

Chapter 3

Emerging and Re-emerging Infectious Diseases

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3.1 Definition

Emerging infectious diseases (EIDs) are characterized by a new or an increased occurrence within the last few decades. They include the following categories:

1. Emerging diagnosis of infectious diseases: old diseases that are newly classified as infectious diseases because of the discovery of a responsible infectious agent,
2. Newly emerging infectious diseases,
3. Re-emerging infectious diseases: reoccurrence or new outbreaks of old infectious diseases with important public health relevance, and
4. Emerging resistance: increasing resistance of infectious agents to antimicrobial substances.

3.2 Factors Contributing to Emergence

Human activities that change the ecology of the microbial world are important factors for the emergence of infectious diseases on a macro- and microlevel, which was noted in the Institute of Medicine (IOM) report in 1992. The main factors that were listed are deforestation, change in air quality, and climate. The report was updated in 2003 when additional factors were included: human susceptibility to infection (HIV, aging population), changing ecosystems, poverty and social inequality, war, famine, lack of political will (e.g., breakdown of public health), and the intent of harm (bioterrorism). The convergence model of the various factors shows that environmental factors interact with genetic and biological factors, social and political, as well as economic factors. Figures 3.1 and 3.2 demonstrate examples of different categories of EIDs and the influencing factors on the macro-, meso- and microlevel.

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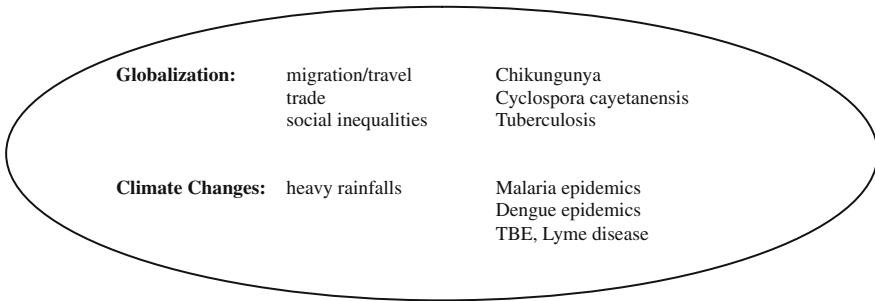


Fig. 3.1 Categories of emerging infectious diseases (EIDs) with examples

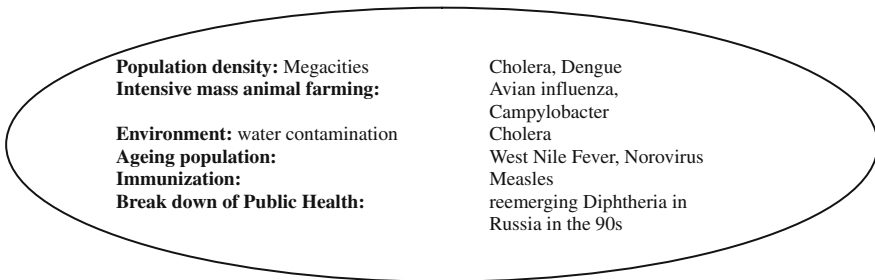
An interdisciplinary consortium recently analyzed 335 EID events between 1940 and 2004 (Jones et al. 2008) and demonstrated nonrandom global patterns. It gave analytical support that EID events rose significantly over time with a peak incidence in the 1980s concomitant with the HIV pandemic. EID events are dominated by zoonoses (over 60%), originating mostly in wildlife (almost 72% of zoonoses, e.g., hantavirus infections). The authors showed that 54% of EID events were caused by bacteria or *Rickettsia*, including a large number of drug-resistant microbes. They proved that new EID events are significantly associated with socioeconomic, environmental, and ecological factors, which can provide a basis for identifying regions where new EIDs are most likely to originate (emerging disease “hot spots”). They showed that the risk of wildlife zoonotic and vector-borne EIDs is high in lower latitudes where reporting effort is low. Population density is the most important driver for EID events in zoonotic wildlife and non-wildlife transmission, drug resistance, and the vector-borne transmission mode. The trends in the last decade were the following:

- The proportion of viral diseases compared to other infectious agents,
- The zoonotic wildlife transmission type,

Macro Level



Meso Level



Micro Level

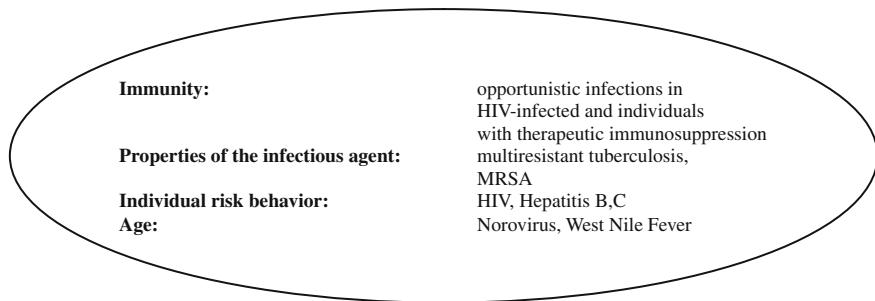


Fig. 3.2 Factors contributing to the emergence of infectious diseases with examples

- c. The vector-borne transmission mode, and
- d. The non-drug-resistant pathogens increased their proportion of EID events compared to the previous decade.

The “hot spots” for EID events were located in India for all four categories (zoonotic wildlife, zoonotic non-wildlife, drug resistance, and vector borne), clustered in densely populated areas throughout the world for zoonotic pathogens from wildlife, and were found for non-wildlife zoonotic diseases mainly in western

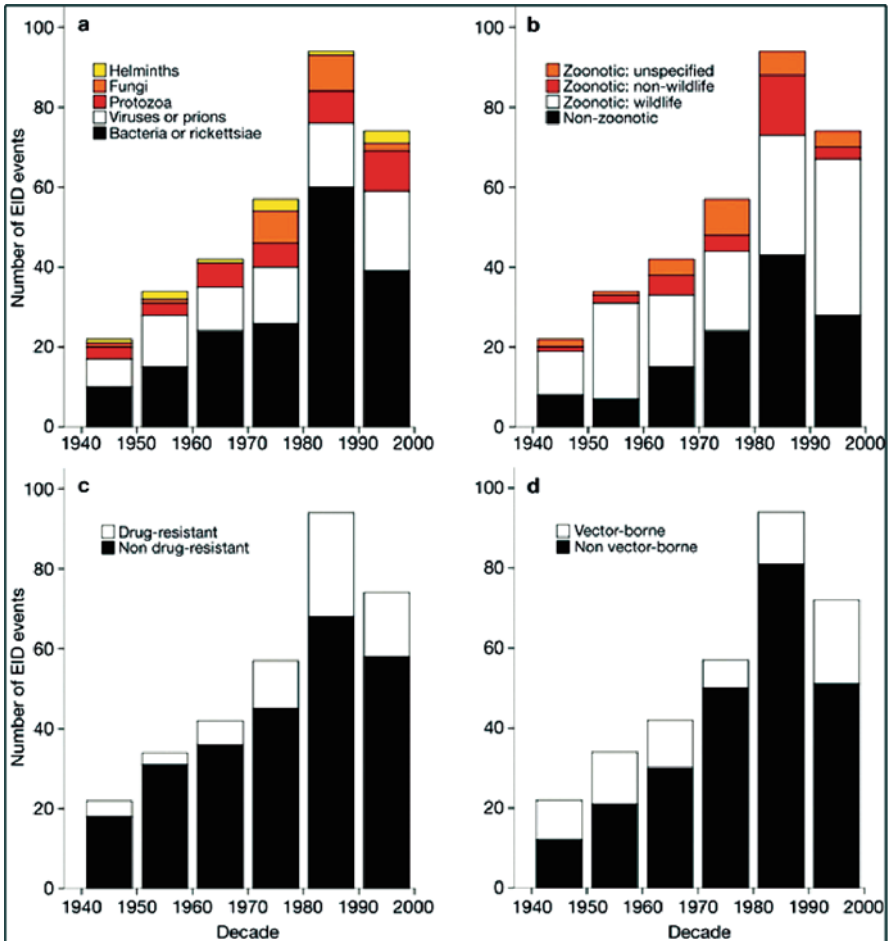


Fig. 3.3 Number of EID events per decade. Adapted from Nature 451, 990–993 (2008)

Europe including Great Britain as well as in India, China, and Japan. Emerging vector-borne disease events concentrated in densely populated subtropical and tropical regions mostly in India, Indonesia, China, sub-Saharan Africa, and Central America (see Figs. 3.3, 3.4, and 3.5).

3.3 New Infectious Agents in Old Diseases

The identification of new infectious agents in old diseases with unknown etiology is still the basis in many epidemiological studies. Such newly detected bacteria and viruses in the last few decades are listed in Table 3.1.

