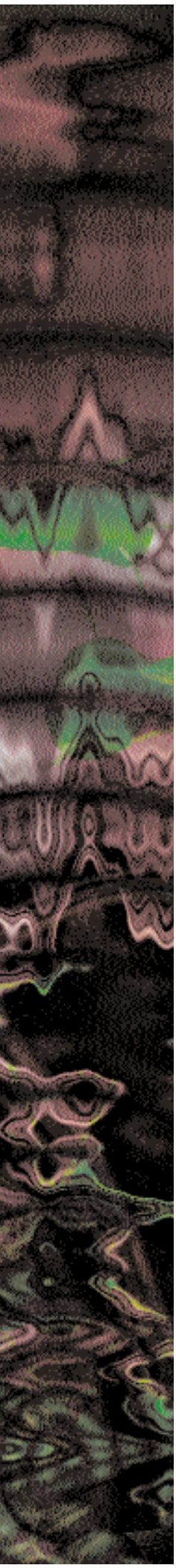

Changing patterns of infectious disease

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Despite a century of often successful prevention and control efforts, infectious diseases remain an important global problem in public health, causing over 13 million deaths each year. Changes in society, technology and the microorganisms themselves are contributing to the emergence of new diseases, the re-emergence of diseases once controlled, and to the development of antimicrobial resistance. Two areas of special concern in the twenty-first century are food-borne disease and antimicrobial resistance. The effective control of infectious diseases in the new millennium will require effective public health infrastructures that will rapidly recognize and respond to them and will prevent emerging problems.

For most of the twentieth century, the predominant feeling about the treatment, control and prevention of infectious diseases was optimism. In 1931, Henry Sigerist wrote[1], 'Most of the infectious diseases … have now yielded up their secrets…. Many illnesses … had been completely exterminated; others had [been brought] largely under control….' Between 1940 and 1960, the development and successes of antibiotics and immunizations added to this optimism, and in 1969, Surgeon General William H. Stewart[2] told the United States Congress that it was time to 'close the book on infectious diseases'. With victory declared, increasing emphasis was directed at the non-infectious diseases such as cancer and heart disease. Often, research on infectious disease or activities on their prevention and control were de-emphasized and resources were reduced or eliminated. As recently as the 1980s, pharmaceutical companies, believing that there were already enough antibiotics, began reducing the development of new drugs or redirecting it away from antibiotics[3,4]. In much of the developed world, the public had forgotten the impact of infectious diseases on previous generations and shared in the confidence that modern medicine and technology would prevail.

This optimism was soon shaken by a series of outbreaks and epidemics of new, re-emerging and antimicrobial-resistant infections. Legionnaire's disease, Ebola virus, HIV, 'flesh-eating' bacteria and 'mad cow disease' (bovine spongiform encephalopathy) were among the topics that began to appear in both scientific journals and the popular press. These diseases, occurring both in the developing and developed worlds, indicated that much was still unknown about infectious diseases. At the beginning of the twenty-first century, infectious diseases were once again capturing the attention of public health workers, academics, government and the general public. Here I will review how infectious diseases changed during the twentieth century, why infectious diseases have been emerging, and what will be necessary to address this important public health problem in the twenty-first century.

Infectious diseases in the twentieth century

At the beginning of the twentieth century, infectious diseases were the leading cause of death worldwide. In the United States, three diseases — tuberculosis, pneumonia, and diarrhoeal disease — caused 30% of deaths[5] (Fig. 1a). The average life expectancy was 47, in large part because of the high infant and childhood mortality from infection. A child born in 1900 had almost a 10% chance of dying between the ages of one and four, often from pneumonia or diarrhoeal disease[6]. In the autobiography of his depression-era childhood, *Angela's Ashes,* Frank McCourt described the devastation of losing three of six siblings to infections and almost dying of typhoid fever himself. This experience was not unusual for much of the world.

Surprisingly, by 1900, morbidity and mortality from infectious diseases had already considerably improved in much of the developed world. Between 1700 and 1900, the average life expectancy in Britain had increased from 17 to 52 years[7], and the death rate from tuberculosis had fallen by 80% (ref. 8). The improvement in life span and decreases in mortality from infectious disease were attributed to a series of factors that were decreasing host susceptibility and curtailing disease transmission: better nutrition and housing, safer food and water, and improved hygiene and sanitation (Fig. 2).

