CHAPTER 34

INFECTIOUS DISEASES

JAN VON OVERBECK

The impact of SARS on society and the economy was enormous, especially in Asia. This type of epidemic is not new, but the media reaction had considerable impact. For society, the investigation of an unfolding epidemic is essential to assess the potential impact and to implement measures to contain it. The insurance business is faced with the same necessities, and to determine early whether it should adapt its business processes.[1] In recent years, the infectious disease threat has diverged considerably from its previous patterns of epidemiology. As a result, new pathogens, or newly recognized diseases involving known pathogens, are being reported at an unprecedented rate. The phenomenal growth of international travel and trade has vastly increased the speed and ease with which pathogens and vectors can cross continents to cause outbreaks, epidemics and, on occasion, establish permanent residence in new areas. No country acting alone can defend its borders against this threat. Efficient defense requires a global system for gathering infectious disease intelligence, detecting outbreaks quickly and collaborating to contain their spread.

SURVEILLANCE AND RESPONSE SYSTEMS[1,2]

Surveillance systems keep the world alert to changes in the infectious disease threat and provide the background data needed to detect an unusual event, whether this involves an upsurge in cases of a well-known endemic disease, the appearance of a previously unknown pathogen or an outbreak caused by the deliberate use of a biological agent to cause harm.

In April 2000, the World Health Organization (WHO) launched the Global Outbreak Alert and Response Network (GOARN)[2] as a mechanism for keeping the volatile microbial world under

R. D. C. Brackenridge et al. (eds.), *Brackenridge's Medical Selection of Life Risks*

close surveillance and ensuring that outbreaks are quickly detected and contained. This network links 110 existing networks in real time. These networks possess much of the data, expertise and skill needed to keep the international community alert to outbreaks and ready to respond.

Procedures for alert and response have four phases: systematic collection of reports or rumors of new outbreaks; outbreak verification; communication of confirmed facts to selected partners and the world at large; and containment, including coordination of international assistance when required. An innovative tool that gathers real-time disease intelligence supports the first phase. This is the Global Public Health Intelligence Network (GPHIN), an electronic surveillance system developed for WHO in partnership with Health Canada. GPHIN heightens vigilance by continuously and systematically monitoring websites, news wires, local online newspapers, public health e-mail services, and electronic discussion groups for rumors of outbreaks. In this way, the WHO is able to scan the world for informal news that gives cause for suspecting an unusual disease.

Six main criteria are used to determine whether an event is of potential international concern:

1. A previously unknown disease.
2. Serious health impact or unexpectedly high rates of illness and death.
3. Potential for spread beyond national borders.
4. Potential for interference with international travel or trade.
5. A nation's capacity to contain the outbreak.
6. Suspected accidental or deliberate release.

From July 1998 to August 2001, WHO verified 578 outbreaks, of which 56% were initially picked up by GPHIN. These outbreaks occurred in 132 countries, indicating the system's broad geographical coverage. Twenty-two countries, many affected by continuing conflict, had 10 or more verified outbreaks of potential international significance. The most frequently reported outbreaks were cholera, meningitis, hemorrhagic fever, anthrax and viral encephalitis.

Traditionally, one of the main factors undermining the effectiveness of infectious disease surveillance has been the reluctance of countries to report outbreaks out of concern this news would negatively impact travel, trade and tourism. Costs from outbreaks may escalate when reactions are inflamed by sensational media coverage. Widespread and sometimes exaggerated media coverage of the 1994 plague epidemic in India contributed to trade and tourism losses in the range of USA$2 billion. Public alarm over the safety of beef, sparked by the epidemic of bovine spongiform encephalopathy, prompted the European Union to introduce a series of very expensive control measures (estimated cost of USA$2.8 billion in 2001). With costs of this magnitude, countries with fragile economies are understandably reluctant to report the occurrence of outbreaks that are certain to result in severe economic losses. New forces at work in an electronically interconnected world are beginning to break down the traditional reluctance of countries to report outbreaks. The Nipah virus outbreak and the SARS epidemic are two recent examples of reporting delay.

RISKS FOR THE LIFE INSURANCE BUSINESS[1]

Despite the overwhelming amount of media attention given to SARS and West Nile Virus (WNV), neither disease has reached the critical mass to impact life insurance pricing or routine underwriting practices. However, a major risk from any epidemic for the insurance business is reputation. An over-reaction to a perceived major risk, through restrictive underwriting and/or large premium increases, can have a negative impact on an individual company, or even the industry as a whole. Conversely, an underestimation of the risk may lead to losses that may have to be shared by all policy-holders through dividend reductions or premium increases. The key objective is to maintain a focus on the epidemiological conclusions drawn from the available data and to avoid being distracted by the level of the media reaction. Good data combined with competent analysis is a prerequisite not only for public health, but also for the proper evaluation of insurance risks.

Life insurance may be influenced by increased mortality. In addition to the basic data, life insurers need to know the attack rates and the case-fatality rates, as well as the demographics of

these two variables. This data must then be compared with the normal fluctuation of infectious disease prevalence in the affected country. An obvious example is an influenza epidemic, which is a big biological killer. For in-force business, an assessment is necessary to evaluate a possible increase in reserves. With respect to new business, updated underwriting guidelines may also be necessary to avoid anti-selection. For example, the incubation period of SARS is estimated to be 10 days, which would be a rational time to postpone applications from people thought to be at high risk. The problem is more difficult where high-risk individuals are not easily identified and the incubation period of a disease is very long. With an incubation period of 15 years, bovine spongiform encephalopathy (mad cow disease) for example, can infect its victim some time before the disease is identified, making underwriting and pricing practically impossible.

BACTERIAL INFECTIONS

Most bacterial infections can be cured with antibiotics, but a few are highly resistant to antibiotic treatment. The more common bacterial infections that require underwriting attention are listed alphabetically below.

Actinomycosis

Cervicofacial actinomycosis is a chronic disease characterized by abscess formation, draining sinus tracts, and fistulae. Human actinomycosis is primarily caused by *A. israelii*. Dental infections and oromaxillocial trauma are common antecedent events. Dissemination occurs almost exclusively by direct invasion. Clinically it can mimic a number of other conditions and should be included in the differential diagnosis of any soft tissue swelling. Cervicofacial actinomycosis requires prolonged courses of antibiotics, and surgery may also be necessary.

Any application should be postponed for at least 1 year after completion of a documented successful treatment. Thereafter an offer with an extra mortality of 100% can be considered.

Anthrax[3]

Anthrax is an uncommon illness. Twenty-two confirmed or suspected cases were reported from the CDC in 2001. From 1984 through 1997, only three cases of cutaneous anthrax were reported to the CDC. The control of anthrax infection is linked to decreased use of imported raw material of animals and to a successful immunization program.

Three major anthrax syndromes exists: cutaneous; inhalation; and pharyngeal and gastrointestinal anthrax. The symptoms that occur are due to the actions of three exotoxins produced by *B. anthracis*, a sporulating Gram positive coccobacillus. It can often be identified on Gram stain from infected material. *B. anthracis* is highly susceptible to antibiotics.

Standard rates are appropriate after full recovery.

Botulism (*Clostridium botulinum*)[4]

Botulism is a rare but life-threatening neuroparalytic syndrome resulting from a neurotoxin of *Clostridium botulinum*. The first investigation of botulism occurred in the 1820s with a case series report of hundreds of patients with 'sausage poisoning' in a German town. *C. botulinum* is actually a heterogeneous group of Gram-positive, rod-shaped, spore-forming, obligate anaerobic bacteria. They are ubiquitous.

Botulism of any type usually requires hospitalization. Mortality for patients with mild disease is low, with complete recovery within 1–3 months. Patients with severe disease may need long treatment and are left with neurological deficits.

Standard rates can be offered 6 months after full recovery.

Brucellosis

Brucellosis (also called undulant, Mediterranean or Malta fever) is a zoonotic infection with protean manifestations. Four species, *Brucella melitensis* (goat), *B. suis* (hogs), *B. abortus* (cattle) and *B. canis*, are known to cause disease in humans. *Brucella* sp. are Gram-negative facultative intracellular rods.

Brucellosis is a cause of fever of unknown origin. The onset of symptoms of brucellosis may be abrupt or insidious, and virtually any organ system can be involved. Therefore diagnosis is often delayed. Several antibiotic regimens can be used, but none are 100% effective because some patients will relapse after therapy. Most relapses occur within 3 months and almost all within 6 months after therapy completion.

Standard rates can be offered 6 months after documented full recovery.

Cat scratch disease

Cat scratch disease (CSD) is characterized by self-limited regional lymphadenopathy. CSD involves ocular, neurological and visceral organ involvement. *Bartonella* (formerly *Rochalimaea*) *henselae* is the etiologic agent of CSD. CSD usually results from a cat scratch or bite.

CSD mainly occurs in an immunocompetent individual and has a benign clinical course. CSD presents as a localized cutaneous and lymph node disorder. Rarely the organisms may spread to other organs. Localized disease generally has a self-limited course, whereas those with disseminated disease can have life-threatening complications. Among immunocompromised individuals (mainly HIV), *B. henselae* can cause bacillary angiomatosis, peliosis hepatis and splenitis. The diagnosis of CSD is primarily a clinical one. Laboratory tests can confirm the diagnosis: a positive *B. henselae* antibody test; a positive Warthin–Starry stain on a tissue specimen; a positive polymerase chain reaction (PCR). The differential diagnosis of CSD primarily includes other infectious and malignant causes of lymphadenopathy.

Standard rates can be offered after full recovery and in cases where the diagnosis is well established.

Chlamydial infections[5]

Chlamydia infections are the most common cause of bacterial sexually transmitted disease (STD) in both men and women. A large proportion of patients have few or no symptoms, thus providing an ongoing reservoir for further transmission. *Chlamydia trachomatis* is a small Gram-negative bacterium.

Chlamydia pneumoniae causes lower respiratory tract infection among children, and most commonly in persons aged 65 to 79 years. Atypical pneumonia by convention is used to refer to infection by *Mycoplasma pneumoniae*, *Legionella* sp. and *C. pneumoniae*.

Psittacosis (or Parrot Fever, ornithosis) is usually a disease with prominent systemic manifestations and some respiratory symptoms. *Chlamydia psittaci* is transmitted to man predominantly from birds. The disease usually occurs sporadically but outbreaks are documented.

Trachoma is a granular conjunctivitis. It is treated effectively with antibiotics.

Standard rates can be offered after full recovery.

Cholera[6]

Cholera is caused by a Gram-negative bacterium *Vibrio cholerae*. Severe, watery diarrhea that can rapidly produce dehydration is the cardinal clinical sign. Cholera remains endemic in developing countries of Asia and Africa. In the past decade, *V. cholerae* of the O1 serotype has caused epidemics in South and Central America, while a new serogroup with epidemic potential, O139, has spread from the Indian subcontinent throughout Asia and the Middle East. Only *V. cholerae* of the O1 and O139 serotypes are responsible for epidemic cholera in humans. All other serotypes are grouped as 'non-O1' strains and are associated with sporadic cases of gastroenteritis. *V. cholerae* O1 occurs in two biotypes, known as 'classical' and 'El Tor'.

Standard rates can be offered after full recovery.

Clostridium difficile colitis (antibiotic-associated colitis)[7]

Clostridium difficile is a common hospital-acquired infection, affecting patients following antibiotic treatment. It colonizes in the human intestinal tract only after the normal gut flora has been altered by antibiotic therapy. The disease spectrum is very broad: asymptomatic carrier state, pseudomembranous colitis, and severe fulminant disease with toxic megacolon. Infection with *C. difficile* may complicate the course of ulcerative colitis or Crohn's disease. Approximately

15–20% of patients treated for C. *difficile* infection relapse following discontinuation of therapy.

Standard rates can be offered after full recovery. If an underlying condition is present, this should be rated appropriately.

Enteritis

Diarrheal disease is the second most common cause of death worldwide, and is the leading cause of childhood death. Most cases of acute diarrhea are self-limited. Different strains of *Escherichia coli*, *Campylobacter*, *Shigella* and *Salmonella* are frequent causes of enteritis, particularly travelers' diarrhea. Each can produce severe dysentery and spread to various organs throughout the body. Antibiotics are both preventative (unclear indication) and curative.

Standard rates can be offered after full recovery.

Erysipelas

Erysipelas is an infection of the superficial epidermis, producing marked swelling. Beta-hemolytic streptococci (primarily group A) cause the vast majority of cases. The resulting local changes are unique to erysipelas and are not seen in other forms of cellulitis. The systemic toxicity signs are promptly controlled with antimicrobial treatment. Complete clearing of the skin changes may require 2 or more weeks.

Standard rates can be offered after full recovery.

Helicobacter pylori infections[8]

Helicobacter pylori (Gram-negative spiral bacteria) was identified in the 1980s and the two scientists who identified it received the medicine Nobel price in 2005. In 1994, the NIH Consensus Conference recognized *H. pylori* as one of the causes of gastric and duodenal ulcers. Later in that year, the International Agency for Research on Cancer (IARC) declared *H. pylori* to be a group I human carcinogen for gastric adenocarcinoma.

Treatment of *H. pylori* in patients with duodenal ulcers decreases the risk of recurrence. Treatment also reduces the risk of gastric cancer, but difficulties with screening and treatment have to be addressed before broad prevention can be contemplated.

Standard rates can be offered after full recovery.

Gas gangrene (*Clostridium perfringens*)

Clostridial gas gangrene occurs in three different settings: traumatic, recurrent, and spontaneous or non-traumatic. The first two types are principally caused by *C. perfringens*, the third most commonly by *C. septicum*. Most of these latter cases occur in patients with gastrointestinal portals of entry such as adenocarcinoma. Prompt medical care, especially surgical management including prompt removal of the devitalized tissue, results in a very low mortality.

Standard rates can be offered after full recovery.