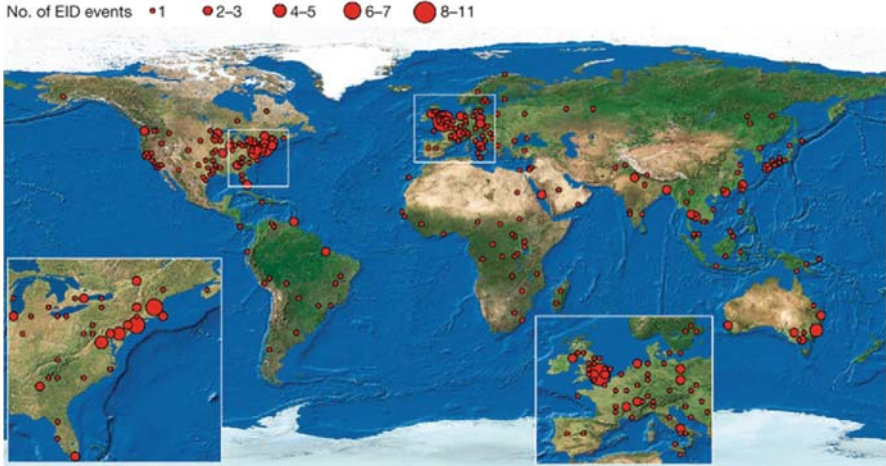
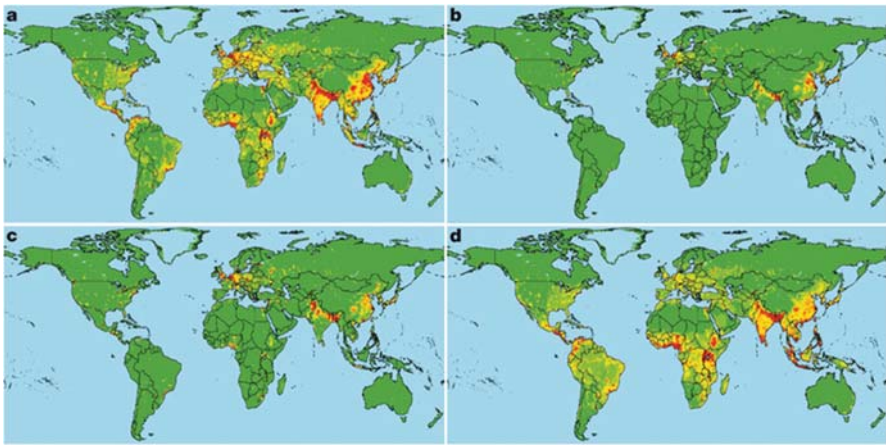


Fig. 3.4 Global richness map of the geographic origins of EID events from 1940 to 2004. Adapted from Nature 451, 990–993 (2008)



- a. zoonotic pathogens from wildlife
- b. zoonotic pathogens from non-wildlife
- c. drug-resistant pathogens
- d. vector-borne pathogens

Fig. 3.5 Global distribution of relative risk of an EID event; (a) zoonotic pathogens from wildlife, (b) zoonotic pathogens from non-wildlife, (c) drug-resistant pathogens, (d) vector-borne pathogens. Adapted from Nature 451, 990–993 (2008)

Table 3.1 New infectious agents of old diseases that had been classified as infectious diseases in the last decades

Infectious agent	Discovery year	Disease
<i>H. pylori</i>	1983	H.p.-gastritis Peptic ulcer Stomach cancer MALT lymphoma
<i>B. burgdorferi</i>	1982	Lyme disease (borreliosis) Erythema chronicum migrans Arthritis Neuroborreliosis
Hepatitis C virus (HCV)	1989	Hepatitis C
Hepatitis E virus (HEV)	1983/1990	Hepatitis E
<i>Chlamydia pneumoniae</i>	1986	Community-acquired pneumonia Coronary heart disease
<i>Tropheryma whipplei</i>	1992	Morbus whipple
<i>Bartonella henselae</i>	1994	Cat scratch disease Bacillary angiomatosis
Human papillomavirus (HPV)	1983	Cervix carcinoma

3.3.1 Emerging Diagnosis of Infectious Diseases

3.3.1.1 *Helicobacter pylori*-Associated Diseases

Since the detection of *Helicobacter pylori* in 1983, this infection has been identified as the causative agent in 90% of B-gastritis cases. The risk of duodenal ulcer is increased by 4–25-fold in patients with *Helicobacter*-associated gastritis. WHO declared *H. pylori* as a carcinogen of first order because of its potential to enhance the risk of stomach carcinoma and MALT lymphoma in long-term infection. In high-prevalence regions for *H. pylori*, the frequency of stomach carcinoma is significantly higher compared to low-endemic areas (Correa et al. 1990). The identification of *H. pylori* facilitates curative treatment of most associated diseases in individuals. But the most important epidemiological effect on associated diseases is attributed to increased hygienic standards in industrialized countries with a substantial reduction of *H. pylori* prevalences in younger age cohorts.

Transmission of *H. pylori* occurs mainly in childhood. In western developed countries the overall prevalence is around 30%, higher in older age groups due to a cohort effect, and this increases with low socioeconomic status (Rothenbacher et al. 1989). In countries with low hygienic standards the prevalences are still high in younger age groups and reach 90% in developing countries. In developed countries, migrant subpopulations from less-developed regions show significantly higher prevalences in comparison to the nonmigrant population (Mégraud 1993).

3.3.1.2 Lyme Disease, Tick-Borne Encephalitis

Since the early 20th century, a characteristic expanding skin lesion, erythema migrans (EM), and an arthritis associated with previous tick bites were known.

Molecular investigations in conserved ticks showed that ticks had been infected with *Borrelia* for many decades. Increased outdoor activities facilitated contacts between humans and ticks in the 1970s and the 1980s and increased transmission of *Borrelia* to humans at the northeastern coast of North America, leading to the discovery of *Borrelia burgdorferi* in 1981 by Willy Burgdorfer. Three different stages of the disease that describe the stage of infection and the involvement of different organ systems are known: stage 1, early localized infection; stage 2, early but disseminated infection; and stage 3, late stage with persistent infection.

Lyme disease is endemic at the east coast and in Minnesota in the United States, in eastern and central Europe, and Russia. Seroprevalence rates that reflect about 50% of nonclinical infections vary between 2 and 18% in the general population in Germany (Hassler et al. 1992; Weiland et al. 1992). In high-risk groups like forest workers in Germany the prevalences reach 25–29% (Robert Koch Institute 2001a). In ticks (*Ixodes*) the prevalences are between 2 and 30% depending on the geographical area and the testing method used [immunofluorescence test, IFT and polymerase chain reaction (PCR)]. In most studies the main risk factors of infection are age (children: 4–9 years, adults 35–60 years), outdoor activities, skin contacts with bushes and grass, and the presence of ticks in domestic animals (Robert Koch Institute 2001b). The probability of infection (seroconversion) after a tick bite in Germany is 3–6% and the probability of a clinical disease is 0.3–1.4%. The probability that the bite of an infectious tick leads to infection in the host is 20–30%. This depends on the time duration that the tick is feeding on the human body. Since the detection of the etiologic infectious agent and the subsequent development of laboratory diagnostic tests in the 1980s, the number of reported cases of Lyme disease has increased from 0 to 16,000 per year, indicating that it is an “emerging diagnosis.” The reported numbers vary depending on the reproduction of the hosting rodents for ticks as well as the contacts between humans and nature (Spach et al. 1993).

Ticks may live for several years and their survival, reproduction rate, and activity are directly affected by changes in seasonal climate through induced changes in vegetation zones and biodiversity, hence causing local alterations of the tick’s habitat and in the occurrence of animals that are carriers of different pathogens (like small rodents). Several studies in Europe have shown that in recent decades the tick *Ixodes ricinus*, transmitting Lyme borreliosis and tick-borne encephalitis (TBE), has spread into higher latitudes (e.g., Sweden) and altitudes (e.g., Czech Republic, Austria), and has become more abundant in many places. Such variations have been shown to be associated with recent variations in climate. As a result, new risk areas of both diseases have recently been reported from the Czech Republic. Climate change in Europe seems likely to facilitate the spread of Lyme borreliosis and TBE into higher latitudes and altitudes, and to contribute to extended and more intense transmission seasons. Currently, the most effective adaptive strategies available are TBE vaccination of risk populations and preventive information to the general public (Danielova et al. 2004; Lindgren et al. 2006; Materna et al. 2005).

An effective vaccine was licensed for *B. burgdorferi* in 1999. In Europe, where different variants of *Borrelia* are present (mostly *B. afzelii* and *B. garinii*), this vaccine is not protective. Trivalent vaccines for Europe are in clinical trials.

3.3.1.3 Norovirus

In recent years, norovirus infections are increasingly recognized as the cause of large outbreaks of diarrheal diseases in the general population, school classes, nursing homes, hospitals, and cruise ships in western countries with peaks in colder seasons (winter epidemics) (Centers of disease control 2006; Verhoef et al. 2008; Robert Koch Institute 2008a). This is a typical example for emerging diagnosis due to increasing availability of routine PCR testing for these viruses in stool samples. Noroviruses (family *Caliciviridae*) are a group of related, single-stranded RNA viruses first described in an outbreak of gastroenteritis in a school at Norwalk, Ohio, in 1968. Five genogroups are known. Immunity seems to be strain specific and lasts only for limited periods, so individuals are likely to get the infection repeatedly throughout their life. It is estimated that noroviruses are the cause of about 50% of all food-borne outbreaks of gastroenteritis. For several years there has been an ongoing epidemic in several European countries due to drift variants of a new genotype (GG II.4jamboree) previously unknown to this nonimmune population (Robert Koch Institute 2008a).

