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Lessons from the outbreak in the Netherlands: transmission and epidemiology of Q fever

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Outline

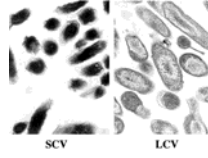
- Introduction
- Transmission
- Epidemiology and control measures
- Current situation
- Lessons learned from the Dutch outbreak



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Introduction: microbiology


- *Coxiella burnetii*
 - Small obligate Gram-negative coccobacillus
 - Intracellular
- Two morphological states:
 - LCV: large cell variant
 - Intracellular metabolically active form
 - SCV: small cell variant
 - Extracellular, survives in environment
- Phase variation: chromosome deletions lead to irreversible change in lipopolysaccharides
 - Infection with phase I
 - Change to phase II in human cells



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Introduction: infection in animals


- Usually no symptoms when infected with *C. burnetii*
- Most important symptoms in animals:
 - Abortion
 - Stillbirth
 - Early lamb mortality
- Symptomatic and asymptomatic animals shed *C. burnetii* in feces, urine, milk, and products of pregnancy
- High seroprevalence in animal populations but few human cases



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Introduction: infection in humans



- Acute Q fever:
 - Asymptomatic in >60% of cases
 - Fever (95%)
 - Flu-like illness
 - Pneumonia
 - Hepatitis
 - Low mortality
- Chronic Q fever (1-3% of all patients):
 - Endocarditis
 - Vascular infection
 - High mortality



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Introduction


- Monday 16.40: The Val de Bagnes *Coxiella* outbreak (O. Peter)
- Monday 17.00: The *Coxiella* outbreak in Lavaux (G. Greub)
- Tuesday 11.00: Chronic Q fever (C. Bleeker-Rovers)
- Wednesday 11.20: Acute Q fever (S. Keijmel)
- Wednesday 11.40: Serological diagnosis of Q fever (O. Peter)

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Transmission


- Transmission through inhalation of infected aerosols and consumption of raw milk
- Mainly found in goats and sheep
- Rodents, dogs, cats, and cows, buffalos, bears, camels, etc.
- C. burnetii* detectable 500-1000 meters from source in the air
- Dose-response effect, but a single bacterium can cause seroconversion
- No human-to-human transmission, except:
 - Blood transfusion
 - Aerosols during delivery in a Q fever infected woman



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Epidemiology in the world

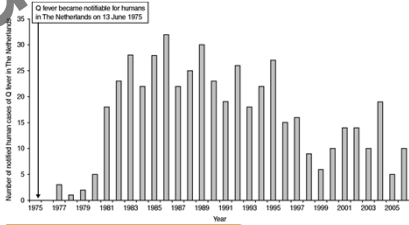
- Small outbreaks everywhere except Antarctica and New Zealand
- Transmission not always obvious:
 - 1948, Hamilton, USA: 6 laundry workers infected by contaminated clothing from Rocky Mountain Laboratory
 - Patients >20 km from laboratory



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Epidemiology in the Netherlands until 2007

- Before 2007: 10-20 cases/year
- Notifiable disease for humans since 1975
- Predominantly farmers and veterinarians
- Seroprevalence before 2007: 2.7%



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Epidemiology in the Netherlands until 2007

- 2005: Sudden rise in abortions on goat farms: Q fever
- 2007: Human outbreak in Herpen:



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Epidemiology in the Netherlands 2007: Herpen

- Small village in a rural area in the south of the Netherlands
- May 2007:
 - General practitioner contacts the local public health agency: unusual high number of patients with pneumonia
 - Medical microbiologist local hospital contacts the same public health agency because of severe pneumonia in 2 healthy patients from the same household



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Q fever!



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Q fever!

