

# 6

## Pandora's box

Pandora was the first woman to be created. She was fashioned from clay by Hephaestus at the request of Zeus. The gods gave her every advantage they were able to grant. Zeus then gave her a box to present to the man who married her. He planned to destroy man, who had been created by Prometheus, by giving the man Pandora as a wife. Knowing that Prometheus would be too wise to accept the gift, Zeus persuaded his less cautious brother Epimetheus to marry her. Later Pandora, against the instructions of the gods, opened the box and let loose upon the world all evils and diseases. In the bottom of the box only Hope remained.

Ancient Greek myth

Most of the zoonoses already discussed in this volume lead to death only in an infected human following a prolonged untreated infection. The zoonoses discussed in this chapter are less benign, and entirely more sinister. Their very names – anthrax, Ebola, plague and rabies – carry an echo of unspeakable evil. This may only be a fantasy or a folk memory, yet the facts speak for themselves. Once infected, the chance of mortality with any of these agents is much higher than with other zoonoses, especially if treatment is delayed once symptoms appear.

Having been demonised by our media in books, films and newspapers (the image of Dustin Hoffmann fighting against an epidemic of massive mortality in *Outbreak* is an enduring one for all who have seen it), where does the truth lie? This chapter sets out to answer some of the following questions: how dangerous are these infections? What are the mortality statistics? What are the available treatments, if any?

Although not endemic in the UK, all of these diseases could appear here carried by fomites, animals or humans, depending on their mechanism of spread. If robust measures were not put in place rapidly on the appearance of an initial case, a pestilence of biblical proportions could ensue. It is not for nothing that one of the horsemen of the apocalypse is named as pestilence or plague.

As has been mentioned in Chapter 1, our temperate climate, geographical isolation and quarantine system give the UK a degree of

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protection against the more dramatic manifestations of serious zoonoses. The system of quarantine certainly has afforded us comprehensive protection against rabies for many years, and the advent of a well-regulated system of pet passports is unlikely to compromise that system. In contrast, we cannot quarantine human beings except in rare and exceptional circumstances. Not all immigrants to our country – be they animal or human – stop at the immigration office on the way in, nor can we tell if they are infected if they do. Migrating birds are believed to have been responsible for the outbreak of West Nile virus in New York which killed eight people between September 2000 and September 2001. They do not stop at borders for a health check.

Historically, the bubonic plague was introduced into the country by rats from ships, and the epidemiology of the Black Death began with the first cases being seen at Melcombe in Dorset. The likelihood of a recurrence of plague from such a source is reduced by inspections and mandatory fumigation of vessels as well as the system of public health measures aimed at controlling the rodent populations. Nevertheless there still remains a risk, and the price of safety is constant vigilance. Part of any system of vigilance has to be the education of healthcare professionals in the signs and symptoms associated with these diseases and this chapter aims to forward that objective.

It is not only animals and humans that travel today; goods are transported from far and near to fuel the appetite of our domestic market. Fomites transfer or objects contaminated with spores are particularly important in the transmission of anthrax. Recently the importation by both tourists and commercial companies of items made from goatskins in Haiti and the Dominican Republic has been banned as these items have been shown to be contaminated with anthrax spores.

There is another dimension to several of the diseases examined in this section. Biological warfare has been the subject of a wide debate in modern society. It has a long and less than glorious history linking the catapulting of dead animals and humans into besieged strongholds by our ancestors to the possibility of Scud missiles loaded with anthrax being fired from Iraq into Israel. Biological warfare is banned by international treaty, and enforced by United Nation inspection. However, as recent events in the USA have shown, this is not sufficient to prevent individuals or states pursuing this route in the hope of causing mega-death to their adversaries. Some of the organisms discussed in this chapter have the potential to be biological agents for weapons of mass destruction. This also helps link these zoonoses in readers' minds with

the everyday world of media reportage and will perhaps dispel some of the wilder journalistic assertions.<sup>1</sup>

### **Anthrax**

*(Malignant pustule, woolsorter's disease, charbon, malignant oedema, splenic fever)*

Anthrax is an acute bacterial disease of animals and humans which can cause rapid fatality (hence the old English name of 'struck' for the disease in cattle). It is caused by *Bacillus anthracis*, a Gram-positive, encapsulated, spore-forming bacterium which spores rapidly on contact with oxygen. When cultured it produces dense colonies on agar with long chains of bacteria forming so-called 'medusa-head colonies' from their shape and appearance.

This disease occurs worldwide and is an occupational hazard for those involved in processing the wool, hide, hair or bones of animals, such as farmers, slaughterers, skinnners, hideworkers, tanners and woolworkers. Most mammals are susceptible to the disease. It is most commonly seen in cattle; goats, sheep, horses and pigs can also contract the disease.

Anthrax is a notifiable disease in the UK. Notification also applies to animals suspected of having died of the disease. Carcasses must be disposed of by burning or by liming followed by deep burial. Definitive diagnosis is not always possible as opening or moving suspect carcasses is also prohibited.

Luckily, the disease is rare in the UK. The most recent case occurred in August 2000 in Bradford after a man involved in the wool trade was diagnosed as having the cutaneous form. After treatment he survived.<sup>2</sup>

Many of the non-fatal cases in the USA associated with the handling of contaminated mail have also been of the cutaneous form.

An outbreak in 1979 at Sverdlosk, Russia, seems to have been related to an accidental release from a biological weapons research facility. Sixty-six people died, although the authorities claim that the cases resulted from the ingestion of poorly cooked infected meat.<sup>3</sup>

A large outbreak in Zimbabwe from October 1979 to March 1980 caused more than 6000 (mostly cutaneous) cases. In Paraguay 25 cutaneous cases were seen in 1987 following the slaughter of an infected cow. Currently the Department of Health (DoH) considers South and Central America, southern and eastern Europe, Asia, Africa, the Caribbean and

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the Middle East as areas where the disease may occur in significant amounts.

### Disease in animals

Anthrax in animals often follows the grazing of pasture infected with viable spores. The spores are resistant to a wide range of climatic conditions and can remain in contaminated ground for many years. In one reported incident from Hawaii, a cow died after grazing a pasture where the carcass of a cow suspected of having died of the disease 20 years previously was buried. Animals may also demonstrate in-species spread from infected meat or by close contact with an infected beast.

Symptoms in animals are usually acute, with high fever of sudden onset, localised swellings and profuse bleeding from orifices. Death usually occurs 24–72 hours after onset. Animals may be found dead or moribund.

### Transmission

The spores present in the animal's blood or secretions, infected pastures, hides and bone or meat. Transmission to humans follows contact with these spores.

### Disease in humans

The disease presents in distinct forms in humans depending on the route of infection. These are:

1. Cutaneous, following physical contact with spores and their subsequent inoculation into wounds or abrasions.
2. Pulmonary, following inhalation of spores from infected hides.
3. Intestinal, following ingestion of spores or organism in undercooked meat from infected carcasses.

Infected individuals display the disease after a variable incubation period depending on route of infection. The cutaneous form develops after 2–10 days, the pulmonary after 1–5 days and the intestinal after 2–5 days.