Legionnaires' disease[9]

Legionella was first identified in 1976 during an outbreak at an American Legion Convention in Philadelphia. Since then it has been identified as a relatively common cause of both community-acquired and hospital-acquired pneumonia. The most common risk factors for patients to acquire *Legionella* are cigarette smoking and chronic lung disease. The mortality ranges from 16 to 30% if untreated (or use of inactive antibiotics). Awareness, improved early diagnostic methods, and better therapies have reduced mortality to $< 10\%$. Overall prognosis depends on rapid antibiotic treatment.

Standard rates can be offered after full recovery, provided there is no underlying disease such as COPD.

Leprosy[10]

See also Chapter 36.

Leprosy is an ancient deforming disease caused by *Mycobacterium leprae*, which is still poorly understood and often feared by the general public. The outlook for patients has dramatically improved over the last three decades with the introduction of multi-drug treatment.

In endemic regions the possibility of leprosy should always be considered in any patient from

endemic regions with skin lesions and/or enlarged nerve(s) accompanied by sensory loss.

Leptospirosis[11]

Leptospirosis is a zoonosis with protean manifestations caused by the spirochete *Leptospira interrogans*. Various mammals are the natural reservoir. Synonyms for the disease are Weil's disease, Swineherd's disease, rice-field fever, cane-cutter fever, swamp fever, mud fever, hemorrhagic jaundice, Stuttgart disease and Canicola fever. Leptospirosis is distributed worldwide, but the majority of cases occur in the tropics. Humans become infected after exposure to environmental sources (animal urine, contaminated water or soil, or infected animal tissue). In humans the disease is often sporadic, but outbreaks may occur involving a common source of contamination.

After full recovery, standard rates can be offered.

Lyme borreliosis[12]

Lyme disease is a multisystem inflammatory disease caused by at least three closely related *Borrelia* species, all included broadly within the general term *B. burgdorferi* sensu lato ('in the broad sense'). They are spread by the bite of infected Ixodes ticks: I. scapularis in the eastern, north central and southern USA; I. pacificus in the western USA; I. ricinus in Europe; and I. persulcatus in Asia.

The clinical manifestations can be divided into three phases: early localized, early disseminated, and late or chronic disease. The erythema migrans (EM) is the main characteristic of the *early localized* disease. It occurs in up to 90% of patients, usually within 1 month of the tick bite. *Early disseminated disease* occurs days to months after the tick bite. It may appear without preceding EM and can be the first manifestation of *B. burgdorferi* infection. Cardiac (conduction block, myocarditis) involvement is observed in up to 8% of untreated patients. The cardiac signs usually resolve spontaneously. Neurological symptoms appear in up to 10% of untreated patients. Meningitis due to Lyme disease resolves spontaneously. *Late Lyme disease* occurs months to years after the onset of infection. It can be the first manifestation and not be preceded by other features of Lyme disease (the early stages may have been missed). Treatment with the standard antibiotics is generally successful for each of the stages of Lyme disease. Relapses occur only rarely, but need a second course of antibiotics to achieve cure. Some individuals residing in endemic areas may also be re-infected. Healthy individuals may test positive for antibodies to *B. burgdorferi* after exposure to *B. burgdorferi* without having experienced Lyme disease. Antibodies do not protect from future infections with *B. burgdorferi* or clinical manifestations of the disease.

Insurance can be offered 3 months after complete recovery, but if low-grade symptoms continue a debit of +50% is indicated.

Osteomyelitis

Osteomyelitis is an acute or chronic infection of the bone that results in inflammatory destruction of the bone, bone necrosis, and new bone formation. Hematogenous spread and a local focus of infection can cause osteomyelitis. From a clinical perspective, acute and chronic osteomyelitis have to be managed differently as the etiology, treatment and prognosis differ considerably.

Acute osteomyelitis (< 6 weeks) is usually the phase of osteomyelitis occurring before necrotic bone develops. The timing of clinical signs is variable as bone destruction intensity is different according to the site of infection (e.g. vertebral infection, osteomyelitis occurring with prostheses). In contrast, chronic osteomyelitis (> 6 weeks) is usually easily recognized. Diagnosis difficulties arise in patients with a painful orthopedic prosthesis, a decubitus ulcer, or a foot ulcer associated with peripheral vascular disease or diabetes. Treatment of chronic osteomyelitis is challenging and requires surgery as well as long courses of antibiotics.

If recovery is complete, standard rates can be offered. If diabetes or peripheral vascular disease is present, particular care is needed in evaluation of the risk, and a minimum debit of +50% should be made in addition to the rating for the vascular disease or diabetes.

See also Chapter 34.

Plague[13]

Plague is caused by an aerobic pleomorphic Gram-negative rod *Yersinia pestis*. Plague is a zoonosis primarily affecting rodents. Survival of the bacillus is dependent upon the flea–rodent interaction. Humans are accidental hosts. Foci of plague are present on most continents. The largest enzootic plague area is in North America, followed by the former Soviet Union. In 1994 a plague epidemic was reported in India. Plague has also been listed among possible bioterrorism agents.

Different forms of plague occur in humans: bubonic, septicemic and pneumonic. They differ in clinical features, severity and outcome. Prompt treatment of the infection is essential for prognosis. Mortality is estimated to be between 60 and 100% in untreated cases compared to less than 15% with treatment.

Standard rates can be offered after full documented recovery.

Pneumonia[14]

Community-acquired pneumonia (CAP) remains a common and serious illness. Pneumonia is a leading cause of death, predominantly in the sick and older age groups. Mortality rates are at about 1% in the outpatient setting, but can be as high as 25% in hospitalized patients.

Clinical and radiographic presentation of pneumonia often does not allow an etiological diagnosis. Serologic studies are required for etiologic diagnosis, especially in atypical pneumonia. These tests take time, need sequential samples and are expensive. Therefore they are not useful in the usual clinical setting. *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* or *legionella* sp. are the most common causes of atypical pneumonia and account for 7–20% of CAP for which a pathogen can be identified.

Mycobacterium tuberculosis infection is worldwide still a very important cause of disease. Pulmonary manifestations of tuberculosis (TB) include primary, reactivation, endobronchial, and lower lung field infection. Complications of TB can also involve the lung, including hemoptysis, pneumothorax, bronchiectasis and, in some cases, extensive pulmonary destruction (*see also* Chapter 23).

The explosion of *Pneumocystis carinii* pneumonia (PcP) was tightly linked to the HIV-AIDS epidemic. Before 1981, PcP was only seen in patients with underlying malignancy and other forms of immunosuppression. The incidence of PcP peaked between 1987 and 1988 and has declined since then as a result of effective PcP prophylaxis (*see also* Chapter 35).

Uncomplicated bacterial or viral pneumonia can be offered standard rates after full recovery. Pneumonia in patients with other impairments should be carefully assessed and rated appropriately for the underlying disease (TB, HIV).

Pyelonephritis

See Chapter 27.

Salmonellosis[15]

Salmonellae cause a broad range of infections: gastroenteritis, enteric fever, bacteremia, endovascular infections and focal infections (e.g. osteomyelitis, abscesses). They are facultative anaerobic Gram-negative bacilli and usually transmitted via the oro–fecal road. They can persist for long periods of time in the gastrointestinal tract. The 2000-plus serovars of *Salmonella* can be characterized by three major antigens: the somatic O antigen, the flagellar H antigen, and the surface Vi antigen. The O-antigen is widely used to divide Salmonella into serogroups (A, B, C1, C2, D, E).

The epidemiology of typhoidal and non-typhoidal Salmonella infections is quite different. Typhoid fever and paratyphoid fever are severe systemic illnesses characterized by sustained fever and abdominal symptoms. *Salmonella typhi*, or *Salmonella paratyphi* A, B or C, are the etiologic agents. Treatment of typhoid fever has been complicated by the development and rapid dissemination of antibiotic resistance. The development of multidrug resistant (MDR) strains were linked to numerous outbreaks in the Indian subcontinent, South-East Asia, Mexico, the Arabian Gulf, and Africa. This requires the use of

fluoroquinolones and third-generation cephalosporins as first-choice antibiotics for typhoid fever until the antimicrobial susceptibilities is confirmed.

Non-typhoidal salmonellosis has increased steadily over the years and is tightly associated with bacterial food-borne infections resulting from improperly handled food. Non-typhoidal Salmonellae is associated with animal reservoirs and therefore with farming products, especially eggs and poultry. Salmonellae can be transmitted transovarially from hens to intact egg shells. It is estimated that in the USA there are approximately 2 million cases and about 500 to 2000 deaths annually related to non-typhoidal salmonellosis. *S. enteritidis*, *S. typhimurium* and *S. heidelberg* were the serotypes most frequently isolated in recent years. The majority of these *S. enteritidis* outbreaks were related to eggs. It can also be acquired via the fecal–oral route (humans, animals).

All types of salmonella infection, including typhoid, respond to antibiotics. Antibiotic resistance is starting to be an important issue. If full recovery is documented and there is no underlying disease, standard rates can be offered.

Shigellosis

Shigella species are a common cause of bacterial diarrhea and dysentery. The bacteria is not as sensitive to stomach acid as many other pathogens, so that as few as 10–100 organisms can cause disease. Fever associated with diarrhea suggests infection with invasive bacteria (e.g. *Shigella*, *Salmonella*, *Campylobacter*, enteroinvasive *Escherichia coli*), enteric viruses, or a cytotoxic organism (e.g. *Clostridium difficile*).

The severity of disease varies according to the bacterial serogroup. *S. sonnei* commonly causes mild watery diarrhea, while *S. dysenteriae* 1 or *S. flexneri* commonly causes dysenteric symptoms (bloody diarrhea). In a normal healthy host the disease is self-limited and lasts no more than 7 days when left untreated. Several intestinal complications can occur that may lead to long-term morbidity.

Standard rates can be offered after full recovery.

Tetanus (*Clostridium tetani*)

Clostridium tetani produces an exotoxin that causes intermittent spasms of voluntary muscles. The muscles of chewing are commonly affected, hence the term lockjaw. Stiffening of the jaw and facial muscle spasm are followed by generalized spasm of muscles throughout the body leading to respiratory distress, asphyxia and death. The widespread use of tetanus immunization has made the disease uncommon. Rapid treatment with antitoxin, a tetanus toxoid booster injection, wound debridement and antibiotics can lead to complete recovery.

Standard rates can be offered after full recovery.

Toxic shock syndrome

Toxic shock syndrome (TSS) associated with *S. aureus* was first described in children. In 1980, 812 documented cases of menses-related TSS were reported. They occurred mostly in young Caucasian women. Clinical illness arose during menstrual periods and was associated with the use of highly absorbent tampons. *S. aureus* TSS may also present without association to menstrual bleeding. Differential diagnostic considerations should include streptococcal TSS, which is most often associated with severe local pain and tenderness often linked to a local trauma. The distinction is important as patients with streptococcal TSS often require immediate surgical debridement of the involved site.

After full recovery standard rates can be offered.

Trepanematoses (endemic)

Within this group of spirochetal infections yaws, pinta or bejel (endemic syphilis) are grouped. All test positive for syphilis, and these are not true false-positive results because all the routine laboratory tests for syphilis do not distinguish between the various types of *Treponema*. The differential diagnosis between the endemic non-venereal treponematoses and venereal syphilis is made by the epidemiology and clinical picture. These non-venereal spirochetal infections are seen in warm, humid areas such as Mexico,

Central and South America, and Africa. They are spread by skin contact and are primarily skin diseases, but they can form gummas and affect bones. Skin granulomas are common and heal with scar formation. They are not fatal and are cured with penicillin. No debits are needed after successful treatment.

Tuberculosis[16–19]

See also Chapter 23.

Tuberculosis (TB) remains a major infectious disease worldwide. It is endemic in most developing countries. The HIV-AIDS epidemic is clearly linked to resurgence of TB in both developed and developing countries. Mortality rates range from 50 to 80% in untreated smear-positive individuals to 30% in areas with poor control programs, and less than 5% when directly observed therapy (DOT) is implemented successfully. Increasing resistance to first-line drugs isoniazid (INH) and rifampin (RMP) is a very worrisome problem with important public health consequences. In this regard, susceptibility testing is essential in order to select effective therapy.

The lungs are the primary site for TB infection following inhalation of the organism. Pulmonary TB is the most frequent manifestation of both primary and reactivated disease. Identifying patients with active pulmonary TB is essential to initiate prompt therapy and also to prevent further transmission of the disease. Extrapulmonary TB is a challenging diagnosis and depends heavily upon a high index of clinical suspicion. Extrapulmonary TB is more common among HIV-infected individuals and should raise the suspicion of a double infection.

The HIV epidemic has deeply changed the spectrum of pulmonary disease in patients with HIV[18] infection. Worldwide, millions of people harbor a double infection, especially in developing countries. TB is the most common pulmonary complication of HIV in Africa, and at least one-third of all cases occur in HIV-infected patients. TB should be suspected not only in HIV patients with pulmonary symptoms, but also in those with weight loss, or fever of unknown origin. Patients with severe immunosuppression are very likely to have atypical findings (clinical, radiological) as well as disseminated infectious disease.

Before offering terms to a client with a history of TB, the following information should be collected: diagnostic criteria (pulmonary, extra-pulmonary), treatment (combination and duration), an HIV test. For extra-pulmonary tuberculosis the HIV status must be known. If the client is HIV-negative, a postponement period of 1 year after completion of treatment is necessary (relapse risk). Thereafter, terms can be offered with an extra-mortality of +50%, or a temporary extra premium (5 per 1000) for 2 years.

Tularemia

Tularemia is a zoonosis caused by the Gram-negative bacterium *Francisella tularensis*. Synonyms include Francis' disease, deer-fly fever, rabbit fever, trappers' ailment, and Ohara's disease. Tularemia is known to occur predominantly in the northern hemisphere. Following contact with infected animals or vectors humans are accidental hosts. Infected patients present with abrupt onset of fever, chills and headache. The incubation period is between 2 and 10 days. Some symptoms and signs are related to the site of entry as well as with the principal organ systems involved. Six distinct clinical syndromes have been recognized in patients with *Francisella* infection: ulceroglandular, glandular, typhoidal, pneumonic, oropharyngeal and oculoglandular. The diagnosis of tularemia is difficult and requires a good knowledge of the clinical presentation and the epidemiologic history. The diagnosis can be confirmed serologically by tube agglutination or ELISA.