Although deaths from many infectious diseases were already declining, the introduction of antimicrobial agents in the mid-twentieth century accelerated these declines even further. In England and Wales, deaths from childbed fever, caused by *Streptococcus pyogenes*, fell by more than 50% after the introduction of sulphadiazine[9]. In the United States, deaths from infectious disease declined at an annual rate of 8.2% between 1938 and 1952; the most prominent decreases were in tuberculosis and pneumonia[10]. These decreases coincided with the beginning of the era of antibiotics. The influence of immunization was also striking: in 1952, 57,879 cases of paralytic poliomyelitis were reported in the United States; by 1965, there were 72 (ref. 11). The eradication of smallpox in 1977, also a triumph of immunization, was one of the greatest accomplishments of public health. Between 1900 and 1980, mortality from infectious disease fell from 797 to 36 per 100,000 (ref. 10). By the end of the twentieth century, in most of the developed world, mortality from infectious diseases had been replaced by mortality from chronic illnesses such as heart disease, cancer and stroke (Fig. 1b). In 1997 these three conditions caused 62% of all deaths in

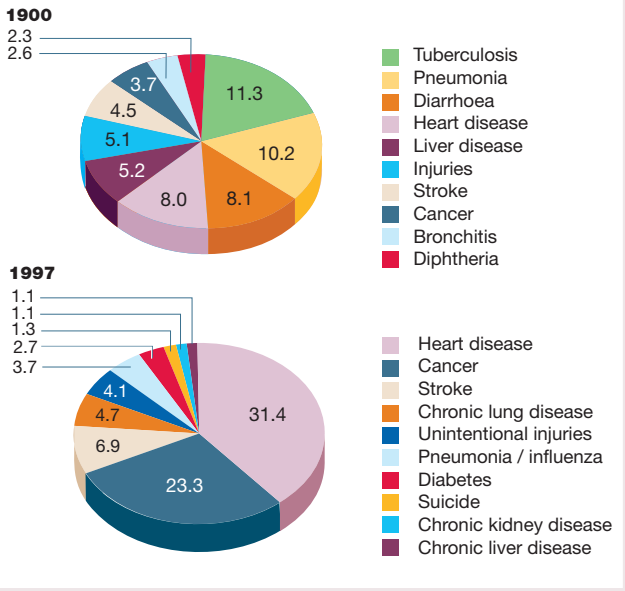

Figure 1 The ten leading causes of death in the United States in 1900 and 1997. Infectious diseases that were the most important causes of death at the beginning of the twentieth century have been replaced by chronic diseases.

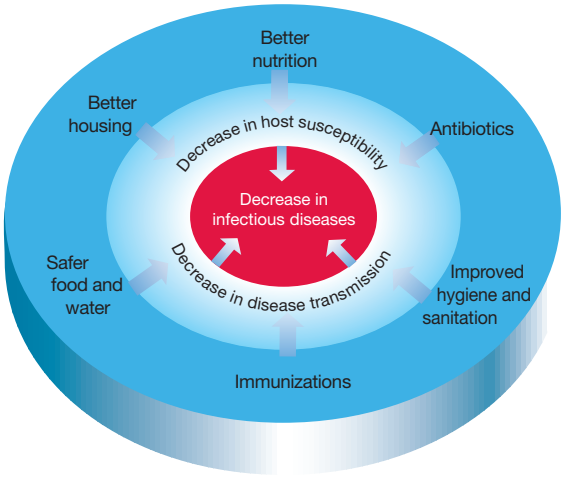

Figure 2 Factors influencing the decrease in infectious diseases in the twentieth century. Most factors led to decreases in host susceptibility and/or disease transmission.

the United States. Between 1900 and 1997, the average life span had increased by about 60% to more than 76 years[12].

The developing world had not had the same success with infectious diseases: there they remained the major cause of morbidity and mortality. In 1998, the World Health Organization estimated that infectious diseases caused over 13 million deaths — almost a quarter of the 54 million deaths worldwide[13]. Among the most common causes of mortality were the three diseases that had been so common in the developed world at the beginning of the twentieth century: pneumonia (3.5 million), diarrhoeal disease (2.2 million) and tuberculosis (1.5 million). Other important infectious causes of death were AIDS (2.3 million), malaria (~1.1 million) and measles (1.0 million). Many of these deaths, particularly from pneumonia and diarrhoeal disease, occurred in small children. The societal and technological advances that had influenced infectious diseases in the developed world had less of an effect in the developing world.