As a result of an analysis of 232 outbreaks in the United States between 1997 and 2000, direct contamination of food by a food handler was the most common cause (57%), person-to-person transmission was less prevalent (16%), and even less frequently waterborne transmission could be proved (3%) (Centers for Disease Control 2006). Vomiting is a frequent symptom of norovirus enteritis and may result in infectious droplets or aerosols causing airborne or contact transmission. This may explain the difficulty to stop outbreaks in hospitals, nursing homes, and similar settings despite precautions to prevent fecal–oral transmission. Also on cruise ships, person-to-person transmission is most likely in those closed settings, and drinking tap water is a risk factor as well (Verhoef et al. 2008).

3.3.1.4 Hepatitis E

Searching for an agent which causes large outbreaks of enterically transmitted non-A hepatitis in Asia and other parts of the world, the hepatitis E virus (HEV) was first described in 1983 and cloned and sequenced in 1990 (Reyes et al. 1990). Meanwhile, HEV has been shown to be a zoonotic virus circulating in pigs and other animals. It is implicated in about 50% of sporadic cases of acute hepatitis in developing countries and associated with a high case fatality rate in the third trimester of pregnancy (10–25%). HEV is a major cause of large epidemics in Asia, and to a lesser extent in Africa and Latin America, typically promoted through postmonsoon flooding with contamination of drinking water by human and animal feces.

Recent data show HEV also to circulate in European countries and to be associated with severe and fatal disease not only during pregnancy but also in the elderly and in patients with chronic liver conditions. In patients with solid organ transplants, HEV may even cause chronic hepatitis and liver cirrhosis (Kamar et al. 2008). A recombinant HEV vaccine candidate has demonstrated a high protection rate of approximately 95% during clinical trials in Nepal (Shrestha et al. 2007).

3.3.1.5 Cervix Carcinoma and Human Papillomavirus Infection

For 30 years, specific human papillomaviruses have been linked to certain human cancers and have been identified as causative agents of malignant proliferations. In the 1980s the detection of papillomavirus DNA from cervical carcinoma biopsies were published, showing that HPV types 16 and 18 are the most frequent (Dürst et al. 1983; Boshart et al. 1984). The relation of HPV infections and cancer is further discussed in Chapter 23.

3.4 Newly Emerging Infections

Definition: only infections that are newly discovered in humans are listed in this chapter: HIV, new variant of Creutzfeldt–Jakob disease (vCJD), hemorrhagic uremic syndrome (HUS) caused by enterohemorrhagic *Escherichia coli*, viral hemorrhagic fevers like Hanta, Lassa, Ebola, and Marburg fever, Nipah virus encephalitis, monkeypox, human ehrlichiosis, severe acute respiratory syndrome (coronavirus infection, SARS), and avian influenza (H5N1) (see Fig. 3.1 and Table 3.2).

Table 3.2 Newly emerging infectious diseases

Infectious agent	Discovery year	Disease	Important outbreak; prevalence
Hantaan virus	1976	Hemorrhagic fever with renal syndrome (HFRS)	More than 3,000 cases in 1951 in US soldiers in the war of Korea, case fatality rate 5%
Puumala virus		HFRS	Central and northern Europe (seroprevalence up to 3%), outbreak in Germany 2007
Dobrava (central and southeast European variant)		HFRS	Central and southeast Europe (seroprevalence 2.4% in lumbermen in Brandenburg, Germany)
Various types of hantaviruses Muerto Canyon, Sin Nombre, Louisiana et al.	1993	Hantavirus pulmonary syndrome (HPS)	First outbreak in the United States through favorable climatic conditions for the chronically infected deer mice population, 465 cases until 2007, case fatality rate 35%
Nipah virus (related to Hendra virus)	1999	Encephalitis	1997/1998 in Malaysia among butchery workers, 265 cases, case fatality rate 40%, disease transmission by infected pigs, in India 66 cases in 2001 Outbreaks in Bangladesh since 2001
West Nile virus	1999	Encephalitis	Since 1999 at the east coast of the United States, spread in the whole country within 4 years

Table 3.2 (continued)

Infectious agent	Discovery year	Disease	Important outbreak; prevalence
<i>V. cholerae</i> 0139 Bengal	1992	Cholera	Originated from India and Bangladesh, epidemic with 200,000 cases in seven Asian countries
<i>Cyclospora cayetanensis</i>	1993	Long-lasting diarrhea	1996/1997 outbreaks in the United States with 1465 diseases through contamination of imported strawberries
Presumably PrPSc (Prion), presumably identical to BSE virus	1996	New variant of Creutzfeldt–Jakob Disease (vCJD)	First cases in 1994/1995 in the United Kingdom, 163 deaths in the United Kingdom until June 2008
<i>Ehrlichia chaffeensis</i> , <i>E. ewingii</i> , etc.	1986, 1994, 1999	Human monocytogenic and granulocytogenic ehrlichiosis	Several clinical cases, seroprevalence in lumbermen in Brandenburg, Germany, in 2000 6.2%
Coronavirus	2002	Severe acute respiratory syndrome (SARS)	8097 cases between 11-2002 and 2004 (China, Hong Kong, Taiwan, Singapore, Canada), case fatality rate 9.6%
Influenza virus H5N1	1996 in a farmed goose in China, 2003 first human confirmed cases from China	Avian influenza	Since 2003 until June 2008, 385 confirmed human cases with 243 deaths in China, Vietnam, Thailand, Indonesia, Cambodia, Azerbaijan, Djibouti, Egypt, Iraq, Turkey, Laos, Myanmar, Nigeria, Pakistan, Bangladesh
Influenza virus A H1N1	2009 in children and mostly young adults in Mexico	New influenza A H1N1	Since 2009, outbreak in Mexico with further spread to neighborhood countries, North and South America, Europe, Asia, and Africa (56,000 cases worldwide by the end of June 2009)

These infections mostly have their origin in zoonotic wildlife (e.g., avian influenza, monkeypox, hantavirus, Nipah virus, and filoviruses) or livestock (e.g., vCJD). Factors promoting the spread of these infections in humans are contacts with wildlife, mass food production of animal origin, and globalization (migration, transportation of goods and vectors) (see Fig. 3.2).

In addition, new strains or variants of well-known pathogens have emerged showing increased or altered virulence such as *Clostridium difficile* ribotype 027 or *Staphylococcus aureus* strains expressing the Panton–Valentine leukocidin (see also Chapter 22).

The epidemiology of HIV is treated in Chapter 18 and that of avian influenza and new influenza H1N1 in Chapter 16.

3.4.1 New Variant of Creutzfeldt–Jakob Disease

In the year 1995, 3 years after the peak of the BSE epidemic in the United Kingdom, with an annual incidence rate in cows of 6.636 per million bovines aged over 24 months, the first mortalities in humans with a new variant of Creutzfeldt–Jakob disease were observed in the United Kingdom. Until 2007, smaller incidence rates of BSE cases had been reported by 21 other European countries in indigenous bovines and up to more than 43,000 per million in 2004 in Ireland. From 1999, BSE started to increase in Switzerland and Portugal, from 2004 in Spain and in recent years has spread to eastern European countries (Organisation Mondiale de la Santé Animale 2008). The infectious agent is a self-replicating protein, a “prion.” The source of infection for cows is infectious animal flour. The transmission to humans occurs through oral intake of cow products, most likely undercooked meat and neural tissues as well as transplants of cornea, dura mater, contaminated surgical instruments, or the treatment with hypophyseal hormones extracted from animal tissues. After a statutory ban on the feeding of protein derived from ruminants to any ruminant and the export ban of all cow products from England, the epidemic of BSE in cows and the occurrence of human infections decreased in the United Kingdom since 2004. By June 2008 the total number of deaths in definite/probable cases of vCJD in the United Kingdom was 163 (The National Creutzfeldt–Jakob Disease Surveillance Unit 2008). Only a few numbers of vCJD were reported from other European countries and the United States (WHO 2008).

3.4.2 Nipah Virus Encephalitis

Nipah virus encephalitis was first observed in 1997/98 in Malaysia. The disease was transmitted by pigs to laborers in slaughterhouses and showed a lethality of 40%. The infectious agent was detected in 1999 (Chua et al. 2000; Lam and Chua 2002). Since then, several outbreaks of Nipah virus infections have been observed in Asian countries: Singapore in 1999, India 2001, and Bangladesh since 2003 (WHO 2004a; Harit et al. 2006). The virus has been isolated repeatedly from various species of fruit bats, which seem to be the natural reservoir (Yob et al. 2001).