Standard rates can be offered after full recovery.

Rickettsial infections

Rocky Mountain spotted fever (RMSF) is a potentially lethal but usually curable tick-borne disease due to *Rickettsia rickettsii*. This Gram-negative, obligate intracellular bacterium has a predilection for human endothelial cells. The spectrum of disease of *R. rickettsii* ranges from mild to fulminant.

Epidemic typhus is a potentially lethal, louse-borne, exanthematous disease caused by *Rickettsia*

prowazekii. *R. prowazekii* is one of three members of the typhus group of *Rickettsia* known to cause human illness. *Murine (endemic) typhus* is an uncommon flea-borne infectious disease caused by *Rickettsia typhi*. The disease is mainly diagnosed in the developing world and can be controlled by improving hygiene and rat control efforts.

Rickettsialpox is an uncommon, mite-borne rickettsial disease caused by the agent *Rickettsia akari*. The disease was named rickettsialpox because of its resemblance to chickenpox.

Standard rates can be offered 6 months after full documented recovery.

VIRAL INFECTIONS

There are innumerable viruses and viral diseases. Vaccination is an important preventive tool and should be broadly implemented through efficient public health programs (e.g. measles vaccination). The common respiratory and intestinal viral infections as well as influenza present no problem for insurance after full recovery.

The more common viral infections that require underwriting attention are listed alphabetically below.

Aseptic meningitis

A number of viruses produce aseptic meningitis. The most common are enteroviruses, but other viruses are relatively frequent causes of viral meningitis: herpes simplex virus (HSV), human immunodeficiency virus (HIV) and lymphocytic choriomeningitis virus (LCMV). The great majority of patients with aseptic meningitis have a self-limited course with no need for specific treatment. Clinically it is essential to promptly recognize patients presenting with similar symptoms and other etiologic agents requiring immediate treatment.

Standard acceptance for life insurance can be made after documentation of full recovery.

Cytomegalovirus

The seroprevalence rates for cytomegalovirus (CMV) infection varies greatly worldwide, ranging between 40 and 100% of the adult population. Seroprevalence correlates inversely with a country's socioeconomic development. The spectrum of disease linked to CMV is very broad and diverse. Acute infection is commonly asymptomatic or produces only non-specific symptoms in the immunocompetent host. A broad variety of presentations have been described, ranging from a mild 'viral syndrome' to a common form of infectious mononucleosis. In a small number of patients, there is a marked systemic and organ-specific involvement that may be associated with significant morbidity. CMV infections in immunocompromized patients (transplantation, HIV) cause substantial morbidity and mortality. Acute infection of pregnant women can be associated with congenital CMV in newborns, which may present with severe impairment.

If HIV testing is negative, standard rates are appropriate after full recovery.

Encephalitis

See Chapter 30.

Epstein–Barr virus [20,21]

Epstein–Barr virus (EBV) is a widely disseminated herpes virus. The transmission requires close contact between susceptible persons and asymptomatic EBV shedders. The majority of primary EBV infections are unapparent. Approximately 90–95% of adults test positive for EBV.

EBV is the etiologic agent of infectious mononucleosis and persists without symptoms for life in all infected adults. Reactivation of disease is uncommon with EBV infection. It may be associated with severe complications in transplant recipients. It is associated with the following tumors: B cell lymphomas, T cell lymphomas, Hodgkin disease and nasopharyngeal carcinoma. After full recovery of infectious mononucleosis standard rates can be offered.

Burkitt's lymphoma (BL) is the most common childhood malignancy in equatorial Africa. This clinically obvious tumor is typically localized in the jaws of young patients. One possible etiology is that recurrent malaria attacks provide a chronic stimulus for proliferation of EBV infected B lymphocytes.

Nasopharyngeal carcinoma (NPC)[20,21] is a rare malignancy, except in some parts of Asia. In southern China the age-adjusted incidence rate is around 55 per 100,000. The association of EBV with NPC is strong and consistent. EBV can be detected in every anaplastic nasopharyngeal carcinoma cell. Patients with NPC have elevated titers of antibodies to various parts of EBV. These tests are useful for diagnosis purposes. In contrast, the value for screening normal population is still under investigation. In one Taiwanese study, 9699 persons were tested for IgA EBV-antibodies and neutralizing antibodies against EBV-specific DNAase. The relative risk for NPC was 32.8 and 4.0 for subjects who tested positive for both or one marker, respectively, compared to those testing positive for neither antibody.

Non-Hodgkin lymphomas (NHL) occur approximately 60 to 100 times more frequently than expected in patients infected with HIV. These tumors are often associated with EBV infection.

Hantavirus

Old World (HFRS) and New World (HCPS) hantaviruses are carried by wild rodents and can be transmitted directly to man. Endemic and epidemic episodes are often related to natural rodent eruptions. Patients acquire the infection via aerosols of rodent excreta. The incubation period is between 1 and 6 weeks. Fever and progressive capillary leak syndrome dominate the clinical picture, affecting primarily the retroperitoneal space, the kidney or the pulmonary vascular bed. The mortality rate is generally high but depends upon the species of virus.

Standard rates can be offered 6 months after full recovery.

Hepatitis B[22–28]

See also Chapter 26.

Hepatitis B virus (HBV) infection is a global public health problem. It is estimated that there are more than 300 million HBV carriers in the world, of whom over 250,000 die annually from HBV-related liver disease. Furthermore, the rates of HBV-related hospitalizations, cancers and deaths in the USA have more than doubled during the past decade. This may be due to the delay in implementation of universal vaccination (which was instituted in 1991), the influx of immigrants from endemic areas, improved diagnosis, and better documentation of infection.

The prevalence of HBV carriers varies from 0.1–2% in low prevalence areas (USA and Canada, Western Europe, Australia and New Zealand), to 3–5% in intermediate prevalence areas (Mediterranean countries, Japan, Central Asia, Middle East, and Latin and South America), to 10–20% in high prevalence areas (South-East Asia, China, sub-Saharan Africa). HBV is transmitted by percutaneous or permucosal exposure to infectious body fluids, for example by sexual contact with an infected person, and perinatally from an infected mother to her infant.

In areas of high endemicity, the lifetime risk of HBV infection is $> 60\%$ and most infections occur at birth or during early childhood, when the risk of chronic infection is greatest. Because most early childhood HBV infection are asymptomatic, there is little recognition of acute disease, but rates of chronic liver disease and liver cancer are high. The major determinants of infection include exposure to an HBsAg-positive mother or sibling. The contribution of perinatal transmission to the overall burden of disease is related to the prevalence of HBeAg among pregnant women. In areas where the mothers are both HBsAg- and HBeAg-positive, 70–90% of infants will become infected if not given immunoprophylaxis (antibodies and vaccine). Of infants born to HBsAg-positive but HBeAg-negative mothers, approximately 5–20% are infected at birth. Infants of HBsAg-positive mothers who are not infected at birth are still at increased risk of HBV infection during early childhood through household contact with the infected persons.

In areas of moderate endemicity, the lifetime risk of HBV infection is 20–60% and infections occur in all age groups. Recognition of acute disease is common because most infections occur in adolescents and young adults. Acute disease among adults tends to occur in the same risk groups as in developed countries. Generally, in areas of moderate endemicity, 2–7% of pregnant women are HBsAg-positive and $< 20\%$ of these

are HBeAg-positive; thus, perinatal transmission accounts for a small proportion (10–20%) of the persons with chronic infection.

In areas of low endemicity, the lifetime risk of infection is < 20% and most infections occur among adults in well-defined risk groups. In the USA, the prevalence of chronic HBV is 0.35%, with 5% of the general population having evidence of prior HBV infection. High-risk groups for HBV infection include intravenous drug users, homosexual men, persons who have heterosexual contact with multiple partners, household contacts of persons with chronic HBV infection, hemophiliacs, hemodialysis patients and staff, inmates of long-term correctional facilities, persons with occupational exposure to blood and infectious body fluids, and institutionalized persons with developmental disabilities.

Hepatitis B virus

HBV is a member of the *hepadnavirus* family. The mature HBV virion is a 42-nm, spherical, double-layered 'Dane particle', which has an outer surface envelope of protein, lipid and carbohydrate enclosing an electron-dense, 28-nm slightly hexagonal core. The genome of HBV is a partially double-stranded circular DNA molecule having 3200 nucleotides. The organization of the HBV genome is unique, because all regions of the viral genome encode protein sequences, including the nucleocapsid (hepatitis B core antigen, HBcAg), envelop glycoprotein (hepatitis B surface antigen, HBsAg), DNA polymerase, and a protein from the X gene. The DNA polymerase exhibits reverse transcriptase activity, and genomic replication occurs via an intermediate RNA template. HBeAg is a polypeptide virtually identical to HBcAg, which contains a slightly longer 'precore' region; this directs the HBeAg polypeptide toward secretion into blood. Infected hepatocytes are capable of synthesizing and secreting massive quantities of non-infective surface protein (HBsAg), which appears in cells and the serum as spheres and tubules of approximately 22 nm in diameter; this may occur with replication of infectious virus or without replication.

When HBV enters the hepatocytes, the genome moves into the nucleus and is converted into a covalently closed circular DNA. This is transcribed to form an RNA intermediate that can move into the cytoplasm, where the virus polymerase uses reverse transcription to convert it into a new circular DNA. The virus polymerase is the site of action of the new reverse transcription inhibitors that are used to treat chronic HBV infection.

The host's immune attack against HBV is the cause of liver injury, mediated by a cellular response to small epitopes (antigens) of HBV proteins, especially HBcAg, presented on the surface of the liver cell. HLA class I- restricted CD8 + cells recognize HBV peptides fragments derived from intracellular processing and presentation on the hepatocyte surface by class I molecules. This process leads to the direct killing of liver cells by the CD8+ cytotoxic T lymphocytes.

The different immune responses in patients in whom the virus is cleared successfully and those in whom it is not depend on the match between the HBV peptides presented by the host's major-histocompatibility-complex molecules and the specific T-cell-receptor repertoire of the host. If sufficient recognition and activation occur, all infected cells are destroyed, viral replication is aborted, and antibodies to HBsAg prevent the reinfection of hepatocytes. If the response is inadequate, the infection continues. It is hypothesized that chronic infection is related to weak T-cell response to the viral antigens. While neonatal immune tolerance to viral antigens appears to play an important role in viral persistence among persons infected at birth, the basis of a poor T-cell response in adults is not well understood.

Clinical manifestations

The clinical manifestations of HBV infection range from subclinical hepatitis to symptomatic hepatitis and, in rare instances, fulminant hepatitis during the acute phase. The chronic phase can range from an asymptomatic carrier state to chronic hepatitis, cirrhosis and hepatocellular carcinoma (HCC). The clinical presentation and outcome of HBV infection depend on the age at infection, the level of HBV replication and the immune status of the host. Perinatal or childhood infection is usually associated with few or no symptoms, but with a high risk of chronicity, whereas adult-acquired infection is

usually associated with symptomatic hepatitis, but a low risk of chronicity.

The consequences of acute HBV infection are highly variable. The incubation period ranges from 6 weeks to 6 months. Symptomatic infections vary in severity from mild to fulminant. Clinical signs and symptoms of acute HBV infection include fever, anorexia, nausea, malaise, vomiting, jaundice, dark urine, clay-colored or pale stools and abdominal pain. Occasionally, extra-hepatic manifestations occur and include skin rashes, arthralgias and arthritis. Fulminant hepatitis occurs in about 1–2% of persons with acute disease with a case-fatality ratio of 60–90%.

Chronic infection is defined as the presence of HBsAg in serum for at least 6 months or the presence of HBsAg and the absence of anti-HBc immunoglobuline M (IgM). The risk of developing chronic infection varies inversely with age and is highest (90%) for infants infected during the perinatal period. Between 25 and 50% of children infected between 1 and 5 years of age develop chronic infection, compared to 6–10% of acutely infected older children and adults.

Persons with chronic HBV infection have a substantially increased risk of developing chronic liver disease, including cirrhosis of the liver and HCC. The age at which chronic infection occurs may alter the risk of developing the disease. Prospective studies indicate that up to 25% of persons who acquire HBV infection as infants and young children develop either HCC or cirrhosis, compared to 15% of adolescents and young adults who acquire chronic HBV infection. The risk of HCC diminishes with resolution of chronic HBV infection.

Persistently HBsAg-positive patients with serum alanine aminotransferase (ALT), as well as other liver chemistries in the normal range, are termed asymptomatic HBV carriers or inactive HBsAg carriers. Most of these individuals are HBeAg-negative, and most have normal or minimally abnormal results of liver biopsy on initial evaluation.

Laboratory parameters

Because the clinical symptoms of HBV are indistinguishable from other forms of hepatitis, definitive diagnosis is dependent on serologic testing for HBV infection. Using serology it is possible to distinguish acute HBV infection, the replicative and non-replicative phases of chronic HBV infections, and the recovery phase.

Hepatitis B surface antigen (HBsAg) is the serologic hallmark of HBV infection. HBsAg appears in the serum 1–10 weeks after an acute exposure to HBV, before the onset of hepatic symptoms or elevation of ALT. In patients who subsequently recover, HBsAg usually becomes undetectable after 4–6 months. Persistence of HBsAg for more than 6 months implies progression to chronic HBV infection.

The disappearance of HBsAg is followed by the appearance of hepatitis B surface antibodies (anti-HBs). In most patients, anti-HBs persist for life, thereby conferring long-term immunity. In some patients, however, anti-HBs may not be detectable until after a window period of several weeks to months, during which neither HBsAg nor anti-HBs can be detected. During this period, diagnosis of HBV infection is made by the detection of IgM antibodies against hepatitis B core antigen (IgM anti-HBc).