The cutaneous form, once known as malignant pustule, is responsible for 98% of cases worldwide. After the incubation period, a papular spot develops on the skin. This papule becomes vesicular and turns black in the centre. This forms an eschar (a plug of dead tissue, skin and blood) which causes necrosis of the underlying tissue and then sloughs off. There is very little pain or tenderness associated with the condition,

although local lymph nodes usually swell. Extensive oedema affecting the whole limb or upper body is often seen and is important in differentiating the disease from tick-borne disease where an eschar may also be present. Some patients will display fever, lethargy, sickness and severe headache. The skin lesion will often heal without treatment, but there is a 5–20% risk of untreated cases progressing to septicaemia or meningitis with fatal consequences after the eschar sloughs. Cutaneous spread to other people is possible.

Pulmonary anthrax, known as woolsorter's disease, follows inhalation of spores from infected hides or wool. It presents as a flu-like illness after the incubation period, followed by cough and severe shortness of breath. This develops into respiratory failure and can be fatal within 24 hours, usually following septicaemic spread.

All of the fatal cases seen in the US terrorist attacks during 2001 have been from the pulmonary form. Prior to the extensive number of cases seen, this form of the disease was believed to be fatal in all cases regardless of the rapidity with which treatment was commenced. This has proved erroneous, with death only occurring in 40% of cases.<sup>4</sup> There are still no known cases stemming from pulmonary spread from existing patients to other individuals, although precautions have been taken to prevent such an eventuality.

Intestinal anthrax follows ingestion of infected meat. The rarity of the condition is related to the low incidence of the disease in meat in developed countries, and the unlikely nature of ingesting enough viable spores or organisms to cause disease.

Severe copious diarrhoea occurs after the incubation period. Half of untreated cases will die.

### Diagnosis

Identifying the causative organism in blood smears makes the diagnosis. Growing samples on standard culture media leads to the development of characteristic colonies, with the bacterium showing centrally placed spores. Immunofluorescent and enzyme-linked immunosorbent assay (ELISA) techniques can also be used.

### Treatment

Anthrax is susceptible to most common antibiotics. There are reports of rare strains being found which are resistant to either penicillin or doxycycline.<sup>5</sup>

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Drug regimes culled from the literature include: Benzlpenicillin (penicillin G) 2 million units (IU) intravenously every 4 hours, tetracycline 500 mg by mouth 6-hourly, ciprofloxacin 400 mg intravenously every 12 hours or doxycycline 100 mg intravenously every 12 hours. There is little clinical experience with these regimes, although they have been used experimentally in laboratories. Therefore they must be treated with some caution, except for the penicillin dose regime.<sup>6,7</sup>

### Prevention

A vaccine derived from a cell-free filtrate of killed bacteria is available and licensed for human use in the UK. Supplies are kept by the Public Health Laboratory Service (PHLS), and are usually issued for use in workers considered to be at a high occupational risk. The vaccination regime consists of three doses given over a period of 6 weeks with a booster dose given after 6 months. An annual booster is necessary to maintain immunity. A vaccine is also available for animals, but it is only for emergency use and is obtained through the Ministry of Agriculture, Fisheries, and Food (MAFF: now the Department for Environment, Food, and Rural Affairs (DEFRA)).

Prophylactic use of antibiotics may also be appropriate. The *British National Formulary (BNF)*<sup>8</sup> has no recommendations; in contrast, in the American literature drugs of choice are tetracyclines, including doxycycline and ciprofloxacin. The recommended regimes are doxycycline 100 mg every 12 hours by mouth, ciprofloxacin 500 mg by mouth 12-hourly. Due to the persistence of spores in tissues following contact with dense inocula, it may be necessary to continue prophylaxis for 4–6 weeks after exposure. Vaccination may be necessary during antibiotic prophylaxis to give protection after discontinuing the drug therapy.

Physical prevention methods are based on preventing or limiting contact with infected animals or their hides, hair or meat. All surface wounds should be disinfected and covered. Physical disinfection of hides and hair is considered to be good practice in the tanning and wool industry. The use of formaldehyde as a disinfectant is carried out by specialist companies for imports of hide, bones and bone meal (much reduced in volume since the advent of bovine spongiform encephalopathy (BSE)) and wool. Heat treatment is also used. Animals suspected of having died of the disease are to be handled in accordance with bio-hazard procedures. Suitable protective clothing and filtered ventilation helmets should be worn.

Spores may be killed by heat with autoclaving or boiling infected materials or instruments where appropriate. In areas where anthrax is endemic, meat should be thoroughly cooked or avoided.

Formaldehyde and glutaraldehyde are effective disinfectants for dealing with local contamination and spillages, though it is recommended that clothing and other articles of victims should be incinerated carefully.

#### Potential as a biological warfare agent

Anthrax can be cultured successfully and its spores harvested. The spores can then be turned into a dry powder. During the First World War, the Germans produced sugar lumps inoculated with anthrax for feeding to allied draught horses. There were also incidents of bags of powder containing anthrax spores being dropped from German aircraft. In 1942–1943, the British conducted trials on Gruinard Island off the north-west coast of Scotland to investigate the feasibility of biological warfare using anthrax. (The island was finally declared safe in 1990.) In an associated programme, the UK developed cattle cakes inoculated with anthrax for retaliatory strikes against Germany. These were to have been dropped from bomber aircraft in the event of a German strike. In Germany warheads containing anthrax were developed for attachment to V1 and V2 weapons. The escalation of hostilities that such weapons would have caused led to neither side employing them offensively.<sup>7</sup>

In Japan during the 1990s, the Aum Shinrikyo cult released anthrax spores in Tokyo. Luckily there were no fatalities. Following the Iran–Iraq war and the Gulf War, Iraq was shown to have produced shells and missile warheads packed with spores.

Many authorities view anthrax as the greatest threat for use in biological warfare or terrorism. With the cases caused by contaminated mail in the USA in the aftermath of the events of September the 11th, it has become apparent that as a terrorist weapon it has a tremendous potential to cause widespread concern with some fatalities, even when the potency has not been enhanced by finely grinding the powder containing the spores.

#### **Ebola**

*(African haemorrhagic fever; Ebola haemorrhagic fever)*

Ebola is probably one of the most emotive and dramatic zoonotic infections. It is caused by a virus similar in form to Marburg virus but

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distinguished by differences in antigen testing profile. The virus is named after a river in the Democratic Republic of the Congo (formerly Zaire). Classified as an RNA filovirus, it shows strange branching and filamentous forms displayed by no other viral group. There are four subtypes of the virus. The three demonstrated to be pathogenic in humans are Ebola–Ivory Coast, Ebola–Sudan, and Ebola–Zaire. The fourth, Ebola–Reston, has been shown to be pathogenic in apes but not for infected humans. This last type was identified in monkeys imported from the Philippines into Italy and North America for laboratory use. Several research workers became infected with the virus, although none became ill.<sup>9</sup>

Ebola haemorrhagic fever was first recognised in 1976, when large outbreaks occurred in southern Sudan and neighbouring northern Zaire. Since then it has appeared sporadically in these and other areas of Africa. There has been only one case recorded outside Africa with a single non-fatal case in a laboratory in the UK following a needlestick injury. The pathogenic forms of the virus are not known to be native to other continents.

