ELSEVIER

Antiviral Research 57 (2003) 121–127

Antiviral Research

www.elsevier.com/locate/antiviral

Hantavirus

Jan P. Clement*

Laboratory of Clinical and Epidemiological Virology, Department of Microbiology and Immunology, Rega Institute and Leuven University Hospitals, Kapucijnenvoer 33, BE-3000 Leuven, Belgium

Received 25 September 2002; accepted 8 October 2002

Abstract

When hantaviruses hit the headlines with the advent in May 1993 of a new disease in the USA, and later in the New World from Canada to south Argentina, called "hantavirus pulmonary syndrome" (HPS), speculations in the lay press rose from the very beginning around the possibilities of a biological warfare (BW) weapon. Indeed, the responsible agent of HPS, hantavirus, was almost unknown at that moment in the New World, was airborne, seemed to target preferentially young adults, and induced a devastating cardio-pulmonary collapse with a high case-fatality rate (50%), often within hours. It quickly became clear, however, that the same scourge had been known for many years in the Old World under different and mostly milder presentations. With the rapidly increasing knowledge about hantaviruses, it also became clear that they lack many of the potentials of an "ideal" BW weapon, as will be explained in this paper.

Keywords: Hantavirus (HTV); Hantavirus pulmonary syndrome (HPS); Hemorrhagic fever with renal syndrome (HFRS); Nephropathia epidemica (NE); Rodent-borne infection; Biological warfare (BW); Vaccines

1. Description of the virus

In contrast to the other viral hemorrhagic fever (VHF) viruses considered as potential agents for biological warfare (BW), hantaviruses (HTVs) are the only VHF viruses with a worldwide distribution, with documented clinical cases on the Eurasian landmass and the American continent. HTV was genetically characterized as a new genus in the *Bunyaviridae* family (Schmaljohn et al., 1985), where it is the only nonarthropod-borne pathogen. HTVs possess a tripartite, single-stranded, negative sense RNA genome enclosed in circular nucleocapsid structures and consisting of three segments designated as small (S), medium (M) and large (L).

HTVs are transmitted to man via aerosols of infectious excreta (urine, faeces, saliva) from chronically infected, but apparently healthy small mammals, mainly wild rodents and formerly also laboratory rats.

Based first on serotyping by plaque reduction neutralization tests (PRNT), and later confirmed and extended by polymerase chain reaction (PCR) genotyping, more than 30 different HTV "types" have been distinguished so far, at least half of which are of clinical relevance (Sheshberadaran et al., 1988; Xiao et al., 1994; Hjelle et al., 1995; Clement et al., 1998; Peters and Khan, 2002). Each serotype has its own specific main rodent reservoir of the *Muridae* family, its own geographical spread, and induces in humans a more or less specific clinical picture (Table 1). Clinical presentation of Old World HTVs is called "hemorrhagic fever with renal syndrome" (HFRS), consisting of sudden fever, severe lumbalgia, acute renal failure (ARF) and particularly thrombocytopenia. HFRS is mainly caused by rat-transmitted Seoul (SEO) worldwide, Hantaan (HTN) in the Far East, and Puumala (PUU) in Russia and Western Europe. "New" European pathogenic serotypes are Dobrava (DOB), with a documented presence in Central and Eastern Europe, and Amur (AMR) in East Siberia.

In the New World, the lung is the main target of Sin nombre virus (SNV) and other SNV-like agents. They cause an acute pulmonary oedema, often worsened by cardiac depression. This "hantavirus pulmonary syndrome" (HPS) has been described only since May 1993 (Nichol et al., 1993; Duchin et al., 1994) and had originally a case-fatality rate of about 50%. Phylogeny and epidemiology of HTVs are closely linked to those of their respective rodent reservoirs, and both have undergone a long-standing coevolution. This probably explains the marked differences between hantaviroses spread by the murid subfamilies *Arvicolinae* (Old World voles) and *Murinae* (Old World rats and mice), *versus* those spread by *Sigmodontinae* (New World rats and mice).

* Tel.: +32-16-33-2160; fax: +32-16-33-2131.
E-mail address: jan.clement@uz.kuleuven.ac.be (J.P. Clement).

