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Risk Profile Humaan Schmallenbergvirus

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Situation assessment

On November 18th, 2011 scientists from the Friedrich Loeffler institute in Germany identified the presence of viral sequences in serum from cattle affected by a specific febrile syndrome. The sequences show homology to the L, M, and S gene segments of viruses from the family *Bunyaviridae*, genus *Orthobunyavirus.* Full details of the virus characterization are needed before definitive conclusions can be drawn about the taxonomic assignment. However, based on the preliminary data, the virus – named Schmallenberg virus- is most related to genomic sequences of Shamonda-, Aino-, and Akabane-virus, all grouped within the Simbu serogroup and known as viruses that may cause illness in ruminants(1).

Based on the findings sofar, the infection is considered to be the likely cause of a clinical syndrome that occurred in late summer in cattle (fever, decreased milk-production, diarrhea) in Germany and the Netherlands, and more recently in sheep in The Netherlands (intra-uterine malformations). Evidence for association of the virus with the illness in cattle and sheep in The Netherlands comes from the detection of viral gene sequences by RT-PCR in a significant proportion of sera from cattle with the syndrome while 150 sera from healthy cattle were negative. Furthermore, the virus was detected in brain material from lambs with congenital abnormalities (Communicated by Beer, Freidrich Loeffler institute, Van der Poel, CVI, Vellema, Kock, Mars GD)

Sofar, Schmallenberg virus has been identified in the North Rhine-Westphalia (Germany) and the Netherlands. Based on an initial assessment of the clinical syndrome in The Netherlands, the infection appears to be dispersed across the country with no apparent geographic clustering.

As the family *Bunyaviridae* contains several medically important viruses, a risk assessment was made to identify potential human health risks.

Taxonomy

Family: Bunyaviridae
Genus: Orthobunyaviruses
Putative serogroup: Simbu serogroup (classification solely based on sequence data!).
Virus: Schmallenberg virus.

Viruses in the family *Bunyaviridae* are classified into five genera: *Orthobunyavirus, Hantavirus, Nairovirus, Phlebovirus* and *Tospoviruses*. The *Bunyaviridae* are enveloped, negative sense RNA viruses whose genome comprises three segments: small (S), medium (M) and large (L). The S segment encodes for the nucleocapsid and a nonstructural protein, NSs. The M segment encodes for the surface glycoproteins Gn and Gc, whereas the L segment encodes the viral polymerase (2). The surface proteins mediate attachment, cell fusion and haemagglutination, and therefore are thought to contain important virulence determinants. Neutralizing antibodies are reportedly directed against epitopes on the G1 surface glycoprotein.

Medically important viruses within the family are amongst others Oropouche virus (genus *Orthobunyavirus*), Crimean-Congo hemorrhagic fever virus (genus *Nairovirus*), Sandfly fever virus and Rift-Valley fever virus ((both genus *Phlebovirus*), Sin Nombre virus and Puumalavirus (genus *Hantavirus*). At least 30 orthobunyaviruses have been associated with human disease, causing self-limiting, although sometimes severe, febrile illness (e.g. Oropouche virus).(3, 4).

For the purpose of this risk assessment, we focus on information on viruses belonging to the *Orthobunyavirus* genus. This contains some 170 virus isolates, assigned to 48 distinct species, covering 18 serogroups, including the Simbu serogroup (5). Serogroups within the genus are based on cross-hemagglutination inhibition and antibody neutralization relationships, and are further clustered into 5 serocomplexes. The Simbu serogroup comprises 25 viruses of which Akabane virus, Aino virus, Shamonda virus, Shuni virus, Jatobal virus, Oropouche virus and Iquitos virus are examples. Phylogenetic analysis has distinguished Simbu viruses that affect ruminants (Akabane, Aino, Shamonda) from the medically relevant viruses Oropouche and Iquitos virus, suggesting that they are epidemiologically distinct.

Transmission cycle.

Orthobunyaviruses are mainly transmitted by mosquitoes (*Culicidae*) or midges (*Culicoides*) and the natural life-cycles of the viruses involve a limited number of warm-blooded vertebrates, which can act as amplifying hosts and may aid in dissemination of virus through migration. Infection of these hosts is usually inapparent, although the animals develop sufficient viremia for biting arthropods to acquire infection. Humans are usually considered dead-end hosts. Exceptions are found in the Simbu serogroup, to which the Schmallenberg virus putitatively belongs: humans infected with Oropouche virus and Iquitos virus develop significant viremia such that uninfected midges can acquire the virus (3). As a consequence of this, epidemic spread of these viruses resulting in dengue-like outbreaks has been observed, particularly in South America (Iquitos virus: Amazon region of Peru; Oropouche virus: Brazil, Panama, Peru, and Trinidad.). The Shamonda-, Aino-, and Akabane-viruses to which the Schmallenberg virus is closely related at the nucleotide level (1) are all mainly transmitted by Culicoides spp.

