# Microbial Zoonoses and Sapronoses

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# Chapter 1
# Introduction

**Abbreviations**

| | |
|---|---|
| AIDS | Acquired immune deficiency syndrome |
| AR | Agglutination reaction |
| BA | Blood agar |
| BHI | Brain heart infusion agar |
| BSL | Biosafety level, 1 to 4 |
| BSC | Biosafety cabinet, I to III |
| CCHF | Crimean-Congo haemorrhagic fever |
| CDC | Centers for Disease Control and Prevention, USA |
| CEE | Central European encephalitis |
| CFT | Complement-fixation test |
| CNS | Central nervous system |
| CSF | Cerebrospinal fluid |
| CT | Computerized tomography |
| CTF | Colorado tick fever |
| ECDC | European Centre for Disease Prevention and Control, Stockholm |
| EEE | Eastern equine encephal(omyel)itis |
| ELISA | Immunoenzymatic serological test |
| EMC | Encephalomyocarditis |
| FMDV | Foot-and-mouth-disease virus |
| FAO | Food and Agriculture Organization of the United Nations |
| HCPS | Hantavirus cardio-pulmonary syndrome |
| HIT | Haemagglutination-inhibition test |
| HIV | Human immunodeficiency virus |
| HFRS | Haemorrhagic fever with renal syndrome |
| HPAI | Highly pathogenic avian influenza |
| HPS | Hantavirus pulmonary syndrome |
| HUS | Haemolytic-uremic syndrome |
| IF, IFA | Immunofluorescence microscopy, immunofluorescence assay |
| JE | Japanese encephalitis |
| KFD | Kyasanur forest disease |
| LB | Lyme borreliosis |

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| | |
|---|---|
| LCM | Lymphocytic choriomeningitis |
| LD | Lethal dose |
| LI | Louping ill |
| MID | Minimum infectious dose |
| MLD | Minimum lethal dose |
| MLST | Multilocus sequence typing |
| MRSA | Methicillin-resistant *Staphylococcus aureus* |
| MVE | Murray Valley encephalitis |
| NFD | Natural focus of disease/infection (singular or plural) |
| OHF | Omsk haemorrhagic fever |
| OIE | World Organization for Animal Health |
| ONN | O'nyong nyong |
| PCR | Polymerase chain reaction |
| PFGE | Pulse-field gel electrophoresis |
| RDPA | Reaction of diffuse precipitation in agar (gel), immunodiffusion test |
| RES | Reticuloendothelial system |
| RFLP | Restriction fragment length polymorphism |
| RLB | Reverse line blot (molecular detection technique) |
| RIHA | Reaction of indirect (passive) haemagglutination |
| RMSF | Rocky Mountain spotted fever |
| RSSE | Russian spring-summer encephalitis |
| RT-PCR | Reverse transcription polymerase chain reaction |
| RVF | Rift Valley fever |
| SARS | Severe acute respiratory syndrome |
| SFG(R) | Spotted fever group (rickettsiae) |
| SFN; SFS | Sandfly fever Naples; Sandfly fever Sicily |
| SGA | Sabouraud glucose (dextrose) agar |
| s.l. | *sensu lato* |
| SLE | St. Louis encephalitis |
| SSH | Snowshoe hare virus |
| s.s. | *sensu stricto* |
| TBE | Tick-borne encephalitis |
| TC | Tissue (in fact, cell) culture |
| TOT | Transovarial transmission |
| TST | Transstadial transmission |
| vCJD | New variant of Creutzfeld-Jakob disease |
| VEE | Venezuelan equine encephal(omyel)itis |
| VNT | Virus-neutralisation test |
| VSV | Vesicular stomatitis virus |
| WB | Western blotting |
| WEE | Western equine encephal(omyel)itis |
| WHO | World Health Organization |
| WNV | West Nile virus (WNF, West Nile fever) |
| YF | Yellow fever |

This book originated while lecturing a graduate course in microbiology called first "Zoonoses", and later more specifically "Microbial Zoonoses and Sapronoses" at the Faculty of Science, Masaryk University in Brno, in the years 1992–2009. It presents an up-to-date survey of the problems of microbial zoonoses and sapronoses, and can be used not only by microbiologists but also zoologists or students of veterinary and human medicine including Ph.D. students.

Preparing a modern review of this turbulent discipline has been difficult. In the last two decades or so, we have encountered a number of new emerging infectious diseases (e.g. SARS, Ebola, Nipah, hantavirus pulmonary syndrome) or diseases newly recognized (Lyme borreliosis, ehrlichiosis, anaplasmosis), re-emerging (West Nile fever in Europe), geographically expanding (West Nile encephalitis in the Americas), starting to occur at altitudes higher than before (TBE and LB in Europe), with an increasing incidence (campylobacterosis, or salmonellosis after 1988), those changing the range of hosts and vectors or caused by agents modifying their characteristics (virulence, antibiotic resistance) and clinical symptoms they produce in the host. A number of these emerging diseases has been due to the ability of some pathogens to cross the "species barrier" of their hosts, as observed with, e.g., vCJD, avian and swine influenza, SARS or AIDS. It has been estimated that from a total of about 177 (re)emerging diseases, zoonoses present as much as 75% (Taylor et al. 2001, Woolhouse and Gowtage-Sequeria 2005). A number of zoonoses and insect-borne diseases (malaria, dengue, filariosis, trypanosomiases, leishmaniasis) jeopardise the lives of millions of people every year.

Another problem in writing this book has been frequent and profound changes in nomenclature and taxonomy of many zoonotic and sapronotic agents (e.g., *Ehrlichia, Anaplasma,* other rickettsiae, *Pneumocystis, Rhinosporidium*, microsporidia). In addition, the number of known zoonotic and sapronotic aetiological agents of human diseases is high and growing steadily (more than 815 today: Woolhouse and Gowtage-Sequeria 2005), and it has been necessary to take in consideration only the important ones while neglecting those that are regarded as "minor" at present. Intentionally, more emphasis is given in this book to the ecological aspects of zoonoses and sapronoses (haematophagous vectors of the diseases and their bionomics; vertebrate hosts of zoonoses; habitats of the agents and their geographical distribution; natural focality of the diseases) than to clinical and therapeutic details.

