

# Factors and determinants of disease emergence

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## Summary

Emerging infectious diseases can be defined as infections that have newly appeared in a population or are rapidly increasing in incidence or geographic range. Many of these diseases are zoonoses, including such recent examples as avian influenza, severe acute respiratory syndrome, haemolytic uraemic syndrome (a food-borne infection caused by certain strains of *Escherichia coli*) and probably human immunodeficiency virus/acquired immune deficiency syndrome.

Specific factors precipitating the emergence of a disease can often be identified. These include ecological, environmental or demographic factors that place people in increased contact with the natural host for a previously unfamiliar zoonotic agent or that promote the spread of the pathogen. These factors are becoming increasingly prevalent, suggesting that infections will continue to emerge and probably increase. Strategies for dealing with the problem include focusing special attention on situations that promote disease emergence, especially those in which animals and humans come into contact, and implementing effective disease surveillance and control.

## Keywords

Avian influenza – Emerging infection – Infectious disease surveillance – Infectious disease – Nipah virus – Severe acute respiratory syndrome – Zoonosis.

## Introduction

Recent years have witnessed an increasing number of apparently novel infectious diseases in both animal species and humans. Notable recent events have included human populations becoming infected with highly pathogenic avian influenza (HPAI) and severe acute respiratory syndrome (SARS).

In 2004 alone, HPAI (subtype H5N1) has caused severe outbreaks in both poultry and humans in Thailand, Vietnam and other regions of Asia. From January to late September 2004, a total of over 40 human cases (with at least 30 deaths) had been reported in Vietnam and Thailand. The disease SARS, due to a newly identified coronavirus, caused 8,098 cases of human disease (with 774 deaths) in 2003, and at least 12 reported cases in 2004 (although some of these were due to laboratory infection, in Asia). Other infectious diseases that have emerged in the last few decades include, as follows:

– human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS)

- Rift Valley fever
- hantavirus pulmonary syndrome
- West Nile fever in the United States of America (USA)
- Lyme disease
- haemolytic uraemic syndrome (HUS), a food-borne infection caused by certain strains of *Escherichia coli* (serotype O157:H7 in the USA, with a variety of other serotypes elsewhere in the world).

Even monkeypox, a viral infection normally confined to the African rainforest, made an appearance in the USA in 2003, through an unexpected connection in the companion animal trade (3). All of these infections are zoonotic. In fact, zoonotic infections account for many of the most novel human diseases, crossing from their natural hosts into the human population.

Infections can be defined as 'emerging' if they have newly appeared, or are rapidly increasing in incidence or geographic range. Although the occurrence of these

diseases may appear to be sudden and inexplicable, factors responsible for their emergence can be identified in virtually all cases that have been carefully studied.

Infectious disease emergence can be viewed operationally as a two-step process. The first step is the introduction of the agent into a new host population. The second step is the further dissemination of the agent within the new host population. Sometimes, this agent may even establish itself in the new host. Most emerging infections appear to be caused by pathogens already present in the environment, which have been given an opportunity to infect new host species or populations. On relatively rare occasions, a new variant of the pathogen may also evolve and cause a new disease. The infection 'emerges' when it reaches a new population and is noticed.

The process by which infectious agents may cross species or become disseminated from isolated groups into new populations can be called 'microbial traffic'. A number of activities increase microbial traffic and, as a result, promote disease emergence, sometimes with epidemic consequences. Most emerging infections, and even antibiotic-resistant strains of common bacterial pathogens, usually originate in one geographic location (where they initially evolved) and then spread to new places.

Zoonotic diseases are of great importance in this regard. The numerous examples of infections which originated as zoonoses suggest that the 'zoonotic pool' – introductions of infections from other species – is an important and potentially rich source of emerging diseases. Periodic and continuing discoveries of new zoonoses suggest that the zoonotic pool remains a key source. As one example among many, the Henipaviruses (Hendra virus in Australia and Nipah virus in Asia) were unknown to humans before the 1990s, but have probably long existed in the fruit bat (*Pteropus*) species, which are the natural reservoirs for these viruses (5, 24).