### Transmission

The natural reservoir of Ebola virus is unknown at present. It has been postulated that the natural reservoir could be bats. Recently scientists from the Institut Pasteur, Paris, have detected it in small rodents in the Central African Republic.<sup>10</sup> There is still work to be done to discover how the rodents transmit the virus to apes and monkeys which have previously been identified as the link to human infection. The handling of ill or dead infected chimpanzees was shown to be the source of human infection in the outbreaks in the Ivory Coast and Gabon.

The main concern for countries outside Africa stems from the latent period of the infection. In theory it would be possible for an infected individual to carry the disease into a city or country where unrecognised the disease could rapidly spread. Mortality rates have been as high as 90% in some outbreaks so the fear is not unfounded.

### Disease in humans

The virus has an incubation period of between 2 and 21 days after exposure and infection in humans before clinical signs are seen. Weak-

ness and lethargy follow a sudden onset of fever with a temperature as high as 39°C. Muscle and joint pain are seen in most cases, with sore throat, headache and occasionally hiccups. More severe symptoms follow with anorexia, nausea, vomiting and diarrhoea. The development of a severe skin rash and mental confusion is concurrent with the progression of the illness. Kidney and liver damage occurs and catastrophic internal and external haemorrhage leads to death towards the beginning of the second week. The virus is present in high concentrations in the blood, tissue fluids and most organs of the body. Patients lucky enough to survive require extended periods of care.

Human-to-human transmission occurs following direct contact with the blood, secretions or semen of infected patients. Following the first confirmed or index case transmission occurs to those in closest contact with the victim. These can be friends, family or healthcare workers. Nosocomial spread or spread from a clinic or hospital to staff or other patients has occurred several times in major outbreaks, leading to high mortality rates. In Africa limitations on availability of disposable equipment and protective clothing have also led to transmission. The disease can also be sexually transmitted through semen up to 7 weeks after clinical recovery. All Ebola virus subtypes have displayed the ability to be spread through aerosols under research conditions, although aerosol spread has not been demonstrated during outbreaks.

### Outbreak statistics

Between June and November 1976 the Ebola virus infected 284 people in Sudan, with 117 deaths. During the outbreaks 76 of the 230 staff at Maridi Hospital contracted Ebola fever, with 41 subsequently dying. In Zaire there were 318 cases and 280 deaths in September and October 1976.

There was an isolated case in Zaire in 1977 and a second outbreak in Sudan in 1979. One human case of Ebola haemorrhagic fever and several cases in chimpanzees were confirmed in the Ivory Coast in 1994 when a scientist contracted the disease after conducting an autopsy on a wild chimpanzee found dead with signs of haemorrhagic disease. Fortune favours the foolish and the brave and he spontaneously recovered.

In Gabon, Ebola haemorrhagic fever was first documented in 1994 and two outbreaks occurred in February 1996 and July 1996, with 37 cases and 21 deaths in Makokou, related to cooking a chimpanzee and 61 cases and 45 deaths in Booue.

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A large epidemic occurred in Kikwit, Zaire, in 1995 with 315 cases, 244 of whom died. This outbreak was thought to have occurred after the index case handled a monkey and smoked its flesh.

Ebola virus infections were not reported again until the autumn of 2000 when an outbreak occurred in the Gulu district of northern Uganda. This is the first outbreak ever documented in Uganda. As of 19 December 2000, the Ugandan Ministry of Health reported cumulative figures for all affected districts of 421 cases, including 162 deaths. Spread had been dramatic both in the community and hospitals, with healthcare workers amongst the dead.<sup>11</sup>

The outbreak was finally declared over by the World Health Organization (WHO) at the end of February 2001.<sup>12</sup> The final official death toll was 224. Including this outbreak, there have been approximately 1500 cases with over 1000 fatalities since the identification of the virus.

### Treatment

There is no therapeutic treatment for the disease. Supportive measures, such as rehydration by intravenous fluids, blood transfusion, use of nutritional supplements (again by intravenous route) and management of kidney failure, can improve the outcome of the disease. Rapid treatment of secondary infections is also very important, especially in the convalescent patient. During the Kikwit outbreak in 1995, eight patients were given blood donated by survivors. Seven of the eight patients recovered, probably as a result of the conferred immunity, although this treatment has not been properly clinically evaluated.

### Prevention

Any imported apes which have not been bred in captivity must be strictly quarantined. For best practice this should be extended to all primates, as the Ebola-Reston variety was found in apes previously held in a facility in Manila where fresh-caught and captive-bred apes were mixed.

Strict hygiene measures should be employed. Appropriate protective clothing should be worn at all times.

Suspected Ebola haemorrhagic fever is a notifiable disease in the UK, both domestically and to the World Health Organization (WHO). For healthcare workers strict barrier nursing and the use and careful disposal of gloves, syringes, needles and dressings are essential. All clinical

specimens have to be handled according to guidelines for extremely hazardous substances. Immediate disposal of bodies in secure body bags with prompt burial or cremation is necessary during an outbreak.

Case contacts or individuals exposed in laboratories must be placed under health surveillance for 3 weeks after their last possible exposure to infection. If there is the onset of febrile symptoms they must be placed in strict isolation until diagnostic test results are obtained.

In Africa, as the infection route is still unclear, prevention of Ebola poses a major problem. Educating healthcare workers and others to identify a suspected case early and to be able to isolate the patient with appropriate barrier nursing techniques is seen as the main thrust of current limitation strategies. The main obstacle to the success of such a strategy is the availability of sterile materials, protective clothing and appropriate facilities. Usually once a case has been confirmed by diagnostic tests an outbreak is already underway.

## Plague

*(The Black Death, bubonic and pneumonic plague)*

Any book about zoonoses would not be complete without a section on plague, and any section on plague must detail the historic importance of the ravages associated with the disease. Even today, it is not unusual to see children in the playground singing and acting out 'Ring-a-ring o'roses, a pocket full of posies, a-tishoo, a-tishoo, we all fall down'. This anonymous nursery rhyme, originating in the middle of the 17th century, is a graphic and simple representation of the effects of an outbreak of pneumonic plague. The importance of rat control is emphasised in the same way, with the telling of the tale of the Pied Piper of Hamelin.

Historians differ in their view of the worst results of epidemic plague, and the numbers of casualties quoted for pandemics are probably in legal terms 'unsafe'. The widest geographic epidemics are usually known as pandemics and the consensus of opinion is that in recorded history there have been three outbreaks which could be thus classified.

The first to spread across Europe started in the 6th century, and was known as the Plague of Justinian. There were widespread fatalities. This outbreak was seen as a visitation by God on a sinful people; however, the religiosity it engendered was no protection against flea bites and disease.

