

Global Aspects of Emerging and Potential Zoonoses: a WHO Perspective

Many new human pathogens that have emerged or reemerged worldwide originated from animals or from products of animal origin. Many animal species as well as categories of agents have been involved in the emergence of diseases. Wild (e.g., bats, rodents) as well as draught animals (e.g., horses) and food animals (e.g., poultry, cattle) were implicated in the epidemiologic cycles of these diseases. Many of the agents responsible for new infections and diseases in humans were viruses (e.g., hantaviruses, lyssaviruses, and morbilliviruses), but bacteria, especially enteric bacteria (e.g., *Salmonellae* and *Escherichia coli*) and parasites (e.g., *Cryptosporidium*) of animal origin, were also involved in major food and waterborne outbreaks. The public health relevance of some of these agents (e.g., new lyssaviruses and morbilliviruses) is not yet fully assessed. In addition the zoonotic nature of some other human diseases, such as Ebola and the new variant form of Creutzfeldt-Jakob disease, is suspected but not yet demonstrated. Finally, the possible future use of xenografts may lead, if precautions are not taken, to the emergence of new diseases called xenozoonoses.

Emerging and Reemerging Zoonotic Diseases

In both the developing and industrialized worlds, a number of zoonoses have emerged either as new pathologic entities or as already known agents, appearing in areas or species in which they had not been previously reported. In addition known zoonotic agents have reemerged sometimes after many years of absence in areas where they had been reported before. In this connection, limited and sometimes important outbreaks of otherwise endemic zoonoses such as rabies, brucellosis, leptospirosis, anthrax, a number of zoonotic foodborne diseases (caused by *Salmonella enteritidis*, *Salmonella typhimurium*, and *Escherichia coli*) and arbovirus infections involving production animals (Venezuelan equine encephalitis, Congo-Crimean hemorrhagic fever) have continued to appear in many industrialized and developing countries. Some examples of both emerging and reemerging zoonotic infections are given below.

Emerging Zoonoses

S. typhimurium in the United Kingdom

Multidrug-resistant *S. typhimurium* DT 104 initially emerged in cattle in 1988 in England and Wales. Subsequently, the strain has been isolated from poultry, sheep, pigs, and horses. Antimicrobial therapy is used extensively to combat

S. typhimurium infection in animals. The evolution of a strain resistant to the commonly used antibiotics has made infections with *S. typhimurium* DT 104 in food animals difficult to control and likely to remain a zoonotic problem. Furthermore, in *S. typhimurium* DT 104 of R-type ACSSuT, multiple-drug resistance has become an integral part of the genetic material of the organism. Unlike other salmonella serotypes, multidrug-resistant *S. typhimurium* DT 104 is, therefore, likely to retain its resistance genes even when antimicrobial drugs are no longer used. Unlike *S. enteritidis*, which is mainly associated with poultry and eggs, multidrug-resistant *S. typhimurium* DT 104 can be found in a broad range of foods. Outbreaks in the United Kingdom have been linked to poultry, various meats and meat products, and unpasteurized milk. In addition to infections from contaminated food, cases have also occurred from human contact with infected cattle. A small proportion of cases may have been caused by pets such as cats and dogs, which can also be infected with this strain of *Salmonella*. Like humans, pets probably acquire the infection through consumption of contaminated raw meat, poultry, or poultry-derived products. The emergence of *Salmonella* strains resistant to antibiotics in common use is important to clinicians, microbiologists, and those responsible for the control of communicable disease.

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Equine Morbillivirus in Australia

Equine morbillivirus (EMV) was isolated in September 1994 in Queensland, Australia. Fourteen horses died as a result of infection with EMV in southeast Queensland during September 1994. Seven additional horses were infected by the virus and were humanely killed. The first death (of a mare) attributed to the infection occurred on 9 September 1994. The virus produced severe damage to the lungs with the accumulation of massive amounts of fluid. Two persons who had close contact with the sick mare became infected with the virus and also had respiratory illness, in one case with fatal consequences. During October 1995, a third human infection with EMV was diagnosed. The infected man came from a property in Mackay where two horses had been diagnosed as dying from avocado poisoning and snakebite during August 1994.