Co-existence of HBsAg and anti-HBs has been reported in approximately 25% of HBsAg-positive individuals. In these instances, the antibodies are unable to neutralize the circulating virus. These individuals should be regarded HBV carriers.

Hepatitis B core antigen (HBcAg) is an intracellular antigen that is expressed in infected hepatocytes. It is not detectable in the serum.

Hepatitis B core antibody (anti-HBc) can be detected throughout the course of HBV infection. During acute infection, anti-HBc is predominantly of the IgM class (as is the case in most acute forms of infectious diseases). IgM anti-HBc is the sole marker of HBV infection in the window period between the disappearance of HBsAg and the appearance of anti-HBs (seroconversion). The detection of IgM anti-HBc indicates acute HBV infection. IgM anti-HBc, however, may remain detectable for up to 2 years after the acute infection. Furthermore, the titer of IgM anti-HBc may increase to detectable levels during exacerbation of chronic hepatitis B. IgG anti-HBc persists along with anti-HBs in patients who recover from acute hepatitis B and also persists in

association with HBsAg in those who progress to chronic HBV infection.

Isolated presence of anti-HBc in the absence of HBsAg and anti-HBs has been reported in 0.4–1.7% of blood donors in low prevalence areas and in 10–20% of the population in endemic countries. Isolated detection of anti-HBc can occur in three settings:

1. During the window period of acute hepatitis B infection (when the anti-HBc is predominantly of the IgM class).
2. Many years after recovery from acute hepatitis B, when anti-HBs has fallen to undetectable levels.
3. After many years of chronic HBV infection, when the HBsAg titer has decreased below the level of detection.

The clinical significance of isolated anti-HBc is unclear.

Hepatitis B e antigen (HBeAg) is generally considered to be a marker of HBV replication and infectivity. The presence of HBeAg is usually associated with the detection of HBV DNA in serum and higher rates of transmission of HBV infection. Most HBeAg-positive patients have active liver disease, but HBeAg-positive patients with perinatally acquired HBV infection and HIV-positive patients may have normal serum ALT levels and minimal inflammation in the liver. In general, seroconversion from HBeAg to hepatitis B e antibody (anti-HBe) is associated with the disappearance of HBV DNA in serum and remission of liver disease. A small proportion of patients, however, continue to have active liver disease and detectable HBV DNA in serum. The latter group of patients may have low levels of wild-type HBV or the presence of a stop codon mutation in the precore region that prevents the production of HBeAg.

HBV replication is best assessed by the detection of HBV DNA in serum using qualitative or quantitative assays. The sensitivity limit of these assays depends on the techniques used, being 10^5–10^6 viral equivalents/ml for hybridization on signal amplification assays and 10^2–10^3 viral equivalents/ml for PCR assays. The clinical significance of detecting HBV DNA by hybridization and by PCR is quite different. Generally, detection by PCR has the same significance as detection by HBsAg testing and indicates current HBV infection. In contrast, detection by hybridization indicates significant viral replication and a high probability of active disease (similar to HBeAg).

Recovery from acute hepatitis B is usually accompanied by the disappearance of HBV DNA in the serum as determined by non-PCR based assays; HBV DNA, however, may remain detectable for many years using PCR assays. This observation suggests that HBV persists after clinical recovery but is contained by the immune system. Similarly, in patients with chronic HBV infection, spontaneous or treatment-induced HBeAg seroconversion is usually accompanied by the disappearance of HBV DNA in serum by non-PCR based assays; PCR assays, however, often remain positive except in patients who have had HBsAg serconversion.

The major clinical role of serum HBV DNA assays is to assess candidacy for and response to antiviral therapy in patients with chronic HBV infection. Patients with high pretreatment serum HBV DNA levels are less likely to respond to interferon therapy. It is not clear if the pretreatment serum HBV DNA is also predictive of response to treatment with nucleoside analogs.

The purpose of a liver biopsy is to assess the degree of liver damage and to rule out other causes of liver disease. The histologic diagnosis of chronic hepatitis should include the etiology, grade of necroinflammatory activity, and stage/extent of fibrosis. Several numerical scoring systems have been established to permit statistical comparisons of necroinflammatory activity and fibrosis. Histologic findings may help predict prognosis. However, it must be recognized that liver histology can improve significantly in patients who have sustained response to antiviral therapy or spontaneous HBeAg seroconversion. Liver histology can also worsen rapidly in patients who have recurrent exacerbations or reactivations of hepatitis. Liver biopsies can also be used for immunohistochemical staining for HBsAg and hepatitis B core antigen.

Diagnostic algorithm

The serologic diagnosis of *acute HBV infection* is based on the presence of HBsAg and IgM

anti-HBc. Nearly all patients who present clinically with an acute HBV infection are HBsAg-positive, however about 10% of cases will be negative for HBsAg at the time of the test. Testing for IgM anti-HBc identifies all acutely infected patients, regardless of whether HBsAg is still present. HBeAg and HBV DNA are typically present during the acute phase of illness, but because their identification adds little useful information, they are not routinely measured.

Chronic HBV infection is defined operationally as the persistence of HBsAg for at least 6 months. The highest risk for HBV persistence is found in neonates born to women who are HBsAg-positive and have high levels of HBV DNA. Of these neonates, 80–90% progress to chronic infection. In contrast, only 30% of children infected before 6 years of age develop chronicity. Among adults infected by HBV, more than 95% recover completely. In about 1–5%, persistent infection may be associated with chronic hepatitis or an asymptomatic carrier state. In general, persistent infection occurs with a higher frequency in males than in females and among individuals with impaired immunity. Among adults with acute HBV infection, high serum levels of HBsAg, HBeAg and HBV DNA during the first few weeks of infection appear to predict progression to chronic infection.

Diagnostic criteria for chronic HBV (NIH):

1. HBsAg-positive > 6 months
2. Serum HBV DNA > 10^5 copies/ml
3. Persistent or intermittent elevation in ALT/AST levels.
4. Liver biopsy showing chronic hepatitis.

Diagnostic criteria for inactive HBsAg carrier state (NIH):

1. HBsAg-positive > 6 months
2. HBeAg-negative, anti-HBe-positive
3. Serum HBV DNA < 10^5 copies/ml
4. Persistently normal ALT/AST levels
5. Liver biopsy confirms absence of significant hepatitis.

Treatment of HBV chronic infection

Liver injury leading to cirrhosis occurs in patients with active replication but is minimal in those whose HBV DNA levels are negative despite persistence of HBsAg. Therefore, patients with active replication are most in need of treatment. Although many of these patients will have minimal evidence of liver inflammation, the presence of persistent viremia portends liver disease, if not now, then at a later date.

Indications for therapy include evidence of ongoing viral replications:

- presence of HBeAg and HBV DNA for at least 6 months
- persistent elevation of liver enzymes
- evidence of chronic HBV infection on liver biopsy.

The objective of treating chronic HBV infection is to halt progression of liver injury by suppressing viral replication or eliminating infection. Sustained loss of the markers of active viral replication (HBeAg, HBV DNA) results in biochemical, clinical and histologic remission. In general, seroconversion from HBeAg to anti-HBe is associated with disappearance of HBV DNA in serum and remission of liver disease.

Interferon-alpha has been available for the past decade for treating chronic hepatitis B. A favorable outcome to interferon-alpha therapy is associated with factors such as adult-acquired disease, high baseline ALT, low baseline HBV DNA, absence of cirrhosis, and female gender. The arrival of nucleoside analogue treatment marks a new era in the treatment of chronic hepatitis B. Lamivudine, nucleoside analogue, was the first specific oral antiviral agent available for treatment of chronic HBV. Clinical research data indicate that lamivudine has few side-effects and that it reduces not only necroinflammatory activity but also reverses fibrosis. The major drawback of lamivudine monotherapy is the emergence of resistant HBV with mutation of the tyrosine-methionine-aspartate-aspartate (YMDD) motif at the catalytic domain of the viral transcriptase/DNA polymerase. Incidence of YMDD mutants rises from 15 to 32% in the first year to 67–69% by the fifth year of treatment.

Other nucleosid analogues such as adefovir and tenofovir are further alternatives in the treatment of HBV infections. Adefovir has the great

advantage of being effective despite the presence of YMDD mutants.

Periodic screening for HCC

In longitudinal prospective studies, carriers of HBV have clearly been shown to be at increased risk of developing HCC. HCC may have a long asymptomatic stage lasting 2 years or longer. In the majority of patients, the cancer begins as a single tumor that is often encapsulated. The doubling time of HCC has been estimated to range from 2 to 12 months, with a median of 4 months. There is considerable evidence that HCC can be detected early when persons with chronic HBV or HCV infection receive periodic screening. Although there is strong evidence that long-term survival can occur in some patients with small HCC if they are treated surgically, no randomized trials of carriers undergoing periodic screening compared with those not screened have been reported. In addition, it is important to note that a high false-positive rate of alpha fetoprotein (AFP) in HBV carriers with chronic hepatitis or cirrhosis may result in expensive (and risky) evaluations such as radiographic procedures and liver biopsy.

Among the laboratory tests that have been used for screening, AFP has been studied the most extensively. The sensitivity of AFP testing depends on the cut-off level employed. The normal level of AFP is less than 8–12 ng/ml. If a level of 20 ng/ml is used, the sensitivity for small HCC ranges from 50 to 75%. The specificity of AFP is above 90% in studies that include not only individuals with chronic hepatitis or cirrhosis but also carriers in inactive state. The negative predictive value is greater than 99%. However, positive predictive value is low, ranging from 9 to 30%. AFP levels that rise in a step-like manner strongly suggest the presence of HCC, and persons with persistent mild elevation of AFP (< 200 ng/ml) are at a higher risk of HCC than those with a single increased value.

Ultrasound (USA) is the only radiological test that has been prospectively studied as an imaging tool for HCC surveillance. The sensitivity for small HCC ranges from 68 to 87% and false-positive rate from 28 to 82%. Regenerating nodules, seen in patients with cirrhosis, are the most common reason for false-positive results. USA is considerably more expensive than AFP and, in most countries, requires a radiologist. In addition, USA is very operator-dependent. However, USA is more sensitive for small HCC than AFP. The combination of AFP and USA appears to be superior to either one alone.

Vaccination

Effective vaccines for HBV have been available since 1981. The initial strategy for vaccination, which targeted high-risk groups such as intravenous drug users, attendees of STD clinics, inmates of correctional institutions, homosexual men, patients undergoing hemodialysis, and health care workers, has been ineffective. More recently, a broader use of the vaccine has begun to dramatically reduce the prevalence of infection, the development of HBV carrier state, and the incidence of HCC.

Anti-HBs is the protective, neutralizing antibody responsible for immunity to HBV infection. Passive immunization, i.e. the administration of exogenous, preformed anti-HBs in the form of HBIG prepared from donors who have recovered from HBV infection, is rarely used alone. Active immunization, i.e. use of HBV vaccine, and combined active–passive immunization (HBV vaccine and HBIG) are the preferred approaches. HBsAg is the active immunogenic material in commercially available yeast-recombinant HBV vaccines (Recombivax HB and Engerix-B). The vaccines contain HBsAg particles but lack HBV DNA, HBcAg, HBeAg or pre-S sequences. They are safe, immunogenic, effective, but expensive. Plasma-derived HBV vaccines, also containing HBsAg particles, are relatively inexpensive but have the small risk linked to blood products.

The immune response to active immunization by vaccination is limited alone to anti-HBs; the response to natural infection with HBV involves induction of both anti-HBc and anti-HBs. Titers (level of antibody) of anti-HBs after vaccination are usually lower than those found after natural infection. Breakthrough infections in vaccinated individuals can be attributed to hyporesponsiveness or non-responsiveness to HBV vaccine. Anti-HBs titers after vaccination diminish with time. Whereas anti-HBs levels also fall after natural

infection, the duration of protection is lifelong in nearly all instances of natural infection.

Underwriting hepatitis B infection

Good underwriting requires the understanding of the natural history and serologic markers of HBV infection. It is important to realize that chronic HBV infection is a silent disease in the early stages. By the time symptoms develop, patients are already in the advanced stage of disease, when treatment is ineffective or too late. Rates of progression to cirrhosis and HCC vary according to the state of the immune system, the age of the patient, the serologic stage of infection, and geographic and genetic factors. The relative risk of death due to cirrhosis for HBsAg carriers, as compared with normal persons, ranges from 12 to 79, and the relative risk of HCC ranges from 148 in Alaska to 30–98 in the Far East.

The challenges for the underwriter are:

1. To recognize and assess the chronic HBV carrier: inactive HBsAg carrier or chronic hepatitis B infection?
2. To recognize late complications of established chronic HBV infection: risk for cirrhosis, risk for HCC? Antiselection?

Recognize and assess chronic HBV infection

Most patients with chronic HBV infection are asymptomatic unless they have progressed to decompensated cirrhosis. The main challenges will be to recognize the potential problem according to the local epidemiology, vaccination programs and testing procedures. In a high endemicity area such as Asia, the basic mortality will include most of the HBV-related mortality, therefore the overmortality rating must be adapted to the region where underwriting is done. However, the awareness of HBV-related problems in Asia will also increase the risk of antiselection, as potential insured will often have been screened and investigated already. This would especially apply to healthy HBV carriers, in particular for HBsAg- and HBeAg-positive clients. Therefore the ratings must be adapted and not only in regard to prevalence, but also to how the medical community assesses these cases.

Before accepting a case with chronic HBV infection, the underwriter must collect the complete HBV serology (at least HBsAg, anti-HBs, HBeAg, anti-HBe) and liver enzyme profiles (if possible three sets over a year). If the patient had a biopsy or another investigation such as HBV DNA it should also be available at the underwriting stage. If a patient is treated for chronic hepatitis B, the full treatment documentation should be available, especially the follow-up studies to assess the relapse risk.

With this information, the underwriter can distinguish three different risk situations and rate them accordingly:

1. Inactive (healthy) HBV carrier (HBsAg-positive, HBeAg-negative, liver enzymes normal or near normal).
2. Chronic HBV carrier (HBsAg-positive, HBeAg-positive, elevated liver enzymes).
3. Chronic HBV disease.