The outbreak now termed the Second Pandemic or the Black Death started from a natural focus somewhere in Mesopotamia in

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western Turkey during the 11th century. Plague-infected rats and their associated fleas, carried aboard trading ships, spread the Black Death from Tana in the Crimea, Ukraine, to Messina in Sicily in 1347. In the ensuing European plague, which endured up to the end of the 17th century, it is variously estimated that a quarter to a half of the population died as a result of this disease alone. At the height of the epidemic in the 14th century, the effect upon all aspects of social and international development was profound: large swathes of land in Europe became uninhabited. The epidemic in the UK in the 1660s, which caused the Plague of London and other local outbreaks, stemmed from this pandemic. Although important in British history, it was insignificant in world terms, with only 70 000 fatalities.

The third and last pandemic occurred during the late 19th century. It owed its rapid spread to commercial shipping, with infected rats becoming stowaways on fast steam packets leaving Hong Kong and Canton in 1894 for many other ports the world over. Within a decade it had spread to over 70 ports on five continents. Coming as it did at a time when scientific endeavour and disciplines were developing, the bacterium, its association with rats and the rat flea as a vector were soon identified, allowing prevention strategies to be put in place.

### The disease

The pathogen responsible for plague is *Yersinia pestis*, a Gram-negative coccobacillus. A facultative anaerobe, the bacterium is capable of forming an encapsulated spore swiftly when exposed to the air. The risk of infection from the spores, which are able to survive under suitable conditions for prolonged periods of time, has been considered a significant risk in archaeological excavations of burial sites.

During the Second World War, part of the Blitz upon London was aimed at disturbing the plague pits used for burials during the Plague of London three centuries previously, in the hope of releasing viable spores into the environment. Had this succeeded, the death toll from this disease, let loose in a city with increasing rodent numbers, poor sanitation and a displaced human population, would doubtless have been high.

This was not the first use of the disease as a weapon of war. Corpses of humans and animals which had died of this and other diseases have in the past been hurled into besieged cities using catapults. This stratagem was used in the hope and certainty of infecting the

garrison from the earliest recorded incidents of siege warfare until modern times. In 1346 a Tartar army besieging the city of Kaffa, in what is now Turkey, suffered from plague. They threw their dead into the city over the walls, and the resulting epidemic forced the defenders to surrender.

Plague has been identified as a pathogen at the centre of several countries' programmes of biological warfare development. Russia is known to have a genetically manipulated strain, designed for use. Both North Korea and Israel are known to have studied the use of this pathogen extensively in an offensive military role. If employed, the pathogen would be delivered using an air-borne route, so giving pneumonic plague to victims.

#### Wild foci

Wild plague foci, where suitable rodent populations and habitat conditions exist, are found in the western USA, some countries in South America, extensive areas of north-central, eastern and southern Africa, Madagascar, Iran, and also along the frontier between Yemen and Saudi Arabia, Central and South-east Asia, and portions of the Former Soviet Union<sup>13</sup> (Figure 6.1).



**Figure 6.1** Sylvatic (wild) plague foci across the world. Data from Dennis *et al.*<sup>14</sup>

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These foci are associated with dry areas, usually where desert or prairie-type landscapes form. Foci are normally away from urban areas because of their inaccessibility, or their inhospitable nature. It is therefore unusual to find human cases emanating from wild foci sources; however, in the USA where there has been rapid expansion of urban areas and isolated condominium building, an increasing number of human cases come from this source.

Rodents in a natural plague focus become immune to the disease. However, if they spread from the focus into another distinct rodent population, especially one linked to an urbanised site, infection of a susceptible population of rodents may produce massive fatalities. This can lead to the phenomenon known as rat-fall, where a large number of rodent corpses are seen in open areas. Associated with this event are usually reports of fleas biting humans: the rat fleas leave the corpses in search of new hosts, and this results in disease transfer.

### The world picture

The WHO made the latest worldwide study of plague in 1997. In that year there were 5419 cases of the disease reported, with 274 deaths. More than 70% of cases were in Africa and the country with the highest number was Madagascar, with more than half of the reported total occurring there. Interestingly, there has been a small but steady rise of numbers of cases annually since the mid 1980s. This may be due to a true increase in cases, or just better detection and reporting. Plague is one of only three infectious diseases subject to the International Health Regulations. All confirmed cases should be reported to the WHO.<sup>14</sup>

In Africa, plague was reported from six countries – Madagascar, Malawi, Mozambique, Tanzania, Zambia and Zimbabwe. The total number of cases in 1997 was 5101, with 261 fatalities. Of these, 2863 were reported from Madagascar, with 176 deaths.

The whole of the American continent – Central, North and South America – only reported 44 cases in 1997. Bolivia reported a single case, Peru had 39 cases and the USA reported four cases, with one being fatal. The cases were reported from Arizona, Colorado and California.

Five Asian nations reported 274 cases, with 12 fatalities. These were in China, Indonesia, Kazakhstan, Mongolia and Vietnam. China had 43 cases, Indonesia six, Kazakhstan one, Mongolia four, Vietnam 220. Of the deaths, 10 were in Vietnam. It is possible that reporting from these countries might be incomplete.

### Epidemiology

In terms of the development of an epidemic, the re-emergence of plague in India in 1994 after a gap of reported cases of nearly 30 years is interesting. In 1993 a severe earthquake hit areas previously identified as having wild plague foci. The resulting devastation allowed the rat population to increase dramatically, with a corresponding increase in the population of their associated fleas. In August 1994 a village in the Beed district reported rat-fall and subsequent flea nuisance. An outbreak of bubonic plague followed, with 596 cases but no fatalities.

A separate outbreak in Gujarat followed flooding associated with a record monsoon rainfall. During the clean-up operation, workers came into contact with infected animal corpses. The initial cases turned into secondary pneumonic plague, and subsequently, during an influx of people into Surat City for a religious festival, an outbreak of pneumonic plague ensued. Of 151 cases, 52 died.

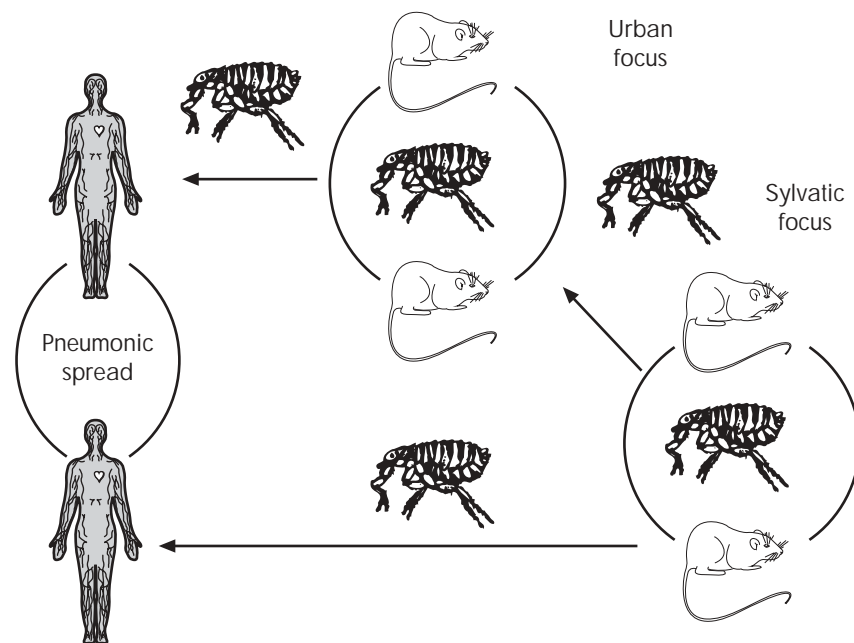
The area of most concern in plague infection is currently Madagascar. A strain of *Y. pestis* showing multiple antibiotic resistance has emerged there.<sup>15</sup> The island has an unusual animal population: rodent species are widespread, leading to an atypical pattern of foci with a higher risk to the human population. The majority of cases are bubonic, due to the virtually universal source of infection being primary contact with rodent fleas.<sup>16</sup>