At the end of the twentieth century there were worrying trends in both the developed and the developing worlds. New infectious diseases and microorganisms were being recognized: Legionnaire's disease, toxic shock syndrome, Lyme disease, HIV, Nipah virus, hantavirus, *Escherichia coli* O157:H7, 'flesh-eating' bacteria, and many others. Infectious diseases were also being recognized as the cause of chronic illnesses; *Helicobacter pylori*, for instance, is now known to be the cause of peptic ulcers. New infectious agents, such as Ebola or Marburg virus, had the potential for rapid international spread. Diseases such as cholera, tuberculosis, dengue fever, yellow fever and malaria, which had once been controlled in many parts of the world, were re-emerging. Resistance to antimicrobial agents was becoming a serious global problem. Even in the developed world, infectious disease mortality was increasing. In the United States from 1981 to 1995, this increase was at a rate of 4.8% per year from 36 to 63 deaths per 100,000 (ref. 10).

In 1992, the Institute of Medicine (IOM), recognizing these trends, published a report[14] entitled *Emerging Infections: Microbial Threats to Health in the United States*. This report defined an emerging infection as a "new, reemerging, or drug-resistant infection whose incidence has increased in the last two decades, or whose incidence threatens to increase". The report examined this emergence, identified factors that were influencing it, and suggested approaches to addressing the problem.

Factors influencing emergence

The IOM report identified six factors (Fig. 3) as influencing the emergence of infectious diseases. Many of these factors increase the susceptibility of populations to infectious diseases or increase the exposure to or transmission of infectious agents. Emergence is often the consequence of societal and technological change and is frequently unexpected and unpredictable. In most instances the emergence of a specific agent results from a complex interaction of several factors that can vary even by geographic area. For example, vancomycin-resistant enterococci (VRE) emerged in hospitals in the United States because of antibiotic use combined with inadequate infection control practices and simultaneous increases in the number of susceptible persons in intensive-care units. In Europe, the emergence of VRE might have also been influenced by the agricultural uses of avoparcin, a glycopeptide antibiotic used in Europe as an animal growth promoter. Ironically, some factors that have resulted in a decline in one disease can contribute to an increase in another. The development of refrigeration, for instance, made food safer by inhibiting the growth of most food-borne pathogens, but it provided an advantage to organisms such as *Listeria* or *Yersinia* that can grow in the cold.

The recurring theme throughout all of these factors that influence the emergence of infectious diseases is change. During the twentieth century, tremendous societal and technological changes occurred, and these are likely to continue or accelerate in the twenty-first century. It is useful to examine how these changes have influenced infectious disease emergence so that we can anticipate some of the challenges of the new century.

Changes in demographics and behaviour

Demographic changes fall into several broad areas: changes in population, such as the increasing prevalence of persons with susceptibility to infection; societal changes, such as increases in two-income or single-parent families (which in turn lead to a greater use of day care for children and subsequently to an increase in disease transmission); and movements of infected or high-risk populations

by immigration. Changes in behaviour include various factors from increases in recognized risky behaviours, such as unsafe sex or the use of alcohol or drugs, to risks that are often unrecognized, such as recreational activities, exposures to new geographic areas and patterns of use of antimicrobial agents.

One of most important demographic factors influencing the emergence of infectious diseases has been the increase in susceptible populations. Ageing of the population, increases in underlying diseases, and technological advances in health care have all contributed. At the beginning of the twentieth century, for instance, less than 5% of the US population was over 65; by 2040 it is estimated that more than 25% will be that age or older[15]. Ageing contributes to susceptibility to many bacterial diseases, even in the absence of other underlying conditions. Thus, with an ageing population, there are more persons that are susceptible to certain diseases and a larger group that might sustain transmission. Similar increases are occurring in the number of persons with underlying diseases or conditions that contribute to susceptibility. Malnutrition contributes to susceptibility to infectious diseases in many parts of the developing world. The HIV epidemic in Africa has produced an enormous population of susceptible persons[16]. Other diseases such as diabetes, autoimmune diseases, malignancies and renal failure can also suppress host defences and increase the likelihood of infection. The prevalence of many of these chronic conditions is increasing, in part because the life span of patients can now be prolonged. Between 1935 and 1995 the prevalence of diabetes in the US population increased from 0.5% to 3% (ref. 17). This is directly related to causative factors such as obesity but also to improvements in medical technology, including the availability of insulin. It is estimated that, including undiagnosed cases, there could be more than 16 million persons with diabetes in the United States.

