy. Importantly, it may help prevent the chronic carrier state even if given after infection has occurred. The vaccine should be given at 0, 1, 2 and 12 months, with the first dose (including HBIG) within 12 hours. The vaccine should be given preferably in one arm; the immunoglobulin can be given in the buttock or other arm. Babies of carrier mothers should be tested for HBsAg at 12 months.

Activity 17.10

Given the information above, to whom would you give HB vaccine in your country?

Feedback

In England, HB vaccine is used selectively. It is given routinely to:

- babies of HBsAg-positive mothers or mothers who had acute HB during pregnancy
- injecting drug users
- those who change sexual partners frequently
- close family contacts of cases and high-risk carriers
- those who adopt children from high-risk countries unless the child shown not to be a carrier
- frequent blood product recipients (e.g. haemophiliacs)
- patients with chronic renal failure requiring dialysis
- heath care workers and students in some professions if likely to be in regular contact with blood (including morticians and embalmers)
- prisoners
- frequent travellers to high endemic countries
- those working or living in residential institutions for those with learning disabilities

This list is highly specific for one country and your list should also be influenced by the epidemiology of HBV infection in your country and the resources available. Universal immunization may be justified in your country. With a selective regimen, babies born to HBsAg-positive mothers would probably be the first priority in most countries.

HBIG should be given with the vaccine to all those who need protection immediately. This includes:

- babies of HBsAg carrier mothers who are e-antigen positive, who do not have e markers (or e markers undetermined), or who developed acute HB infection during pregnancy;
- people who have a needlestick injury, or were in contact with contaminated blood through conjunctiva or fresh skin injury.

Other methods of prevention focus on preventing exposure. Health education and information given to members of the public as well as health care workers are useful. Needle exchange schemes for drug users, tracing of contacts and infection control in medical settings, including sharps bins, are effective. Screening of blood, as discussed, is essential.

Hepatitis C

In 1989, HCV long suspected as the cause of non-A non-B (NANB) hepatitis was identified. It is responsible for about 90 per cent of post-transfusion NANB hepatitis.

The epidemiology of HCV is similar in some ways to that of HBV, in that both are blood-borne, have a long incubation period and cause chronic hepatitis. Some of the risk groups are the same. Nevertheless there are some substantial differences.

HCV is a spherical enveloped RNA virus of the flavivirus family. It mutates easily while replicating within humans, so that many variants may exist within one person. Like HBV, it is blood-borne, though less contagious. The incubation period is six to eight weeks (range 2–26 weeks). At least 90 per cent of infections are asymptomatic, and 80–85 per cent lead to chronic infection. Long-term complications include hepatitis, cirrhosis or carcinoma. A characteristic feature of infection with HCV is its persistence. HCV RNA can be detected in many human fluids, though only blood/plasma/serum/body organs have been shown to be infectious. There are six major genotypes, and these show a worldwide distribution. Virus sequencing is used to identify a common source of infection.

Serological course of hepatitis C infection

HCV induces a persistent antibody; no protective antibody has been detected. During the acute phase of infection liver enzymes may be raised in the blood, and rise intermittently in persistent cases. Probably no more than 20 per cent of patients mount an immune response strong enough to minimize viral damage (see Figure 17.3).

Epidemiology of hepatitis C

Hepatitis C is recognized by the WHO as a global public health problem, with an estimated 170 million carriers worldwide. It is spread by:

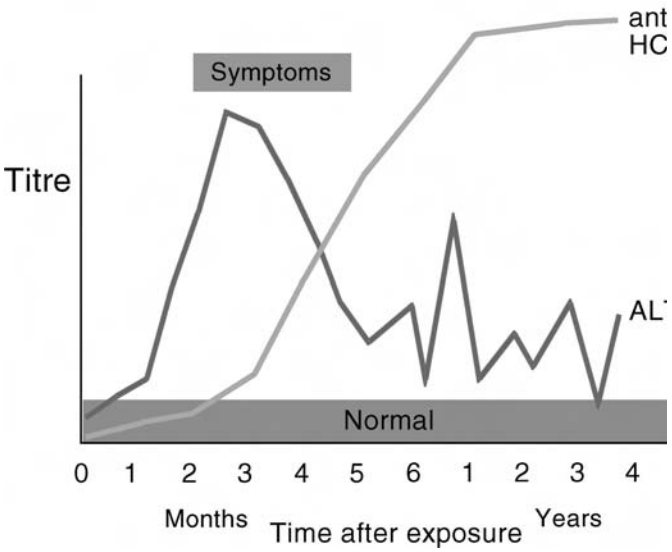

Figure 17.3 Hepatitis C virus infection: typical serological course
Source: Centers for Disease Control, USA

- transfusion – blood/blood products
- organ transplants from an HCV carrier
- needle sharing
- other needlestick injuries
- other needlestick risks (e.g. body piercing)
- multiple sexual contacts
- mother-to-baby perinatally

Some people have multiple risk factors. In most cases, risk factors are unidentifiable or may not be reported. Because of screening, transfusion as a cause of infection is rare in most developed and middle-income countries, and drug abuse is the main risk. HCV is much less easily transmissible sexually or vertically than HBV.

About 1 per cent of the western European population is estimated to have been infected with HCV, compared with 2 per cent in Asia and 5 per cent in Egypt. In a country such as the UK, 40–60 per cent of drug users may be seropositive, compared with 0.19–0.28 per cent of health care workers. Rates of less than 2 per cent are found in renal units, though this can vary with unit. The UK, in common with Denmark and Finland, has rates in blood donors of <0.1 per cent, compared with <0.3 per cent in France and Germany.

HCV infection is now the most common cause of chronic hepatitis in westernized countries and an important reason for liver transplants. Transplanted livers tend to get reinfected, suggesting that the virus infects organs other than the liver. A needlestick or other contact with HCV will not necessarily lead to infection. Estimated HCV transmission rates are as follows:

- needlestick from an infected individual: 1.8 per cent (0–10 per cent)
- perinatal from an HIV negative HCV-infected mother: <10 per cent

- perinatal from an HIV-positive HCV-infected mother: >10 per cent
- sexual: <5 per cent in monogamous relationships
- Household: 0.5–13 per cent
- Breastfeeding: 0 per cent (although breast milk may contain HCV RNA)

Activity 17.11

In a high or middle income country that screens blood donors for HCV, what age and sex distribution for HCV carriers would you expect to find?

Feedback

The commonest risk factor would be drug abuse, with homosexual and heterosexual transmission the second most common risk. Thus most cases would be in young adult males (Figure 17.4).

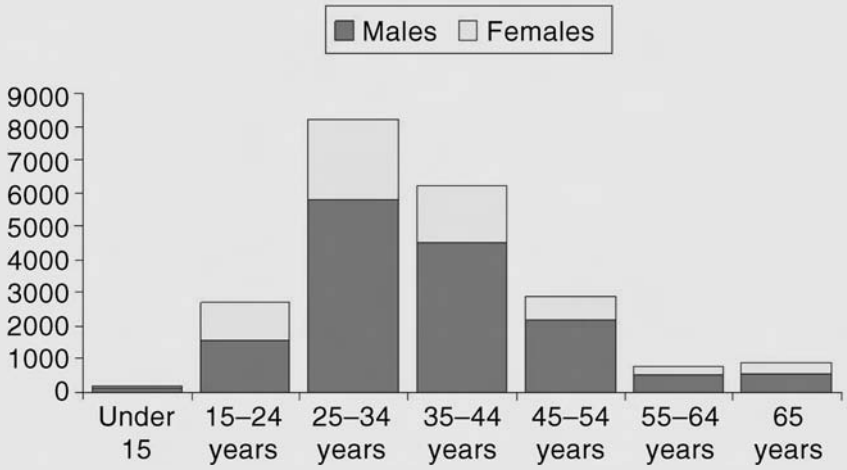

Figure 17.4 Age/sex distribution of confirmed HCV infections, 1997–2001

Source: HPA, London

Surveillance of hepatitis C

The objectives of surveillance for HCV are similar to those for HBV. The sources of data are also similar.

Activity 17.12

Reported incidences of acute hepatitis A, B and C are likely to be underestimated. Why? Which is likely to be most seriously underestimated?

Feedback

Note that the question is about *acute* hepatitis. Both hepatitis B and hepatitis C cause asymptomatic infections. The asymptomatic rate for hepatitis C is particularly high, so surveillance of acute hepatitis C is likely to be the most seriously underestimated. The high asymptomatic rate also explains the high proportion of unknown sources of infection in cases. Hepatitis A also causes asymptomatic infections, though these are mainly in children. Hepatitis A causes a milder illness than the other two types of hepatitis, which may make it less likely to be reported or notified.