0166-3542/02/$ – see front matter
PII: S0166-3542(02)00205-X

Table 1
Pathogenic hantavirus genotypes known up to 2001

Hantavirus serotype	Main rodent vector (geographical spread)	Human illness (type of spread)
1. **Hantaan** (**HTN**)	*Apodemus agrarius* (striped field mouse) (Asia, Eastern Russia and Southern Europe)	Severe: KHF, EHF, HFRS (rural)
2. **Seoul** (**SEO**)	*Rattus norvegicus* (brown rat) (worldwide)	Intermediate: HFRS (urban and rural)
3. **Puumala** (**PUU**)	*Clethrionomys glareolus* (red bank vole) (Eurasian continent)	Mild: NE (rural)
4. **Dobrava** (**DOB**)	*Apodemus flavicollis* (yellow necked field mouse) (Balkan, Central and Eastern Europe, Middle-East)	Very severe HFRS (rural?)
5. **Sin nombre virus** (**SNV**)	*Peromyscus maniculatus* (deer mouse) (Canada and USA)	HPS
6. **New York** (**NYV**)	*Peromyscus leucopus* (white-footed mouse) (Canada and Eastern USA)	HPS
7. **Black Creek Canal** (**BCC**)	*Sigmodon hispidus* (hispid cotton rat) (Eastern and Southern USA to Venezuela, Peru)	HPS
8. **Bayou** (**BAY**)	*Oryzomys palustris* (marsh rice rat) (Louisiana)	HPS
9. **Rio Mamoré** (**RMV**)	*Oligoryzomys microtis* (small-eared rice rat) (Bolivia and Peru)	HPS
10. Monongahela (MON)	*P. maniculatus nubiterrae* (forest form) (Canada and Eastern USA)	HPS
11. **Laguna Negra** (**LN**)	*Calomys laucha* (white paunch mouse) (Paraguay and Bolivia)	HPS
12. **Andes** (**AND**)	*Oligoryzomys longicaudatus* (southern) (Argentina, Chile, Uruguay)	HPS
13. Juquitiba (JUQ)	Unknown (Brazil)	HPS
14. Araraquara (ARA)	Unknown (Brazil)	HPS
15. Castelo dos Sonhos (CAS)	Unknown (Brazil)	HPS
16. Hu 39694	Unknown (Central Argentina)	HPS
17 Orán (ORN)	*Oligoryzomys longicaudatus* (northern) (North Western Argentina)	HPS
18. Lechiguanas (LECH)	*Oligoryzomys flavescens* (Central Argentina)	HPS
19. Choclo (CHO)	*Oligoryzomys fulvescens* (Panama)	HPS
20. Amur (AMR)	*Apodemus peninsulae* (Korean field mouse) (Far Eastern Russia)	HFRS

EHF: Epidemic hemorrhagic fever; HFRS: hemorrhagic fever with renal syndrome; HPS: hantavirus pulmonary syndrome; KHF: Korean hemorrhagic fever; NE: nephropathia epidemica. Genotypes in bold are those for which at least one (rodent or human) virus isolate exists.

2. Military importance of (Old World) hantaviruses

Few viruses have such an impressive, almost exclusively military past. In fact, until the description of HPS in the USA in 1993, most of the outbreaks were reported in military in the field—with the exception of laboratory outbreaks induced by SEO-infected laboratory rats or PUU-infected bank voles, and the large, but often unreported mixed HTN and SEO epidemics in the (mainly rural) populations of East China.

Paradoxically enough, Western medicine first "discovered" hantavirus disease under its severe Far-Eastern form, later called "Korean hemorrhagic fever" (KHF), during the Korean War (1951–1953). US Army physicians were suddenly confronted with a up to then unknown acute febrile illness with multi-organ dysfunction (mainly ARF, hemorrhages, and sometimes shock), bearing a mortality rate between 5 and 10%, and affecting over 3000 United Nation troops (Earle, 1954). Despite a sustained investigative effort by a special Hemorrhagic Fever Commission of the US Army, it was not until 1976 that Lee and coworkers discovered a virus-specific antigen in the lungs of a Korean striped field mouse (*Apodemus agrarius Coreae*), which subsequently led to the isolation and characterization of the responsible agent in 1977 (Lee et al., 1978), the same year that Ebola virus was first identified. This first prototype agent was called Hantaan (HTN), after the river which runs near to the famous 38th parallel between North and South Korea, where most of the battles were fought, but where also most of the KHF cases were recorded. So even the name of the virus has a military consonance.

Only later on it became clear that an European variant of the same illness had probably affected thousands of German troops during World War II in Finnish Lapland (Stuhlfauth, 1943). During World War I, a similar epidemic struck French (Ameuille, 1916) as well as British (Bradford, 1916) and German soldiers. Various military authors described the disease as "néphrite de guerre", "trench nephritis" or "Kriegsnephritis", respectively. Captain W.L. Brown suspected as early as 1916 that the agent was of viral origin, and implicated even the same agent as responsible for the epidemic of renal disease observed during the American Secession War, the first armed conflict in which trench warfare was used (Brown, 1916).

In former Yugoslavia, the first epidemic after the World War II took place in 1952 in Fruska Gora (Bosnia) during major maneuvers of the Yugoslavian army, resulting in the first description of HFRS in the Balkans (Heneberg et al., 1962). The first isolation in Europe of a murine Hantaan-like HTV serotype was performed on the urine of a Greek soldier who was infected during maneuvers in Porogia (N-Greece) and suffered from acute respiratory distress (ARDS) and ARF (Antoniadis et al., 1987).