Once introduced, an infection might then be disseminated (step two). Fortunately, zoonotic infections vary greatly in this capability. Despite the great number of possible zoonoses, relatively few succeed in establishing themselves within the human population. There are many aspects to the species barrier, including non-specific and induced immunity, receptor specificity and even the effects of host body temperature (15, 23). Much remains to be understood. Many of the zoonotic agents that have caused the most dramatic outbreaks, such as Ebola, Lassa fever and Nipah viruses, have caused human disease with a rapid course and high mortality, but these agents are poorly transmitted from person to person.

The disease SARS has, of course, been a notable recent exception (18), thus (rightfully) attracting a great deal of

attention from the world health community. While influenza also varies greatly in its ability to spread, the major epidemic strains have shown explosive transmissibility (17).

However, even if a zoonotic agent is not able to spread readily from person to person and establish itself in the human population, other mechanisms, such as nosocomial infection, might be able to transmit the infection. Indeed, for many of these infections, including Ebola, Lassa fever and SARS, the major secondary spread has been within healthcare settings, through breaches in infection control or contaminated injection equipment.

In addition, as with the classic zoonoses such as rabies, if the reservoir host or vector becomes more widely disseminated or there is more frequent human contact, the microbe can appear in new places. Bubonic plague and rat-borne hantavirus infections are among the historical infections that have spread as their rat hosts have been introduced into new locations.

Factors that promote one or both of the steps discussed above (introduction and dissemination) will tend to precipitate the emergence of a disease. It is surprising how often disease emergence is the unintended consequence of human actions. At other times, natural causes, such as changes in climate, can be responsible. Table I summarises the factors responsible for emergence and lists several examples of infections that have emerged or increased.

Any categorisation of these factors is, of course, somewhat arbitrary but should fairly represent the underlying processes that cause diseases to emerge. Table I essentially uses the categories developed in the original 1992 Institute of Medicine report on emerging infections (12), with additional definitions from the first emerging infections plan of the USA Centers for Disease Control and Prevention (CDC) (2).

Factors responsible for the emergence of diseases include the following:

- ecological changes, such as those due to agricultural or economic development or anomalies in climate
- human demographic changes and behaviour
- travel and commerce
- technology and industry
- microbial adaptation and change
- the breakdown of public health measures.

It should be noted that these categories need not be mutually exclusive.

Another recent Institute of Medicine report (13), which was intended to reassess current knowledge on emerging

**Table 1**  
**Factors in infectious disease emergence: some examples (categories should not be considered mutually exclusive as several factors may contribute to the emergence of a particular disease)**

Factor	Examples of specific factors	Examples of disease emergence
Ecological changes (including those due to economic development and land use)	Agriculture, dams, changes in water ecosystems, deforestation/reforestation, flood/drought, famine, climate change	Rift Valley fever (dams, irrigation), Argentine haemorrhagic fever (agriculture), Hantaan or Korean haemorrhagic fever (agriculture), hantavirus pulmonary syndrome in the south-western United States of America, 1993 (weather anomalies)
Human demographics, behaviour	Societal events: population migration (movement from rural areas to cities), war or civil conflict, economic impoverishment, urban decay, factors in human behaviour such as the commercial sex trade, intravenous drug use, outdoor recreation, use of childcare facilities and other high-density settings	Spread of human immunodeficiency virus and other sexually transmitted diseases, spread of dengue (urbanisation)
International travel and commerce	Worldwide movement of goods and people, air travel	Dissemination of human immunodeficiency virus, dissemination of mosquito vectors such as <i>Aedes albopictus</i> (Asian tiger mosquito), rat-borne hantaviruses, introduction of cholera into South America, dissemination of O139 (non-O1) cholera bacteria (via ships)
Technology and industry	Food production and processing: globalisation of food supplies, changes in food processing and packaging  Health care: new medical devices, organ or tissue transplantation, drugs causing immunosuppression, widespread use of antibiotics	Food production processes: haemolytic uraemic syndrome (certain <i>Escherichia coli</i> strains from cattle contaminating meat and other food products), bovine spongiform encephalopathy, Nipah virus (pigs), avian influenza, severe acute respiratory syndrome (probably)  Ebola and human immunodeficiency virus (health care and medical technology, contaminated injection equipment), opportunistic infections in immunosuppressed patients, Creutzfeldt-Jakob disease from contaminated batches of human growth hormone
Microbial adaptation and change	Microbial evolution, response to selection in the environment	'Antigenic drift' in influenza virus, possibly genetic changes in severe acute respiratory syndrome coronavirus in humans, development of antimicrobial resistance (human immunodeficiency virus, antibiotic resistance in numerous bacterial species, multi-drug-resistant tuberculosis, chloroquine-resistant malaria)
Breakdown in public health or control measures	Curtailed or reduction in disease prevention programmes; lack of, or inadequate, sanitation and vector control measures	Resurgence of tuberculosis in the United States of America, cholera in refugee camps in Africa, resurgence of diphtheria in former Soviet republics and Eastern Europe in the 1990s