Prevention of hepatitis C

Screening of blood and organ donors has been highly successful, so that transmission by this route is now rare. In the absence of a vaccine, prevention of hepatitis C infection through other routes is limited. The mainstays are:

- health education
- risk reduction (e.g. needle exchange schemes)

Hepatitis D

Hepatitis D (or delta virus) is unusual. It is a defective RNA virus that needs help from HBV to cause infection and for replication. The inner core contains the D antigen and the outer core is made up of HBsAg. Two forms of infection occur. With co-infection, infection occurs simultaneously with acute HBV in a previously uninfected person. A more severe form of acute hepatitis than HB alone is often the result. With superinfection, a person already with chronic HBV infection gets reinfected with HBV/HDV. Superinfection may lead to fulminant infection or accelerate the progression of chronic liver disease. In asymptomatic HBsAg carriers, superinfection may produce hepatitis. The routes of transmission are the same as with HBV except perinatal infection is rare. HDV infection is commoner in Italy, the Middle East, parts of Africa and South America. About 5 per cent of HBsAg carriers also have HDV.

Activity 17.13

From the description given above, what risk group would you expect to be particularly likely to be infected with HDV?

Feedback

Intravenous drug users because of repeated injections with contaminated needles and needle sharing. Some sexual groups may also be at risk.

Hepatitis E

Hepatitis E is a newly-discovered hepatitis virus which is transmitted by the faecal-oral route. It first came to prominence, before it was identified, by causing an extensive waterborne outbreak affecting many thousands in India in 1955. Waterborne outbreaks are still the predominant type, and remain virtually confined to developing countries (see Figure 17.5); gross faecal contamination of water is usually present. War zones are vulnerable. Sporadic cases also occur, and HEV is said to account now for more than half the sporadic acute viral hepatitis cases in endemic parts of the world.

Figure 17.5 Geographical distribution of hepatitis E: outbreak or confirmed infection in >25% of sporadic non-ABC hepatitis

Source: Emerson and Purcell (2004)

Person-to-person transmission is much less common than with hepatitis A – in families in Nepal, rates were 2.4 per cent with HEV compared to 10–20 per cent with HAV. However, some cases have occurred in travellers who have visited endemic countries, and nosocomial transmission has been documented. Foodborne infection has also been documented, including one outbreak attributed to raw wild boar meat and another to venison. Evidence is accumulating that swine may be the natural host, and other animal hosts may well be discovered. Primates can be infected experimentally. There is also some evidence that transmission of HEV by blood may occur during the short viraemic phase. Immunity to HEV after natural infection appears to be long-lasting.

The incubation period is 40 days (range 15–60 days). The period of infectivity following acute infection lasts probably about 14 days after illness onset. In sporadic cases young adults aged 20 to 30 tend to have the highest attack rates. Symptomatic infections in children appear to be rare. Although overall the fatality rate is between 0.5 and 3 per cent, pregnant women are particularly vulnerable to severe HEV infection, and the fatality rate in this group is 20 per cent, higher in the third trimester. Intrauterine transmission is common – foetal loss can occur and there is high perinatal morbidity and mortality.

Hepatitis E is a single-stranded positive-sense RNA virus, with some characteristics in common with members of the family *Caliciviridae*. It has been classified as a distinct unassigned genus. The virus can be cultured in the laboratory. Diagnosis, not yet universally available, requires laboratory amplification of viral genomes found in serum and faeces during the acute phase of the disease, or detection of specific antibodies during convalescence (Emerson and Purcell 2004). The serological course of infection is shown in Figure 17.6.

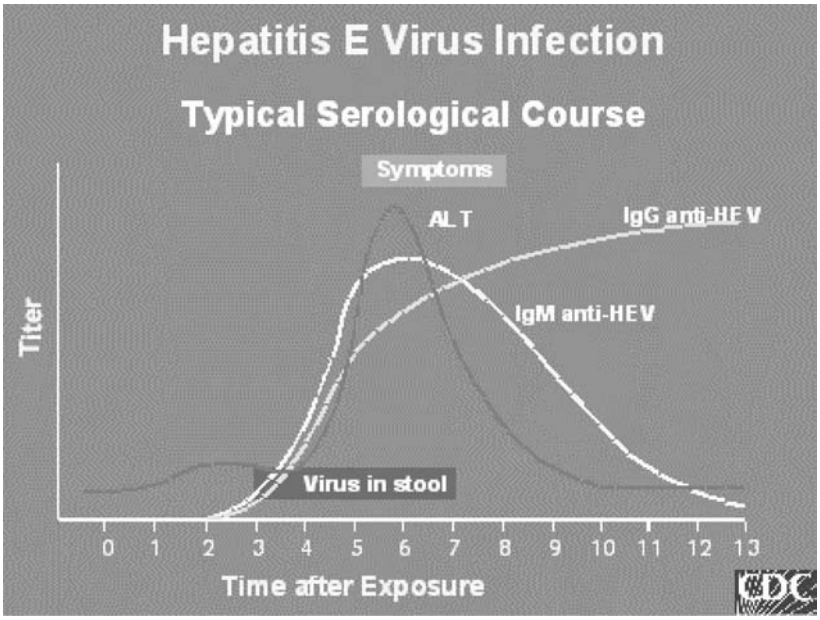

Figure 17.6 Serological course of hepatitis E
Source: CDC Centers for Disease Control, USA

Travellers to, or those living in, developing countries should boil all suspect or raw water and avoid eating undercooked meat, especially from wild animals. Pregnant women should be particularly careful. A recombinant vaccine is undergoing trials.

Activity 17.14

From clues in the descriptions given above, do you think the dose of HEV required to cause symptoms is likely to be small or large?

Feedback

Large. Waterborne outbreaks are not very common and the water is usually heavily contaminated. The secondary attack rate in contacts is low.

Summary

You have learnt how the hepatitis viruses have epidemiological similarities with each other as well as significant differences. Hepatitis A and E are spread by the faecal-oral route and do not cause chronic infections. HA is confined to humans, is highly infectious, and transmission can be food-borne, or case-to-case. HE is less infectious, is transmitted mainly by water, case-to-case transmission is uncommon, and it is probably a zoonosis. HB, HC and HD are blood-borne, confined to humans and cause chronic infections. Their modes of transmission are similar, although HB is far more contagious than HC. HC infection is transmitted less commonly sexually or vertically.

References

Emerson SU and Purcell RH (2004) Running like water – the omnipresence of hepatitis E, *New England Journal of Medicine*, 351: 2367–8.

Pebody RG *et al*. (1998) Foodborne outbreaks of hepatitis A in a low endemic country: an emerging problem? *Epidemiology and Infection*, 120: 55–9.

Said S *et al*. (1985) Seroepidemiology of hepatitis B in a population of children in central Tunisia, *International Journal of Epidemiology*, 14(2): 313–17.

Further reading

Nelson KE and Thomas DL (2001) Viral hepatitis, in KE Nelson *et al*. (eds) *Infectious Disease Epidemiology, Theory and Practice*. Aspen Publishers, Inc., Frederick, MD.

Salisbury DM and Begg NT (eds) (1996) *Immunisation against Infectious Disease*. Department of Health, Welsh Office, Scottish Office, DHSS (Northern Ireland), London.

Useful websites

CDC: http://www.cdc.gov/ncidod/diseases/hepatitis/.
HPA: http://www.hpa.org.uk/infections/topics_az/list.htm#H.
WHO: http://www.who.int/mediacentre/factsheets/en/#H.
Viral Hepatitis Prevention Board: www.vhpb.org.

18 HIV and sexually transmitted infections

Overview

In this chapter you will be encouraged to think about the public health importance of HIV and sexually transmitted infections (STIs) and how the surveillance of these diseases is more complex than many other infectious diseases. At times HIV is considered as a STI but at other times needs to be considered as a blood-borne virus. Many of these infections can spread, at least in the early stages, without being recognized, and failure to diagnose and treat can facilitate further spread. Therefore, active and enhanced surveillance may be necessary. You will learn about: methods of surveillance for these diseases; outbreaks and responses to them; trends and endemic levels of infection; and methods of control.

Learning objectives

After studying this chapter you will be better able to:

- **describe methods of HIV and STI surveillance including their dependence on the structure of the health care system**
- **describe the importance of active surveillance in the recognition of the introduction of HIV (or STIs) into a country**
- **explain the need to ensure surveillance actively links with, and drives the agenda of, prevention programmes**

Key terms

Active surveillance Active case-finding with encouragement of those seeing such cases to report them. Also useful for infections which may be overlooked if not actively looked for or incentives to report not present.

Enhanced surveillance A form of active surveillance where a more comprehensive set of information is collected than would ordinarily be obtained from passive surveillance.

Passive surveillance Routine reporting without active attempts to ensure a high rate of completeness.

***Pneumocystis carinii pneumonia* (PCP)** A rare infection of the lungs affecting the immunosuppressed; now classified as a fungal infection.