Reservoirs.
Orthobunyaviruses, Simbu serogroup are found in a wide variety of reservoirs including wildlife (sloths, marmosets) and livestock (cattle, pigs, goats). Akabane virus has been found in cattle, buffalo, sheep, camels, deer goats, horses and dogs. Zoonotic and human-to-human transmission has been described for Oropouche virus and is suggested for Iquitos virus.

Vectors.
The Shamonda-, Aino-, and Akabane-viruses, all closely related to Schmallenberg virus at the nucleotide level, are transmitted mainly by *Culicoides* spp. (1). Mosquitoes have been implicated also, but their role is expected to be minor compared to that of midges.
The national checklist states 26 species of *Culicoides* to occur in the Netherlands, which is about half the number found in neighbouring Germany. During the recent bluetongue outbreak, *Culicoide*s spp. were captured in the near vicinity of cattle throughout the Netherlands. The survey showed that *C. imicola*, the principal vector for bluetongue virus in Africa and Southern Europe, is not present in the Netherlands. Subsequently, it was demonstrated that local *Culicoides* involving multiple species were responsible for the transmission of bluetongue in the Netherlands (6, 7). Elsewhere in the world, Akabane virus, Shamonda virus and bluetongue virus are transmitted by *Culicoides* belonging to at least three subgenera, including the subgenus *Avaritia.* In Australia Akabane virus is transmitted by the same *Culicoides* species that transmits bluetongue virus, namely the cattle dung inhabiting *C. brevitarsis* (8). In Southern Europe bluetongue virus is transmitted by *C. imicola*, the known vector for Shamonda virus in Nigeria (9) and which, like *C. brevitarsis,* belongs also to the subgenus *Avaritia.* Other virus vectors belonging to this subgenus are *C. dewulfi*, *C. obsoletus, C. scoticus* and *C. chiopterus,* all implicated in the transmission of bluetongue in Northern Europe, including the Netherlands. Other *Culicoides* found quite frequently in association with cattle in the Netherlands are various species of the subgenus *Culicoides*, better known as the Pulicaris Complex, and includes *C. pulicaris,* which has been implicated also in the transmission of bluetongue (6, 10) .

The bluetongue outbreak in the Netherlands demonstrated clearly that endemic *Culicoides* not previously implicated in the transmission of the virus, are in fact efficient vectors

Little is known about host preferences of midges. Little is known about the host preferences of midges in Europe. Two recent studies (11, 12) conducted in northern Europe deal with the feeding habits of midges belonging to two subgenera, i.e. *Avaritia* and *Culicoides*:
The first study involved some of the most common and abundant species of biting midges found in Denmark, i.e. *Culicoides obsoletus*, *C. scoticus*, *C. pulicaris* and *C.punctatus*. The blood meals of 115 freshly engorged midges were identified and revealed that a variety of mammal and avian hosts had been attacked; these included cattle, roe deer, horse, mallard and wood pigeon. Cattle were the preferred host and constituted 73.9% of the total bloodmeals identified; unexpectedly,the common wood pigeon was the next most commonly attacked host, with a frequency of 18.3% (11).
In the second study, conducted in Germany, a total of 177 *Culicoides* blood meals were analysed; 115 (65%) tested positive for vertebrate blood. Of these 63.5% were assigned to a species; cattle again proved to be the most attractive host (79.5%, n = 58) even in the immediate presence of other large vertebrates . Pigs and/or horses maintained on the same farm, were attacked also by biting midges, but at a distinctly lower rate (pigs 13.7%, horses 2.7%). Game animals appeared to be less attractive as only a few engorged midges had taken a blood meal from

red deer (4.1%). None of the 177 blood meals analysed tested positive for sheep (12).

These results show that biting midges of the *C. pulicaris* and *C. obsoletus* species groups feed on a wide range of vertebrate hosts, but with a distinct preference for cattle even in the near presence of other types of livestock.

Clinical manifestation of orthobunyaviruses in human.
Currently, Schmallenberg virus has not been related to human disease. Shamonda-, Aino-, and Akabane-virus which are genetically most related to the Schmallenberg virus are only found in livestock. However, zoonotic potential of this virus cannot be excluded as

1) Viruses within the Simbu serogroup (Oropouche virus and Iquitos virus) are known to be zoonotic and cause human outbreaks (13).
2) Genetic reassortment among members of the same serogroup within the Orthobunyavirus genus occurs in nature and has led to the emergence of new viruses, occasionally with increased pathogenicity. This may increase the zoonotic potential of these viruses as reassortment might lead to change of host reservoirs (14-17).
3) Viruses within other serogroups of the genus orthobunya are zoonotic. Examples: California encephalitis virus, La Crosse encephalitis virus, Tahyna virus, Bataivirus, Inkoovirus, Snowshoe hare virus.

Oropouche virus, that like Schmallenberg virus is a member of the Simbu serogroup, causes a febrile disease often associated with headache, dizziness, photophobia, skin rash, myalgias, arthralgias and malaise, which may be long lasting and sometimes relapsing 2-3 weeks after initial onset of symptoms (18). Patients with Oropouche fever usually recover after 2–3 weeks of disease without known sequelae or recorded mortality (19). The very limited information available indicates that Oropouche virus infection is associated with viremia that declines quickly until the fifth or sixth days of illness (18), and that the virus has been recovered from the cerebral spinal fluid **(**CSF) in association with clinical meningitis (20).