# Chapter 2
# Types of Human Disease by Source of the Infectious Agent

In general, the source of infection for human beings is another human, or an animal, or the environment (extra-animal substrate). In line with this we can distinguish human infectious diseases as anthroponoses, zoonoses and sapronoses, respectively. The names have been derived from the *Greek* "νόσος" (nosos) = disease; "ανθρόπος" (anthropos) = man; "ζωός" (zoos) = living (animal); "σαπρός" (sapros) = decayed.

| Type of human disease | The source of infection (habitat of the agent) | Man-to-man transmission |
|---|---|---|
| Anthroponosis | Human | Common |
| Zoonosis | Animal | Uncommon or rare |
| Sapronosis | Abiotic substrate | Very rare |

Anthroponoses are diseases transmissible only from man to man. Typical microbial anthroponoses are typhoid fever (typhus abdominalis, caused by *Salmonella typhi*), paratyphoid fever, shigellosis (bacillary dysentery, the agents are *Shigella* spp.), whooping cough (the agent is *Bordetella pertussis*), diphtheria (*Corynebacterium diphtheriae*), streptococcal diseases (tonsillitis, scarlet fever, erysipelas), syphilis (*Treponema pallidum*), yaws (*Treponema pertenue*), gonorrhoea (*Neisseria gonorrhoeae*), *Haemophilus* infections (including Brazilian purpuric fever), chancroid (ulcus molle, *Haemophilus ducreyi*), tuberculosis caused by *Mycobacterium tuberculosis*, leprosy, trachoma (inclusion conjunctivitis) and lymphogranuloma venereum (*Chlamydia trachomatis*), chlamydial pneumonia and cardiovascular disease, mycoplasmal pneumonia, peptic ulcer disease, pneumococcal pneumonia, invasive group A streptococcal infections, meningococcal disease, common cold, epidemic influenza (except for that caused by certain types of zoonotic orthomyxoviruses – avian, swine or equine), poliomyelitis, some types of viral hepatitis (A, B, C), epidemic viral gastroenteritis, rubella, measles (morbilli, rubeola), mumps (infectious parotitis), epidemic haemorrhagic conjunctivitis, infectious mononucleosis, cytomegalovirus infection, smallpox (variola), herpes simplex, chickenpox (herpes zoster, caused by varicella-zoster virus), AIDS, ringworm caused by *Trichophyton rubrum, Epidermophyton floccosum* and some other

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species of dermatophytes, candidosis, *Pneumocystis* pneumonia (caused by human genotypes of *P. jirovecii*), some microsporidial infections, cryptosporidiosis (human genotypes), giardiasis (human genotype), trichomoniasis, amoebiasis (amoebic dysenteria, *Entamoeba histolytica*), and several other human diseases.

Zoonoses are diseases transmissible from animal to man. The term was invented by Rudolf Virchow during his study of trichinellosis in 1855. In general, zoonoses are not transmissible by contact from the patient to other people, although there are notable exceptions with haemorrhagic fevers Lassa, Machupo, Ebola, Marburg, CCHF, or SARS, plague etc. The term used earlier for diseases transmissible from animals to man was "anthropo-zoonoses". By analogy, a term "zoo-anthroponoses" was used for diseases transmissible the other way, from man to animals; however the number of the latter is limited (e.g., influenza, tuberculosis). Regrettably, many epidemiologists started to use these both terms in a reverse order (zooanthroponoses as diseases transmissible from animals to man), or promiscuously. The WHO therefore suggested using "zoonoses" as the official term, and that the two previous terms should no longer be used. According to an expert commission of WHO/FAO the definition of zoonoses reads as follows: "*Zoonoses are diseases and infections which are naturally transmitted between vertebrate animals and man*" (WHO Tech Rep Ser 169, 1959). This definition was confirmed also by the third and fourth report of this Commission (WHO Tech Rep Ser 378, 1967; WHO Tech Rep Ser 682, 1982).

The number of known zoonoses is growing steadily, at present exceeding 250, about 80 of which are common. From the zoonoses discovered in recent decades we can mention for instance Lyme borreliosis, anaplasmosis, HFRS and other haemorrhagic fevers Lassa, Marburg and Ebola, hantavirus pulmonary syndrome, SARS or Nipah fever. However (and luckily), only a limited number of zoonoses can cause extensive outbreaks – e.g., salmonellosis, Q fever, yellow fever, Japanese encephalitis, West Nile fever, chikungunya, RVF and American equine encephalomyelitides. Other zoonoses attract public (and media) attention due to their high lethality, sometimes associated with a high contagiosity for attending medical personnel (haemorrhagic fevers).

The transmission of zoonotic agents from animal to man can be realized either directly, or indirectly, *via* a vector (usually a haematophagous, i.e. blood-feeding member of the phyllum *Arthropoda*); in the latter case we can speak about obligate or facultative vector transmission (so-called "meta-zoonosis" according to WHO 1967).

Zoonoses can further be divided according to the habitat or ecosystem where their agents circulate as: (i) synanthropic, with an urban (anthroponotic, domestic) cycle where the source of human infection are most often domestic animal or synanthropic vertebrates bound to human dwellings; or (ii) exoanthropic, with a sylvatic (feral) cycle, and their reservoir is in the countryside outside human dwellings – in so-called natural foci. The first group of zoonoses forms, e.g., vesicular stomatitis, brucellosis, bovine tuberculosis, glanders, listeriosis, erysipeloid or ringworm caused by *Trichophyton verrucosum* and *Microsporum canis.* These diseases are transmissible usually percutaneously, aerogenically, alimentarily or per conjunctiva, and often present typical occupational diseases in farmers, butchers and veterinary

doctors. The second group form classic diseases with natural focality in the sense of J. N. Pavlovsky, e.g. tick-borne encephalitis and other arboviroses, tularaemia, plague or scrub typhus, where man acquires the infectious agent after entering a natural focus, commonly by the attack of an haematophagous vector. However, there does not exist a clear distinction between these two groups of zoonoses, and a number of zoonoses exhibit both urban and sylvatic patterns of circulation – yellow fever, American trypanosomiasis, plague.

Sapronoses are diseases transmissible to man from an abiotic substrate in the environment – soil, water, decaying plants, animal excrement, carrion and other substrata. The most important feature is that the sapronotic agent replicates actively in these abiotic substrata – it is not the mere persistence of the microbe in the environment, nor secondary contamination of environmental objects with the agent from animal sources. The source of infection is therefore not an animal or man. Sapronotic agents are capable of reproduction both in abiotic environment (saprophytic phase) and in the organisms of homoiothermous vertebrates including man (parasitic phase). They show a "dual life": saprophytic and parasitic (pathogenic). In particular, many human mycoses belong to sapronoses, especially visceral ones, like coccidioidomycosis, histoplasmosis, blastomycosis, emmonsiosis, cryptococcosis, and also some bacterial (legionellosis) and protozoan (primary amoebic meningoencephalitis, naegleriosis) diseases, but no viral, rickettsial or chlamydial diseases (because obligate intracellular parasites are unable to reproduce extracelullarly).