Rabies in Australia

On 24 May 1996, a black flying fox with signs of neurologic illness was found in Ballina, New South Wales, Australia, and was submitted for autopsy. Histopathologic examination of the brain showed severe nonsuppurative encephalitis. Tissues were examined for EMV infection at the Animal Research Institute, Brisbane. Additional fixed tissues were sent for EMV and rabies testing. Results were negative for EMV. However, immunoperoxidase testing on fixed brain tissue was positive for *Lyssavirus* antigen and was subsequently confirmed by immunofluorescence testing. Subsequent investigations have indicated that the *Lyssavirus* present is not classic rabies, serotype 1. A range of cell cultures and mice inoculations were carried out to characterize the specific *Lyssavirus* involved.

Rabies in the United Kingdom

Since 30 May, four people in the vicinity of Newhaven, on the south coast of England, were thought to have been in contact with an insectivorous bat with rabies. After the bat was caught and humanely killed, on 3 June, the carcass was examined, and the diagnosis of rabies was confirmed. In the past 30 years, three human deaths have been associated with bat rabies in Europe, one in Finland and two in the former Soviet Union. Bat rabies is mainly confined to serotine bats in Europe, particularly in Denmark, northern Germany, and the Netherlands. Serotine bats are relatively uncommon in the United

Kingdom. In the United States, four cases of human rabies, caused by different variants of rabies viruses associated with insectivorous bats, were reported in 1995.

Reemerging Zoonoses

Venezuelan Equine Encephalitis in Colombia and Venezuela

An outbreak of Venezuelan equine encephalitis (VEE), which began in early September 1995, was reported on the border between Colombia and Venezuela. As of 21 September 1995, 825 human cases of VEE had been reported, with five confirmed by laboratory analysis and four resulting in death in Venezuela, mainly in the state of Zulia. In Colombia, more than 450 cases have been reported in the Department of La Guajira. VEE is the most severe of several viruses causing disease in horses and can be transmitted to humans by mosquito bites. Most infections are relatively mild, and symptoms include abrupt onset of severe headache, chills, fever, muscular pain, nausea, and vomiting. Clinical cases occur in 11% to 20% of the exposed population, and death occurs in fewer than 1% of those cases. Large-scale epidemics of VEE occurred in Colombia, Peru, Trinidad, and Venezuela in the 1950s and Central America and Mexico in the late 1960s, reaching the United States (Texas) in 1971. Outbreaks can be prevented by the regular immunization of horses in the framework of public health programs.

Leptospirosis in Nicaragua

On 1 November 1995, health authorities in Nicaragua established a task force to determine the cause of an unidentified illness that affected hundreds of residents of the Achuapa area, causing some 15 deaths. A task force investigated the nature and origins of the unknown disease, whose symptoms ranged from high fever to internal bleeding. On 6 November 1995, tests conducted by the Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, USA, indicated that the cause of the disease that killed at least 16 people in Nicaragua was an unusual form of leptospirosis. Initial reports that the disease was dengue fever, which has been common in the region, were ruled out after several autopsies showed severe respiratory hemorrhaging, and laboratory tests for dengue fever proved negative. Tests on three of the four

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specimens were positive for leptospirosis. Leptospirosis, while not rare in the Americas or Asia, usually affects the liver or kidneys, rather than the respiratory system.