Sexually transmitted diseases (STDs) Infections transmitted sexually and causing symptoms which can be acute, or the long-term result of an earlier infection.

Sexually transmitted infections (STIs) May be asymptomatic and not currently causing disease.

Introduction

HIV and STIs are of public health importance for several reasons. These are listed in Table 18.1

Table 18.1 Public health importance of HIV and STIs

Occur worldwide
High impact on mortality (HIV)
Impact on morbidity (HIV and STIs) (TB/HIV overlap; pelvic inflammatory disease; decreased fertility)
Communicable but can be 'hidden' unless actively looked for (e.g. chlamydia, HIV)
Epidemiology – mainly young adults but may affect children through mother to child transmission
cost – direct health care costs – indirect (years of potential life lost – for HIV especially) – cost in terms of chronic disease and infertility
Prevention – behaviour change possible but difficult to achieve
No vaccines (though development work ongoing and HPV vaccine is almost ready for wider-scale use)
STIs interact to facilitate transmission of each other (ulcerative STIs facilitate HIV transmission etc.)
STI/HIV treatment and control highly politicized; for HIV, long term and not curable – treatment ongoing and expensive
HIV capable of rapid spread through other behaviours (e.g. sharing needles)

Source: HPA Centre for Infection

Many diseases can be sexually transmitted but the focus in this chapter is on those principally transmitted sexually:

- HIV
- syphilis
- gonorrhoea
- herpes simplex
- genital warts and human papillomavirus (HPV) infection
- chlamydia
- lymphogranuloma venereum (LGV)

Sexual health encompasses more than STIs and includes contraception, fertility and more general aspects of satisfaction from sexual relationships. Health more generally, and also sexual health, is wider than the absence of disease. Although the impact of such issues on STIs and their control cannot be ignored, this chapter mainly considers the surveillance of STIs and their control rather than the wider sexual health agenda. In contrast to many of the other communicable diseases considered in this book, HIV and STIs need to be actively looked for or they will go unrecognized, continue to spread and result in considerable morbidity and mortality at a later stage.

Methods of surveillance

Common to many surveillance systems is information on age, sex, ethnic group and other demographic variables. In enhanced surveillance for HIV/STIs, useful information includes: number of sexual partners; use of sex workers; heterosexual, homo- or bisexual behaviours; previous STIs and previous HIV test history. Such detail may not be possible to collect in all cases but may be possible on a subset of cases, or on all cases from certain clinics. Enhanced surveillance may be important in the early phases of a newly-introduced STI (e.g. lymphogranuloma venereum in 2004 in Europe) or in a sharp increase of infections (e.g. syphilis in 2003 in the UK). Such enhancements should facilitate understanding of the sexual behaviours underlying changing transmission patterns. Where infection is widespread, enhanced surveillance might assist in obtaining certain information but more comprehensive data collection is unlikely to be justified in all instances.

Activity 18.1

List the reasons why surveillance of HIV is more complex than for many other infections. Which of these are shared by other STIs? Asterisk these on your list.

Feedback

Table 18.2 HIV surveillance

HIV infection
Initial infection is asymptomatic or non-specific
Chronic illness/disease – many years before symptoms
Diagnosed infection may be a very small part of the total
Transmission may be affected by stage of diagnosis
Societal/social context
Stigma and discrimination
Mobility of young adults
Marginalized behaviours associated with spread (injecting behaviour; sex between men; sex work)
Fear/irrational reactions
Serious illness, usually sexually transmitted – shame/rejection
Epidemiology
Different risk groups
Importance of 'core groups' which are often difficult to reach
Rapidly changing trends possible
Wide variation in prevalence possible (geography, age, sex, risk group)
Effect of resistance to antivirals (or antibiotics for bacterial STIs)
Health care
Testing invasive and may be barriers (or perceived barriers)
Quality control on specimens important
Many diagnoses may be made in the private health sector
Strict confidentiality necessary
Personal identifiers to look at duplication from more than one centre

Source: HPA Centre for Infection

Probably all of these could be asterisked as they are shared with some or many other STIs.

The behaviours listed in Table 18.2 do not pose the same risk for all STIs. The reasons why the epidemiology of HIV and STIs differs so much between countries are only partially understood. Much of the differences in transmission is based around (a) sexual behaviour/number of partners, for example, concurrency (more than one partner at the same time) anal sex, role of sex workers, trauma etc.; (b) the presence of one STI which can facilitate the transmission of others (e.g. ulcerative STIs facilitate HIV transmission from the HIV infected partner if they have the ulcerative STI, and acquisition by the HIV uninfected partner if they have the ulcerative STI); and (c) protective behaviours such as condom use, delayed first intercourse etc.

There are no simple answers to overcoming barriers to surveillance of HIV and STIs – indeed, understanding the transmission patterns and wider knowledge of these may be actively discouraged by some within society for political, religious or social reasons. Part of your public health duty will be to try to convince such opinion-formers that one of the first steps in control of HIV and STIs is to understand accurately the way they are spreading within your society – and this may (and probably will) need active surveillance (and for some, enhanced surveillance systems).

Table 18.3 Methods of HIV and STI surveillance

Case reporting
AIDS
New diagnoses of HIV (from laboratories or clinicians)
Deaths from HIV/AIDS (CD4 cell counts)
Anti-viral resistance
Unlinked anonymous surveys ('blinded' surveys)
Screening results (e.g. antenatal HIV and syphilis screening, chlamydia screening)
Behavioural surveillance

Source: HPA Centre for Infection

Table 18.3 gives the broad categories relevant to the reporting of HIV in particular. The combination of surveillance systems chosen depends on the stage of the HIV epidemic(s) within your country. The WHO/UNAIDS have helpfully classified these into:

- low level: HIV prevalence has not consistently exceeded 5 per cent in any defined sub-population;
- concentrated: HIV prevalence over 5 per cent in at least one defined sub-population but below 1 per cent in pregnant women in urban areas;
- generalized: HIV prevalence consistently over 1 per cent in pregnant women.

Activity 18.2

If you were setting up new or enhanced HIV surveillance in a low prevalence or concentrated epidemic situation and had decided to introduce HIV case reporting, what issues would you need to be particularly aware of? Think what opposition you might experience in setting up such systems and how you would therefore try to overcome it? Why are there so many possible HIV surveillance systems?

Feedback

Prior to introducing such a system the case definition for the laboratory-confirmed cases needs to be agreed with microbiological/virological colleagues. The laboratories are generally excellent at reporting correctly diagnosed cases, but may have limited additional information needed for enhanced surveillance (i.e. behavioural data etc.). Other issues related to how you would undertake HIV case reporting are covered in Table 18.4 (applicable also to other STIs).

Table 18.4 How is HIV and STI surveillance undertaken?

Legally	– with regard to data protection and human rights
Confidentially	– only collect the level of patient identifiers that are strictly necessary – if possible avoid using names or other 'high level' identifiers; ensure staff handling the data are trained in confidentiality
Ethically	– do you need an ethics committee's approval and even if not, how would you set up a system that is within ethical guidance in your country?
Responsibly	– it is possible that a system you set up might have consequences for longer-term surveillance of other diseases? Proceed with caution, involving others, especially the clinicians you are expecting to report
With regard to public health action	– you are collecting information for the purposes of understanding and control of HIV and STIs: 'surveillance with a purpose'
Locally as well as nationally	– ensure data collected can be used at a variety of levels within your health care system – locally, regionally and nationally
Collaboratively	
International	– are cases being seen internationally? If so is international collaboration on case definition, study design etc. appropriate?
Collaboration within county with other health professionals and possibly voluntary groups (you will need the trust of the public and professionals)	
Tailored to the health care system	– the system you set up must be capable of operating within your health care system
In addition the system set up must be: affordable sustainable specific to your context but with a view to the national or international picture	

Source: HPA Centre for Infection

Unlinked anonymous surveys

One particular form of surveillance to consider is unlinked anonymous testing, the mechanism for which is shown in Figure 18.1.

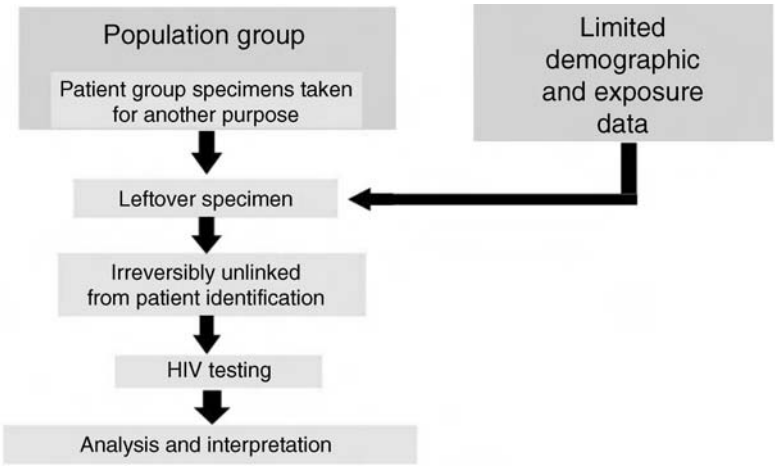

Figure 18.1 Unlinked anonymous testing – methods

Source: Unlinked Anonymous Prevalence Monitoring Programme, Health Protection Agency

Activity 18.3

When applying unlinked anonymous testing to blood specimens taken as part of a woman's antenatal care, what useful information can be obtained and what are some of the possible biases and problems? Look at the data in Figure 18.2 – obtained from such a programme within the UK. What does it show?