Medical technology is also increasing the survival of persons with other conditions that might render them susceptible to infection. Between 1960 and 1980, effective chemotherapy increased the five-year survival for persons with Hodgkin's disease from 40% to 76% (ref. 18). Persons with malignancies are often at risk of infections during chemotherapy, but some might have lifelong susceptibility to certain infections even after the successful treatment of their malignancy. Improvements in the technology of intensive care units (ICUs) and of organ transplantation have increased their use but have also caused the numbers of susceptible persons to increase and have provided opportunities for the emergence of new diseases. The increase in ICU patients has contributed to both the emergence of antimicrobial resistance and a greater incidence of fungal diseases. Debilitated patients, multiple courses of powerful antimicrobial drugs, long periods in hospital and often inadequate practices for controlling infection are factors in the emergence of methicillin-resistant staphylococci, VRE and a variety of multidrug-resistant Gram-negative rods. Some of the same factors have contributed to the emergence of fungal diseases, such as disseminated *Candida* infections, which in the 1980s increased 11-fold in hospital patients in the United States[19]. Organ transplantation has created one of the most susceptible populations and consequently has brought about increases in infections with *Listeria*, mycobacteria, viral agents and moulds[20]. Some of the moulds, such as *Aspergillus* spp. and fungi with low pathogenicity, were uncommon or previously unrecognized as causes of human disease.

Human behaviour has provided more opportunities for exposure to and transmission of new and re-emerging infection and have increased selective pressure for antimicrobial resistance. Sexual activity is an important behavioural risk factor that has contributed to emergence. The rapid spread of HIV in heterosexual populations in parts of Africa was facilitated by social and economic factors that encouraged multiple sexual partners[16]. In the western world, the sexual revolution that began in the 1960s was associated with increases in sexually transmitted diseases. The appropriate and inappropriate use of antimicrobial drugs to treat or prevent the increasing number

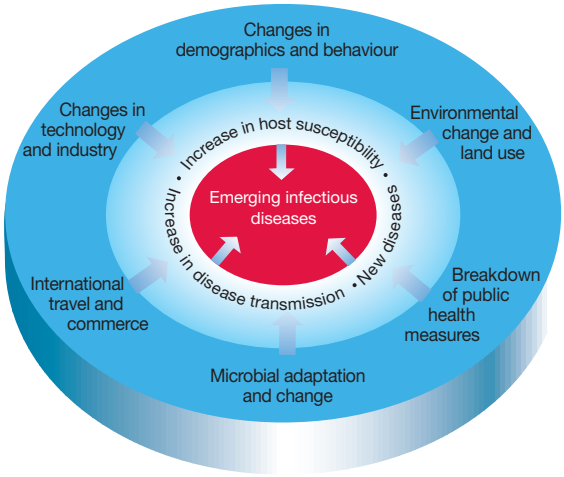

Figure 3 Factors leading to the emergence of infectious diseases. Changes in society, technology, environment and microorganisms are leading to increases in host susceptibility and/or disease transmission and the evolution of new or drug-resistant microorganisms.

of sexually transmitted infections contributed to the emergence of drug resistance in gonorrhoea and chancroid. Other behaviours are also risk factors for emergence. Smoking has been associated with pneumococcal disease[21]. Intravenous drug use has been associated with sexually transmitted diseases, including HIV[22]. Changing eating habits are exposing people to new foods with unfamiliar risks, to foods eaten without further preparation or to foods prepared outside the home. Thus, the increase in spending on food prepared or consumed outside the home between 1970 and 1990 parallels the increase in the percentage of food-borne outbreaks occurring outside the home[23]. Recreational activities or moves to new geographic areas can also pose new risks. Spelunking (potholing) has been associated with outbreaks of histoplasmosis; another mycosis, coccidioidomycosis, has increased in part because previously unexposed persons moved or retired to areas in the southwestern United States where the fungus is endemic[24].

