

Chapter 41

Dangerous Viral Pathogens of Animal Origin: Risk and Biosecurity

Zoonotic Select Agents

Jean-Paul Gonzalez and Gavin Macgregor-Skinner

Abstract Most of emerging infectious diseases affecting humans are of animal origin and transmitted under natural circumstances from either, wild or domestic vertebrate animals giving the way of zoonotic infection or epidemics. Zoonotic diseases carry a common ancient history between human and animals as a result of pathogen exchanges involving transgression of the species barrier. Nowadays, several agents have been targeted for their potential to be a major risk for human and animal populations and, have been characterized by their potential to be highly pathogenic and/or transmissible, and lacking of any means of protection. Those agents have been listed as “Select Agents” having the potential to pose a severe threat to both human and animal health, as well as to animal and plant products. Several of the most dangerous agents responsible of viral hemorrhagic fever are review in this chapter including: Ebola virus, Marburg virus, Rift valley fever virus, Kyasanur forest virus, Omsk hemorrhagic fever virus, Alkhurma hemorrhagic fever virus.

41.1 Introduction

More than 75% of recently emerging infectious diseases affecting humans are of animal origin; about two third of all human pathogens have an animal source as a natural reservoir (Taylor et al. 2001). The nosologic term of “Zoonosis” has been crafted to gather all transmissible diseases harboring a potential to infect both human and animal (Palmer et al. 2001). Zoonosis (i.e. zoonotic diseases) are transmissible diseases between animals and man with an infectious (microbes and

J.-P. Gonzalez (✉)
Emerging Diseases and Biosecurity, Metabiota Inc., Suite 600,
1 Sutter St, San Francisco, CA 94104
e-mail: jpgonzalez@Metabiota.com

G. Macgregor-Skinner
Department of Public Health Sciences, College of Medicine,
The Pennsylvania State University, Hershey, USA
e-mail: gum13@psu.edu

prions) or parasitic origin. In another term, a zoonotic disease represents any animal disease communicable to human and/or vice versa. Ultimately, zoonosis can be transmitted from animals to humans, directly or indirectly, sometimes by a vector or an intermediate host, or also from humans to other animals. This is considered as reverse zoonosis and called anthroponotic disease, or zoonanthroponosis. Zoonoses can be of viral (Yellow Fever, HIV, hantavirus), bacterial (tularemia, leptospirosis, lyme disease), rickettsial (Q-fever), fungal (aspergillosis, histoplasmosis), parasitic (giardiasis, cryptosporidiasis), or prions (Creutzfeldt–Jakob disease) origins. Also the mechanisms of transmission are the main factors driving the risk of human infection. Infectious agents are transmissible under natural circumstances from wild or domestic vertebrate animals to humans. They can also be transmitted from animal products causing foodborne diseases, e.g. *Escherichia coli* O157:H7, *Campylobacter*, *Calicivirus*, or *Salmonella*.

The origin of zoonotic diseases occurred probably when humans came in close contact (scavenging or hunting) with wild animals. Indeed, several zoonoses have been known since early prehistoric times. The first hominids were in direct contact with animal groups which previously appeared on Earth some 540 million years ago (ya.). The history of mankind, starting with *Australopithecus*, begins about 5 million ya. and coincides with the first contact and potential of microbe exchanges between fauna and this human precursor. Also, one of the most ancient hominids, *Australopithecus*, was not hunter, but a pretty game (!) hunted by large and powerful carnivorous. Also sick and infected individuals were eaten by such large predators, and human epidemics turned short (Debré and Gonzalez 2013). Earlier *Homo* species from the Pleistocene era (2.6 million–11,700 ya.) utilized larger animals for subsistence (Rabinovich et al. 2008) including mammoths, long horned bisons, saber-toothed cats, giant ground sloths, among others mammals of North America, Asia, and Europe. It is quite acceptable that these creatures were able to exchange their parasites, e.g. intestinal and blood parasites or fur ectoparasites, with humans.

Hunting remained a crucial component of hunter-gatherer societies before the domestication of livestock and the dawn of agriculture 11,000 ya. First attempts to domesticate dogs, goats, and sheep, occurred as early as 15,000–9,000 ya., giving rise to domestic zoonotic parasitic disease. Ultimately, about 1000 ya., 22 species were domesticated including dog, goat, sheep, cattle, camel, pigs, and chicken. Later, during the Neolithic period, when agricultural practices appeared, domestication was well under way supporting the appearance of e.g. flea-or louse-transmitted bacterial zoonoses or pyogenic infections after contact to wild and domestic animals. In fact, in prehistoric times, when human populations were organized in small tribes with a limited number of 100–200 individuals, the human population was actually an accidental victim of infectious diseases, developing rapidly an herd immunity and leaving the pathogens to infect and survive in the more abundant animal populations (e.g. anthrax, rabies, tularemia, cysticercosis) (Debré and Gonzalez 2013).

Indeed, zoonotic diseases carry a common history between human and animals as a result of pathogen exchanges involving a transgression of the species barrier. Altogether, such events occur in a variety of situations involving different hosts,

vectors, the pathogens natural cycle's, and the ability of a pathogen to target specific host cells or organs sharing some structural identity between taxonomically distant species (i.e.: human to non-human mammal species).

41.1.1 Zoonotic risk

Essentially, a zoonotic risk exists and increases with the frequency of contact between infected animals and uninfected permissive human hosts, as well as with the capacity of a pathogen to infect both.

Transgressing the Species Barrier The pathogen species-jumping ability is relevant from wild as well as domestic animal species that can transmit their own microbes to human. The species barrier can easily be violated when species are sympatric and/or taxonomically closely related (e.g.: Arenavirus and different rodent species). Although some pathogens have a high infectious specificity and are usually restricted to infect one host species, some of them can pass the species barrier after a mutation or genetic re-assortment (e.g.: the SARS coronavirus from chiropteran to Palm civet, avian influenza from bird to pig) and/or after an alteration of the permissive host (e.g. due to immunodeficiency). Ultimately, zoonotic diseases result from parasites, *sensu lato*, that can live apparently harmlessly in a natural host while producing disease upon entry into a different host. Some prominent examples are e.g. HIV having a non-human primate origin and influenza viruses generated from pig and bird viruses after genetic re-assortment, both subsequently evolving to be adapted to a human-to-human virus transmission.

Disease Emergence in Humans A variety of classical human viral diseases are suspected to be the consequence of such a virus jump from animal to human. The origin of such species-jumping leading to disease emergence in the human population takes place in different situations generally associated with human behavior. As mentioned above, the first pathogen exchanges between humans and animals probably occurred sequentially from hunting wild animals to animal domestication.

For example, it is hypothesized that the following diseases originated from either domestic and wild animals: smallpox from rodents more than 10,000 ya., common cold rhinovirus from cattle more than 4,000 ya., influenza from pigs more than 8,000 ya., measles from cattle plague 300 ya., HIV from non-human primates (NHP) less than 100 ya. (Hughes 2010).

Human Population at Risk While many of the zoonotic microbial agents (e.g. the bacteria causing tuberculosis or diphtheria) are resident in domestic mammals and birds, farmers, breeders and all those involved in food animal production are at risk, since the growing contact between humans and wildlife clearly increases the zoonotic risk (e.g. the example of Ebola fever) (Daszak et al. 2000). This can be caused either by encroachment of human activity into wilderness areas or by movement of wild animals into areas of human activity (Artsob 2004).

There are undoubtedly many zoonotic agents waiting in Nature that have the potential to be introduced into humans. Among animal reservoirs with a high and manifest risk for zoonotic transmission are the NHP because of their genetic closeness to humans (Gonzalez et al. 2013) and pigs because of the similarity of their digestive, respiratory and immune systems with the human ones (Martien et al. 2012).

Besides the “natural” risk of an emergence of a certain zoonosis that is directly linked to pathogen evolution (i.e.: change in pathogenicity) and ecology (e.g., extreme weather events, natural catastrophies, climate change), more cryptic threats exist and are a cause of concern: the possibility of zoonotic emergence from xenotransplantation from an infected animal biological product (Allan 1996) and the deliberate release of infectious agents into human or animal populations by people (Atlas 2001).

Altogether, most of the factors involved in zoonotic emergence are of human origin, e.g. occupational (poaching, hunting, butchering), due to individual behavior (pets, eating bush meat), by man-made environmental changes (landscape fragmentation, protected area parks and recreational activities), or through social behavior (migration).

41.1.2 Biosecurity

Biosecurity is a set of preventive measures designed to reduce the risk of infection by multiple actions (quarantined pests, contain invasive alien species, master viable genetically modified organisms [GMO], identify pathogen genetic shift, etc.) modulated by the foundations of risk in line with the assessment of biological risk. To this end, scientific research became the principal actor in a complex process aimed at understanding and mastering the emergence of pathologies (Gonzalez and Fair 2013).

Risk Assessment The biological risk can be either of natural (i.e.: the random encounter of the pathogen, the natural host and human), accidental (i.e.: unexpected “spill over” of the pathogen that infect another host including human), or deliberate origin (i.e.: an individual—criminal—or a group—terrorist—undertaking taking action to infect human or animals). Preventive measure needs a risk assessment with respect to the identified pathogen and its potential to target human and animal (or vector) populations. Several pathogens have been identified as particularly dangerous in that matter regarding their intrinsic characteristics. Ultimately, human and animal populations can consequently be identified concerning their vulnerability to the agent (i.e.: pathogenicity and occurrence in the same environment) (Table 41.1).

Select Agents Several classes of diseases and agents have been identified as presenting a particular high level of danger including hemorrhagic fever of viral or bacterial origin, infectious neurological syndromes, severe respiratory syndromes among others. Also, regarding the pathogenicity of infectious agents (virulence) and infectiousness (potential to spread) with respect to the risk for either the general

Table 41.1 Common human and animal highly pathogenic viruses

| Virus family | Virus name | Geographical origin | Hosts: Main/secondary | Vector | Transmission and public health issues | Risk assessment | Human pathogenic | Reference |
|--------------|--------------------------------|---------------------|---|----------|---------------------------------------|-----------------|--|-----------------------------|
| Arenavirus | Barmah forest | Australia | Possums, kangaroos and wallabies | Mosquito | HT: by bites from infected mosquitoes | Z | Mild illness, ILS (pain) recovery | Marshall et al. (1982) |
| | Venezuelan equine encephalitis | America | Horse/zebra, donkey | | HT: Zoonosis fever epizootics | SA/P3/ | ILS/ENC | Gardner et al. (2008) |
| | Chapare ^a | America | Rodent, potentially but no evidence yet? -? | | HT: ? | SA/P4 | H, HF: ILS + vomiting + hemorrhagic signs | Delgado et al. (2008) |
| Arenavirus | Jumín ^a | Argentina | <i>Calomys musculinus</i> (dry lands vesper mouse or corn mouse) | | HT: rodent biological fluid | SA/P4/ | H, HF: neurological signs; mortality 20–30% | Maiztegui (1975) |
| | Lassa fever ^a | Africa | <i>Mastomys natalensis</i> (natal multimammate mouse) | | HT: rodent biological fluid | SA/P4/ | H, HF: + neurological signs; mortality 30% during epidemics | Buckley et al. (1970) |
| | Lujó virus | Africa | Rodent, potentially but no evidence yet? | | HT: ? | SA/P4/ | H/HF: 80% fatalities | Paweska et al. (2009) |
| | Lymphocytic Choriomeningitis | WW | Mice with weight loss, retardation of growth and hair development, often lethal | | HT: mice | Z | H: two phase, ILS and meningitis- encephalitis; E: neurological damage | Armstrong and Lillie (1934) |
| | Machupo ^a | Bolivia | <i>Calomys callosus</i> (large vesper mouse) | | HT: rodent | SA/P4/ | H/HF: slow onset with influenza like fever + Petechial; 30% mortality | Johnson et al. (1966) |

Table 41.1 (continued)

| Virus family | Virus name | Geographical origin | Hosts: Main/secondary | Vector | Transmission and public health issues | Risk assessment | Human pathogenic | Reference |
|--------------|------------------------------|------------------------|--|---|---------------------------------------|-----------------|---|----------------------------|
| | Sabia | Brazil | Rodent ? | | HT: aerosol | SA/P4/ | H/HF one fatal case among 3 known; E: 1 death/3 | Coimbra et al. (1994) |
| | Guanarito ^a | Brazil | <i>Zygodontomys brevicauda</i> (short-tailed cane mouse) | | HT: rodent | SA/P4/ | H/HF 23.1% mortality | Salas et al. (1991) |
| Bornavirus | Borna | WW | Horse/cattle, sheep, dog | | HT: rodent ? | Z | P/NS | Lipkin (2007) |
| Bunyavirus | Oropouche fever | Brazil | Sloth | Mosquito | HT: mosquito bite | Z | P/meningitis | Anderson et al. (1961) |
| Coronavirus | SARS- coronavirus (SARS-CoV) | Asia/pandemic | <i>Panguma larvata</i> /bats? And | | HT: Civets direct contact | SA/P3-4 / | H/acute RS, 10% mortality | Peiris et al. (2003) |
| Filovirus | Ebola ^a | Central Africa | Bats fruit eating | | HT: Bats | SA/P4 / | H/HF 70% mortality | Yun (2012) |
| | Marburg ^a | Central Africa | Bats | | HT: Bats | SA/P4/ | H/HF 25+% mortality | Yun (2012) |
| Flavivirus | Dengue fever | Asia, Africa, Americas | Monkey? | <i>Aedes aegypti</i> , <i>A. albopictus</i> | HT: Mosquito | P2 | H/Fever to HF | Petersen and Gubler (2003) |
| | Eastern equine encephalitis | Americas | Horse | Ticks | HT: Mosquito | SA/P3-4/ | H/ENC 25% + mortality | Zacks and Paessler (2010) |
| | Kyasanur forest disease | Southeast Asia | Monkey | Ticks | HT: ticks | SA/P4/ | H/HF ENC 3-5% mortality | Work et al. (1959) |
| | Omsk hemorrhagic fever | Siberia | Rodents | Ticks | HT: tick | SA/P4/ | H/ILS to HF, mortality 1-10% | Chumakov et al. (1948) |
| | Tick-borne encephalitis, TBE | | | | | | | Barrett et al. (2008) |

Table 41.1 (continued)

| Virus family | Virus name | Geographical origin | Hosts: Main/secondary | Vector | Transmission and public health issues | Risk assessment | Human pathogenic | Reference |
|--------------|--|-----------------------|------------------------------------|----------|---|-----------------|-----------------------|---------------------------|
| Hantavirus | TBE far eastern subtype | Europe | Game | Ticks | HT + tick bite | SA/P4/ | H/ENC, mortality 1-2% | |
| | TBE Siberian subtype | Siberia | | Ticks | HT + tick bite | SA/P4/ | H/ENC, mortality 1-2% | |
| | West Nile virus | WW | Horse/bird | Mosquito | HT: Mosquito bite | Z | H/ENC | |
| | Western equine encephalitis | Americas | Horse | | HT: Mosquito bite | Z | H/ENC mortality 35% | Zacks and Paessler (2010) |
| | Yellow fever | Africa, South America | Monkeys | Mosquito | HT: Mosquito bite | Z/P3 | H/HF, ENC | Monath et al. (2008) |
| Henipavirus | Hantaviruses (except KHF) | WW | Rodents | | HT: rodent feces, urine | Z/P3 P4 | H/HF—ReS | Lee (1989) |
| | Korean hemorrhagic fever, KHF ^a | Asia | Rodent | | HT: rodent feces, urine; S and S; E; | Z | H/HF | Lee et al. (1978) |
| | Puumala | Europe | Rodents | | HT: rodent feces, urine | Z | P/ReS | Brummer et al. (1980) |
| | Hendra | Australia | Bats | Horses | HT: + bat urine, animals? | SA/P4/ | H/NS—RS | Field et al. (2009) |
| Herpesvirus | Nipah | Asia (Africa?) | Bats | | HT: + bat urine, human? | SA/P4/ | H/RS | Halpin et al. (2000) |
| | Cytomegalovirus (B Herpes) | WW | Primates | | HT: direct contact | ? | + mild (fever) | Michaels et al. (2001) |
| | Herpes simian B | WW | Monkey macaque | | HT: direct contact | Z | H/ENC | Gay and Holden (1933) |
| | Lymphocryptovirus (LCVs) gammaherpesvirus | WW | Primates (Old world and new world) | | Direct contact, saliva; Epstein-Barr virus (EBV), human LCV | | ? | Ablashi et al. (1978) |

Table 41.1 (continued)

| Virus family | Virus name | Geographical origin | Hosts: Main/secondary | Vector | Transmission and public health issues | Risk assessment | Human pathogenic | Reference |
|----------------|---|---------------------|---|----------|--|-----------------|------------------|------------------------|
| Nairovirus | Crimean-Congo haemorrhagic fever ^a | Africa, Asia | Cattle | Ticks | HT: tick bite | SA/P4 | HF | Chumakov et al. (1968) |
| | Influenza A virus H1N1 | WW | Pigs/birds | | HT: Influenza syndrome | Z | H/ILS + RS | Suarez et al. (2000) |
| Orthomyxovirus | Influenza A virus: Highly Pathogenic Avian influenza (HPAIV) ^a | WW | Ducks, shore birds, gulls (natural reservoirs of AIV ^c) | | Several AI strains infect human (H5N1, H7N2, H7N3, H7N, H9 H9N2, H9N and, H10N7) | USDA SA | H/RS | Chan PK (2002) |
| | Newcastle disease | WW | Avian | | HT: direct contact | USDA SA | P/conjunctivitis | Nelson et al. (1952) |
| Phlebovirus | Rift Valley fever | Africa | Cattle | Mosquito | HT: mosquito bite | SA/P3-4 / | H/HF | |
| Poxvirus | Monkeypox | Central Africa | Monkeys | | HT: direct contact, bite | SA/P4/ | Skin lesions | Ladnyj et al. (1972) |
| | Orf | WW | Sheep goat | | HT: direct contact (skin wound) | Z | P/MD | Geraut (2006) |
| Retrovirus | Human Immunodeficiency, HIV (ref. to SIV) | WW | NHP | | HT (Historical: see Hahn et al.) | Z | HP/P3 | Hahn BH, et al. (2000) |
| | Simian Foamy (SFV) | Africa | Primates | | HT: monkey bite | Z | Asymptomatic | Wolfe et al. (2004) |
| | Simian Immunodeficiency (SIV) | Africa | Primates | | HT: ? | S | Asymptomatic (?) | Switzer et al. (2010) |

Table 41.1 (continued)

| Virus family | Virus name | Geographical origin | Hosts: Main/secondary | Vector | Transmission and public health issues | Risk assessment | Human pathogenic | Reference |
|--------------|--|---------------------|-----------------------|--------|---------------------------------------|-----------------|--|----------------------------|
| Rhabdovirus | Simian T-cell Leukemia (STLV) | Africa | Primates | | HT: ? | P | Asymptomatic (?) | Mahieux and Gessain (2011) |
| | Rabies | WW | Canids (lethal) | Feline | HT: bite | Z | H Neurological syndrome; 100% fatal/NS | |
| | Vesicular stomatitis (VS) ^a | Americas | Horses, cattle, pigs | | HT: aerosolization or direct exposure | USDA SA | H/IL | |

WW worldwide, HT human transmission (+ : positive, ? : unknown), SA national institute of allergy and infectious diseases select agent (see ref.), SA USDA select agent of veterinary importance (see ref. and Table 41.2), P (3-4) p level of security = (ref. CDC), H highly pathogenic, ILS influenza like syndrome, P potentially pathogenic, S suspected, MD mild disease, NS neurological syndrome, ReS renal syndrome, RS respiratory syndrome, WW world wide, HF hemorrhagic fever, SA select agent, USDA SA USDA select agents, Z recognized as zoonotic

^a potential biological weapon

^b Select Agents Regulations (42 CFR Part 73, 7 CFR Part 331, 9 CFR Part 121) in the Federal Register on March 18, 2005

^c domestic and wild avian species (including chickens, turkeys, ducks, domestic geese, quail, pheasants, partridge, parrots, gulls, shorebirds, seabirds, emu, eagles, and others). cause disease in horses, pigs, whales, and seals; expanding to others mammalian species, i.e. cats, dogs, foxes, leopards, tigers, civets, pigs, raccoons

human population or laboratory workers, they have been classified as P3–4 level of containment agents (Richmond and McKinney 1999).