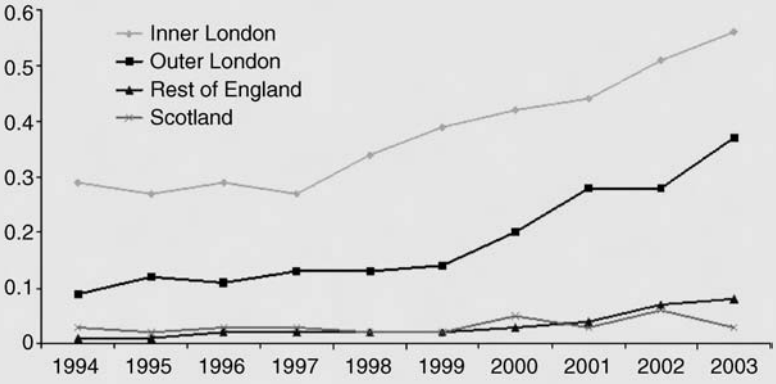

Figure 18.2 Overall[1] prevalence of HIV infection in pregnant women[2] by area of residence, England and Scotland, 1994–2003

[1] Tested through Newborn infant dried blood spots taken for metabolic screening

[2] Includes previously diagnosed, those diagnosed through antenatal screening and those remaining undiagnosed

Source: Unlinked Anonymous Prevalence Monitoring Programme, Health Protection Agency

Feedback

Unlinked anonymous testing of blood specimens reduces the bias introduced by knowledge of only diagnosed HIV infection. Thus the increase seen in Figure 18.2 is likely to be real.

Outbreaks and responses: HIV

As well as longer-term surveillance, public health practitioners working in HIV/STI have to respond to acute/semi acute 'outbreak' situations. To understand how surveillance contributed to the initial descriptions of HIV spread within the USA, consider the data taken from the Morbidity and Mortality Weekly Reports (MMWR) in June, July and August 1981.

On 5 June 1981 there was an initial case description of what appeared to be a 'new' syndrome: five cases of various infections including *Pneumocystic carinii* pneumonia (PCP), not usually seen in people with normally functioning immune systems. They were given the name 'opportunistic infections' and were seen often in combination with a rare malignancy, Kaposi's sarcoma (KS), previously restricted to elderly males and seldom up to that point seen in younger people. All were described in Los Angeles.

Activity 18.4

If you were the investigating public health practitioner, what would you like to know? Start with basic epidemiology and work through to questions which may enable you to better understand what might be causing this.

Feedback

Before any kind of analytical or descriptive epidemiological study is undertaken you need a case definition. This may (and probably will) need refinement and change in the light of ongoing developments. The basic epidemiological parameters of time, person and place should be your starting point.

- *Time*: are these clustered in time or are they a case series going back over many years? Is there any suggestion of seasonality?
- *Person*: basic demographic variables – age, sex, occupation, ethnicity, any contact between the individuals, any other possible links – from leisure activities to travel history etc., any behaviours shared in common – e.g. could this be a drug-induced immune suppression?
- *Place*: was there clustering in any part of the city, any suggestion of environmental exposure?

The next key question might be whether other similar cases have been seen by clinicians in other parts of Los Angeles or in other cities.

In the light of what was found, the initial case definition adopted was 'a disease at least moderately predictive of a defect in cell mediated immunity occurring in a person with no known cause for diminished resistance to that disease' (this was almost two years before the discovery of HIV). Active surveillance was necessary as clinicians were not aware of what needed reporting etc. By July 1981 active surveillance had identified:

- 10 additional cases of PCP in Los Angeles and San Francisco;
- 26 cases of KS over a two-year period, 20 in New York, and 6 in Los Angeles and San Francisco;
- age range 26–51; six patients had died; all were homosexual males;
- ethnicity: 25 of 26 were white.

Activity 18.5

What are the key questions at this stage of your investigation of this cluster? (although this is now an extended cluster as the New York cases in particular spread back over two years).

Feedback

One of the key questions at this stage was whether this was increased recognition of something which had been going on for some time or a new syndrome. (This question, discussed in Chapter 5, is often more complex than it seems.) Because these young men were profoundly ill and some had already died most, if not all, would have almost certainly presented to hospital. They would have been seen by a general physician, infectious disease specialist, dermatologist (KS), gastroenterologist (chronic diarrhoea and wasting), chest physician (acute pneumonia or recurrent pneumonias) or intensive care physician. Thus, actively asking about such cases, and looking for unexpected deaths from pneumonia especially in younger adults might have revealed whether this was a departure from normal. However, the numbers were small and there are many causes of pneumonia even in young adults, most of which will be unconnected with this 'new' syndrome. Other questions include:

- Was it just homosexual men? The term gay related immune deficiency (GRID) was used before AIDS (acquired immunodeficiency syndrome), because all the initial recognized cases had been in gay men.
- Could the cause be chemical? A drug widely used in the gay community as a smooth muscle relaxant was the most likely suspect.
- Or was it infectious? Initial suspicion fell on a virus known to produce some immune suppression – cytomegalovirus virus.

By the end of August 1981 the following data were published in the *Morbidity & Mortality Weekly Report*:

- 108 cases: male 107, female 1;
- clinical: KS: 47, PCP: 53, both KS and PCP: 7;
- ethnicity: White: 79, Black: 12, Hispanic: 11, Not known: 6;
- Sexual preference of males: Homosexual: 95, Heterosexual: 6, Not known: 6.

Activity 18.6

If you were in charge of public health at a high level in New York state or California at that time what additional questions would you seek arising out of these data?

Feedback

The single female case may prove useful in understanding something about this new syndrome – 'outliers' in any outbreak may give clues to aetiology, exposure etc. (see Chapter 5). However, first check that this case was not misreported (wrongly reported as female). It is worth checking such 'outlier' cases before building a hypothesis which you may later regret!

In addition to wrongly reported data, some of the information you receive may be 'soft' (i.e. not very reliable). One such item could be the sexual preference of males. For some men who are not open about their sexuality there may be difficulties in admitting their sexual preference to clinic or ward staff. Hence the six 'heterosexual' cases should be treated with caution – these may be men who have had only heterosexual sex; men who have occasionally had sex with another man but whose main preference is heterosexual; or men whose preference is homosexual but have difficulty admitting this to others. Moreover, in some societies being the insertive partner in a relationship with another man is not thought of as being homosexual – only the receptive partner is regarded as homosexual. The general point here is that you need to understand what clinicians are reporting to you and in addition understand what patients are telling the clinicians – there is a complexity and sensitivity in reporting sexual practice which needs to be understood and not necessarily taken at face value. It is difficult to comment on the ethnicity data without either looking at rates or having at least some knowledge of the size of the ethnic groups in the areas from which you are receiving surveillance data.

Outbreaks and responses: LGV

Lymphogranuloma venereum (LGV) is an STD caused by a variety of *Chlamydia trachomatis*. Until recently it was almost exclusively seen in Africa, South-East Asia, Central and South America and the Caribbean. It was very rare in North America and western Europe. However, from 2003 onwards cases began to be seen in several countries of western Europe – among the first countries to recognize this was the Netherlands.

Activity 18.7

Thirteen cases of LGV were diagnosed from April to November 2003 and reported by local health authorities in one of the major Dutch cities. Describe how you would investigate this and what you would want to set up in terms of ongoing surveillance. Try to be as specific as you can in your answer and write it down before reading the feedback below.

Feedback

Establish an outbreak control team composed of public health personnel, STI clinicians, microbiologists, academic researchers with an interest in sexual health, representatives from your Ministry of Health, those with responsibility for resource allocation etc. (Chapter 6). Now develop a case definition, defining how the cases are to be microbiologically confirmed and whether this is to be done locally, in one reference laboratory within the country, or sent outside the country. Start collecting data for an epidemiological study and consider the following:

- A good descriptive epidemiology of cases with some of the enhanced data listed earlier in this chapter.
- A case control study – what are the questions you want to answer and how are you going to recruit your controls? Would you need ethical approval for such a study?
- A cohort study – have you identified a population at high risk and which you have the resources to follow up over a longer time period?

