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Van:

Verzonden: woensdag 11 juni 2008 10:42

Aan:

Ministerie van Landbouw, Natuur en Voedselkwaliteit

CC:

Onderwerp: Brief naar de Tweede Kamer over Q-koorts

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Aan:

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Beste mensen,

Bijgaand de brief zoals die gisteren om 17.00 uur naar de Tweede Kamer is verzonden. In de brief is zoveel als mogelijk rekening gehouden met uw aller inbreng. De komende dagen houd ik mij bezig om afspraken verder vorm te geven. Mochten er vragen zijn hoe één en ander gaat verlopen of over onduidelijkheden dan ben ik uiteraard daar altijd voor bereikbaar.

Met vriendelijke groeten,

h.

Ministerie van Landbouw, Natuur en Voedselkwaliteit  
Directie Voedselkwaliteit en Diergezondheid (VD)

(68)

Re Q fever

Van: |  
Verzonden: woensdag 11 juni 2008 16:48 |  
Aan:  
Onderwerp: Re: Q fever

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en nog een.

Met vriendelijke groet,

\*\*\*\*\*

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----- Original Message -----

From:  
To:  
Sent: Wednesday, June 11, 2008 2:37 PM  
Subject: Q fever

Hallo

was leuk je meteen weer tegen te komen nu ik net bij LNV binnen ben!

Ik zal me iets meer in Q fever moeten gaan verdiepen,

Heb hier echter geen toegang tot de literatuur.  
Heb jij toevallig eea digitaal zodat ik me wat kan inlezen?

Zo niet dan kom ik gewoon een keer bijpraten,

Dank en groet!

27 Re Q fever

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**ADVIES Q-KOORTS**

**VAN DE INTERDEPARTEMENTALE WERKGROEP ZONNOSEN**

**JANUARI 1999**

Fout! Bladwijzer niet gedefinieerd. **ADVIES Q-KOORTS**

**VAN DE INTERDEPARTEMENTALE WERKGROEP ZONNOSEN**

**JANUARI 1999**

Dit advies is een product van de Interdepartementale Werkgroep Zoönosen

De schrijversgroep van het Advies Q-koorts had de volgende samenstelling:

- . Inspectie W&V, Dienst Oost
- . Erasmusuniversiteit, MGZ
- . RIVM, LIS

en

ID-DLO

De Interdepartementale Werkgroep Zoönosen had de volgende samenstelling:

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- . RVV - Centraal
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- . Ministerie van VWS, IGZ

en

. ID-DLO

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## 1 *Inleiding*

De naam Q-koorts is in feite een afkorting voor "Query Fever". Deze naam is ontleend aan de ontdekking in 1935 door Derrick in Brisbane, van een destijds nieuwe ziekte bij slachthuispersoneel en melkveehouders in Queensland, Australië met onbekende oorzaak. Nu weten we dat *Coxiella (C.) burnetii* de verwekker is.

*C. burnetii* is een Gram-negatieve, intracellulaire bacterie, uit de orde Rickettsiales. De mens is eindgastheer voor dit microorganisme, hetgeen inhoudt dat het zich bij de mens niet kan handhaven. Dit is wel het geval bij een groot aantal zoogdieren (bv. rund, schaap, geit, varken, en sommige wilde dieren, bv. hert) en vogels die zo als reservoir fungeren. Onduidelijk is of kleine huisdieren zoals honden en katten tussen- dan wel eindgastheer zijn. De rickettsiae infecteren met name monocyten en macrophagen: hier overleven zij intracellulair bij een lage pH (4.8) en weerstaan zo de werking van intracellulaire enzymen, die betrokken zijn bij het doden van het organisme.

Buiten de gastheer kan het organisme in een spore-achtige vorm overgaan en is dan zeer resistent tegen fysische invloeden waardoor het lange tijd in de omgeving kan overleven.

*C. burnetii* is oorzaak van een zöonose.

## 2 *Voorkomen bij de mens.*

Tot het begin van de jaren tachtig werd Q-koorts in Nederland als een uiterst zeldzame ziekte beschouwd. In de vijftiger jaren werd m.b.v. de Complement Binding Reaction (CBR) voor het eerst serologisch onderzoek verricht naar het voorkomen van *C. burnetii* infecties bij slachthuispersoneel, bij patiënten met atypische pneumonie, en bij vee. Er werden in eerste instantie geen antistoffen aangetoond. De eerste drie gevallen van klinische Q-koorts in Nederland bij de mens dateren uit 1956. Sinds 1979 nam het aantal patiënten in ons land toe. Omdat aanknopingspunten voor een buitenlandse besmettingsbron ontbraken, terwijl wel



en 24-62% bij bloeddonoren (Rotterdam 24%, Groningen 60% en Maastricht 62%). Percentages sero-positieven zijn volgens diverse studies significant hoger bij mensen die beroepshalve of uit liefhebberij intensief contact hebben met dieren (veehouders, dierenartsen, dieren-opzetters, wolspinsters): 46 - 84% positieven (studies tussen 1968 en 1984).

In Nederland worden ca 20 klinische gevallen per jaar gemeld (Q-koorts is aangifteplichtig). In 1996 waren er 13 ziekenhuisopnamen met gemiddeld 11 verpleegdagen. Toen het RIVM nog primaire diagnostiek verrichtte toonde men in het eigen verzorgingsgebied meer gevallen van Q-koorts infectie aan dan er meldingen van klinische gevallen waren in de rest van Nederland. Bovendien kennen veel infecties een subklinisch verloop. Daarom moet voor ons land rekening gehouden worden met een substantiële onderrapportage via de melding aangifteplichtige ziekten.

### **3 Ziektebeeld bij de mens**

Q-koorts is een gegeneraliseerde infectieziekte met een hematogene verspreiding van de verwekker. Afwijkingen kunnen daarom in alle organen voorkomen. Vaak wordt de diagnose niet gesteld omdat de infecties frequent subklinisch verlopen.

We kennen diverse vormen van Q-koorts infectie: een acute vorm, een luchtweginfectie, en een chronische vorm, waaronder endocarditis en een granulomateuse hepatitis. Na een incubatietijd van 2-6 weken verlopen de meeste infecties subklinisch of lijken op griep. De verwekker verspreidt zich met het bloed in het lichaam en kan in alle orgaansystemen terechtkomen. Daarom kunnen symptomen zeer divers zijn: zoals hoge, vaak remitterende, koorts (38.5 - 40.5°C), hoofdpijn, spierpijn, koude rillingen, anorexia, misselijkheid, braken, diarree en relatieve bradycardie.

Verder kan in de acute vorm pneumonie, hepatitis, meningo-encefalitis, myocarditis, pericarditis en exantheem met koorts optreden; in de chronische vorm kan endocarditis, osteomyelitis, en abortus optreden. De chronisch vorm komt nogal eens vaker voor bij patiënten met immunodeficiëntie (HIV, kwaadaardige tumoren, therapie met steroïden). Deze complicaties kunnen zich in chronische gevallen tot 10 jaar na de primaire infectie nog voordoen. Een heel scala aan ziektebeelden kan dus geassocieerd worden met Q-koorts.

Meestal geneest Q-koorts spontaan, na 1-2 weken. De mortaliteit van onbehandelde gevallen is lager dan 1%.

### **4 Voorkomen bij het dier**

*C. burnetii* kan bij alle landbouwhuisdieren, gezelschapsdieren en vele wilde dieren, inclusief vogels voorkomen. Ook zijn er rapporten van infecties bij amfibieën en reptielen (bv. een python).

In Nederland bleek in 1986 21.4% van het melkvee (n=1160), 3.5% van de schapen (n=3603) en <1% van de geiten seropositief. Uit latere gegevens (1992) waren 13% honden (n=688) en 10% katten (n=441) positief. Percentages positieve rundersera die voor exportdoeleinden worden onderzocht vertonen sinds 1995 een duidelijke stijging (zie Tabel 1).

Tabel 1. Percentages Q-koorts positieve runderen, geiten en schapen in Nederland m.b.v. CBR (serologie ID-DLO, Lelystad)

jaar	rund		geit		schaap	
	%	(n)	%	(n)	%	(n)
1994	0	(290)	-		-	
1995	0.6	(861)	-		18	(43)
1996	5.4	(3784)	4	(1249)	100	(3)
1997*	8.2	(3018)	-		87	(53)

Fout! Bladwijzer niet gedefinieerd. (\* t/m september 1997)

Het aanbod monsters voor serologisch onderzoek stijgt de laatste jaren. De sera werden in het algemeen aangeboden voor exportonderzoek. Van de weinige schapensera die zijn onderzocht, vallen de hoge percentages positieven op.

