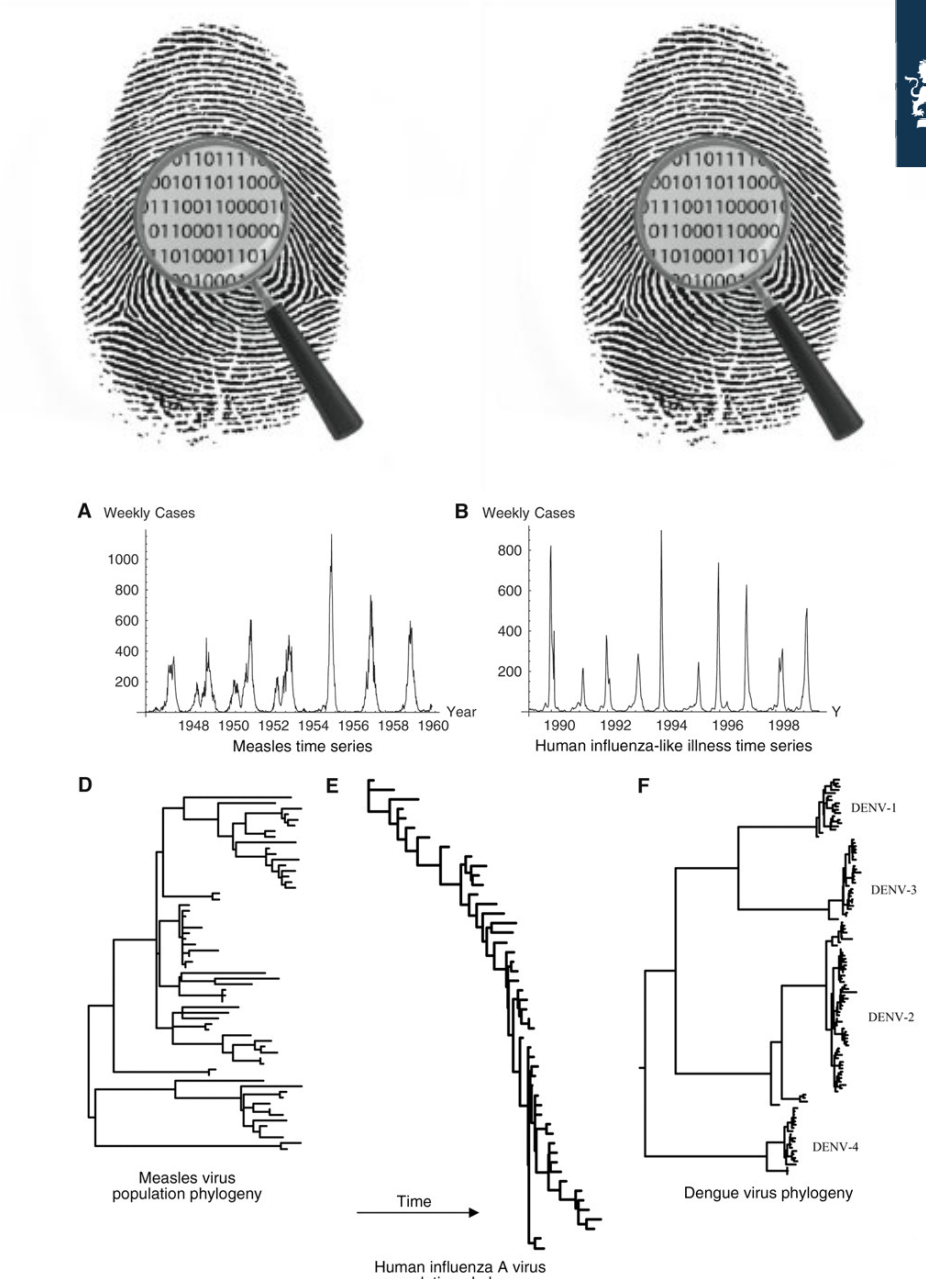


Rijksinstituut voor Volksgezondheid
en Milieu
Ministerie van Volksgezondheid,
Welzijn en Sport

Human risk profile and response to Schmallenberg virus

Marion Koopmans
Professor of public health virology

April 2nd, Brussels

19-11-2011

Promed report FLI, bunyavirus associated with disease in cattle
RFI to FLI about potential zoonotic risk, and protocol for detection