You may experience difficulties in such an investigation as to who 'owns' the data and how results are communicated. This is one of the reasons why an outbreak control team is important and achieves a wider acceptance of the course of action. You will need some form of patient identifiers so that you can recognize duplicate reports. However, there is real sensitivity around STI data and this needs to be handled very carefully with due regard to data protection and confidentiality guidance within your country. You are collecting the data with the purpose of trying to prevent further cases so if you are able to elucidate particular risk factors this may enable targeted health promotion among men who have sex with men (many of the cases were found to be HIV positive also).

What was actually undertaken is covered in CDC (2004) and Gotz (2004).

Trends and endemic levels of infection: HIV

Figure 18.3 illustrates HIV cases reported in the UK from 1985 to 2003. The most striking change is in the increasing number of new diagnoses in heterosexuals, especially from 1998 onwards. More detailed surveillance data (see Figure 18.4) show this as being part of the impact of the worldwide epidemic on the UK as most of these were in people from Africa or who had acquired their infection there. However, the continued numbers of new diagnoses in men who have sex with men (most of which were acquired within the UK) is also a concern.

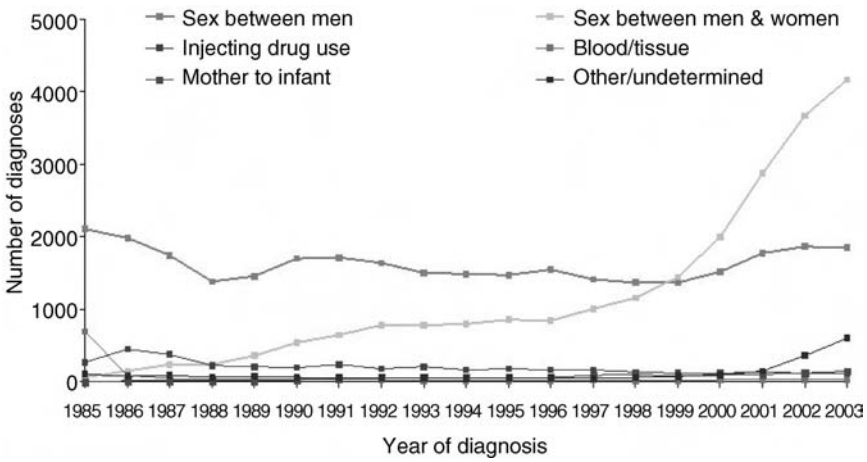

Figure 18.3 Number of new HIV diagnoses by year of diagnosis and probable route of exposure, UK reports to the end of 2004

Source: HIV/STI Department, Health Protection Agency

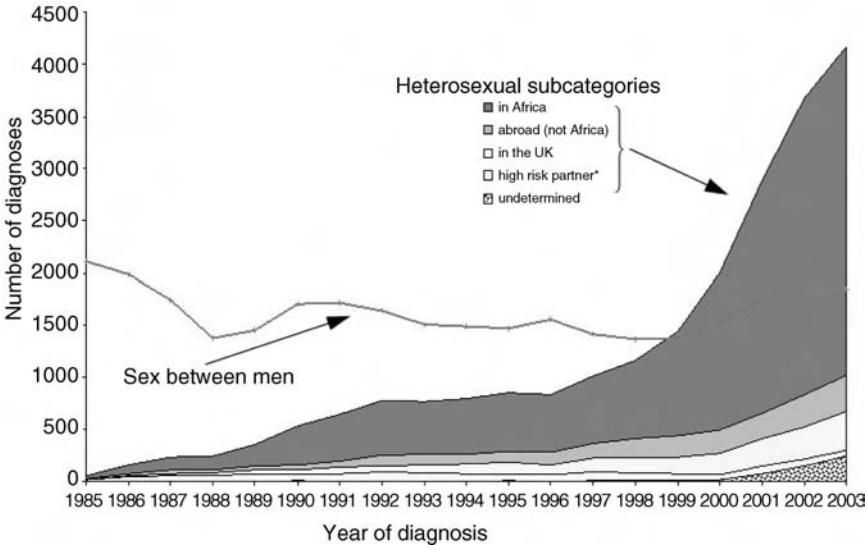

Figure 18.4 UK HIV diagnoses by the two main routes of transmission (Reports received by end of 2004)

Numbers for 2003 will increase as further reports are received and follow-up continues
* High risk partner included people infected through sex between men, injecting drug use or receipt of blood or blood products

Source: HIV/STI Department, Health Protection Agency

Trends and levels of infection: chlamydia

Figure 18.5 shows Chlamydia diagnoses from 1995 to 2003.

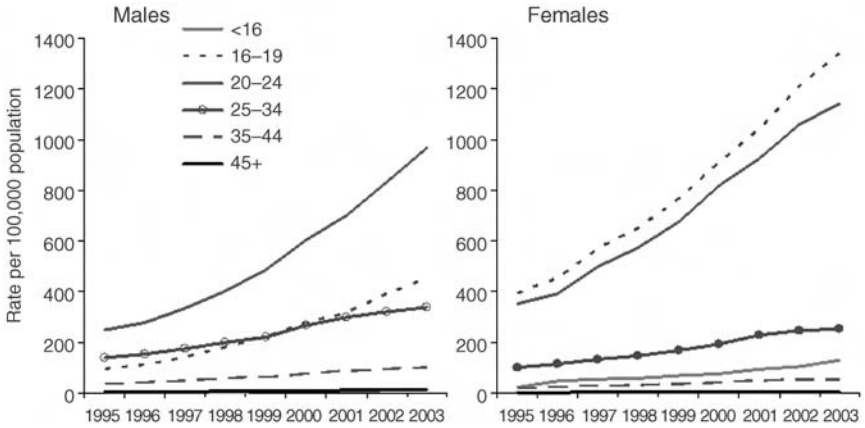

Figure 18.5 Rates of diagnoses of uncomplicated genital chlamydial infection by sex and age group, GUM clinics, United Kingdom,* 1995–2003

* Data are currently unavailable from Scotland for 2001, 2002 and 2003

Source: KC60 statutory returns and ISD(D)5 data, Health Protection Agency

Activity 18.8

Describe the trends seen. What factors affect them? From these data can you say that the incidence (i.e. new infection acquisition) of chlamydia is increasing and if not why not?

Feedback

These data will be dependent on who is getting tested. Most people with Chlamydia have no symptoms and so testing policy will strongly determine who gets diagnosed. If over this time period there has been encouragement of people to be tested then the increase could be artefactual and just as high rates might have been present in 1995 if the same testing pattern had applied. In addition the sensitivity and specificity of the diagnostic tests may have altered the trends. (STI clinics in the UK are called genitourinary medicine (GUM) clinics.)

Trends and levels of infection: syphilis

Figure 18.6 charts trends in syphilis rates for Germany, the Netherlands and the UK over the period 1997 to 2002.

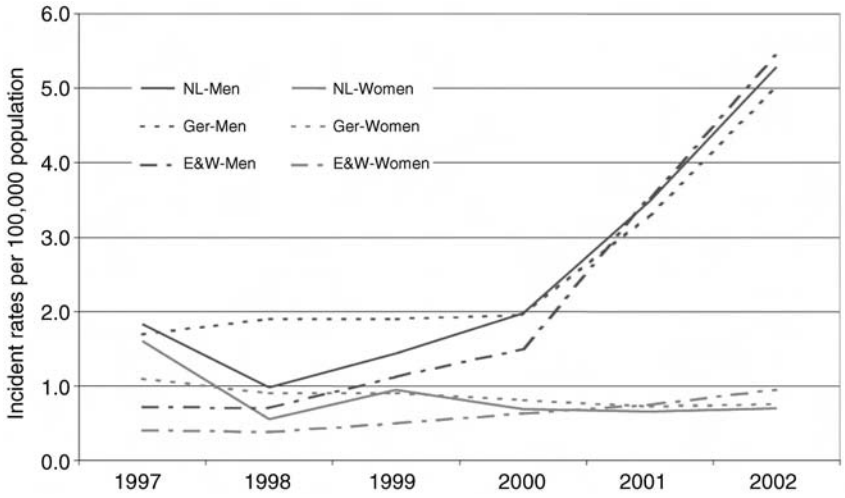

Figure 18.6 Resurgence syphilis 1997–2002 by sex – England and Wales, the Netherlands and Germany

Source: European Surveillance of sexually transmitted infections

Activity 18.9

Describe what you see. What features or risk groups might this suggest?

Feedback

The trend lines are remarkably similar in these three western European countries and incidence rates increased markedly in men since 2000. Further surveillance information shows this to be largely in men who have sex with men, many of whom are HIV infected and a significant proportion (at least 30 per cent within England and Wales) is due to oral sex.

Behavioural trends

Figure 18.7 shows sharing of injecting equipment in injecting drug users (histograms) and the UK levels of hepatitis B and C in injecting drug users (percentage prevalence on y axis).