Recente onderzoeken (1992) in andere landen, bv. in Japan geven hoge percentage seropositieven bij diverse diersoorten: rund 47%, schaap 28%, geit 23% en hond 15%; in Duitsland (1991) zijn ca 30-50% van alle rundveebestanden serologisch positief. In de UK bleek de seroprevalentie in diverse populaties van de bruine rat te variëren van 7-53% (n=313). Boerderijen met schapen in combinatie met andere landbouwhuisdieren scoorden de hoogste percentages seropositieve ratten (39-53%). Australië werd en wordt beschouwd als een belangrijk endemisch gebied, maar in een recente studie (1997) op 617 runderen was slechts één dier serologisch positief (CBR).

Bij honden en katten uit verschillende gebieden over de hele wereld zijn antistoffen tegen Q-koorts aangetoond.

## 5 *Ziekteverschijnselen en pathologie bij het dier*

### 5.1 Ziekteverschijnselen

Met uitzondering van abortus geeft *C. burnetii* in het algemeen bij dieren geen symptomen. Hematogene verspreiding met nesteling en vermeerdering in diverse organen vindt wel plaats: in uier, uierlymfeklieren, en placenta. De melkproductie kan desondanks onveranderd hoog blijven en een normaal aspect blijven vertonen. Verder kan *C. burnetii* zich lange tijd handhaven in lever, milt, lymfeklieren, nieren, ovaria en hersenen. Tijdens de dracht kan de infectie weer actief worden met uitbundige vermeerdering van de organismen in de placenta. Zo kunnen tijdens een abortus of geboorte hoge aantallen organismen worden uitgescheiden met placenta, vruchtvliezen, feces of urine. Ook kunnen moederdieren met hoge aantallen coxiella's in de placenta toch à terme jonge kalveren of lammeren ter wereld brengen die goed levensvatbaar zijn en geen klinische symptomen vertonen.

Fout! Bladwijzer niet gedefinieerd.

## 5.2 Pathologie

Bij volwassen dieren komen kenmerkende pathologische laesies voor die zich meestal beperken tot de placenta. Deze typische laesies zijn identiek bij rund, schaap en geit, met exudatie en necrose in de placentaire villi en met karakteristieke micro-kolonies van *C. burnetii* (gemodificeerde Ziehl-Neelsen, Gimenez, Machiavello of Giemsa kleuring) in de trophoblastcellen. Geïnfecteerde cellen hebben een karakteristiek schuimachtig uiterlijk met vele niet-gekleurde vacuolen, terwijl de intracellulaire pleomorfe staafjes als insluitlichaampjes omgeven zijn door een lichtblauw cytoplasma. De geaborteerde vruchten kunnen histologisch een bescheiden granulomateuse hepatitis en een monocyttaire bronchiolitis vertonen.

## 6 Diagnostiek

### 6.1 Klinische diagnostiek bij de mens

Er bestaat een grote verscheidenheid aan klinische symptomen: hoofdpijn, spierpijn, ano-rexie, misselijkheid, braken, koorts, transpiratie, diarree, hoesten en pijn op de borst. Verder kunnen begeleidende symptomen voorkomen: lichtschiuwheid, conjunctivitis, licht ontstoken keel en een gegeneraliseerde lymfeklierontsteking. De pneumonie van de acute vorm kan aanleiding zijn tot ernstige longklachten; de hepatitis van de chronische vorm kan geelzucht geven, terwijl de endocarditis hartklepaandoeningen met circulatieproblemen kan geven. Vanwege deze grote verscheidenheid aan klinische symptomen is casuïstische diagnostiek waarbij men geen andere ziekteoorzaak kan vaststellen erg moeilijk en aanvechtbaar.

Men mag de diagnose Q-koorts dus pas stellen na zorgvuldige interpretatie van alle klinische symptomen, in combinatie met de aanwezigheid van antistoffen en andere beschikbare laboratorium-gegevens.

### 6.2 Serologische diagnostiek bij mens en dier

Diagnostiek bij mens en dier geschiedt door het aantonen van specifieke antistoffen in serum van zieke patiënten of in convalescent serum. Hiervoor worden meestal de Complement Binding Reactie (CBR) of een Immuno Fluorescentie Test (IFT) met het Q-koorts antigeen gebruikt. Men onderscheidt twee antigene fases (I en II). Het antigeen van de virulente fase I, komt voor in gastheer en vector, en induceert hoge titers antistoffen bij chronische infecties; het antigeen van de avirulente fase II induceert antistoffen in de acute fase en komt vrij na bv ei-passage. In geval van acute infecties worden dus alleen antistoffen tegen fase II antigenen gevonden, bij chronische infecties vind men antistoffen tegen fase I en tegen fase II antigenen, vaak in hoge titers.

Een viervoudige stijging of hoger in CBR of IFT van IgG antistoffen (tegen fase I of II antigenen) in gepaarde sera, verzameld in de acute en reconvalescent fase, bevestigt de diagnose. In de IFT is de aanwezigheid van IgM alleen al voldoende voor een diagnose. In de humane diagnostiek wordt de CBR alleen gebruikt voor het aantonen van acute Q-koorts. De test is positief bij 65% van de patiënten in de tweede week na infectie en bij 90% in de 4de week.

Andere serologische testen die in de literatuur vermeld worden zijn de micro-agglutinatie-methode, radio-immuno-precipitatie en een Enzyme-linked Immunosorbent Assay (ELISA).

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se, speeksel en urine, of uit placenta's of melk van dieren. Hiervoor is een proefdierbesmetting nodig (bv. intra-peritoneale inoculatie van cavia's of hamsters), gevolgd door seriële passages in de dooierzak van bevruchte kippeneieren. Isolatie na experimentele besmetting van cavia's wordt bevestigd door deze dieren op seroconversie te controleren. Vanwege de gezondheidsrisico's voor laboratoriumpersoneel is isolatie van coxiella's niet gangbaar. Met name dierproeven en ei-passages geven een groot risico voor laboratoriuminfectie. Naast eipassage kan agens-detectie plaatsvinden in "schoon" materiaal (bv bloed of hartkleppen) door middel van isolatie in celkweek en Polymerase Chain Reaction (PCR). Voor veel klinisch materiaal zijn deze technieken dus niet geschikt. Voor typering kan sinds kort een DNA finger-printing methodiek gebruikt worden.

## 7 Transmissie

Coxiella kan zich via twee cycli in de natuur handhaven: één in wilde dieren (bv knaagdieren, buideldieren, das, en hert) waarbij teken vaak als vector fungeren. Er zijn meer dan 40 soorten teken beschreven die met *C. burnetii* geïnfecteerd kunnen worden, behorend tot de families Ixodidae en Argasidae. De tweede cyclus verloopt in landbouwhuisdieren, is niet afhankelijk van vector overdracht, maar kan aërogeen via inhalatie van besmette aërosolen of besmette stofdeeltjes verlopen. Ook is interactie tussen deze cycli mogelijk waarbij landbouwhuisdieren via teken besmet raken. Voor de mens is de tekenbeet waarschijnlijk niet van belang.

Voor katten is er in de literatuur enige casuïstiek waaruit zou blijken dat kort na het werpen het nest een bron van infectie voor de mens zou kunnen zijn. Eventuele risico's voor de mens op infectie door kleine huisdieren zijn nooit gekwantificeerd.

Horizontale overdracht van mens op mens bv. via seksueel contact is theoretisch mogelijk, maar wordt niet als belangrijk beschouwd. Verticale overdracht van moeder op kind tijdens de geboorte of via de moedermelk is ook mogelijk. De frequentie van een dergelijke transmissie is onbekend. Analyse (in 1985) van 51 ziektegevallen wees uit dat 18 patiënten jonger waren dan 3 jaar. Sero-epidemiologisch onderzoek gaf aan dat 63% van de kinderen in de leeftijdsgroep van 0-4 jaar en woonachtig op veehouderijen IgG antistoffen tegen *C. burnetii* bezaten. Bij 14 van 22 seropositieve vrouwen werd *C. burnetii* uit de placenta geïsoleerd en bij 11 van deze 14 tevens uit de moedermelk. Hieruit blijkt dat wel ernstig rekening gehouden moet worden met - verticale - besmetting van pasgeboren kinderen door de eigen moeder.

## **8 Preventie en behandeling van ziekte bij de mens**

Van belang is een goede voorlichting over het infectiegevaar aan risicogroepen: e.g. veehouders, laboratorium- en slachthuispersoneel. Bij acute humane infectie kan een medicatie met tetracyclines (oxytetracycline, chloortetracycline, doxycycline) en macroliden (erythromycine) gedurende een periode van 3 weken de ziekteduur bekorten. Voorts wordt in de literatuur als medicatie rifampicine, quinolonen en trimethoprim genoemd. Behandeling dient vroeg te vlna

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mogelijk na het zien van de eerste symptomen te beginnen en volgehouden te worden tot 5 dagen na verdwijnen van de laatste symptomen. De behandeling van een chronische infectie is wezenlijk anders, hier is een combinatietherapie gedurende enkele jaren noodzakelijk.