For practical reasons, several agents have been targeted for their potential to be a risk for human and animal populations and characterized according their potential to be highly pathogenic or to be highly transmissible—in particular by aerosols—and the lack of any means of protection, e.g. by a vaccine. Those agents have been listed by HHS and USDA as “Select Agents” having the potential to pose a severe threat to both human and animal health, (potentially plant health), or to animal and plant products. Among these 45 Select Agents (33 viruses and 12 bacteria) 31 (69%) are zoonotic, while the remaining are known to infect only animals (Table 41.2)¹.

Risk Mitigation and International Perspective Major factors have to be taken in account in order to reduce the risk of transmission between animals and humans. Besides reducing the direct contact among the two populations, tools and strategies to fight zoonoses has to be specifically developed. Select Agents have to be surveyed for their emergence, circulation and evolution. Highly pathogenic agents, as well as Select Agents, have to be diagnosed and handled by well-trained workers in certified appropriate laboratory structures (P3 and P4 laboratories, etc.) and their circulation controlled (i.e.: shipping, transferring from one laboratory to another, etc.).

41.2 Highly Pathogenic Viral Zoonoses

41.2.1 *Viral Hemorrhagic Fevers (VHF)*

Viral Hemorrhagic Fevers (VHF) appear as a whole clinical entity characterized by (high) fever and bleeding that can progress to shock and death. The first severe VHF identified was the Ebola Hemorrhagic Fever (1976), although the Marburg virus was isolated and characterized earlier in 1967; Marburg virus, however, appears in the medical literature as part of the nosocomial framework of VHF only in 1977 when published aside with the Ebola virus (Bowen et al. 1977). Later, several already known VHF joined the concept including: the Hemorrhagic Fevers with Renal failure (known since 1951), the Hantavirus in 1978 (Lee et al. 1978); the Lassa fever and Bolivian and Argentine HF, Yellow Fever, Rift Valley Fever, Crimean Congo Hemorrhagic fever (CCHF), and others. The group of VHF was identified as a nosologic entity associated with viruses belonging essentially to five distinct families of RNA viruses: the four Arenaviridae, Filoviridae, Bunyaviridae, and Flaviviridae. Only recently in September 2012 scientists reported the isolation of a member of the Rhabdoviridae family responsible for VHF in the Bas-Congo district of the Democratic Republic of Congo (Grard et al. 2012). Several VHF share many important features: (1) many of them may be transmitted by arthropod-borne agents

¹ <http://www.selectagents.gov/Select%20Agents%20and%20Toxins%20Exclusions.html>.

Table 41.2 Common human and animal highly pathogenic viruses

| HHS select agents (zoonotic) | USDA select agents (not zoonotic) | |
|---------------------------------------|---|-------------------------------------|
| Virus | Bacteria/Rickettsia | Virus |
| Chapare | <i>Bacillus anthracis</i> ^a | African horse sickness |
| Crimean-Congo haemorrhagic fever | <i>Brucella abortus</i> | African swine fever |
| Eastern equine encephalitis | <i>Brucella melitensis</i> | Avian influenza |
| Ebola ^a | <i>Brucella suis</i> | Classical swine fever |
| Guanarito | <i>Burkholderia mallei</i> ^a | Foot-and-mouth disease ^a |
| Hendra | <i>Burkholderia pseudomallei</i> ^a | Goat pox |
| Junin | <i>Coxiella burnetii</i> | Lumpy skin disease |
| Lassa fever | <i>Francisella tularensis</i> ^a | Newcastle disease virus |
| Lujo | <i>Rickettsia prowazekii</i> | Peste des petits ruminants |
| Machupo | <i>Yersinia pestis</i> ^a | Rinderpest virus ^a |
| Marburg ^a | | Sheep pox |
| Monkeypox | | Swine vesicular disease |
| Nipah | | |
| Kyasanur forest disease | | |
| Omsk hemorrhagic fever | | |
| Rift valley fever | | |
| Sabia | | |
| Tick-borne encephalitis complex | | |
| Variola major (Smallpox) ^a | | |
| Variola minor (Alastrim) ^a | | |
| Venezuelan equine encephalitis | | |

HHS (US department of) health and human Services, USDA US department of agriculture

^a Tier 1 Agent

(usually mosquito vector), (2) person-to-person transmission is possible through direct contact with infected patients, their blood or other body fluids; (3) natural animal reservoirs are mainly rats and mice, but also domestic livestock, monkeys or other NHP may serve as intermediate hosts. Moreover, with the increasing international travel, these mainly tropical viruses may now be imported into non-endemic countries thus posing a major global risk for human public health. Furthermore, several of these agents have been associated with nosocomial outbreaks involving health care and laboratory workers.

Due to special biosecurity concerns, we will mainly focus in the following on Filoviruses, RVFV, other flavivirus responsible of hemorrhagic fevers, Kyasanur Forest disease and Omsk HF. Alkhurma HF virus is cited in cursory detail because its limited geographic distribution.

41.2.1.1 Filoviruses (Ebola and Marburg)

Filoviruses

Ebola and Marburg viruses are the only members of the genus *Filovirus* in the *Filoviridae* family and can cause severe hemorrhagic fever in humans and NHP.

The genus *Marburgvirus* consists of a single species, *Marburg marburgvirus*, with 2 member viruses, Marburg virus (MARV) and Ravn virus (RAVV).

The genus *Ebolavirus* contains five species: *Bundibugyo ebolavirus*, *Zaire ebolavirus*, *Reston ebolavirus*, *Sudan ebolavirus*, and *Tai Forest ebolavirus*, whose members are Bundibugyo virus (BDBV), Ebola virus (EBOV), Reston virus (RESTV), Sudan virus (SUDV), and Tai Forest virus (TAFV), respectively (Kuhn et al. 2010). Ebola-Reston is the only known Filovirus that does not cause severe disease in humans; however, it can still be fatal in monkeys and it has been recently recovered from infected pigs in South-East Asia. A third, tentative genus (“*Cuevavirus*”) has been suggested for a novel filovirus, Lloviu virus (LLOV; species “*Lloviu cuevavirus*”), which has not yet been isolated in culture. With the exception of RESTV and possibly LLOV, all of these viruses cause severe and often fatal viral hemorrhagic fever (VHF) upon infection in humans (Negredo et al. 2011).

The Pathogen

Ebola and Marburg viruses are elongated filamentous molecules, highly variable in length, and are typically between 800–1000 nm long, and can be up to 1400 nm long due to concatamerization, with a uniform diameter of 80 nm. The viral fragment is pleomorphic, and may appear in the shape of a “6”, a “U”, or a circle, and it is contained within a lipid membrane. Each virion contains one molecule of single-stranded, negative-sense viral genomic RNA, complexed with the proteins *NP*, *VP35*, *VP30*, and *L* (Kiley et al. 1982; Sanchez et al. 1992; Geisbert and Jahrling 1995; Mwanatambwe et al. 2001; Pringle 2005).

Pathogenesis

Two independent studies reported that Ebola virus cell entry and replication requires the cholesterol transporter protein Niemann-Pick C1 (NPC1). The studies described that when cells from Niemann Pick Type C1 patients were exposed to Ebola virus in the laboratory, the cells survived and appeared immune to the virus, further indicating that Ebola relies on NPC1 to enter cells. The same studies described similar results with Ebola's cousin in the filovirus group, Marburg virus, showing that it too needs NPC1 to enter cells (Carette et al. 2011; Côté et al. 2011). Furthermore, NPC1 was shown to be critical to filovirus entry because it mediates infection by binding directly to the viral envelope glycoprotein (Côté et al. 2011). Miller et al. (2012) confirmed the findings that NPC1 is a critical filovirus receptor that mediates infection by binding directly to the viral envelope glycoprotein and that the second lysosomal domain of NPC1 mediates this binding. Carette et al. (2011) showed mice that were heterozygous for NPC1 were protected from lethal challenge with mouse adapted Ebola virus. Together, these studies suggest NPC1 may be a potential therapeutic target for an Ebola anti-viral drug.

Clinical Signs

Ebola and Marburg virions enter the host cells through endocytosis and replication occurs in the cytoplasm. Upon infection, the virus targets the host blood coagulative and immune defense system and leads to severe immunosuppression (Harcourt et al. 1999).

Ebola virus disease is clinically indistinguishable from Marburg virus disease, and both are similar to many other diseases prevalent in Equatorial Africa (Grolla et al. 2005).

Early signs of infection are non-specific and flu-like, and may include sudden onset of fever, asthenia, diarrhea, headache, myalgia, arthralgia, vomiting, and abdominal pains (Bwaka et al. 1999). Less common early symptoms such as conjunctival injection, sore throat, rashes, and bleeding may also appear. Shock, cerebral oedema, coagulation disorders, and secondary bacterial infection may co-occur with onset of infection (Feldmann 2010). Hemorrhagic symptoms begin 4–5 days after onset, which includes hemorrhagic conjunctivitis, pharyngitis, bleeding gums, oral/lip ulceration, hematemesis, melena, hematuria, epistaxis, and vaginal bleeding. Hepatocellular damage, marrow depression (such as thrombocytopenia and leucopenia), serum transaminase elevation, and proteinuria may also occur. Persons that are terminally ill typically present with obtundation, anuria, shock, tachypnea, normothermia, arthralgia, and ocular diseases. Hemorrhagic diathesis is often accompanied by hepatic damage and renal failure, central nervous system involvement, and terminal shock with multi-organ failure. Contact with the virus may also result in symptoms such as severe acute viral illness, malaise, and maculopapular rash. Pregnant women will usually abort their foetuses and experience copious bleeding. Fatality rates range between 50 and 100%, with most dying of dehydration caused by gastric problems (Casillas et al. 2003).

Diagnosis can be confirmed by virus isolation, ELISA to detect viral antigens or patient antibodies in serum or organ homogenates, RT-PCR, immunohistochemistry, and electron microscopy of tissue sections and/or biopsies (Grolla et al. 2005).

Ebola and Marburg virus are morphologically indistinguishable; laboratory studies are extremely hazardous and should be performed in a Biosafety Level 4-equivalent containment Level 4 facility. Laboratory researchers have to be properly trained in BSL-4 practices and wear proper personal protective equipment.

Ebola Virus Epidemiology

Occurrence of Ebola and Marburg virus disease has been primarily limited to countries in sub-Saharan Africa. The name, Ebola, comes from the Ebola River in the Democratic Republic of the Congo, where it was first found in 1976. Marburg virus was first discovered in 1967 and is named after the German city of Marburg.

Ebola virus disease (EVD) was first described after almost simultaneous viral hemorrhagic fever outbreaks occurred in Zaire and Sudan in 1976 (WHO 1978a). EVD is believed to occur after an ebolavirus is transmitted to a human index case via contact with an infected animal host. Human-to-human transmission occurs via direct contact with blood or bodily fluids from an infected person (including embalming of a deceased victim) or by contact with contaminated medical equipment such as needles. In the past, explosive nosocomial transmission has occurred in under-equipped African hospitals due to the reuse of needles and lack of implementation of universal precautions. Aerosol transmission has not been observed during natural EVD outbreaks, although there are reports suggesting or suspecting aerosol transmission between NHP or in humans based on epidemiological observations (Dalgard et al. 1992; Jaax et al. 1995; Johnson et al. 1995; Roels et al. 1999). The potential for widespread EVD epidemics is considered low due to the high case-fatality rate, the rapidity of demise of patients, and the remote rural areas where infections occur.

Marburg Virus Epidemiology

In 1967, simultaneous outbreaks occurred in laboratory workers handling African green monkeys imported from Uganda in Marburg, Frankfurt (Germany), and Belgrade (Yugoslavia, now Serbia). There were 25 reported primary laboratory-acquired cases with seven deaths. The 25 cases arose from contact and accidents with blood and tissues from infected African green monkeys and six secondary cases (medical personnel, one spouse) developed from the primary cases (Siegert 1972). Between 1975 and 1987, isolated cases were reported in South Africa (originating from Zimbabwe), Kenya, Zimbabwe, Kenya, and the Democratic Republic of Congo (Gear 1977; Smith et al. 1982). A large long running outbreak occurred between 1998 and 2000 in the Democratic Republic of Congo, resulting in 154 cases and 128 deaths, and two different Marburg viruses, MARV and RAVV,

co-circulated and caused disease (Bausch et al. 2006). The largest outbreak to date occurred in 2004 and 2005 centered in Uige, Angola where 374 cases were reported with 329 deaths (Roddy et al. 2010). Since 2007, a number of cases have been reported in Uganda, some of which have been diagnosed into other countries (i.e. USA, The Netherlands) in individuals returning from Uganda (CDC 2003; Timen et al. 2009). Marburg virus has been isolated from blood; serum; secretions, including respiratory and throat secretions; semen; urine; and various tissues and organs from human or animal hosts, or their homogenates (Fisher-Hoch 2005).

Crossing the Species Barrier and Transmission—Ebola Virus

Between 1976 and 1998, from 30,000 mammals, birds, reptiles, amphibians, and arthropods sampled from outbreak regions, no *Ebolavirus* was detected apart from some genetic traces found in six rodents (*Mus setulosus* and *Praomys sp.*) collected from the Central African Republic (Pourrut et al. 2005). Traces of EBOV were detected in the carcasses of gorillas and chimpanzees during outbreaks in 2001 and 2003, which later became the source of human infections. However, the high lethality from infection in these species makes them unlikely as natural reservoir (Pourrut et al. 2005). Plants, arthropods, and birds have also been considered as possible reservoirs; however, bats are considered the most likely candidate. Bats were known to reside in the cotton factory in which the index cases for the 1976 and 1979 outbreaks were employed, and they have also been implicated in Marburg virus infections in 1975 and 1980 (Pourrut et al. 2005). Of 24 plant species and 19 vertebrate species experimentally inoculated with EBOV, only bats became infected (Swanepoel 1996). The absence of clinical signs in these bats is characteristic of a reservoir species. In a 2002–2003 survey of 1030 animals that included 679 bats from Gabon and the Republic of the Congo, 13 fruit bats were found to contain EBOV RNA fragments (Leroy et al. 2005). As of 2005, three types of fruit bats (*Hypsignathus monstrosus*, *Epomops franqueti*, and *Myonycteris torquata*) have been identified as being in contact with EBOV. They are suspected to represent the EBOV reservoir hosts (Pourrut et al. 2007).

The existence of integrated genes of filoviruses in some genomes of small rodents, insectivorous bats, shrews, tenrecs (insectivora from Madagascar), and marsupials indicates a history of infection with filoviruses in these groups as well. However, it has to be stressed that infectious Ebola virus have not yet been isolated from any nonhuman animal (Taylor et al. 2010).

Transmission between natural reservoirs and humans are rare, and outbreaks are usually traceable to a single index case where an individual has handled the carcass of a gorilla, chimpanzee, or duiker (a small antelope species) (Peterson et al. 2004). The virus then spreads person-to-person, especially within families, hospitals, and during some mortuary rituals where contact among individuals becomes more likely (Hewlett and Amolat 2003).

The virus can be transmitted through body fluids. Transmission through oral or conjunctiva exposure is likely and has been confirmed in NHP (Jaax et al. 1995).

Filoviruses are not naturally transmitted by aerosol. They are, however, highly infectious as breathable 0.8–1.2 µm droplets in laboratory conditions; because of this potential route of infection, these viruses have been classified as Category “A” biological weapons (Johnson et al. 1995; Leffel and Reed 2004)².