Data such as these emphasize the importance of strengthening needle exchange programmes to try to prevent ongoing transmission of these blood-borne viruses. Sexual behavioural surveillance may be organized differently and is often via surveys carried out regularly (e.g. annually) rather than ongoing surveillance. Although more research than surveillance, the British National Sexual Attitudes & Lifestyles Survey is a national survey (around 20,000 people surveyed) which was first carried out in 1990 and repeated in 2000 (Fenton *et al.* 2001). This gives much detailed information on sexual behaviour.

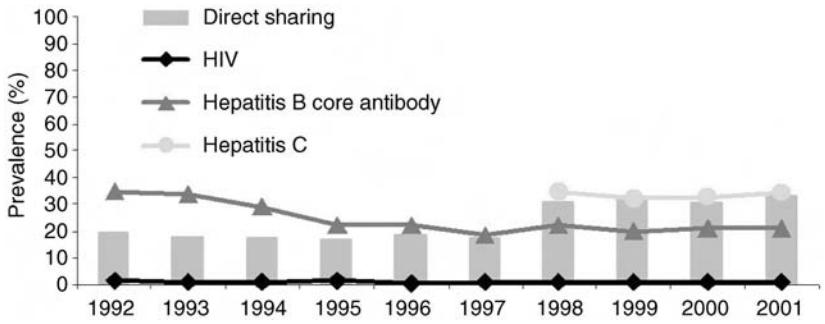

Figure 18.7 Prevalence of HIV, hepatitis B core antibody, hepatitis C and trends in direct sharing in injecting drug users in England and Wales: 1992–2001

Source: Unlinked Anonymous Prevalence Monitoring Programme, HIV/STI department, Health Protection Agency

Response: surveillance into action and methods of control

The WHO/UNAIDS lists the main uses of surveillance data as:

- situation analysis
- strengthen commitment
- resource mobilization
- targeting interventions
- planning and evaluation of interventions
- programme assessment and evaluation

Activity 18.10

Think through what from this list is relevant in your country to the situation with HIV/STIs.

Feedback

The following covers some of the interventions which are possible.

Internationally

Vaccines: much work is currently going on to develop an HIV vaccine and other STI vaccines (HPV, HSV).

Treatment: research work in developing new anti-HIV drugs continues, with drug manufacturers linking with academic departments undertaking research at a molecular level into how HIV attaches to cells etc.

Nationally

Behaviour change: surveillance data may have identified particular risk groups which can

be targeted with specific sexual health promotion advice. It is necessary to work at a strategic and operational level – both with the Ministry of Health and with voluntary agencies and local statutory groups who are in a position to undertake the specific interventions. An important part of behaviour change is advice in particular situations. In order to get messages to the general population, reaching school-age children is important. In this way, hopefully, responsible attitudes to sexual relationships will be created and when sexual activity commences this will be something they want to do, rather than something they later regret. Specific groups at high risk can also be targeted (e.g. sex workers).

Surveillance data can also assess the impact of such interventions in behaviour change or in new STI rates. Targeting specific groups needs to be undertaken cautiously so as not to further stigmatize such groups. Such action is possible especially if voluntary organizations or those at higher behavioural risk themselves are involved.

Because STIs can facilitate the transmission of each other, prompt diagnosis and treatment will contribute to lessening transmission. Surveys of patient access to treatment may be helpful in understanding barriers to access and ways in which services could be altered or strengthened to enable better access. Late diagnosis of HIV may contribute to further spread as it is known that HIV transmission occurs with increased frequency at higher viral loads. Hence if an HIV infected person is unaware of their HIV status, has a high viral load and continues to practise unsafe sex, then HIV transmission is more likely to occur in sexual partners. When people come for diagnosis and treatment it is often an appropriate time to give specific advice on sexual behaviour, condom use etc.

It is important that any interventions involve key people (e.g. Ministry of Health, academics, health promotion specialists, STI clinicians, public health professionals, microbiologists/virologists, voluntary groups). New ideas may arise or specific interventions be more appropriately targeted if this wider ownership of interventions occurs.

Complexity vs. 'sound-bites'

There is a complexity to HIV and STI surveillance and to the interpretation of the data. However, politicians especially prefer sound-bites – brief messages which are capable of catching the headlines. In working with health promotion, journalists and politicians it is important that together you work out what is valid to say in summarizing trends or in highlighting behavioural risk. An example combining data from many UK HIV surveillance systems is shown in Table 18.5.

Table 18.5 Estimate of prevalent HIV infections among adults in the UK at the end of 2003

	2002	2003		
Exposure category	**Total**	**Number diagnosed†**	**Number undiagnosed‡¥**	**Total**
Sex between men	**22,600**	**18,100**	**6,400 (26%)**	**24,500**
Injecting drug use:	**1,700**	**1,400**	**400 (22%)**	**1,800**
Sex between men and women				
Male	**10,600**	**6,700**	**4,200 (39%)**	**10,900**
African	*6,300*	*4,100*	*2,000*	*6,100*
Non-African	*4,300*	*2,600*	*2,200*	*4,800*
Female	**13,900**	**11,800**	**3,300 (22%)**	**15,100**
African	*9,100*	*8,700*	*1,400*	*10,100*
Non-African	*4,800*	*3,100*	*1,900*	*5,000*
Total (heterosexual)	**24,500**	**18,500**	**7,500 (29%)**	**26,000**
Blood products¶	**700**	**700**	**0**	**700**
Grand total	**49,500**	**38,700**	**14,300 (27%)**	**53,000**

† Numbers diagnosed were obtained from SOPHID and SCIEH, adjusted for under-reporting and failure to access services

‡ Numbers undiagnosed derived for England and Wales and Scotland using data from Natsal 2000 and the UA programme in an extension of the method previously described {6231}

¥ Numbers undiagnosed for Northern Ireland derived by using exposure specific factors

¶ All cases infected through blood and blood products or tissue were assumed to be diagnosed

Source: Health Protection Agency

Summary

You have learnt about the importance of the multiple layers sometimes needed in surveillance, as described in Chapter 1. In the absence of effective vaccines, the control of STIs is complex and requires input from a wide variety of disciplines.

References

CDC (2004) *Lymphogranuloma venereum* among men who have sex with men – Netherlands 2003–4, *Morbidity & Mortality Weekly Report*, 53(42): 985–8.

Fenton KA *et al.* (2001) Sexual behaviour in Britain: sexually transmitted infections and prevalent genital Chlamydia trachomatis infection, *Lancet*, 358: 1851–4.

Gotz H *et al.* (2004) Preliminary report of an outbreak of *Lymphogranuloma venereum* in homosexual men in the Netherlands, with implications for other countries in Western Europe, *Eurosurveillance Weekly*, 8(4). www.eurosurveillance.org/ew/2004/040122.asp#1.

Useful websites

More up-to-date information of the LGV situation in Europe and the UK can be obtained, together with details of current surveillance methods, from www.essti.org (Europe) and www.hpa.org.uk/ (UK). www.unaids is also useful.

19 Hospital-acquired infections

Overview

In this chapter you will learn about some epidemiological aspects of hospital-acquired infection (HAI). HAI causes considerable morbidity and mortality worldwide. Health care associated infection (HCAI) is a wider term that includes infection acquired in primary care, community clinics, nursing homes and other health care facilities. It also includes occupational infections acquired by staff. Many of the health care problems associated with the wider term have been described elsewhere in this book.

Learning objectives

After studying this chapter you will be better able to:

- **describe the worldwide burden of HAI and the most important causes**
- **explain the importance of surveillance in HAI**
- **understand the interaction of factors causing HAI**
- **explain the basic steps of infection control to prevent HAI**

Key terms

Carrier A person who is asymptomatic but may transmit infection to others.

Colonization When an organism colonizes and multiplies in a part of the body but is not causing infection, though it may cause infection later, either in the host or someone else.

Contamination Presence of an organism on a generally inanimate surface or liquid, usually without multiplication.

Opportunistic pathogens Infections caused by normally innocuous organism(s), which become pathogenic when the body's immunological defences are compromised, e.g. *Pneumocystis pneumonia* in HIV.

Pseudomembranous colitis An inflammation of the colon characterized by yellowish-white plaques which may coalesce to form a 'membrane'.

Septicaemia Bacterial infection of the bloodstream, popularly called 'blood poisoning'.

Introduction

By definition, HAIs occur when:

- a patient has been admitted for another reason;
- infection not present or incubating at admission and usually appearing >48 hours later;
- an infection is acquired in hospital.