Enterohemorrhagic *E. coli* Infection in Japan

An outbreak of enterohemorrhagic *E. coli* (EHEC) infection among schoolchildren was announced in Sakai City (population ca. 800,000), in the region of Osaka, Japan, in July 1996. Most of the reported cases were in children 6 to 12 years of age from 62 public elementary schools of the municipality. EHEC serotype O157 was detected in patients' stool samples. School lunch, which was prepared in individual schools from the foods delivered by a central supply station, was the suspected cause of this outbreak; the responsible food is still unknown. Epidemiologic investigation has shown that fresh radish sprouts (*kaiware-daikon*) were among the foods eaten by the schoolchildren. However, samples of radish seeds and sprouts, water, and soil from the environment of the farm concerned and stool samples from the farm workers showed no trace of this organism. As of 26 August 1996, 9,578 cases of *E. coli* serotypes O157:H7 and O157:H- infection, in both outbreaks and sporadic infections resulting in 11 deaths, had been reported in Japan. Although most of the cases are believed to be foodborne, the responsible foods have not been identified with certainty except in a few isolated cases. Investigations of outbreaks in other countries have established that animals, especially cattle, are major reservoirs of Shiga-like toxin producing *E. coli* and that foods of bovine origin, such as ground beef and unpasteurized milk, are the principal sources of human infection. The possibility that the source of the responsible agent is of animal origin should be further investigated in Japan.

Potential Zoonoses

The natural cycle of Ebola is not known, and its reservoir (i.e., the vertebrate playing an essential role in the maintenance of the agent and its life cycle, if one exists) remains to be identified. On the other hand, exposure to the agent of bovine spongiform encephalopathy (BSE), a known disease of cattle, is suspected to be the origin of a new variant form of Creutzfeldt-Jakob disease (CJD) in humans in the United Kingdom. These potential zoonoses have very recently had a considerable impact on public health, animal production, and

laboratory animal sectors worldwide in view of the need to minimize the risks for humans.

Bovine Spongiform Encephalopathy

BSE is a fatal disease of cattle that first came to the attention of the scientific community in November 1986 with the appearance in cattle of a newly recognized form of neurologic disease in the United Kingdom. Between November 1986 and 31 May 1996, approximately 160,000 cases of this newly recognized cattle disease were confirmed on approximately 33,400 farms. The disease is now on the decline in the United Kingdom. Epidemiologic studies suggested that the source of disease was cattle feed prepared from carcasses of dead ruminants. Modifications to the process used for preparing cattle feed introduced in 1981 to 1982 may have been a risk factor by not eliminating the agent from the feed. By May 1996, BSE had been reported from 10 countries and areas outside the United Kingdom. In one group of countries—France, Portugal, the Republic of Ireland, and Switzerland—the disease occurred in native cattle and could be linked to importation of potentially infected cattle feed from the United Kingdom. In another group—the Falkland Islands, Oman Sultanate, Germany, Canada, Italy, and Denmark—cases were only identified in cattle imported from the United Kingdom.

BSE is associated with a transmissible agent, the nature of which is not yet fully understood, and is one of several forms of transmissible brain disease of animals. A number of similar severe and fatal neurologic human diseases are due to non-conventional agents. These diseases include kuru, a disease that was transmitted by human ritual handling of bodies and brains of the dead and was identified in Papua, New Guinea in the 1950s, and the various forms (i.e., sporadic, familial, and iatrogenic) of CJD, a rare disease with a worldwide distribution.

After the identification of BSE, because the above human and animal diseases shared a number of characteristics, including their ability to be transmitted experimentally to a range of animals, the World Health Organization (WHO) held, or coorganized as a regular activity, four consultations during 1991 to 1995 to study these diseases (called transmissible spongiform encephalopathies). An express purpose of these consultations was to review the possible human public health implications of animal spongiform encephalopathies, with a special emphasis on BSE.