Recognize late complications of established chronic HBV infection

The sequelae of chronic HBV infection vary from an asymptomatic healthy carrier state to the development of cirrhosis, hepatic decompensation, HCC and death. The prognosis appears to vary with the clinical setting. Long-term follow-up studies of HBsAg-positive blood donors (most of them HBeAg-negative) have shown that the majority remain asymptomatic with a very low risk of cirrhosis or HCC. The prognosis is very different in HBV-infected patients from endemic areas and in patients with chronic HBV infection. The estimated 5-year rates of progression are: chronic hepatitis to cirrhosis 12–20%; compensated cirrhosis to hepatic decompensation 20–23%; and compensated cirrhosis to HCC 6–15%. Among Chinese patients with chronic HBV infection, the lifetime risk of liver-related death has been estimated at 40–50% for men and 15% for women.

When chronic HBV infection is evaluated by the underwriter, the potential presence of complications and aggravating factors (alcohol) must be assessed, especially when the client is older and male. The main arguments will be the liver enzymes profile, the presence or absence of HBeAg

and the clinical statement of the attending physician. Special care at underwriting stage must be given when there is a treatment history as this is a marker of disease severity.

Hepatitis C[29–37]

See also Chapter 26.

Hepatitis C infection represents a true silent viral pandemic. A clear understanding of the epidemic and the disease are necessary for good underwriting. The natural history has been difficult to assess, because of the usually silent onset of the acute phase as well as the frequent lack of symptoms during the early stage of chronic infection. The public awareness will increase testing for HCV and therefore many new cases will be diagnosed. To avoid antiselection, the insurance industry must be well prepared to assess the impact on different products and to evaluate individual cases.

It is estimated that about 170 million people worldwide are infected with HCV. The seroprevalence rate is about 1% in Western Europe and North America, 3–4% in some Mediterranean and Asian countries, and up to 10–20% in parts of Central Africa and Egypt. HCV is parenterally transmitted. With the introduction of anti-HCV screening of blood and blood products in 1990, new cases of post-transfusion HCV have virtually disappeared and intravenous drug use has become the major identifiable mode of transmission in many countries. The current risk of infection from blood that is negative for HCV antibodies in the USA is less than 1/103,000 transfused units, the residual risk resulting from blood donations that occur in the interval between infection and the development of detectable antibodies ('window period' estimated to be less than 12 weeks). The transfusion-associated risk has decreased from 0.45% to 0.001% per unit of blood transfused.

The main issues for underwriting are to establish a cost-effective screening strategy for this silent epidemic and a rational assessment procedure for HCV cases. The Centers for Disease Control and Prevention recommend that testing for HCV should be routine in patients at increased risk for infection, including those who ever injected illegal drugs, received clotting factors made before 1987, received blood/organs before July 1992, were ever on chronic hemodialysis, or have evidence of liver disease. Testing should also be performed based upon the need for exposure management including: healthcare, emergency and public safety workers after needle stick/mucosal exposure to HCV-positive blood, children born to HCV-positive women. The need for testing is uncertain in the following groups: recipients of transplanted tissue, intranasal cocaine or other non-injecting illegal drug users, those with a history of tattooing, body piercing, history of sexually transmitted diseases or multiple sex partners, long-term steady sex partners of HCV-positive persons. These criteria are also useful for insurance purposes.

The lack of systematic screening of blood donors continues to result in HCV transmission in countries with developing or traditional economies. In addition, large-scale immunization and parenteral therapy programs as well as surgical and dental procedures with inadequately sterilized equipment have been important routes of transmission in these countries. HCV transmission has been described in nosocomial settings, including organ transplantation. Occupational needle-stick injuries from anti-HCV-positive sources result in seroconversion in about 3% of recipients; thus representing a transmission risk between that of HIV (about 0.3%) and hepatitis B virus (about 30% in unvaccinated recipients). Intranasal cocaine use has been identified as a possible mode of transmission ('straw sharing'). Sexual transmission is rare and correlates with high-risk sexual practices. Mother-to-infant transmission has been observed, but the risk is probably less than 5% unless the mother is co-infected with HIV. There is no proven association between transmission and the type of delivery or maternal breast-feeding. Household transmission is uncommon. Intriguingly and important for underwriting, in clinical practice no epidemiologic factor can be identified in up to 40% of patients with hepatitis C ('sporadic hepatitis C').

Because many of those with chronic HCV infection are asymptomatic, population-based serologic studies are needed to estimate the prevalence in the general population that best reflects the insured population. The prevalence of HCV

among blood donors does not reflect the prevalence in the general population, because even first-time donors are a highly selected group that has been screened for risk factors associated with various infectious diseases. On the other hand, the prevalence among liver transplant patients is overestimated as it is also a highly biased group of patients. Based on a USA population-based study (NHANES III), it was estimated that about 2.7 million people are chronically infected with HCV (positive RNA test). People who use illegal drugs or engage in high-risk sexual behavior have the highest risk of infection. Considering the same mode of transmission patients with a positive HCV test should also be tested for HIV and hepatitis B.

Virology

HCV is a positive-strand RNA virus that belongs to the family of flaviviruses; the most closely related human viruses are hepatitis G virus, yellow fever and dengue virus. The natural targets for HCV are hepatocytes and, possibly, B lymphocytes (antibody-producing cells). Viral replication is extremely robust, and it is estimated that more than 10 trillion virion particles are produced per day, even during the chronic phase of infection. The HCV genome consists of about 9400 nucleotides with one large open-reading frame encoding for a polypeptide (about 3000 amino acids long), which is then processed into 10 mature structural and regulatory proteins. Replication occurs through an RNA-dependent RNA polymerase that lacks a 'proofreading' function, which results in the rapid evolution of diverse but related quasi-species within an infected person and represents a major challenge with respect to immune-mediated control of HCV.

Major differences in the nucleotide sequences of HCV isolates are found throughout the genome and indicate the presence of distinct HCV genotypes, defined as having nucleotide divergence of more than 20%. Different genotypes have been reported to alter disease severity, change treatment response, and influence virus–host interaction and the potential for vaccine development. The most common genotypes in the USA and Western Europe are 1a and 1b. Genotype 1b has been reported to be associated with higher HCV RNA levels in the infected host, more advanced diseases, and suboptimal response to currently accepted therapy. Genotypes 1b, 2a and 2b are common in Japan and Taiwan; genotype 3 has been described in Thailand, Northern Europe and Australia; genotype 4 is predominant in the Middle East; genotype 5 is prevalent in South Africa; and genotype 6 has been reported in Hong Kong. The genotype is of importance for research and clinical trial, but not for underwriting because the test is not readily available and its clinical significance is still uncertain.

The mechanisms responsible for liver injury in acute and chronic HCV infection are poorly understood. In primary HCV infection, liver cell damage coincides with the development of the host immune response and not with infection and viral replication. The liver is the 'battlefield' of this immune response and the 'wounded' are the hepatocytes. Hepatocyte necrosis appears to be mediated by cellular mechanisms involving both CD4+ and CD8+ T cells. This cell-mediated immune response appears to be polyclonal, that is, directed against many HCV epitopes (antigenes). In addition, persistent viral replication often occurs without evidence of liver cell damage, suggesting that HCV is not directly cytopathic. The immune response against HCV, therefore, plays a central role in HCV pathogenesis but does not induce a protective immunity.

Acute HCV infection

HCV infection is infrequently diagnosed during the acute phase of infection. The incubation period for acute HCV following transfusion or accidental needle stick has been reported to average 6–7 weeks, but may range from 2 to 26 weeks. In adults with acute HCV infection, prospective studies have reported that up to 40% had some type of symptomatic illness and 15–30% had jaundice.

The course of acute HCV is variable, although its most characteristic feature is fluctuating ALT patterns. Normalization of ALT may occur and suggest full recovery, but is frequently followed later by ALT elevations (without further symptoms), indicating chronic disease. Fulminant hepatic failure following acute HCV infection is rare. Persistent HCV infection develops after the onset

of acute HCV in most persons (74–86%), even in those with no biochemical evidence of active liver disease. No clinical or epidemiological features among patients with acute HCV infection have been found to be predictive of chronic infection. Moreover, a variety of ALT patterns have been observed in these patients during follow-up, and some patients may have prolonged periods (12 or more months) of normal ALT activity although they have histologically confirmed chronic hepatitis.

Chronic HCV infection

The natural history of chronic HCV has been analyzed in several retro- and prospective studies. While no increased mortality was found in the retrospective Veterans Administration study, other studies indicated that chronic HCV frequently progresses to cirrhosis and HCC. On the other hand, recent studies in highly selected cohorts have again shown a more benign course. Two studies describing women who had received anti-D-immunoglobulin contaminated by HCV in the late 1970s, showed that after 17–20 years, more than 95% of those who underwent a liver biopsy had evidence of hepatic inflammation, but in most it was slight or moderate. Half had fibrosis, with only 2% having cirrhosis and 3–15% pre-cirrhosis bridging fibrosis. Although these findings may be generally reassuring for the majority of infected persons, the high prevalence of the disease still translates into a large number of persons with clinical sequelae of disease. In addition, these figures may be an underestimate, because of the high percentage of favorable factors in the cohorts studied and the short duration of follow-up.

A recent systematic review[32] has demonstrated that estimates of disease progression in chronic HCV infection are strongly influenced by study methodology. Higher estimates arose from studies of people with transfusion-acquired infection and those referred to specialist liver clinics, compared to those involving community-based studies and people newly diagnosed at blood donor screenings. Factors previously shown to influence disease progression in chronic HCV infection in individual studies have included older age at HCV infection, male gender and heavy alcohol intake. Each of these factors was found to be associated with higher estimates of disease in this review, and had different distribution across study types. Older age at infection largely explains the higher estimates for blood transfusion-acquired HCV infection, while selection biases probably explain the higher estimates of disease progression in liver clinic series. Based largely on estimates from community-based studies, it appears that less than 10% of people who acquire HCV infection in young adulthood will develop cirrhosis within 20 years. However, further follow-ups of community-based cohorts are necessary to determine disease progression in the third and fourth decade of chronic HCV infection. Once cirrhosis is established, the rate of HCC development is 1–4% per year. HCV infection appears to be responsible for a substantial proportion of the recently observed increase in HCC incidence and mortality. Although recent experimental evidence raises the possibility that HCV might operate through direct pathways in promoting malignant transformation of hepatocytes, it is generally believed that HCC associated with chronic hepatitis C develops through a general pathway of increased liver cell turnover, induced by chronic liver injury and regeneration, resulting in multiple and stepwise genetic alterations.

Chronic HCV infection has been associated with a number of extra-hepatic manifestations, including mixed cryoglobulinemia, glomerulonephritis, lichen planus, and porphyria cutanea tarda. Cryoglobulins are detectable in up to one third of patients with chronic HCV, while the clinical syndrome of mixed cryoglobulinemia occurs in only 1–2% of patients. These impairments are usually rated separately.

Diagnosis and laboratory testing

Diagnosis of hepatitis C is based on serologic assays that detect HCV-specific antibodies (anti-HCV) and on molecular assays that detect HCV RNA.

Second- and third-generation anti-HCV enzyme-linked immunosorbent assays (ELISAs) are highly sensitive as well as specific and represent the primary diagnostic assay. Anti-HCV tests are less sensitive in immunocompromized individuals or hemodialysis patients. For those patients, a

negative ELISA does not exclude HCV infection, and reverse transcriptase PCR (RT-PCR) should be performed. The recombinant immunoblot assay (RIBA) is a supplemental assay that can be used to confirm a positive ELISA, particularly in low-risk populations. In this scenario, a negative RIBA will make further testing unnecessary. In contrast to hepatitis B (surface antigen), no routine serological test for a viral antigen is yet available.

The molecular assays currently available are reverse transcriptase by (RT)-PCR and the branched DNA (bDNA) assay. With RT-PCR the viral RNA is reverse transcribed into complementary DNA (cDNA), which is then amplified by PCR. In the bDNA assay, the signal resulting from a specific hybridization of capture and detection probes with the viral RNA is amplified. Because viral RNA is unstable, the appropriate processing of samples is critical to minimize the risk of false-negative results. Qualitative HCV RNA assays are based on the PCR technique and have a lower limit of fewer than 100 copies of HCV RNA per milliliter. These are the tests of choice for the confirmation of viremia and the assessment of treatment response. Three commercial tests are currently available to quantitate the degree of viremia (bDNA and two RT-PCR). All systems deliver reliable but not easily comparable results because no standardized system of expressing the viral load has been established. The viral load has been shown to be relevant to the outcome of anti-HCV therapy but not to predicting the likelihood of disease progression.

HCV becomes positive by RT-PCR as early as 1–2 weeks after infection and 4–6 weeks before anti-HCV seroconversion. The determination of HCV RNA is, in principle, important for selecting patients for antiviral therapy and for the assessment of its efficacy. Measurement of HCV RNA should not be used as a primary test to confirm or exclude the diagnosis, but it is useful as a confirmatory test in patients whose results on recombinant immunoblots (RIBA) are indeterminate.

Liver biopsy

Histological evaluation of a liver biopsy specimen remains the gold standard for determining the activity of HCV-related liver disease, and histological staging remains the only reliable predictor of prognosis and the likelihood of disease progression. A liver biopsy can determine the necro-inflammatory activity (grading) and the degree of fibrosis (staging), and also allows recognition or exclusion of coexisting liver pathologies (such as alcoholic liver disease or hemochromatosis). Therefore, a biopsy is generally recommended for the initial assessment of those with chronic HCV infection. However, a liver biopsy is not considered mandatory before treatment is initiated and some recommend a biopsy only if treatment does not result in sustained remission.

Treatment possibilities

In general, treatment is currently recommended for patients with persistently (> 6 months) elevated aminotransferase levels, anti-HCV and RNA serum positivity, and at least moderate degrees of inflammation, necrosis and fibrosis on liver biopsy. Additional factors that come into consideration are, among others, the age and general condition of the patient, the duration of HCV infection, the risk of developing cirrhosis, the likelihood of response to therapy, comorbidity, and the patient's personal and professional plans. Importantly, impairment of quality of life during treatment should be discussed with the patient.