The term "sapronosis" and its definition were introduced into epidemiology by Russian microbiologist V. I. Terskikh (1958) in the article entitled "On diseases of humans and animals caused by microbes capable of reproduction in external milieu . . .", and for further use it was accepted by Somov and Litvin (1988), Krauss et al. (1997), Hubálek (2003) and others. The definition of sapronoses reads after Krauss et al. (1997): *Krankheiten*, *deren Erreger keine Wirbeltiere als Reservoir erfordern*, *weil sie in Wasser*, *Boden*, *auf Pflanzen usw. vorkommen und von dort aus auch Vertebraten infizieren können*.

The difference between zoonoses and sapronoses is sometimes fuzzy to vague, and a disease can be called, depending on circumstances, either zoonosis or sapronosis (e.g., listeriosis, pseudotuberculosis, anthrax).

A characteristic feature of a majority of zoonoses and sapronoses is that man is a dead-end host in the epidemic process (inter-human transmission is absent), although his or her disease can often be serious, even fatal. The pathogenic agent is evolutionarily not adapted to its accidental new host. From an ecological point of view, all pathogenic microorganisms are parasites of their hosts (animals or plants). The evolution of parasitism in today's pathogens proceeded along the trajectory saprophyte (commensal) → facultative (occasional) parasite → obligate parasite. An obligate parasite as a rule does not kill its host on which it is evolutionarily adapted (the untimely death of the host would lead to a bad fate for it), while unusual, incidental but susceptible hosts (man in our case) where parasitic co-evolution has not occurred can be severely harmed or killed.

Classification of infectious diseases into anthroponoses, zoonoses and sapronoses is a combination of an anthropocentric view (i.e. treating only diseases

of humans, while not those of animals) and ecological view (studying the habitats in which the infectious agent lives: Hubálek 2002).

We can distinguish six classes of zoonoses and sapronoses according to systematic arrangement of their aetiological agents:

I Viroses
II Bacterial diseases
III Mycoses
IV Protozoan diseases
V Helminthoses (invasions: cestodes, trematodes, nematodes)
VI Diseases caused by arthropods (infestations)

However, we will concentrate on microbial zoonoses and sapronoses in this monograph, leaving aside diseases caused by multicellular organisms (helminths and arthropods, i.e. invasions and infestations). The agents of the classes IV–VI belong to the field of parasitology, and cause the so-called parasitic zoonoses and sapronoses.

# Chapter 3
# A History of Zoonoses and Sapronoses and Research into Them

The history of these diseases and of their study is given in a brief chronological review of the most important events (important epidemics) and milestones of their study (relevant microbiological discoveries). In some historical data it is difficult to differentiate between the year of discovery and the year of its publication.

Eighteenth century BC, Babylonian codex Eshuna: "mad dogs" (most probably rabies).

Fourth century BC, Talmud: notes on mad dogs in Israel.

1320 BC, Bible: a description of a plague epidemic among the Philistines (enlarged lymphatic nodes, overpopulation of "mice" at the same time).

556 BC, China: a description of rabies.

435 BC, HIPPOKRATES: "*Epidemion*" (the causes of diseases are in environment).

429–426 BC, THUCYDIDES: the "plague of Athens" killed about one-quarter (75,000–100,000) of the citizens of Athens during the siege by the Spartan army (the "Peloponnesian wars", 431–404 BC) while not affecting besieger, and for 3 additional years thereafter. When the Athenian navy was dispatched later against Sparta, it was also heavily affected by the disease: one-quarter of 4,000 soldiers died, including the commander Pericles and his two sons. The symptoms described by Thucydides involve high fever, facial erythema, pustular rash to ulcers on the skin (sometimes gangrenes), bleeding from gums, tongue and throat, conjunctivitis, cough, sneezing, runny nose, diarrhoea, severe vomiting, dehydration, sleeping distress; and some of those who survived lost their toes and fingers, vision or memory. According to the symptoms and some epidemiological features, as the most probable cause of this epidemic could be regarded epidemic louse-borne typhus, while plague is improbable; additional alternative hypotheses have included ergotism or smallpox; some authors also considered (but as much less probable causes) abdominal typhus, malaria, dengue, WN fever, Ebola haemorrhagic fever, CCHF, gastrointestinal anthrax or brucellosis. (In our opinion, a combination of epidemic typhus with ergotism is a feasible hypothesis). In any event, this outbreak contributed significantly to the decline of Athens.

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224 BC, China: the first major epidemic of plague reported.

First century, SUSRUTA (a Brahmin priest in India) and COLUMELLA (an educated Roman farmer): the spread of fevers is caused by "biting flies".

100, RUFUS from Ephesus: a description of bubonic plague in Libya, Egypt and Syria (here was plague known since third century BC).

541–546: 1st plague pandemic ("Justinian", Byzantine Caesar) started in Egypt, continued in Palestine, Syria, Constantinople, and engulfed the whole known world including Europe (Italy, Spain, France, Germany, Denmark, England), central Asia and China (an estimated 100 million persons succumbed out of about 142 million contracting the disease).

1321, Florencia: "*Statuti sanitari*": rule of the city how to behave when there occurs an epidemic.

1346–1352, 2nd plague pandemic ("The Black Death") in Europe – it started already in about 1330 in central Asia, where almost entire populations of Tatars and Saracens had succumbed. During the siege of the Genoan fortress of Caffa (today's Theodosia) in the Crimea, Tatars catapulted the cadavers of their soldiers that had succumbed to plague within (the first "biological warfare"); Genoan merchants escaped the fortress but spread the plague to Constantinople and Messina. The ensuing pandemic engulfed the whole Italy, Dalmatia, France, England and Norway in 1348; then Germany and Moravia in 1349; and Poland, Russia (for instance in Smolensk died all citizens except for five persons) in 1350–1351. In Europe, one-quarter of inhabitants succumbed (about 25 million), and an estimated 25 million died in Asia [the pandemic probably considerably contributed to the fall of the Mongolian empire] and Africa earlier; 1361, 1371 and 1380–1382 saw follow-up outbreaks in Europe.