Crossing the Species Barrier and Transmission—Marburg Virus

The natural reservoirs of Marburg viruses remain to be identified unequivocally. However, the isolation of both MARV and RAVV from bats and the association of several MVD outbreaks with bat-infested mines or caves strongly suggest that bats are involved in Marburg virus transmission to humans. Avoidance of contact with bats and abstaining from visits to caves is highly recommended, but may not be possible for those working in mines or people dependent on bats as a food source. Monkeys are susceptible but are incidental hosts and individuals handling infected monkeys or their fluids and cell cultures of Marburg virus have become ill (Towner et al. 2009; Timen et al. 2009; Swanepoel et al. 2007).

In 2009, the isolation of infectious MARV was reported from healthy Egyptian rousettes (*Rousettus aegyptiacus* or Egyptian fruit bat) (Towner et al. 2009). This isolation, together with the isolation of infectious RAVV, strongly suggests that Old World fruit bats are involved in the natural maintenance of marburgviruses. Further studies are necessary to establish whether Egyptian rousettes are the actual hosts of MARV and RAVV or whether they get infected via contact with another animal and therefore serve only as intermediate hosts.

The first experimental infection study of *Rousettus aegyptiacus* with MARV provided further insight into the possible involvement of these bats in MARV ecology. Experimentally infected bats developed relatively low viremia lasting at least five days, but remained healthy and did not develop any notable gross pathology. The virus also replicated to high titers in major organs (liver and spleen), and organs that might possibly be involved in virus transmission (lung, intestine, reproductive organ, salivary gland, kidney, bladder and mammary gland). The relatively long period of viremia noted in this experiment could possibly also facilitate mechanical transmission by blood sucking arthropods or infection of susceptible vertebrate hosts by direct contact with infected blood (Paweska et al. 2012).

Biosecurity of Filoviruses

Filoviruses (Ebola viruses and Marburg viruses) are listed as World Health Organization Risk Group 4 Pathogens, National Institute of Allergy and Infectious Diseases (NIAID) Category A Priority Pathogens, Select Agents, and Centers for

² National Institutes of Health, National Institute of Allergy and Infectious Diseases. Category A, B & C Priority Pathogens. 2013. <http://www.niaid.nih.gov/topics/biodefenserelated/biodefense/pages/cata.aspx> Accessed May 27, 2013.

Disease Control and Prevention (CDC) Category “A” Bioterrorism Agents due to the absence of prophylaxis or treatment regimens, their high lethality (up to 90% in larger outbreaks), their high infectivity ($LD_{50} = 1$ virion in rodent models), and their stability in artificial aerosols. Research on infectious filoviruses requires Biosafety Level 4 (BSL-4) laboratories.

Filoviruses can survive up to 4–5 days on contaminated surfaces, and can survive in liquid or dried material for a number of days (Belanov et al. 1996; Bray 2003). They are susceptible to sodium hypochlorite, beta-propiolactone, 3% acetic acid (pH 2.5), phenolic disinfectants, formaldehyde and paraformaldehyde, 1% glutaraldehyde, formalin, lipid solvents, and detergents such as SDS. They are physically inactivated by heating for 30–60 min at 60 °C, boiling for 5 min, gamma irradiation (1.2×10 – 1.27×10 rad), and UV radiation (Elliott et al. 1982; Kurata et al. 1983; Mitchell and McCormick 1984; Mahanty et al. 1999).

Ebola Vaccine

Most of the Ebola virus VP proteins are capable of eliciting protective immune responses and therefore are important to consider as potential components of a vaccine to protect humans from Ebola hemorrhagic fever. An “Ebola Δ VP30” strain replication incompetent virus as been generated with a lack of the gene encoding for the VP30 protein, therefore it cannot replicate and do not form infectious progeny in wild-type cells. The genome is stable, without a single event of virus replication; experimental infection of animals did not cause disease in infected animals (Halfmann et al. 2008, 2009).

41.2.1.2 Arenavirus

Arenaviruses are negative stranded RNA viruses of the *Arenaviridae* family. They naturally and chronically infect asymptomatic rodent host-reservoirs. Each rodent species is persistently infected by a specific virus and represents a model of virus-host coevolution (Gonzalez et al. 2007). One exception is made with the Tacaribe virus that has been isolated from naturally infected chiropteran (Downs et al. 1963).

Clinical Signs Several arenaviruses can accidentally infect humans and are responsible for mild to severe zoonotic diseases. Although the arenavirus prototype species, Lymphocytic Choriomeningitis Virus of mice (LCMV) is responsible for a neurological syndrome in humans, at least seven out of the 24 arenavirus species are known to be highly pathogenic for humans and responsible of Viral Hemorrhagic Fever (VHF). Six of them are classified as Select Agents ⁽³⁾ including the South American Arenaviruses (Guanarito from Venezuela, Junín from Argentina,

³ http://www.selectagents.gov/resources/List_of_Select_Agents_and_Toxins_2012-12-4-English.pdf.

Machupo and Chapare from Bolivia and Sabía from Brazil) and the African one, Lassa Fever Virus (from Guinea, Nigeria and Sierra Leone). Also the Lujo virus, not yet a Select Agent, has been recently described in AustralAfrica and represents an emerging potential threat for the region (Paweska et al. 2009).

Although bleeding tendencies are often recorded but not always life threatening, a high mortality of 30% of infected patients can occur during epidemics. Four others arenaviruses including Flexal (Brazil), Pichinde (Columbia), Tacaribe (Trinidad and Tobago) and White Water Arroyo (California) viruses have been found to potentially infect humans and potentially represent also highly dangerous agents (for a review, Gonzalez et al. 2007).

Epidemiology Asymptomatic infections of rodents are generally suspected to be associated with an insufficient or inappropriate host immune response (Hayes and Salvato 2012) resulting in chronic viremia and/or viruria which leads to shedding of the virus into the environment via urine or faeces.

Exceptionally, chronic infection may have a deleterious effect on their reservoir's fitness, which reduces rodent host fertility (Webb et al. 1975). NHP can be experimentally infected, but there is no evidence that these viruses are pathogenic for domestic animals (e.g.: livestock, cats, dogs), while exotic pets (hamster, mice, etc.) represent a potential source of infection.

Besides the specific association between "arenavirus species—rodent species", the geographic range of an arenavirus ecologic niche appears to be more restricted than the one of its rodent reservoir-host with a more circumscribed enzootic domain, which is often limited by natural barriers (e.g. rivers, elevations, climate, food access). This appears as one of the major characteristics of the epidemiological and dispersion patterns of arenaviruses and therefore VHF associated with them (Salazar-Bravo et al. 2002).

Argentine HF (Junín virus) was identified in the early 1940s in Argentina and described in the 1950s in the rural area of Buenos Aires province, while the virus was characterized only in 1958. Today the virus distribution extends to 150,000 km² of the Pampa. The Vesper mouse (*Calomys* spp.) is the natural host and direct rodent-to-human transmission occurs via ingestion of contaminated food or water, inhalation of rodent urine infested particles or via direct contact of broken skin with rodent excrements. Currently, Argentine HF remains a major and severe enzootic disease of public importance in Argentina with an endemic risk of crossing the natural barrier of the Rio Paraná and spill over to the closest neighboring countries of Uruguay (Polop et al. 2008).

Bolivian HF (BHF) (Machupo virus) was identified after several outbreaks of BHF in 1963 in the Beni province of Bolivia. Although BHF incidence increases late during the rainy season, small outbreaks are a dominant feature of the epidemiological pattern with several years of dormancy thereafter. The natural host *Calomys callosus* invades houses during floods of the rainy season resulting in close contact and human infection (Kilgore et al. 1997).

Chapare virus was isolated once from a fatal human case of hemorrhagic fever during a unique reported outbreak of HF that occurred in 2003 in the Chapare River

region close to Cochabamba in Bolivia, the original setting of Machupo virus responsible of the BHF (Delgado et al. 2008). There is no information concerning an eventual natural rodent host.

Venezuela HF emerged in 1989, with several cases that occurred in the central plains of Venezuela. A new Guanarito virus was isolated and named after the region where the first outbreak occurred (Salas et al. 1991). The main affected populations are settlers moving into cleared forest areas to practice small agriculture. *Zygodontomys brevicauda* appears to be the principal host (i.e.: reservoir) of the virus.

Lassa fever (LF) was described in 1956 in the eponym village of Lassa. LF occurs in rural West Africa, and appears to be hyper-endemic in Sierra Leone with an antibody prevalence of 8–52%, Guinea (4–55%) and Nigeria (21%). Natural transmission of Lassa virus (LASV) occurs from its domestic, ubiquitous, prolific and common multimammate rodent virus reservoir, *Mastomys natalensis*. As for other Arenaviruses it is transmitted to humans directly through rodent urine and faeces or indirectly by contaminated food. Person-to-person transmission has been described posing a risk for healthcare workers. The virus can also be contracted by an airborne route or by direct contact with infected human blood, urine, or semen, up to three months after clinical recovery. LF is a prominent threat outside the endemic area with several imported cases in Germany (Gunther et al. 2000), Japan (Hirabayashi et al. 1988), the United States (Holmes et al. 1990), the United Kingdom (Kitching et al. 2009) among others. About 80% of patients experience a mild or asymptomatic infection. LF has a relatively low mortality rate up to 5%. Among the endemic countries, it is estimated that LF is responsible for about 5000 deaths a year. Pregnant women have the greatest risk of fatality. After an incubation period of 1–3 weeks an acute illness develops while the virus infects every tissue from the mucosa (e.g., intestine, lungs and urinary system) and subsequently progresses to the vascular system. Initial non-specific symptoms include fever, facial swelling, muscle fatigue, conjunctivitis and mucosal bleeding. Later on there might develop gastrointestinal tract bleeding, bloody vomiting, dysphagia, melena, accompanied with cough, dyspnea worsening to cardiovascular system dysfunctions (pericarditis, tachycardia) and hepatitis; finally hearing deficit, meningo-encephalitis and seizures occur. Death is due to multiorgan failure. With respect to this multiple organ infection and accompanying HF signs differential diagnoses include other VHF's such as Ebola or Marburg, malaria or influenza (Yun and Walker 2012; for a review⁴).

After LASV, Lujo virus is the second known to date human pathogenic arenavirus of Africa. Among the five identified cases in 2008, four died; the fifth case was treated with ribavirin early after onset of clinical disease and survived. It has been only reported from a few patients from Zambia and from a subsequent nosocomial outbreak in South Africa (Briese et al. 2009). A natural reservoir has not yet been identified.

⁴ <http://www.cdc.gov/ncidod/dvrd/spb/mnpages/dispages/lassaf.htm>; <http://www.pasteur.fr/ip/easysite/pasteur/fr/presse/fiches-sur-les-maladies-infectieuses/fievre-de-lassa>.

Sabia virus was first isolated from a fatal case of Brazilian HF (BrHF) in the village of Sabia, outside of Sao Paulo, Brazil in 1990 (Lisieux et al. 1994). Two other non-fatal accidental infections were later recorded (Gandsman et al. 1997). Chapare virus infected patients were also clinically considered as BrHF cases. Both viruses do not have an identified reservoir, however, like the other arenaviruses, they naturally appear to have only a limited geographical distribution.

Crossing the Species Barrier Transmission Virus transmission within rodent populations occurs through vertical (mother to progeny), or horizontal routes (directly through bites or indirectly by contacts with urine or feces). Arenavirus transmission from natural rodent hosts to humans occurs through contacts with infected rodent biological fluids (i.e. blood, saliva or urine), when people (through rodent bites, trapping or eating rodents) are directly exposed to the infected rodent, or indirectly, when exposed to food contaminated with rodent urine and/or by inhalation of infested rodent excreta. Also, human-to-human transmission may occur and arenaviruses can be transmitted through aerosolized particles and sperm fluid. Moreover, transmission to humans may occur by accidental inoculation with infected body fluids and through tissue transplantation (Emonet et al. 2006; Paweska et al. 2009).

Biosecurity, Therapy and Prevention

Prevention of arenavirus infection consists of interrupting virus transmission from rodents to humans, and from humans to humans. Rodent control seems to be efficient only in certain conditions (i.e.: urban settings). Hospital based nursing barrier appears highly efficient, including personal protective measures (gloves, masks and gowns), good hygiene and appropriate sterilization of equipment. The highest-risk of infection occurs during unprotected contact with body fluids from an infected person. Linens should be handled per CDC guidelines⁵. Environmental surfaces and contaminated equipment are properly disinfected by 1:10–1:100 dilution of sodium hypochlorite or other EPA-registered disinfectants. The viruses can also be inactivated by ultraviolet, gamma irradiation, temperatures of 56 °C for 20 min and, by a pH less than 5.5 or greater than 8.5.

One anti-virus drug against arenavirus infection has been identified: Ribavirin® is an anti-viral drug that interferes with RNA viral replication. It has been proved to be an efficient treatment against LASV if administered early and might in some cases also be effective against other arenaviruses including BHF, Sabia virus or Lujo virus. Also it has been shown to be effective in advanced stages of LASV infection by reducing the virus load (McCormick et al. 1986; Barry et al. 1995; Enria et al. 1994; Kilgore et al. 1997, Briese et al. 2009).

Several antiviral molecules are under development with the most promising one directed to interfere with arenavirus cell entry (Larson et al. 2008; York et al. 2008; Charrel et al. 2011). Although hyperimmune serum has been effectively used in

⁵ <http://www.cdc.gov/mmwr/preview/mmwrhtml/00037085.htm>.

several instances, clinical experiences are limited and only circumstantial reports are available. Hyperimmune serum treatment has been used successfully for AHF patients and a plasma bank was established in Argentina (Maiztegui et al. 1979). Also, neutralizing antibodies contained in Human immune plasma appear to be effective in patients with BHF by reducing viremia. However, LASV infection only leads to a limited neutralizing antibody reaction and hyperimmune serum treatment is not applicable.

Among all arenaviruses, only one vaccine, i.e. the live attenuated Junín virus vaccine Candid #1, has been conclusively developed and produced: its immunogenicity and efficacy in humans was proven to be greater than 84% without causing any serious adverse effects (Maiztegui et al. 1998). Other vaccines tested in animal models include: an attenuated recombinant LASV vaccine using vesicular stomatitis virus as vector that causes a protective immune response in NHP against a lethal LASV challenge (Geisbert et al. 2005); an attenuated Lassa/Mopeia construct ML-29 virus demonstrated protection against LASV challenge in guinea pigs and Rhesus macaques (Lukashevich et al. 2008); a yellow fever 17D vaccine expressing LASV glycoprotein precursor protected also guinea pigs against LASV challenge (Bredenbeek et al. 2006; Charrel and de Lamballerie 2010 for review).

41.2.1.3 Rift Valley Fever

Rift Valley Fever (RVF) is a viral zoonosis that primarily affects domestic livestock and also humans in Africa. RVF present a clinical spectrum from mild fever to fatal hemorrhagic syndrome. RVF virus is spread by infected *Aedes* spp. or *Culex* spp. mosquitoes. RVF virus is a member of the Phlebovirus genus of the Bunyaviridae family.

Clinical Signs Only a small percentage of patients develops a severe form of the disease including: ocular disease with retinal lesions (0.5–2% of patients); meningo-encephalitis (<1%) with headache, loss of memory, confusion, convulsions, and coma; hemorrhagic fever (<1%) starting with severe liver impairment, jaundice, followed by hemorrhage, vomiting blood, melena, purpuric rash, nose and gums bleedings, or menorrhagia. Hemorrhagic forms have a case-fatality as high as 50%. The virus may be detected in blood for up to ten days.

RVFV is also able to infect many animal species causing particularly severe disease in domesticated animals including cattle, sheep, camels and goats. Sheep are very sensitive to infection: 90% of infected lambs die, and abortion occurs in up to 100% of infected pregnant ewes.

Epidemiology Human infections can result from direct contact with infected animal biological products, by handling of animal tissue during slaughtering or butchering, conducting veterinary procedures, or from the disposal of carcasses or fetuses. Consequently, herders, slaughterhouse workers, farmers and veterinarians are at high risk of infection. The virus can infect humans through inoculation (i.e.: wound), inhalation of aerosols, by ingesting unpasteurized or uncooked milk or

from mosquito bites. To date, no human-to-human transmission of RVF has been documented. Outbreaks of RVF occur essentially in rural environment (see WHO⁶ for review).

RVF may occur as large outbreaks when heavy rains favor intense breeding of mosquito vectors. Deaths of newborn animals and abortion in pregnant sheep, goats, and cattle may happen and humans can become infected by contact with infected animal tissues or by mosquito bites. The active circulation of RVFV in Africa and the Arabian Peninsula constitutes a threat for human and animal health all over the African continent and beyond (Grobbelaar et al. 2011).

Biosecurity and Prevention Rift Valley fever belongs to the Select Agent list. It is a potential biological weapon particularly because of its high pathogenicity and its potential to be airborne transmitted (Borio et al. 2002)

Basic nursing barrier and standard infection control precautions are recommended to avoid RVFV transmission to health care workers.

A live-attenuated MP-12 RVFV strain has been developed as a vaccine; the vaccine has been shown to protect bovine and ovine dams against RVFV challenge and is safe and efficacious for use in neonatal calves and lambs (Morris et al. 1997). Another live attenuated RVFV vaccine lacking the NSs and NSm genes cannot be transmitted by mosquitoes (Bird et al. 2011; Crabtree et al. 2012).

41.2.1.4 Kyasanur Forest Disease

The Kyasanur Forest Disease (KFD) is a tick-borne VHF endemic to and geographically limited to Karnataka State of Central-West India (Work and Trapido 1957). The KFD virus belongs to the Flaviviridae family.

In the early 1990s a new and close related highly pathogenic virus (more than 30% mortality rate), the Alkhurma virus, was isolated in Saudi Arabia and represents another threat for the local population (Charrel et al. 2001).

Clinical Signs

After an incubation period of 3–8 days, KFD starts with a sudden onset of fever, headache, severe muscle pain, cough and dehydration: later on a gastrointestinal syndrome and bleeding occurs. 10% of the patients develop low blood pressure and pancytopenia. Some patients show a biphasic form and experience after 2 weeks a second phase of fever and neurological syndrome leading to a case fatality rate (CFR) of 3–5%. Approximately 400–500 cases of KFD occur in India per year.