The burden of HAI worldwide is considerable. A WHO survey covering 55 hospitals in 14 countries and four regions showed an overall prevalence of 8.7 per cent, with the highest rates in the eastern Mediterranean and South-East Asian regions. In the UK, about 1 in 11 patients in hospital (9 per cent) has a HAI, making an estimated total of 100,000 patients a year. The cost of increased length of stay (LOS) and treatment is thought to be about £1000 million a year. The equivalent figures for the USA are 5 per cent, 2 million cases and >$2 billion. Litigation adds to these costs. Mortality is significant and many patients survive treatment including surgery only to succumb to HAI. LOS makes up most of the extra cost: the average increase for surgical wound infections was 8.2 days (range 3.0 in gynaecology – 19.8 in orthopaedics (Coella *et al.* 1993)) proving a cost burden to the hospital and the patient. Yet up to one third of HAI is potentially preventable.

The main clinical sites of HAIs are:

- blood (septicaemia);
- urinary tract;
- respiratory tract;
- skin/wound/surgical site;
- gastrointestinal tract.

Gastrointestinal infections have become more important recently because of norovirus and *Clostridium difficile*. Other sites include central nervous system, eye, ear, nose and throat. Each of these has its own HAI definition (Garner *et al.* 1988).

Activity 19.1

1 In what type of wards and patients would you expect the highest rates?

2 What hospital-associated procedure would you expect is most associated with HAI?

Feedback

1
- intensive care units
- surgical (especially orthopaedic) wards
- elderly, very young
- patients with underlying disease or immunosuppressed

2 The use of an indwelling device, whether it be in the bloodstream, urinary or respiratory tracts.

Main types of HAI

Septicaemia accounts only for about 5 per cent of HAI but has a high mortality. It is most commonly associated with an intravascular device, and with intensive care units. Coagulase-positive and negative staphylococci and enterococci are common pathogens. Fungal (candida) septicaemia also occurs. Septicaemia can also follow on from vascular catheter site infection, urinary tract infections (UTIs) wound and other infections.

UTIs account for about 40 per cent of HAI. As with septicaemia, these are mostly associated with an indwelling catheter. The commonest infecting organisms are the Gram-negative intestinal flora – *E. coli* and other enterococci; *Pseudomonas aeruginosa* and candida are the commonest pathogens.

Pneumonia is the second most common HAI after UTI. It has a high fatality rate. Patients who are intubated or on ventilators are at greatest risk. Infecting organisms may derive from the upper respiratory tract or upper gastrointestinal tract, or from contaminated respiratory equipment. Viral infections, including influenza, can also cause nosocomial infection. With legionnaires' disease the source is invariably from the environment.

Surgical site infections (SSIs) include wound infections or deeper infections. Risk factors include host and surgical factors. SSIs often occur after discharge. The commonest organisms are *Staphylococcus aureus*, pseudomonads, coagulase negative staphylococci, enterococci and fungi. The National Nosocomial Infection Surveillance system in the USA developed a risk index based on the wound class, ASA index and duration of surgery. The wound class increases in four stages: clean, clean-contaminated, contaminated and dirty. The ASA index is based on the anaesthetist's score of the patient's underlying risk factors. High scores mean high risks of infection. Comparing individual surgeons' SSIs was found to reduce rates of SSI.

It is important to differentiate causes of diarrhoea common in hospital patients (e.g. laxative- or antibiotic-induced) from HAI. HAI infections include *Clostridium difficile*, rotavirus, norovirus and salmonella, although almost any gastrointestinal organism transmissible from person-to-person can cause HAI. Outbreaks of norovirus are common in hospitals and can be particularly difficult to control.

Activity 19.2

1 From what you already know about norovirus (see Chapter 16), why do you think it is difficult to control?

2 Some of these characteristics are shared by shigella, which is a less common cause of HAI. Why do you think this is?

Feedback

1 The small dose, ability to spread on fomites and staff hands, and probably even in the air, together with the high resistance of the virus and vulnerable patients, facilitate spread.

2 Shigella is more susceptible to the environment (light, dryness, heat) than norovirus, and is not known to be airborne. Being less common it is less likely to be brought into hospital.

Clostridium difficile is the commonest pathogen associated with antibiotic-induced diarrhoea and pseudomembranous colitis in hospitals. It can be acquired from the environment (spores can persist for five months on surfaces), hands of staff, other patients and medical equipment. Length of stay is closely correlated with acquisition. In most cases infection is asymptomatic. Symptoms may be triggered by antibiotics and the presence of risk factors such as age and debility of the patient (with about 80 per cent >65), antidiarrhoeal drugs and insertion of tubes/enemas into the gastrointestinal tract.

MRSA is important because staphylococci are virulent, and resistance to several commonly-used antibiotics decreases treatment options. It has a higher case fatality rate than sensitive staphylococci. It is increasing in incidence and prevalence in the UK and other European countries, the USA and elsewhere. It can be spread between patients both within hospitals and in the community.

Risk factors

Activity 19.3

Using some first principles of epidemiology, list the main factors which you expect will influence whether HAI will occur.

Feedback

It is probably best to think of the host, the agent and the environment. Host factors will include age, sex and health status of the patient. Agent factors include the virulence of the organism and the site of inoculation. The environment encompasses general hygiene and cleanliness of the patients' surroundings; cleanliness or sterility of all invasive apparatus including ventilators; air-conditioning systems; plumbing systems; spaces between beds; facilities for handwashing etc.

The probability of HAI (I_p) depends on the virulence (V) and dose (D) of the organism, the receptive host site of contact (S), the time of contact (T) and the combined force of the host defences (H_d). It can be expressed as follows (Hierholzer 1996):

$$\frac{Ip = V \times D \times S \times T}{Hd}$$

The environment is the background ('playing field') on which HAI occurs, and will influence the four factors in the numerator. It includes new technologies which are important to patient care but may present new opportunities to invading organisms.

Surveillance of HAI

The choice of numerator in HAI can be quite complex. Possibilities are surveillance by organism or condition (clinical). Organism surveillance is most commonly used, and is specific, easy to use and ideal for outbreak detection. However, it is not sensitive – it depends on appropriate microbiological samples being taken and proving positive, and some important HAIs have a low microbiological diagnosis rate. Condition surveillance can be, and often is, combined with organism surveillance to increase sensitivity, and enhances teamwork between ward and infection control staff. On the other hand, ward staff are less likely to be alert to clinical conditions which need to be reported.

The list below is not necessarily complete but gives examples of the important organisms:

Respiratory tract:	legionella
	penicillin-resistant pneumococcus
	influenza
Surgical site infections:	methicillin-resistant *Staphylococcus aureus* (MRSA)
	vancomycin-resistant enterococci
Gastrointestinal tract:	*Clostridium difficile*
	norovirus, rotavirus
	salmonella
	shigella
Urinary tract infection:	vancomycin-resistant enterococci
Septicaemia:	MRSA
	vancomycin-resistant enterococci
Any site:	MRSA
	vancomycin-resistant enterococci
	M. tuberculosis
	S. pyogenes

The alert conditions could include any type of infectious diarrhoea and food poisoning, SSI, tuberculosis, legionellosis, chickenpox (and similar childhood illnesses which may affect vulnerable patients), scabies and other skin infestations including impetigo, viral haemorrhagic fever etc.

Activity 19.4

What would you use as a denominator?

Feedback

Possibilities are admissions, discharges, patient days, number of procedures or even number of days with a device associated with HAI. Admissions and discharges are easiest to use but all the others can be useful if data are available. Incidence and prevalence surveys can be undertaken. Prevalence data give a broad measure of the extent and spectrum of HAI in a hospital, but like many prevalence surveys of short-term events may not be representative. Incidence data can provide information on rates of infection and time at risk, and can be more easily used for comparisons within and between hospitals, but is more labour intensive and therefore expensive.

Prevalence surveys show higher rates of infection than incidence surveys because HAI increases length of stay so more patients than you would expect will be included in a prevalence survey.

Activity 19.5

What sources of data for surveillance of HAI are available?

Feedback

Case note review is ideal but can be labour intensive. Otherwise microbiology reports, clinical diagnoses and antibiotic records can be used. Total continuous surveillance to detect all infections is very resource-intensive and may not produce the best results. Priority-directed, site-specific surveillance is preferred, especially when resources are limited – being more flexible, it can be adapted for specific needs and problems.

Prevention of HAI

Clearly the use of invasive medical devices warrants utmost care. Only use if necessary and adopt scrupulous hygiene methods when inserting them. Keep them in for as short a time as possible. Routine hand-washing before and after any contact not just with a patient but also with other potentially contaminated objects is the backbone of HAI control. Disinfectant soaps are recommended in wards with high-risk patients, such as intensive care units. All potentially infectious body material, such as blood, urine, saliva and tissue should be safely disposed of. Special boxes for sharps should be available. Gloves, masks and gowns should be used where advised.

On a broader basis, a dedicated infection control team which undertakes surveillance and control is essential. Agreed policies should be made and in force. Such policies should cover everything from cleaning of the environment, through hygiene measures required of staff, to immunization of staff and an antibiotic policy. Good surveillance with regular informative bulletins is useful in itself, and it

has been shown that producing surgeon-specific HAI rates reduces the rates. Audits of wards and theatres can have a useful effect.