1348, Venezia: "*Magistrato della Sanità*": probably first hygienic office for control of plague and other diseases.

Fifteenth century, a new epidemic of plague in Germany, France and Russia.

1490, Granada: during the siege of the town kept by Maurs, a total of 17,000 Spanish soldiers succumbed to epidemic louse-borne typhus.

1493–1495, Haiti – Hispañola: first description of yellow fever (dengue?).

1528, Naples: 14,000 French besiegers succumbed to epidemic (louse-borne) typhus.

1542, Hungary: 30,000 people died from epidemic typhus.

1545, Mexico: an epidemic of haemorrhagic fever "cocolitztli" (aetiology has remained unexplained).

1546, FRACASTORO: "*De contagione et contagiosis morbis et eorum curatione*" – first theory of infectious diseases caused by germs ("*seminaria morbi*"); he

described three modes of infection (*contagiosis morbis*) – *per contactum; per fomites* (indirectly – via clothes, bedding, things); *ad distans* (via air).

1554, AGRICOLA: a treatise on plague ("*De peste libri III*").

1575–1577, an epidemic of plague in Italy (Milan and Venezia 70,000 victims, etc.).

1585, Milan: a pact between Milan and Swiss cities for control of plague (commerce etc.).

1606–1620, big outbreaks of plague in Germany, France, Switzerland, Italy.

1647–1648, an extensive epidemic of yellow fever in the Caribbean – Little Antilles (Barbados → St. Cristof → Guadeloupe), Yucatan and Cuba (e.g., in Havana one-third of citizens died); the disease was imported from West Africa during the slave trade (viraemic slaves and infected *Aedes aegypti* mosquitoes on ships).

1648–1649, Prague: a major epidemic of plague in the city besieged by Swedish soldiers at the end of the Thirty-Year's War.

1653–1654, plague in southern, western and northern (Sweden) Europe with a great number of victims (e.g., London 60,000; Genova 50,000; Amsterdam 50,000).

1675–1684, another extensive epidemic of plague in Europe (central) spreading from Poland to Moravia, Bohemia (13,000 victims in Prague alone), Austria, Germany etc.: schools and churches were closed and public religious services forbidden; *magistri sanitatis* (directors of health) and plague regulations (including obligatory notification of sick and dead persons) were installed in many towns; preventive measures were fixed for physicians, priests−confessors, and friars attending patients and dying persons; quarantine was imposed on foci of infection.

1709, plague in Poland, Hungary and Russia.

1713–1715, plague in Vienna (Austria), spread to Prague (Bohemia) by an infected tailor, and later to Moravia (Olomouc); the last plague epidemic in central Europe.

1720, plague in Marseille.

1737, plague in Mesina and environs (46,000 victims).

1741, an epidemic of yellow fever in Portugal and Spain (e.g., 10,000 victims in Cadiz).

1759, the first veterinary school in the world founded in Lyon.

1762, big outbreak of YF in Cuba.

1778, great YF epidemic in Senegal.

1779, extensive epidemic of sandfly (pappataci) fever among French soldiers in the Mediterranean (Italy) during the Napoleonic wars.

1779, big outbreak of dengue fever in Indonesia (on the island of Java).

1788, ANDRIEVSKI: human and animal anthrax are identical (autoinoculation).

1791, The Royal Veterinary College founded in London.

1793, Philadelphia (USA): yellow fever killed 10% citizens of the town.

1802–1803, YF epidemics in Portugal and Spain (80,000 victims), and on Haiti (29,000 French soldiers).

1804, ZINKE: experimental transmission of rabies by saliva from infected animals to healthy ones.

1817, beginning of pandemic cholera: India → China, Japan, Indonesia, Russia → Baltic, England, and Ireland, then → North America, Mexico.

1820, ERNST: dermatomycosis of a man, the source was a diseased cattle.

1839–1841, SCHÖNLEIN and GRUBY: the cause of human and animal favus is a fungus.

1849–1855, POLLENDER and REYER: microscopic detection of the anthrax agent (rods) in the blood of diseased sheep and humans.

1850, FRESENIUS: a description of avian aspergillosis and cultivation of the agent (*Aspergillus fumigatus*).

1851, Paris: 1st international conference on preventive measures against cholera, plague and YF.

1853, New Orleans, USA: YF (29,000 cases, 8,000 succumbed to the disease).

1854, BEAUPERTHUY: hypothesis on the transmission of YF by mosquitoes.

1855, SNOW: a monograph "*On the mode of communication of cholera*" (John Snow found that water from a certain pump on Broad Street in London was the source of infection with cholera that caused death of more than 500 people in August 1854; he laid the foundations of descriptive epidemiology).

1859, LAMBL: description of a protozoan *Cercomonas intestinalis* (now *Giardia lamblia*) as a cause of diarrhoea.

1863–1865, DAVAINE: experimental transmission of anthrax.

1866, GRAWITZ and REMAK: cultivation of the favus agent (*Trichophyton*) and demonstration of its pathogenity by autoinoculation (Remak) – cf. 1839.

1867, LISTER: introduction of aseptical and antiseptical techniques during chirurgical operations.

1870, Brazil: a big outbreak of YF.

1867–1873, OBERMAIER: description of the agent of endemic recurrent typhus (spirochete *Borrelia recurrentis*) in the blood of patients [he died 1873 after autoinoculation of a blood sample taken from a patient with cholera].

1873, LÖSCH: unraveled amoebic diarrhoea (*Entamoeba histolytica*).

1874, MÜNCH: confirmed the finding of Obermaier; a theory on transmission of spirochetes by lice, fleas and other insects.

1876, KOCH: cultivation of the anthrax agent (*Bacillus anthracis*) and detection of its ability to form spores: foundings of scientific research of infectious diseases (so-called Koch's postulates for verification of the disease agent).

1877, MANSON: mosquitoes are biological vectors of filariae *Wuchereria bancrofti* on Taiwan (first evidence on participation of mosquitoes in the transmission of diseases).

1878, plague in the Astrakhan region of Russia (Lower Volga), with 416 victims (the last outbreak of plague in Europe).

1878, an extensive epidemic of YF in the USA (132 towns were hit; 75,000 cases – 16,000 persons died).

1880, LAVERAN: discovery of the aetiological agent of malaria (*Plasmodium*) in the blood of patients [Nobel prize 1907].

1880, RITTER described psittacosis in 7 patients in Switzerland, acquired from exotic birds.