Modified from (21)

infections, further divides some of these categories and suggests a few additional ones, such as bioterrorism or intentional use. However, the fundamental organising principles remain the same. It is notable that most of the classical agents listed in association with bio-warfare and

bio-terrorism are also zoonotic, including, among others:

- anthrax
- plague
- tularaemia
- various haemorrhagic fever viruses.

## Ecological changes, agricultural development and food handling

Ecological changes, including those due to agricultural or economic development, are among the most frequently identified factors in disease emergence. Ecological factors usually precipitate emergence by placing people in contact with a natural reservoir or host, which harbours an existing infection that was previously unfamiliar to humans. This may occur either by increasing proximity or, often, by changing conditions to favour an increased population of the microbe or its natural host. The emergence of Lyme disease in the USA and Europe was probably due largely to reforestation, which increased the population of deer and the deer tick, the vector of Lyme disease. The movement of people into these areas placed a larger population in close proximity to the vector.

Agricultural development, one of the most common ways in which people alter the environment and interact with it, is often a factor in disease emergence. Hantaan virus, the cause of haemorrhagic fever with renal syndrome (Korean haemorrhagic fever), is generally considered responsible for at least 100,000 human cases of disease each year in the People's Republic of China and has probably been known in Asia for centuries. The virus is a natural infection of the field mouse, *Apodemus agrarius*. The rodent flourishes in rice fields and people usually contract the disease during the rice harvest from contact with infected rodents. Junin virus, the cause of Argentine haemorrhagic fever, is an unrelated virus with a history remarkably similar to that of Hantaan (14). The conversion of grassland to maize cultivation apparently favoured a rodent that was the natural host for this virus, and human cases increased in proportion to the expansion of maize agriculture. Additional examples are likely to appear as new areas are placed under cultivation.

Perhaps more surprisingly, it has also been suggested that pandemic influenza may have an agricultural origin. Strains causing the frequent annual or biennial epidemics generally result from a mutation in response to host immune selection ('antigenic drift'), but pandemic influenza viruses do not generally arise by this process. Instead, gene segments from two influenza A strains re-assort themselves to produce a new virus that can infect humans. Usually the novel gene segments are of avian origin (17). Evidence amassed by several researchers indicates that waterfowl, such as ducks, are major reservoirs of influenza (17, 27). Humans appear to be relatively resistant to direct infection by most avian influenza viruses (23) (hence the current and justified concern over the human cases of avian influenza infection in Asia), but pigs may be more readily susceptible and

could serve as 'mixing vessels' for new mammalian influenza strains (17, 27).