In endemische gebieden dient consumptie-melk gekookt te worden.

In Australië is een effectief vaccin aanwezig en is vaccinatie verplicht in bepaalde beroepsgroepen. Het betreft een formaline-geïnactiveerd bacterine vaccin, gebaseerd op fase I organismen en werd gebruikt ter bescherming van slachthuispersoneel in endemische streken. Dit bleek voor een periode van tenminste 5 jaar effectief. Verder bestaan er een subunit vaccin op basis van zuur extractie en een vaccin op basis van een levende geattenueerde stam (M44) dat vnl. fase II antigenen produceert. Men gebruikt dergelijke vaccins ook voor laboratoriumpersoneel dat daadwerkelijk betrokken is bij isolatie van *C. burnetii*. Deze vaccins zijn niet commercieel verkrijgbaar.

## **9 Wering en bestrijding bij het dier**

Probleembedrijven zijn bedrijven waarbij serologisch hoge titers antistoffen gevonden worden, mogelijk vergezeld van acute abortusproblemen bij de landbouwhuisdieren. Het kan moeilijk zijn om veehouders op dergelijke bedrijven te overtuigen van de noodzaak om hygiënische maatregelen te nemen, vaak vanwege de afwezigheid van ziekteverschijnselen. Deze maatregelen zijn gericht op hygiëne rond de geboorte.

Voorafgaand aan het afkalven/aflammeren dienen drachtige dieren van de rest van de kudde te worden gescheiden en gehuisvest op een locatie waar reiniging en desinfectie goed mogelijk is. Na de geboorte is grondige desinfectie van grondoppervlak en al het materiaal dat door contact met placenta en vruchtwater en vruchtvliezen is gecontamineerd noodzakelijk. Placenta en vruchtvliezen zelf dienen ter destructie te worden afgevoerd.

Verzorgers en personeel dienen tijdens de geboorte en bij de reiniging en desinfectie erna voorzorgen te nemen tegen infectie door contact of inhalatie: dragen van plastic of rubber handschoenen en van mondkapjes.

Vaccinatie van landbouwhuisdieren op probleembedrijven met de hierboven genoemde bacterine vaccins is theoretisch mogelijk, maar is in Nederland niet gangbaar.

## **10 Wettelijke aspecten**

### **10.1 Wetgeving in relatie tot de mens**

In 1976 werd de ziekte opgenomen in het Uitvoeringsbesluit van de Wet Bestrijding Infectieziekten en Opsporing Ziekteoorzaken (WBIZ) groep B, en werd daarmee aangifteplichtig. In de nieuwe Infectieziektenwet, die binnenkort van kracht wordt, zal de ziekte opgenomen worden onder artikel 2, lid c van de "Regels ter afwending van de gevaren van Infectieziekten", en geldt er meldingsplicht voor het hoofd van het laboratorium.

Volgens de Warenwet dient rauwe melk voorafgaand aan consumptie eerst gepasteuriseerd of gekookt te worden. Nalatigheid in deze, of consumptie van rauwmelkse producten zoals boerenkaas afkomstig van seropositieve runderen betekent dus een potentieel risico voor infectie.

### **10.2 Wetgeving in relatie tot het dier**

Artikel 15 lid 2, sub c. van de Gezondheids- en welzijnswet voor dieren (GWWD) bepaalt dat de Minister van LNV een dierziekte als besmettelijke dierziekte kan aanwijzen indien de ziekte naar het oordeel van de Minister van WVC (nu VWS) "een ernstig gevaar voor de volksgezondheid oplevert". De toelichting maakt duidelijk dat dit artikel met name betrekking heeft op zoönosen, ook die waarbij het dier slechts als vector optreedt en slechts de gezondheid van de mens in het geding is. Op dit moment is Q-koorts niet in de regeling aangewezen.

Artikelen 77 t/m 81 stellen eisen aan vee (en pluimvee) bestemd voor uitvoer, en deze verschillen afhankelijk van het land van bestemming. In het geval van Q-koorts zouden deze slaan op de CBR serologie. Voor intracommunautaire handel worden geen eisen gesteld ten aanzien van Q-koorts. Een aantal Derde Landen eisen wel onderzoek, alvorens export daarvan van vee of sperma plaats mag vinden.

## **11 Aandachtspunten voor onderzoek**

### **11.1 Motivatie**

Onze huidige kennis van pathogenese, transmissie, epidemiologie en diagnostiek van *C. burnetii* infecties bij mens en dier is zeer beperkt en daarmee de mogelijkheden tot adequate preventie en bestrijding. Enerzijds fungeren onze landbouwhuisdieren als reservoir, anderzijds kan het agens onder wijzigende ecologische omstandigheden buitengewoon infectieus worden. Daarom heeft *C. burnetii* de potentie om onverwacht epidemische vormen aan te nemen. Daarbij komt het uitgesproken zoönotisch karakter van het agens, plus de stijging in de laatste jaren van het aantal seropositieve runderen en schapen in Nederland. Tenslotte is de

grote diversiteit van klinische symptomen, het voorkomen van infecties bij zeer jonge kinderen en het subklinisch verloop bij veel gevallen er oorzaak van dat de diagnose waarschijnlijk vaak wordt gemist. Dit leidt tot langere ziekteduur en mogelijk langere opnameduur in ziekenhuizen als ongewenst gevolg. Bovendien leidt het tot onderrapportage.

Bovengenoemde constatering is belangrijke argumenten voor meer en gericht onderzoek.

#### 11.2 Vraagstelling voor epidemiologisch onderzoek

- \* Hoe uitgebreid is *C. burnetii* aanwezig bij landbouwhuisdieren en gezelschapsdieren, gedifferentieerd naar diersoort en geografische regio in Nederland?  
Dit is te meten door serologisch onderzoek op runder- en schapenbedrijven, inclusief onderzoek naar risicofactoren op die bedrijven. Bij zelfkazende boeren en andere kleine zuivelaars, en op kinderboerderijen bestaat vanwege het risico van humane infectie een extra indicatie voor dergelijk onderzoek.  
Vanwege de onduidelijke rol die honden en katten spelen bij de mogelijke transmissie naar de mens is nader onderzoek naar het voorkomen van de infectie bij kleine huisdieren geïndiceerd.
- \* Hoe uitgebreid is de humane populatie in contact gekomen met *C. burnetii*, gedifferentieerd naar risicogroep en geografische regio in Nederland.
- \* Zijn er algemene relaties aantoonbaar tussen het voorkomen van *C. burnetii* bij landbouwhuisdieren en gezelschapsdieren, en humane populaties?

#### 11.3 Vraagstelling voor transmissie onderzoek

Onder andere in verband met preventie, bestrijding en bronopsporing is kennis vereist van factoren die bijdragen aan de transmissie van *C. burnetii* van dier naar mens.

In dit kader kan onderzoek worden gedaan naar de betekenis van kinderboerderijen, naar de eventuele overleving van *Coxiella* in melk na pasteurisatie, naar de overleving van *Coxiella* in rauwmelkse producten (bv boerenkaas), naar het belang van andere dierlijke producten (bv. wol) en naar de rol van teken en wilde fauna.

#### 11.4 Vraagstelling voor diagnostisch onderzoek

Om bovenstaand onderzoek te kunnen uitvoeren dienen een aantal operationele vragen te worden beantwoord.

- \* Op welke wijze kan de verspreiding van *C. burnetii* onder dier en mens in Nederland doelmatig worden gevolgd? Hierbij kan naast de bestaande serologische controle van dieren die voor export zijn bestemd, worden gedacht aan de regelmatige controle van melk en andere producten van dierlijke oorsprong bestemd voor humane consumptie en aan adequate registratiesystemen van infectie en/of ziekte bij dier en mens.

- \* Welke serologische test is het meest geschikt voor routinematige screening op *C. burnetii* bij dier en mens? Hierbij moet worden gedacht aan (de ontwikkeling van) een robuuste - standaard - methode, die zowel vanuit het oogpunt van sensitiviteit, specificiteit en herhaalbaarheid, als vanuit het oogpunt van kosten-effectiviteit geschikt is voor grootschalig gebruik.
- \* Kunnen PCR en genotyperings technieken effectief worden toegepast bij de studie van de epidemiologie en transmissie van *C. burnetii*? Dergelijke technieken kunnen van belang blijken omdat hierdoor het agens direct kan worden aangetoond in verdacht materiaal. Zo zijn deze technieken nuttig voor eventueel pathogenetisch onderzoek.
- \* Om *Coxiella* te isoleren, te typeren en te vermeerderen, zou, wellicht als alternatief voor de huidige -vanwege de kans op laboratorium-besmetting riskante - eikweek, een weefselkweek opgezet kunnen worden met minder risico voor humane infectie. Dit zou ook nuttig kunnen zijn voor eventuele vaccinontwikkeling.