1880–1881, PASTEUR and TOUSSAINT: vaccine against anthrax (an attenuated culture of *B. anthracis*) successfully demonstrated in a public experiment on sheep (25 vaccinated, 25 controls) in Pouilly-le-Fort.

1881, FINLAY: hypothesis on transmission of YF by the mosquito *Aedes aegypti* in Cuba (cf. also 1854).

1881, KOCH: introduction of solid nutrient media (with gelatine and agar) for isolation and cultivation of pure cultures of microbes.

1882, PASTEUR: serum against rabies tested on animals.

1882–1883, LÖFFLER and SCHÜTZ: discovery of the agents of erysipeloid and glanders, and vaccination of swines against erysipeloid.

1884, GRAM: differential staining of bacteria for microscopy.

1884, NICOLAIER: microscopical evidence of the agent of tetanus.

1884, LICHTHEIM: pathogenicity of the fungus *Absidia corymbifera* for humans.

1885, PASTEUR: antiserum to rabies tested on man.

1885, CARRIÓN: fatal autoinfection with bartonellosis (connection between *verruga peruana* and *febris Oroya*).

1886, BRUCE: isolation of the agent (*Brucella melitensis*) from victims with "Maltese fever" and its experimental transmission to monkeys.

1886, an epidemic of yellow fever in the USA (20,000 victims).

1888, GÄRTNER: *Salmonella enteritidis* is a common agent of the human and cattle disease (58 human patients after eating meat from a diseased cattle = first description of food-borne human salmonellosis).

1888, Paris: Pasteur Institute founded.

1888, BABES: an intraerythrocytic protozoon is the agent of cattle piroplasmosis (described as *Haematococcus bovis*, renamed by Starkovici *Babesia bovis* in 1893).

1889, KITASATO: cultivation of tetanus bacterium (*Clostridium tetani*).

1890, EPPINGER: isolation of *Nocardia asteroides.*

1891, Berlin: Institute for Infectious Diseases (today called Robert Koch Institute) founded.

1892, LÖFFLER: isolation of *Salmonella typhimurium.*

1892, BEHRING and KITASATO prepared tetanus antiserum.

1893, SMITH and KILBORNE observed transmission of Texas cattle fever (piroplasmosis, caused by *Babesia bigemina*) by ticks *Boophilus annulatus* (first detection of transmission of a pathogen by ixodid ticks, including demonstration of both TST and TOT).

1893, MORANGE: transmission of psittacosis from parrots to humans.

1894–1930 (. . .1955), 3rd pandemic of plague started in Hongkong after dispersal from continental China; rats and their fleas spread the disease on ships to many harbours in the world (Japan, India, Europe, Africa, Americas and Australia): 30 million persons were affected, 12 millions of them died.

1894, YERSIN and KITASATO: isolation of the plague agent (*Yersinia pestis*) during the epidemic in Hongkong.

1895, BUSSE and SANFELICE discovered (and cultivated) the agent of human cryptococcosis.

1895, BRUCE: *Trypanosoma brucei* is transmitted by tsetse fly *Glossina morsitans.*

1897, OGATA explained the role of rats and the flea *Xenopsylla cheopsis* in the epidemics of plague.

1897, BANG: isolation of the agent of livestock brucellosis (*Brucella abortus*).

1897, FLÜGGE: evidence of transmission of epidemic typhus by the body louse.

1897, van ERMENGEM proved the aetiology of botulism (toxin of *Clostridium botulinum*).

1898, Liverpool: first School of Tropical Medicine in the world founded (Ross, Dutton).

1899, London School of Hygiene and Tropical Medicine founded (P. Manson).

1898, ROSS in birds and GRASSI in man explained epidemiology of malaria (its transmission by *Anopheles* mosquitoes) [1902 Nobel prize to Ross].

1898, SCHENCK discovered the agent of sporotrichosis (*Sporothrix schenckii*).

1898, GILCHRIST and STOKES: fungal aetiology of blastomycosis.

1900, Hamburg: Institute for Maritime and Tropical Diseases (today called Bernhard Nocht Institute for Tropical Medicine) founded.

1900, OPHÜLS and MOFFITT isolated the agent of coccidioidomycosis.

1898–1900, an extensive epidemic of YF in Cuba.

1900–1901, REED, CARROLL, LAZEAR and AGRAMONTE ("Yellow Fever Commission"): first evidence of the transmission of the YF agent by arthropods (*Aedes aegypti* – experimental mosquitoes were supplied by C. Finlay – cf. 1881) to a susceptible man; during the experiments J. Lazear infected himself unintentionally and died (first fatal laboratory infection with a virus); beginnings of arbovirology.

1901, GORGAS: eradication of the YF vector *Ae. aegypti* in Havana (larvicide control by oil; a similar action he headed in Panama during the building of the Canal, 1905).

1901, RICKETTS: isolation of the agent of blastomycosis (with autoinoculation).

1901–1902, DUTTON and BRUCE: human sleeping sickness is caused by *Trypanosoma gambiense* transmitted by the tsetse fly *Glossina palpalis.*

1902, AUJESZKY: propagation of pseudorabies virus (aetiology of *morbus Aujeszky*).

1903, NEGRI observed elementary bodies of rabies virus in the CNS of rabid animals.

1903, GRAHAM demonstrated transmission of dengue fever by mosquitoes in Lebanon.

1904–1905, DUTTON and TODD (Kenya), KOCH (east Africa), ROSS and MILNE (Uganda) elucidated the aetiology of African recurrent fever (spirochete *Borrelia duttoni*) and proved experimentally its vector (*Ornithodoros moubata*, including TOT) and susceptibility of monkeys to this disease (Dutton and Todd infected themselves at autopsy of the monkeys, and Dutton died due to the infection); this disease had already been known to Livingstone (as "human tick disease") in 1857.

1904, GAFFKY: isolation of *Clostridium botulinum.*

1905, ZAMMIT isolated *Brucella melitensis* from goat milk.

1906, RICKETTS discovered the agent of Rocky Mountain spotted fever and described its transmission (including TOT) by *Dermacentor* spp. ticks.

1906, BANCROFT found that the mosquito *Aedes aegypti* is the only vector of dengue.

1906, DARLING described histoplasmosis as protozoan disease (an error, cf. 1934).