⁶ <http://www.who.int/mediacentre/factsheets/fs207/en/>.

Epidemiology⁷

Although the main hosts of KFDV are rodents, shrews, bats, and monkeys may also carry the virus. Cattle, goats and sheep may become infected without playing a role in the transmission of the disease. KFDV is transmitted from the bite of an infected tick, principally *Haemaphysalis spinigera* (Work et al. 1959).

Crossing the Species Barrier

Humans can get infected from tick bites or by contact with an infected animal (often sick monkeys: *Presbytis entellus* or *Macaca radiata*). KFDV is common in young adults exposed during the dry season in the forest.

Biosecurity and Prevention

A formalin-inactivated tissue-culture vaccine has been used for vaccination campaigns since the early 1990s in the endemic area of India with an efficacy of 79.3–93.5% after respectively one or two doses (Dandawate et al. 1994).

41.2.1.5 Omsk Hemorrhagic Fever

The tick-borne arbovirus Omsk Hemorrhagic Fever Virus (OHFV) is a member of the Flaviviridae family and classified as a biosafety level 4 virus. Several tick species can transmit the virus including *Dermacentor reticulatus*, *D. marginatus* and *Ixodes persulcatus*.

Clinical Signs As for KHFD, after a one week-incubation period, a first clinical phase of infection, begins with several symptoms including fever, chills, headache, muscular pain, rash, and cervical adenopathy. After two weeks a neurological syndrome appears sometimes accompanied by a hemorrhagic syndrome with severe platelet loss and leucopenia. A third of patients develops pneumonia, nephritis, meningitis, or a combination of these complications. The CFR ranges from 1 to 10%, surviving patients acquire life-long immunity

Epidemiology

The geographic distribution of the OHFV appears restricted to western Siberia (Kharitonova and Leonov 1985) in Omsk, Novosibirsk, Kurgan, and Tyumen oblasts. The main hosts of OHFV are rodents and in particular the non-native

⁷ <http://www.phac-aspc.gc.ca/lab-bio/res/psds-ftss/kyasanur-eng.php#note10>.

muskrat (*Ondatra zibethica*) as a natural OHFV reservoir. Muskrat was imported to Siberia from Canada in the 1920s and the virus finds a particular receptive host to replicate and spread efficiently.

The sylvatic cycle of OHFV involves rodents and in particular the non-native muskrat as a natural OHFV reservoir, but also water voles (*Arvicola terrestris*), while most animals within endemic areas can be infected and bitten by the tick vectors. OHFV survives in water and is transferred to humans via contaminated water or an infected tick.

Crossing the Species Barrier Humans become infected through tick bites or contact with blood, feces or urine of infected muskrats (and other hosts). Gamasid mites are also thought to play a minor role in transmission within the sylvatic cycle. OHFV can also spread through milk from infected goats or sheep.

Prevention

Preventing OHF consists of avoiding tick exposure; consequently persons engaged in farming, forestry, and hunting (i.e.: Siberian muskrat) are at highest risk of infection.

41.2.2 *Viral Encephalitis*

41.2.2.1 Eastern Equine Encephalitis

The Pathogen Eastern equine encephalitis virus (EEEV) is a member of the genus Alphavirus, family Togaviridae. Other medically important alphaviruses found in the Americas include Western equine encephalitis virus (WEEV) and Venezuelan equine encephalitis virus (VEEV). EEEV has a single-stranded, positive-sense RNA genome. The virus particles are spherical and have a diameter of 60–65 nm (Snyder et al. 2009). Of the four lineages of EEEV, Group I is endemic in North America and the Caribbean and causes most human disease cases; the other three groups (IIA, IIB, and III) cause primarily equine illness in Central and South America (Zacks and Paessler 2010).

Clinical Signs The incubation period for Eastern equine encephalitis virus (EEEV) disease ranges from 4 to 10 days. EEEV infection can result in one of two types of illness, systemic or encephalitic (involving swelling of the brain, referred to as EEE). The type of illness will depend on the age of the person and other host factors. It is possible that some people who become infected with EEEV may be asymptomatic.

Systemic infection has an abrupt onset and is characterized by chills, fever, malaise, arthralgia and myalgia. The illness lasts 1–2 weeks, and recovery is complete when there is no central nervous system involvement. In infants, the encephalitic

form is characterized by abrupt onset; in older children and adults, encephalitis is manifested after a few days of systemic illness. Signs and symptoms in encephalitic patients are fever, headache, irritability, restlessness, drowsiness, anorexia, vomiting, diarrhea, cyanosis, convulsions, and coma.

EEE is the most severe of the arboviral encephalitis entities and has a mortality of 50–75% (Petersen and Gubler 2003). Death usually occurs 2–10 days after onset of symptoms, but can occur much later. Of those who recover, 15–50% are left with disabling and progressive mental and physical sequelae, which can range from minimal brain dysfunction to severe intellectual impairment, personality disorders, seizures, paralysis, and cranial nerve dysfunction. Many patients with severe sequelae die within a few years (Zacks and Paessler 2010).

No human vaccine against EEEV infection or specific antiviral treatment for clinical EEEV infections is available. Patients with suspected EEE should be evaluated by a healthcare provider, appropriate serologic and other diagnostic tests ordered, and supportive treatment provided.

Epidemiology EEEV is transmitted to humans through the bite of an infected mosquito. Human EEEV cases occur relatively infrequently, largely because the primary transmission cycle takes place in and around swampy areas where human populations tend to be limited. Overall, only about 4–5% of human EEEV infections result in EEE. EEEV infection is thought to confer life-long immunity against re-infection. It does not confer significant cross-immunity against other alphaviruses (e.g., Western Equine Encephalitis Virus), and it confers no cross-immunity against flaviviruses (e.g., West Nile Virus) or bunyaviruses (e.g., La Crosse Virus).

In the United States, about six human cases of EEE are reported annually. Most cases of EEE have been reported from Florida, Georgia, Massachusetts, and New Jersey. EEEV transmission is most common in and around freshwater hardwood swamps in the Atlantic and Gulf Coast states and the Great Lakes region. Between 1964 and 2010, there were 270 confirmed cases of EEE in the US. Several states in the northeastern USA have seen increased virus activity since 2004. Between 2004 and 2006, there were 17 equine cases and at least 13 human cases of EEE reported in Massachusetts. In 2006, approximately 500,000 acres (2000 km²) in southeastern Massachusetts were treated with mosquito adulticides to reduce the risk of humans contracting EEE. Subsequently, between 2007 and 2010, there were two confirmed human cases and six equine cases reported to CDC and USDA respectively.

In October 2007, a citizen of Livingston, West Lothian, Scotland became the first European victim of this disease. The man had visited New Hampshire during the summer of 2007 on a fishing vacation, and was diagnosed as having EEEV on 13 September 2007. He fell ill with the disease on 31 August 2007, just one day after flying home.^[5]

In 2012, 209 equine cases of EEE were reported from 19 US States, and 15 human cases of EEE reported from six US States. In 2012, two residents of Vermont were confirmed to have EEE, and this was the first time the illness had been reported in this state.

Crossing the Species Barrier Eastern equine encephalitis virus (EEEV) is maintained in a cycle between *Culiseta melanura* mosquitoes and avian hosts in freshwater hardwood swamps. *Cs. melanura* is not considered to be an important vector of EEEV to humans, because it feeds almost exclusively on birds. Transmission to humans requires mosquito species capable of creating a “bridge” between infected birds and uninfected mammals such as some *Aedes*, *Coquillettidia*, and *Culex* species.

Wild birds are the main reservoir for transmission of EEEV. Humans, horses, and other animals (domestic fowl, feral pigs, cattle and rodents) are not significant reservoir hosts (Zacks and Paessler 2010). Amphibians and reptiles are a possible reservoir for the virus to overwinter. Mosquitoes and infected eggs are also a reservoir for the viruses (Pfeffer and Dobler 2010).

Person-to-person transmission has not been reported for EEEV viruses. Direct bird-to-human infection can occur, although humans and horses are not amplifying hosts as virus titers in their bodies are insufficient to infect mosquitoes. Eggs of mosquitoes can be infected by the female (Pfeffer and Dobler 2010).

Horses are susceptible to EEEV infection and some cases are fatal. EEEV infections in horses, however, are not a significant risk factor for human infection, because horses (like humans) are considered to be “dead-end” hosts for the virus (i.e., the concentration of virus in their bloodstreams is usually insufficient to infect mosquitoes). (Zacks and Paessler 2010).

Biosecurity and Prevention All residents of and visitors to areas where virus activity has been identified are at risk of infection with EEEV, particularly persons who engage in outdoor work and recreational activities in these areas. Persons over age 50 and younger than age 15 are at greatest risk for severe disease (encephalitis) following infection. EEEV infection is thought to confer life-long immunity against re-infection.

EEEV is difficult to isolate from clinical samples; almost all isolates (and positive PCR results) have come from brain tissue or CSF. Laboratory acquired infections have been reported, and accidental parenteral inoculation, contact of the virus with broken skin or mucous membranes, and bites from infected laboratory arthropods or rodents are the primary hazards associated while working with these viruses.

EEEV do not persist in the environment, and are susceptible to many common disinfectants including 1 % sodium hypochlorite, 70 % ethanol, 2 % glutaraldehyde and formaldehyde. EEEV can be inactivated by exposure to 50 % ethanol at concentration for 60 min, also by moist or dry heat, or by drying, or by UV rays (Aguilar et al. 2005).

EEEV was one of more than a dozen agents that the United States researched as potential biological weapons before the nation suspended its biological weapons program. Samples taken from people and animals with suspected EEEV infection should be handled by trained staff working in Biosafety Level 3 (BSL-3/ABSL-3) **containment** laboratories (CDC 2007).

41.2.2.2 Venezuelan Equine Encephalitis

The Pathogen Venezuelan equine encephalitis virus (VEEV) is a spherical arbovirus that belongs to the *Togaviridae* family and is an alphavirus (Atasheva et al. 2010). It is 70 nm in diameter and has an enveloped single stranded RNA genome (Gardner et al. 2008).

The Venezuelan equine encephalomyelitis complex contains at least six viral subtypes, I–VI. Subtype I, the Venezuelan equine encephalomyelitis virus (VEEV), is divided into five antigenic variants or serovars, AB to F. Some of the other five subtypes also have official species names; subtype II is known as Everglades virus, subtype III as Mucambo virus, and subtype IV as Pixuna virus.

VEE complex viruses are divided into epizootic (or epidemic) and enzootic (or endemic) groups. The epizootic viruses, which are amplified in equines and are responsible for most epidemics, are found in VEEV subtypes I-AB and I-C. The remaining viruses, including VEEV I-D, VEEV I-E and variants in subtypes II-VI are enzootic (sylvatic) subtypes. These viruses are generally found in limited geographic areas, where they usually occur in natural cycles between rodents and mosquitoes. The enzootic subtypes are typically non-pathogenic for horses and are not amplified in this host; however, in 1993 an enzootic I-E variant was responsible for an outbreak of VEE among horses in Mexico (Weaver et al. 2004).

Clinical Signs In humans, VEEV usually causes mild to severe influenza-like symptoms; 4–14% of cases, however, develop neurological complications (Gardner et al. 2008). Children and young adults are more likely to develop encephalitis; however, fatalities in humans are rare reaching about 1% of all reported cases (de la Monte et al. 1985). Usually, flu-like symptoms such as headache, myalgia, fatigue, vomiting, nausea, diarrhoea, pharyngitis and fever appear abruptly, 2–5 days after exposure to the virus. The VEE virus can also cause retro-orbital and occipital headaches as well as leucopenia and tachycardia. Symptoms of encephalitis, only appearing in a minority of cases, occur 4–10 days after exposure and include somnolence, convulsions, confusion, photophobia, and coma. Fatal human cases are usually caused by encephalitis as well as brain, lung and gastrointestinal bleeding (Weaver et al. 2004). Long-term neurological damage can be caused by this virus and it can infect the foetus in pregnant women causing birth defects and stillbirths (de la Monte et al. 1985). Generally, the symptoms last between 3 and 8 days and can be biphasic, recurring 4–8 days after the initial symptoms (Sidwell et al. 1967).

Enzootic VEEV usually infects horses sub-clinically or cause mild symptoms. Epizootic subtypes may cause a generalized acute febrile disease with or without neurologic signs. Asymptomatic infections also occur.

Fatal VEE has been reported in various mammals including rabbits, goats, dogs and sheep during epizootics. Some VEE viruses also kill laboratory rodents including hamsters, guinea pigs and mice; however, natural reservoir hosts for enzootic strains usually remain asymptomatic. Experimentally infected, NHP develop a non-specific febrile illness similar to human disease.

Epidemiology Epizootic VEE viruses (VEEV I-AB and I-C) are found in South and Central America. Most VEE epidemics occur in northern and western South America, but some may spread into adjacent countries, including the US. Enzootic VEE viruses have been found in Mexico, parts of the US, and South and Central America.

The virus was first observed in horses in 1935 after outbreaks in Columbia, Venezuela and Trinidad, and was isolated in 1938. In the 1960s, over 200,000 human cases and 100,000 equine deaths were reported in Colombia and smaller epidemics occurred in Venezuela and Mexico. Between 75,000 and 100,000 infections were reported in Venezuela and Colombia in 1995. The outbreaks usually occur after a season of heavy rains, due to increases in the mosquito population (Weaver et al. 2004).

VEE can be widespread in human populations during epidemics; more than 10% of the population in an area may be affected. Between epidemics, sporadic cases of VEE are caused by enzootic viruses. Humans are highly susceptible to VEE; approximately 90–100% of exposed individuals become infected, and nearly 100% develop clinical signs. However, most infections are mild. Less than 1% of adults develop encephalitis, with approximately 10% of these cases ending in death; the overall CFR in adults is less than 1%. Very young or elderly patients are more likely to develop severe infections. Encephalitis, with a CFR of 35%, occurs in approximately 4% of children less than 15 years of age. More severe disease, with a higher incidence of neurologic signs, might occur in both children and adults after a biological attack with aerosolized virus.

Instances of person-to-person transmission have not been reported for the VEE virus, although an infected individual can transmit the virus to mosquitoes. Generally, humans and equines become infected by mosquitoes of the **Psorophora** and **Ochlerotatus** genus. Equines can spread the virus to each other through aerosols and to mosquitoes via bites (Pfeffer and Dobler 2010)

Crossing the Species Barrier There are two types of cycles involved in the VEE virus. The enzootic cycle is maintained by rodents and mosquitoes. The epizootic cycle implicates horses, mosquitoes and humans, although there is the potential for the virus to affect many other animal species (Pfeffer and Dobler 2010). Horses are the amplifying host in the cycle and are necessary for a larger outbreak of VEE (de la Monte et al. 1985).

VEEV is typically spread by mosquitoes, although certain types of ticks and mites can spread the virus as well (Weaver et al. 2004). The **Culex (Melanoconion)** mosquito is normally responsible for the dispersal of the enzootic strain of the VEE virus (Zacks and Paessler 2010). **Ochlerotatus taeniorhynchus**, **Psorophora confinnis**, **Psorophora columbiae**, **Ochlerotatus sollicitans**, **Mansonia titillans** and **Anophelis aquasalis** are some of the species of mosquitoes known to carry the epizootic varieties of the VEEV (Weaver et al. 2004).

VEE epidemics typically begin in horses, with human cases developing weeks later: Unlike EEE outbreaks, which usually end with the onset of colder temperatures, VEE epidemics can last for several years. Epizootic subtypes of VEEV can

cause significant morbidity and mortality in equids; the infection rate can be as high as 90%, and the morbidity rate varies from 10–40% in some areas to 50–100% in others. The CFR in horses is 38–90%. Fatal infections have also been reported in goats, rabbits, dogs and sheep during epizootics, as well as in laboratory rodents infected with some isolates.

Most enzootic VEEV subtypes do not result in serious disease or deaths in horses, but limited outbreaks of encephalitis have been reported with some variants.

Rodents are usually the natural hosts for enzootic VEEV, but birds are involved in a few cycles. The maintenance host for epizootic VEEV between outbreaks is unknown; during epidemics, these viruses are amplified mainly in equids.

Epidemic VEEV can cause serious disease in horses, mules, burros, donkeys and zebras. During epizootics, fatal cases have also been reported in domesticated rabbits, dogs, goats and sheep. Cattle, pigs, bats and opossums can also be infected. Experimental infections have been reported in NHP, guinea pigs, mice and hamsters; some isolates are fatal for laboratory rodents, although they are usually asymptomatic in their normal rodent hosts.

Biosecurity and Prevention VEEV can be found in the body fluids of horses, and transmission by direct contact or aerosols is theoretically possible in this species. However, natural transmission of VEEV between horses or from horses to humans has not been seen. Infected laboratory rodents can also shed this virus, and people have been infected after exposure to aerosolized debris from cages.

Vaccinations of equines with the TC-83 vaccine and protection against mosquitoes (protective clothing, insecticides) are some of the proposed ways to reduce VEE outbreaks. While the TC-83 vaccine is recommended for laboratory workers, there is no licensed vaccine available for the general population (Weaver et al. 2004).

Arboviruses may be present in blood, cerebrospinal fluid, urine and exudates. The virus may be found in nasal, eye and mouth secretions of infected animals as well as in contaminated animal bedding. The greatest risks when working with VEEV are exposure to infected aerosols, accidental subcutaneous inoculation, and contact with broken skin or contaminated animal bedding. VEEV is stable in dried blood and exudates as well as in freeze dried materials (aerosols) (Chosewood and Wilson 2009). One viral infectious particle injected subcutaneously is enough to infect an individual with VEEV (Collins and Kennedy 1983).

Like other enveloped viruses, VEEV virus is susceptible to disinfectants such as 1% sodium hypochlorite, 4% formaldehyde, 2% glutaraldehyde, 70% ethanol, 3–6% hydrogen peroxide, 2% and peracetic acid (Collins and Kennedy 1983). Microbial inactivation is possible using moist or dry heat (Block 2001). Togaviruses can be inactivated by 15 min of heat at 65 °C (Lelie et al. 1987).