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The sudden announcement on 20 March 1996 by the United Kingdom of a cluster of 10 human cases identified with what appears to be a variant of CJD necessitated a fifth and sixth consultation at WHO because the results of the investigation indicated that, although there was no direct evidence of a link, the most likely hypothesis was that these cases might be related to exposure to BSE in the United Kingdom. The fifth consultation reassessed current recommendations in light of these new developments and issued recommendations to further minimize risks for consumers particularly in relation to foods and food products of animal origin. This was achieved through the organization of expert consultations first held in April 1996. The sixth consultation by WHO was organized in May 1996 to propose to its member states a protocol for global surveillance of the new variant form of CJD and identify the main areas for research on these diseases. Other consultations may be held when new findings with a bearing on public health become available.

Ebola and Ebola-related Viruses

In 1976, Ebola attracted worldwide attention with the outbreaks of Yambuku, Zaire, with 318 cases and Nzara, Sudan, with 284 cases, characterized by very high case-mortality rates (53% in Sudan and 88% in Zaire). In the first cases at the origin of the outbreaks (index cases) the patients may have had contacts with infected animals or their products (bats and/or rodents in Sudan, meat from monkeys or wild antelopes in Zaire), but contact could not be proven, and investigations of the possible animal reservoir remained inconclusive.

During 1977 to 1989 a small number of suspect, sporadic cases, or relatively small outbreaks were reported (e.g., in Nzara, 1979). In 1989, a new Ebola-related virus was isolated from macaques originally captured in the wild in the Philippines dying from acute hemorrhagic fever and imported into the United States. The same virus, called Reston, was isolated again in different animal colonies in macaques imported from the same country in 1990 (United States), 1992 (Italy), and 1996 (United States).

In 1994, 15 years after the last Ebola outbreak (Nzara, 1979) reported in Africa, a Swiss ethologist became infected by a new Ebola variant after doing a postmortem on a chimpanzee from the Tai forest in Côte d'Ivoire. The infection was demonstrated in this chimpanzee, and a number of deaths reported in these animals in 1994 in the

Tai forest were associated with this agent. Other outbreaks may have occurred in the chimpanzee population of the Tai forest before 1994. In January 1995, a new Ebola epidemic was reported in Kikwit, Zaire, with 315 cases and 244 deaths. The initial source of the infection of this outbreak may have been a forest worker involved in charcoal making. A year later, in January 1996, an outbreak occurred in Makokou, Gabon, with 37 cases and 21 deaths. The investigation of this outbreak showed that most patients had contacts with dead chimpanzees that they butchered. In October 1996, a second outbreak was reported in the Makokou region. The number of cases was 24 with 17 deaths on 12 November 1996. The index case was a hunter who fell ill in July 1996 and died in August in Booue hospital 200 km from Makokou.

Nothing definite is known on the reservoir of Ebola virus. A number of hypotheses have been proposed involving rodents or insects and even viruses of plant origin. It is generally agreed that the species of monkeys and apes in which the virus stains have been isolated so far are only victims of the disease, because in view of the high mortality rates usually observed, these populations could not sustain themselves or the agent for very long. These animals, however, participate in virus amplification by facilitating further virus transmission, including to humans, through handling of monkey carcasses or consumption of their meat. The identification of a new variant of Ebola in chimpanzees in its natural environment is a unique opportunity; so far the agent was only isolated from monkeys captured in the wild but (at time of the disease) located far from their natural environment. WHO, in collaboration with scientists from many countries including Switzerland, France, the United Kingdom, Sweden, Canada, and the United States, has, therefore, initiated a multidisciplinary study in the Tai forest in Côte d'Ivoire to identify the natural reservoir of the virus on the basis of the behavior of the chimpanzees. This identification would be essential to understanding the mechanisms for transmission in nature and facilitating the prevention of future Ebola outbreaks.

Xenografts and Xenozoonoses

Successful xenotransplantation (the transfer of animal organs or tissues into human recipients) may quickly become a biomedical reality. The development of immunosuppressive drug protocols to prevent both organ rejection and graft vs.

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host disease, as well as advances in surgical techniques is opening the door to a field that can save thousands of human lives each year.