3.4.3 West Nile Encephalitis

West Nile is a mosquito-borne flavivirus that was first isolated from a woman with a febrile illness in Uganda in 1937. From the 1950s, West Nile fever endemicity and epidemics started being reported from Africa and the Middle East. Severe neurological symptoms were thought to be rare. More recent epidemics in northern Africa,

eastern Europe, and Russia suggested a higher prevalence of meningoen­cephalitis with case fatality rates of 4–13%. In 1999, West Nile virus was identified as the cause of an epidemic of encephalitis at the east coast of the United States (Nash et al. 1999). A seroepidemiological household-based survey showed that the first outbreak consisted of about 8,000 infections of which about 1,700 developed fever and less than 1% experienced neurological disease (Mostashari et al. 2001). Since then, epidemics occur during summer months in North America each year, with an estimated 35,000 febrile illnesses and over 1,200 encephalitis or meningitis cases in the United States in 2007 (Centers for Disease Control 2008). Age above 50 years is the main risk factor for developing severe disease. The virus is transmitted mainly by *Culex* mosquitoes, but also by sandflies, ceratopogonids, and ticks, with birds as reservoir hosts and incidental hosts such as cats, dogs, and horses. Efforts are made to reduce the transmitting mosquito population and to prevent mosquito bites through personal protection as well as to prevent transmission through blood donations by screening (Centers of Disease Control 2008).

3.4.4 Severe Acute Respiratory Syndrome (SARS)

The first case of SARS occurred in Guangdong (China) in November of 2002, leading to an outbreak with 7082 cases in China and Hong Kong (8096 cases worldwide) until July 2003. The case fatality rate was 9.6%. A new coronavirus (SARS-CoV) was identified as the causative agent (Drosten et al. 2003), being transmitted first by infected semidomesticated animals such as the palm civet and subsequently from human to human. Some cases were exported to other countries, causing smaller outbreaks there, Canada being the most affected country outside Asia with 251 cases, before control of transmission was effective. Eight thousand and ninety-six cases were reported worldwide, until July 2003, then further transmission stopped (besides one more case of laboratory transmission in 2004), indicating an efficient international cooperation in disease control (WHO 2004b). Recently, SARS-CoV has been found in horseshoe bats, which seem to be the natural reservoir of the virus.

3.4.5 Hantavirus

About 150,000–200,000 cases of hemorrhagic fever with renal syndrome (HFRS) caused by hantaviruses are reported annually worldwide, with more than half in China, many from Russia and Korea, and numerous cases from Japan, Finland, Sweden, Bulgaria, Greece, Hungary, France, and the Balkan with different death rates depending on the responsible virus, ranging from 0.1% in Puumala to 5–10% in Hantaan infections (Schmaljohn and Hjelle 1997).

Hantaviruses are transmitted from rodent to rodent through body fluids and excreta. Only occasionally do humans get infected. Different types of hantaviruses are

circulating in Europe and the eastern hemisphere, predominantly Puumala virus, Dobrava virus, and Tula virus, adapted to different mouse species. Depending on the virus type the case fatality rate is between 1 and 50%. As an example, the annual rate of reported cases in Germany was about 100 cases per year from 2001 onward. This started to change in 2005 with 448 reported cases and rose dramatically to 1687 cases in 2007. That year, hantavirus infections were among the five most reported viral infections in Germany. Reasons for the rise in human infections were an increase in the hosting rodent population due to a very mild winter 2006/2007 and an early start of warm temperatures in spring which led to favorable nutritional situations for the mice influencing their population dynamics. In addition, favorable climatic conditions enhanced the outdoor behaviors of humans facilitating transmission in rural areas (Robert Koch Institute 2008b; Hofmann et al. 2008).

Since 1993, a previously unknown group of hantaviruses (Sin Nombre, New York, Black Creek Canal, Bayou—in the United States and Canada; Andes, in South America) emerged in the Americas as a cause of hantavirus pulmonary syndrome (HPS), an acute respiratory disease with high case fatality rates (approx. 35%), causing a new, significant public health concern. A total of 465 cases had been reported until March 2007 in 32 states, most of them in the western part of the United States (Centers for Disease Control 2007).

3.4.6 *Filoviruses and Lassa Virus*

Lassa virus was detected for the first time in 1969 during an outbreak affecting nurses in a missionary hospital in Lassa, Nigeria. However, the disease had previously been described in the 1950s. Lassa virus is enzootic in a common peridomestic rodent in West Africa, the multimammate rat *Mastomys natalensis*, which is chronically infected and sheds the virus in urine and saliva. Human infection through direct or indirect contact with rats or their excretions is rather common in some West African countries and estimates from seroepidemiological and clinical studies suggest that there are several hundred thousand cases annually. However, only a minority of infections seems to progress to severe hemorrhagic disease with a case fatality rate of 5–30% in hospitalized cases. The virus can be transmitted by close person-to-person contact and nosocomial spread has been observed under poor hygienic conditions.

Marburg and Ebola viruses, which were first detected during outbreaks in 1967 and 1975, respectively, have so far been observed only during several limited outbreaks and a few isolated cases in certain countries of sub-Saharan Africa. However, very high case fatality rates (25–90%), the occurrence of outbreaks that were difficult to control in resource-poor settings, and the obscure origin of these viruses have attracted considerable public interest worldwide. Recently, evidence was found for both Marburg and Ebola viruses to occur in certain species of bats that probably constitute the natural reservoir of these filoviruses (Towner et al. 2007).

Although the disease burden of these viral hemorrhagic fevers is low, they gained considerable international attention due to

- their high case fatality rates,
- the risk of person-to-person transmission,
- several imported cases to industrialized countries, and
- fears of abuse of these agents for bioterrorism.

As a consequence, considerable resources have been invested, even in non-endemic countries, in the setting up of task forces and high containment facilities for both laboratory diagnostic services and treatment of patients using barrier nursing.

3.4.7 *C. difficile* Ribotype 027

This highly virulent strain of *C. difficile* expresses both cytotoxins A and B and, in addition, the binary toxin CDT, an ADP-ribosyltransferase. Due to a deletion in the regulatory *tcdC* gene, the synthesis rates of toxin A and B are increased by 16- and 23-fold, respectively. This strain was detected in 2000 for the first time in Pittsburgh, USA. Since then it has spread to Canada, and in 2003 it reached Europe causing multiple outbreaks in hospitals and nursing homes (Warny et al. 2005). *C. difficile* 027-associated colitis has shown high case fatality rates (10–22%) and an increased relapse rate. Containment of outbreaks in hospitals and other institutions necessitates isolation of patients or cohorts and strict hygienic measures.

3.5 Re-emerging Infectious Diseases

During recent decades, a large variety of well known infectious diseases has shown regional or global re-emergence with considerable public health relevance (Table 3.3). Globally, tuberculosis is probably the most important re-emerging infectious disease. In developing countries, TB infection still is extremely common and, in the wake of the HIV pandemic, the percentage of those developing overt disease has increased dramatically. Worldwide, TB is the most common opportunistic infection in patients with AIDS. The significance of TB and HIV/TB coinfection is reviewed in Chapters 16 and 18.

The re-emergence of some infectious diseases is closely related to the lack or the breakdown of basic infrastructures as seen in periurban slums and in refugee camps in developing countries, or as a consequence of war, breakdown of the civil society, or natural or man-made disasters. Cholera is a formidable example for both re-emergence and epidemic spread under those conditions.

Another important group of re-emerging infectious diseases is caused by various vector-borne infections, such as malaria, dengue fever, and yellow fever. These major vector-borne diseases are treated in more detail in Chapter 21. In addition,

Table 3.3 Re-emerging infections of public health relevance

Disease	Current epidemiology
Tuberculosis, malaria, cholera, dengue fever	See Chapters 16, 17, and 21
Yellow fever	See Chapter 21 Numerous outbreaks in Africa and South America; in 2008 new outbreaks in southern Brazil, Argentina, and Paraguay Single cases in uprooting workers and gold miners in the Amazon area; in 2007–2008 new outbreak in southern Brazil, Paraguay and Argentina; single imported cases in industrialized countries (Germany, United States, and others)
Japanese encephalitis	Increasing in rural areas of Southeast Asia, spreading to the West (epidemics in northern India, Nepal, Sri Lanka); since 1995 some cases in Torres Islands (Australia)
Crimean-Congo hemorrhagic fever	Small tick-borne or human-to-human transmission-borne epidemics in 2001 (Kosovo, Albania, Iran, Pakistan, South Africa), small outbreaks in Turkey since 2002, 438 cases (27 deaths) reported in 2006
Meningococcal meningitis	Pandemic since 1996 in West Africa; epidemic with serogroup W135 in pilgrims to Mecca 2000 and 2001 with imports and contact infections in several European countries
Plague	Several epidemics in the 1990s in India, Tanzania, Madagascar (deriving from known zoonotic infections, facilitated by increased rat population and slums and poor hygiene)
Rift Valley fever	Epidemics in humans and productive livestock in North Africa and sub-Saharan Africa; in 1997–1998, outbreaks in Kenya and Somalia (heavy rainfalls, El Niño); in 2000, first occurrence outside Africa in Saudi Arabia and Yemen; in 2006–2007, outbreaks in Kenya and Tanzania
Ross River fever	Spread in Australia and to Oceania, some epidemics
Sleeping sickness	Re-emergence in areas with political destabilization, high mortality (Angola, Congo, south Sudan)
Visceral leishmaniasis	Increasing numbers in south Sudan, northeast India, west China; increasing occurrence as opportunistic infection in HIV-infected persons mainly in southwest Europe (i.v. drug user) and northeastern Brazil
Rabies	India, Nepal, China (outbreaks in dog farms)
Cholera	Tanzania, Zanzibar
Chikungunya fever	Large outbreaks in La Réunion and other Indian Ocean islands with further spread to Sri Lanka, India in 2007–2008, autochthonous outbreak in Italy in 2007

there are a variety of re-emerging infections transmitted by arthropod vectors such as various arboviral diseases and some protozoal diseases other than malaria (i.e., leishmaniasis, human African trypanosomiasis). The reasons for the emergence of several vector-borne diseases are rather variable and may range from climatic factors (e.g., global warming, rainfall), lack or breakdown of control, to changes in agriculture and farming and in human behavior (e.g., outdoor activities). These factors are usually quite specific for each of these diseases and largely depend on the specific ecology of the agent, its vectors, and reservoirs.