### Disease in animals

The primary wildlife reservoirs of plague are rodent species. The rat, either the domestic black rat (*Rattus rattus*) or the urban brown rat (*R. norvegicus*), is the most important reservoir and rodent vector. Other species may be involved depending on the site and situation of the natural foci involved. Under the normal circumstances in a natural wild focus, the disease cycles within the rodent population and is transferred by fleas which are often specific to the rodent species involved (Figure 6.2).

Other animal species capable of carrying, amplifying or transmitting plague include goats, dogs, cats, squirrels, camels and rabbits. Dogs usually have a brief illness and often recover; cats are not so fortunate. They will often have severe fatal infection with high fever, swollen lymph nodes, pneumonic symptoms and encephalitis. Cats have caused human infection, usually following bites or scratches or inhalation by the human of aerosolised cat secretions. Other non-rodent species are also theoretically able to infect humans via similar routes.

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**Figure 6.2** Plague cycle from sylvatic (wild) focus to urban rodent focus and humans.

### Transmission

The infection of the first, and sometimes only, victim in an outbreak can almost be classed as accidental, following bites from rodent fleas, either in a natural focus or following a rat-fall. The infection may also follow direct contact with rodents, especially if they are butchered or skinned. The route of infection under these circumstances can be by direct transfer of blood, ingestion of infected tissue or inhalation of infected aerosols of blood or mucus. There is some evidence that fomites spread by knives or other instruments used to slaughter or butcher rodents is also possible.

Once an infected host has been bitten, the bacterium is ingested and multiplies in the flea's gut. The bacterium secretes a coagulase, causing an occlusive clot to form in the mid-gut of the flea. This causes blood from a previous bite to be regurgitated during the next bite, due to the obstruction, and the structure of the flea's mouth parts. Inevitably this leads to transfer of the bacteria in the most efficient manner possible. Once infected, fleas can remain infective for a period of weeks or months. The coagulated mass can also ultimately kill the flea. The

inoculum necessary to initiate clinical disease, if delivered by the bite of a flea, is believed to be a single viable organism.<sup>17</sup>

The usual route of infection for humans is by rat flea bite. There have also been cases of plague being transmitted from human to human via the bite of a human flea. This is believed to be extremely rare.

### Disease in humans

The course that the disease then takes depends upon the route of infection and the symptoms displayed. Cases are classified as bubonic, septicaemic, meningial, pharyngeal or pneumonic plague.

#### *Bubonic plague*

This is the classic pattern of infection following the bites of infected fleas or inoculation of a wound with contaminated material. Following infection, an incubation period of 2–6 days is normally seen. As with many other diseases, the initial signs and symptoms following inoculation can be very generalised and non-specific, but with an acute onset. A fever with headache, chills, fatigue, sickness, joint pain and sore throat are the first clinical signs, indistinguishable from infection with other pathogens.

Following these initial symptoms, and with persistent fever which may increase, there is a progressive swelling of the lymph nodes. This usually commences with the node nearest the site of inoculation. The nodes become tender and are known as buboes, hence the condition's name. Vomiting and muscle pain with delirium usually follow. The swollen nodes fill with pus and the disease spreads, both through the lymphatic system and the blood stream. The skin over the node becomes reddened, shiny and swollen.

On treatment the reddening starts to resolve. However the buboes, especially the first, only subside over a period of time. The initial site can remain swollen for weeks and may require surgical removal for full recovery to take place. In untreated cases, more than half of patients will die.

#### *Septicaemic plague*

Primary septicaemic plague does not present with a bubo. There is a high fever, with gastrointestinal disturbance. Symptoms may be confused with urinary tract or chest infections, appendicitis or a viral infection. Pneumonic plague may develop. The disease is progressive, and mediated

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by an endotoxin secreted by the pathogen. There is an overwhelming immunological response, resulting in a type of anaphylactic shock. Intravascular coagulation may occur with multiple organ failure and respiratory distress, thrombosis and subdermal haemorrhage leading to the blackening and focal necrosis (the symptom from which the sobriquet 'Black Death' comes) of the skin. Meningeal plague can be present, as can ophthalmic involvement and hepatic or splenic abscesses.

### *Meningeal plague*

Usually seen as a complication of bubonic or septicaemic plague, it can also be a primary infection. Fever, headache, stiffness of the neck, with increasing delirium and confusion followed by coma are normally seen. The pathogen can be isolated from cerebrospinal fluid. Most cases follow delayed, inappropriate or bacteriostatic antibiotic therapy. The use of any antibiotic incapable of crossing the blood-brain barrier carries with it the risk of developing this form of disease.

### *Pharyngeal plague*

Pharyngeal plague follows inhalation and deposition in the nose, mouth or throat of large droplets of infected pulmonary exudate or ingestion of infected raw or undercooked meat. Clinical signs mimic bacterial or viral pharyngitis, with severe lymph node swellings. The only way of characterising the infection and the responsible pathogen is by identification from a throat swab and subsequent culture. The course of the disease is variable; however, it normally progresses to a bubonic infection if the patient survives for long.

### *Pneumonic plague*

Patients suffering from bubonic or septicaemic plague may have a dissemination of infection to form a focus in the lungs, known as secondary pneumonic infection. Although their infection remains mainly bubonic, and the clinical course is relatively unaltered, they can develop cough with production of aerosolised infected pulmonary exudate. This can transfer infections to other individuals who then develop a primary pneumonic form of the disease. Once individuals display pneumonic symptoms they are extremely contagious and the spread of the disease within human outbreaks is usually by this rapid route, without the further involvement of rodents or fleas. For the infection to spread, other individuals need to be within 2 m of an actively coughing patient.

Humid overcrowded living areas encourage and promote human-to-human spread.

Pneumonic plague is the form of the disease associated with the highest rate of fatality. The prepatent period is very short: 24–72 hours after exposure. The initial symptoms are similar to other forms of the disease but there is marked physical weakness and respiratory difficulty. A productive cough with copious thin sputum, gradually increasing chest pain, breathing difficulties and the coughing of blood are progressive signs as the condition worsens. Deterioration is very rapid and death occurs within 3 days in almost all untreated patients.