War activities, and even field exercises mimicking war conditions, often lead to a disruption of the natural habitat of wild rodents, thus putting the soldier at risk. In January 1990, US troops freshly arrived from the American continent or partly derived from US troops stationed already in Germany,

camped for yearly maneuvers under tents near the Danube river in the area of Ulm, one of the most endemic regions for HTV infections in Germany. The bivouac site appeared infested with wild mice, and many rodent burrows were seen under and between the tents. We documented a total of 24 acute PUU-induced HFRS cases, 14 of which had to be hospitalized with varying degrees of ARF (Clement et al., 1996).

During the recent armed conflict in Bosnia-Herzegovina, where soldiers were exposed to the miseries of war (including rodents), a major outbreak concerning primarily Bosnian military in the field was reported, with more than 300 cases to be hospitalized (Hukic et al., 1996; Lundkvist et al., 1997a). For the first time, a mixed epidemic of mild arvicoline PUU, together with severe murine DOB was documented. For the latter, *Apodemus flavicollis*, a wood mouse also present in West Europe, was involved. During the same war, a 19-year-old British soldier stationed in Bosnia as a member of the UNPROFOR was reported as presenting with HTV-induced ARF combined with ARDS, urgently needing intubation and ventilation in a local military field hospital, followed by emergency repatriation by air and intensive care therapy in London, UK (Stuart et al., 1996). Another 24-year-old Canadian military was working as a radio-operator in the besieged city of Sarajevo, in the UN Headquarters, a building infested with rodents. In July 1992, he developed sudden fever, diarrhea with melaena, and rapidly progressive ARF, for which he needed emergency evacuation by helicopter to the University Hospital at Zagreb (Croatia) (Clement et al., 1994). Both individual infections were initially described as SEO-induced, but with the increased knowledge about the "new" DOB, another related but distinct murine serotype, appeared in retrospect almost certainly caused by this clinically more severe serotype.

3. Facts and fictions about biowarfare (BW) implications of hantaviruses

For all these reasons, it is not surprising that the only laboratory in the Western hemisphere with an almost 40-years uninterrupted experience in HTV research is the United States Army Medical Research Institute for Infectious Diseases (USAMRIID), initiated under President Franklin Roosevelt in 1943 at Fort Detrick, Maryland, as a response to suspicions during World War II that Germany and Japan were developing a BW program. As a result, the few New World scientists involved in HTV research 25 years ago were almost without exception to be found in the American military. But this interest was from the beginning not aimed at developing HTV into a BW agent, since the few HTVs known in these pioneer years (HTN, SEO, PUU, and the American, but apathogenic isolate, Prospect Hill) possessed little, if any, BW potentials as such. USAMRIID research was rather first directed towards classifying this emerging virus, and developing diagnostic tools for it (Schmaljohn et al., 1985, 1990; Chu et al., 1994; Xiao et al., 1994) As a remarkable accomplishment in serology, the clinical diagnosis of KHF in hundreds of soldiers fallen ill during the Korean War was confirmed by modern techniques almost 40 years after the facts. Thanks to the diligent efforts of the then Hemorrhagic Fever Commission, a unique collection of more than 600 lyophilized sera from 245 patients admitted with KHF between December 1951 and August 1954, was preserved for posterity, allowing ELISA IgM and IgG testing in 1990. Of these patients, 94% (230/245) possessed HTN antibodies, and most sera contained high titered IgM (LeDuc et al., 1990). Early USAMRIID attention was also paid to the epidemiological study of HTV in human and rodent populations worldwide (LeDuc et al., 1986), and the study of antiviral treatment (ribavirin) in HTN epidemics (i.e. mainly in the PR of China) (Huggins et al., 1991). Nowadays, vaccine development has become the main research topic at USAMRIID (Chu et al., 1995; McClain et al., 2000).

With the discovery in 1993 of lethal HPS in the Four Corners region of the USA, rumors in the lay press went that a "new, deadly virus" may have escaped from a military lab involved in BW research. Indeed, the agent appeared to be airborne, and victims of the early outbreak were mostly previously healthy young adults (even marathon runners), some of them dying within hours from a sudden, intractable pulmonary oedema. It later became clear that the virus of this mysterious disease had been in place for millions of years in different species of New World sigmodontine rodents (see Table 1), and HPS cases have now been noted, not only in the USA, but also in Argentina, Brazil, Canada, Chile, Panama, Paraguay and Uruguay. Between 1993 and 2000, a total of 550 cases of HPS have been confirmed in the Americas (Hooper and Li, 2000), a much lower number than the about 100,000–150,000 other HTV cases per year noted worldwide. The oldest descriptions (1931) and the most important epidemics are to be found in PR of China, where the accumulated number of officially registered cases in the whole country from 1950 to 1990 reached a total of 904,995 with an average morbidity of 2.69 per 100,000 inhabitants and an average case-fatality rate of 4.3%. The peak year was 1986, during which 115,985 serologically confirmed cases were recorded, with a total of 2,561 deaths (fatality rate: 2.2%) and a morbidity of 11.08 per 100,000 (Chen and Qiu, 1993). Thus, when high lethality of SNV and SNV-like infections remains a serious problem in the Western hemisphere (fatality rate still about 40%), a high incidence of mixed HTN and SEO infections was only noted in the Far East, but so far high fatality rates and high incidence numbers never occurred together in the same region.