Known past pandemic influenza viruses have generally come from the People's Republic of China. Some years ago, Scholtissek and Naylor suggested that integrated pig-duck agriculture, an extremely efficient food production system traditionally practised in certain parts of the People's Republic of China for several centuries, puts these species in close contact and provides a natural laboratory for creating new influenza recombinants (27). More recently, it has been suggested that, with high-intensity agriculture and the movement of livestock across borders, suitable conditions may now exist not only in Asia, but also in Europe and elsewhere (17). The recent outbreaks of avian influenza in humans suggest that poultry farming also provides opportunities for exposure to novel influenza viruses (16). Although it has usually been thought that avian influenza strains are rarely able to infect humans directly, recent events suggest that exceptions can occur, leading researchers to realise that influenza continues to evolve both as an agricultural and a human disease threat. Concern is increased by uncertainty about the origins of the virus responsible for the great influenza pandemic of 1918 to 1919. While this pandemic virus was apparently of avian origin, it is not yet known whether the virus first re-assorted itself in another species (such as the pig) or entered the human population directly from an avian source (26).

The human infections with avian influenza occurring in Asia have prompted a re-evaluation of the pathways by which pandemic influenza strains are introduced into the human population (26). As a result of these recent events, much attention has also recently been focused on live animal markets, and other settings in which different species may be housed closely together at high densities. An important role for these markets has been suggested in the emergence of both HPAI (16, 17) and SARS (8). In each case, a zoonotic infection was introduced into a human agricultural worker or food handler who became infected from a food animal source. In some cases, especially with SARS, the infection was then transmitted to others.

Although HIV-1 remains more problematic as an example, and the exact source and mode of introduction remain uncertain, the best current evidence suggests that HIV-1 is also originally zoonotic, perhaps introduced originally from non-human primates, possibly several times (10, 25). Although it is not known exactly how HIV-1 first entered the human population (1), handling of infected animal carcasses in the 'bush meat' trade has been suggested as a possible source and remains the best candidate so far (10, 29). If so, this scenario for introduction would be similar in many ways to the suggested scenario for the introduction of SARS through the handling of food animals.

## Technology, industry and globalisation

The two possibilities of disease spread through high-density settings and through the global movement of people and goods are closely related. The term 'high density' characterises many industries in modern society, including agriculture and food production in industrialised countries. High-intensity production of food animals may allow a pathogen which is present in a small subpopulation to become more widespread. The *E. coli* strains that cause HUS may once have existed in relatively limited subpopulations of cattle, but then spread widely as cattle from diverse sources were brought together in high-density settings.

In operations such as food production chains, which process or use products of biological origin, modern production methods yield increased efficiency and reduced costs, but can increase the chances of accidental contamination and amplify the effects of such contamination. A pathogen present in some of the raw material may find its way into a large batch of the final product, as happened with the contamination of hamburger meat by the *E. coli* strains that cause HUS. In fact, the CDC have recently stated, 'The contamination of raw ingredients from infected food-producing animals and cross-contamination during processing is a more prevalent cause of food-borne disease than is contamination of foods by persons with infectious or contagious diseases (4).

Another likely example of the interspecies transfer of a pathogen through industrial processes involves bovine spongiform encephalopathy. This disease, which emerged in the 1980s in cattle and was later associated with new variant Creutzfeldt-Jakob disease in humans, was probably caused by an interspecies transfer of scrapie from sheep to cattle. The transfer seems to have occurred when changes in rendering processes led to incomplete inactivation of the scrapie agent in sheep byproducts which were fed to cattle (20, 28).

These problems are further compounded by globalisation, which allows agents to be introduced from other countries and even continents. The recent outbreak of monkeypox in the USA is one demonstration of this. Monkeypox is an orthopoxvirus closely related to variola (smallpox) virus, but normally found in the rainforests of central Africa. Various rodent species are thought to be its natural reservoir (6). In 2003, cases of monkeypox were identified in humans who purchased companion animal prairie dogs (*Cynomys* spp.) from a supplier in the midwestern USA (3, 9). The prairie dogs had been housed with African rodents which were infected with the monkeypox virus. After contracting the virus, some of the prairie dogs (who

became sick themselves) passed the infection on to their human owners. There were 71 reported human cases (35 of which were confirmed by laboratories), in six states (3).