3.5.1 Cholera

Cholera, an acute diarrheal infection transmitted by fecally contaminated water and food, had been endemic for centuries in the Ganges and Brahmaputra deltas in the 19th century before it started to spread to the rest of the world. Since 1817, six pandemics caused by the classical biotype of *Vibrio cholerae* were recorded that killed millions of people across Europe, Africa, and the Americas. It has been a major driving force for the improvement of sanitation and safe water supply. The seventh pandemic was caused by the El Tor biotype, first isolated from pilgrims at the El Tor quarantine station in Sinai in 1906. It started in 1961 in South Asia, reached Africa in 1971, and is still ongoing. After more than hundred years, cholera spread to the Americas in 1991, and beginning in Peru, a large epidemic hit numerous Latin American countries with 1.4 million cases and more than 10,000 fatalities reported within 6 years.

Out of the 139 serogroups of *V. cholerae*, only O1 and O139 can cause epidemics. The serogroup O139, first identified in Bangladesh in 1992, possesses the same virulence factors as O1 and creates a similar clinical picture. Currently, the presence of O139 has been detected only in southeast and east Asia, but it is still unclear whether *V. cholerae* O139 will extend to other regions.

Since 2005, the re-emergence of cholera has been noted in parallel with the ever-increasing size of vulnerable populations living in unsanitary conditions. Cholera remains a global threat to public health and one of the key indicators of social development. While the disease is no longer an issue in countries where minimum hygiene standards are met, it remains a threat in almost every developing country. The number of cholera cases reported to the WHO during 2006 rose dramatically, reaching the level of the late 1990s. A total of 236,896 cases were notified from 52 countries, including 6,311 deaths, an overall increase of 79% compared with the number of cases reported in 2005. This increased number of cases is the result of several major outbreaks that occurred in countries where cases had not been reported for several years such as Sudan and Angola. It is estimated that only a small proportion of cases – less than 10% – are reported. The true burden of disease is therefore grossly underestimated.

The absence or the shortage of safe water and sufficient sanitation combined with a generally poor environmental status are the main causes of spread of the disease. Typical at-risk areas include periurban slums where basic infrastructure is not available, as well as camps for internally displaced people or refugees where minimum requirements of clean water and sanitation are not met. However, it is important to stress that the belief that cholera epidemics are caused by dead bodies after disasters, whether natural or manmade, is false. On the other hand, the consequences of a disaster—such as disruption of water and sanitation systems or massive displacement of population to inadequate and overcrowded camps—will increase the risk of transmission.

3.6 Vector-Borne Diseases

3.6.1 *Chikungunya Fever*

Chikungunya virus, an arbovirus belonging to the alphavirus group, is transmitted by various mosquitoes. The virus was first isolated in Tanzania in 1952 and since then has caused smaller epidemics in sub-Saharan Africa and parts of Asia with low public health impact. In 2005, the largest epidemic ever recorded started in east Africa, spread to Réunion and some other islands of the Indian Ocean, and then spread further to Asia, with more than 1.5 million cases in India alone so far. Characteristics of the disease are high fever and a debilitating polyarthritis, mainly of the small joints that can persist for months in some patients. Now, for the first time, severe and fatal cases have been observed that may be due to certain mutations of the epidemic strain (Parola et al. 2006).

The Asian tiger mosquito *Aedes albopictus* has proved to be an extremely effective vector in recent epidemics causing high transmission rates in big cities and leading to epidemics with high public health impact. This southeast Asian mosquito species has been shipped by transport of used tires and plants harboring water contaminated with larvae to other continents and, since 1990, *Ae. albopictus* has successfully spread in Italy and other parts of southern Europe. In August 2007, an outbreak of chikungunya fever occurred in northern Italy with more than 200 confirmed cases. The index case was a visitor from India who fell ill while visiting relatives in one of the villages and further transmission was facilitated by an abundant mosquito population during that time, as a consequence of seasonal synchronicity (Rezza et al. 2007).

3.6.2 *Ross River Fever*

Ross River virus (RRV) is another arbovirus of the alphavirus group that causes an acute disease with or without fever and/or rash. Most patients experience arthritis or arthralgia primarily affecting the wrist, knee, ankle, and small joints of the extremities (epidemic polyarthritis). About one-quarter of patients have rheumatic symptoms that persist for up to a year. The disease can cause incapacity and inability to work for months. It is the most common arboviral disease in Australia with an average of almost 5,000 notified cases per year. RRV is transmitted by various mosquito species and circulates in a primary mosquito–mammal cycle involving kangaroos, wallabies, bats, and rodents. A human–mosquito cycle may be present in explosive outbreaks which occur irregularly during the summer months in Australia and parts of Oceania. Heavy rainfalls as well as increasing travel and outdoor activities are considered as important factors contributing to the emergence of RRV epidemics.

3.6.3 *Japanese Encephalitis (JE)*

This flavivirus is transmitted by certain *Culex* mosquitoes and is a leading cause of viral encephalitis in Asia with 30,000–50,000 clinical cases reported annually. It occurs from the islands of the Western Pacific in the east to the Pakistani border in the west, and from Korea in the north to Papua New Guinea in the south. Only 1 in 50–200 infections will lead to encephalitis, which is, however, often severe with fatality rates of 5–30% and with a high incidence of neurological sequelae.

Despite the availability of effective vaccines, JE causes large epidemics and has spread to new areas during recent decades (e.g., India, Sri Lanka, Pakistan, Torres Strait islands, and isolated cases in northern Australia). JE is particularly common in areas where flooded rice fields attract water fowl and other birds as the natural reservoir and provide abundant breeding sites for mosquitoes such as *Culex tritaeniorhynchus*, which transmit the virus to humans. Pigs act as important amplifying hosts, and therefore JE distribution is very significantly linked to irrigated rice production combined with pig rearing. Because of the critical role of pigs, JE presence in Muslim countries is low.

3.6.4 *Crimean–Congo Hemorrhagic Fever (CCHF)*

Crimean–Congo virus is a bunyavirus causing an acute febrile disease often with extensive hepatitis resulting in jaundice in some cases. About one-quarter of patients present hemorrhages that can be severe. Fatality rates of 7.5–50% have been reported in hospitalized patients. CCHF is transmitted by *Hyalomma* ticks to a wide range of domestic and wild animals including birds. Human infection is acquired by tick bites or crushing infected ticks, and also by contact with blood or tissue from infected animals that usually do not become ill but do develop viremia. In addition, nosocomial transmission is possible and is usually related to extensive blood exposure or needle sticks. Human cases have been reported from more than 30 countries in Africa, Asia, southeastern Europe, and the Middle East. In recent years, an increase in the number of cases during tick seasons has been observed in several countries such as Russia, South Africa, Kosovo, and Greece. In Turkey, where before 2002 no human CCHF cases had been observed, a total of 2,508 confirmed cases, including 133 deaths, were reported between 2002 and June 2008. The emergence of CCHF has been associated with factors such as climatic features (temperature, humidity, etc.), changes of vector population, geographical conditions, flora, wildlife, and the animal husbandry sector.

3.6.5 *Rift Valley Fever (RVF)*

RVF is a mosquito-borne bunyavirus infection occurring in many parts of sub-Saharan Africa. It infects primarily sheep, cattle, and goats, and is maintained in nature by transovarial transmission in floodwater *Aedes* mosquitoes. It has been shown that infected eggs remain dormant in the dambos (i.e., depressions) of east

Africa and hatch after heavy rains and initiate mosquito–livestock–mosquito transmission giving rise to large epizootics. Remote sensing via satellite can predict the likelihood of RVF transmission by detecting both the ecological changes associated with heavy rainfall and the depressions from which the floodwater mosquitoes emerge.

Transmission to humans is also possible from direct and aerosol exposure to blood and amniotic fluids of livestock. Most human infections manifest themselves as uncomplicated febrile illness, but severe hemorrhagic disease, encephalitis, or retinal vasculitis is possible. In 1977, RVF has been transported, probably by infected camels to Egypt, where it caused major epidemics with several hundred thousand infections of humans. It has been suggested that introduction of RVF may be a risk to other potentially receptive areas such as parts of Asia and the Americas. Floods occurring during the El Niño phenomenon of 1997 in east Africa subsequently gave rise to large epidemics and further spread to the Arabian Peninsula. Most recent epidemics occurred in 2006 and 2007 following heavy rainfalls in Kenya, Somalia, and Sudan, causing several hundred deaths. Besides mosquito control, epidemics are best prevented by vaccination of livestock.