PUU is the most important HTV serotype in Europe and West Russia, causing a mild and self-remitting form of HFRS (also called Nephropathia epidemica or NE), where complete restoration to normal within 2–3 weeks is the rule. Hemorrhagic symptoms are rare (22%) and minor in NE (petechiae, nose bleeding, etc.). Each year, thousands of NE cases are recorded in West Russia, about a thousand of cases

in Finland, and a few hundred of cases in the rest of Europe. In Belgium alone, we recorded between 1985 and 1999 more than 800 seroconfirmed NE cases (Clement, 1999). However, NE has a very low fatality rate (<0.5%) and dialysis as a treatment for ARF is required in less than 5% of most European series (Colson et al., 1995; Clement et al., 1998).

Finally, DOB was documented so far in a few hundred cases in the Balkan (Hukic et al., 1996; Lundkvist et al., 1997a) and in West Russia (Lundkvist et al., 1997b). DOB infections can bear a fatality rate of up to 12%, mainly due to hemorrhagic shock. Of all HTV serotypes known so far, DOB seems to possess the most outspoken hemorrhagic potential, making it a true VHF virus. The fact that its rodent reservoir *A. flavicollis* is the only HTV host with a known spread encompassing the Middle East is at first sight not a reassuring idea, but this knowledge has to be interpreted with caution (see below). So far, no data are available concerning the presence or not of DOB (or for that matter, of any other HTV) in the Middle East, but we recently found DOB-like infections in Israëli patients suspected with leptospirosis, i.e. with patients presenting ARF, minor hemorrhages and thrombocytopenia (Clement, unpublished findings).

4. Biowarfare (BW) potential of hantaviruses

Although still rumored by laypersons as such, the "new" HTVs (i.e. the lethal American SNV and SNV-like agents) have little potential for a development into utilizable BW agents, and even less so the clinically milder "old" HTVs (i.e. the Old World pathogens, see Table 1). In fact, HTVs do not even figure in most lists and articles on bioterror. In perhaps the most authoritative and complete list of all, issued by the Center of Disease Control (CDC) in Atlanta, USA (htpp://www.bt.cdc.gov/Agent/agentlist.asp) "hantavirus" (not specified) is mentioned only under Category C, together with Nipah virus, also discussed in this Special Issue. Category C has the lowest priority as a risk to national security, and means the lowest potential for use as BW agent. This is in contrast to the other VHF viruses, such as filoviruses (Ebola and Marburg) and arenaviruses (Lassa and Machupo), all listed under Category A, having the highest priority. Indeed, if HTVs are mentioned at all in discussions about bioterror, they are invariably listed together with these other VHF agents, reputedly having in common a symptomatology of capillary leak syndrome, and of hemorrhages. However, this is an awkward classification, since as we have seen, hemorrhages are rare or minor in most Old World HTV infections, and are absent altogether in all North American SNV(-like) infections. As a word game, one could say that at least SNV, NY, MON, BAY, and BCC (Table 1), together with the European PUU, are in fact most often "*non*hemorrhagic VHF agents", a rather confounding factor for the attending physician. Major hemorrhagic complications are present in a minority of DOB, and to a lesser extent in HTN-cases, whereas they are truly exceptional in SEO and PUU cases. Only very recently it has become clear that South American HTVs, and in particular AND, have also the potential of inducing severe gastrointestinal bleedings and even frank hemorrhagic shock, a finding so remarkable that HPS could now finally be branded this year as "the new American hemorrhagic fever" (Peters and Khan, 2002). However, it also became clear that that mild and even asymptomatic SNV(-like) infections are also possible, as was demonstrated in American seroprevalence studies, with, for example, prevalences as high as 40% in Paraguay and Argentina, in people without any history of HPS (Ferrer et al., 1998).

The definition of a "bioterrorist weapon" is not necessarily synonymous to that of a "biological weapon", since production of the latter can be dependent of a heavy scientific infrastructure, and can, if necessary, be very demanding on technical grounds. The "ideal" bioterrorist agent should preferably possess three characteristics, perhaps not coincidentally all phrased also—be it in other words—under Category C of the CDC list:

A. Easy to produce.
B. Easy to spread, by natural (i.e. person-to-person) or technical means (i.e. preferably by aerosols).
C. Inducing infections hard to treat and/or to prevent.

No such ideal bioterrorist agent is at hand for the moment, and HTVs have in part "quality C" only. No single species or subspecies of HTVs known so far meets all characteristics A + B + C in full.