#### 11.5 Vraagstelling voor humaan/medisch onderzoek

- \* In hoeverre is er sprake van onderdiagnostiek en onderrapportage in Nederland?
- \* Welke factoren beïnvloeden de ernst van de ziekteverschijnselen bij de mens. Hierbij kan gedacht worden aan leeftijd, aan bepaalde bronnen of transmissieroutes (intensiteit van contact met dieren) die een ernstiger klinisch beeld als gevolg kunnen hebben. Welke groepen mensen risico lopen dient beter in beeld te komen.
- \* Wat is de rol van verticale transmissie van *C. burnetii* bij de mens van moeder op kind? Welke maatregelen zijn geëigend om het risico van neonatale besmetting via de moeder te beperken?

## 12 *Conclusies en aanbevelingen*

### 12.1 Conclusies

- \* *C. burnetii* komt endemisch voor in Nederland.
- \* Serologisch onderzoek toont hogere percentages infecties aan bij personen die intensief contact hebben met dieren en hun producten, dan bij de overige bevolking.
- \* Serodiagnostiek geeft een stijgende graad van infecties van met name rundvee weer.
- \* Hiermee stijgt ook het risico voor humane infecties.
- \* De meeste Q-koorts infecties bij de mens verlopen subklinisch maar de complicaties in chronische gevallen zijn ernstig en moeilijk te behandelen.
- \* Het is waarschijnlijk dat de ca 20 meldingen per jaar door het missen van de diagnose en onderrapportage in werkelijkheid een veelvoud van dit getal bedraagt.
- \* Er is geen medicamenteuze behandeling van dieren beschikbaar.



- \* Consumptie van ongepasteuriseerde melk en melkproducten vormen een potentieel risico voor humane infectie.
- \* Transmissie naar de mens kan plaatsvinden langs verschillende routes o.a. via besmette stofdeeltjes en aërosolen afkomstig van dieren, van moeder op kind en via consumptie van besmette zuivelproducten. Het is onbekend welke van deze routes onder Nederlandse condities belangrijk zijn.

Inspectie W&V, Regio Oost, 29 januari 1999.

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Coxiella\_serologie\_en\_kliniek\_Marseille\_Am.J.Med\_1992[1].pdf;  
Coxiella\_via\_melk\_Epid\_Inf\_2006[1].pdf; CT12-05-Tissot-Dupont-jni04[1].pdf;  
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hierbij een tweede poging; haalde je oude en nieuwe mailadres door elkaar.

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(69A)

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## Verwerpen: vermindert het risico voor mens en dier

### Abortus: drachtverlies bij het lammen

Drachtige schapen en geiten kunnen hun lammeren verwerpen. Dit voortijdig dood ter wereld brengen van de lammeren kan verschillende oorzaken hebben. Van de ziektekiemen die besmettelijk verwerpen kunnen veroorzaken, zijn de meeste niet zonder risico voor de mens. Een aantal gerichte maatregelen kan deze risico's voor de mens verkleinen.

### Administratie

Een goede administratie is een wezenlijk onderdeel van de bedrijfsvoering, ook in de agrarische sector. De meeste schapen- en geitenhouders houden een registratie bij van gedekte dieren. Dit maakt het mogelijk om oorzaken van eventuele problemen tijdens de dracht, zoals abortusproblemen, beter op te kunnen sporen.

### Algemene aanpak

De oorzaken van abortus bij kleine herkauwers kunnen infectieus en niet-infectieus zijn.

Bekende voorbeelden van niet-infectieuze oorzaken van abortus zijn een hond tussen de schapen, ziekte bij het moederdier, te weinig ruimte aan de voerbak en daardoor ontstane beschadiging van de vrucht en in sommige gevallen verkeerd gebruik van medicijnen of het zodanig uitvoeren van behandelingen dat dit met de nodige stress gepaard gaat.

Bekende oorzaken van besmettelijke abortus bij schape en geit zijn: *Toxoplasma gondii*, *Chlamydomphila* abortus, *Listeria monocytogenes*, *campylobacter*, *salmonella*, *border disease-virus*, *Yersinia pseudotuberculosis*, *Coxiella burnetii*, *Leptospira hardjo*, *Brucella* soorten en schimmels.

Uitgebreide achtergrondinformatie over deze ziektekiemen en de risico's daarvan voor de mens staan beschreven op [www.capraovis.nl](http://www.capraovis.nl).

### 8.1.1.1. Kleine herkauwers

De houder van kleine herkauwers die te maken krijgt met abortus onder zijn dieren, doet er verstandig aan zijn dierenarts te raadplegen. Samen zullen zij tot een aanpak moeten komen. Als zij er samen niet uitkomen wil GD daar graag bij helpen. Het allerbelangrijkste is namelijk, zeker als het om meerdere gevallen gaat, om eerst achter de oorzaak te komen.

### 8.1.2.2. Algemene aanpak

Bij het optreden van abortus op een bedrijf worden de volgende algemene maatregelen geadviseerd:

1. Verwijder het verwerpene dier uit het koppel.
2. Stuur verworpen vrucht en nageboorte op voor onderzoek.
3. Bied overige verworpen vruchten en nageboorten aan ter destructie.
4. Ontsmet, indien mogelijk, de plaats waar vrucht, vruchtwater en nageboorte terecht zijn gekomen.
5. Laat een ooi of geit die heeft verworpen geen andere lammeren zogen.
6. Zwangeren, jonge kinderen, ouderen en mensen met een verminderde weerstand zouden direct en indirect contact met verwerpene kleine herkauwers moeten vermijden. Op een bedrijf met een abortusprobleem moeten zij niet assisteren, niet in de stallen komen en geen contact hebben met de ongewassen kleren van iemand die heeft geassisteerd bij een verlossing.
7. Verwerk melk van verwerpene dieren niet rauw tot producten.
8. Stof, mest, hooi en stro kunnen op een besmet bedrijf verwekkers bevatten en voorkomen moet worden dat de wind voor verspreiding zorgt.
9. Rijd mest en stro bij voorkeur uit bij rustig weer en werk dit zo spoedig mogelijk onder.

### 3.2.9 Spoorzoek

Stuur, indien mogelijk, niet alleen de verworpen vrucht maar ook de nageboorte op voor onderzoek naar de Gezondheidsdienst voor Dieren. Van een niet-afgekomen nageboorte is meestal wel een gedeelte te mogelijk zijn. Bijna even belangrijk als het opgestuurde materiaal is de bij dat materiaal geleverde anamnese (het verhaal met de ziektebeschrijving). Daarbij gaat het vooral om:

- het stadium van de dracht,
- de leeftijd van de ooi,
- het aantal dieren dat heeft geaborteerd,
- het eventueel ziek zijn van de ooi,
- de vraag of er wel of geen problemen in een vorig jaar waren,
- de vraag of het zelfgefokte of aangekochte ooiën betreft,
- het soort voer dat wordt verstrekt,
- eventueel andere opmerkelijke feiten.

De diagnostiek is niet altijd eenvoudig en vaak moet meerdere keren materiaal voor onderzoek worden aangeboden. Bovendien is onderzoek niet gratis. Als eenmaal een diagnose is gesteld is daarmee het probleem nog niet opgelost: niet voor alle oorzaken bestaat een goede behandeling en gerichte preventieve maatregelen zijn ook niet altijd mogelijk. Toch raden wij het instellen van een behandeling zonder diagnose om een aantal redenen ten stelligste af.

### 3.3.11 Verlosving

Een schapen- of geitenhouder moet de oorzaak van zijn abortusprobleem kennen om gericht te kunnen ingrijpen. Nog belangrijker is het om te weten of de ziektekiem die de problemen veroorzaakt risico's heeft voor de mens: heel veel abortusverwekkers bij kleine herkauwers zijn namelijk niet zonder risico voor de mens. Mensen met een verminderde weerstand, jonge kinderen, oude mensen maar vooral zwangere vrouwen lopen een verhoogd risico om zelf ziek te worden na contact met zo'n ziektekiem. Zolang geen onderzoek heeft plaatsgevonden en dus nog niet vaststaat of er sprake is van besmettelijk verwerpen, is voorzichtigheid geboden. Op bedrijven waar nog geen diagnose is gesteld, zouden bovengenoemde risicogroepen niet moeten helpen tijdens de aflamperiode. Ze zouden ook niet in de stal moeten komen en zelfs niet contact moeten hebben met de ongewassen kleren van de partner die geassisteerd heeft bij een verlossing. Ook zouden bezoekers moeten worden geweerd uit de stal.