Activity 19.6

Why are HAIs likely to continue to increase?

Feedback

There are four reasons:

- increasingly vulnerable patients – older age, immunosuppressed
- antibiotic-resistance
- new infections
- new technologies

The trend towards a more rapid turnover of patients and shorter lengths of stay may have a slight reversing effect.

Summary

You have learnt that HAI is a considerable problem worldwide. It depends on a complex interaction of host, agent and environmental factors. About a third of the total burden is thought to be preventable. Control depends on effective surveillance, good hygiene, effective management and workable policies.

References

Coella R *et al.* (1993) The cost of infection in surgical patients: a case study, *Journal of Hospital Infection*, 25: 239–50.

Garner JS *et al.* (1988) CDC definitions for nosocomial infections, *American Journal of Infection Control*, 16: 128–40.

Hierholzer W (1996) Principles of infectious disease epidemiology, in C. Glen Mayhall (ed.) *Hospital Epidemiology and Infection Control*. Williams and Wilkins, Baltimore, MD.

Useful websites

HELICS: http://helics.univ-lyon1.fr.
Hospital Infection Society (UK): www.his.org.uk/.
Infection Control Nurses Association (UK): www.icna.co.uk.
National Audit Office (England): www.nao.org.uk/publications/nao_reports/9900230.pdf.
UK PHLS: www.hpa.org.uk/infections/publications/ninns/hosacq_HAB_2002.pdf.

US/CDC: www.cdc.gov/ncidod/hip/surveill/NNIS.htm.
WHO: www.who.int/csr/resources/publications/drugresist/whocdscsreph200212.pdf.

Glossary

Active surveillance Active case-finding with encouragement of those seeing such cases to report them. Also useful for infections which may be overlooked if not actively looked for or incentives to report not present.

Acute hypotension Sudden loss of blood pressure.

Acute poliomyelitis A viral infection which causes paralysis of any muscle in the body. Most infections are asymptomatic; risk of paralysis increases with age at first infection. Spread mainly by faecal-oral route. Live (oral) and inactivated (injection) vaccines are available.

Anaerobic organisms Those that require absence of oxygen for growth.

Arbovirus An arthropod-borne virus, i.e. spread by an insect.

BCG vaccination Insertion of Bacille Calmette-Guerin, a modified attenuated tubercle bacillus, intradermally to stimulate immunity. Efficacy is limited.

Biofilm Slime, a film of biological matter which sticks to surfaces.

Carrier A person who is asymptomatic but may transmit infection to others.

Cervical lymphadenitis Enlarged lymph glands in the neck, usually caused by various conditions including TB.

Colonization When an organism colonizes and multiplies in a part of the body but is not causing infection, though it may cause infection later, either in the host or someone else.

Contamination Presence of an organism on a generally inanimate surface or liquid, usually without multiplication.

Diphtheria A bacterial infection caused by *Corynebacterium diphtheriae*. It may produce a white membrane which can block the upper respiratory tract, or a toxin which can damage the heart, often fatally.

DTP polio vaccine Diphtheria, tetanus and pertussis vaccines given as one injection in three doses at under 1 year of age, together with oral **polio** vaccine.

Emetic Producing vomit.

Enhanced surveillance A form of active surveillance where a more comprehensive set of information is collected than would ordinarily be obtained from passive surveillance.

Epidemic A large outbreak usually affecting an extensive area or several countries.

Excess mortality The number of deaths in excess of that which occurs in a non-epidemic or baseline year.

FDA Federal Drug Administration, a body in the USA that approves all drugs for sale in the country.

Fomites Inanimate materials which are likely to carry infection.

Ghôn focus The initial lesion in the lung.

Guillain-Barré syndrome A complication of campylobacter and other infections which presents as a symmetrical paralysis of limbs and sometimes the respiratory muscles.

Hepatitis An inflammation of the liver, caused by a variety of agents, including chemicals and viruses.

Hepatitis (viral) Hepatitis is an infection and inflammation of the liver caused by a number of viruses, named alphabetically from A to G.

Horizontal transmission Case-to-case, usually in childhood.

Immunoglobin M (IgM) Antibodies that are usually produced first in an immune response and are later replaced by other types of antibody.

Immunoglobulin Five classes of protein (A, D, E, G, M) that play an essential role in the body's immune system by attaching to foreign substances, such as bacteria, and assisting in destroying them.

Intussusception A blockage of the intestine which can be fatal. Thought to be caused by some viruses and associated with rotavirus vaccine.

Lyme disease An infection spread by ticks, causing skin rash, cardiac and neurological disease.

Measles An extremely infectious viral disease with serious complications. Before the vaccine, infection in childhood was virtually universal.

Methicillin resistant staphylococcus aureus (MRSA) Another increasing and important public health problem, not only in hospitals now but also in the community.

Miliary Disseminated tuberculosis.

Motor end plate Where nerve meets muscle and releases a chemical, acetylcholine, causing the muscle to contract. Important in botulism.

Multidrug-resistant tuberculosis (MDR-TB) An increasing and important public health problem. It makes the management and treatment of TB more difficult, especially as the drug-resistant strains can be transmitted from person to person.

Nosocomial infection Infection acquired in hospital.

Operational (technical, productive) efficiency Using only the minimum necessary resources to finance, purchase and deliver a particular activity or set of activites (ie avoiding waste).

Opportunistic pathogens Infections caused by normally innocuous organism(s), which become pathogenic when the body's immunological defences are compromised, e.g. *Pneumocystis pneumonia* in HIV.

Outbreak Usually localized. These terms are not precise.

Pandemic A worldwide epidemic.

Passive surveillance Routine reporting without active attempts to ensure a high rate of completeness.

Phage (bacteriophage) A virus which parasitizes a bacterium, and reproduces within it. Can be used for typing (e.g. salmonella) and determining virulent strains.

***Pneumocystis carinii pneumonia* (PCP)** A rare infection of the lungs affecting the immunosuppressed; now classified as a fungal infection.

Primary complex of Ranke The primary lung lesion with enlarged lymph nodes at hilum of lung (hilar lymphadenopathy).

Prions Proteins which can enter cells and convert intracellular proteins into replica prions, causing infection. Human-to-human transmission occurs through blood transfusion, growth hormone injections, tissue transplants, food.

Pseudomembranous colitis An inflammation of the colon characterized by yellowish-white plaques which may coalesce to form a 'membrane'.

Reye syndrome Rare serious condition affecting infants and young children, causing brain and liver disease; associated with use of aspirin.

Rheumatic fever A generalized response to infection with group A streptococci involving joints and heart. Heart valve changes often became permanent. Rheumatic heart disease was a common cause of death until recently.

Scarlet fever An infection caused by a streptococcus. A toxin produced by the streptococcus makes the skin turn red. It had a high mortality in the early part of the twentieth century. It is susceptible to penicillin.

Secular (temporal) trends Changes over a long period of time, generally years or decades.

Septicaemia 'Blood poisoning' – a more than transient invasion of the blood with a bacterium.

Sexually transmitted diseases (STDs) Infections transmitted sexually and causing symptoms which can be acute, or the long-term result of an earlier infection.

Sexually transmitted infections (STIs) May be asymptomatic and not currently causing disease.

Silicosis A widespread disease of the lung caused by inhaled silica particles.

Subacute sclerosing panencephalitis (SSPE) A rare fatal complication of measles, causing a slow deterioration of brain function (panencephalitis). Now rare in countries with effective measles immunization programmes.

Tenesmus A continual feeling of wanting to defaecate without necessarily being able to.

Toxoplasma gondii A protozoon not considered as a cause of food poisoning although it can infect beef. Can be hazardous to the foetus if consumed by pregnant women.

Tuberculin test/PPD A standard solution for testing previous exposure to TB prepared from tubercle bacilli, injected intradermally into the forearm.

Tuberculomas A tuberculous abscess, a large solid lesion with necrotic centre.

Vaccine effectiveness The final outcome of a vaccine programme in controlling a disease, dependent on uptake and efficacy.

Vaccine efficacy (VE) The protective rate of a vaccine – per cent protected by the vaccine if 100 per cent uptake.

Vaccine failure When infection occurs despite receiving a full course of an effective vaccine.

vCJD (Variant Creutzfeldt Jakob disease) A fatal brain disease caused by prions, spread from cows with a brain infection.

Vertical transmission Mother to foetus.

Whirlpool spa A warm bath with built-in whirlpools and water jets, often shared by several people. Water is recycled after filtering and disinfection. Also known as jacuzzis, named after Candido Jacuzzi, an Italian-American.

Whooping cough A bacterial infection caused by *Bordetella pertussis*. It causes a paroxysmal cough, especially severe in babies.

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