4.1. HTVs are hard to produce

HTVs are notoriously difficult to isolate in tissue culture, necessitating serial blind passages. Moreover, these viruses are noncytopathic, making plaque assays hard to interpret and impractical. HTV isolation is not only long and tedious, but also dangerous for the surrounding personnel, thus requiring biosafety level (BSL)-3 or even BSL-4 laboratories. This explains why of the 25 New World HTVs listed in a recent review, only 10 could be isolated so far from rodent or (exceptionally) from human tissues (Monroe et al., 1999), the rest being characterized only by PCR techniques: "virology without a virus" (Clement et al., 1995).

Virus isolation is further hampered by the fact that in man viremia is often low and short-lived, explaining why the vast majority of HTV isolates are from rodent, and not from human origin. In fact, the first human isolate from the serum of an American HPS case was reported only very recently in a 10-year-old Chilean boy, who died from AND-induced HPS (Galeno et al., 2002). The viremic serum sample was obtained 2 days before the symptoms began, and 6 days before death, when the serum was still IgG and IgM negative. This and other recent findings suggest that HTV viremia, as quantified by PCR, most often occur in the prodromal phase, and, if still present at hospitalization, may rapidly decline, through a build-up of neutralizing antibodies, the titer of

which seems to be an important factor in the determination of the clinical severity (Terajima et al., 1999; Padula et al., 2000). Even high viral loads on admission, as assessed by quantitative PCR, were not contributive to a higher yield of multiple isolation attempts of HPS agents in the New World (Peters and Khan, 2002).

Symptoms leading to hospitalization are probably due to host-related cellular immune responses, rather than to the viremia itself. A BW agent depending mainly on the highly variable individual immune responses of the attacked victim, instead of the intrinsic pathogenic capacities of the agent itself, is less interesting for a terrorist. Last but not least, adaptation of a HTV (in this case, PUU) to growth in cell culture can result in a reduction of infectivity of this virus (Lundkvist et al., 1997c). If confirmed for other HTVs, this would mean a major handicap for the use as BW weapon.

4.2. HTVs have a very peculiar transmission way

Except for the aerosol transmission from rodent excreta and secreta to humans and other rodents, surprisingly little is known about potential other ways of transmission. Human infection after a rodent bite is highly exceptional (Dournon et al., 1984). Laboratory infections from handling blood specimens or HTV-infected tissues have not been documented so far. HTV-infected rodents present only a limited period of viremia, after which they develop neutralizing antibodies, but they go on excreting (mainly via the urine) infectious virus apparently life-long, an immunological paradox. This means that not even the blood, but only some excretory organs (kidneys, lungs, salivary glands) and their excreta could be considered as a source for the high mass production of lethal virus, a hard start for a BW program outside securized laboratories. Moreover, HTV-infected rodents are not readily recognizable, since they remain apparently healthy for the rest of their life, and transmission to man is a dead end for the virus. Humans do not secrete HTVs in substantial amounts during infection, and apparently unequivocal man-to-man transmission has so far been documented for one single serotype (AND) in one single case in Argentina. Hereby a doctor contracted the illness after having treated a patient with HPS that had traveled from the endemic area El Bolsón to Buenos Aires (Padula et al., 1998). This seems the only case of man-to-man transmission so far, since in all other so-called contact or family cases in Chile and Argentina, infection from domestic or peridomestic rodents could not be ruled out. The mechanism(s) of this possible interhuman transmission of AND are far from elucidated.

Virtually nothing is known about the survival of HTVs in free nature, which is an essential point for the use of artificial HTV aerosols to be considered for BW purposes.

4.3. Some HTV infections can be treated or prevented

Ribavirin, a broad-spectrum antiviral with known efficacy against other VHF agents such as Lassa, is also active against Old World HTVs, such as HTN, at least when given early enough, and in sufficiently high intravenous doses. As shown in a field trial in mainland China, this treatment can be life-saving (Huggins et al., 1991). However, the same treatment has given disappointing results so far in the management of American HPS cases (Chapman et al., 1999), and other medication schemes of immunomodulation of cytokines such as tumor necrosis factor (TNF)-alpha are still experimental.

Formalin-inactivated vaccines derived from brains of suckling rodents have been developed, and used now since more than 10 years in South and North Korea (Lee et al., 1990; Kim et al., 1991). In the latter, the protection rate in 1.2 million people was reported to be between 88 and 100%. In the PR of China and in the early 1980s, several inactivated vaccines derived from cell cultures have been developed against SEO, or against SEO and HTN, and are produced now in millions of doses per year (Hooper and Li, 2000).

In the USA, the long-standing USAMRIID policy of developing vaccines for the military stationed in endemic areas was obviously strongly boosted with the advent in 1993 of HPS. However, handling of dangerous BSL-3 level agents was avoided from the very beginning, and various approaches of recombinant DNA technology were preferred (Hooper and Li, 2000). Since elicited neutralizing antibodies, mainly directed against envelope glycoproteins 1 and 2 appeared not always cross-protective (Chu et al., 1995), the ultimate goal remains a recombinant DNA vaccine containing a panel of immunogens protecting against the most important HTV pathogens.