During the Cold War, both the United States biological weapons program and the Soviet biological weapons program researched and weaponized VEEV. In April 2009, the U.S. Army Medical Research Institute of Infectious Diseases at Fort Detrick reported that samples of VEEV were discovered missing during an inventory of

a group of samples left by a departed researcher. The report stated the samples were likely among those destroyed when a freezer malfunctioned.

41.2.2.3 Tick-Borne Encephalitis

The Pathogen Tick-borne encephalitis virus (TBEV) is a single-stranded RNA virus that belongs to the genus *Flavivirus*, and was initially isolated in 1937. TBEV has three subtypes: European, Siberian, and Far Eastern, and is the most important arthropod-borne virus in Europe (Ramelow et al. 1993; Barrett et al. 2008).

The family Flaviviridae includes other tick-borne viruses affecting humans and these viruses are closely related to TBEV and Russian Spring Summer encephalitis, such as Omsk hemorrhagic fever virus in Siberia, Al Khumra virus in Saudi Arabia, and Kyasanur Forest disease virus in India. Louping ill virus (United Kingdom) is a member of this family; it causes disease primarily in sheep and has been reported as a cause of a TBE-like illness in laboratory workers and persons at risk for contact with sick sheep (e.g.: veterinarians, butchers) (see above paragraphs 5.2.1.4 and 5.2.1.5).

Clinical Signs Tick-borne encephalitis (TBE) is a human viral infectious disease involving the central nervous system. The disease most often manifests as meningitis, encephalitis or meningoencephalitis. Although TBE is most commonly recognized as a neurologic disease, mild febrile illnesses can also occur. Long-lasting or permanent neuropsychiatric sequelae are observed in 10–20% of infected patients. Approximately two thirds of infections are asymptomatic. The median incubation period for TBE is 8 days (range, 4–28 days). The incubation period for milkborne exposure is usually shorter (3–4 days). Hemmer et al. (2005) recommended that tickborne encephalitis should be included in the differential diagnosis of meningoencephalitis in northeastern Germany, even if the patient has not been in tickborne encephalitis–endemic areas.

Among patients with central nervous system involvement, approximately 10% require intensive care and 5% need mechanical ventilation. Clinical course and long-term outcome vary by subtype of TBEV. The European subtype is associated with milder disease, a case-fatality ratio of <2%, and neurologic sequelae in up to 30% of patients. The Far Eastern subtype is often associated with a more severe disease course, including a case-fatality ratio of 20–40% and higher rates of severe neurologic sequelae. The Siberian subtype is more frequently associated with chronic or progressive disease and has a case-fatality ratio of 2–3%.

Epidemiology Tick-borne encephalitis (TBE) has become a considerable public health risk in several European countries, and on average, between 1990 and 2009, nearly 8500 cases of TBE were reported annually in Europe including Russia, although with considerable variability in incidence from year to year (Suss 2011). Many factors contribute to this increase: expanding tick populations due to climatic factors (Randolph 2009; Randolph 2010), social and behavioral changes (Kriz et al. 2004), as well as changes in land use and leisure activities (Sumilo et al. 2007).

Reporting of TBE cases has improved as it is a notifiable disease in 16 European countries, including 13 European Union (EU) Member States (Austria, Czech Republic, Estonia, Finland, Germany, Greece, Hungary, Latvia, Lithuania, Poland, Slovak Republic, Slovenia, Sweden) and three non-EU Member States (Norway, Russia and Switzerland) (Donoso et al. 2008).

TBE is endemic in temperate regions of Europe and Asia (from eastern France to northern Japan and from northern Russia to Albania) and up to about 4921 ft (1500 m) in altitude. Russia has the highest number of reported TBE cases, and western Siberia has the highest incidence of TBE in the world. Other countries where the incidence is high include the Czech Republic, Estonia, Germany, Hungary, Latvia, Lithuania, Poland, Slovenia, Sweden, and Switzerland. High vaccination rates in Austria have reduced the incidence of TBE; however, unvaccinated travelers to this country are still at risk. European countries with no reported cases are Belgium, Iceland, Ireland, Luxembourg, the Netherlands, Portugal, Spain, and the United Kingdom (Suss 2008). Asian countries known to be endemic for TBE include China, Japan, Mongolia, and South Korea (Lu et al. 2008; Walder et al. 2006).

Crossing the Species Barrier TBEV is transmitted to humans through the bite of an infected tick of the *Ixodes* species, primarily *I. ricinus* (European subtype) or *I. persulcatus* (Siberian and Far Eastern subtypes). The virus is maintained in discrete areas of deciduous forests. Ticks act as both vector and virus reservoir, and small rodents are the primary amplifying host. Tickborne encephalitis (TBE) can also be acquired by ingesting unpasteurized dairy products (such as milk and cheese) from infected goats, sheep or cows, and reports of this route of infections come from Slovakia, Poland, the Baltic States, and other Eastern European countries (Kerbo et al. 2005; Vaisviliene et al. 2002; Balogh et al. 2010). TBEV transmission has infrequently been reported through laboratory exposure and by slaughtering viremic animals. Direct person-to-person spread of TBEV occurs only rarely, through blood transfusion or breastfeeding (Dumpis et al. 1999).

TBE is also emerging in Europe's canine population, and the numbers of clinical cases in dogs are expected to increase (Leschnik et al. 2002; Beugnet and Marié 2009). Humans are accidental dead-end hosts for ticks and for TBEV as, humans do not transmit the disease despite showing noticeable viremia (Heinz 2008)⁸.

Biosecurity and Prevention Reducing exposure to ticks is the best method to prevent TBE in humans. It is also recommended to avoid consuming unpasteurized dairy products (Rendi-Wagner 2004). Repellents or insecticides provide unreliable protection against tick bites, and there is no specific antiviral treatment for TBE; therapy consists of supportive care and management of complications (Ginsberg and Stafford 2005).

Being a zoonosis, TBE cannot be easily eliminated from endemic areas. However, the introduction of large-scale vaccination campaigns has proven to be highly effective in reducing the burden of disease. In Austria, where the vaccination coverage in the general population has reached approximately 90%, the number of

⁸ <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=18848>.

clinical cases could be reduced to about 10%, as compared to the prevaccination era (Heinz et al. 2007). In most highly TBE-endemic countries, large-scale vaccination campaigns are not implemented (Heinz 2008). The risk of acquiring TBE in a highly endemic area in Austria was calculated at approximately 1/10,000 per person-month (Rendi-Wagner 2004). WHO (WHO 2012) recommends tick bite prevention in endemic areas during the summer months; only at-risk travellers should be offered vaccination. Travellers are considered to be at risk when hiking or camping in rural and forested areas up to altitudes of 1400 m (WHO 2012).

41.2.3 Other Severe Clinical Syndromes

41.2.3.1 Monkeypox

The Pathogen *Monkeypox* is a viral disease caused by the Monkeypox virus, an orthopoxvirus. Human cases have been reported from nine countries in central and western Africa where the disease is endemic—Democratic Republic of Congo, People's Republic of Congo, Central African Republic, Gabon, Cameroon, Nigeria, Cote d'Ivoire, Liberia, and Sierra Leone.

The virus was first identified in the State Serum Institute in Copenhagen, Denmark, in 1958 during an investigation into a pox-like disease among monkeys. Monkeypox virus is pathogenic for both animals and humans: Human monkeypox infection was first identified in 1970 in a 9 month old child in the town of Basankusu, Equateur Province, Democratic Republic of Congo and initially NHP were suspected as the source of outbreaks (Ladnyj et al. 1972; Marrennikova et al. 1972).

Over the next year, six further human cases of monkeypox infection were reported in Liberia, Sierra Leone and Nigeria (Foster et al. 1972). From 1970 to 1979, 47 human cases of monkeypox were identified, 38 of which were from Zaire, and the majority were in close proximity to the tropical rainforest (Nalca et al. 2005). A total of 79 cases were subsequently reported over the next 12 years. In 1996–1997 a major outbreak involving 88 cases occurred; between 2001 and 2002 51 human cases were reported in the Democratic Republic of Congo (Hutin et al. 2001; Heymann et al. 2008).

During May and June 2003, the first cases of human monkey pox disease outside of the African continent were reported in an outbreak in Midwestern United States (Illinois, Indiana, Kansas, Missouri, Ohio and Wisconsin) due to direct contact with ill prairie dogs that were kept or sold as pets and which had been recently exposed to imported Monkeypox virus-infected West African rodents from Ghana (Reed et al. 2004).

There were ten confirmed cases and nine probable cases of monkeypox between September and December of 2005 reported in Unity, Sudan (now South Sudan). The particularly intriguing aspect of this outbreak is the evidence of possible human-to-human transmission. In this case, a traditional healer was linked to three of the four transmission chains in the outbreak. The healer had a confirmed case of monkeypox, and a number of the monkeypox patients were either children whom

the healer had recently treated for illnesses or young adults who had gone to him for a tooth extraction procedure (removal of the incisors to signify passage into adulthood is a cultural tradition in this part of Sudan) (Nakazawa et al. 2013).

Clinical Signs Monkeypox disease is characterized by the onset of non-specific symptoms which can include fever, headache, backache, and fatigue during a prodromal period of 2–3 days (Reynolds et al. 2006). This is followed by a 2–4 week period in which a rash develops and progresses from macules, to papules, to vesicles, and then to pustules, followed by umbilication, scabbing and desquamation (CDC 2003). The rash is usually confined to the trunk, but can spread to the palms and soles of the feet, occurring in a centrifugal distribution (Parker et al. 2007). Lesions can also develop on mucous membranes, in the mouth, on the tongue, and on the genitalia (Nalca et al. 2005). The pathogenicity of monkeypox is similar to that of smallpox except for the pronounced lymphadenopathy associated with monkeypox and generally milder symptoms (Heymann 2008). Lymphadenopathy is thus considered to be a key distinguishing feature of monkeypox (Weber and Rutala 2001). The CFR is approximately 1–10% in Africa, with higher death rates among young children (Parker et al. 2007). In children unvaccinated against smallpox, the case-fatality rate ranges from 1 to 14% (Heymann 2008). In addition, children may be more susceptible to monkeypox due to the termination of regular smallpox vaccinations following the worldwide eradication of the disease in 1980.

The incubation period varies from 6 to 16 days. The number of lesions varies from a few to several thousands, affecting oral mucous membranes (in 70% of cases), genitalia (30%), and conjunctivae (20%), as well as the cornea.

There are no drugs or vaccines available for monkeypox, although vaccination against smallpox has been proven to be 85% effective in preventing monkeypox in the past (Parker et al. 2007). Prophylactic vaccination with the smallpox vaccine may be useful within 4 days and up to 14 days after initial contact with a confirmed monkeypox case (CDC 2007).

Epidemiology Monkeypox affect all age groups; however, children under age of 16 have constituted the greatest proportion of cases (Heymann 2008).

Infections of index cases result from direct contact with blood, bodily fluids, or rashes of infected animals. In Africa, human infections have been documented through handling of infected monkeys, Gambian rats or squirrels.

Secondary transmission is human-to-human, resulting from close contact with infected respiratory tract excretions, with skin lesions of an infected person or with recently contaminated objects. Transmission via droplet respiratory particles has also been documented. Transmission can also occur by inoculation or via the placenta (congenital monkeypox). There is no evidence to date that person-to-person transmission alone can sustain monkeypox in the human population.

The differential diagnoses include usually smallpox, chickenpox, measles, bacterial skin infections, scabies, medicamentous allergies and syphilis.

Monkeypox can be definitively confirmed by a number of different tests (ELISA, antigen detection tests, PCR, virus isolation).

Crossing of the Species Barrier In Africa, monkeypox infection has been found in many animal species: rope squirrels, tree squirrels, Gambian rats, striped mice, door-mice and NHP. Doubts persist on the natural history of the virus and further studies are needed to identify the exact reservoir of the monkeypox virus and how it is maintained in nature.

In the USA, the virus is thought to have been transmitted from African animals to a number of susceptible non-African species (like prairie dogs) with which they were co-housed.

Multiple events of human-to-human transmission have been reported, but sustained Monkeypox virus infection cycles among humans have not been documented (Damon et al. 2006; Formenty et al. 2010).

Likos et al. (2005) investigated phylogenetic relationships between Monkeypox virus isolates by examining five whole-genome sequences and confirmed the existence of two distinct groups: the first group contained isolates from the Congo Basin (Congo Basin clade), and the second group included isolates from countries in western Africa. Differences in epidemiologic and clinical features between Monkeypox virus isolates (e.g., higher morbidity and CFR caused by the Congo Basin clade) support the differentiation between these two clades.

Biosecurity and Prevention During monkeypox outbreaks, close contact with other patients is the most significant risk factor for monkeypox virus infection. In the absence of specific treatment and a vaccine, the only way to reduce infection in people is by raising awareness of the risk factors and educating people about the measures they can take to reduce exposure to the virus.

Public health educational messages should focus on the following risks.

- Reducing the risk of human-to-human transmission. Close physical contact with monkeypox infected people should be avoided. Gloves and protective equipment should be worn when taking care of sick people. Regular hand washing should be carried out after caring for or visiting patients.
- Reducing the risk of animal-to-human transmission. Efforts to prevent transmission in endemic regions should focus on thoroughly cooking all animal products (blood, meat) before eating. Gloves and other appropriate protective clothing should be worn while handling sick animals or their infected tissues, and during slaughtering procedures.

Restricting or banning the movement of small African mammals and monkeys may be effective in slowing the expansion of the virus outside Africa.

Captive animals should not be inoculated with smallpox. Instead, infected animals should be isolated from other animals and placed into immediate quarantine. Any animals that might have come into contact with an infected animal should be quarantined and observed for monkeypox symptoms for 30 days.

Health-care workers caring for patients with suspected or confirmed monkeypox virus infection, or handling specimens from them, should implement standard infection control precautions. Healthcare workers and those treating or exposed to patients with monkeypox or their samples should consider being immunized against

smallpox. However, the smallpox vaccination should not be administered to people with compromised immune systems.

Samples taken from people and animals with suspected monkeypox virus infection should be handled by trained staff working in Biosafety Level 3 (BSL-3/ABSL-3) **containment** laboratories (CDC 2007). Orthopoxviruses are susceptible to 0.5% sodium hypochlorite, chloroxylenol-based household disinfectants, glutaraldehyde, formaldehyde, and paraformaldehyde; and are inactivated by heat (autoclaving and incineration) (Butcher and Ulaeto 2005). Orthopoxviruses are stable at ambient temperatures when dried (CDC 2007).

41.2.3.2 Severe Acute Respiratory Syndrome

The Severe Acute Respiratory Syndrome (SARS) Coronavirus (SARS-CoV) is responsible for an acute and often fatal respiratory syndrome that was identified for the first time in the Guangdong province of South China in 2003 (Peiris et al. 2003). SARS-CoV consequently expanded encompassing 37 countries and created the first emerging pandemic of the twenty-first century.

Clinical Signs SARS-CoV may cause an often-severe illness marked initially by systemic symptoms of muscle pain, headache, and fever, followed in 2–10 days by a respiratory symptoms (cough, dyspnea, and pneumonia) and a marked lymphocytopenia. Increased respiratory distress led to a CFR of 9.6% (Smith 2006).

Epidemiology SARS emerged as a unique pandemic starting as an epidemic in Guangdong Province, China in November 2002. It further expanded from person to person worldwide as a pandemic in less than 9 months and ultimately infected more than 8000 persons killing more than 700. The pandemic ended in May 2004.

The virus is supposed to have originated from its natural host, a horseshoe bat (*Rhinolophus sinicus*). Subsequently, it is thought to have been transmitted to and mutated within a secondary host, the palm civet (*Panguma larvata*) serving also as an amplification host, before it was passed into humans as a new human-pathogenic virus, the SARS-CoV (Zhong et al. 2003). SARS-CoV was found to infect also raccoon dogs (*Nyctereutes* sp.), ferret badgers (*Melogale* spp.) and domestic cats. SARS-CoV emerged several times from the same intermediate host, the palm civet, to transgress the species barrier and infect humans. Nevertheless, SARS-CoV seems to have also emerged several times in the past in the province of Guangdong, but remained unnoticed as potential epidemic risk. The conclusion was that bats acted as a reservoir of SARS-CoV with the potential to infect other mammals including humans (Li et al. 2005).

Likewise but surprisingly, ten years after the SARS-pandemic, a novel human coronavirus (HCoV-EMC) emerged in the Middle East in 2012 (Bermingham et al. 2012). The HCoV-EMC was identified following respiratory infections with a clinical presentation of severe acute respiratory syndrome of a Qatari man in a British hospital and, a woman who died in Saudi Arabia. The virus consequently caused 12 other confirmed cases and five deaths worldwide (Saudi Arabia, Jordan, and

Britain). HCoV-EMC, that appears distant genetically from the former SARS-CoV, seems to have a zoonotic origin naturally infecting chiropteran species (Kelland 2013; Kindler et al. 2013).

Crossing of the Species Barrier SARS-CoV appears to have transgressed efficiently and successively two species barrier from bat to carnivores to humans and, ultimately, be highly pathogenic for the later with the potential to infect human pulmonary and intestinal epithelium (Sims et al. 2008).

Interestingly, HCoV-EMC appears genetically in the same phylogenetic clade as other bat coronaviruses (Chan and Poon 2013).

In the past decade chiropterans have been confirmed as hosts or reservoirs of several emerging diseases including SARS, nipah, hendra, Ebola, Marburg and rabies viruses posing a zoonotic risk (Gonzalez et al. 2008).

Prevention Because SARS-CoV may be transmitted by aerosol (i.e. aerosolized droplets from coughing), and due to its physical stability in the environment, the low or absent protective immunity in the human population, and the lack of effective antivirals or vaccines, infection control against SARS relied primarily on the prevention of person-to-person transmission (see for review Cheng et al. 2007).