To avert this outcome, antibiotic therapy must be commenced within 18–24 hours of clinical onset. Development of concurrent septicaemic plague and associated complications make supportive therapy and nursing difficult.

### Diagnosis

The WHO recommends that immediately a diagnosis of human plague is suspected on clinical and epidemiological grounds, appropriate specimens for diagnosis should be obtained and the patient should be started on specific antimicrobial therapy without waiting for laboratory results. Victims suspected of having the pneumonic form should be placed in isolation wards and barrier-nursed.

Confirmation of the diagnosis follows isolation, culture and identification of *Y. pestis* from specimens. Staining with Wayson or Giemsa stain leaves the pathogen showing a distinctive bipolar appearance. On microscopic examination they have a distinctive 'safety-pin' shape. Serological testing, ELISA and antibody testing can also be used if available. In some cases, diagnosis is only confirmed retrospectively by autopsy.

### Treatment

The first response to plague infection is antibiotics. The following notes come from various WHO documents. Any cases seen in the UK would be treated at specialist level, therefore the notes are here for information only and included for the sake of completeness.

*The aminoglycosides: streptomycin and gentamicin*

Streptomycin is the most effective antibiotic against *Y. pestis* and the drug of choice for treatment of plague, particularly the pneumonic

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form. Therapeutic effect may be expected with 30 mg/kg per day (up to a total of 2 g/day) in divided doses given intramuscularly, to be continued for a full course of 10 days of therapy or until 3 days after the temperature has returned to normal. Gentamicin can be used at doses of 3 mg/kg per day in adults, 6–7.5 mg/kg per day in children, and 7.5 mg/kg per day in infants.<sup>14</sup>

### *Chloramphenicol*

Chloramphenicol is a suitable alternative to aminoglycosides in the treatment of bubonic or septicaemic plague and is the drug of choice for treatment of patients with meningial, ophthalmic or pleural complications. A dose of 50 mg/kg per day administered in divided doses either parenterally or orally for 10 days is usually adequate in both adults and children over 1 year. Chloramphenicol may be used in conjunction with either streptomycin or gentamicin.

### *Tetracyclines*

The tetracyclines are bacteriostatic, and their use can lead to the development of complications. However, they are deemed suitable for use in uncomplicated cases. Tetracycline at a dose of up to 2 g/day in adults and 25–50 mg/kg per day in children over 9 years is recommended. Doxycycline may also be used at a dose of 200 mg/day in both adults and children over 9 years. As normal when using this class of drugs, a loading dose may be necessary. Tetracyclines can be used in addition to other agents.

### *Other antibiotics*

Ciprofloxacin has been shown to be effective against *Y. pestis* in laboratory and animal studies. However this and other fluoroquinolones have not yet been used in human cases. Penicillins, cephalosporins and macrolides have been shown to be ineffective or of variable effect in the treatment of plague and they should not be used for this purpose.<sup>18</sup>

### **Prophylaxis**

Healthcare workers or others who come into close contact with infected patients should receive prophylactic treatment. It may also be suitable for scientific fieldworkers investigating plague foci. Tetracycline, doxycycline or co-trimoxazole are currently used. Chloramphenicol has

fallen from favour, due to the incidence of severe side-effects. Dosages used are: tetracycline 1–2 g/day in divided doses, doxycycline 100–200 mg/day and co-trimoxazole 1.6 g/day at 12-hourly intervals.<sup>18</sup>

### Prevention

Vaccination is available; however, the likelihood of travellers contracting plague is very low. People going to work or live in areas where there is a known wild focus may be vaccinated. Laboratory workers who could be exposed to plague through clinical samples should be vaccinated in endemic areas, especially if investigating the focus. Development of immunity takes at least 1 month postimmunisation. Immunisation with the vaccine does not protect against developing primary pneumonic plague, so workers in risk areas, especially if geographically isolated, should be educated about signs and symptoms and encouraged to carry suitable antibiotics for immediate use if required. The vaccine is available through specialised centres, such as the Hospital for Tropical Diseases and the DoH. It is an unlicensed product, although if needed this is probably not significant.<sup>19</sup>

Avoiding exposure to rodents and their fleas, and controlling rodents and their fleas, remain the best methods of prevention. Domestic and companion animals in endemic areas should be treated for fleas, and bites and scratches avoided wherever possible.<sup>20</sup>

### Rabies

*(Hydrophobia)*

In Chapter 1 it was stated that the UK benefits from certain geographic advantages in respect of zoonoses. Rabies is one of the most outstanding examples. The last indigenous case of rabies was in 1902, and after a nationwide campaign and enforcement of a system of strict quarantine the country was declared disease-free. The continued enforcement of these regulations and the strict rules relating to the issuing of pet passports has maintained the UK in this status; however, this is not true of continental Europe. The area where the disease is considered to be endemic advanced toward the coast of the English Channel at approximately 16 km (10 miles) each year during the last decade, and had engulfed Paris at one point. A massive concerted effort by the French government of vaccinating wildlife by using inoculated baits has led to the disease being pushed back towards the French border with other European states during the past 12 months.

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During the last quarter of 2000 the WHO European rabies monitoring centre reported 1662 cases in Europe. Of these, 70% occurred in wild animals and 29% in domestic animals. There were only four human cases, all of which occurred in the Former Soviet Union.

Cases in domestic animals totalled 488, of which cats and dogs were the most significant pet species. Cases in cattle represent nearly half of the total, but onward transmission is unlikely. Bats are a significant reservoir for the disease in certain European countries; cases of bat rabies are usually only detected when they bite other animals or humans, therefore it is difficult to know the true incidence in the bat population. As the general public tends to associate rabies and dogs, it is advisable to remind individuals travelling to countries where the disease is endemic that bats and cats are also to be treated with caution, and to avoid contact with them if at all possible.

Most cases seen in European countries are designated as arising from 'fox-mediated rabies', where foxes are the main reservoir and vector. Other large and small mammals, including rodents, are less significant hosts.

Only Turkey has 'dog-mediated rabies', where wild and feral dogs form the main disease reservoir. The southern portion of the Former Soviet Union is unique in having a mixed pattern of dog- and fox-mediated infection.

European countries considered to be rabies-free are Albania, Finland, Greece, Iceland, Ireland, Italy, Macedonia, Norway, Portugal, Sweden, Switzerland and the UK and Northern Ireland. All other countries either have the disease or have had a case within the last 2 years.

Elsewhere in the world the disease is found in most countries and areas and some countries have high levels of disease incidence. These include areas of North, Central and South America, India, South-east Asia and Africa. In different geographical areas, different major animal reservoirs will be seen, linked to the most effective carnivore or scavenger species. Any other mammal in any country may become rabid, although not a primary vector or reservoir species. This said, canine rabies is considered to be the most significant animal reservoir worldwide.<sup>21</sup>

In 1996, the last year for which figures are available, over 33 000 human deaths from rabies were reported. The majority occurred in the countries forming the Indian subcontinent. The WHO suggests that there is significant underreporting of casualty figures, so the total death toll annually is well in excess of the figure given.