## Evolution: adaptation and change

Microbes, like all other living things, are constantly evolving. The emergence of antibiotic-resistant bacteria as a result of the ubiquity of antimicrobials in the environment is an evolutionary lesson on microbial adaptation, as well as a demonstration of the power of natural selection. Selection for antibiotic-resistant bacteria and drug-resistant parasites has become frequent, driven by the wide and sometimes inappropriate use of antimicrobial drugs in a variety of applications. Pathogens can also acquire new antibiotic resistance genes from other, often non-pathogenic, species in the environment, selected for or perhaps even driven by the selective pressure of antibiotics.

Many viruses show a high mutation rate and can rapidly evolve to yield new variants. A classic example is antigenic drift in influenza. It also appears likely that the SARS coronavirus underwent some genetic changes (such as a 29-base deletion) as it passed through the human population from its original host (8). While the significance of these genetic changes is still uncertain, it is possible that such genetic changes increased the transmissibility of the SARS coronavirus in humans.

## Breakdown of public health measures and deficiencies in public health infrastructure

Re-emerging diseases are diseases which were once decreasing, but are now rapidly increasing again. Classical public health and sanitation measures have long served to minimise dissemination and human exposure to many pathogens which are spread by traditional routes (such as water or food), or are preventable by immunisation or vector control. However, the pathogens themselves often still remain, in small pockets of infection, and may therefore re-emerge if circumstances allow. Often these circumstances are breakdowns in disease prevention and control measures.

Thus, re-emerging infectious diseases are often conventionally understood and well-recognised public health threats for which (in most cases) previously active



public health or control measures have been allowed to lapse. This is a situation that unfortunately now applies all too often, in both developing countries and the inner cities of the industrialised world. The appearance of re-emerging diseases may often be a sign of the breakdown of public health measures. It should also be a warning against complacency when considering infectious diseases.

## Conclusions

The historical processes that have given rise to the emergence of 'new' infections throughout history continue today. In fact, they are accelerating, because the conditions of modern life ensure that the factors responsible for disease emergence are more prevalent than ever before. Speed of travel and global reach allow microbes rapid access to new populations. The SARS epidemic was one recent example, but surely the future will bring others.

Humans are not powerless, however, against these processes. Both science and political will are necessary. Knowledge of the factors underlying disease emergence can help to focus resources on the key situations and areas worldwide, as well as assist in developing more effective prevention strategies to stop emerging infections at their source. Monitoring the 'human-animal interface' in agricultural settings and urban food animal handling, as well as in the wild, is essential. The first people to become infected with SARS were reportedly food handlers in the southern People's Republic of China who prepared civet meat (*Paguma larvata*) for restaurant patrons (8). While it is still not definitively known that the palm civet was the specific, original source of the SARS coronavirus, it appears likely that the virus was introduced from an animal species through such food production and handling processes. Appropriate protective measures, such as personal protective equipment and good husbandry practices (including better separation of livestock species), might conceivably have prevented the outbreak of SARS, or the deaths due to H5N1 HPAI in agricultural workers in Asia.

Another high priority is effective global disease surveillance to give early warning of emerging infections (11, 22). This must be linked to incentives, such as national development, and be supported by a well-

resourced infrastructure to enable an appropriate rapid response. New technologies in communications, informatics and diagnostics provide essential tools that can strengthen surveillance and make it possible for the first time to try to 'outrun' the microbes. Communications is an important example. The growth of the Internet and the World Wide Web in recent years has been instrumental in enabling instant or 'real-time' worldwide communications. 'ProMED-mail' is an e-mail list which began in 1994 as a prototype system for reporting and discussing emerging infections. It now numbers almost 30,000 subscribers throughout the world, and is available on the Web ([www.promedmail.org](http://www.promedmail.org)). A variety of electronic information-sharing capabilities were used effectively by the World Health Organization (WHO) and other agencies during the last SARS outbreak, and proved invaluable in speeding progress. Similarly, molecular diagnostic methods and other advances in diagnostic technology have added greatly to the capability for rapid recognition and response.