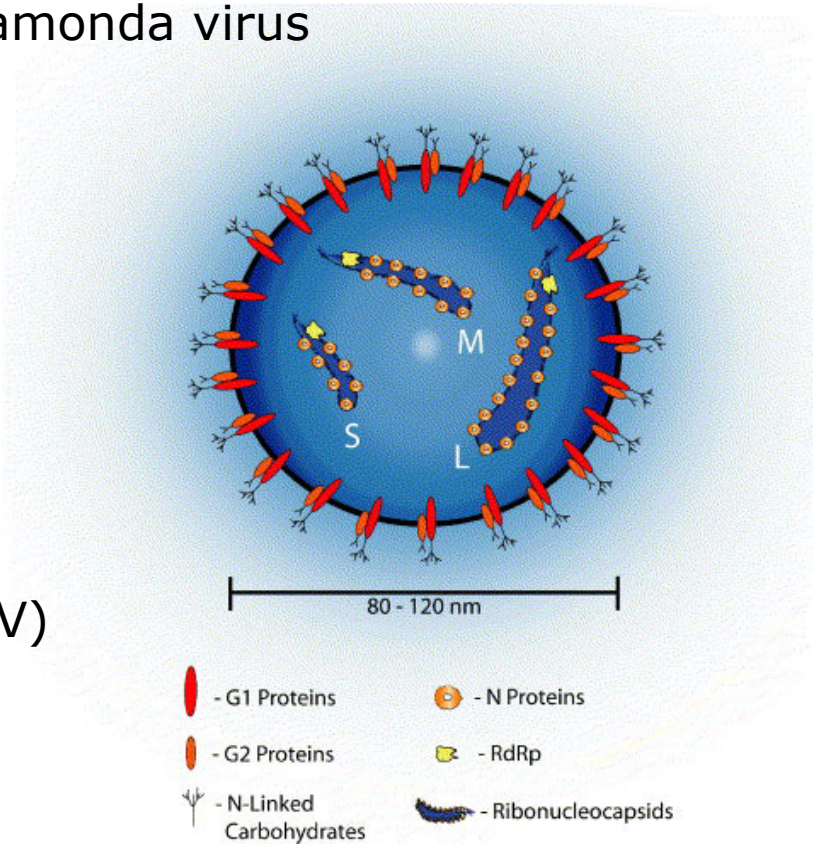
Discussion in national human/veterinary threat alert meeting
Suspected link to disease noted in The Netherlands
Risk assessment human health

- What is the pathogen?
- What is known about its taxonomic status?
- What is known about related viruses?
    - Evidence for zoonotic transmission
    - Evidence for abrupt changes
    - Epidemiology

Taxonomic classification SBV

- L-segment: 69% homology with Akabane virus
- M-segment: 71% homology with Aino virus
- S-segment: 97% homology with Shamonda virus

Family: *Bunyaviridae*
Genus: *Orthobunyaviruses*
Serogroup: Simbu serogroup
Virus: Schmallenberg virus (SBV)



Beer et al., 2012

Bunyaviruses known to infect humans

genus	serogroup	species	Geografical distribution	Vector	Reservoir	Human pathogen
Nairovirus	Crimean-Congo haemorragic fever group	Crimean-Congo haemorragic fever virus	Europe, Turkey, Afrika	tick	Humans, ruminants, rodents, birds	**yes**
Phlebovirus	Phlebotomus fever group	Rift Valley fever virus	Afrika, Middle-East	mosquito	Rodents, cattle	**yes**
		Toscana virus	Europe, Asia, Afrika	sandfly	unkown	**yes**
	SFTS	SFTS virus	China	tick	unknown	**yes**
Hantavirus	-	Puumalavirus	Europe	-	Rodents	**yes**
Orthobunyavirus	Simbu group	Oropouche virus	South-Amerika	mosquito midge	Humans, sloths, marmosets	**yes**
		Iquitos virus	South-Amerika	midge	Humans, unknown	**yes**
		Akabane virus	Asia, Israël, Australia	midge	ruminants	No
		Shamonda virus	Afrika	midge	ruminants	No
		Aino virus	Asia	midge	ruminants	**Antibodies**
		Shuni virus	Afrika	midge	ruminants	**Antibodies**
	California Encephalitis group	California encephalitis virus	North-Amerika	mosquito	rodents, lagomorphs	**yes**
		La Crosse virus	North-Amerika	mosquito	Rodents, lagomorphs	**yes**
		Tahyna virus	Europe	mosquito	Birds, lagomorphs	**yes**
	Bunyamwera group	Batai virus	Europe, Asia, Afrika	mosquito	Birds	**yes**
		Cache Valley virus	North-Amerika	mosquito	Deer, ruminants	**Yes**