Nadere informatie kunt u ook vinden op:  
[www.capraovis.nl](http://www.capraovis.nl)  
[www.gddeventer.com](http://www.gddeventer.com)  
[www.rivm.nl](http://www.rivm.nl)  
[www.ggd.nl](http://www.ggd.nl)



De Gezondheidsdienst voor Dieren

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(69B)

# Q fever

Neil R Parker, Jennifer H Barralet, Alan Morton Bell

Q fever is a zoonosis with many manifestations. The most common clinical presentation is an influenza-like illness with varying degrees of pneumonia and hepatitis. Although acute disease is usually self-limiting, people do occasionally die from this condition. Endocarditis is the most frequent chronic presentation. Although Q fever is widespread, practitioner awareness and clinical manifestations vary from region to region. Geographically limited studies suggest that chronic fatigue syndrome and cardiovascular disease are long-term sequelae. An effective whole-cell vaccine is licensed in Australia. Live and acellular vaccines have also been studied, but are not currently licensed.

## Introduction

Edward Derrick named the illness he described in 1937 as Q [for query] fever,<sup>1</sup> "until fuller knowledge should allow a better name".<sup>2</sup> Within 10 years, the bacterium was described, reservoirs found, and the route of infection elucidated,<sup>1</sup> but the name has persisted—perhaps because researchers like using it in their article titles.<sup>3,4</sup> This review is primarily written for generalists, particularly those responsible for rural communities.

Derrick's description of nine Q fever cases from Queensland<sup>2</sup> is the fourth most cited article from the *Medical Journal of Australia*.<sup>5</sup> The name *Coxiella burnetii* reflects the almost simultaneous isolation of the organism by American and Australian researchers. Cox identified bacteria from ticks collected near Nine Mile Creek in Montana,<sup>6</sup> while Burnet's isolates came from Derrick's patients.<sup>7,8</sup>

## Microbiology

*C burnetii* was originally named *Rickettsia burneti* since it shares some characteristics with the Rickettsiae, such as being an obligate intracellular organism and having a tick reservoir. However, sequencing of the *C burnetii* 16S rRNA<sup>9</sup> and genome<sup>10</sup> has identified substantial homology with *Legionella pneumophila*.<sup>11</sup> Both these bacteria are in the gamma subdivision of the proteobacteria, distantly placed from Rickettsiae which belong in the alpha subdivision.<sup>12</sup> Although the adjective "rickettsial" is still applied to *C burnetii*,<sup>13-16</sup> this is not taxonomically correct.<sup>17</sup>

*C burnetii* is a pleomorphic gram-negative coccobacillus (figure 1).<sup>18</sup> Although the full life-cycle remains unclear,<sup>17,19</sup> small-cell variants (SCV) and large-cell variants (LCV) are easily distinguishable by electron microscopy.<sup>17</sup> The SCV is resistant to heat, pressure, and chemical agents<sup>17,20</sup> and survives well in the environment, whereas the LCV multiplies in the host monocyte or macrophage.<sup>17</sup>

After passive entry into the host-cell phagosome, *C burnetii* delays the fusion of the phagosome with lysosomes, presumably using this delay to change from SCV to LCV.<sup>17,21</sup> *C burnetii* uses the acidic (pH 4-8) fused phagolysosome as its "nursery".<sup>11</sup>

*C burnetii* has two antigenic states. Bacteria obtained directly from patients or laboratory animals are in phase I, but those obtained after repeated passage through

embryonated hens' eggs are in phase II.<sup>18</sup> During phase variation, chromosome deletions result in irreversible cell lipopolysaccharide changes.<sup>22</sup> The antibody response in acute disease is primarily to phase II organisms.<sup>18</sup> However, inactivated vaccines made from phase II organisms are poorly protective, so phase I bacteria are used in vaccine production.<sup>21</sup>

*C burnetii* isolates are genetically homogenous,<sup>9</sup> but can be differentiated by restriction fragment length polymorphisms, with related strains generally coming from adjacent geographic regions.<sup>24</sup>

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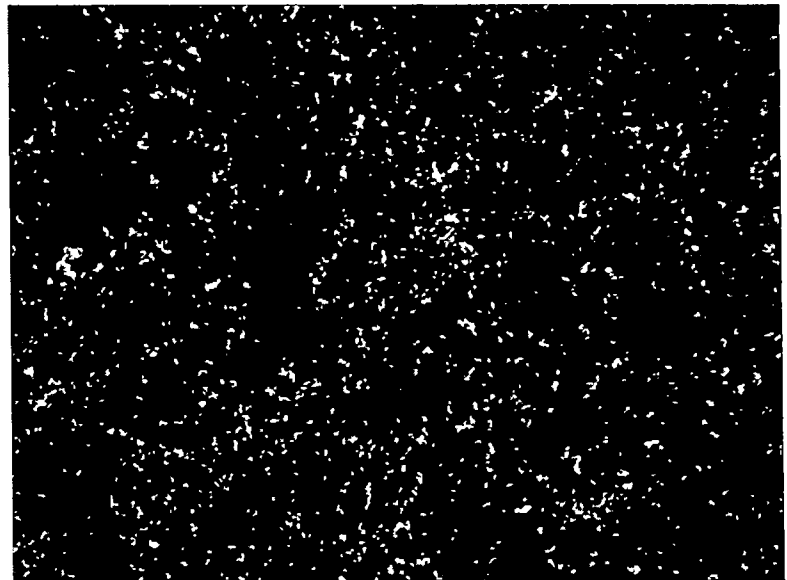


Figure 1: Positive serological reaction by indirect immunofluorescence assay. Fluorescent *C burnetii* bacteria (with permission from Cassy Faux, Queensland Health Pathology and Scientific Services).

## Search strategy and selection criteria

In September 2004, we searched for articles published in English from 1999 using MEDLINE, Biological Abstracts, Embase, PsycINFO, and CINAHL. A search with the terms "Coxiella", "burnetii", "burneti", "coxiellosis", "coxiell", and "Q fever" identified 309 journal articles. We also read older papers cited in these, or already known to the authors, and some papers published after September, 2004.

Panel 1: Case Study 1

A 59-year-old man had a sudden onset headache followed

Frank hepatitis with jaundice is rare,<sup>9</sup> but hepatomegaly and raised liver enzyme measurements are common. In a series from an Australian hospital, only one of 111

afebrile. On transfer to the intensive care unit of the regional hospital, a working diagnosis of viral encephalitis was made. His CSF had an elevated protein (1100 mg/L), an elevated white cell count ( $86 \times 10^6/L$ , 99% mononuclear cells) but a normal glucose test. He improved, and 5 days later was discharged back to his local hospital.

Q fever indirect immunofluorescence tests were positive on day 7 (see below).

Q fever antibodies

85% of those tested had abnormal liver function test results.<sup>11</sup> One of nine cases in Derrick's original series<sup>7</sup> was jaundiced.

**Chronic disease**

Endocarditis accounts for 60–70% of chronic Q fever<sup>12</sup> and in Marseille, France 15% of endocarditis is caused by *C burnetii*.<sup>16</sup> Fever is often absent, and vegetations are usually absent or small.<sup>16,17</sup> There is an average of

premature birth, and 43% abortion or neonatal death.<sup>49</sup> *C burnetii* may also cause problems in the absence of acute disease. A Canadian study of 4588 pregnancies recorded that seropositive women were three times more likely to have a current or previous neonatal death.<sup>14</sup>

#### Q fever in children

Most of the published articles on Q fever in children are case reports. A recently published review provides a good overview.<sup>15</sup> Although Q fever is believed to be rare in children, this might be because the diagnosis is often missed.<sup>15</sup>

The clinical presentation of Q fever in children is similar to that in adults, predominantly a self-limited febrile illness,<sup>50</sup> although some deaths are reported.<sup>15</sup> Chronic infection includes osteomyelitis and endocarditis,<sup>15,50,51</sup> and fever can relapse.<sup>52</sup> As in adults, asymptomatic infection is common.<sup>15,53</sup>

In Australia, Q fever might not be included in the differential diagnosis of febrile illness in children because it is seen as a disease of adult farmers and abattoir workers.<sup>54</sup> However, the disease has been recorded in children as young as three years of age in Queensland (unpublished notification data).