Iquitos virus, a member of the Simbu serogroup to which Schmallenberg virus belongs, causes illness that includes symptoms of fever, general malaise, headache, retro-orbital pain, myalgia, arthralgias and chills. Respiratory manifestations were observed in 38% of the cases.
Gastrointestinal manifestations in 75% of the cases, including diarrhea, vomiting, nausea (13).

There have been no reports of unusual human illness form the regions where Schmallenberg virus has been identified. The veterinary health service indicates that farmers from affected farms have been specifically asked for symptoms of illness, and have reported none (Kock, pers. comm..)

Human diagnostics.
In Europe Oropouche virus diagnostics are available in Hamburg (Bernhard-Nocht-Institut
für Tropenmedizin, dr. Schmidt-Chanasit). This includes IFA, reverse-transcriptase (rt) PCR, VI. However, based on the findings sofar, it is unlikely that these methods would be suitable to detect exposure to Schmallenberg virus in humans.

For Oropouchovirus, real-time- (RT-) PCR showed high titers of Oropouchevirus in acute-phase serum samples from febrile patients. A study in South America

showed serological evidence for infection in 113 of 119 acutely febrile patients with paired serum samples. Oropouche virus infections were confirmed by seroconversion (n=76) or high antibody titers (n=37), determined both by HI assay and IgM-ELISA (21)

Currently there is no serology available for Schmallenberg virus. A commercially available test for detection of antibodies to Akabane virus did fail to detect antibodies in serum from Schmallenberg virus infected cattle (Beer , pers. comm.). This indicates that serological tests that are currently available for Simbu serogroup viruses might not be applicable for Schmallenbergvirus . Therefore, diagnostics currently rely on detection of viral infection by RT-PCR. For this purpose, the Friedrich Loeffler institute has shared information with the CVI and RIVM in The Netherlands. Validation of the use of RT-PCR for diagnosis of infection requires more data on infection kinetics.

Scientists from the FLI have isolated the virus and are able to culture it in hamster cells (Beer pers. comm.) This will enable the development of IFA-based tests and neutralization assays that can be used for antibody detection.

Risk factors for human exposure.
In general, infection risk for humans of arboviruses is closely related to high densities of infected arthropods. High population densities of the midge vector of Oropouche virus coincide with human epidemics (22). Given the viremic phase, blood-borne transmission of these viruses is possible.

There is no evidence for direct zoonotic transmission of Simbu serogroup viruses from ruminants to humans. If there would be a potential for direct zoonotic transmission, presence at or in the direct surroundings of affected farms would be expected to be a risk factor. The birth defects in lambs have resulted in an increased need for assistance from veterinarians during parturition (Vellema, pers. comm.). There is no information about possible presence of virus in amniotic fluid. From the California serogroup of orthobunyaviruses it is known that these viruses are susceptible to common disinfectants (1% sodium hypochlorite, 2% glutaraldehyde, 70% ethanol, formaldehyde) like all lipid enveloped viruses. They are sensitive to heat; infectivity lost at 50-60°C for at least 30 min) and do not survive outside the host for long periods (23).

Conclusion/recommendations.
1) Based on the considerations mentioned above, zoonotic transmission of Schmallenbergvirus can not be excluded but is considered unlikely.

2). The clinical syndrome associated with Schmallenberg virus in cattle peaked during the months August and September. Currently the circulation/transmission of Schmallenberg virus in cattle seems to have faded out. The recent increase in delivery of malformed lambs – if proven to be related to the infection- is likely resulting from intra-uterine exposure during prior months.

3). If one would assume that Schmallenberg virus has zoonotic potential, there is no acute risk for human population at present (December 2011) when considering the vectorial transmission route (most likely midges). However, exposure risk during abortion or delivery of affected ruminants due to Schmallenberg virus is unknown.

4). There have been no reports of unusual illness in humans in the months when the cattle syndrome peaked.

5) The outbreak in cattle in Germany and the Netherlands could reoccur in the vector season in 2012 (based on epidemiology other orthobunyaviruses and bluetongue virus: survival in midges during winter). In this case these outbreaks should be monitored closely from a public health perspective: an increased awareness for putative zoonotic events is indicated, for instance by implementation of a surveillance system.

6) We advice to initiate a monitoring system for diseases among professionals (farmers, veterinarians) that have been in close contact with abortion products or who conducted deliveries of affected calves/lambs. They will be advised to contact the local municipal health services. The national center for control of infectious diseases (LCI) will coordinate this system.

7) Currently, diagnostic methods for this virus are limited to RT-PCR, and have not been validated. Improved diagnostic methods will be developed in the near future. The CIb is in contact with the FLI and CVI to prepare for laboratory response, in case such is needed.

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