Reusken and Koopmans, NTMM 2012; ECDC risk assessment, december 2011

Bunyaviruses known to infect humans

genus	serogroup	species	Geografical distribution	Vector	Reservoir	Human pathogen
Nairovirus	Crimean-Congo haemorragic fever group	Crimean-Congo haemorragic fever virus	Europe, Turkey, Afrika	tick	Humans, ruminants, rodents, birds	yes
Phlebovirus	Phlebotomus fever group	Rift Valley fever virus	Afrika, Middle-East	mosquito	Rodents, cattle	yes
		Toscana virus	Europe, Asia, Afrika	sandfly	unkown	yes
	SFTS	SFTS virus	China	tick	unknown	yes
Hantavirus	-	Puumalavirus	Europe	-	Rodents	yes
Orthobunyavirus	Simbu group	Oropouche virus	South-Amerika	mosquito midge	Humans, sloths, marmosets	**yes**
		Iquitos virus	South-Amerika	midge	Humans, unknown	**yes**
		Akabane virus	Asia, Israël, Australia	midge	ruminants	No
		Shamonda virus	Afrika	midge	ruminants	No
		Aino virus	Asia	midge	ruminants	**Antibodies**
		Shuni virus	Afrika	midge	ruminants	**Antibodies**
	California Encephalitis group	California encephalitis virus	North-Amerika	mosquito	rodents, lagomorphs	**yes**
		La Crosse virus	North-Amerika	mosquito	Rodents, lagomorphs	**yes**
		Tahyna virus	Europe	mosquito	Birds, lagomorphs	**yes**
	Bunyamwera group	Batai virus	Europe, Asia, Afrika	mosquito	Birds	**yes**
		Cache Valley virus	North-Amerika	mosquito	Deer, ruminants	**Yes**

Reusken and Koopmans, NTMM 2012; ECDC risk assessment, december 2011

Bunyaviruses known to infect humans

genus	serogroup	species	Geografical distribution	Vector	Reservoir	Human pathogen
Nairovirus	Crimean-Congo haemorragic fever group	Crimean-Congo haemorragic fever virus	Europe, Turkey, Afrika	tick	Humans, ruminants, rodents, birds	yes
Phlebovirus	Phlebotomus fever group	Rift Valley fever virus	Afrika, Middle-East	mosquito	Rodents, cattle	yes
		Toscana virus	Europe, Asia, Afrika	sandfly	unkown	yes
	SFTS	SFTS virus	China	tick	unknown	yes
Hantavirus	-	Puumalavirus	Europe	-	Rodents	yes
Orthobunyavirus	Simbu group	Oropouche virus	South-Amerika	mosquito midge	Humans, sloths, marmosets	**yes**
		Iquitos virus	South-Amerika	midge	Humans, unknown	**yes**
		Akabane virus	Asia, Israël, Australia	midge	ruminants	No
		Shamonda virus	Afrika	midge	ruminants	No
		Aino virus	Asia	midge	ruminants	**Antibodies**
		Shuni virus	Afrika	midge	ruminants	**Antibodies**
	California Encephalitis group	California encephalitis virus	North-Amerika	mosquito	rodents, lagomorphs	yes
		La Crosse virus	North-Amerika	mosquito	Rodents, lagomorphs	yes
		Tahyna virus	Europe	mosquito	Birds, lagomorphs	yes
	Bunyamwera group	Batai virus	Europe, Asia, Afrika	mosquito	Birds	yes
		Cache Valley virus	North-Amerika	mosquito	Deer, ruminants	Yes