One of the strongest influences on the emergence of resistance has been the unnecessary use of antimicrobial agents. In many parts of the world, antibiotics are available over the counter. Even in countries in which use is more controlled, their use is often unnecessary[25]. Many of the antimicrobial drugs prescribed to outpatients are for the treatment of upper-respiratory infections. Because most of these infections are viral, the antimicrobial agents are ineffective and unnecessary. In 1992, 18% of the 110 million courses of outpatient antibiotics prescribed in the United States were for upper-respiratory infections, providing strong selective pressure for the emergence of resistance in bacterial pathogens such as *Streptococcus pneumoniae*[26].

Changes in technology and industry

The twentieth century witnessed a number of technological advances that improved life and health and often transformed industry. However, some of these technologies were unexpectedly associated with the emergence of disease. Air-conditioning cooling towers were linked to Legionnaire's disease, super-absorbent tampons to toxic shock syndrome, and the fast-food hamburger to *E. coli* O157:H7. In the food industry especially, tremendous changes have occurred in how food is produced, preserved and processed. Antimicrobial agents used for promoting growth and preventing and treating disease in animals have facilitated large-scale, lower-cost production

but have contributed to the emergence of drug resistance in *Salmonella* and *Campylobacter* that are transmitted through the food chain to humans. Changes in rendering and in the feeding of rendered materials to food animals contributed to the emergence of 'mad cow disease'. There has been an increased emphasis on foods with a longer shelf life or more natural foods preserved only by refrigeration. This latter phenomenon has provided conditions favourable to *Listeria*, an organism that grows at refrigeration temperatures. The food industry has changed drastically, with consolidations and mergers leading to a broad geographic distribution of products. Thus, the typical food-borne outbreak vehicle that was once the home-made potato salad at the local church supper has now become any one of a number of commercial products distributed in multiple states or countries[27].

Environmental change and land use

Changes in environment and in land use are global activities that include both natural and man-made changes. In the developing world, these include the encroachment on the tropical rain forest, which poses a risk for the emergence of new haemorrhagic fever viruses. They also include the impact of growing megapolises often with inadequate hygiene and sanitation. As pointed out by Laurie Garrett, author of *The Coming Plague*[28], these cities are time bombs for the emergence and transmission of infectious diseases. The spread of cholera in Latin America during the 1990s was facilitated by such conditions. In the developed world, agricultural practices have contributed to blooms of pfiesteria and toxic algae. Conservation efforts, such as preserving deer populations, have led to the spread of Lyme disease. Climate change, whether natural or man-made, is also contributing to the emergence of infectious diseases. In 1993, in the southwestern United States, increased rainfall led to increased vegetation, larger rodent populations, more rodent–human contact and the first recognized outbreak of hantavirus in North America[29]. Similarly, in 1997 higher water temperatures in the Pacific Northwest, caused by El Niño, provided unusual conditions that were favourable for the growth of *Vibrio parahaemolyticus* and resulted in shellfish-associated outbreaks of disease[30].

International travel and commerce

One of the most impressive changes of the twentieth century has been in the ease of international travel. Travel that once required months has been reduced to hours, converting the world into a global village. Such travel facilitates the global transmission of diseases spread by person-to-person contact such as shigellosis or gonorrhoea. Respiratory infections, too, can spread more rapidly, as demonstrated by the outbreaks of influenza associated with Alaskan cruises[31]. The recent outbreak of a vector-borne agent, West Nile virus, in the northeastern United States could have been caused by the introduction of an infected bird or person[32]. Specific strains of drug-resistant *Strep. pneumoniae* or *Neisseria gonorrhoeae* have been traced between continents, suggesting that they were transmitted by human travel. Diseases that would normally have a limited geographic distribution have become part of the differential diagnosis of the unwell traveller. The febrile emergency-room patient in the local hospital can easily be a refugee or an immigrant or even a tourist returning from Africa with malaria or schistosomiasis. As with infected travellers, contaminated food can also move rapidly from continent to continent. International food-borne disease outbreaks have become more common and have introduced new pathogens to an area, such as the recent outbreaks in the United States of *Cyclospora* associated with imported raspberries[33].