1907, CHAGAS found that the "kissing bug" *Triatoma infestans* can transmit *Trypanosoma cruzi.*

1908, NICOLLE and MANCEAUX discovered *Toxoplasma gondii.*

1908, AFZELIUS described specific skin lesions called *erythema* (*chronicum*) *migrans* in some patients after attack of the tick *Ixodes ricinus* on them in Sweden (Lyme borreliosis – cf. 1982 and 1983).

1909, KLEINE described development of *Trypanosoma brucei gambiense* in the fly *Glossina palpalis.*

1909, DOERR, FRANZ and TAUSSIG carried out experimental transmission of the pappataci fever to volunteers by phlebotomines.

1909–1912, NICOLLE, SERGENT and FOLEY proved experimentally the transmission of epidemic typhus by body louse and discovered also so-called eclipse phase of pathogen in the vector [Nobel prize 1928].

1911, FRANCO et al. discovered in Columbia an alternative, forest cycle of yellow fever ("jungle YF") – confirmed in full in 1932 (SOPER), with monkeys and mosquitoes other than *Ae. aegypti* participating in the jungle cycle.

1911–1912, McCOY and CHAPIN isolated the agent of tularaemia from an ill ground squirrel (*Citellus beecheyi*) in the area of Tulare (California).

1911–1912, ZABOLOTNY et al. demonstrated plague in exoanthropic rodents (marmots, susliks) in Russia.

1912, SPLENDORE isolated dimorphic pathogenic fungus *Paracoccidioides brasiliensis.*

1913, PROWAZEK and ROCHA da LIMA: demonstration of the agent of epidemic typhus (*Rickettsia prowazeki*) in the body louse [S. Prowazek got laboratory infection and died of typhus in 1915].

1915, INADA and UHLENHUTH isolated *Leptospira icterohaemorrhagiae.*

1915, LANE and MEDLAR demonstrated the agent of chromoblastomycosis (*Phialophora verrucosa*).

1918, CLELAND and CAMPBELL isolated (by intracerebral inoculation of rhesus monkey) the virus of Murray Valley encephalitis from the CNS of three dead persons during an epidemic in Australia (the very first isolation of an arbovirus).

1918–1920, the pandemic of "Spanish flu" caused death of at least 21 million people (the aetiological agent originated with great probability from an avian influenza virus).

1920, STOKES passaged the yellow fever agent.

1920, FRANCIS found that the agent of tularaemia in ground squirrels, hares and rabbits is transmissible to human.

1921, BOYD and CRUTCHFIELD isolated the agent of maduromycosis (*Monosporium apiospermum*).

1923, SPENCER and PARKER found evidence that the vector of RMSF is the tick *Dermacentor andersoni.*

1924, SPENCER prepared a phenolized vaccine against RMSF.

1924, PARKER, SPENCER and FRANCIS: *D. andersoni* tick is also vector of tularaemia.

1925, RAMON and DESCOMBEY prepared anatoxin (vaccine) against tetanus *Clostridium tetani* (vaccine).

1926, MURRAY isolated *Listeria monocytogenes.*

1926, de KRUIF published a very successful book "Microbe Hunters".

1926, SILLER, HALL and HITCHENS demonstrated transmission of dengue to volunteers by *Aedes aegypti* mosquitoes.

1927, STOKES, BAUER and HUDSON verified that the agent of yellow fever is a filterable virus; the use of rhesus monkey for arbovirus isolation.

1927, RAMON applied vaccination against tetanus (toxoid).

1927–1928, a big outbreak of dengue fever in Athens, Greece.

1928, EVANS discovered that *Brucella abortus* causes undulating fever in humans.

1928, FLEMING observed antibacterial effect of the fungus *Penicillium notatum* on staphylococci (penicillin – cf. 1940).

1928, EPSTEIN and TARASOV demonstrated *Leptospira grippotyphosa* as the agent of "harvest fever" in Europe.

1929–1930, BEDSON et al. identified the agent of psittacosis (as a "virus") during a winter pandemic in USA and Europe, caused by importation of green Amazon parrots from Argentina.

1930, POOL, BROWNLEE and WILSON isolated louping ill virus from the CNS of sheep in Scotland and demonstrated the aetiology of LI by inoculating it to healthy sheep.

1930, THEILER first used white mouse (inoculated intracerebrally) for isolation of arboviruses.

1930, NAGAYO, KAWAMURA et al. demonstrated the transmission of tsutsuga-mushi fever by larval trombiculid mites ("chiggers").

1930–1932, DAUBNEY, HUDSON and GARNHAM isolated RVF virus from sheep.

1931, GOODPASTURE and WOODRUFF used chicken embryos for cultivation of viruses.

1931–1933, MEYER, ROSENBUSCH et al. isolated WEE virus from the brain of horses in California (first isolation of an arbovirus in USA).

1932, MacLEOD and GORDON demonstrated transmission of LI virus to sheep by the tick *Ixodes ricinus.*

1932, McCOY and BEDSON explained the aetiology of psittacosis (ornithosis).

1932, de KRUIF published another successful book about infectious diseases including zoonoses "Men Against Death".

1932–1933, MUCKENFUSS et al. isolated SLE virus from a patient.

1933, GILTNER, SHAHAN, TEN BROECK and MERRIL isolated EEE virus from CNS of dead horses during an extensive outbreak in USA (EEE virus was isolated from humans in USA later, in 1938).

1934, DeMONBREUN cultivated the agent of histoplasmosis, and found it to be a fungus [cf. 1906].

1934, LOVE and JUNGHERR isolated zoonotic simian B virus (*Herpesvirus simiae*).

1934, ARMSTRONG and LILLIE recovered LCM virus.

1934, PANOV reported on severe clinical symptoms and epidemiology of Russian spring-summer encephalitis in Siberia to the Ministry of Health of the USSR, and asked for a research expedition to be sent for detailed investigation of the disease.

1934, an epidemic of HFRS in Korea (aetiology unexplained at that time).

1935, DOMAGK reported about prontosil (he discovered the sulphonamide already in 1932) [Nobel prize 1939].

1935, vaccination of sheep against louping ill in Great Britain (the vaccine was formalinised, but contaminated with scrapie prions and caused the spread of scrapie in Britain).

1935, isolation of Japanese encephalitis virus from CNS of a deceased patient in Tokyo.

1935–1937, DERRICK described Q fever among slaughterhouse workers in Australia.

1936–1937, DAVID, DRBOHLAV, KŘIVINKA and VRLA: a big outbreak of tularaemia among rodents, hares, and then humans (>500 patients) in Lower Austria, west Slovakia and south Moravia (Czechland).