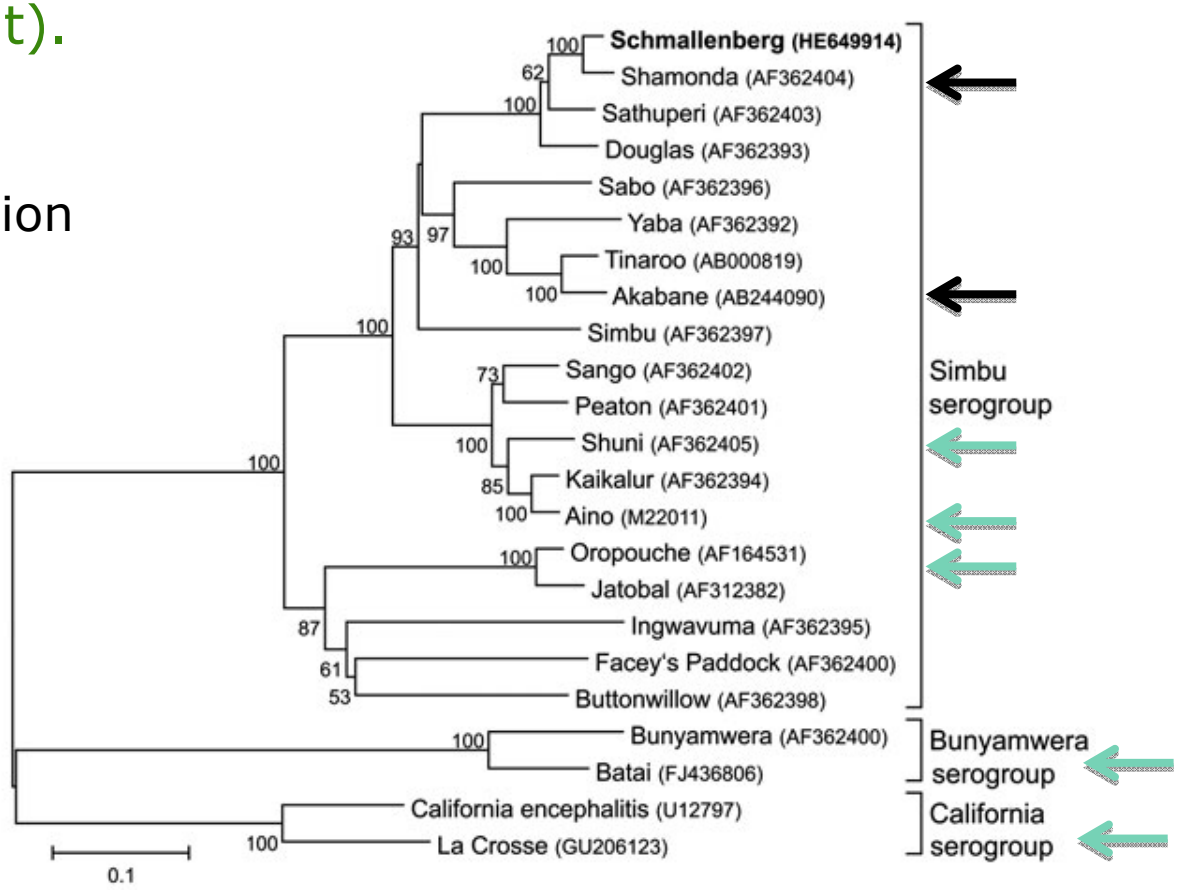
Reusken and Koopmans, NTMM 2012; ECDC risk assessment, december 2011

Orthobunya phylogeny

S-segment based (701 nt).

← No zoonotic infection

← zoonotic infection



Beer *et al.*, *2012*

Conclusion

- There are several zoonotic viruses within the same serogroup
- Genetic reassortment may generate novel viruses with unknown properties
  - emergence of new bunyaviruses with increased pathogenicity has been described.
  - putative host switching (zoonotic transmission).
- SBV is a previously unknown virus with unknown characteristics (vs BTV).
- On the basis of available data, zoonotic infections could not be excluded

Preparedness questions (checklist)

- What is known about (human) disease
- Kinetics of shedding in animals
- (environmental) Stability of pathogen
- Diagnostic options and their interpretation
  - Methods, pro and con's
  - validation
  - Sampling frame
  - Safety
  - Surge capacity
  - …….