Current standard therapy consists of subcutaneous application of 3 million units IFN-alpha three times per week combined with oral application of 1000 to 1200 mg ribavirin per day. Patients with genotype 1 should be treated for 12 months and patients with genotype 2 and 3 for 6 months. IFN-alpha and ribavirin operate through direct antiviral effect and by boosting the immunologic defence mechanisms (immunomodulating effects). Contraindication to therapy with IFN and ribavirin include decompensated liver cirrhosis, autoimmune hepatitis or other autoimmune diseases, a history of depression or psychosis, pregnancy, the lack of reliable contraception methods (teratogenicity of ribavirin), cardiopulmonary diseases, leukopenia, thrombocytopenia, and conditions that impair compliance with therapy.

Patients who become HCV RNA-negative during therapy, and remain so for more than 6 months after the end of treatment, have a

sustained response and usually remain negative. Patients who are HCV RNA-negative at the end of treatment but become positive again at 6 months of follow-up are classified as relapsers. Relapsers of previous IFN monotherapy should be retreated with combination therapy. There is no established therapy for non-responders. These patients should be referred to specialized centers and treated only within controlled clinical trials.

A significantly increased sustained response rates have been achieved with the use polyethylenglycol (PEG)-conjugated IFN-alpha as compared to conventional IFN-alpha. Pegylated IFNs have replaced the conventional because they are more effective and have to be injected only once weekly due to their prolonged half-life. Sustained response rates achieved with PEG-IFN-alpha and ribavirin range from 35 to 70%, which is higher than the response rates to combination therapy with conventional INF-alpha and ribavirin, but the results of any large, prospective, randomized controlled trials have yet to be released.

HCV-infected patients with persistently normal transaminases should not be treated. The benefit of currently available antiviral therapy in children or the elderly, in patients with acute hepatitis, in patients coinfected with HIV or HBV, and in organ transplant recipients is not established. Liver cirrhosis due to chronic HCV is the leading indication for liver transplantation in many Western countries. This is inevitably followed by recurrent infection of the allograft. However, in contrast to hepatitis B, recurrent HCV following transplantation is typically mild and only slowly progressive.

Underwriting HCV infection

The spectrum of liver disease observed in patients demonstrating seropositivity for HCV covers the spectrum from asymptomatic blood donors with normal liver function tests and no apparent sequelae, to acute and chronic hepatitis, HCC and hepatic failure requiring liver transplantation. Good underwriting requires the understanding of the different faces of HCV infection and the collection of sufficient data to make a decision. The first step is to have a clear idea of how the HCV infection was originally suspected and ultimately diagnosed. This allows for the categorization of the risk as described in the following.

Elevated ALTs and ASTs

Aminotransferase levels are sensitive indicators of liver-cell injury and are helpful in recognizing hepatocellular diseases such as hepatitis. Both aminotransferases (AST, ALT) are normally present in the serum at low levels, usually < 30–40 U/l. The normal range varies widely among laboratories. Both enzymes are released into the blood in increasing amounts when the liver cell membrane is damaged. Necrosis of liver cells is not required for the release of the aminotransferases. In fact, there is poor correlation between the degree of liver cell damage and the level of the aminotransferases. If the results of repeated tests are abnormal, further evaluation is indicated. The first step is to obtain a complete history and work-up in order to identify the most common causes of elevated aminotransferases, i.e. alcohol-related liver injury, chronic hepatitis B and C, autoimmune hepatitis, hepatitis steatosis, non-alcoholic steatohepatitis and hemochromatosis. Concerning HCV, a reflex testing of anti-HCV antibodies is recommended if elevated aminotransferases are found on routine testing. If anti-HCV is positive, it may be useful to confirm this finding with RIBA. HCV RNA should not be used to screen patients, but only to confirm a doubtful RIBA test.

HCV infection without clinical symptoms

As the most remarkable and alarming aspects of HCV infection are its high rate of persistence and its ability to induce chronic liver disease, any positive serological results for HCV require further assessment. The underwriter must look for data to estimate the risk of chronic hepatitis and the progression rate toward cirrhosis: transmission route, date of infection and laboratory data. The minimum set of data consists of three sets of aminotransferase measurements during the last year and a HCV RNA test. If the patient was clinically investigated, all the available data should be submitted to the underwriter, especially if a liver biopsy was performed. This is essential as the correlation between the aminotransferases and the histology is poor. If the data is not

provided, the underwriter must be very cautious as non disclosure is very likely.

HCV infection with clinical symptoms

Symptomatic patients usually have more advanced disease and are usually fully investigated before treatment is proposed. These applicants have a high risk of complication and should be evaluated very carefully before an offer is made. Most symptomatic patients will have a liver biopsy before treatment is started and as this investigation is critical to the evaluation of a risk, it should be made available to the underwriter. If a patient is treated, it is essential to postpone the applicant until 6 to 12 months after completion of treatment.

Treated HCV infection

Treated patients are usually those with chronic hepatitis with more advanced inflammation and fibrosis. The therapeutic goal is to stop or at least to delay the process. Before accepting an applicant with a history of treated HCV, the underwriter should receive complete information about the reason for treatment (including the liver biopsy results) and the outcome of therapy (ALT profile, RNA value before and after treatment, if done biopsy after treatment). The main issue is the stage of hepatitis before treatment and if there is a relapse, of the inflammation after treatment (values at 6 or 12 months after stopping treatment).

Herpes zoster[38]

Chickenpox is caused by varicella-zoster virus (VZV) in susceptible hosts and latent infection follows in the sensory dorsal root ganglia. Reactivation of this latent VZV infection within the sensory ganglia results in herpes zoster or 'shingles', restricted to a dermatome. Herpes zoster is reported in all age groups, but older age groups account for the highest incidence, linked to the decline in VZV-specific cell-mediated immunity. Herpes zoster may recur in a small proportion of patients.

Skin bacterial superinfection can delay the healing of the zoster lesions and post-herpetic neuralgia can be very painful and problematic. Herpes zoster can rarely also extend to the central nervous system, resulting in meningeal inflammation and clinical meningitis.

HIV-infected patients, transplant recipients, and other patients with immunosuppression are at substantial risk for severe VZV related complications.

If no other disease is present and the HIV test is negative, standard rates can be offered after full recovery.

Molluscum contagiosum

Molluscum contagiosum is caused by poxvirus, which leads to chronic localized skin infection. The infection is usually self-limited and spontaneously resolves after a few months in immunocompetent patients. Lesions can persist much longer, be more numerous and widespread in immunocompromized individuals. In the HIV-infected patient, molluscum lesions can resolve after starting highly active antiretroviral therapy. There is no serious risk of life or health in the non-immunocompromized patient.

Poliomyelitis[39]

Paralytic poliomyelitis was a major cause of morbidity and death throughout the world during the first half of the 20th century. In 1954 the inactivated polio vaccine was introduced, resulting in a dramatic decline of new polio cases.

Poliomyelitis is an acute, febrile illness associated with aseptic meningitis and weakness or paralysis of one or more extremities. It is caused by a neutropic virus that attacks the anterior horn cells of the spinal cord, producing lower motor neuron paralysis of related muscles. Infection due to wild-type poliovirus no longer occurs in the western hemisphere. The WHO has an international eradication program making very good progress in the rest of the world. Exceptional cases continue to occur as a complication of live, attenuated oral polio vaccine use.

Applicants who have been rehabilitated and are working can be accepted at ordinary rates unless deformity interferes with vital functions (*see* Chapter 34). For patients with PPS, rating, if any, would depend on the degree of disability (e.g. the ADL score).

Rabies

The virus is transmitted to humans by a bite from an infected animal, usually a dog, but it can be a bat, fox, skunk or raccoon. Untreated, death will result. With appropriate treatment and after full recovery standard rates can be offered.

Respiratory syncytial virus

Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract infection in infants and children less than 1 year old. Infection with this virus is associated with up to 80,000 pediatric hospitalizations and 500 deaths each year, and is increasing in frequency. Standard rates can be offered after full recovery.

Warts

These are contagious skin growths caused by human papilloma virus. They are common and eventually disappear spontaneously. However, warts caused by certain serotypes of human papilloma virus can become malignant, especially in a person with a compromized immune system. Standard rates are appropriate provided there is no other disease present. For discussion of genital warts, *see* the section on sexually transmitted diseases.

West Nile virus

West Nile (WN) virus is a flavivirus that is a member of the Japanese encephalitis virus antigenic complex. WN virus is one of the most widely distributed arboviruses. Birds are the primary amplifying hosts, and the virus is maintained in a bird–mosquito–bird cycle. Humans and other vertebrates, such as horses, are incidental hosts and are thought to play a minor role in the transmission cycle. Nearly all human infections are caused by mosquito bites. Transmission through transplanted organs and blood transfusion are also rarely possible.

In 1999 WN virus emerged in New York, causing 62 cases of encephalitis and seven deaths. The exact manner in which WN virus came to the USA remains unknown. However, because it first appeared in a major international gateway, travel and commerce may have played a major role. The incubation period of WN virus ranges from 3 to 14 days. National surveillance documented persons with illness caused by WN virus, mostly encephalitis and meningitis each year since 1999: 62 cases in 1999, 21 in 2000, and 66 in 2001. Only 20% of persons infected with WN virus develop fever, and only half of these had visited a physician for this illness. Since that time, the virus has dramatically spread, and by September 2002, WN virus activity had been detected in many states in the USA.

Most infected individuals are asymptomatic. Mild illness, known as WN fever, is a self-limited febrile illness difficult to distinguish from other viral illnesses. CNS manifestations are rare but may be serious. Encephalitis or meningoencephalitis are more common than meningitis in contemporary outbreaks. Treatment of WN virus infection is supportive.

Six months after full recovery standard rates can be offered.

FUNGAL INFECTIONS

Superficial (external) fungus infections

Three types of superficial fungi/dermatophytes causes most of the infections: *Epidermophyton, Trichophyton* and *Microsporum*. These infections have varied clinical presentations. An unusual clinical picture and/or failure to respond to treatment should raise the suspicion of an underlying immunologic problem.

Candida species are another common cause of fungus infections. *Candida* is considered normal flora in the gastrointestinal and genitourinary tracts. The clinical manifestations are broad, ranging from local mucous membrane infection to widespread dissemination. *Candida* invades and causes disease usually when an imbalance of the normal physiology is present, especially when hormones or the immune response is affected. Vulvovaginal candidiasis is the most common form of mucosal candidiasis and is linked to a hormonal imbalance. Antibiotics, steroids, diabetes mellitus, HIV infection, intrauterine devices and diaphragm use are further common

risk factors for vulvovaginal candidiasis. Chronic mucocutaneous candidiasis is a rare syndrome and an underlying HIV infection or a T cell defect should be suspected that usually has its onset in childhood but also is found in HIV-infected individuals.

If there is no underlying condition, standard rates can be offered.

Systemic (internal) fungus infections

The fungal infections discussed below are seen mostly in individuals with a compromised immune system (including AIDS). In healthy persons the organisms may be present but will cause no active disease.

Aspergillosis

Aspergillus is common and is present in decaying vegetation and compost piles. In most cases it becomes invasive in humans only if the immune system is compromised. It is possible to consider making an offer of insurance, but only if the cause of the compromised immune state has improved and aspergillosis has been cured, in which case the rating depends on that needed for the underlying disease.

Aspergillosis is sometimes seen in patients with eosinophilic pneumonia (Loeffler's syndrome). When the infection is brought under control the appropriate rating is that needed for the eosinophilic pneumonia.

Superficial aspergillosis infection can occur in the external ear. This presents no hazard to life; standard rates can be offered even while the individual is under treatment.

Blastomycosis

Infection due to *Blastomyces dermatidis* is, fortunately, not common. It is of gradual onset, and the means by which a person becomes infected is not fully understood. It is infrequent in AIDS patients. Treatment is effective. One year after recovery +50 is appropriate for 1–2 years provided that there is no underlying immune deficiency.

Candidiasis

When *Candida* sp. becomes invasive the individual usually has a compromised immune system. Invasion can be found in the esophagus, brain, intestinal tract, kidneys, lungs or heart and can be treated, but the outcome usually depends on the predisposing condition. If the underlying condition is alleviated or removed then a high substandard offer might be considered after 2 years.

Coccidiomycosis

Coccidiomycosis is due to *Coccidioides immitis* and may be a self-limiting respiratory illness ('valley fever'). Often there are virtually no symptoms. With full recovery standard rates can be offered. Progressive coccidiomycosis is a commonly fatal infection and is usually associated with AIDS. If there is recovery and the immune system is intact high substandard (+200) rates may be possible 2 years after recovery; the rating may be reduced progressively to standard after the fifth year.

Cryptococcosis

Cryptococcus neoformans infection starts in the lung and may spread to the meninges resulting in cryptococcal meningitis. It can also infect the kidneys and prostate gland. It occurs frequently in patients with AIDS. If there is no underlying disorder of the immune system, +200 can be offered 2 years after full recovery; this can be reduced progressively to standard rates over the next 3 years.

Farmers' lung

This is a hypersensitivity reaction to inhaling spores of *Aspergillus* sp. in moldy hay; the fungi themselves are not infecting the patient. Treatment includes avoiding the exposure and a short course of corticosteroids. Standard rates can be offered after full recovery (*see* Chapter 23).

Histoplasmosis

The primary acute infection due to *Histoplasma capsulatum* manifests itself as pneumonitis. Often

there is recovery without treatment. Unless there is a heavy inhalation of the *Histoplasma* spores, the course is benign. Standard rates can be offered on recovery. Progressive disseminated infection is usually fatal; this is most often seen in AIDS. If there is full recovery in an individual without a compromised immune system, +200 can be charged 2 years after full recovery and this can be progressively reduced to standard rates after the 5th year.