1937, THEILER released an attenuated vaccine (17D) against YF [Nobel prize 1951].

1937–1939, ZILBER, LEVKOVICH, CHUMAKOV, SMORODINTSEV, SHUBLADZE, PAVLOVSKY et al.: description of aetiology of RSSE (virus

isolation) and its epidemiology (*Ixodes persulcatus*) in Siberia; laboratory infection and untimely death of three investigators (N.V. Kagan, V.I. Pomerancev, N. Utkina) and chronic RSSE in M.P. Chumakov.

1938, BECK and WYCKOFF: isolation of VEE virus from horses in Venezuela.

1939, PAVLOVSKY formulated the paradigm on natural focality (nidality) of diseases.

1939, MÜLLER discovered insecticide effects of DDT (dichlordiphenyl-trichloethane), a compound synthetized by ZIEDLER already in 1874 [Nobel prize to MÜLLER in 1948].

1940, SMITHBURN et al. isolated WN virus from the blood of a patient in West Nile district, Uganda.

1940, FLOREY, CHAIN and HEATLEY prepared purified penicillin (cf. 1929), industrial production started in 1941 [Nobel prize to A. Fleming, E.B. Chain and H.W. Florey in 1945].

1940, SMORODINTSEV demonstrated viral aetiology of HFRS.

1941, HIRST introduced haemagglutination test and HIT in virological diagnostics (influenza, etc.).

1941, MEYER described two human cases of ornithosis acquired from a sick feral pigeon (in New York City).

1942, EMMONS and ASHBURN discovered adiasporomycosis (emmonsiosis) in North-American rodents.

1943–1944: KIMURA and HOTTA isolated dengue virus.

1943–1944, WAKSMAN, UGIE and SCHATZ discovered streptomycin [Nobel prize to S.A. Waksman 1952].

1944, WOODWARD synthetized quinine [Nobel prize 1965].

1944, SABIN et al. isolated viruses of pappataci fever (SFN, SFS) from the blood of patients and detected the vector (*Phlebotomus papatasi*).

1944, FLORIO et al. demonstrated experimental transmission of CTF virus by ixodid ticks.

1946–1947, CHUMAKOV et al. explained viral aetiology of Crimean haemorrhagic fever.

1946, Center for Disease Control (CDC) founded in Atlanta, USA (renamed as Centers for Disease Control and Prevention in 1994).

1946, HUEBNER, POMERANTZ and JELLISON discovered the agent of rickettsial pox and its vector (*Allodermanyssus* mites).

1947, CHUMAKOV et al. first isolated OHF virus (from a patient).

1947–1948, BURKHOLDER and DUGGAR proposed the wide-spectrum antibiotics chloramphenicol and tetracycline for treatment of rickettsial and other microbial diseases.

1949, The Gamaleya Institute for Epidemiology and Microbiology (of the USSR Academy of Medical Sciences) founded in Moscow.

1949, ENDERS, WELLER and ROBBINS used cell cultures (primary rhesus monkey kidney) for isolation and propagation of viruses [Nobel prize 1956].

1949–1950, KREJČÍ, GALLIA and RAMPAS isolated TBE virus from the blood and CSF of patients and from *Ixodes ricinus* ticks in Czechland.

1951, "The Rockefeller Foundation Virus Program": a total of 30 million USD were released for arbovirus investigations over the world until 1970 (>60 new viruses were isolated).

1951, BLAŠKOVIČ, BÁRDOŠ, RAŠKA et al. explained a big outbreak (>600 patients) of milk-borne TBE in Rožňava, east Slovakia.

1951–1954, outbreaks of HFRS among American soldiers during the Korean war (aetiology remained unexplained at that time; cf. 1956–1958).

1952, TAYLOR et al. isolated Sindbis virus from the mosquito *Culex univittatus* in Egypt.

1952–1953, Chikungunya virus was isolated during epidemics in Tanzania and Uganda.

1952, HAMMON and REEVES isolated the virus of California encephalitis from mosquitoes and detected first three cases of fatal encephalitis in children.

1953–1954, SMORODINTSEV and GREŠÍKOVÁ demonstrated experimentally the ability of the TBE virus to be transmitted by milk (cf. 1951).

1954, CHAMBERLAIN et al. used chicken embryos for isolation of arboviruses.

1955, plague in the Asian seaports Rangun, Bombay, Madras and some others (>12 million people died only in India).

1955, TAYLOR et al. used newborn laboratory mice as the most sensitive substrate for isolation of arboviruses.

1955–1957, WORK and TRAPIDO studied a big outbreak among monkeys in Kyasanur forest (southwest India), followed by an epidemic in humans; the agent was *Flavivirus* KFD, isolated also from ticks *Haemaphysalis spinigera*.

1957, SKRABALO and DEANOVIC described first case of human babesiosis (caused by *Babesia divergens*, Slovenia).

1958, PARODI, CASALS, BUCKLEY et al. described an epidemic of Argentine haemorrhagic fever with a high fatality rate, and isolated the agent (arenavirus Junin).

1958, BÁRDOŠ and DANIELOVÁ isolated Ťahyňa bunyavirus from *Aedes* mosquitoes in east Slovakia (the very first human pathogenic mosquito-borne virus isolated in Europe).

1958, SIMPSON isolated the agent of Congo haemorrhagic fever (CCHF virus).

1959, HADDOW et al.: a big outbreak of ONN fever in Uganda (2 million persons affected), the alphavirus isolated.

1960, MacKENZIE et al.: an epidemic of severe haemorragic fever ("el typho negro") in San Joaquin, Bolivia (cf. 1964–1965).

1960, BÁRDOŠ and SLUKA: certain summer flu-like cases of humans ("Valtice fever") in south Moravia (Czechland) are caused by Ťahyňa bunyavirus.

1961, Oropouche fever in Brazil, outbreak with 11,000 patients (but first cases revealed already in 1955).

1962–1964, a big outbreak of VEE in Venezuela and Columbia.

1964, GREŠÍKOVÁ and LIBÍKOVÁ isolated Tribeč/Lipovník virus (Kemerovo group) from ixodid ticks in Slovakia.

1964–1965, JOHNSON, MacKENZIE, KUNS and WEBB isolated the agent of Bolivian haemorrhagic fever (arenavirus Machupo) from humans and rodents.

1965, THOMPSON et al. isolated LaCrosse bunyavirus from the brain of a child killed by California encephalitis.