- 168 notified cases until the end of the year



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Epidemiology in the Netherlands 2007


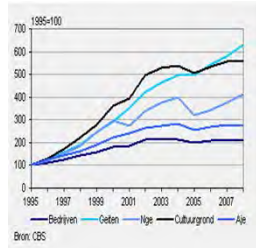


Reported human cases Contaminated goat farms

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Goat farming in the Netherlands

- Explosive growth of number of goat farms and number of goats per farm
- >400 farms
- Total >350,000 goats





Bron: CBS

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Epidemiology in the Netherlands 2007: Herpen

- April 2007: large commercial goat farm with abortion storm
- April 2007: average temperature of 13.4 °C (4.4 °C higher than the 1977–2006 average)
- April 2007: easterly wind more prominent than in the 30 previous years and very little rain
- Multiplex qPCR on samples from animals from infected farm:
 - Urine and milk samples negative
 - Vaginal swabs and manure samples all positive for *C. burnetii*
- Multiplex qPCR on environmental samples:
 - Water from drinking buckets negative
 - Samples from straw, swabs from floors and walls, insects from a UV-lamp all positive for *C. burnetii*



Karagiannis et al. Epidemiol Infect 2009;37:1283–1294

Transmission the Netherlands

- Surface swabs and aerosol samples collected inside stables and around 6 Q fever-affected ruminant farms
- Optimized multiplex qPCR for the detection of *C. burnetii* DNA: all samples positive

De Bruin et al. J Appl Microbiol 2013;114(5):1395-404

Epidemiology in the Netherlands 2007: Herpen

- Case control study in Herpen:
 - Risk factor for Q fever:
 - Contact with manure, hay, and straw
 - Living in the eastern part of the village close to ruminant farms
 - Contact with animals and consumption of raw milk products were not significant risk factors
- Outbreak in Herpen and surrounding areas caused by infected goat farm with abortion storm
- Outbreak in Herpen considered as an isolated incident:
 - Unusual weather conditions in combination with
 - Unusual high number of abortions on large goat farm

Kirgejannis et al. Epidemiol Infect 2009;137:1283-1294

Epidemiology in the Netherlands 2008

- University Medical Centre Nijmegen (20 km north of Herpen):
 - April 2008: 3 admissions from nearby psychiatric institution
 - Young patients (35-54y) with pneumonia
 - Common exposition: "therapeutic cuddling" with abandoned lamb

Q fever!

Koene et al. Epidemiol Infect 2011;139(1):13-18

Epidemiology in the Netherlands 2008: Nijmegen

Figure 2. Confirmed and possible Q-fever cases in a psychiatric care institution by day of illness onset April - June 2008 (n=45)

Date	Confirmed case	Possible case
11-Apr	1	0
25-Apr	1	0
9-May	2	4
23-May	1	1
6-Jun	1	0

Koene et al. Epidemiol Infect 2011;139(1):13-18

Control measures 2008

- June 2008: national outbreak management team
 - Q fever notifiable disease in animals in case of >5% abortions in sheep or goats
 - Spread of manure from infected farms prohibited for a period of 90 days after diagnosis
 - No entry for not strictly necessary visitors for a period of 90 days after positive results
- August 2008:
 - Coxevac vaccine limited availability and not registered: exemption
 - Voluntary vaccination of non-pregnant goats and sheep in a 45 km zone around Uden

Epidemiology in the Netherlands 2007-2008

2007: <200 cases

2008: 1000 cases

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Minister of Agriculture Minister of Health Head of Dutch National Institute for Public Health and the Environment

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Control measures 2009

- February 2009:
 - Control of rodents
 - Spread of manure from all farms within 30 days of lambing season prohibited
- April 2009:
 - Obligatory vaccination of all goats and sheep in the province of North-Brabant and some surrounding areas

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Epidemiology in the Netherlands 2009:

- Case control study:
 - 146 cases and 431 address-matched controls
 - Relation between visiting farm X and developing Q fever?
- Farm X:
 - "Lamb-viewing days" every weekend in February and March 2009
 - 12,000 visitors

Whelan et al. Epidemiol Infect 2012;140(5):858-864

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Epidemiology in the Netherlands 2009:

	Univariable matched ^a OR			Multivariable matched OR		
	OR	95% CI	P	OR	95% CI	P
Demographics						
Age (yr)	Ref.	Ref.		Ref.	Ref.	
40-49 yr	1.7	(0.9-3.2)	0.094	5.4	(1.9-15.3)	0.001
≥60 yr	1.2	(0.6-2.3)	0.594	3.8	(1.3-10.6)	0.012
Gender (male)	1.8	(1.1-2.9)	0.013			
Visits to agricultural sites and events						
Visited Farm X	24.2	(8.4-69.7)	0.000	43.3	(9.4-200.1)	0.000
Visited site Y	1.2	(0.4-3.5)	0.773			
Visited site Z	1.9	(0.9-3.7)	0.076			
Other agricultural site for recreational visit (unspecified)	1.4	(0.5-3.4)	0.520			
Other public event with animals	2.1	(0.7-6.2)	0.186			
Visited other sheep or goat farm, not otherwise named						
Other contact with animals						
Work in industry related to a agriculture	0.6	(0.1-4.9)	0.620			
Pets at home	0.9	(0.6-1.4)	0.671			
Farm animals at the home-place	1.8	(0.4-8.1)	0.473			
Sheep at home						
Goats at home						
General health						
History of medical problems	1.5	(1.0-2.3)	0.054	1.6	(0.9-2.8)	0.084
History of Q fever prior to February 2009						
Current smoker	2.0	(1.3-3.0)	0.002	2.2	(1.3-3.8)	0.006
Occurrence of disease in households						
Another person in the household with Q fever in 2009	10.3	(2.2-48.7)	0.003	4.8	(0.6-36.1)	0.126

Whelan et al. Epidemiol Infect 2012;140(5):858-864

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Epidemiology in the Netherlands 2008-2009

2008: 1000 cases 2009: >2300 cases

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Minister of Agriculture Minister of Health Head of Dutch National Institute for Public Health and the Environment

Control measures 2009

- October 2009:
 - Obligatory bulk tank milk testing for *C. burnetii* 1x/2 months
 - Transport of animals prohibited
 - Visitors prohibited
- December 2009:
 - Breeding and extension ban: life-long breeding ban for 55,000 animals
 - Obligatory bulk tank milk testing 1x/2 weeks





Control measures 2009-2010

- December 2009:
 - Obligatory culling of all pregnant sheep and goats on infected farms
 - >50,000 animals were culled

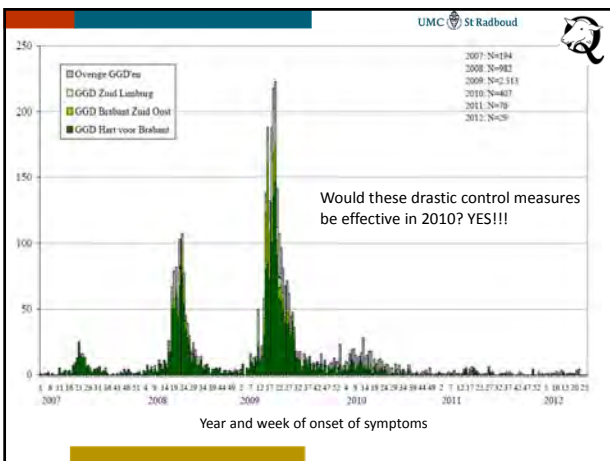
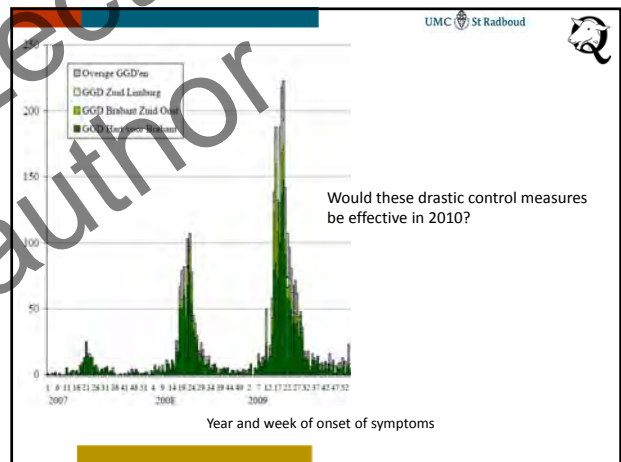



Q fever among culling workers

- 517 culling workers using personal protection equipment (filtering facepiece masks, gloves, overalls, hairnets)
- 246 culling workers participated in the study
- Pre- and post-cull blood samples: serology using ELISA
- Seroconversion in 17.5%
- Risk factors for seroconversion:
 - Univariable model: total hours worked, farm size, and working inside the stable
 - Multivariable model: working >100 hours on the farm and working inside the stable
- Additional preventive measures needed!
- Vaccination of culling workers should be considered