PARASITIC INFECTIONS

Amebiasis

See Chapter 36.

Giardiasis

See Chapter 36.

Malaria

See Chapter 36.

Pediculosis

This is a condition due to lice which can be seen in the scalp, the body or the genital area (crabs). Treatment is effective. Lice can be the vectors of organisms that cause relapsing fever, epidemic typhus and trench fever, all of which are uncommon in North America. No debits are required for pediculosis.

Pinworms (enterobiasis)

This is a very common parasitic infestation, especially in children. Symptoms are perianal and vulvar itching, but there may be no symptoms. Treatment is effective and no debits are required.

Scabies

This infestation of the skin is caused by *Sarcoptes scabiei*. There is intense itching. Treatment is effective and no debits are needed.

Toxoplasmosis

See Chapter 35.

Trichinosis

This parasitic infection is caused by *Trichinella spiralis*. The infection occurs when inadequately cooked pork containing encysted larvae is eaten by man. The envelope of the cysts is digested in the stomach and duodenum releasing the larvae which quickly undergo sexual maturity and produce young larvae, some of which migrate in the blood stream to various organs, but mainly to muscles. The active infection and migration cause an allergic reaction, fever, eosinophilia, aching muscles and edema of the face, particularly the upper eyelids. After about 3 months the larvae will have become encysted and the disease becomes quiescent. The prognosis is generally good and there are no long-term complications. A history of proven trichinosis can be accepted at standard rates of premium.

Trichomoniasis

See the section below on sexually transmitted diseases.

Other worm infestations

These include roundworm, hookworm, threadworm, whipworm and tapeworm. These infestations do not usually affect mortality and no debits are required. Echinococcus, flukes and schistosomiasis can produce problems for travelers and cause health difficulties in tropical climates (*see* Chapter 37).

SEXUALLY TRANSMITTED DISEASES

Sexually transmitted diseases (STDs) are highly and easily communicable and were extremely common until the mid-1980s when AIDS became known. Because of AIDS there has been a desirable trend toward 'safe sex' and the incidence of all types of STD has dropped, although an increase

in the last few years has been observed. As there is the potential for significant increases in mortality in people with AIDS, it is sensible to consider obtaining an HIV antibody test whenever underwriting an applicant who has any one of the STDs.

Many STDs are curable provided both sexual partners are treated at the same time. If they are not, there is often a ping-pong ball effect, with recurring infections.

Some of the diseases discussed in this chapter may be acquired without sexual contact; situations in which this can occur will be mentioned in the discussion on the diseases.

Acquired immune deficiency syndrome (AIDS)

See Chapter 35.

Balanitis

This is an infection of the foreskin or glans penis, usually seen in non-circumcised males. The most common cause is yeast infection, but the infection can be herpes, trichomonas, gonorrhea or syphilis, and it can be a manifestation of Reiter's syndrome (*see below*). In the absence of any other evidence of STD no debits are required.

Chancroid

Chancroid is a major cause of genital ulcer disease in the developing world. In sub-Saharan Africa, for example, chancroid is the predominant cause of genital ulcers. Since the onset of HIV and AIDS, chancroid cases have increased in the developed world. It is a risk factor for HIV infection as the transmission risk is significantly increased. *Hemophilus ducreyi* is the etiologic agent. The incubation period of chancroid is between 4 and 10 days. The infection begins as an erythematous papule that rapidly evolves into a pustule, which then erodes into an ulcer and drains through inguinal lymph nodes. It responds well to antibiotics.

Standard rates can be offered 6 months after recovery provided there is no HIV infection.

Chlamydia

Chlamydia trachomatis, a small Gram-negative bacterium, is the most common cause of bacterial STD in both men and women. Most of the infected individuals are asymptomatic and therefore an ongoing reservoir for transmission of the infection.

C. trachomatis is the most commonly identified cause of urethritis after gonococcal infection. *C. trachomatis* is also responsible for other syndromes in men like proctitis, epididymitis, some cases of prostatitis, and reactive arthritis or Reiter's syndrome.

Most infections with *C. trachomatis* in women are also asymptomatic. The clinical picture ranges from cervicitis to pelvic inflammatory disease, which is a major cause of infertility. Cervical infection is the most common chlamydial syndrome, but only 50% of women will have symptoms. Treatment of chlamydia infection is important to prevent pelvic inflammatory disease and infertility.

There may be some transmission synergies between STDs and HIV infection. Therefore, HIV testing should be performed routinely in this group of patients. If an HIV infection is excluded, standard rates can be offered.

Gonorrhea

The infecting organism is *Neisseria gonorrheae*. It can cause urethritis, epididymitis, cervicitis, vaginitis and salpingitis. Sterility may result in women. Bacteremia may occur and, rarely, can proceed to meningitis, pericarditis or endocarditis. Arthritis is an occasional complication. Treatment with antibiotics is effective. Gonorrhea and syphilis are often seen together so it is also appropriate to test for syphilis and HIV. Standard rates may be offered after full recovery.

Granuloma inguinale

This is seen almost exclusively in the tropics. It is thought to spread by sexual contact. A red nodule swells to a granulomatous mass in the perianal area in both men and women. The disease can

be cured with antibiotic treatment. Standard rates can be offered 6 months after recovery.

Herpes simplex

USA seroepidemiologic surveys estimate that about 500,000 cases of new genital HSV infections occur annually. The infection is frequently under-recognized as most cases are sub-clinical. While both HSV-1 and HSV-2 cause genital herpes infections, HSV-2 is still the main cause of herpetic genital ulcer disease in men and women. Genital ulcer disease in several studies has been linked to a greater risk for transmission of HIV-1. HSV is linked to about 75–80% of genital ulcer disease in Western countries, whereas chancroid and syphilis are more frequent etiologic agents in other regions.

If there is no risk for HIV transmission, standard rates can be offered.

Lymphogranuloma venerum

Lymphogranuloma venereum (LGV) is a genital ulcer disease caused by *Chlamydia trachomatis* (L1, L2 and L3 serovars). This infection is found most frequently in tropical and subtropical regions. The diagnosis is difficult to establish on clinical grounds alone and requires serologic testing.

If treated early, standard rates can be offered after full recovery. If the infection has progressed beyond the initial lesion any offer should be postponed until 1 year after full recovery.

Non-specific urethritis

Chlamydia is responsible for at least half of all non-specific urethritis (NSU) infections; other organisms include trichomonas, but often the organism is not defined. Dysuria is the predominant symptom, although there may be virtually no symptoms at all. With full recovery standard rates may be offered.

Pediculosis

This lice infection can be transmitted sexually. It is easily treated and no debits are needed.

Syphilis[40,41]

Syphilis is a chronic infection caused by the bacterium *Treponema pallidum*. The manifestations of disease are notoriously protean. First described at least 500 years ago, syphilis has a fascinating and diverse history. *T. pallidum* cannot be grown *in vitro*, which is an important handicap for research.

Nearly all new syphilis infections are sexually acquired. Vertical transmission is possible in utero or at delivery. Syphilis is easily transmissible during early disease (primary and secondary stage) with an estimated transmission rate of 30%. Transmission requires exposure to open lesions with organisms present. The incubation period varies from 10 to 90 days.

Congenital syphilis

Transmission of syphilis to the fetus is through the placenta if the mother has untreated syphilis during her pregnancy. Since the early 1980s there has been a great increase in the incidence of congenital syphyilis. If treated early with penicillin, recovery may be complete. In late congenital syphilis, defined as at age over 2 years, prolonged penicillin treatment is required and the serological tests for syphilis may always remain positive. Nerve deafness is often a sequel and may be permanent. Standard rates can be considered after 5 years of age.

Primary syphilis

The first manifestation of syphilis is a papule, which is typically painless, at the site of inoculation. This soon ulcerates to produce the classic chancre(s) of primary syphilis, a 1–2 cm painless ulcer with a raised, indurated margin that may be genital or extragenital. The ulcer is associated with mild to moderate regional lymphadenopathy that is often bilateral. Chancres heal spontaneously within 3–6 weeks, even in the absence of treatment.

Secondary syphilis

Secondary syphilis is a phase of systemic dissemination. It begins between 6 weeks and 6 months after the appearance of the primary chancre in

about 25% of untreated patients. A generalized maculopapular skin rash involving the palms and soles and mucous membranes is the hallmark of this stage, but it can be missed in the clinical setting. The rash of secondary syphilis typically resolves spontaneously within 2–6 weeks. Generalized lymphadenopathy accompanies the skin rash. Large genital lesions called condylomata lata, are diagnostic and very infectious. Spirochetes can be found in the cerebrospinal fluid (CSF) of around 40–50% of patients with early syphilis, but neurological manifestations are rare at this stage.

Latent syphilis

Latent disease is usually subclinical, although clinical relapses may occur. Syphilis is rarely transmitted during the latent phase, with the exception of perinatal transmission during pregnancy.

Tertiary syphilis

Tertiary syphilis occurs in approximately one-third of untreated patients. The disease is now rarely seen because most patients are treated at an earlier stage. Clinical manifestations include gumma formation, cardiovascular disease and/or CNS changes (neurosyphilis). Such manifestations usually develop 5–20 years after the disease has become latent. Late syphilis can develop in individuals who never experienced clinically symptomatic primary or secondary syphilis.

Laboratory tests

T. pallidum cannot be cultured in the laboratory. Presently, the disease can only be identified by direct visualization of the organism or by serology. Direct visualization of the spirochete from a moist lesion with dark-field microscopy is the quickest and most direct method for diagnosing primary and secondary syphilis. Experienced staff are required for this technique and therefore its use is limited to specialized STD clinics. Serologic testing is an indirect method of diagnosis and relies upon a humoral immune response to infection. There are two types of serologic tests for syphilis: non-treponemal tests (VRRL: Venereal Disease Research Laboratory; RPR: Rapid Plasma Reagin test) and treponemal tests (FTA-ABS: fluorescent treponemal antibody absorption; MHA-TP: microhemagglutination test for antibodies to *Treponema pallidum*). *Non-treponemal tests* (tests for reagin antibodies) are based upon the reactivity of to a cardiolipin-cholesterol-lecithin antigen. They measure IgG and IgM antibodies and are used as a screening test as they are inexpensive and easy to perform. The results are reported as a titer of antibody. They can be used to follow the response to treatment. *Treponemal tests* are used as confirmatory tests when the non-treponemal tests are positive. These qualitative tests detect antibodies directed against treponemal cellular components. False-positive tests for syphilis are observed at a rate of approximately 2% in the general population, independently of which test was performed. Some of these false-positive tests are associated with unrelated disease. As the test may revert to negative it is useful to repeat such a test after a period of 6 months. Chronic false-positive tests are associated with autoimmune disorders (particularly systemic lupus erythematosus), intravenous drug use, chronic liver disease, and HIV infection.

If there is a history of syphilis, it must be investigated before an offer can be made. Serologic testing must be performed, including an HIV test. After full documented recovery, standard rates can be offered. If there is a doubt about late complications or incomplete treatment the case must be postponed and investigated. A positive VDRL should remind the underwriter that this person is at risk for future HIV infection.

Yaws, bejel, pinta

These occur in hot, humid equatorial countries. They are non-venereal, endemic, syphilitic diseases caused by spirochetes (*see* 'treponematoses' *above*). The chancres are usually found on the legs and not the genitalia, but scrapings from these early lesions reveal treponemal spirochetes. Screening and specific tests for syphilis are positive and the final diagnosis is made from the epidemiology and clinical patterns of the local disease.

Trichomoniasis

This is a common infection caused by a protozoan organism. It can be without symptoms or there may be urethritis or vaginitis. It is easily cured with metronidazole provided that both sexual partners are treated at the same time. No debits are needed.

Warts

Condylomata acuminata is one of the most common viral STDs and is caused by human papilloma virus (HPV) infection. HPV are highly infectious and primarily sexually transmitted double-stranded DNA viruses. Most infections are transient and clear within 2 years. A persistent infection with HPV serotypes 16 and 18 is associated with an increased risk of developing a squamous cell carcinoma. Intermediate risk subtypes can cause high-grade dysplasia, which persists without progressing to an invasive stage. Low-risk subtypes are less frequently associated with lower genital tract dysplasia or benign condylomas.

If there is no underlying disease (e.g. HIV) and after successful treatment, standard rates can be offered.

EMERGING INFECTIONS[42]

Epidemic-prone diseases, such as cholera, dengue, influenza, meningitis, plague, yellow fever and food-borne diseases, pose an almost constant threat to human populations. They are well adapted to human transmission, either directly from person to person, through transmission by insects and other disease vectors, or by contamination of food or the environment. These diseases are generally well understood and, in most cases, effective measures are available for their control.

Previously unknown infectious agents that have crossed the species barrier from animal to humans can cause unexpected or unusual disease events. Infectious agents that appear in a new geographical area can also cause unexpected events. Finally, biologic agents that have been deliberately engineered and were introduced by acts of bioterrorism can cause unusual disease events. The ability to detect emerging or unexpected diseases depends on sensitive surveillance. Adequate background data on usual disease events in a particular geographical area or under specific climatic conditions facilitate the recognition of the unusual.

The appearance of new diseases is unpredictable. Their detection is problematic and they are frequently misdiagnosed, even in the most advanced countries, e.g. HIV in the USA and Europe in the1980s. These new diseases are poorly understood as they emerge, and therefore difficult to treat and to control. When the dynamics of transmission are unknown, epidemics can take a long time to contain. While some emerging pathogens are not well adapted to human populations, and lack the potential for sustained epidemic spread, they are frequently associated with high mortality, as they occur in new and often highly susceptible hosts.

WHAT DATA DO WE NEED?

Epidemiology is based on two fundamental assumptions. First, human disease does not occur at random. Second, systematic investigation of different populations and subgroups within populations at different places or times can identify causal and preventive factors. Epidemiology defines the who, what, when, where, how and why of infectious diseases. The 'who' is the population at risk for infection. The 'what' is the scope and impact of infections. The 'when' are the temporal trends. The 'where' is the geographic location of the disease. The 'how' defines the reservoirs of disease and the mechanisms of transmission. The 'why' addresses risk factors, or the reasons disease affects some persons but not others.