1967, CHUMAKOV isolated the agent of Crimean haemorrhagic fever in Russia (CCHF virus).

1967–1968, SIEGERT, MARTINI, HENNESSEN, STILLE et al.: three clusters of Marburg haemorrhagic fever cases (31 patients, 7 died) in pharmaceutical laboratories in Germany (Behringwerke AG in Marburg, and also Frankfurt) and in Serbia (Beograd) that were acquired from rhesus monkeys imported from Uganda in 1967.

1969, BUCKLEY, CASALS and DOWNS isolated Lassa arenavirus from the blood of a missionary during an epidemic in Nigeria.

1970, a big outbreak of Rocio (flavivirus) fever in Brazil.

1970, monkeypox in humans, Zaire (DR Congo). The virus was originally isolated from ill macaques by VON MAGNUS already in 1958.

1972, DOHERTY: a large outbreak of Ross River fever in Australia (but the virus was first isolated from mosquitoes in 1959, and then a number of human cases were reported up to 1970).

1972–1977, BUTZLER, SKIRROW et al.: *Campylobacter jejuni* causes epidemic bacterial gastroenteritis in humans.

1975, discovery of simian B herpesvirus, fatal for humans but benign for monkeys.

1976, NIME et al. found that *Cryptosporidium parvum* caused acute diarrhoea in humans (an epidemic with some 400,000 cases in Milwaukee, Wisconsin).

1976–1977, SHOPE, BEARE, CRAIG et al.: an epidemic of swine influenza among army recruits in Fort Dix, New Jersey (USA), the virus isolated; in a follow-up, 135 million USD were released for the US national vaccination campaign (however, Guillain-Barré syndrome developed in at least 1,500 of 40 million vaccinees).

1976–1977, McDADE, SHEPARD et al.: an outbreak of atypical pneumonia called "Legionnaires' disease" in a Philadelphia hotel (34 from 221 sick legionnaires died); isolation of the agent (*Legionella pneumophila*).

1976–1978, LEE, LEE and JOHNSON isolated the agent of HFRS in Korea and elsewhere (Hantaan bunyavirus).

1976–1979, BOWEN, JOHNSON, PATTYN, SUREAU, McCORMICK, et al.: extensive outbreaks of Ebola haemorrhagic fever in Zaire and Sudan, and recovery of the agent (a new filovirus).

1977–1978, a major epidemic of RVF in Egypt (18,000 persons with the disease, hundreds died).

1979–1980, BRUMMER-KORVENKONTIO et al. detected the agent of *nephropathia epidemica* in Finland (Puumala hantavirus).

1979–1980, an extensive epidemic of Ross River fever in Polynesia (more than 60,000 people affected).

1980, 2nd big epidemic of Oropouche fever in Amazonia.

1982, PRUSINER: infectious agents in spongiform encephalopathies are specific proteins ("prions") [Nobel prize 1997].

1982–1983, RILEY et al.: enteropathogenic *Escherichia coli* O157:H7 was the cause of epidemic haemorrhagic enterocolitis (hamburgers, USA) and of haemolytic-uraemic syndrome.

1982, BURGDORFER et al. clarified the aetiology of Lyme disease (an ixodid tick-borne spirochete), observed in Old Lyme (Connecticut, USA) since 1975, and clinically described as rheumatic arthritis in 1977.

1983, STEERE et al. isolated the agent of Lyme disease (*Borrelia burgdorferi*).

1983, MONTAGNIER, BARRÉ-SINOUSSI, GALLO et al. isolated a lymphotropic retrovirus (lentivirus HIV) from patients with AIDS, a syndrome described in 1981.

1985, MULLIS introduced PCR in microbiology.

1986–1987, MAEDA et al. described human tick-borne monocytic ehrlichiosis.

1988, GLIGIČ et al. isolated the agent of HFRS in Serbia (Dobrava hantavirus).

1989–1991, haemorrhagic fever in Venezuela (Guanarito arenavirus isolated).

1990–1992, REGNERY, WELCH et al. isolated the causative agent of cat-scratch fever (*Bartonella henselae*).

1991, ANDERSON, DAWSON et al. isolated the agent of human monocytic ehrlichiosis (*Ehrlichia chaffeensis*).

1993, TEMPEST, CHEEK, NICHOL, PETERS, KSIAZEK, CHILDS, LeDUC, ELLIOTT, JAHRLING, SCHMALJOHN et al.: an epidemic of lethal pulmonary syndrome among Navaha Indians in the "Four Corners" region (southwestern USA), and isolation of the agent (Sin Nombre hantavirus).

1994, BAKKEN, DUMLER, CHEN et al. described human tick-borne granulocytic anaplasmosis, and detection of the agent (*Anaplasma phagocytophilum*) in *Ixodes scapularis* ticks in USA.

1994–1995, MURRAY, SELVEY et al. isolated Hendra paramyxovirus from ill horses and from a man in Australia.

1996, WILL et al. reported occurrence of a new variant Creutzfeld-Jakob prion disease (vCJD) that is pathogenic for man (since 1994) and linked to the epizootic of bovine spongiform encephalopathy ("mad cows disease") that appeared in Great Britain in 1986.

1996, an outbreak of West Nile encephalitis in Romania (>500 patients).

1998, PHILBEY, KIRKLAND, ROSS et al. isolated a new Menangle paramyxovirus in Australia (pigs, humans, fruit bats).

1998–99, SIT and BING isolated a new Nipah paramyxovirus during a big outbreak (pigs, humans) in Malaysia.

1999 –2006, a very surprising epidemic of West Nile encephalitis in New York after an importation of WNV (probably from Israel), with a following spread over whole North (later also Central and South) America; closely before this event, big WN outbreaks in southern Russia and Israel.

2002, an extensive epidemic of SARS in southeast Asia, exported later to other countries (Canada etc.).

2005, founding of the "European Centre for Disease Prevention and Control" (ECDC), Stockholm.

2005–2006, a major epidemic of avian influenza (H5N1) in Asia, with a following wave-like rapid spread to Europe and Africa; the strain also infected 504 humans and caused 299 deaths (WHO, as of 12 August 2010); most cases have been reported from Indonesia (168), Vietnam (119), and Egypt (111).

2005–2007, to date the largest epidemic of chikungunya fever on islands in Indian Ocean (Réunion Island etc.), in India etc. (about 280,000 cases – 213 persons died).

2005–2010 (still ongoing), a major outbreak of Q fever in the Netherlands (at least 3,500 human cases up to 2009).