A risk of disease transmission is present in any transplantation system. In allotransplantation, disease transmission is a major cause of illness and death in recipients. This is largely due to the required level of recipient immunosuppression but is also attributable to infected, but usually asymptomatic, human donors. Cases of viral, bacterial, fungal, and parasitic transmission are documented. In some cases, the presence of the infectious agent was known before transplantation. The decision was made to proceed because of the lack of alternative donors. The field of xenotransplantation also brings with it the potential for introducing unwanted animal-origin infectious agents, both known and as yet unknown, into the human population. These agents could cause disease in their new host. Dissemination beyond the original recipient into the general population could lead to epidemics. Xenotransplantation, therefore, has the potential for being both of great benefit and of detriment to humans. WHO is developing guidelines to ensure the development of xenotransplant donors free of zoonotic and other agents representing a potential risk for the recipient.

Reasons for the Increasing Trend—Control Measures

As shown in this paper, in both the developing and industrialized worlds, a number of zoonoses have emerged either as new pathologic entities or as already known agents, appearing in areas or species where they had not been previously reported or where they had seemingly disappeared. The reasons for this increasing trend are complex, but some have been identified as follows: 1) alteration of the environment affecting the size and distribution of certain animal species, vectors, and transmitters of infectious agents of humans; 2) increasing human populations favoring an increased level of contact between humans and infected/affected animals; 3) industrialization of foods of animal origin; changes in food processing and consumer nutritional habits; and, 4) increasing movements of people as well as trade of animals and animal products and decreasing activities for the surveillance and control of major zoonoses.

Although the prevalence of major zoonoses, such as brucellosis, tuberculosis, and dog rabies,

has been greatly reduced in the industrialized world, these diseases have not been eliminated altogether; zoonoses prevention and control will remain an area of major concern in most developing countries. Recent observations show that expenses related to the prevention of zoonotic diseases in humans are likely to increase dramatically in these countries in the near future if no programs for their control and elimination in animal reservoirs are implemented. Diseases such as brucellosis, rabies, and bovine tuberculosis will certainly be brought under control during the first decade of the second millennium, but this will require constant efforts for the next 15 to 20 years. Also, as the trade of animal products and the movements of people become more intense, the risks of introduction/reintroduction of certain diseases in a country increase. It is very likely, in view of the foreseeable global changes over the next few decades (e.g., population growth, urbanization, and climatic changes), that this trend will continue and even increase. Human disease patterns will be affected by high densities and movements of human populations within and between countries and changes in lifestyles; animal disease patterns will be affected by changing land-use patterns, new farming practices, displacement of animals, and environmental contamination.

Infectious diseases, including zoonoses, will remain the major health problems in most developing countries, together with opportunistic infections, including zoonotic diseases as a very important component. In industrialized countries, where cardiovascular diseases and cancers will remain the main causes of illness and death in spite of the AIDS pandemic, special attention will need to be paid to human-animal relationships especially with groups at higher risk such as the elderly, who already represent a significant part of the population of industrialized countries, as well as children and childbearing women, HIV-infected persons, and AIDS patients.

As zoonoses and animal diseases with the potential to affect human health likely will continue to emerge and reemerge, zoonoses surveillance will need to be reinforced and maintained at the national and international levels. In view of the foreseeable unplanned urbanization phenomenon and the associated lack or shortage of basic facilities, a strategy to respond to human and animal health problems in an urban environment will need to be developed for cities of

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both industrialized and developing countries. Comprehensive plans will need to be developed to reduce the rural-urban migration flow to reverse the current and anticipated trend. Major components of these plans should include improving rural employment and food availability by promoting animal production projects and improving health through zoonoses control and reduction of environmental pollution related to animal rearing.

Further collaboration is essential between all professions involved in food technology development, food industry control, and promotion of new production techniques at the primary production level in order to ensure food protection and response to the needs of the world population.

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