The Australian Q fever vaccine is not recommended for paediatric use. Prevention is therefore limited to avoidance of activities that place children at risk of infection, which is not always possible for children living on farms.<sup>50</sup>

#### Long-term sequelae

In 1996, *The Lancet* published two letters describing protracted fatigue following acute Q fever.<sup>55,56</sup> Symptoms

#### Panel 2: Clinical syndromes associated with Q fever

##### Acute disease

###### Common presentation

"Flu-like" illness, with varying degrees of pneumonia and hepatitis

###### Less common presentations

##### Neurological

Encephalitis, meningoenzephalitis, encephalomyelitis, meningitis, cerebellitis

Guillain-Barré syndrome, neuritis (including optic, brachial, and mononeuritis multiplex)

Myelitis and peripheral neuropathy, polyradiculopathy, extrapyramidal neurological disease

##### Gastrointestinal

Gastroenteritis, pancreatitis, splenic rupture, mesenteric panniculitis, acalculous cholecystitis

##### Genital

Orchitis, epididymitis, priapism

##### Cardiac

Myocarditis, pericarditis, myopericarditis

##### Haematological

Haemolytic uraemic syndrome, haemophagocytosis, anaemia (haemolytic and transient hypoplastic), rhabdomyolysis, bone marrow necrosis

##### Endocrine

Thyroiditis, inappropriate secretion of antidiuretic hormone

##### Cutaneous

Maculopapular or purpuric rash, erythema nodosum,

##### Renal

Glomerulonephritis,

##### Other

**Panel 3: Case Study 2**

A 58-year-old teacher's aide developed fever with sweats and chills, headache, myalgia and joint pains, together with loss of appetite. Five days later she travelled 1 h to the closest town to see her doctor. Initially, she was too ill to return. Serological tests done 1 month after the onset of illness and 2 days after returning to work showed a ratio of complement fixation test titre to phase II antigen of 1:2048. 5 weeks later this had fallen to 1:512. During the first week of recovery, tasks she had previously done easily, such as sewing, had to be carefully sequenced one step at a time. Although initially a source of great concern, improvement was rapid.

The illness occurred during lambing season, and the patient's husband was a farmer. Thus, she was in contact with newborn lambs and also with goats, pigs, dogs and cats. The season had been dry, and there were more sheep than usual around the house to facilitate hand feeding. She regularly washed her husband's clothes. The patient had been aware a vaccination programme had been ongoing in the nearest town, but had not been able to get to it.

She has a pre-existing "leaky" heart valve and needs follow up serology to look for the development of Q fever endocarditis.

The clinician suspecting Q fever must check for heart valve disease and immunosuppression, because these conditions predispose to the development of endocarditis.<sup>19</sup>

**Serology**

In 1995, Raoult and Marrie wrote that diagnosis is based exclusively on serology,<sup>12</sup> a statement that remains true for most clinical practice. Significant titres may take 3–4 weeks to appear,<sup>12,15</sup> so treatment should be started as soon as a clinician suspects the disease to be present. Only 39 of 100 people presenting with Q fever were positive on their first test.<sup>67</sup> People who are sero-negative when acutely ill are understandably reluctant to re-test once they are well, especially in rural areas where testing requires considerable travel (panel 3).<sup>68</sup> A history of illness in others with similar exposures can help, and in Australia, exposure to native animals is also important (panel 4).

Indirect immunofluorescence (IF) is the reference method for serological diagnosis.<sup>15,69</sup> Enzyme immunoassay (EIA) and complement fixation (CF) tests are also in routine use.<sup>69</sup> CF tests take longer to become positive, and are less specific and less sensitive than IF tests.<sup>15,69</sup> EIA tests have been promoted recently, but are no better than IF tests.<sup>69</sup> Serological cross-reactions occur with other infections<sup>4</sup> including legionellosis<sup>70</sup> and leptospirosis.<sup>69</sup>

In an apparent paradox, antibodies to the phase II organism are high in acute disease, and antibodies to the phase I organism are raised in chronic disease.<sup>18</sup> For acute Q fever, a four-fold rise in paired sera gives the highest specificity, but sufficiently elevated single IF tests also have good specificity. Raoult and co-workers judged an IF IgM ratio of 1:50 with a 1:200 IgG ratio to be 100% specific in their laboratory.<sup>18</sup> In

Queensland, individual samples with IF IgM titres of 1:160 or CF titres of 1:64 or more meet notification criteria if there is a compatible illness, but this CF criterion can miss nearly 50% of cases.<sup>69</sup> There is considerable variation in cut-off titres used, which might be explained by regional differences in background positivity.<sup>15</sup>

IF titres to phase I antigen of 1:800 or more are considered diagnostic for endocarditis.<sup>18</sup> Both IgG and IgA titres are usually high, although IgA titres add nothing to diagnostic precision.<sup>71</sup> Phase II IgG titres are the same or lower and IgM might be absent.<sup>18</sup> In persistent infection during pregnancy, phase I antibodies are usually high.<sup>45</sup>

IgM antibodies are usually undetectable after 4 months,<sup>18</sup> but can last 12 months or more.<sup>71,72</sup> CF antibodies usually fall within 3 years,<sup>71</sup> whereas nearly all of 92 people still had IgG to phase II antigen detectable by IF, 12 years after an outbreak.<sup>53</sup>

**PCR testing**

PCR holds the promise of timely diagnosis, since it should be positive before antibodies are detectable. However, the sensitivity of serum PCR has been disappointing. Of 100 patients with Q fever, only 18 were PCR positive.<sup>67</sup> There is also on-going controversy over PCR methods, with some tests branded insensitive and claims that others produce false positives through cross-contamination.<sup>62,74</sup> Serum contains few intracellular organisms, and use of buffy coat specimens may increase test sensitivity.<sup>67</sup> PCR is highly sensitive on tissue samples such as heart valves, which have higher numbers of bacteria.<sup>47</sup>

**Panel 4: Case Study 3**

A 20-year-old man became ill on December 25 with fever, cough, chest pain, and myalgia. He visited his doctor on January 1—the same day his 17-year-old brother also developed fever, cough, myalgia, and vomiting. A third, 14-year-old brother became ill just over a month later, with similar symptoms. He was not admitted to hospital, but the older brothers spent 2 and 4 days, respectively, as in-patients, and both were off work for 2 weeks. 6 months later, the oldest brother still had fatigue, sweats, and chills. Serological testing identified all three as having Q fever. The oldest brother's IF IgG titre rose from <1:10 to 1:40 in 5 days, and the other brothers both had IF IgM titres of 1:1280.

All lived in a rural area, and all three were kangaroo shooters, including the youngest who helped out at a local "chiller box" where commercial shooters bring animals they have harvested. The older brothers worked at a local kangaroo meat and processing works as well as having recent contact with sheep and on a cotton farm, respectively.



### Histology and other laboratory results

Histological findings are generally non-specific. Doughnut granulomas are characteristic but not specific for Q fever chronic hepatitis.<sup>9</sup> Immunostaining of tissue is useful<sup>17</sup> with both fresh and formalin-fixed samples.<sup>18</sup> In acute disease, the white cell count is usually normal, thrombocytopenia is present in 25% of cases, and liver enzymes are often elevated.<sup>18</sup>

### Disease management

#### Acute disease

Doxycycline, 100 mg twice daily for 14 days<sup>75</sup> is recommended for acute illness. Antibiotic treatment lessens the time in which the patient has fever,<sup>42</sup> and hastens recovery from pneumonia.<sup>14</sup> In a randomised controlled trial<sup>76</sup> and in retrospective studies, doxycycline outperforms other antibiotics including erythromycin.<sup>42,44</sup> Newer macrolides and fluoroquinolones show promise.<sup>42,75,77</sup> Starting antibiotic therapy after the third day of fever might not change outcomes,<sup>9</sup> although in the randomised trial cited above, the average duration of fever before starting antibiotics was 4.3 days,<sup>76</sup> and unlike the time before antibiotics were available, fever rarely lasts more than a month.<sup>12</sup> Anti-inflammatory agents could be useful when symptoms do not respond to antibiotics.<sup>78,79</sup> Co-trimoxazole is recommended for children younger than 8 years, and the newer macrolides might also prove useful.<sup>15</sup>

#### Chronic disease

Life-long antibiotic treatment has been recommended for endocarditis,<sup>9</sup> but 18 months of doxycycline (100 mg, twice daily) and hydroxychloroquine (200 mg, three times daily) could be enough.<sup>9,80</sup> Chloroquine raises the pH in the phagolysosome,<sup>12</sup> increasing the efficacy of doxycycline. Chloroquine levels between 0.8 mg/L and 1.2 mg/L,<sup>80</sup> and doxycycline levels over 5 mg/L<sup>15</sup> are associated with the best response. Most patients treated with this regimen have photosensitivity, and regular heart and eye examinations are needed.<sup>80</sup>

Treatment should continue until IgA and IgG antibodies to phase I antigen fall below 1:200,<sup>9</sup> although targets of <1:800 for IgG and <1:50 for IgA have also been recommended.<sup>80</sup> Follow-up for life might be needed.<sup>9</sup> Haemodynamic problems could require valve replacement,<sup>9</sup> and pericarditis can cause cardiac tamponade and require urgent intervention.<sup>27</sup>