Whelan et al. Emerg Infect Dis 2011;17(9): 1719-1723



Human vaccination

- Human vaccine available: Q-VAX[®], a purified suspension of *C. burnetii* prepared from the Phase 1 Henzerling strain of the bacterium
- Licensed only in Australia
- Previously used in healthy persons with high-risk occupation
- In these people high effectiveness and safety
- Side effects when vaccine is given after prior infection
- Serology alone not enough
- Additional skin test needed



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Human vaccination the Netherlands 2010-2011

- July 2010: Dutch Health Council decides for vaccination of patients at high-risk for developing severe complications of Q fever = chronic Q fever
- NOT vaccination of the entire population
- NOT vaccination of those working in the livestock industry
- Reasons:
 - Assumption that the veterinary control measures would be sufficiently effective in decreasing the risk of infection in people
 - Limited evidence about the effectiveness and safety of the vaccine in the general population
 - Benefit of preventing complications high-risk patients outweighed the concerns about vaccine effectiveness and safety

Isken et al. Vaccine 2013;31(23):2617-2622

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Human vaccination the Netherlands 2010-2011

- General practitioners: selection of patients:
 - History of endocarditis or heart valve disease
 - Large arterial aneurysms or vascular grafts or prosthesis
- Exclusion criteria:
 - Pregnancy
 - Age <16 years
 - Previous Q fever infection: positive serology and/or positive skin test

Isken et al. Vaccine 2013;31(23):2617-2622

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Human vaccination the Netherlands 2010-2011

- Vaccination between January and June 2011
- Many minor side effects: injection site reaction in two thirds
- Only one serious adverse event related to vaccination (extended injection site reaction)

Isken et al. Vaccine 2013;31(23):2617-2622

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Q fever in the Netherlands 2007-2013

Year	Number of reported cases
2007	168
2008	1000
2009	2354
2010	504
2011	81
2012	66
2013	17

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Q fever in the Netherlands 2007-2013

Hilken Deuren

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C. burnetii in Dutch blood donors


- May 2009: 1004 serum samples collected from blood donors living in the area with the highest Q fever incidence:
 - 12.2% positive serology for Q fever (IFA)
 - 0.3% contained C. burnetii DNA
- Follow-up samples from 543 donors:
 - 10 seroconversions
- Incidence 5.7% per year: 10-fold higher than local number of reported clinical cases (0.47% per year)

Hogema et al. Transfusion 2012;52(1):144-150

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Serologic prevalence

- Seroprevalence study in catchment area of Jeroen Bosch Hospital
- Using a very conservative cut-off titre of $\geq 1:128$ for *C. burnetii* phase II IgG
- Seroprevalence 10.7% (vs. 2.4% before outbreak)
- 32,200–48,900 persons in the catchment area have been infected by *C. burnetii*
- Exceeds the number of notified patients with symptomatic acute Q fever in this region by 50- to 75-fold!




Kampschreur et al. Epidemiol Infect 2013;141(4):847-51

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Epidemiology 2013

- Incidence of acute Q fever appears to be “back to normal”
- Still increasing numbers of patients with chronic Q fever
- Many of these patients present acutely with life-threatening complications without knowing of a previous Q fever infection
- No notification system for chronic Q fever or Q fever related mortality
- Major challenges in 2013:
 - Early detection and treatment of patients who are at risk for chronic Q fever
 - Optimal treatment of known patients with chronic Q fever



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Lessons learned from the Dutch outbreak

- Main causes of the large Q fever outbreak in the Netherlands:
 - Many susceptible humans in highly populated area (497 inhabitants/km²)
 - Close proximity to aborting small ruminants in large commercial farms
 - Initially perfect weather conditions for spread of the infection
- In addition to good monitoring and surveillance systems, continuing clinical awareness necessary to assess Q fever outbreaks
- Early and sometimes drastic control measures necessary to halt outbreak:
 - Obligatory vaccination of all goats and sheep very effective
 - Culling of all unvaccinated pregnant animals was very effective
 - Human vaccination of risk groups should be considered at an early stage

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Questions?