3.6.6 *Leishmaniasis*

Leishmaniasis, a protozoal transmitted by sandflies, has shown a sharp increase in the number of recorded cases and spread to new endemic regions over the last decade. Presently, 88 countries are affected with an estimated 12 million cases worldwide. There are about 1.5 million new cases of cutaneous and mucocutaneous leishmaniasis, a nonfatal but debilitating disease with 90% of cases occurring in Afghanistan, Brazil, Bolivia, Iran, Peru, Saudi Arabia, and Syria.

The incidence of visceral leishmaniasis (VL), a disease with a high fatality rate when untreated, is estimated at around 500,000 per year. The situation is further aggravated by emerging drug resistance (Table 3.4) and the deadly synergy of VL/HIV coinfection. Epidemics usually affect the poorest part of the population and have occurred recently in Bangladesh, Brazil, India, Nepal, and Sudan.

For many years, the public health impact of the leishmaniasis has been grossly underestimated. They seriously hamper socioeconomic progress and epidemics have significantly delayed the implementation of numerous development programs.

The spread of leishmaniasis is associated with factors favoring the vector such as deforestation, building of dams, new irrigation schemes, and climate changes, but also with urbanization, migration of nonimmune people to endemic areas, poverty, malnutrition, and the breakdown of public health.

3.7 Emerging Resistance

Antimicrobial resistance of epidemiological relevance has emerged as a major problem in the treatment of many infectious diseases (Table 3.4). Resistance is no longer a problem that predominantly affects the chemotherapy of bacterial infections. It

became increasingly important in parasitic and fungal diseases, and despite the short history of antiviral chemotherapy, it already plays a prominent role in the treatment of HIV infection and other viral diseases. Resistance is also a problem in some of the emerging infections and will further complicate their treatment and control.

Resistance of bacterial pathogens has become a common feature in *nosocomial infections*, especially in the ICU and in surgical wards. Currently, the number one problem in most hospitals is *S. aureus* resistant to methicillin (MRSA, see Chapter 22). However, common problems of resistance also extend to other major bacterial pathogens such as enterococci, various gram-negative enteric bacilli, and pseudomonas species. Resistance has developed not only to standard antibiotics (e.g., penicillins, cephalosporins, aminoglycosides, macrolides, or quinolones) but also to second-line antibiotics including carbapenems, glycopeptides, and newer quinolones. However, there is considerable geographic variation. In 2006, the European Antimicrobial Resistance Surveillance System (EARSS), a network of national surveillance systems, reported vancomycin-resistant rates among enterococci ranging from none in Iceland, Norway, Romania, Bulgaria, Denmark, and Hungary to 42% of *Enterococcus faecium* strains in Greece (EARSS 2006). A surveillance study conducted in the United States hospitals from 1995 to 2002 showed that 9% of nosocomial bloodstream infections were caused by enterococci and that 2% of *E. faecalis* isolates and 60% of *E. faecium* isolates were vancomycin resistant (Wisplinghof et al. 2004).

Rates and spectrum of antibacterial resistance of *E. coli* and other gram-negative enteric bacilli may differ considerably from one hospital to the other. In some important pathogens of hospital-related infections such as *Klebsiella*, *Enterobacter*, and *Pseudomonas* species, resistance to almost all available antimicrobials has been observed. This may complicate the choice of an effective initial chemotherapy considerably. Therefore, each hospital has to monitor the epidemiological situation of resistance regularly, at least for the most important bacteria causing nosocomial infections, such as staphylococci, enterococci, gram-negative enteric bacilli, and pseudomonas.

Even in *community-acquired infections*, there has been a considerable increase in resistance problems. At present, approximately 15% of pneumococcal isolates in the United States are resistant to penicillin, and 20% exhibit intermediate resistance. The rate of resistance is lower in countries that, by tradition, are conservative in their antibiotic use (e.g., Netherlands, Germany) and higher in countries where use is more liberal (e.g., France). In Hong Kong and Korea, resistance rates approach 80%. In addition, about one-quarter of all pneumococcal isolates in the United States are resistant to macrolides. This rate is even higher in strains highly resistant to penicillin, and increasingly there is multiresistance against other antibiotics such as cephalosporins.

The prevalence of meningococci with reduced susceptibility to penicillin has been increasing, and high-level resistance has been reported in some countries (e.g., Spain, United Kingdom). Although high-dose penicillin is effective in infections with strains of intermediate resistance, most national and international guidelines recommend broad-spectrum cephalosporins such as ceftriaxone as first-line

drugs. However, in most developing countries, penicillin and chloramphenicol are the only affordable drugs.

In recent years, certain strains of community-acquired *S. aureus* with resistance to methicillin (cMRSA) have been observed which produce a toxin (Panton–Valentine leukocidin) that is cytolytic to PMNs, macrophages, and monocytes, and which are an emerging cause of community-acquired cases and outbreaks of necrotic lesions involving the skin or the mucosa, and in some patients also of necrotic hemorrhagic pneumonia with a high case fatality (Vandenesch et al. 2003).

Development of resistance is mainly determined by two factors:

- The genetic potential of a certain pathogen, i.e., mobile elements such as plasmids, transposons, or bacteriophages, genes coding for resistance, and mutation rate.
- The selection pressure caused by the therapeutic or the para-therapeutic application of antimicrobial drugs.

In the hospital these factors are supported by

- microbial strains that are highly adapted to this environment (e.g., rapid colonization of patients, resistance to disinfectants),
- an increasing percentage of patients who are highly susceptible to infections due to old age, multimorbidity, immunosuppression, extended surgery, and invasive procedures, and
- the frequent use of broad-spectrum antibiotics or combinations of antimicrobial drugs.

Another source of resistant bacteria has been identified in mass animal production and the use of antimicrobials as growth promoters (e.g., the glycopeptide avoparcin, the streptogramin virginiamycin) or as mass treatment in the therapy or the prevention of infections.

The inadequate use of antimicrobial drugs is also an important factor responsible for the development of resistance in community-acquired infections. This is especially true in developing countries where only a limited spectrum of antibiotics is available, where shortage of drugs often leads to treatment that is underdosed or too short, and where uncontrolled sale and use of antibiotics is commonplace. As a consequence, resistance of gonococci is extremely frequent in southeast Asia, and resistance of *Salmonella typhi*, *Shigella*, and *Campylobacter* to standard antibiotics is common. Some of the still effective second-line antibiotics have to be given parenterally or are not available because they are too costly.

A typical example of the consequences of insufficient chemotherapy due to lack of compliance and/or unavailability of drugs is the alarming increase in multiresistance and extreme resistance in TB (see Chapter 16). Resistance is also a problem in parasitic diseases such as malaria (see Chapter 21), leishmaniasis, or African trypanosomiasis. *Plasmodium falciparum* developed resistance against all major antimalarial drugs as soon as they were used on a broad scale. Resistance had contributed significantly to the increase in malaria-associated morbidity and mortality

observed in many endemic areas (Wongsichranalai et al. 2002). A recent report on failures of the new artemisinin combination treatment for *P. falciparum* malaria at the Thai–Cambodian border supports fears of the development of resistance to this most promising class of drug at present (Dondrop et al. 2009).

Resistance against antiviral drugs has developed almost from the beginning of antiviral chemotherapy (Table 3.4). In the treatment of HIV infection, the risk of development of resistance has been drastically reduced by the combination of several drugs with different mechanisms of action (see Chapter 18). However, drug resistance remains the Achilles' heel of the highly active antiretroviral therapy (HAART) and may be at a considerable risk of expanding HAART to the developing world.

Table 3.4 Important resistance of infectious agents to antibiotics and chemotherapeutics

<i>Agent/disease</i>	<i>Frequent or significant resistances against</i>
<i>Staphylococcus</i>	Penicillin, methicillin, glycopeptides
<i>Enterococcus</i>	Glycopeptides, multiresistance
Enterobacteria (<i>E. coli</i> , <i>Klebsiella</i> , <i>Enterobacter</i> et al.)	Broad-spectrum penicillins, cephalosporins (ESBL) ^a , quinolones, etc., multiresistance also against last-choice antibiotics
<i>Pseudomonas</i> spp. <i>S. typhi</i>	Numerous antibiotics including last-choice antibiotics Chloramphenicol, ampicillin, cotrimoxazole, quinolones, multiresistance in Thailand, Laos, Vietnam
<i>Shigella</i>	Ampicillin, tetracycline, cotrimoxazole, quinolones
<i>Campylobacter</i>	Quinolones
Pneumococci	Penicillin, cephalosporins, macrolides
Meningococci	Penicillins
Gonococci	Penicillins, tetracycline, quinolones
<i>H. pylori</i>	Nitroimidazoles
Cholera	Tetracycline, cotrimoxazole, quinolones (still rare)
Mycobacteria	INH, rifampicin, other antimycobacterials, multiresistance, and extreme resistance
<i>Mycobacterium leprae</i>	Dapsone
Plasmodia	Chloroquine, sulfa/pyrimethamine, mefloquine, quinine, atovaquone, multiresistance
Leishmania	Antimony drugs, especially in India and Sudan
Trypanosomes	Pentamidine, suramin, melarsoprol (especially east Africa)
Schistosomes	Praziquantel (Senegal, Egypt)
Fungi	Azol derivatives, flucytosine, amphotericin B (still rare)
HIV	All antiretrovirals
HSV	Acyclovir
CMV	Ganciclovir and others
HBV	Lamivudine, adefovir, vaccine escape mutants

^aExtended-spectrum beta-lactamases

Today, we have to realize that as we develop antimicrobial drugs, microbes will develop strategies of counterattack. Antimicrobial resistance occurs at an alarming rate among all classes of pathogens. Even in rich countries it causes real clinical

problems in managing infections that were easily treatable just a few years ago. In life-threatening infections such as sepsis, nosocomial infections, or falciparum malaria, there is a substantial risk that the initial chemotherapy might not be effective. In addition, the delay caused by inadequate treatment might favor transmission to other people and support the spread of resistant pathogens (e.g., multiresistant TB). Last but not the least, surveillance and control and the necessity to use expensive second-line drugs or combinations of antimicrobials are enormous cost factors. For developing countries this is a major limitation in the treatment and control of infections caused by resistant agents. So, in many ways, emerging resistance contributes to the emergence of infectious diseases.