41.3 Conclusion and Perspectives

Humans and animals did host, share and exchange their pathogens since prehistoric times.

A literature review by Olival, Bogich, Karesh et al. (pers. comm. 2013) on virus isolation from different animal hosts shows that NHP, primates and small domestic ungulates are the mammals that share the most virus species with humans; when corrected for the number of species and by the respective sampling/research methods, monkeys, rodents and bats are the most important reservoirs for zoonotic agents. Moreover, if we focus on known viruses and correct for the number of species and sampling per taxonomic order, chiropterans appear to potentially harbor three and six time more different virus species than rodents and NHP, respectively. Also Rodent and Chiropteran are one of the most species richness among the vertebrate orders, they harbor a variety of viruses that can be potentially infectious for human. Moreover, apes share a so close relationship by nature with human, i.e. >90% of genomic identity, that they theoretically can easily exchange pathogens and pass such “thin” inter species barrier from NHP to Human Primates.

There is no more *terra incognita* on Earth. Humans, by migratory habits, professional or recreation occupations explored already the entire natural environments on the planet, stepping into the immense variety of its ecosystems. While the vast ocean is still open for discovery, zoonotic risk is not out of the scope. As an example, humans are more likely to interact with pinnipeds, than with any other marine mammals and a newly described influenza from seals may potentially infect humans (White et al. 2013). Influenza B virus as well as measles can be shared by

human and seals. Also it is well documented that transmission occurs from human to animals like *Coxiella burnetii* found infecting seals in Alaska. Moreover, *Streptococcus agalactiae*, a member of human gastrointestinal normal flora, is known to infect sea mammals as well as other marine fauna including fishes (!) among others (Delannoy et al. 2013; Duncan et al. 2012).

Understanding the fundamentals of virus emergence from an animal reservoir and its transmission to humans—but also from one animal species to another—as well as mastering the territories at risk with regard to their environments—including biological and physical environmental components (i.e. increase of the human population, climate change and exceptional weather or natural events)—are essential for controlling and preventing zoonoses and potentially emerging zoonoses.

Viruses will continue to pass the species barrier without geographical borders and acquire new abilities to survive within new hosts without losing their intrinsic pathogenic potential.

More than 60% of 335 emerging infectious diseases identified since 1940 have a zoonotic origin. Among them more than two third are from wildlife animal (Jones et al. 2008). Furthermore, specific territories or domains of emergence, within a given environment, where people, livestock and wildlife encounter each other, have been identified and characterized. An analysis of all documented events has led to develop a spatial and temporal approach for a better understanding of dynamic risk factors (so-called drivers) associated with disease emergence (Souris et al. 2010). By understanding these variable drivers of different scales (e.g. from molecular to spatial, including environmental factors) using computing assisted analysis and mathematical models we might finally be able to predict and hopefully prevent emerging zoonotic infections (Morse et al. 2012). Obviously, theoretical models will have always to be sustained by accurate survey networks coupled with multi-disciplinary research. Several of these drivers have to be carefully monitored, e.g. human expansion and its propensity to invade animal territories (i.e. protected area), the emergence of new pathogens from the natural fauna, ecological and environmental conditions, human and animal behaviors, socioeconomic changes, etc.

Biodiversity plays a role in both directions, favoring the risk of exposure to new potentially pathogenic agents and protecting the host against unknown microbes. On one hand, biodiversity exists for the microorganisms as well as for all the other animals, such increasing the variety of potential human pathogens that have not yet “jumped” from animals to humans. On the other hand, the biodiversity of the human major histocompatibility complex, MCH, helps to prevent infection by new pathogens. Eventually, new pathogens may adapt to a new human host (humanization) and ultimately resist to disappearance (i.e. drug resistance) (Maillard and Gonzalez 2006).

Climate change and societal behavior favor the encounters of hosts, vectors and pathogens that never “met” before: Human and animal populations are highly reacting to climate change (e.g.: mosquitoes) and move or expand towards new territories. Human density, i.e. risk of encounter/transmission from animals to humans, and changes in behavior (pets, hunting) are the driver of emerging zoonoses.

Survey and networking, connected to research, molecular biology and/or virus discovery are the strategic key to predict and prevent the emergence of new zoonoses as well as the next pandemic zoonosis (Gonzalez et al. 2011). Moreover technological advances in molecular diagnostics, mathematical modeling, communication, and informatics enable a targeted global surveillance of emerging and previously unknown infections in both human beings and other species (Morse et al. 2012).

References

- Ablashi DV, Pearson G, Rabin H, Armstrong G, Easton J, Valerio M & Cicmanec J (1978) Experimental infection of *Callithrix jacchus* marmosets with Herpesvirus ateles, Herpesvirus saimiri, and Epstein Barr virus. *Biomedicine* 29, 7-10. with heated, noncytopathogenic Herpesvirus saimiri. *Nat New Biol* 242:28-30
- Aguilar PV, Paessler S, Carrara AS, Baron S, Poast J, Wang E, Moncayo AC, Anishchenko M, Watts D, Tesh RB, Weaver SC (2005) Variation in interferon sensitivity and induction among strains of eastern equine encephalitis virus. *J Virol* 79(17):11300-11310. doi:10.1128/JVI.79.17.11300-11310.2005
- Allan JS (1996) Xenotransplantation at a crossroads: prevention versus progress. *Nat Med* 2:18-21
- Anderson CR, Spence L, Downs WG, Aitken TH (1961) Oropouche virus: a new human disease agent from Trinidad, West Indies. *Am J Trop Med Hyg* 10:574-578. PMID 13683183
- Anthony SJ, St Leger JA, Pugliares K, Ip HS, Chan JM, Carpenter ZW, Navarrete-Macias I, Sanchez-Leon M, Saliki JT, Pedersen J, Karesh W, Daszak P, Rabadan R, Rowles T, Lipkin WI (2012) Emergence of fatal avian influenza in New England harbor seals. *MBio* 3(4):e00166-e00112. doi:10.1128/mBio.00166-12
- Armstrong C, Lillie RD (1934) Experimental lymphocytic choriomeningitis of monkeys and mice produced by a virus encountered in studies of the 1933 St. Louis encephalitis epidemic. *Pub Health Rep* 49:1019-1027
- Artsob H (2004) Emerging and nonemerging arboviral diseases and the veterinary/public health interface. *Can Vet J* 45(12):1021-1022
- Atasheva S, Fish A, Fornerod M, Frolova EI (2010) Venezuelan equine Encephalitis virus capsid protein forms a tetrameric complex with CRM1 and importin alpha/beta that obstructs nuclear pore complex function. *J Virol* 84(9):4158-4171. doi:10.1128/JVI.02554-09
- Atlas RA (2001) Bioterrorism before and after September 11. *Crit Rev Microbiol* 27:355-379
- Balogh Z, Ferenczi E, Szeles K, Stefanoff P, Gut W, Szomor KN, Takacs M, Berencsi G (2010) Tick-borne encephalitis outbreak in Hungary due to consumption of raw goat milk. *Journal of Virological Methods* 163(2):481-485
- Barrett P, Plotkin S, Ehrlich H (2008) Tick borne encephalitis virus vaccines. In: Plotkin S, Orenstein W, Offit P (eds) *Vaccines*. Saunders Elsevier, Philadelphia, pp 841-856
- Barry M, Russi M, Armstrong L et al (1995) Brief report: treatment of a hazard group laboratory-acquired *Sabia* virus infection. *N Eng J Med* 333:294-295
- Bausch DG, Nichol ST, Muyembe-Tamfum JJ, Borchert M, Rollin PE, Sleurs H, Campbell P, Tshioko FK et al (2006) Marburg hemorrhagic fever associated with multiple genetic lineages of virus. *N Engl J Med*. 355(9):909-919. doi:10.1056/NEJMoa051465
- Belanov EF, Muntianov VP, Kriuk VD, Sokolov AV, Bormotov NI, P'iankov OV, Sergeev AN (1996) Survival of Marburg virus infectivity on contaminated surfaces and in aerosols. *Vopr Virusol* 41(1):32-34
- Bermingham A, Chand MA, Brown CS, Aarons E, Tong C, Langrish C, Hoschler K, Brown K, Galiano M, Myers R, Pebody RG, Green HK, Boddington NL, Gopal R, Price N, Newsholme W, Drosten C, Fouchier RA Zambon M (2012) Severe respiratory illness caused by a novel coronavirus, in a patient transferred to the United Kingdom from the Middle East, September 2012. *Euro Surveill* 17(40):20290

- Beugnet F, Marie JL (2009) Emerging arthropod-borne diseases of companion animals in Europe. *Vet Parasitol* doi:10.1016/j.vetpar.2009.03.028
- Bird BH, Maartens LH, Campbell S, Erasmus BJ, Erickson BR, Dodd KA, Spiropoulou CF, Cannon D, Drew CP, Knust B, McElroy AK, Khristova ML, Albariño CG, Nichol ST (2011) Rift valley fever virus vaccine lacking the NSs and NSm genes is safe, nonteratogenic, and confers protection from viremia, pyrexia, and abortion following challenge in adult and pregnant sheep. *J Virol* 85(24):12901–12909
- Block SS (ed) (2001) *Disinfection, sterilization, and preservation* (5th edn). Lippincott Williams & Wilkins, Philadelphia
- Borio L, Inglesby T, Peters CJ et al (2002) Hemorrhagic fever viruses as biological weapons: medical and public health management. *JAMA* 287(18):2391–2405
- Bowen ET, Lloyd G, Harris WJ, Platt GS, Baserville A, Vella EE (1977) Viral haemorrhagic fever in southern Sudan and northern Zaire. Preliminary studies on the aetiological agent. *Lancet* 1(8011):571–573
- Bray M (2003) Defense against filoviruses used as biological weapons. *Antiviral Res* 57(1–2): 53–60
- Bredjenbeek PJ, Molenkamp R, Spaan WJ, Deubel V, Marianneau P, Salvato MS, Moshkoff D, Zapata J, Tikhonov I, Patterson J, Carrion R, Ticer A, Brasky K, Lukashevich IS (2006) A recombinant yellow fever 17D vaccine expressing Lassa virus glycoproteins. *Virology* 345(2): 299–304
- Briese T, Paweska JT, McMullan LK, Hutchison SK, Street C et al (2009) Genetic detection and characterization of Lujo virus, a new hemorrhagic fever-associated arenavirus from Southern Africa. *PLoS Pathog* 5(5):e1000455. doi:10.1371/journal.ppat.1000455
- Brummer-Korvenkontio M, A Vaheri, T Hovi, CH von Bonsdorff, J Vuorimies, T Manni, K Penttinen, N Oker-Blom, J Lähdevirta (1980) Nephropathia epidemica: Detection of antigen in bank voles and serological diagnosis of human infection *J. Inf. Dis.*, 141:131–134
- Buckley SM, Casals J (1970) Lassa fever, a new virus disease of man from West Africa. III. isolation and characterization of the virus. *Am J Trop Med Hyg* 19:680–691
- Butcher W, Ulaeto D (2005) Contact inactivation of orthopoxviruses by household disinfectants. *J Appl Microbiol* 99(2):279–284
- Bwaka MA, Bonnet MJ, Calain P, Colebunders R, De Roo A, Guimard Y, Katwiki KR, Kibadi K, Kipasa MA, Kuvula KJ, Mapanda BB, Massamba M, Mupapa KD, Muyembe-Tamfum JJ, Ndaberey E, Peters CJ, Rollin PE, Van den Enden E, Van den Enden E (1999) Ebola hemorrhagic fever in Kikwit, Democratic Republic of the Congo: clinical observations in 103 patients. *J Infect Dis* 179(Suppl 1):S1–7. doi:10.1086/514308
- Carette JE, Raaben M, Wong AC, Herbert AS, Obernosterer G, Mulherkar N, Kuehne AI, Kranzusch PJ, Griffin AM, Ruthel G, Dal Cin P, Dye JM, Whelan SP, Chandran K, Brummelkamp TR (2011) Ebola virus entry requires the cholesterol transporter Niemann-Pick C1. *Nature* 477(7364):340–343. doi:10.1038/nature.10348
- Casillas AM, Nyamathi AM, Sosa A, Wilder CL, Sands H (2003) A current review of Ebola virus: pathogenesis, clinical presentation, and diagnostic assessment. *Biol Res Nurs* 4(4):268–275
- Centers for Disease Control and Prevention (CDC) (2003) Multistate outbreak of monkeypox—Illinois, Indiana, and Wisconsin. *MMWR Morb Mortal Wkly Rep* 52(23):537–540
- Centers for Disease Control and Prevention (CDC) (2007) In: Richmond JY, McKinney RW (eds) *Biosafety in microbiological and biomedical laboratories (BMBL)* (5th edn). US GPO, Washington, DC
- Centers for Disease Control and Prevention (CDC) (2008) Imported case of Marburg hemorrhagic fever—Colorado. *MMWR Morb Mortal Wkly Rep* 58(49):1377–1381
- Chan PK (2002) Outbreak of avian influenza A (H5N1) virus infection in Hong Kong in 1997. *Clin Infect Dis* 34(suppl 2):S58–S64
- Chan RWY, Poon LLM (2013) The emergence of human coronavirus EMC: how scared should we be? *MBio* 4(2):e00191–e001913 doi:10.1128/mBio.00191-13
- Charrel RN, de Lamballerie X (2010) Zoonotic aspects of arenavirus infections. *Vet Microbiol* 140:213–220

- Charrel RN, Zaki AM, Attoui H, Fakeeh M, Billoir F, Yousef AI, de Chesse R, De Micco P, Gould EA, de Lamballerie X (2001) Complete coding sequence of the Alkhurma virus, a tick-borne flavivirus causing severe hemorrhagic fever in humans in Saudi Arabia. *Biochem Biophys Res Commun* 287(2):455–461
- Charrel RN, Coutard B, Baronti C, Canard B, Nougairede A, Frangeul A, Morin B, Jamal S, Schmidt CL, Hilgenfeld R, Klempa B, de Lamballerie X (2011) Arenaviruses and hantaviruses: from epidemiology and genomics to antivirals. 2011. *Antiviral Res* 90(2):102–114. doi:10.1016/j.antiviral. 2011.02.009. PMID:21356244
- Cheng VC, Lau SK, Woo PCY, Yuen KY (2007) Severe acute respiratory syndrome coronavirus as an agent of emerging and reemerging infection *Clin Microbiol Rev* 20(4):660–694
- Chosewood LC, Wilson DE (eds) (2009) Biosafety in microbiological and biomedical laboratories (5th edn). CDC–NIH, Washington, DC
- Chumakov MP (1948) [Results of a study made of Omsk hemorrhagic fever (OL) by an expedition of the Institute of Neurology] » *Vestnik Acad Med Nauk SSSR*. 2:19-26 (in Russian)
- Chumakov MP, Butenko AM, Shalunova NV, Mart'yanova LI, Smirnova, WE, Bashkirtsev VN., Zavadova TI, Rubin SG, Tkachenko EA, Karmy-Sheva VY, Reingold VN, Popov GV, Savinov, AP (1968) New data on the virus causing Crimean hemorrhagic fever (CHF). *Vopr. Virusol*. 13, 377 (in Russian; in English, NAMRU3-T596)
- Coimbra TLM, Nassar ES, Burattini MN, de Souza LTM, Ferreira IB, Iray MR, Travassos da Rosa APA, Vasconcelos PFC, Pinheiro FP, LeDuc JW, Rico-Hesse R, Gonzalez J-P, Jahrling PB, Tesh RB (1994) New arenavirus isolated in Brazil. *Lancet* 343(8894):391–392
- Collins CH, Kennedy DA (eds) (1983) *Laboratory-acquired Infections* (4th edn). Butterworth-Heinemann, Oxford
- Côté M, Misasi J, Ren T, Bruchez A, Lee K, Filone CM, Hensley L, Li Q, Ory D, Chandran K, Cunningham J (2011) Small molecule inhibitors reveal Niemann-Pick C1 is essential for Ebola virus infection. *Nature* 477(7364):344–348. doi:10.1038/nature10380
- Courgnaud V, Van Dooren S, Liegeois F, Pourrut X, Abela B et al (2004) Simian T-cell leukemia virus (STLV) infection in wild primate populations in Cameroon evidence for dual STLV type 1 and type 3 infection in agile mangabeys (*Cercocebus agilis*). *J Virol* 78(9):4700–4709
- Crabtree MB, Kent Crockett RJ, Bird BH, Nichol ST, Erickson BR, Biggerstaff BJ, Horiuchi K, Miller BR (2012) Infection and transmission of Rift Valley fever viruses lacking the NSs and/or NSm genes in mosquitoes: potential role for NSm in mosquito infection. *PLoS Negl Trop Dis* 6(5):e1639
- Dalgard DW et al (1992) Combined simian hemorrhagic fever and Ebola virus infection in cynomolgus monkeys. *Lab Anim Sci* 42:152–157
- Damon IK, Roth CE, Chowdhary V (2006) Discovery of monkeypox in Sudan. *N Engl J Med* 355:962–963
- Dandawate CN, Desai GB, Achar TR, Banerjee K (1994) Field evaluation of formalin inactivated Kyasanur forest disease virus tissue culture vaccine in three districts of Karnataka state. *Indian J Med Res* 99:152–158
- Daszak P, Cunningham AA, Hyatt AD (2000) Emerging infectious diseases of wildlife-threats to biodiversity and human health. *Science* 287:443–449
- Debré P, Gonzalez JP (2013) *Vie et mort des épidémies*. Odile Jacob, Paris, 280 p
- de la Monte S, Castro F, Bonilla NJ, Gaskin deUA Hutchins GM (1985) The systemic pathology of Venezuelan equine encephalitis virus infection in humans. *Am J Trop Med Hyg* 34(1):194–202
- Delannoy CM, Crumlish M, Fontaine MC, Pollock J, Foster G, Dagleish MP, Turnbull JF, Zadoks RN (2013) Human *Streptococcus agalactiae* strains in aquatic mammals and fish. *BMC Microbiol* 13:41. doi:10.1186/1471-2180-13-41
- Delgado S, Erickson BR, Agudo R, Blair PJ, Vallejo E et al (2008) Chapare virus, a newly discovered Arenavirus isolated from a fatal hemorrhagic fever case in Bolivia. *PLoS Pathog* 4(4):e1000047. doi:10.1371/journal.ppat.1000047
- Donoso MO, Schädler R, Niedrig M (2008) A survey on cases of tick-borne encephalitis in European countries. *Euro Surveill* 13(17):pii=18848