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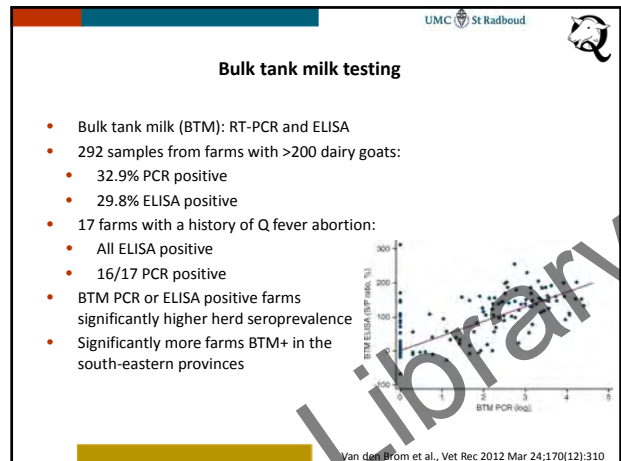
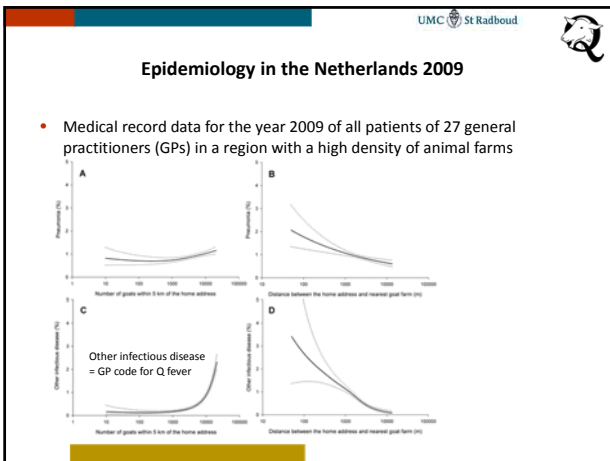
Extra slides

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Introduction: history

- August 1935: Outbreak among abattoir workers: 20/800 ill
- Pathologist Derrick, Queensland Australia: Query fever, limited resources for research
- 1935: Lab of Burnet and Freeman, Melbourne Australia: bacteria in microphages of infected tissue
- 1936: Cox and Davis, Montana USA: isolation of bacteria within ticks
- 1938: Dyer: got infected in the lab: micro-organisms Cox en Burnet identical: *Coxiella burnetii*



Date of implementation	Document code	Measure
12 June 2008	TRCJZ/2008/1622	Q fever notifiable in dairy goats and dairy sheep, notification when over 5% abortions within 30 days at farms with more than 100 animals and when over 3% abortions within 30 days at farms with fewer than 100 animals (abortion rates up to 5% are considered to be more or less normal)
12 June 2008	TRCJZ/2008/1643	Prohibited from removing manure from the stable for 90 days after notification
16 October 2008	TRCJZ/2008/2817	Special dispensation for Coesvae (CEVA) Q fever vaccine to be used in The Netherlands
2 February 2009	TRCJZ/2009/244	Voluntary vaccination in dairy sheep and dairy goats at farms with more than 50 sheep or goats, petting zoos and nursing farms in the affected areas (Fig. 3)
20 April 2009	TRCJZ/2009/1142	Prohibited from farming more than 50 dairy goats and dairy sheep if certain hygienic measures are not implemented, when a vet has control, human measures, rendering facilities and placental tissue tests
1 October 2009	Regulation 40823	Mandatory vaccination of dairy sheep and dairy goats on farms with more than 50 animals, on care farms, petting zoos and zoos in the extended area (Fig. 4) before 1 January 2010
9 December 2009	Regulation 96744	Mandatory bulk tank milk monitoring for Q fever every 2 months
1 January 2010	Regulation 72246	Prohibited from transporting dairy sheep and dairy goats from a positive farm. Vaccinated animals may be transported to positive farms
14 December 2009	Regulation 98748	Victory ban in place at positive farms
16 December 2009	Regulation 99604	Bin on increase of numbers of dairy goats and dairy sheep on a farm
18 December 2009	Letter to Parliament WPK 09-2046-CPM	Bin on reproduction of goats
18 December 2009	Regulation 101785	Mandatory vaccination of dairy sheep and dairy goats, on care farms, petting zoos, zoos on farms open to the public, mobile sheep stocks, and in natural reserves nationwide before 2011
		Mandatory bulk tank milk monitoring for Q fever every 2 weeks
		Prohibited from removing manure from the stable within 30 days after end of lambing season
		If manure has to be removed from the stable, it should be stored on the farm for 90 days
		Culling of all pregnant goats and sheep on Q fever positive dairy goat and dairy sheep farms
		Prohibited from adding sheep or goats to a farm