3.8 Outlook

Despite the availability of effective strategies for treatment and prevention, infectious diseases have remained a major cause of morbidity and mortality worldwide. However, the problems associated with infections are due to considerable changes.

In industrialized countries the mortality caused by infectious diseases has decreased tremendously during more than 100 years. However, during recent years, both mortality and morbidity associated with infections are increasing again. Ironically, this is closely associated with the advances in medicine which have contributed to profound changes in the spectrum of both patients and their infections. Advanced age, underlying conditions, and an altered immune response are common features in the seriously infected hospital patient today. Immunosuppressive therapy is frequently used to treat neoplastic and inflammatory diseases or to prevent the rejection of transplants. Some infections, most notably HIV/AIDS, cause immunosuppression by itself. In the compromised patient, infections are generally more severe or may be caused by opportunistic pathogens that will not harm the immunocompetent host. Antimicrobial treatment is often less effective in these patients and tends to be further complicated by antimicrobial resistance which may manifest itself or develop at a higher frequency in the immunocompromised patient. An increasing percentage of infections are hospital acquired or otherwise health care associated. It is estimated that nosocomial infections affect 1.7 million patients and contribute to approximately 100,000 deaths in US hospitals annually (Klevens et al. 2007). Considering the rising number of elderly and immunocompromised patients, a further increase in severe infections can be predicted.

In developing countries, the significance of infectious diseases has remained high for ages and despite the advances in medicine. Until now, infections are by far the leading cause of both disability-adjusted life years and life years lost. The reasons are obvious and mostly related to poverty and lack of development causing poor and unhealthy living conditions, inadequate health systems, and lack of resources for prevention and treatment. This is, of course, just an integral part of the general socioeconomic problems of developing countries. However, poor health conditions per se are an important obstacle to development, and infections such as HIV/AIDS in

sub-Saharan Africa can be a major cause of lack of development, increasing poverty, and political instability.

Generally, the situation of many developing countries has not improved during the last two decades, and the gap between the first and the third world has increased. However, most of the mortality and morbidity associated with infectious diseases is avoidable. As laid down in the millennium goals, a major task of the world community will be to counteract the imbalance between the industrialized and the developing countries and to find strategies to ensure participation in the progress of modern medicine for all.

Developing countries also carry the main burden of diseases caused by newly emerging and re-emerging infections (Table 3.2 and 3.3). However, the consequences of economical and political crises on emerging infectious diseases are obvious in industrialized countries also—such as the return of diphtheria or the increase in TB and multiresistant TB after the breakdown of the former Soviet Union.

Today, all countries worldwide are affected by emerging infections as well as by emerging antimicrobial resistance. In the age of globalization, travel and transport of people, animals, and goods of all kinds have increased tremendously. As a consequence, infectious agents may travel over long distances and at high speed. This is clearly evident with influenza pandemics or outbreaks such as the SARS epidemic or with imported cases of viral hemorrhagic fever transmissible from person to person. The spread of antimicrobial resistance or the re-emergence of TB seems to be less spectacular, but the consequences may be at least as important in the long run.

Management and control of emerging and re-emerging infectious diseases can be very different from disease to disease and has to allow for all relevant factors of the populations at risk and of the specific disease including the ecology of the agent, its vectors, and reservoirs. However, some basic principles apply to all situations:

- Surveillance
- Information and communication
- Preemptive planning and preparedness
- Provision and implementation of
 - adequate treatment
 - adequate control and prevention
- international cooperation

Active and passive surveillance systems with rapid reporting and analysis of data are essential for the early detection of outbreaks, changes in epidemiology, and other events of public health concern (see Chapters 8 and 9). However, many resource-poor countries do not have functional surveillance systems.

In addition, reporting of infectious diseases may be neglected or delayed because of fears of stigma, international sanctions including trade and travel restrictions, or interference with tourism. Classical examples are plague and cholera, but also recent examples such as the BSE/vCJD crisis in the United Kingdom or SARS originating from China showed undue delays between first occurrence of cases and information to the public. Although, in outbreaks of new and unknown diseases it may be difficult, or even impossible, to predict or assess the magnitude of the problem and the potential consequences, timely and adequate information and communication is not only obligatory, according to international regulations, but also the best strategy to avoid rumors, misbeliefs, panic, or disregard.

In recent years, many countries have installed national plans of action for important epidemiological scenarios and outbreaks such as pandemic influenza, bioterrorism, import of viral hemorrhagic fevers transmissible from person to person, SARS, and comparable diseases or outbreaks. All member states of the World Health Assembly that have so far not been able to install functional surveillance and/or pre-emptive planning are obliged to do so within a maximum of 5 years after their ratification of the new International Health Regulations (WHO 2005).

Preparedness not only means surveillance and planning but also has to include the provision of facilities to adequately treat and, if necessary, to isolate patients with infectious diseases of public health importance and relevant epidemic potential and/or at risk of transmission to other persons including health-care workers. Task forces and high containment facilities for both laboratory diagnostic services and treatment of patients using barrier nursing have been set up in several countries. However, all health facilities of a certain level such as general hospitals should be prepared by their organization and structure to treat patients with infections of public health relevance such as multiresistant TB under appropriate isolation and barrier nursing conditions. This also applies to hospitals in resource-poor countries. Adequate training of health-care workers and strict management have been effective to control outbreaks of highly contagious infections within rural African hospitals lacking sophisticated technical equipments (CDC 1998).

Strategies for control and prevention may be quite different for various emerging infections. Effective vaccinations are available only for some infections and are usually lacking for newly emerging infections (Table 3.5). For the majority of emerging infections, control and prevention have to rely on information, education and exposure prophylaxis, interruption of transmission by vector control and control of reservoir hosts (e.g., rodents), and case finding with early diagnosis and treatment.

For diseases and outbreaks caused by infections of public health relevance that are transmissible from person to person, containment procedures including isolation and treatment of patients under condition of barrier nursing as well as tracking and surveillance of contacts are warranted by national and international health regulations. Here, international cooperation is essential to successfully contain outbreaks and epidemics such as the SARS epidemic in 2003.

Table 3.5 Availability and development of vaccines for emerging infectious diseases

Agent/disease	Available	Under clinical development	Remarks
<i>B. burgdorferi</i>	+		Withdrawn from the market
Chikungunya fever		+	
Cholera, <i>V. cholerae</i> 0139	+ ¹		Oral rCTB ² vaccine, protects against O1 and O139
Dengue fever		+	Quadrivalent vaccines
Filoviruses (Marburg/Ebola)		+	Phase I trials started recently
Hantavirus		+	Hantaan and Seoul virus vaccines
<i>H. pylori</i>		+	
Hepatitis C virus		+	
Hepatitis E virus		+	
HIV/AIDS		+	
Human papillomavirus	+		Two products (type 6/11/16/18; type 16/18)
New Influenza H1N1	+	+	
Influenza virus H5N1	+	+	
Japanese encephalitis	+	+	New cell culture vaccine
Lassa fever			
Leishmaniasis			
Malaria		+	
Plague ¹	+	+	Limited availability, new vaccines in clinical trials
Rift Valley fever	+		Veterinary vaccine in use, limited availability of human vaccine
Ross River fever		+	
Rabies	+		Plus rabies immunoglobulin for PEP
SARS coronavirus			
Sleeping sickness			
Tuberculosis	+ ¹	+	New vaccines in clinical trial
West Nile virus		+	
Yellow fever	+		

¹Partially effective²Recombinant cholera toxin subunit B

3.9 Summary

Despite dramatic progress in their treatment and prevention, infectious diseases are still of enormous global significance with tremendous economic and political implications. Emerging and re-emerging infectious diseases as well as emerging antimicrobial resistance are major challenges to all countries worldwide. For the management of current and future problems, it will be most important to counteract the imbalance between the industrialized world, new economies, and developing countries, and to adequately and timely react to new threats on a global scale.