Descriptive epidemiology involves the collection and analysis of all data that describe the disease in the population. Its main limitations are the under-reporting or the under-ascertainment of cases of a specific disease. The precise number of cases that indicates the presence of an epidemic varies according to the agent, the size and type of population, previous experience or degree of exposure to the disease, and the time and place of occurrence. The identification of an

epidemic also depends on the background frequency of the disease in the area in the specified population during the same season of the year, e.g. influenza. Even a very small number of associated cases of an unrecognized disease may be sufficient to constitute an epidemic. For example, the first report on AIDS involved only four cases of pneumocystis carinii pneumonia in young homosexual men.

The initial stage of investigation should verify the diagnosis of suspected cases and confirm that an epidemic exists. The preliminary investigations also lead to the formulation of hypotheses about the source and spread of the disease, and this, in turn, may lead to immediate control measures. The case definition is an essential step, especially when the cause is not clearly defined. The development of a case definition is an important step that can profoundly affect the outcome of the analysis. For example, a strict clinical case definition may limit the recognized spectrum of disease; whereas a loose case definition may include persons with illness from an entirely different cause. As with diagnostic tests in clinical medicine, it would be desirable in epidemiology to have a case definition that is 100% sensitive and 100% specific; however, this is not realistic. The investigation of the AIDS epidemic started long before the HIV virus was identified, and was based on a CDC case definition that was adapted when new data became available. The main goal is to label clinical cases and classify them in a way that allows further epidemiological investigations.

As an example of a case definition, a suspected case of SARS is defined as documented fever (temperature $> 38^{\circ}C$), lower respiratory tract symptoms, and contact with a person believed to have had SARS or history of travel to an area of documented transmission (according to the WHO). A probable case is a suspected case with chest radiographic findings of pneumonia, acute respiratory distress syndrome (ARDS), or an unexplained respiratory illness resulting in death with autopsy findings of ARDS without identifiable cause.

Three closely interrelated components are important for epidemiology: frequency, distribution and characteristics of diseases. The most basic measure of disease frequency is the simple count of affected individuals. Such information is essential for public health planners and administrators who wish to determine the allocation of health care resources in a particular community. However, count data alone has very limited utility for epidemiologists. To investigate distributions and determinants of disease, it is also necessary to know the size of the source population from which affected individuals were derived, as well as the time period during which the data was collected. The use of such measures allows direct comparisons of disease frequencies between two or more groups of individuals. Incidence rate is defined as the number of times an infection is noted in an observed population during the defined period divided by the number of persons observed in that time. For most infectious diseases, the incidence is reported as an annual rate. Most commonly, an illness is declared reportable by state law, and a formal surveillance system is established. Observed over time, changes in incidence can identify an emerging problem or the effectiveness of prevention or control measures.

The distribution of disease considers who contracts the disease within a population, as well as where and when the disease is occurring. This may involve comparisons between different populations at a given time or comparisons between subgroups of one population. These comparisons are essential to describe the pattern of disease as well as to formulate hypotheses concerning possible causal or preventive factors. A population may be defined by a specific geographic location, host characteristic or exposure. The hospital is a distinct ecosystem with a self-contained human population, unique pathogens and unique mechanisms of transmission. In the SARS epidemic, hospitals served as powerful centers of disease transmission until containment and quarantine were introduced.

The characteristics of disease follows disease frequency and distribution, because knowledge of these is necessary to test an epidemiologic hypothesis. The goal of analytic epidemiology is to identify the risk factors associated with disease. This is typically accomplished by case-control or cohort analysis that attempts to identify different frequencies of characteristics or exposure of

ill (cases) and well (controls) persons. Risk factors are typically characteristics of the ill person, such as age, sex, race, socioeconomic status, area of residence, as well as exposures including foods, smoking, medications, illicit drug use, travel history, daycare attendance, or sexual activity. Great care must be taken in making the distinction between concluding that a factor is associated with a disease and a conclusion that an associated factor is related to cause. Inferring causation requires statistical and logical epidemiologic associations, but proof often requires considerable additional biological studies.

SARS[43–45]

One of the latest of these new emerging infections is the SARS epidemic. Severe acute respiratory syndrome (SARS), an atypical pneumonia characterized by a high rate of transmission to healthcare workers, began in Guangdong Province, China, in November 2002. Subsequent to its introduction to Hong Kong in mid-February 2003, the virus spread to more than 30 countries, causing disease in over 7900 patients across five continents. In many locations, the infection was spread by ill travelers to healthcare workers and household contacts. The global spread of SARS proceeded with unprecedented speed, overwhelming many hospitals and some public health systems in a matter of weeks. On 12 March 2003, the WHO issued a worldwide alert for SARS. A novel corona virus (SCoV) was identified as the etiological agent of SARS, and the virus causes a similar disease in cynomolgus macaques. Human ScoV appears to be an animal virus that crossed to humans relatively recently. The SARS virus may long have had the capacity to infect people, but only recently encountered conditions that facilitated its spread.

East Asia was hit hardest by SARS, with China having 5328 cases up to June 2003, followed by Hong Kong with 1753 cases, and Taiwan with 680 cases. This was the fourth time in recent years that an emerging infectious disease has surprised East Asia. The Nipah outbreak in Malaysia, the enterovirus 71 outbreak in Taiwan, and the influenza H5N1 outbreak in Hong Kong had all disrupted the regional public health infrastructure before SARS.

Outside of Asia, Canada was the country hardest hit by SARS. As of August 2003, there had been 436 probable and suspect SARS cases in Canada, including 44 deaths. The majority of SARS cases and all deaths were concentrated in Toronto and the surrounding Greater Toronto area. The toll on healthcare workers was high: more than 100 became ill and 3 died. The SARS experience illustrated that Canada (as other countries) is not adequately prepared to deal with a true pandemic. In response, Canada's Minister of Health established The National Advisory Committee on SARS and Public Health in early May 2003. The Committee's mandate was to provide a third party assessment of current public health efforts and lessons learned for ongoing and future infectious disease control. The Committee has accordingly recommended strategies that will reinforce the public health system and integrate its components more fully with each other. The report is extremely interesting and valuable and should serve as a working instrument for many other public health systems throughout the world.[45]

AVIAN INFLUENZA ('BIRD FLU')

Avian flu is an infection caused by the influenza virus and occurs naturally in wild birds without symptom. Domestic birds, such as chicken, ducks and turkeys, can be infected from wild birds, often fatally. The H5N1 strain has become endemic in Asia and has recently spread to Europe. The WHO has warned of a substantial risk of an influenza epidemic in the near future, most probably from the H5N1 type of avian influenza virus. Importantly, neither the timing nor the severity of such a pandemic can be predicted with any certainty because of the unpredictable behavior of influenza viruses. Presently, avian influenza A viruses rarely infect humans, with the WHO reporting only 148 cases of H5N1 and 79 resultant deaths between 1997 until the time of writing (14 January 2006). Most of these cases have resulted from direct contact with infected birds or contaminated material, but have not been transmitted from human-to-human.

When human cases occur, information on the extent of influenza infection in animals, as well as humans, and on the circulating influenza virus is needed to assess the epidemic/pandemic risk. The most important question to investigate is whether sustained human-to-human transmission has taken place during a local outbreak. If this has occurred, then the likelihood of a pandemic would be much higher and urgent public health measures would be essential. Accurate predictions of bird flu-related human mortality therefore cannot be made before the pandemic virus emerges and spreads through the population. While a number of estimates of likely casualties have recently been attempted, all such estimates are speculative and should therefore be assessed with caution.

An earlier version of this chapter was written by Robert TE Bishop for the fourth edition. This chapter has been extended and revised to its present form. We hereby gratefully acknowledge the original contribution of Robert TE Bishop.

REFERENCES

1. von Overbeck J. Insurance and epidemics: SARS, West Nile virus and Nipah virus. *J Insur Med* 2003; 35: 24–33.
2. www.who.int/crs/outbreaknetwork/en/ (WHO, accessed 22 October 2003).
3. Swartz MN. Recognition and management of anthrax – an update. *N Engl J Med* 2001; 345: 1621–6.
4. Shapiro RL *et al.* Botulism in the USA: a clinical and epidemiologic review. *Ann Intern Med* 1998; 129: 221–8.
5. Principi N, Esposito S. Emerging role of Mycoplasma pneumoniae and Chlamydia pneumoniae in paediatric respiratory-tract infections. *Lancet Infect Dis* 2001; 1: 334–44.
6. Sack D *et al.* Cholera. *Lancet* 2004; 363: 223–33.
7. Stoddart B, Wilcox MH. Clostridium difficile. *Curr Opin Infect Dis* 2002; 15: 513–18.
8. Suerbaum S, Michetti P. Helicobacter pylori infection. *N Engl J Med* 2002; 347:1175–86.
9. Fields BS *et al.* Legionella and Legionnaires' disease: 25 years of investigation. *Clin Microbiol Rev* 2002; 15: 506–26.
10. Ustianowski AP, Lockwood DN. Leprosy: current diagnostic and treatment approaches. *Curr Opin Infect Dis* 2003; 16: 421–7.
11. Bharti AR *et al.* Leptospirosis: a zoonotic disease of global importance. *Lancet Infect Dis* 2003; 3: 757–71.
12. Hengge UR *et al.* Lyme borreliosis. *Lancet Infect Dis* 2003; 3: 489–500.
13. Krishna G, Chitkara RK. Pneumonic plague. *Semin Respir Infect* 2003; 18: 159–67.
14. Andrews J *et al.* Community-acquired pneumonia. *Curr Opin Pulm Med* 2003; 9: 175–80.
15. Graham SM. Salmonellosis in children in developing and developed countries and populations. *Curr Opin Infect Dis* 2002; 15: 507–12.
16. Frieden TR at al. Tuberculosis. *Lancet* 2003; 362: 887–99.
17. Tufariello JM *et al.* Latent tuberculosis: mechanisms of host and bacillus that contribute to persistent infection. *Lancet Infect Dis* 2003; 3: 578–90.
18. Davies PD. The world-wide increase in tuberculosis: how demographic changes, HIV infection and increasing numbers in poverty are increasing tuberculosis. *Ann Med* 2003; 35: 235–43.
19. Corbett EL *et al.* The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. *Arch Intern Med* 2003; 163: 1009–21.
20. Ayan I *et al.* Childhood nasopharyngeal carcinoma: from biology to treatment. *Lancet Oncol* 2003; 4:13–21.
21. Chien X *et al.* Serologic markers of Epstein-Barr virus infection and nasopharyngeal carcinoma in Taiwanese men. *N Engl J Med* 2001; 345:1877.
22. Fattovich G. Natural history and prognosis of hepatitis B. *Semin Liver Dis* 2003; 23: 47–58.
23. Alter MJ. Epidemiology and prevention of hepatitis *B.Semin Liver Dis* 2003; 23: 39–46.
24. Kao JH and Chen DS. Global control of hepatitis B virus infection. *Lancet Infect Dis* 2002; 2: 395–403.
25. Mahomey FJ. Update on diagnosis, management, and prevention of hepatitis B virus infection. *Clin Microbiol Rev* 1999; 12: 351–66.
26. Yang HY *et al.* Hepatitis B e antigen and the risk of hepatocellular carcinoma. *N Engl J Med* 2002; 347: 168–74.
27. http://www.hepnet.com
28. von Overbeck J. Hepatitis B infection. On the Risk 2002; 4: 50–61.
29. Flamm SL. Chronic hepatitis C virus infection.-JAMA. 2003; 289: 2413–7.
30. Alter MJ *et al.* The natural history of community-acquired hepatitis C in the USA. *N Engl J Med* 1992; 327: 1899–1905.
31. Alter MJ *et al.* The prevalence of hepatitis C virus infection in the USA, 1988 through 1994. *N Engl J Med* 1999; 341: 556–62.

32. Freeman X *et al.* The natural history of chronic hepatitis C: a systematic review. *Hepatology* 34: 809–16.
33. Kenny-Walsh E. Clinical outcomes after hepatitis C infection from contaminated anti-D immune globulin. *N Engl J Med* 1999; 340:1228–33.
34. Lauer GM, Walker BD. Hepatitis C virus infection. *N Engl J Med* 2001; 345: 41–52.
35. Pratt DS and Kaplan MM. Evaluation of abnormal liver-enzyme results in asymptomatic patients. *N Eng J Med* 2000; 342: 1266–71.
36. Shakil AO *et al.* Volunteer blood donors with antibody to hepatitis C virus: clinical, biochemical, virologic, and histologic features. *Ann Intern Med* 1995; 123: 330–7.
37. von Overbeck J. The silent hepatitis C epidemic. On the Risk 2001; 4: 58–67.
38. Gnann JW Jr, Whitley RJ. Clinical practice. Herpes zoster. *N Engl J Med* 2002; 347: 340–6.
39. Aylward RB *et al.* Global health goals: lessons from the worldwide effort to eradicate poliomyelitis. Lancet. 2003; 362: 909–14.
40. Golden MR *et al.* Update on syphilis: resurgence of an old problem. *JAMA* 2003; 290: 1510–4.
41. Walker DG, Walker GJ. Forgotten but not gone: the continuing scourge of congenital syphilis. *Lancet Infect Dis* 2002; 2: 432–6
42. Daszak P *et al.* Emerging infectious diseases of wildlife – Threats to biodiversity and human health. *Science* 2000; 287: 443–9.
43. Donnelly C *et al.* Epidemiological determinants of spread of causal agent of severe acute respiratory syndrome in Hong Kong. *Lancet* 2003; 361: 1761–6.
44. Peiris J *et al.* Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. *Lancet* 2003; 361:1767–72.
45. A report of the National Advisory Committee on SARS and Public Health. Learning from SARS. *Health Canada.* 2003. Available at: www.hc-sc.gc.ca/english/protection/warnings/sars/learning.html. Accessed on October 22, 2003.