- Gardner CL, Burke CW, Tesfay MZ, Glass PJ, Klimstra WB, Ryman KD (2008) Eastern and Venezuelan equine encephalitis viruses differ in their ability to infect dendritic cells and macrophages: impact of altered cell tropism on pathogenesis. *J Virol* 82(21):10634–10646. doi:10.1128/JVI.01323-08
- Downs WG, Anderson CR, Spence L, Aitken THG, Greenhall AH (1963) Tacaribe virus, a new agent isolated from Artibeus bats and mosquitoes in Trinidad, West Indies. *Am J Trop Med Hyg* 12:640–646
- Dumpis U, Crook D, Oksi J (1999) Tick-borne encephalitis. *Clin Infect Dis* 28(4):882–890. doi:10.1086/515195
- Duncan C, Savage K, Williams M, Dickerson B, Kondas AV, Fitzpatrick KA, Guerrero JL, Spraker T, Kersh GJ (2012) Multiple strains of *Coxiella burnetii* are present in the environment of St. Paul Island, Alaska. *Transbound Emerg Dis* doi: 10.1111/j.1865-1682.2012.01353.x.
- Elliott LH, McCormick JB, Johnson KM (1982) Inactivation of Lassa, Marburg, and Ebola viruses by gamma irradiation. *J Clin Microbiol* 16(4):704–708
- Emonet S, Lemasson JJ, Gonzalez JP, de Lamballerie X, Charrel RN (2006) Phylogeny and evolution of old world arenaviruses. *Virology* 350(2):251–257
- Enria DA, Maiztegui JI (1994) Antiviral treatment of Argentine hemorrhagic fever. *Antiviral Res* 23(1):23–31
- Esposito JJ, Sammons SA, Frace AM, Osborne JD, Olsen-Rasmussen M, Zhang M, Govil D, Damon IK, Kline R, Laker M, Li Y, Smith GL, Meyer H, Leduc JW, Wohlhueter RM (2006) Genome sequence diversity and clues to the evolution of variola (smallpox) virus. *Science* 313(5788):807-812
- Feldmann H (2010) Are we any closer to combating Ebola infections? *Lancet* 375(9729):1850–1852. doi:10.1016/S0140-6736(10)60597-1
- Field HE (2009) Bats and emerging zoonoses: henipaviruses and SARS. *Zoonoses Public Health* 56(6-7):278–284. doi:10.1111/j.1863-2378.2008.01218.x.
- Fisher-Hoch SP (2005) Lessons from nosocomial viral haemorrhagic fever outbreaks. *Br Med Bull* 73-74:123–137
- Formenty P, Muntzir MO, Damon IK, Chowdhary V, Opoca ML, Monimart C (2010) Human monkeypox outbreak caused by novel virus belonging to Congo Basin clade, Sudan, 2005. *Emerg Infect Dis* 16:1539–1545
- Foster SO, Brink EW, Hutchins DL, Pifer JM, Lourie B, Moser CR, Cummings EC, Kuteyi OE, Eke RE, Titus JB, Smith EA, Hicks JW, Foege WH (1972) Human monkeypox. *Bull World Health Organ* 46(5):569–576
- Gandsman EJ, Aaslestad HG, Ouimet TC, Rupp WD (1997) Sabia virus incident at Yale University. *Am Ind Hyg Assoc J* 58(1):51–53
- Gay FP, Holden M (1933) Isolation of herpes virus from several cases of epidemic encephalitis. *Proc. Soc. Exp. Biol. Med.* 30:1051–1053
- Gear JH (1977) Haemorrhagic fevers of Africa: an account of two recent outbreaks. *J S Afr Vet Assoc* 48(1):5–8
- Geisbert TW, Jahrling PB (1995) Differentiation of filoviruses by electron microscopy. *Virus Res* 39(2–3):129–150
- Geisbert TW, Jones S, Fritz EA, Shurtleff AC, Geisbert JB et al (2005) Development of a new vaccine for the prevention of Lassa fever. *PLoS Med* 2(6):e183. doi:10.1371/journal.pmed.0020183
- Géraud C (2006) Dermatoses professionnelles. *Traité de pathologie professionnelle et de l'environnement*, 16-533-A-10. Encyclopédie Médico-Chirurgicale. Elsevier Masson SAS
- Ginsberg HS, Stafford KC (2005) Management of ticks and tick-borne diseases. In: Goodman JL, Dennis DT, Sonenshine DE (eds) *Tick borne diseases of humans*. ASM Press, Washington, pp 65-86
- Gonzalez JP, Fair J (2013) From biosecurity to emerging diseases: a relentlessly changing paradigm. *Trop Med Sur* 1:(1). <http://dx.doi.org/10.4172/tpms.1000e102>
- Gonzalez JP, Emonet S, de Lamballerie X, Charrel R (2007) Arenaviruses. *Curr Top Microbiol Immunol* 315:253–288
- Gonzalez JP, Ar Guilh M, Reynes JM, Leroy E (2008) Bat borne viral zoonoses emergence part I synthetic analyses, chapter 6. In: Carol JCP, Kleinau E (eds) *People, health and forests*. Earthscan, London

- Gonzalez JP, Lambert G, Legand A, Debré P (2011) Toward a transdisciplinary understanding and a global control of emerging infectious diseases. *J Infect Dev Ctries* 5(12):903–905
- Gonzalez JP, Prugnolle F, Leroy E (2013) Men, primates, and germs: an ongoing affair. *Curr Top Microbiol Immunol* 365:337–353. PMID: 23239237
- Grard G, Fair JN, Lee D, Slikas E, Steffen I et al (2012) A novel Rhabdovirus associated with acute hemorrhagic fever in Central Africa. *PLoS Pathog* 8(9): e1002924. doi:10.1371/journal.ppat.1002924
- Greene D (1989) *The history of the Peloponnesian War of Thucydides* [trans]. University of Chicago Press, Chicago. pp 115–118
- Grobbelaar AA, Weyer J, Leman PA, Kemp A, Paweska JT, Swanepoel R (2011) Molecular epidemiology of Rift valley fever virus. *Emerg Infect Dis* [serial on the Internet]. <http://dx.doi.org/10.3201/eid1712.111035>
- Grolla A, Lucht A, Dick D, Strong JE, Feldmann H (2005). Laboratory diagnosis of Ebola and Marburg hemorrhagic fever. *Bull Soc Pathol Exot* 98(3):205–209
- Günther S, Emmerich P, Laue T, Kühle O, Asper M, Jung A, Grewing T, ter Meulen J, Schmitz H (2000) Imported lassa fever in Germany: molecular characterization of a new Lassa virus strain. *Emerg Infect Dis* 6(5):466–476. PMID: PMC2627947
- Hahn BH, Shaw GM, Sharp PM, De Cock KM (2000) AIDS as a zoonosis: scientific and public health implications. *Science* 287:607–614
- Halfmann P, Kim JH, Ebihara H, Noda T, Neumann G, Feldmann H, Kawaoka Y (2008) Generation of biologically contained Ebola viruses. *Proc Natl Acad Sci U S A* 105(4):1129–1133
- Halfmann P, Ebihara H, Marzi A, Hatta Y, Watanabe S, Suresh M, Neumann G, Feldmann H, Kawaoka Y (2009) Replication-deficient ebolavirus as a vaccine candidate. *J Virol* 83(8):3810–3815
- Halpin K, Young PL, Field HE, Mackenzie JS (2000) Isolation of Hendra virus from pteropid bats: a natural reservoir of Hendra virus. *J Gen Virol* 81:1927–1932
- Harcourt BH, Sanchez A, Offermann MK (1999) Ebola virus selectively inhibits responses to interferons, but not to interleukin-1beta, in endothelial cells. *J Virol* 73(4):3491–3496
- Hayes M, Salvato M (2012) Arenavirus evasion of host anti-viral responses. *Viruses* 4(10):2182–2196
- Heinz FX (2008). Tick-borne encephalitis: rounding out the picture. *Euro Surveill* 13(17)
- Heinz FX, Holzmann H, Essl A, Kundi M (2007) Field effectiveness of vaccination against tick-borne encephalitis. *Vaccine* 25:7559–7567
- Hemmer CJ, Littmann M, Löbermann M, Lafrenz M, Böttcher T, Reisinger EC (2005) Tickborne meningoencephalitis, first case after 19 years in northeastern Germany. *Emerg Infect Dis* [serial on the Internet]. <http://dx.doi.org/10.3201/eid1104.041110>
- Hewlett BS, Amolat RP (2003) Cultural contexts of Ebola in Northern Uganda. *Emerg Infect Dis* 9(10):1242–1248
- Heymann DL (2008) *Control of communicable diseases manual* (19th edn). American Public Health Association, Washington, D.C.
- Hirabayashi Y, Oka S, Goto H, Shimada K, Kurata T, Fisher-Hoch SP, McCormick JB (1988) An imported case of Lassa fever with late appearance of polyserositis. *J Infect Dis* 158(4):872–875
- Holmes GP, McCormick JB, Trock SC, Chase RA, Lewis SM, Mason CA, Hall PA, Brammer LS, Perez-Oronoz GI, McDonnell MK et al (1990) Lassa fever in the United States. Investigation of a case and new guidelines for management. *N Engl J Med* 323(16):1120–1123
- Hughes AL, Irausquin S, Friedman R (2010) The evolutionary biology of poxviruses. *Infect Genet Evol* 10(1):50–59
- Hutin YJ, Williams RJ, Malfait P, Pebody R, Loparev VN, Ropp SL, Rodriguez M, Knight JC, Tshiko FK, Khan AS, Szczeniowski MV, Esposito JJ (2001) Outbreak of human monkeypox, Democratic Republic of Congo, 1996 to 1997. *Emerg Infect Dis* 7(3):434–438
- Jaax N et al (1995) Transmission of Ebola virus (Zaire strain) to uninfected control monkeys in a biocontainment laboratory. *Lancet* 346(8991):1669–1671
- Johnson E, Jaax N, White J, Jahrling P (1995) Lethal experimental infections of rhesus monkeys by aerosolized Ebola virus. *Int J Exp Path* 76(4):227–236

- Johnson KM, Kuns ML, Mackenzie RB, Webb PA, Yunker CE (1966) Isolation of Machupo virus from wild rodent *Calomys callosus*. *Am J Trop Med Hyg* 15:103–106
- Jones KE, Patel N, Levy M et al (2008) Global trends in emerging infectious diseases. *Nature* 451:990–994
- Kelland K (2013) Deadly new virus well-adapted to infect humans. *Medscape Medical News*. <http://www.medscape.com/viewarticle/779538>
- Kerbo N, Donchenko I, Kutsar K, Vasilenko V (2005) Tickborne encephalitis outbreak in Estonia linked to raw goat milk, May–June 2005. *Euro Surveill* 10(6):E050623–050622
- Kharitonova NN, Leonov YA (1985) Omsk Hemorrhagic Fever. [Trans. S. Korzelska]. Amerind Publishing Co, New Delhi
- Kiley MP, Bowen ET, Eddy GA, Isaäcson M, Johnson KM, McCormick JB, Murphy FA, Pattyn SR et al (1982) Filoviridae: a taxonomic home for Marburg and Ebola viruses? *Intervirology* 18(1-2):24–32
- Kilgore PE, Ksiazek TG, Rollin PE, Mills JN, Villagra MR, Montenegro MJ, Costales MA, Paredes LC, Peters CJ (1997) Treatment of Bolivian hemorrhagic fever with intravenous ribavirin. *Clin Infect Dis* 24(4):718–722
- Kindler E, Jónsdóttir HR, Muth D, Hamming OJ et al (2013) Efficient replication of the novel human Betacoronavirus EMC on primary human epithelium highlights its zoonotic potential. *MBio* 4(1)
- Kitching A, Addiman S, Cathcart S, Bishop L, Krahe D, Nicholas M et al (2009) A fatal case of Lassa fever in London, January 2009. *Euro Surveill* 14(6):pii=19117. <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19117>
- Kriz B, Benes C, Danielova V, Daniel M (2004) Socio-economic conditions and other anthropogenic factors influencing tick-borne encephalitis incidence in the Czech Republic. *Int J Med Microbiol* 293(Suppl 37):63–68
- Kuhn JH, Becker S, Ebihara H et al (2010) Proposal for a revised taxonomy of the family *Filoviridae*: classification, names of taxa and viruses, and virus abbreviations. *Arch Virol* 155(12):2083–2103
- Kurata T, Hondo R, Sato S, Oda A, Aoyama Y, McCormick JB (1983) Detection of viral antigens in formalin-fixed specimens by enzyme treatment. *Ann N Y Acad Sci* 420 192–207
- Ladnyj ID, Ziegler P, Kima E (1972) A human infection caused by monkeypox virus in Basankusu territory, Democratic Republic of the Congo. *Bull World Health Organ* 46(5):593–597
- Larson RA, Dai D, Hosack VT, Tan Y, Bolken TC, Hruba DE, Amberg SM (2008) Identification of a broad-spectrum arenavirus entry inhibitor. *J Virol* 82(21):10768–75
- Lee HW, Lee PW, Johnson KM (1978) Isolation of the etiologic agent of Korean hemorrhagic fever. *J Infect Dis* 137(3):298–308 PMID 24670.
- Lee HW (1989) Hemorrhagic fever with renal syndrome in Korea. *Reviews of infectious diseases* 11 (Suppl 4): S864–876
- Leffel ER, Reed DS (2004) Marburg and Ebola viruses as aerosol threats. *Biosecur Bioterror* 2(3):186–191. doi:10.1089/bsp.2004.2.186
- Lelie PN, Reesink HW, Lucas CJ (1987) Inactivation of 12 viruses by heating steps applied during manufacture of a hepatitis B vaccine. *J Med Virol* 23(3):297–301
- Leroy EM, Kumulungui B, Pourrut X, Rouquet P, Hassanin A, Yaba P, Délicat A, Paweska JT et al (2005) Fruit bats as reservoirs of Ebola virus. *Nature* 438(7068):575–576. doi:10.1038/438575a
- Leschnik MW, Kirtz GC, Thalhammer JG (2002) Tick-borne encephalitis (TBE) in dogs. *Int J Med Microbiol* 6(Suppl 33):66–69
- Li W, Shi Z, Yu M, Ren W, Smith C, Epstein JH, Wang H, Crameri G, Hu Z, Zhang H, Zhang J, McEachern J, Field H, Daszak P, Eaton BT, Zhang S, Wang LF (2005) Bats are natural reservoirs of SARS-like coronaviruses. *Science* 310(5748):676–679
- Likos AM, Sammons SA, Olson VA, France MA, Li Y, Olsen-Rasmussen MA (2005) A tale of two clades: monkeypox viruses. *J Gen Virol* 86:2661–2672
- Lipkin WI, Briese T (2007) Bornaviridae. In: Knipe DM, Howley PM (eds) *Fields virology* (5th edn) pp 1829–1851. Lippincott Williams & Wilkins, Philadelphia
- Lisieux T, Coimbra M, Nassar ES, Burattini MN, de Souza LT, Ferreira I, Rocco IM, da Rosa AP, Vasconcelos PF, Pinheiro FP et al (1994) New arenavirus isolated in Brazil. *Lancet* 343(8894):391–392