Microbial adaptation and change

As society and technology change, so do microorganisms. In some instances, change is the result of selective pressures, such as the use of antimicrobial agents; at other times the cause of microbial change is less clear. A recent example of microbial evolution is the emergence of *E. coli* O157:H7. This bacterium is an important cause of food-borne disease, causing bloody diarrhoea and a potentially fatal illness called the haemolytic uraemic syndrome. It is likely that this organism emerged since 1950, after the acquisition of *Shigella* toxin genes by *E. coli* O55 (ref. 34). This genetic event resulted in a new pathogen that combined the low infectious dose and toxigenicity of *Shigella* with the resistance to adverse environmental conditions that is characteristic of *Salmonella*. This combination of characteristics, coupled with changes in the food industry, are probable explanations for this organism's success.

Breakdown of public health measures

Some infectious diseases have emerged or re-emerged because the public health systems established to prevent or control them have broken down. A variety of elements have contributed to this breakdown, including complacency from past successes against infectious diseases, limited resources and competing priorities in public health, social unrest, wars, and population movements. The global re-emergence of tuberculosis is a good example of several of these factors[35]. In the United States in the early 1980s, tuberculosis was targeted for elimination by the early twenty-first century. The decline in incidence had been consistent and resembled a straight line reaching zero in 2010. In some public health jurisdictions, tuberculosis was rare, and control programmes faced the competing priorities of HIV and chronic diseases. Tuberculosis treatment programmes to ensure compliance and decrease the emergence of drug resistance such as directly observed therapy (DOT) were curtailed. What was not realized was the impact of HIV or immigration on tuberculosis, which soon led to a re-emergence of the disease. In addition, because programmes such as DOT were no longer ensuring appropriate treatment, the cases of tuberculosis that re-emerged were often resistant to multiple antituberculosis drugs. A simultaneous emergence of tuberculosis has occurred in parts of the developing world that have been most affected by the HIV epidemic. In this instance, the often intrinsically high rates of tuberculosis infection, coupled with the immunosuppression of HIV, have resulted in substantial increases in active disease. In the countries of sub-Saharan Africa, annual rates of tuberculosis have increased by as much as 15% (ref. 36).

Emerging infections in the twenty-first century

As was pointed out by the historian George Santayana in *The Life of Reason*, "those who cannot remember the past are condemned to repeat it". The twentieth century was a microcosm of the history of infectious diseases. During one century, most of the developed world experienced vast improvements in health and in the prevention and control of infectious diseases at rates that dwarfed previous centuries. However, much of the improvement was limited in the developing world; both the developed and developing world experienced important health problems in the emergence of new and once-controlled infections. Societal and technological change accounted for both the control and the emergence of infectious diseases. It is likely that such change will continue into the twenty-first century and that the rate of change might accelerate. One lesson learned from history is that change leads to the continued emergence of infectious diseases, and we must be prepared to address this problem. We can never be too complacent about infectious diseases, or we will find ourselves in circumstances as threatening as the re-emergence of multidrug-resistant tuberculosis in the late 1980s or the influenza epidemic of 1918 in which 20–25 million persons perished worldwide[10].

It is likely that researchers in the twenty-first century will identify infectious agents as contributors to many chronic diseases. The infection itself might be symptomatic or asymptomatic. Viral agents, for instance, now are being recognized as causes or important cofactors in a number of cancers. *Chlamydia* or other infections might have a role in coronary heart disease. Ulcers have been linked to *H. pylori* infections. The haemolytic uraemic syndrome has been associated with *E. coli* O157:H7 infections. Guillan–Barré syndrome can follow

Campylobacter infections, and a variety of enteric infections can lead to reactive arthritis or Reiter's syndrome. With a better understanding of both pathogen and host response, the new technologies of the twenty-first century will lead to diagnostic tools that will clarify the role of microorganisms in many chronic diseases.

Two areas deserve particular attention as we begin the new century: food-borne diseases and resistance to antimicrobial agents.

Food-borne disease

Food-borne disease was recognized as a high priority by the IOM[14]: "The potential for foods to be involved in the emergence or re-emergence of microbial threats to health is high, in large part because there are many points at which food safety can be compromised."