As always, research, both basic and applied, will also be vital. There is still much to be learned about the natural ecology of infectious diseases and developing better prognostic epidemiology to predict the emergence and spread of these diseases. While some progress has been made in recent years in predicting disease spread (7, 18, 19), a great deal of work remains. For a variety of reasons, many zoonotic introductions fortunately do not succeed as human diseases (1). There is also a need to understand not only the driving factors of emergence, but also ways in which researchers can differentiate between successful and unsuccessful introductions, and better predict the risks of emergence and transmission.

It is clear that infections will continue to emerge, and that many of these infections will be zoonotic. This emphasises the importance of close co-operation between the veterinary and human health communities, in working together and exchanging information on a regular basis. The World Organisation for Animal Health (OIE) has long demonstrated leadership in surveillance and responding to threats to livestock and other animals. Agencies such as the OIE and WHO must continue their close collaboration in such worldwide efforts. While the task is large, it is essential to human survival. ■

## Facteurs déterminant l'émergence de maladies

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### Résumé

Les maladies infectieuses émergentes peuvent être caractérisées comme des maladies d'apparition récente dans une population donnée ou dont l'incidence, ou la portée géographique, connaissent une rapide expansion. Nombre de ces maladies sont des zoonoses, comme ce fut le cas des épisodes récents d'influenza aviaire, de syndrome respiratoire aigu sévère, de syndrome hémolytique et urémique (une toxi-infection alimentaire due à certaines souches d'*Escherichia coli*), et probablement du syndrome d'immunodéficience acquise/virus d'immunodéficience humaine.

Le plus souvent, les facteurs spécifiques qui accélèrent l'émergence d'une maladie peuvent être reconnus. Ils s'agit notamment de facteurs écologiques, environnementaux ou démographiques qui intensifient les possibilités de contact entre l'homme et l'hôte naturel d'un agent zoonotique antérieurement inconnu, ou qui favorisent la dissémination de l'agent pathogène. Ces facteurs gagnant en importance, une émergence continue, et probablement une propagation accrue des maladies infectieuses sont à craindre. Les stratégies permettant d'affronter le problème consistent à prêter une attention particulière aux situations favorisant l'émergence de maladies, notamment celles où les animaux et les êtres humains sont en contact, et à mettre en œuvre des mesures efficaces de surveillance et de prophylaxie.

### Mots-clés

Influenza aviaire – Maladie émergente – Maladie infectieuse – Surveillance des maladies infectieuses – Syndrome respiratoire aigu sévère – Virus Nipah – Zoonose.



## Factores que propician y determinan la aparición de enfermedades

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### Resumen

Cabe definir las enfermedades infecciosas emergentes como infecciones que han surgido por primera vez dentro de una población o cuya incidencia o alcance geográfico aumentan con rapidez. Muchas de ellas son zoonóticas. Entre otros ejemplos recientes figuran la influenza aviar, el síndrome respiratorio agudo severo, el síndrome hemolítico urémico (infección que se transmite por los alimentos causada por ciertas cepas de *Escherichia coli*) y, probablemente, el síndrome de inmunodeficiencia adquirida (SIDA), provocado por el virus de inmunodeficiencia humana.

A menudo es posible determinar factores concretos que precipitan la aparición de una enfermedad. Se trata de factores ecológicos, ambientales o demográficos que inducen un contacto más intenso de la gente con el anfitrión natural de un agente zoonótico hasta entonces desconocido o que favorecen la propagación del patógeno. La prevalencia de estos factores va en aumento, lo que hace suponer que las infecciones seguirán surgiendo y probablemente

intensificándose. Las estrategias para hacer frente a este problema pasan por centrarse especialmente en las situaciones que favorecen la aparición de enfermedades, sobre todo cuando entrañan contacto entre personas y animales, y por aplicar medidas eficaces de vigilancia y control sanitarios.

#### Palabras clave

Enfermedad infecciosa – Infección emergente – Influenza aviar – Síndrome respiratorio agudo severo – Vigilancia de enfermedades infecciosas – Virus Nipah – Zoonosis.



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