Approximately 50 million doses of various rabies vaccines are used in 10 million humans for postexposure treatments worldwide. No true

figures are available for the incidence in China, although it is known that there is an extensive vaccination programme.

The expense of vaccine as postexposure prophylaxis for patients exposed to animals suffering from the disease or potentially rabid animals is a significant cost for the public health purse in countries or areas where the disease is endemic.

### Rabies in the USA

Zoonoses are often seen as 'emerging diseases', either because the parameters of the relationship between humans and animals has altered in whatever way, or because a disease once believed to be controlled or eradicated has escaped from captivity and is on the rampage again. This is very true of rabies in the USA. Successfully controlled by vaccination and culling policies in domestic animals, new reservoirs of infection have now been identified in wild animal populations, from which infection claims human lives annually. Raccoons and bats are now the most significant animal reservoirs in the USA, while bat-borne rabies is seen as the most significant.<sup>22</sup>

The presence of a reservoir of disease in bats could almost be an excerpt from the script of a Hammer horror film. Bats are difficult to control, they are nocturnal, they are capable of living in large colonies in urban areas, and they are often protected by wildlife preservation statutes. The particular species of bat implicated in the 21 cases seen since 1980 is the silver-haired. This bat species has very sharp, small teeth and a bite could be small, unrecognisable and easily overlooked. In 20 of the 21 cases victims could not identify having been bitten or exposed to contact with a bat, although they or their families recalled bats being present in the patient's work place or home. This has led the US Centers for Disease Control and Prevention to issue guidance to clinicians that aggressive use of postexposure vaccination in individuals suspected of possible exposures to bats should be considered.<sup>23</sup>

### The latest case in the UK

A man who contracted rabies after being bitten by a dog in the Philippines died in hospital in London on 8 May 2001. Hilario Laya, born in the Philippines but resident in the UK for several years, became ill after a trip to visit his family during which he was bitten by a dog. Mr Laya was admitted to the Hospital for Tropical Diseases in London on 30 April 2001 after he had started to show symptoms of rabies and was

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moved into isolation after admission to hospital. He was given a dose of rabies vaccine within an hour of being admitted and before a definite diagnosis was confirmed. On confirmation of the diagnosis he was sedated and moved into an intensive care bed. Sadly, treatment was started too late to alter the outcome.

This case highlights the need for travellers to be educated about this disease, and to realise that a bite from an animal requires medical attention as soon after it occurs as possible.

### Disease in animals

The causative organism is a rhabdovirus, which is shed in large numbers into the saliva of infected mammals. Transmission follows inoculation of a bite wound or abrasion with infected saliva. Any animal suffering from rabies will display symptoms of central nervous system disturbance. After the incubation period and before the 'mad' or excitative phase, the animal may display certain prodromal symptoms. Behaviour will begin to change: animals may display antisocial behaviour becoming solitary, sexually aroused and having increased urinary frequency. The animal shows a lack of appetite for food and will not drink. After a few days the animal may become very excitable and vicious, biting or attacking anything or anybody in close proximity. This phase may be prolonged or short, and in some species it is totally absent. The third or paralytic stage of the disease follows. As paralysis sets in, the animal becomes progressively more docile and death follows rapidly, usually within 10 days of clinical signs beginning.

### Transmission

Humans contract the disease from bites of rabid animals, or by inoculation of wounds with virus-containing saliva. The possibility of airborne droplet transmission has been demonstrated in caves where there are large populations of bats. The possibility of contracting the disease by corneal transplantation from patients dying of undiagnosed disease has also been documented.

### Disease in humans

The virus is localised for a period postexposure in the immediate vicinity of the wound. The area around the site of entry may be painful or itchy. Localised numbness, especially of the limb nearest the site, may be reported. There is a prepatent period following infection: this period

seems to vary according to where the wound is in relation to the central nervous system. The closer the wound, the shorter the period; however, it is usually between 2 and 8 weeks, with variations linked to amount of inoculum and age of the patient – higher inocula and younger patients show more rapid onset of disease. Incubation periods of more than a year have occasionally been reported.

The virus migrates from the point of inoculation during this period, and enters the central nervous system. Early symptoms are very generalised, consisting of fever, headache and lassitude. As the central nervous system involvement begins, more serious clinical signs occur, often with acute onset. Symptoms progress as the neurological involvement increases. These can include insomnia, confusional states, anxiety, paralysis, hypersalivation, with swallowing difficulties caused by spasm of the oesophageal and laryngeal muscles (leading to the classic symptom of foaming at the mouth), altered perception and aggression. The patient may be extremely excited and often has convulsions. Disturbances of normal breathing and cardiac function are also seen. In the final stages of the disease most victims pass through phases of delirium, convulsions, and to almost invariable outcome of death.

The synonym of hydrophobia for the disease relates to the physical difficulties of drinking experienced by humans and animals, which are probably exacerbated by the abnormal mental state that occurs. The duration of the disease is short: death follows within a few days of clinical signs beginning.

Person-to-person transmission is extremely rare; however, precautions should be taken to prevent exposure to the saliva of the diseased person.

### Diagnosis

Diagnosis is often presumptive from the patient's history or presence of bite wounds. The virus can be isolated from bodily fluids or tissue samples and identified by microscopy, after treatment with fluorescent antibody staining techniques. Rabies nucleic acid can also be detected using polymerase chain reaction tests. Isolating and identifying the virus from brain tissue or saliva postmortem often confirms diagnosis.

### Treatment and prevention

Vigorous cleansing of bites or wounds with copious amounts of surfactant disinfectants or soap and water is a vital measure to reduce the risk

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of infection. This must be carried out immediately or as soon after the event as is practicable. In children, any bites are usually on the limbs, head, face or neck and they must be cleaned very thoroughly. Rapid use of postexposure vaccination is recommended.

Postexposure treatment also uses human rabies immunoglobulin (antirabies immunoglobulin) locally infiltrated around the wound site with concurrent administration intramuscularly. The dose used is calculated on a weight basis at a rate of 20 units/kg, split as 50% used locally and 50% intramuscularly. This is available in the UK from PHLS laboratories and regional blood transfusion centres in England and Wales. It is also available from Bio Products Laboratory and the Scottish National Blood Transfusion Service (addresses below).<sup>24</sup>

In patients with overt clinical signs intensive care is required to maintain respiration. If convulsions and seizures are controlled using anticonvulsants, there is a very small chance of survival.

The avoidance of bites and scratches from stray dogs or companion animals in countries where rabies is endemic is the most important part of any prevention strategy. Vaccination programmes in domestic animals, with rigid guidelines on the control of stray or feral dogs, cats and other mammals, are important in reducing risks and reducing exposure in countries where the disease is present. For island nations, rigid control of animal imports and the use of pet passport schemes or quarantine facilities allow their disease-free status to be maintained.

As has been previously mentioned, the vaccination of wild animal populations using inoculated baits has become very important in reducing levels of disease in the wild animal reservoir within endemic areas.