Some clinicians recommend 12 months of doxycycline and hydroxychloroquine for those with a valvulopathy who develop acute Q fever as, if left untreated, a third of patients could develop endocarditis.<sup>39</sup>

Q fever during pregnancy is treated with co-trimoxazole until delivery, and serology to detect recrudescence is needed in subsequent pregnancies.<sup>14,15,48</sup> A year of doxycycline and chloroquine after delivery may prevent recrudescence.<sup>48</sup> Mothers should be advised that both *C burnetii* and doxycycline are excreted in breast milk.<sup>48</sup>

### Transmission and epidemiology

#### Bioterrorism

The incubation period is usually 2–3 weeks,<sup>75</sup> but is dose-dependent<sup>12,81</sup> with 4 days<sup>82</sup> and 6 weeks representing the extremes.<sup>12,61</sup> Claims that a single *C burnetii* organism can cause disease in a susceptible person<sup>11,61,83,84</sup> have contributed to *C burnetii* being classified as a category B bioterrorism agent. Although it has a low case fatality rate, it meets criteria such as ease of manufacture, stability in the environment, and ability to cause disease.<sup>61</sup> Q fever is also part of military history, with some units having rates of over 30% during the Second World War.<sup>20</sup>

The "single organism" theory could have arisen from a report that defined disease as serological response.<sup>81</sup> In this study, low doses induced asymptomatic seroconversion. It is correctly cited by a 1987 review that one organism can initiate infection.<sup>85</sup> However, this report is cited in another, which then claims that "a single microbe will cause substantial disease in nearly any exposed person".<sup>11</sup> As noted previously, asymptomatic infection is common, and this claim overestimates disease attack rates.

#### Animal reservoirs

A wide variety of animals can be infected with *C burnetii*, including: domesticated animals such as cows, goats, sheep, dogs, and cats; non-human primates; wild rodents and small mammals; big game wildlife; and non-mammalian animals, including reptiles, amphibians, birds (domesticated and wild), fish, and many ticks.<sup>46,45,86–88</sup> Although swine become infected and seroconvert, they rarely infect humans.<sup>86</sup>

Animals shed *C burnetii* in milk, faeces, urine, and especially in birth by-products.<sup>17,89–91</sup> A gram of infected placenta can contain enough bacteria to infect 100 000 000 guinea pigs.<sup>90</sup>

Despite some vaccine use,<sup>92</sup> little effort has been made to control *C burnetii* in animals, as economically significant illness is rarely recognised.<sup>45,83,93</sup> The true impact on income is uncertain, since *C burnetii* infection is associated with placentitis, abortion, infertility, and low birth-weight offspring.<sup>94–96</sup> High seroprevalence is associated with reproductive problems in dairy herds.<sup>86,96</sup>

Many seroprevalence surveys in animals have used convenience samples, or have followed human outbreaks, making generalisations difficult. Some reported rates are: in Quebec, 41% of sheep;<sup>97</sup> in East Turkey, 11% of sheep, and 6% of cattle;<sup>93</sup> in the USA, 41% of goats, 17% of sheep, and 3% of cattle;<sup>26</sup> and in Chad, 80% of camels.<sup>98</sup> Rates in dairy cattle in Japan range from 20% to 30%.<sup>41</sup> The seropositivity rate for herds is much higher; for example although only 6% of cattle were seropositive in East Turkey, 35% of herds had at least one seropositive animal.<sup>94</sup> Similarly in Quebec, where 41% of sheep tested positive, this included 89% of tested flocks.<sup>97</sup>

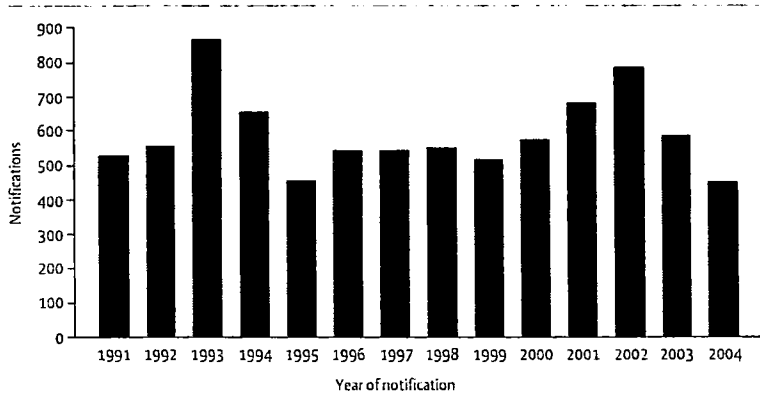


Figure 2: Q fever notifications in Australia by year  
Data extracted from the Australian National Notifiable Diseases Surveillance System (NNDSS).<sup>1,7</sup>

Prevalence increases with more intensive livestock operations.<sup>9</sup> Within herds, the prevalence of positive serology is cyclic,<sup>100</sup> being highest after the parturient period.<sup>101</sup> Chronic infection has been reported more often in cattle and goats than in sheep.<sup>9,47,86</sup> Transmission from animals to humans is influenced by contact between the two, local reservoirs, animal density, species diversity, and other environmental conditions.<sup>89</sup>

#### Direct exposure to animals

Most Q fever infections result from inhalation of infectious aerosol particles from parturient or slaughtered ruminants.<sup>1,47,88</sup> Environmental contamination related to these events lasts for months<sup>89</sup> and possibly years,<sup>102</sup> so inhalation of dust is also important.<sup>89</sup> Cattle, sheep, and goats are the main sources of human infections.<sup>9</sup>

In Australia the association with abattoirs has been emphasised.<sup>1,24</sup> Farming has received less attention as an occupational risk, although farmers were included in the first published series,<sup>2</sup> and now account for the majority of cases, at least in our rural region.<sup>101</sup>

Occupational exposure to animal products, particularly hides and wool, is also a risk, probably through the inhalation of tick faeces,<sup>104</sup> since ticks concentrate the organism in their faeces.<sup>9</sup> Humans rarely, if ever, acquire disease through tick bites.<sup>9</sup> Disease is also associated with consuming unpasteurised dairy products<sup>105</sup> and contact with contaminated clothing.<sup>106</sup>

#### Indirect exposure to animals

Many people with Q fever do not have direct contact with animals.<sup>11,102,107</sup> Windborne spread is well-recognised,<sup>49</sup> and studies suggest the organism can travel several kilometres.<sup>108,109</sup> Rural residents may be infected from trucks carrying cattle, sheep, or contaminated straw.<sup>66,105</sup>

Outbreaks occur in urban areas,<sup>11,66,109</sup> and suburban encroachment into rural areas will bring more people

into proximity with animals. Town planners need to consider the implications of situating saleyards, abattoirs and other animal-related developments near housing, and urban practitioners will need to include Q fever in their differential diagnosis of febrile illness.<sup>110</sup>

#### Person to person spread

Q fever is primarily a zoonosis, and person-to-person spread is rare.<sup>89</sup> There are two early reports of respiratory spread after autopsies,<sup>90</sup> and a recent case report of respiratory nosocomial spread,<sup>111</sup> although the proposed incubation period is long. Q fever has followed bone marrow transplant,<sup>112</sup> and there is one report of transmission by blood transfusion.<sup>111</sup> An obstetrician was infected when attending a pregnant woman, with vertical transmission also occurring in that case.<sup>114</sup> Sexual transmission probably occurs.<sup>115</sup>

#### Case rates

Q fever has been reported from most countries, but not in New Zealand,<sup>116,117</sup> and in a serosurvey, none of 190 Balinese were seropositive.<sup>118</sup>

There is consensus that Q fever is under-diagnosed and under-reported.<sup>11,25,28</sup> In north-western Australia, there were no notifications of Q fever for 15 years, yet 66% of 59 people presenting for vaccination had evidence of immunity.<sup>68</sup> The apparent rate in an area rises and falls with interest in testing,<sup>1,27,14</sup> and the sensitivity of the test.<sup>119</sup> The real incidence presumably varies over time<sup>120</sup> as contacts between people and animals change.<sup>25,92,104,121</sup> If asymptomatic infection is common in children, as suggested by a school outbreak,<sup>51</sup> few cases might be reported in regions where transmission intensity is high and most infections occur in early childhood.<sup>4,45</sup>

From 1991 to 2004, Australia had an average annual incidence of three notifications per 100 000<sup>122</sup> (figure 2) and has more complete national notification than most countries.<sup>9,25</sup> The reported incidence in Australia is strongly associated with the presence of both livestock and abattoirs.<sup>123</sup> Although nationally notifiable in the USA since 1999, data collection is incomplete,<sup>26</sup> with only 21, 26, and 61 cases reported in 2000, 2001, and 2002, respectively.<sup>124</sup> In the UK, about 70 cases a year are identified.<sup>102</sup> In France, between the start of 1994 and the end of 1998, an average of 100 acute and 32 chronic cases of Q fever were diagnosed by the national reference laboratory.<sup>125</sup>

Male-to-female ratios of disease of 5.3:1 have been reported in Australia<sup>121</sup> and 2.5:1 in France.<sup>125</sup> These ratios have been assumed to represent greater occupational exposure in males,<sup>101,107</sup> but higher rates of illness in males might also be due to greater susceptibility,<sup>28</sup> and oestradiol has a protective effect in animals.<sup>126</sup>

#### Serosurveys

Many serosurveys have been undertaken.<sup>89</sup> In a Netherlands study, between 31% and 73% of male blood

donors were seropositive. Females had less than half the rate in males in one town and greater than the rate in males in another. Children younger than 5 years had similar rates to adults from the same area.<sup>119</sup> Lower seroprevalence rates have been found in Nova Scotia (15%)<sup>120</sup> and in blood donors from Kent (4%).<sup>127</sup>

Serosurveys are difficult to compare since researchers use different tests and cut-off points.<sup>26,119,128</sup> The estimation of life-time exposure from prevalence surveys depends upon assumptions about antibody persistence and the effect of re-exposure.<sup>129</sup> These assumptions are sometimes,<sup>28</sup> but not always,<sup>119</sup> made explicit.