At the beginning of the twentieth century there were many challenges to food safety, including diseased animals, unsafe food handling, inadequate food preservation, unsafe water and poor sanitation, and the consumption of raw foods such as milk and shellfish. Food-borne outbreaks of typhoid, scarlet fever, cholera, hepatitis, staphylococcal food poisoning and brucellosis were common. Poor nutrition also contributed to the general susceptibility to infection. The incidence of these food-borne diseases was soon reduced by a series of regulatory and technological changes, including food inspection, hygienic processing, refrigeration, safe canning, food additives and preservatives, and pasteurization. Nutrition was improved by the fortification of food with vitamins and minerals, and social programmes to feed the poor. However, although many of the classic food-borne diseases were on the wane, new diseases were emerging[23]. The technological and societal factors discussed above led to the emergence of non-typhoid salmonellosis, campylobacteriosis, listeriosis, and infections involving *E. coli* O157:H7, *Cyclospora*, calicivirus and *Vibrio vulnificus*. It has been estimated that food-borne illness accounts for 76 million illnesses, 325,000 periods in hospital and 5,000 deaths in the United States annually[37].

In earlier generations, the malnutrition from inadequate amounts or poor quality of food increased people's susceptibility to infections. It is ironic that for present generations, malnutrition from excessive amounts or types of food is increasing susceptibility to infectious diseases by contributing to heart disease, diabetes, hypertension and obesity. In addition to the increases in susceptible populations, as pointed out in the IOM report, there are many points at which the safety of food can be compromised. In the twenty-first century, international commerce and markets will continue to increase, new technologies will affect food production, processing and preservation, and the public will eat more ready-to-eat foods and more meals outside the home. We are increasingly dependent on others to ensure the safety of our food.

Resistance to antimicrobial agents

Antimicrobial resistance was also targeted by the IOM[14]: "Microbes that once were easily controlled by antimicrobial drugs are, more and more often, causing infections that no longer respond to treatment with these drugs". Antibiotics were one of the great discoveries of the twentieth century. However, the emergence of antimicrobial resistance was recognized soon after the discovery of penicillin and has followed the introduction of most every new drug. The problem has greatly escalated as we enter the twenty-first century[38] and a series of microbes that present serious challenges are listed in Table 1. A combination of increased selective pressure from the use of antimicrobials, increased disease transmission and a decline in the development of new antibiotics has raised the spectre of once-treatable infections becoming untreatable. In the hospital, one of the first serious problems was the emergence of VRE. Between 1989 and early 1999, the percentage of VRE isolated from patients in hospital in intensive-care units in the United States increased from 0.4% to 25.9% (ref. 39). Although the enterococcus is less virulent than many other hospital-acquired pathogens, VRE infections were essentially untreatable until the introduction of quinupristin/dalfopristin. A potentially more serious problem is emerging with *Staphylococcus aureus*. Strains already resistant to methicillin are becoming resistant to vancomycin, often the drug of last resort. Because in many hospitals more than 40% of *Staph. aureus* strains are resistant to methicillin, there are ample opportunities for the emergence of vancomycin-resistant strains[39]. At the beginning of the twenty-first century, at least five strains with intermediate resistance to vancomycin have been reported in the United States and Japan[40]. Other drug-resistant bacteria are also posing problems for hospitals. Various Gram-negative bacteria are becoming increasingly resistant to extended-spectrum cephalosporins, some of the newer and most powerful antimicrobial agents.

Resistance to antimicrobial drugs is not just a problem in the hospital environment. Communities have also experienced problems in both the developing and developed worlds. In the 1970s, drug-resistant *N. gonorrheae* and *Haemophilus influenzae* were recognized worldwide. Although other antimicrobial agents were available for those infections, parts of the developing world have experienced outbreaks of drug-resistant bacteria such as *Shigella dysenteriae* for which alternative antimicrobial therapy was often not available[41]. Drug resistance in the developed world has been increasing in food-borne pathogens such as salmonellae and *Campylobacter* and has been attributed to the use of antimicrobials in food animals. Between 1979 and 1994 the frequency of multiple drug resistance in *Salmonella* increased from 17% to 31% (ref. 42). Between 1991 and 1999, ciprofloxacin resistance in *Campylobacter* increased from 0% to 13.6% (ref. 43).