References

- Boshart M, Gissmann L, Ikenberg H, Kleinheinz A, Scheurelen W, zur Hausen H (1984) A new type of papillomavirus DNA, its presence in genital cancer and in cell lines derived from genital cancer. *EMBO J* 3: 1151–1157
- Centers for Disease Control (2008) West Nile virus. <http://www.cdc.gov/ncidod/dvbid/westnile/html>.
- Centers for Disease Control (2007) Case information: hantavirus pulmonary syndrome case count and descriptive statistics. <http://cdc.gov/ncidod/diseases/hanta/hps/>
- Centers for Disease Control (2006) Norovirus: technical fact sheet. <http://www.cdc.gov/ncidod/dvrd/revb/gastro/norovirus-factsheet.htm>
- Centers for Disease Control and Prevention. (1998) World Health Organization: Infection Control for Viral Haemorrhagic Fevers in the African Health Care Setting. Centers for Disease Control and Prevention, Atlanta
- Chua KB, Bellini WJ, Rota PA et al. (2000) Nipah virus: a recently emergent deadly paramyxovirus. *Science* 288: 1432–1435
- Correa P, Fox J, Fontham E (1990) Helicobacter and gastric carcinoma. Serum antibody prevalence in populations with contrasting cancer risks. *Cancer* 66: 2569–2574
- Danielova V et al. (2004) Effects of climate change on the incidence of tick-borne encephalitis in the Czech Republic in the past two decades. *Epidemiol Mikrobiol Imunol* 53 (4): 174–181
- Dondrop AM, Nosten F, Yi P, et al. (2009). Artemisinin resistance in Plasmodium falciparum malaria. *N Engl J Med* 361: 455–467
- Drosten C, Günther S, Preiser W, van der Werf S, et al. (2003) Identification of a novel coronavirus in patients with severe acute respiratory syndrome. *N Engl J Med* 348: 1967–1976
- Dürst M, Gissmann L, Ikenberg H, zur Hausen H (1983) A papillomavirus DANN from a cervical carcinoma and its prevalence in cancer biopsy samples from different geographic regions. *Proc Nat Acad Sci US* 80: 3812–3815
- European Antimicrobial Resistance Surveillance System (2006). Susceptibility results for *E. faecium* isolates. Available at: <http://www.rivm.nl/earss/database/>
- Harit AK, Ichhupujani SG, Gill KS, Shiv Lal, Ganguly NK, Agarwal SP (2006) *Indian J Med Res* 123: 553–560
- Hassler D, Zoller L, Haude M, Hufnagel HD, Sonntag HG (1992) Lyme-Borreliose in einem europäischen Endemiegebiet: Antikörperprävalenz und klinisches Spektrum. *Dtsch Med Wochenschr* 117: 767–774
- Hofmann J, Meisel H, Klempa B, Vesenbeck SM, Beck R, Michel D, et al. (2008) Hantavirus outbreak, Germany 2007. *Emerg Infect Dis* 14: 850–852
- Jones KE, Patel NG, Levy MA, Storeygard A, Balk D, Gittleman JL, Daszak P (2008) Global trends in emerging infectious diseases. *Nature* 451: 990–993
- Kamar N, Selves J, Mansuy JM, et al. (2008) Hepatitis E virus and chronic hepatitis in organ-transplant recipients. *N Engl J Med* 358: 811–817
- Klevens RM, Jonathan JR, Edwards JR, Richards CL et al. (2007) Estimating Health Care-Associated Infections and Deaths in U.S. Hospitals, 2002. *Public Health Report* 122: 160–166
- Lam SK, Chua KB (2002) Nipah virus encephalitis outbreak in Malaysia. *Clin Infect Dis* 34 (Suppl 2): S48–51
- Lindgren E, Jaenson TGT (2006) Lyme borreliosis in Europe: influences of climate and climate change, epidemiology, ecology and adaptation measures. WHO Regional Office for Europe, Copenhagen
- Materna J, Daniel M, Danielova V (2005) Altitudinal distribution limit of the tick Ixodes ricinus shifted considerably towards higher altitudes in central Europe: results of three years monitoring in the Krkonose Mts. (Czech Republic). *Cent Eur J Public Health* 13 (1): 24–28
- Mégraud F (1993) Epidemiology of Helicobacter pylori infection. *Gastroenterol Clin North Am* 22: 73–88

- Mostashari F, Bunning ML, Kitsutani PT, Singer A (2001) Epidemic West Nile encephalitis, New York, 1999: results of a household-based seroepidemiological survey. *Lancet* 358: 261–264
- Nash D, Mostashari F, Fine A, et al. (2001) Outbreak of West Nile virus infection, New York City area, 1999. *N Engl J Med* 14: 1858–1859
- Organisation Mondiale de la Santé Animale (OIE) (2008). http://www.oie.int/eng/info/en_esbincidence.htm
- Parola P, de Lamballerie X, Jourdan J, Rovey C, Vaillant V, Minodier P, Brouqui P, Flahault A, Raoult D, Charrel RN (2006) Novel chikungunya virus variant in travelers returning from Indian Ocean islands. *Emerg Infect Dis* 12: 1493–1499
- Reyes GR, Purdy MA, Kim JP, Luk KC, Young LM, Fry KE, Bradley DW (1990) Isolation of a cDNA from the virus responsible for enterically transmitted non-A, non-B hepatitis. *Science* 247: 1335
- Rezza G, Nicoletti L, Angelini R, Romi R, Finarelli AC, Panning M et al. (2007) Infection with Chikungunya virus in Italy: an outbreak in a temperate region. *Lancet* 370 (9602): 1840–1846
- Robert Koch Institute (2001a). Waldarbeiter-Studie Berlin-Brandenburg 2000 zu zeckenübertragenden und andere Zoonosen. *Epidem Bulletin* 16: 109–110
- Robert Koch Institute (2001b). Risikofaktoren für Lyme-Borreliose: Ergebnisse einer Studie in einem Brandenburger Landkreis. *Epidem Bulletin* 21: 147–149
- Robert Koch Institute (2008a) Norovirus-Winterepidemie 2007/2008 übertrifft die Infektionszahlen der Vorjahre. *Epidem Bulletin* 6: 44–49
- Robert Koch Institute (2008b) Zahl der Hantavirus-Erkrankungen erreichte 2007 in Deutschland einen neuen Höchststand. *Epidem Bull* 19: 147–152
- Rothenbacher D, Bode G, Berg G et al. (1989) Prevalence and determinants of *Helicobacter pylori* infection in preschool children: a population-based study from Germany. *Int J Epidemiol* 27: 135–141
- Schmaljohn C, Hjelle B (1997) Hantaviruses: a global disease problem. *Emerg Inf Dis* 3(2): 95–104
- Shrestha MP, Scott RM, Joshi DM et al. (2007) Safety and efficacy of a recombinant hepatitis E vaccine. *N Engl J Med* 356: 895
- Spach DH, Liles WC, Campbell GL, Quick RE, Anderson DE Jr, Fritsche TR. (1993) Tick-borne diseases in the United States. *N Engl J Med* 329:936–947
- The National Creutzfeld-Jakob Disease Surveillance Unit (NCJDSU) (2008). <http://www.cjd.ed.ac.uk/>
- Towner JS, Pourrut X, Albariño CG et al. (2007) Marburg virus infection detected in a common African bat. *PLoS ONE* 2: e764
- Vandenesch F, Naimi T, Enright M, Lina G, Nimmo G, Heffernan H, Liassine N, Bes M, Greenland T, Reverdy M, Etienne J (2003). Community-acquired methicillin-resistant *Staphylococcus aureus* carrying Panton-Valentine leukocidin genes: worldwide emergence. *Emerg Infect Dis* 9: 978–984
- Verhoef L, Boxman I, Duizer E, Rutjes SA, Vennema H, Friesema IHM et al. (2008) Multiple exposures during a norovirus outbreak on a river-cruise sailing through Europe, 2006. *Eurosurveillance* 13(4–6): 1–6
- Warny M, Pepin J, Fang A, Killgore G, Thompson A, Brazier J, Frost E, McDonald LC (2005) Toxin production by an emerging strain of *Clostridium difficile* associated with outbreaks of severe disease in North America and Europe. *Lancet* 366: 1079–1084
- Weiland T, Kuhn P, Laufs R, Heesemann J (1992) Prevalence of *Borrelia burgdorferi* antibodies in Hamburg blood donors. *Beitr Infusionsther* 30: 92–95
- Who (2008) Variant Creutzfeld-Jakob disease. <http://www.who.int/mediacentre/factsheets/fs180/en/>
- WHO (2004a) Nipah virus outbreaks in Bangladesh. January–April 2004. *Wkly Epidemiol Rec* 23: 168–171
- WHO (2004b) Severe Acute Respiratory Syndrome (SARS). [Http://www.who.int/csr/sars/en](http://www.who.int/csr/sars/en)
- WHO (2005) Revision of the International Health regulations. www.who.int/csr/ihr

- Wisplinghoff H, Bischoff T, Tallent SM, et al. (2004) Nosocomial bloodstream infections in US hospitals: analysis of 24 179 cases from a prospective nationwide surveillance study, *Clin Infect Dis* 39: pp. 309–317
- Wit de M, Widdowson M, Vennema H, de Bruin E, Fernandes T, Koopmans M (2003) Large outbreak of norovirus: The baker who should have known better. *J Infect* 55(2): 188–193
- Wongsichranalai C, Pickard AL, Wernsdorfer WH, Meshnick SR (2002) Epidemiology of drug-resistant malaria. *Lancet Inf Dis* 2: 209–218
- Yob JM, Field H, Rashdi AM, Morrissy C, van der Heide B, Rota P, et al. (2001) Nipah virus infection in bats (order Chiroptera) in peninsular Malaysia. *Emerg Infect Dis* 7: 439–441