Travellers to rabies-endemic countries should be warned about the risk of acquiring rabies, although rabies vaccination is not a requirement for entry into any country. Pre-exposure rabies vaccination should be considered for patients who will be staying a month or more in countries where dog rabies is endemic. The necessity of postexposure rabies prophylaxis after an animal bite should be discussed with patients planning to travel to a non-industrialised country. They should be made aware that vaccination within a few days following a bite is capable of preventing the disease developing.

All travellers to such countries may wish to ensure that they carry sterile packs containing needles and syringes. In the event of needing vaccination, clean equipment will then be available. Travellers should be encouraged to avoid handling, feeding or caressing wild and feral animals unless wearing appropriate protective clothing.

Individuals at risk of occupational exposure, such as workers in laboratories, quarantine facilities, port officials, customs officers, animal and bat handlers and veterinary surgeons, whose employment is likely to carry a higher risk of exposure, should be considered for routine immunisation. Healthcare workers likely to be exposed to patients with the disease must be immunised wherever possible.

#### *Vaccination regimes*

There are wide regional variations in the types of rabies vaccines available. In the UK a human diploid cell rabies vaccine (HDCV: Pasteur Mérieux) is available, as is also a purified chick embryo cell (PCEC) vaccine (Rabipur: MASTA). In other countries, especially developing nations, other products may be in use. These include neural tissue vaccines prepared from sheep or mouse tissue. These vaccines have a high incidence of associated neurological complications; however, they may be the only product available. Some countries also use more modern vaccines prepared on different substrates to those in common use in western Europe or the USA. These include purified Vero cell rabies vaccine (PVRV), and purified duck embryo vaccine (PDEV).<sup>25</sup>

The DoH recommends that for prophylactic use HDCV vaccine should be given in a three-dose schedule on days 0, 7 and 28, with booster doses every 2–3 years if the individual is at continued risk. Where there is a short notice requirement for travellers, two doses given 4 weeks apart may be acceptable provided postexposure treatment is readily available. Booster doses should be given 6–12 months after the first dose, with subsequent doses every 2–3 years if required.

For individuals likely to travel to countries where there is a risk that postexposure therapy may be unavailable, or with products of dubious quality, a comprehensive pre-exposure programme is recommended. Although pre-exposure vaccination does not eliminate the need for additional therapy following an incident, it does simplify post-exposure treatment by removing the need for rabies immunoglobulin and by decreasing the number of doses of vaccine required.

Where it is not known what regime (if any) a patient has been given as prophylaxis, a full postexposure regimen must be adopted unless there is serological evidence of antibody response.

Recommended postexposure regimens differ according to the previous vaccinations given. Fully immunised patients exposed to whatever level of risk should be given two booster doses on days 0 and 3–7. Individuals who have not been previously immunised, or who may have

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inadequate or out-of-date prophylaxis, should receive a course of injections starting as soon as practicable after exposure on days 0, 3, 7, 14 and 30 with a dose of rabies immunoglobulin on day 0.

Healthcare staff who have attended patients suspected of or actually suffering from rabies should be offered immunisation. Four doses of 0.1 ml HDCV at different sites intradermally on the same day have been suggested as adequate, provided the intradermal administration is carried out correctly. This regime is unlicensed.

Concomitant treatment with antimalarials, such as chloroquine and mefloquine, interferes with the antibody response to HDCV. For patients taking these medicines, intradermal vaccination is not recommended. The intramuscular route must always be used.

As with other immunisations, there may be a reaction to the injection. Pain can occur at the injection site, with reddening, swelling or itching. Headaches, nausea, gastrointestinal disturbance, generalised aching and dizziness have been reported. Due to the serious nature of the disease, postexposure programmes must be continued despite mild localised or systemic symptoms, or other factors such as pregnancy. The gluteal muscle must not be used as an administration site, as past experience has shown that there is a poor response to vaccine administered here.

### *WHO recommendations*

The WHO endorses the use of the Essen regimen in postexposure vaccination. This consists of five injections of one dose of vaccine intramuscularly on days 0, 3, 7, 14 and 28. Day 0 is considered to be either the day of the injury or the date at which treatment begins. In theory both should coincide; however, in practice this may not always be the case. In addition to this vaccination scheme, three regimens have been developed to reduce the cost but not the effectiveness of postexposure treatment.

These are the 2.1.1 regimen, where two intramuscular doses of vaccine are given on day 1, and a single-dose booster on days 7 and 21. This scheme is particularly of value where there has been no physical damage, just exposure of skin or abrasions but not wounds to contamination by animal saliva.

The 2.2.2.0.1.1 regimen is for use with PVRV, PCEC vaccine or PDEV. It consists of intradermal injections of one-fifth of the intramuscular dose of vaccine – a dose dependent on the type of vaccine in use – at two sites on days 0, 3 and 7, and at one site on days 30 and 90.

The 8.0.4.0.1.1 regimen is recommended for use where HDCV and purified PCEC vaccine are available. The scheme consists of using a dose of 0.1 ml intradermally at eight different intradermal sites on day 0, four sites on day 7, and one site on days 28 and 90. This scheme is recommended by the WHO for severe exposure where there are single or multiple deep penetrating bites or scratches, or where contamination of mucous membranes with saliva has occurred and where no immunoglobulin is readily available.

As mentioned previously, part of the protection and prevention measures in place in the UK is a strict quarantine system. Recently this has undergone a slight modification to allow a pet passport scheme to be trialled. This section would not be complete without some details of the scheme.

#### *Pet Travel Scheme (PETS)*

This scheme was introduced in the UK in April 2000. The regulations, made under SI 1999 no. 3443 The Pet Travel Scheme (Pilot Arrangements) (England) Order 1999, form the basis of the scheme. It aims not only to prevent rabies entering the UK, but also to prevent establishment of *Echinococcus multilocularis* and certain tick-borne diseases endemic elsewhere in Europe and the rest of the world. It does not replace the quarantine system; however, it does allow cats and dogs, especially hearing dogs for the deaf or guide dogs for the blind, to accompany their owners abroad.

To enter an animal into the scheme, it must have a microchip inserted to identify it permanently, and be verifiably and effectively vaccinated against rabies. A certificate is then issued under the scheme. This allows the animal to enter or leave the UK by specified routes and carriers. Details can be found on the DEFRA website (<http://maff.gov.uk/defra>). Booster injections have to be given as recommended by the rabies vaccine manufacturer to maintain immunity and validity of the certificate.

In addition to this certificate, there is a requirement for the animal to be treated for ticks and tapeworms at least 24 hours before it enters or re-enters the UK. Again a certificate is issued by a vet to verify that the treatment has taken place with approved products on each occasion. These certificates must be obtained before travelling, otherwise the animal may not be accepted by the travel company or may be turned back at the border.

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**Useful addresses**

Bio Products Laboratory (BPL)  
Dagger Lane  
Elstree  
Herts WD6 3BX  
Tel: +44 (0)20 8905 1818

Scottish National Blood Transfusion Service (SNBTS)  
Protein Fractionation Centre  
Ellen's Glen Road  
Edinburgh EH17 7QT  
Tel: +44 (0)131 536 5700

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