CHECKLIST LABORATORIUM PREPAREDNESS, RIVM

1 Patiënten
Basisvragen diagnostiek methode

•welke diagnostiek is beschikbaar voor het stellen van de diagnose bij personen met klachten?
•waar is deze diagnostiek beschikbaar?
•Wat is de kwaliteit van de beschikbare diagnostiek? (bv conform kwaliteitscontroles, detectielimiet)
3a) Wat is de sensitiviteit van de test? (detectielimiet)
3b) Wat is de specificiteit van de test?
3c) Wat is de positief voorspellende waarde?
3d) Wat is de negatief voorspellende waarde?
3e) Wat is er gedaan aan 3e lijnscontroles?
•Is de beschikbare diagnostiek gestandaardiseerd?
•Is er literatuur over beschikbaar?
•Zijn er specifieke aandachtspunten mbt uitvoering of interpretatie?

Basisvragen afname en interpretatie

•Wat is de infectiedynamiek van het pathogeen? (kinetiek immuunresponse, kinetiek uitscheiding).
•Wat is de differentiaal diagnostiek?
•Hoe wordt de diagnostiek gebruikt in de casus definitie?
•Welke materialen worden afgenomen, welke hoeveelheden.
•Zijn er bijzondere beschermingsmaatregelen nodig bij afname (kortsluiten met LCI)
•Op basis van 1-6: keuze maken waar op in te zetten mbt diagnostiekmethodiek: .
•Hoe betrouwbaar zijn de resultaten met de gekozen diagnostiek? Is bevestiging noodzakelijk?
•Waar wordt bevestigingsdiagnostiek gedaan?

Basisvragen capaciteit

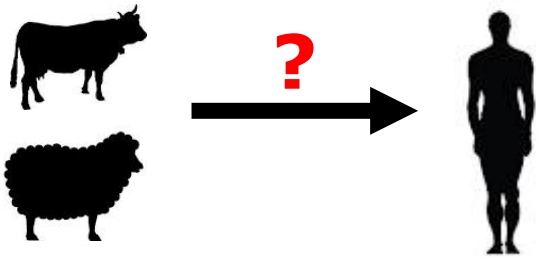
•Wat is de capaciteit van de beschikbare diagnostiek?
•Welke logistieke problemen dienen geadresseerd te worden om deze capaciteit te handhaven? (bv beschikbaarheid reagentia, beschikbaarheid monsterafname materialen).
•Is eigen labrespons noodzakelijk? Indien wenselijk (als er geen adequate diagnostiek beschikbaar is in Nederland of in zeer beperkte capaciteit):
•Wie coördineert de interne laboratorium respons?
•Wie is contact naar respons team/OMT?
•Welke materialen zijn nodig om diagnostiek op te zetten? Hoe komen we hieraan? Wie gaat deze diagnostiek opzetten?
•Wie gaan ingewerkt worden op deze diagnostiek? (expertise, beschikbaarheid 24/7, bevoegdheid)
• Wie regelt de logistiek rond de diagnostiek ? (bestellingen, uitgifte bemonsteringsmaterialen, maken aanvraagformulier, aanpassen unilab, eisen aan manier van verzenden etc.)
•Op welk biologisch veiligheidsniveau wordt het pathogeen ingeschaald?
•Wie maakt SOP's?
•Zijn er speciale maatregelen nodig nav de inschaling van de diagnostiek?
•Hoe is de eindverantwoordelijkheid geregeld m.b.t. de afgifte van diagnostiek uitslagen?
•Wanneer wordt op basis van de huidige capaciteit, opschaling noodzakelijk? (identificatie kantelpunt: overschakelen op opschaling *voordat* de huidige capaciteit uitgeput is).
•Wat zijn de kosten? Hoe worden die vergoed?
•Moet werk worden geherprioriteerd? Wie neemt contact op met opdrachtgevers?