One of the most worrying problems for the community has been the emergence of drug-resistant *Strep. pneumoniae* (DRSP). This poses a serious problem for both the developed world and the developing world. In the developing world this bacterium is a major cause of pneumonia and death in both children and adults. In the United States it causes two million cases of pneumonia and seven million middle-ear infections. The frequency of penicillin resistance varies between hospitals and geographic areas, but between 1993 and 1997 it increased in the United States from 14% to 25% (ref. 44). The increase in antimicrobial resistance has led to the emergence of strains that are susceptible only to vancomycin and has already resulted in changes in the recommended empirical treatment of meningitis in children to include vancomycin. The emergence of antimicrobial resistance has not been limited to bacteria: it is an important public health issue for fungi such as *Candida*, viruses such as HIV, and parasites such as malaria. Even if new antimicrobial agents are introduced, their use will provide selective pressure for the emergence or resistance of these strains. It is likely that antimicrobial resistance will be a serious problem for the twenty-first century.

Addressing emerging infections in the twenty-first century

As the conditions encouraging the emergence of infectious diseases are likely to persist into the twenty-first century, it is necessary to develop flexible strategies to detect and respond to such problems rapidly. Several national and international health organizations have developed plans to address emerging infectious diseases. One plan developed by the Centers for Disease Control and Prevention identifies four major strategies: (1) enhancing surveillance and response, (2) encouraging applied research, (3) strengthening the infrastructure for public health and providing training opportunities, and (4) developing, implementing and evaluating strategies for prevention and control[45]. Activities in each of these areas are often integrated and complementary. Whatever the problem is, surveillance is necessary to detect it and to define its scope and magnitude. Applied research provides new surveillance techniques, new diagnostic methods and potential interventions. Surveillance, applied research, and prevention and control cannot be effective without appropriate infrastructure and training. Finally, all other efforts lead to prevention and control.

Table 1 Antimicrobial-resistant microbes affecting treatment and control of infectious diseases in the twenty-first century

Hospital-acquired infections	
	Methicillin-resistant staphylococci
	Vancomycin-resistant staphylococci
	Vancomycin-resistant enterococci
	ESC-resistant Gram-negative bacteria
	Azole-resistant *Candida*
Community-acquired infections	
	Multidrug-resistant pneumococci
	FQ- and ESC-resistant *Salmonella* (including *S. typhi*)
	Multidrug-resistant *Shigella* (including *Shig. dysenteriae*)
	FQ-resistant gonococci
	Multidrug-resistant *M. tuberculosis*
	Drug-resistant malaria
	Drug-resistant HIV

ESC, extended-spectrum cephalosporin (e.g. ceftriaxone or cefotaxine); FQ, fluoroquinolone (e.g. ciprofloxacin).

The problem of emerging infections cannot be addressed by a procrustean strategy. The relative importance of each strategy varies from problem to problem. The nature of the problem might be different in the developed and developing worlds. For example, addressing antimicrobial resistance is likely to require different strategies for different organisms and different parts of the world. In surveillance strategies, having sentinel centres in hospitals or renal dialysis units might be the most appropriate way of detecting and responding to the first emergence of vancomycin-resistant *Staph. aureus*. In contrast, for *Strep. pneumoniae*, population-based surveillance that determines the extent of resistance in different geographic areas might be better. For some infections, applied research might best be directed towards (1) new antimicrobial agents, (2) mechanisms to decrease host susceptibility through vaccines or immunomodulators, (3) new surveillance techniques, (4) genetic studies to improve our understanding of the host and pathogen, or (5) techniques to improve the use of antimicrobial agents. The infrastructures necessary to treat diseases will be different. Directly observed therapy with its extensive needs for resources is appropriate for tuberculosis but not for other infections. Although specific training needs will vary from problem to problem, a well-trained and flexible workforce will be needed as problems emerge and evolve. Prevention and control measures will also vary. Addressing antimicrobial resistance in *Salmonella* will require the prudent use of antibiotics in animal populations and strategies to prevent food-borne transmission. In contrast, the control of drug-resistant *Strep. pneumoniae* might best be addressed by the development and use of conjugate pneumococcal vaccines and the more prudent use of antimicrobial agents in humans.

History indicates that infectious diseases will remain an ever-changing problem for public health. Effectively addressing these problems will require awareness, flexibility, resources and long-term commitment so that the improvements of the twentieth century can be extended into the developing world and preserved in the developed world. □

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