Interestingly, immunization of bank voles with recombinant nucleocapsid protein N (rN) from different hantaviruses elicited cross-protection, when the voles were subsequently challenged with PUU (de Carvalho Nicacio et al., 2002). Nucleocapsid protein is relatively conserved among different hantaviruses and is highly immunogenic in both laboratory animals and humans.

5. Conclusions

HTV is an unlikely candidate for BW applications, since even the American SNV(-like) agents are not always lethal or hemorrhagic. As such, HTVs cannot be compared with other VHF viruses, which are all listed in Category A of CDC's list of potential BW agents, whereas HTV ranks only under Category C. HTV is very difficult to isolate, even with the means available in the most advanced laboratories. A major obstacle for its use in biological warfare is the lack of interhuman transmission, and the limited amount of evidence that artificial, HTV-loaden sprays would be truly infectious for a substantial period of time. Finally, vaccination programs are already being implemented with success in some Far-Eastern countries with inactivated vaccines against two widespread Old World HTV serotypes, HTN and SEO.

American and European vaccines may be expected in the not too distant future, but will probably be limited for systematic use to the military and to some professions at risk, e.g. foresters and mammalogists.

In fact, another Old World VHF virus, Congo-Crimean hemorrhagic fever (CCHF) virus, seems much better suited for BW: it can readily be cultivated, is highly infective (although not documented so far by aerosol), and is easily transmissible between humans, giving rise to local epidemics and even to nosocomial infections, putting the nursing personnel at high risk. In contrast to HTV infections, CCHF viremia continues throughout disease until the appearance of antibodies in blood heralds clinical recovery, coinciding with the disappearance of circulating virus. The CCHF-induced case-fatality rate of about 30% is much higher than that of most other VHF infections, and no CCHF vaccine is at hand, or even in the pipeline.

References

Ameuille, P., 1916. Du rôle de l'infection dans les néphrite de guerre. Ann. Méd. 3, 298–323.

Antoniadis, A., LeDuc, J.W., Daniel-Alexiou, S., 1987. Clinical and epidemiological aspects of hemorrhagic fever with renal syndrome (HFRS) in Greece. Eur. J. Epidemiol. 3, 295–301.

Bradford, J.R., 1916. Nephritis in the British troops in Flanders. A preliminary note. Q. J. Med. 9, 125–137.

Brown, W.L., 1916. Trench nephritis. Lancet 1, 391–399.

Chen, H.X., Qiu, F.X., 1993. Epidemiological survey: epidemiologic surveillance on the hemorrhagic fever with renal syndrome in China. Chin. Med. J. 106, 857–863.

Chapman, L.E., Mertz, G.J., Peters, C.J., Jolson, H.M., Khan, A.S., Ksiazek, T.G., Koster, F.T., Baum, K.F., Rollin, P.E., Pavia, A.T., Holman, R.C., Christenson, J.C., Rubin, P.J., Behrman, R.E., Bell, L.J., Simpson, G.L., Sadek, R.F., 1999. Intravenous ribavirin for hantavirus pulmonary syndrome: safety and tolerance during 1 year of open-label experience. Ribavirin Study Group. Antiviral Ther. 4, 211–219.

Chu, Y.K., Jennings, G.B., Schmaljohn, C.S., 1995. A vaccinia virus-vectored Hantaan virus vaccine protects hamsters from challenge with Hantaan and Seoul viruses but not Puumala virus. J. Virol. 69, 6417–6423.

Chu, Y.K., Rossi, C., LeDuc, J.W., Lee, H.W., Schmaljohn, C.S., Dalrymple, J.M., 1994. Serological relationships among viruses in the *Hantavirus* genus, family *Bunyaviridae*. Virology 198, 196–204.

Clement, J., 1999. Les maladies à Hantavirus en France et en Belgique. Hantavirus disease in France and in Belgium. Bull. Acad. Nat. Méd. 183, 1363–1375 (in French).

Clement, J., McKenna, P., Avsic-Zupanc, T., Skinner, C.R., 1994. Rat-transmitted hantavirus disease in Sarajevo. Lancet 344, 131.

Clement, J., McKenna, P., Groen, J., Colson, P., Osterhaus, A., Vervoort, T., van der Groen, G., Lee, H.W., 1995. Epidemiology and laboratory diagnosis of hantavirus (HTV) infections. Acta Clin. Belg. 50, 9–19.

Clement, J., McKenna, P., van der Groen, G., Vaheri, A., Peters, C.J., 1998. Hantaviruses. In: Palmer, S.R., Soulsby, E.J.L., Simpson, D.I.H. (Eds.), Zoonoses. Biology, Clinical Practice, and Public Health Control. Oxford University Press, Oxford, pp. 331–351.

Clement, J., Underwood, P., Ward, D., Pilaski, J., LeDuc, J., 1996. Hantavirus outbreak during military manoeuvres in Germany. Lancet 347, 336.