Relevant observations

- Highest circulation/transmission of Schmallenberg virus in period of high vector activity. (August-September)
- Malformations in lambs/calves occurring since december due to intra uterine infections in vector season
- Currently (jan-march) outside vector season -> no acute risk for human population at present when considering the vectorial transmisison route.
- High loads of viral RNA in birthing materials

➢ **IF zoonotic: potential human exposure during vector season AND in direct contact during animal delivery**

Actions / Studies



Phase 1

- Development of human diagnostics
- Monitoring of health complaints in exposed persons
- comparative seroprevalence testing of neutralising antibodies in persons with high risk of (professional) exposure to known affected animals or farms

    - Exposure to birthing materials of infected animals
    - Exposure to vector during summer period

Only if seropositive individuals are found:

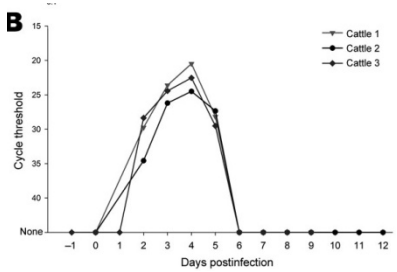
Phase 2: what is the clinical relevance of SBV infection in humans?

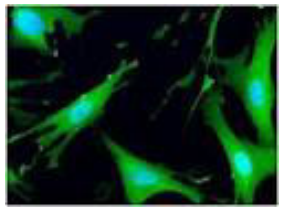
Laboratory response: human diagnostics.

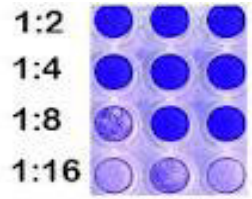
- Real-time RT-PCR: **illness monitoring**
  - Only in first week > short window
  - Detects actual virus presence
  - If positive: confirm by serology and sequencing
- serology: **exposure studies**
  - Longer window for sampling (weeks-months)
  - Neutralising antibodies most specific
  - If positive: repeat against other orthobunyaviruses

NOTE

Tests are **never** completely validated in case of an Emerging Infection !







Cross reactivity:
available data suggests no problems with cross-reactivity to European orthobunyaviruses

Serum >	SBV*	BATV**	Inkoo	TAHV
Virus				
SBV	+++	-	pending	Not available
BATV	-	+++	pending	Not available
INKOO	-	Not available	pending	Not available
TAHV	-	Not available	pending	Not available

*Homologous titer 1/1024
** Homologous titer 64

Sources of information from surveillance

- Questionnaire on illness complaints in farmers, animal health service (no complaints)
- Febrile illness notifications in farmers and their family members, and in veterinarians since Dec 1st 2011 (4 reports, all tested negative by RT-PCR)
- Surveillance of neurological illness for polio eradication: no unusual disease noted
- Surveillance of influenza like illness: no unusual disease noted

Study design

- **Seroprevalence reported** in regions with known orthobunya outbreaks in humans **2-25%**
- **Sample size needed estimated at 200** post exposure for 95% confidence for lowest boundary
- Validation of serology against historic (pre-2011) samples from community, farmers and veterinarians (all negative, n > 250)
- Basic questionnaire (exposure, health complaints, co-morbidities)
- Medical clearance: march 13 th, sampling nearly completed
- **Testing: ongoing**, completed in April
- Data analysis and report: **early May**

Persons involved

Risk profile

- **CHANTAL REUSKEN section chief emerging infections**
- Hans vd Kerkhof, Marieta Braks, Kitty Maassen,
- Roel Coutinho (CIb).
- Rudie Meiswinkel (CMV)
- Wim vd Poel (CVI)
- Petra Kock (GD)
- Martin Beer (FLI, Duitsland)
- Toos Waegemaekers (CIb/GGD)
- Menno de Jong (AMC)
- Ab Osterhaus (EUR)

Response

- Lab response: Chantal Reusken
  - Gert-Jan Godeke, Eveline Kampert, Johan Reimerink, Peter Schielen, Ankje de Vries, Ilse Zutt

- Preparedness and response unit: Hans vd Kerkhof
  - Corien Swaan
  - Leslie Isken
  - Paul van Beek

- Epidemiology: Wilfrid van Pelt
  - Kees vd Wijngaard, Barbara Schimmer
- Teams Municipal health services

VETERINARY

- Jet Mars, Harold vd Heijden (GD)
- Wim vd Poel, Marcel Hulst (CVI)
- Bernd Hoffmann, Martin Beer (FLI, GER)

INTERNATIONAL LAB RESPONSE

- Jonas Chanasit-Schmidt (BNI, GER)
- Manfred Weidmann (UN. Göttingen, GER).
- David Brown, Matthias Niedrig, Andreas Nitsche