- Lu Z, Broker M, Liang G (2008) Tick-borne encephalitis in mainland China. *Vector Borne Zoonotic Dis* 8(5):713–720
- Lukashevich IS, Patterson J (2008) Safety, immunogenicity, and efficacy of the ML29 vaccine for Lassa fever in small non-human primates. *Vaccine* 26:5246–5254
- Mahanty S, Kalwar R, Rollin PE (1999) Cytokine measurement in biological samples after physicochemical treatment for inactivation of biosafety level 4 viral agents. *J Med Virol* 59(3):341–345
- Mahieux R, Gessain A (2011) HTLV-3/STLV-3 and HTLV-4 Viruses: Discovery, Epidemiology, Serology and Molecular Aspects *Viruses*. 2011 July; 3(7):1074–1090. doi:10.3390/v3071074
- Maillard JC, Gonzalez JP (2006) Biodiversity and emerging diseases. *Ann N Y Acad Sci* 1081:1–16
- Maiztegui JI (1975) Clinical and epidemiological patterns of Argentine haemorrhagic fever. *Bull World Health Organ* 52(657):675
- Maiztegui JI, Fernández NJ, Damilano AJ (1979) Efficacy of immune plasma in treatment of Argentine Hemorrhagic Fever and association between treatment and a late neurological syndrome. *Lancet* 2(8154):1216–1217
- Maiztegui JI, McKee KT Jr, Barrera Oro JG, Harrison LH, Gibbs PH, Feuillade MR, Enria DA, Briggiler AM, Levis SC, Ambrosio AM, Halsey NA, Peters CJ (1998) Protective efficacy of a live attenuated vaccine against Argentine hemorrhagic fever. *AHF Study Group. J Infect Dis* 177(2):277–283
- Marrennikova SS, Shelukhina EM, Maltseva NN, Cimiskjan KL, Macevic GR (1972) Isolation and properties of the causal agent of a new varioloid-like disease (monkeypox) in man. *Bull World Health Organ* 46(5):599–611
- Marshall ID, Woodroffe GM, Hirsch S (1982) Viruses recovered from mosquitoes and wildlife serum collected in the Murray Valley of south-eastern Australia, February 1974, during an epidemic of encephalitis. *Aust J Exp Biol Med Sci* 60:457–470
- Martien AM, Groenen A, Archibald L, Uenishi H et al (2012) Analyses of pig genomes provide insight into porcine demography and evolution. *Nature* 491(7424):393–398
- McCormick JB, King IJ, Webb PA, Scribner CL, Craven RB, Johnson KM (1986) Lassa fever. *N Engl J Med* 314(1):20–26
- Michaels MG, Jenkins FJ, St George K, Nalesnik MA, Starzl TE et al (2001) Detection of infectious baboon cytomegalovirus after baboon-to-human liver xenotransplantation. *J Virol* 75(6):2825–2828
- Miller EH, Obernosterer G, Raaben M, Herbert AS, Deffieu MS, Krishnan A, Ndungo E, Sandesara RG, Carette JE, Kuehne AI, Ruthel G, Pfeffer SR, Dye JM, Whelan SP, Brummelkamp TR, Chandran K (2012) Ebola virus entry requires the host-programmed recognition of an intracellular receptor. *EMBO J* 31(8):1947–1960. doi:10.1038/emboj.2012.53
- Mitchell SW, McCormick JB (1984) Physicochemical inactivation of Lassa, Ebola, and Marburg viruses and effect on clinical laboratory analyses. *J Clin Microbiol* 20(3):486–489
- Monath T, Cetron MS, Teuwen DE. (2008) Yellow fever vaccine. In: Plotkin SA, Orenstein WA, Offit PA, eds. *Vaccines*. 5th ed. Philadelphia, PA: Saunders Elsevier; 959–1055
- Morrill JC, Mebus CA, Peters CJ (1997) Safety and efficacy of a mutagen-attenuated Rift Valley fever virus vaccine in cattle. *Am J Vet Res* 58(10):1104–1109
- Morse SS, Mazet JA, Woolhouse M, Parrish CR, Carroll D, Karesh WB, Zambrana-Torrel C, Lipkin WI, Daszak P (2012) Prediction and prevention of the next pandemic zoonosis. *Lancet* 380(9857):1956–1965
- Morvan J, Deubel V, Gounon P, Nakouné E, Barrière P, Murri S, Perpète O, Selekon B et al (1999) Identification of Ebola virus sequences present as RNA or DNA in organs of terrestrial small mammals of the Central African Republic. *Microbes Infect* 1(14):1193–1201. doi:10.1016/S1286-4579(99)00242-7
- Mwanatambwe M, Yamada N, Arai S, Shimizu-Suganuma M, Shichinohe K, Asano G (2001) Ebola hemorrhagic fever (EHF): mechanism of transmission and pathogenicity. *J Nippon Med Sch* 68(5):370–375

- Nakazawa Y, Emerson GL, Carroll DS, Zhao H, Li Y, Reynolds MG, Karem KL, Olson VA, Lash RR, Davidson WB, Smith SK, Levine RS, Regnery RL, Sammons SA, Frace MA, Mutasim EM, Karsani ME, Muntasir MO, Babiker AA, Opoka L, Chowdhary V, Damon IK (2013) Phylogenetic and ecologic perspectives of a monkeypox outbreak, Southern Sudan, 2005. *Emerg Infect Dis* 19(2):237–245
- Nalca A, Rimoin AW, Bavari S, Whitehouse CA (2005). Reemergence of monkeypox: prevalence, diagnostics, and countermeasures. *Clin Infect Dis* 41(12):1765–1771
- Negredo A, Palacios G, Vázquez-Morón S, González F, Dopazo H et al (2011) Discovery of an Ebolavirus-like Filovirus in Europe *PLoS Pathog* 7(10):e1002304. doi:10.1371/journal.ppat.1002304
- Nelson CB, Pomeroy BS, Schroll K, Park WE, Lindeman RJ (1952) An outbreak of conjunctivitis due to Newcastle disease virus (NDV) occurring in poultry workers. *Am J Public Health* 42(6):672–678
- Palmer S, Torgerson SP, Brown DWG (2001) Biology, clinical practice, and public health control. Oxford Textbook of Zoonoses edit. pp. 994, Oxford
- Palmer S, Torgerson SP, Brown DWG (2011) Oxford textbook of zoonoses: biology, clinical practice, and public health control. 992 p. ISBN-10:0198570023
- Parker S, Nuara A, Buller RML, Schultz DA (2007) Human monkeypox: an emerging zoonotic disease. *Future Microbiol* 2(1):17–34
- Paweska J et al (2009) Nosocomial outbreak of novel arenavirus infection: Southern Africa. 2009. *Emerg Infect Dis* 15(10):1598–1602. doi:10.3201/eid1510.090211. PMC 2866397. PMID 19861052
- Paweska JT, Jansen vanVP, Masumu J, Leman PA, Grobbelaar AA et al (2012) Virological and serological findings in *Rousettus aegyptiacus* experimentally inoculated with vero cells-adapted hogan strain of Marburg Virus. *PLoS ONE* 7(9):e45479. doi:10.1371/journal.pone.0045479
- Peiris JSM et al (2003) Coronavirus as a possible cause of severe acute respiratory syndrome. *Lancet* 361:(9366)1319–1325
- Petersen LR, Gubler DJ (2003) Infection: viruses: alphaviruses. In: Warrel DA, Cox TM, Firth JD, Benz EJ (eds) Oxford text book of medicine, (4th edn) Oxford University, Oxford, pp 377–379
- Peterson AT, Bauer JT, Mills JN (2004) Ecologic and geographic distribution of Filovirus disease. *Emerg Infect Dis* 10(1):40–47. doi: 10.3201/eid1001.030125
- Pfeffer M, Dobler G (2010). Emergence of zoonotic arboviruses by animal trade and migration. *Parasit Vectors* 3(1):35. doi:10.1186/1756-3305-3-35
- Polop F, Provencal C, Scavuzzo M, Lamfri M, Caldero'n G, Polop J (2008) On the relationship between the environmental history and the epidemiological situation of Argentine hemorrhagic fever. *Ecol Res* 23:217–225. doi:10.1007/s11284-007-0371-2
- Pourrut X, Kumulungui B, Wittmann T, Moussavou G, Délicat A, Yaba P, Nkoghe D, Gonzalez JP et al (2005) The natural history of Ebola virus in Africa. *Microbes Infect* 7(7–8):1005–1014. doi:10.1016/j.micinf.2005.04.006
- Pourrut X, Délicat A, Rollin PE, Ksiazek TG, Gonzalez J-P, Leroy EM (2007) Spatial and temporal patterns of Zaire ebolavirus antibody prevalence in the possible reservoir bat species. *J Infect Dis* 196(Suppl 2):S176–183. doi:10.1086/520541
- Pringle CR (2005) Order mononegavirales. In: Fauquet CM, Mayo MA, Maniloff J, Desselberger U, Ball LA (eds) Virus taxonomy-eighth report of the international committee on taxonomy of viruses. Elsevier, San Diego, pp 609–614
- Rabinovich R, Gaudzinski-Windheuser S, Goren-Inbar N (2008) Systematic butchering of fallow deer (Dama) at the early middle pleistocene acheulian site of Gesher Benot Ya'aqov (Israel). *J Human Evol* 54:134–149
- Ramelow C, Süss J, Berndt D, Roggendorf M, Schreier E (1993) Detection of tick-borne encephalitis virus. RNA in ticks (*Ixodes ricinus*) by the polymerase chain reaction. *J Virol Methods* 45:115–119. doi:10.1016/0166-0934(93)90145-H
- Randolph SE (2009) Tick-borne disease systems emerge from the shadows: the beauty lies in molecular detail, the message in epidemiology. *Parasitology* 136:1403–1413

- Randolph SE (2010) To what extent has climate change contributed to the recent epidemiology of tick-borne diseases? *Vet Parasitol* 167:92–94
- Reed KD, Melski JW, Graham MB, Regnery RL, Sotir MJ, Wegner MV (2004) The initial detection of human monkeypox in the western hemisphere: association with infected prairie dogs. *N Engl J Med* 350(4):342–350
- Rendi-Wagner P (2004) Risk and prevention of tick-borne encephalitis in travelers. *J Travel Med* 11(5):307–312
- Reynolds MG, Yorita KL, Kuehnert MJ, Davidson WB, Huhn GD, Holman RC, Damon IK (2006) Clinical manifestations of human monkeypox influenced by route of infection. *J Infect Dis* 194(6):773–780
- Richmond JY, McKinney RW (eds) (1999) Biosafety in microbiological and biomedical laboratories (4th edn). ISBN:0-7881-8513-6
- Roddy P, Thomas SL, Jeffs B, Nascimento Folo P, Pablo Palma P, Moco Henrique B, Villa L, Damiao Machado FP et al (2010) Factors associated with Marburg hemorrhagic fever: analysis of patient data from Uige, Angola. *J Infect Dis* 201(12):1909–1918. doi:10.1086/652748
- Roels TH et al (1999) Ebola hemorrhagic fever, Kikwit, Democratic Republic of the Congo, 1995: risk factors for patients without a reported exposure. *J Infect Dis* 179(Suppl 1):S92–97
- Salas R, de Manzione N, Tesh RB, Rico-Hesse R, Shope RE, Betancourt A et al (1991) Venezuelan haemorrhagic fever. *Lancet* 338:1033–1036. doi:10.1016/0140-6736(91)91899-6
- Salazar-Bravo J, Ruedas LA, Yates T. (2002) Mammalian reservoirs of arenaviruses. *Curr Top Microbiol Immunol* 262:25–63
- Sanchez A, Kiley MP, Klenk HD, Feldmann H (1992) Sequence analysis of the Marburg virus nucleoprotein gene: comparison to Ebola virus and other non-segmented negative-strand RNA viruses. *J Gen Virol* 73(Pt 2):347–357
- Scholtissek C (1995) Molecular evolution of influenza viruses. *Virus Genes* 11(2-3):209–215
- Sidwell RW, Gebhardt LP, Thorpe BD (1967). Epidemiological aspects of venezuelan equine encephalitis virus infections. *Bacteriol Rev* 31(1):65–81
- Siegert R (1972) Marburg Virus. In: *Virology monograph*. Springer, New York, pp 98–153
- Siembieda J, Johnson CK, Boyce W et al (2008) Risk for avian influenza virus exposure at human-wildlife interface. *Emerg Infect Dis* 14(7):1151–1153
- Sims AC, Burkett SE, Yount B, Pickles RJ (2008) SARS-CoV replication and pathogenesis in an in vitro model of the human conducting airway epithelium. *Virus Res* 133(1):33–44
- Smith KM, Anthony SJ, Switzer WM, Epstein JH, Seimon T et al (2012) Zoonotic viruses associated with illegally imported wildlife products. *PLoS ONE* 7(1):e29505. doi:10.1371/journal.pone.0029505
- Smith DH, Johnson BK, Isaacson M, Swanapoel R, Johnson KM, Killey M, Bagshawe A, Siongok T et al (1982) Marburg-virus disease in Kenya. *Lancet* 1(8276):816–820
- Smith RD (2006) Responding to global infectious disease outbreaks, lessons from SARS on the role of risk perception, communication and management. *Soc Sci Med* 63(12):3113–3123
- Snyder JE, Jose J, Kuhn RJ (2009). A structural and functional perspective of alphavirus replication and assembly. *Future Microbiol* 4(7):837–856
- Souris M, Gonzalez JP, Shanmugasundaram J, Corvest V, Kittayapong P (2010) Retrospective space-time analysis of H5N1 avian influenza emergence in Thailand. *Int J Health Geogr* 9(3)
- Suarez DL, Schultz-Cherry S (2000) Immunology of avian influenza virus: a review. *Dev Comp Immunol* 24(2-3):269–283
- Sumilo D, Asokliene L, Bormane A, Vasilenko V, Golovljova I, Randolph SE (2007) Climate change cannot explain the upsurge of tick-borne encephalitis in the Baltics. *PLoS ONE* 2:e500
- Suss J (2008) Tick-borne encephalitis in Europe and beyond-the epidemiological situation as of 2007. *Euro Surveill* 13(26)
- Suss J (2011) Tick-borne encephalitis 2010: epidemiology, risk areas, and virus strains in Europe and Asian overview. *Ticks Tick Borne Dis* 2:2–15
- Suzuki Y, Masatoshi Nei (2002) Origin and evolution of influenza virus hemagglutinin genes. *Mol Biol Evol* 19(4):501–509

- Swanepoel R (1996) Experimental inoculation of plants and animals with Ebola virus. *Emerg Infect Dis* 2(4):321–325. doi:10.3201/eid0204.960407
- Swanepoel R, Smit SB, Rollin PE, Formenty P, Leman PA, Kemp A, Burt FJ, Grobbelaar AA, Croft J, Bausch DG, Zeller H, Leirs H, Braack LE, Libande ML, Zaki S, Nichol ST, Ksiazek TG, Paweska JT, International Scientific and Technical Committee for Marburg Hemorrhagic Fever Control in the Democratic Republic of Congo (2007) Studies of reservoir hosts for Marburg virus. *Emerg Infect Dis* 13(12):1847–1851
- Switzer WM, Heneine W (2010) Foamy virus infection of humans. In: Liu D (ed) *Molecular detection of viral pathogens*. CRC Press, Boca Raton pp 131–143
- Taylor DJ, Leach RW, Bruenn J (2010) Filoviruses are ancient and integrated into mammalian genomes. *BMC Evol Biol* 10:193. doi:10.1186/1471-2148-10-193
- Taylor LH, Latham SM, Woolhouse ME (2001) Risk factors for human disease emergence. *Philos Trans R Soc Lond B Biol Sci* 356:983–989
- Timen A, Koopmans MP, Vossen AC, van Doornum GJ, Gunther S, van den Berkmoortel F, Verduin KM, Ditttrich S, Emmerich P, Osterhaus AD, van Dissel JT, Coutinho RA (2009) Response to imported case of Marburg hemorrhagic fever, the Netherlands. *Emerg Infect Dis* 15(8):1171–1175
- Towner JS, Amman BR, Sealy TK, Carroll SAR, Comer JA, Kemp A, Swanepoel R, Paddock CD et al (2009). Isolation of Genetically Diverse Marburg Viruses from Egyptian Fruit Bats (Ron AM Fouchier). *PLoS Pathog* 5(7): doi:10.1371/journal.ppat.1000536
- U.S. Centers for Disease Control and Prevention. Emergency preparedness and response-bioterrorism agents/diseases. <http://www.bt.cdc.gov/agent/agentlist-category.asp>. Accessed 27 May 2013
- U.S. Centers for Disease Control and Prevention (2012) Select agent program. http://www.selectagents.gov/resources/List_of_Select_Agents_and_Toxins_2012-12-4-English.pdf. Accessed 27 May 2013
- Vaisviliene D, Kilciauskiene V, Zygutiene M, Asokliene L, Caplinskas S (2002) TBE in Lithuania: epidemiological aspects and laboratory diagnosis. *Int J Med Microbiol* 291(Suppl 33):179–181
- Walder G, Lkhamsuren E, Shagdar A, Bataa J, Batmunckh T, Orth D, Heinz FX, Danichova A, Khasnatinov MA, Würzner R, Dierich MP (2006) Serological evidence for tick borne encephalitis, borreliosis, and human granulocytic anaplasmosis in Mongolia. *Int J Med Microbiol* 296:69–75. doi:10.1016/j.ijmm.2006.01.031
- Weaver SC, Ferro C, Barrera R, Boshell J, Navarro JC (2004) Venezuelan equine encephalitis. *Annu Rev Entomol* 49:141–174. doi:10.1146/annurev.ento.49.061802.123422
- Webb PA, Justines G, Johnson KM (1975) Infection of wild and laboratory animals with Machupo and Latino viruses. 1975. *Bull World Health Organ* 52(4–6):493–499
- Weber DJ, Rutala WA (2001). Risks and prevention of nosocomial transmission of rare zoonotic diseases. *Clin Infect Dis* 32(3):446–456
- White VC (2013) A review of influenza viruses in seals and the implications for public health. *US Army Med Dep J* 45–50
- WHO (1978a) Ebola haemorrhagic fever in Sudan 1976. *Bull World Health Organ* 56:247–270
- WHO (1978b) Ebola haemorrhagic fever in Zaire 1976. *Bull World Health Organ* 56:271–293
- WHO 2012. International Travel and Health, Chapter 6. http://www.who.int/ith/chapters/ith2012en_chap6.pdf
- Wirth T, Hildebrand F, Allix-Béguec C, Wöbeling F, Kubica T et al (2008) Origin, spread and demography of the *Mycobacterium tuberculosis* complex. *PLoS Pathog* 4(9):e1000160. doi:10.1371/journal.ppat.1000160
- Wolfe ND, Switzer WM, Carr JK, Bhullar VB, Shanmugam V, Tamoufe U, Prosser AT, Torimiro JN, Wright A, Mpoudi-Ngole E, et al. (2004) Naturally acquired simian retrovirus infections in central African hunters. *Lancet*. 363:932–937. doi:10.1016/S0140-6736(04)15787-5
- Work TH, Trapido H (1957) Kyasanur forest disease, a new virus disease in India. *Indian J Med Sci* 11:341
- Work TH, Roderiguez FR, Bhatt PN (1959) Virological epidemiology of the 1958 epidemic of Kyasanur forest disease. *Am J Public Health Nations Health* 49(7):869–874

- York J, Nunberg JH (2006) Role of the stable signal peptide of Junin arenavirus envelope glycoprotein in pH-dependent membrane fusion. *J Virol.* 80(15):7775–7780
- Yun NE, Walker DH (2012) Pathogenesis of Lassa fever. *Viruses* 4:2031–2048
- Zacks MA, Paessler S (2010) Encephalitic alphaviruses. *Vet Microbiol* 140(3-4):281–286. doi:10.1016/j.vetmic.2009.08.023
- Zhong NS, Zheng BJ, Li YM, Poon LL, Xie ZH, Chan KH et al (2003) Epidemiology and cause of severe acute respiratory syndrome (SARS) in Guangdong, People's Republic of China, in February, 2003. *Lancet* 362:1353–1358
- Zinsser H (1935) *Rats, lice and history*. Little, Brown & Co, Boston