Colson, P., Damoiseaux, P., Brisbois, J., Duvivier, E., Levecque, P., Roger, J.M., Bouilliez, D.J., McKenna, P., Clement, J., 1995. Hantavirose dans l'Entre-Sambre-et-Meuse. Acta Clin. Belg. 50, 197–206 (in French).

de Carvalho Nicacio, C., Gonzalez Della Valle, M.O., Padula, P.J., Bjorling, E., Plyusnin, A., Lundkvist, A., 2002. Cross-protection against challenge with Puumala virus after immunization with nucleocapsid proteins from different hantaviruses. J. Virol. 76, 6669–6677.

Dournon, E., Moriniere, B., Matheson, S., Girard, P.M., Gonzalez, J.P., Hirsch, F., McCormick, J.B., 1984. HFRS after a wild rodent bite in the Haute-Savoie and risk of exposure to Hantaan-like virus in a Paris laboratory. Lancet 1, 676–677.

Duchin, J.S., Koster, F.T., Peters, C.J., Simpson, G.L., Tempest, B., Zaki, S.R., Ksiazek, T.G., Rollin, P.E., Nichol, S.T., Umland, E.T., Moolenaar, R.L., Reef, S.E., Nolte, K.B., Gallaher, M.M., Butler, J.C., Breiman, R.F., the Hantavirus Study Group, 1994. Hantavirus pulmonary syndrome: a clinical description of 17 patients with a newly recognized disease. N. Engl. J. Med. 330, 949–955.

Earle, D.P., 1954. Symposium on epidemic hemorrhagic fever. Am. J. Med. 16, 617–793.

Ferrer, J.F., Jonsson, C.B., Esteban, E., Galligan, D., Basombrio, M.A., Peralta-Ramos, M., Bharadwaj, M., Torrez-Martinez, N., Callahan, J., Segovia, A., Hjelle, B., 1998. High prevalence of hantavirus infection in Indian communities of the Paraguayan and Argentinean Gran Chaco. Am. J. Trop. Med. Hyg. 59, 438–444.

Galeno, H., Mora, J., Villagra, E., Fernandez, J., Hernandez, J., Mertz, G.J., Ramirez, E., 2002. First human isolate of Hantavirus (Andes virus) in the Americas. Emerg. Infect. Dis. 8, 657–661.

Heneberg, D., Vuksic, L., Morelj, M., et al., 1962. Epidemic of hemorrhagic fever in certain workplaces in Fruska Gora. Zbornik radova VMA 236–271.

Hjelle, B., Jenison, S.A., Goade, D.E., Green, W.B., Feddersen, R.M., Scott, A.A., 1995. Hantaviruses: clinical, microbiologic, and epidemiologic aspects. Crit. Rev. Clin. Lab. Sci. 32, 469–508.

Hooper, J.W., Li, D., 2000. Vaccines against hantaviruses. In: Schmaljohn, C.S., Nichol, S.T. (Eds.), Hantaviruses. Springer, Berlin, pp. 171–191.

Huggins, J.W., Hsiang, C.M., Cosgriff, T.M., Guang, M.Y., Smith, J.I., Wu, Z.O., LeDuc, J.W., Zheng, Z.M., Meegan, J.M., Wang, Q.N., Oland, D.D., Gui, X.E., Gibbs, P.H., Yuan, G.H., Zhang, T.M., 1991. Prospective, double-blind, concurrent, placebo-controlled clinical trial of intravenous ribavirin therapy of hemorrhagic fever with renal syndrome. J. Infect. Dis. 164, 1119–1127.

Hukic, M., Kurt, A., Torstensson, S., Lundkvist, A., Wiger, D., Niklasson, B., 1996. Haemorrhagic fever with renal syndrome in north-east Bosnia. Lancet 347, 56–57.

Kim, R.J., Ru, C., Kim, G.M., 1991. The special prevention of HFRS in P. D. R. of Korea. Chin. Clin. Exp. Virol. 4, 487–492 (in Chinese).

LeDuc, J.W., Ksiazek, T.G., Rossi, C.A., Dalrymple, J.M., 1990. A retrospective analysis of sera collected by the hemorrhagic fever commission during the Korean conflict. J. Infect. Dis. 162, 1182–1184.

LeDuc, J.W., Smith, G.A., Childs, J.E., Pinheiro, F.P., Maiztegui, J.I., Niklasson, B., Antoniadis, A., Robinson, D., Khin, M., Shortbridge, K., Wooster, M., Elwell, M., Ilbery, P., Koech, D., Rosa, A., Rosen, L., 1986. Global survey of antibody to Hantaan-related viruses among peridomestic rodents. Bull. World Health Organ. 64, 139–144.

Lee, H.W., Ahn, C., Song, J., Baek, L., Seo, T., Park, S., 1990. Field trial of an inactivated vaccine against hemorrhagic fever with renal syndrome in humans. Arch. Virol. (Suppl. 1), 35–47.

Lee, H.W., Lee, P.-W., Johnson, K.M., 1978. Isolation of the etiologic agent of Korean hemorrhagic fever. J. Infect. Dis. 137, 298–308.

Lundkvist, A., Apekina, N., Myasnikov, Y., Vapalahti, O., Vaheri, A., Plyusnin, A., 1997b. Dobrava hantavirus outbreak in Russia. Lancet 350, 781–782.

Lundkvist, A., Cheng, Y., Sjolander, K.B., Niklasson, B., Vaheri, A., Plyusnin, A., 1997c. Cell culture adaptation of Puumala hantavirus changes the infectivity for its natural reservoir, *Clethrionomys glareolus*, and leads to accumulation of mutants with altered genomic RNA S segment. J. Virol. 71, 9515–9523.

Lundkvist, A., Hukic, M., Hörling, J., Gilljam, M., Nichol, S.T., Niklasson, B., 1997a. Puumala and Dobrava viruses cause haemorrhagic fever with renal syndrome (HFRS) in Bosnia-Herzegovina: evidence

of highly cross-neutralizing antibody responses in early patient sera. J. Med. Virol. 53, 51–59.

McClain, D.J., Summers, P.L., Harrison, S.A., Schmaljohn, A.L., Schmaljohn, C.S., 2000. Clinical evaluation of a vaccinia-vectored Hantaan virus vaccine. J. Med. Virol. 60, 77–85.

Monroe, M.C., Morzunov, S.P., Johnson, A.M., Bowen, M.D., Artsob, H., Yates, T., Peters, C.J., Rollin, P.E., Ksiazek, T.G., Nichol, S.T., 1999. Genetic diversity and distribution of Peromyscus-borne hantaviruses in North America. Emerg. Infect. Dis. 5, 75–86.

Nichol, S.T., Spiropoulou, C.F., Morzunov, S., Rollin, P.E., Ksiazek, T.G., Feldmann, H., Sanchez, A., Childs, J., Zaki, S., Peters, C.J., 1993. Genetic identification of a hantavirus associated with an outbreak of acute respiratory illness. Science 262, 914–917.

Padula, P.J., Colavecchia, S.B., Martinez, V.P., Gonzalez Della Valle, M.O., Edelstein, A., Miguel, S.D., Russi, J., Riquelme, J.M., Colucci, N., Almiron, M., Rabinovich, R.D., 2000. Genetic diversity, distribution, and serological features of hantavirus infection in five countries in South America. J. Clin. Microbiol. 38, 3029–3035.

Padula, P.J., Edelstein, A., Miguel, S.D., Lopez, N.M., Rossi, C.M., Rabinovich, R.D., 1998. Hantavirus pulmonary syndrome outbreak in Argentina: molecular evidence for person-to-person transmission of Andes virus. Virology 241, 323–330.

Peters, C.J., Khan, A.S., 2002. Hantavirus pulmonary syndrome: the new American hemorrhagic fever. Clin. Infect. Dis. 34, 1224–1231.

Schmaljohn, C.S., Chu, Y.K., Schmaljohn, A.L., Dalrymple, J.M., 1990. Antigenic subunits of Hantaan virus expressed by baculovirus and vaccinia virus recombinants. J. Virol. 64, 3162–3170.

Schmaljohn, C.S., Hasty, S.E., Dalrymple, J.M., LeDuc, J.W., Lee, H.W., von Bonsdorff, C.H., Brummer-Korvenkontio, M., Vaheri, A., Tsai, T.F., Regnery, H.L., Goldgaber, D., Lee, P.-W., 1985. Antigenic and genetic properties of viruses linked to hemorrhagic fever with renal syndrome. Science 227, 1041–1044.

Sheshberadaran, H., Niklasson, B., Tkachenko, E.A., 1988. Antigenic relationship between hantaviruses analysed by immunoprecipitation. J. Gen. Virol. 69, 2645–2651.

Stuart, L.M., Rice, P.S., Lloyd, G., Beale, R.J., 1996. A soldier in respiratory distress. Lancet 347, 30.

Stuhlfauth, K., 1943. Nachtrag zu dem “Bericht über ein neues schlammfieberähnliches Krankheitsbild bei Deutschen Truppen in Lappland”. Dtsch. Med. Wochenschr. 69, 439–443.

Terajima, M., Hendershot 3rd, J.D., Kariwa, H., Koster, F.T., Hjelle, B., Goade, D.E., DeFronzo, M.C., Ennis, F.A., 1999. High levels of viremia in patients with the Hantavirus pulmonary syndrome. J. Infect. Dis. 180, 2030–2034.

Xiao, S.Y., LeDuc, J.W., Chu, Y.K., Schmaljohn, C.S., 1994. Phylogenetic analyses of virus isolates in the genus Hantavirus, family Bunyaviridae. Virology 198, 205–217.