## Prevention

### Vaccination

The first case of Q fever identified in the USA was laboratory acquired,<sup>9</sup> so vaccines for laboratory staff were soon produced. These were effective, but large local reactions occurred, including sterile abscesses with draining sinuses. The reactions occurred in those with pre-existing immunity, including those previously vaccinated.<sup>24</sup>

Live,<sup>129</sup> whole-cell, and acellular Q-fever vaccines have been developed. A whole-cell vaccine is licensed in Australia (Q-Vax).<sup>29</sup> Acellular vaccines include a trichloroacetic acid (TCA) extracted vaccine (Chemovaccine) from the former Czechoslovakia,<sup>130</sup> and a chloroform-methanol residue (CMR) vaccine from the USA.<sup>111</sup>

The Australian whole-cell vaccine was licensed in 1989.<sup>121</sup> Between 1985 and 1990, no Q fever occurred in 2555 vaccinated abattoir employees, except in two who were already incubating the disease. There were 55 cases in 1365 unvaccinated employees.<sup>54</sup> Vaccine use in Australian abattoirs costs US\$4699 per quality-adjusted life-year (QALY) gained.<sup>29</sup>

Pre-vaccination screening is essential, and includes history, skin test, and serology. Serology is usually by IF at 1:10, and induration at the skin test site is sought one week after intradermal injection of diluted vaccine. The vaccine is only given if there is no history of Q fever disease or vaccination, and the blood test and skin test are both negative.<sup>29</sup>

In non-immune recipients, side-effects are equivalent to routinely administered vaccines.<sup>121</sup> Occasional large local reactions are reported,<sup>121,132</sup> presumably in people with previous immunity not revealed by screening. There has been a report of chronic fatigue syndrome in a vaccine recipient.<sup>60</sup>

The acellular (CMR and TCA) vaccines have been promoted as just as effective as the whole-cell vaccine, but with fewer side-effects.<sup>130,131</sup> However, few data from studies in people are available to support these claims.<sup>130,134</sup> Between 2001, and 2004, 128 878 doses of the Australian whole cell vaccine were distributed (personal communication from CSL Ltd) with post-marketing surveillance in place.<sup>132</sup>

### Other preventive measures

*C burnetii* must be cultured in biosafety level 3 laboratories.<sup>18,55</sup> Sawyer's review provides a summary of preventive measures for animal research laboratories.<sup>65</sup> Excluding individual seropositive animals is inadequate, since seronegative animals can also shed bacteria.<sup>115</sup> Animals should come from seronegative herds. Pregnant women, the immunocompromised, and those with known heart valve defects should be excluded from high risk situations, unless they are immune.<sup>65</sup>

### Future directions

The last decade has seen major improvements in serological diagnosis and the treatment of chronic disease. Serious long-term sequelae have been suggested, and the genome has been mapped.

Q-fever immunology remains a challenge. How does the bacterium thrive in the phagolysosome? Are long-term sequelae caused by persistence of the live organism or by persistence of specific antigens?

What is the incidence of disease, by region, occupation, and age group? Is there significant regional variation in long-term sequelae or disease severity? This information is needed to decide which groups to vaccinate, and to raise awareness about Q fever. Can strains be reliably differentiated, correlated with clinical presentations and linked to specific regions?

A test that is sensitive early in the illness will increase the apparent incidence, and increase the use of doxycycline in acute illness. Whether treatment of acute infection will prevent long-term sequelae and what the best antibiotic is for children and for pregnant women are still unknown. A randomised trial in adults comparing doxycycline with newer antibiotics would be welcome. If *C burnetii* causes pregnancy complications years after initial infection, should all seropositive women of child-bearing age be treated? Can research linking cardiovascular disease and past infection be replicated?

A vaccine not requiring pre-vaccination screening would increase accessibility, especially in remote areas. A vaccine for children is needed, and Derrick's 1973 assertion that "there is scope for a study of the incidence and clinical features of Q fever in Australian children" remains true.<sup>12</sup>

#### Conflict of interest statement

We declare that we have no conflict of interest.

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## Epidemiologic Features and Clinical Presentation of Acute Q Fever in Hospitalized Patients: 323 French Cases

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**PURPOSE:** To contribute to the knowledge of epidemiologic and clinical features of patients hospitalized with Q fever in France.

**METHODS:** We conducted a retrospective analysis of 22,496 sera submitted between 1982 and 1990 to the French National Reference Center for Rickettsial Diseases (NRC). The diagnosis of acute Q fever was based on an IgG titer greater than or equal to 1:200 and an IgM titer greater than or equal to 1:25 against phase II *Coxiella burnetii* antigen on an indirect immunofluorescence test (IFA). Fifteen cases prior to 1985 were diagnosed on the basis of a complement fixation titer greater than or equal to 1:8. A serosurvey of blood donors from Marseille was also conducted in 1988 on 924 sera, using IFA with a cutoff titer of 1:25.

**RESULTS:** The serosurvey conducted in 1988 showed a seroprevalence of 4.03%, without age or sex prediction. The incidence rate of acute Q fever detection at the NRC was 0.58 per 100,000 inhabitants over the 9-year period. Three hundred twenty-three clinical cases were diagnosed, rising from 1 in 1982 to 107 in 1990. In patients hospitalized for acute Q fever, there was a significantly higher sex ratio of males to females (2.3), which, coupled with the age distribution, indicated that elder males, who are overrepresented due to our recruitment bias, are more susceptible to *C. burnetii* infections. The mean age of the patients was 45.5 years, while the risk was increased in the 30 to 39 age group as well

as in the 60 to 69 age group. Usual epidemiologic risk factors were found in 20.1% of the cases. Hepatitis (61.9%) was a more common clinical presentation in our patients with Q fever than pneumonia (45.8%). This might reflect differences in strains of *C. burnetii* or the biology of the host. However, French farmers and stock breeders commonly drink unpasteurized raw milk from their cattle, which might indicate a relationship between hepatitis and infection via the digestive tract.

**CONCLUSION:** Our results indicate that many cases of acute Q fever are undiagnosed. A greater awareness of the disease and more extensive serologic testing of patients with symptoms compatible with Q fever may improve the situation.

Q fever is a worldwide zoonosis due to the rickettsia *Coxiella burnetii*, a strict intracellular organism, living in the phagolysosome of the host cell. The main characteristic of Q fever is its clinical polymorphism. In acute cases, the most common clinical syndromes are self-limited febrile illness of unknown origin, granulomatous hepatitis, pneumonia, or meningoencephalitis. In chronic cases, endocarditis is the main syndrome.

Throughout the world, the most common reservoirs for *C. burnetii* are cattle, sheep, and goats [1]. The organism is found in urine, feces, milk, and birth products of infected animals [2]. Human infections occur following inhalation of contaminated aerosols or ingestion of raw milk or fresh goat cheese. *C. burnetii* is ideally suited for this method of transmission due to its ability to withstand harsh environmental conditions and to its extraordinary virulence [3].

The epidemiology of Q fever in humans varies from country to country, which may reflect differences in strains of *C. burnetii* and in the biology of the host [4]. For example, in Australia, fever of apparent etiology is the most common clinical manifestation of acute Q fever [5], whereas pneumonia is the major syndrome in Nova Scotia [6], and granulomatous hepatitis in Ontario [7].

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The questionnaires were computerized using a database, called Sycvar, developed by the Biostatistics Laboratory of the Faculty of Medicine of Marseille, on a Vax computer. The main feature of Sycvar is its organization with several satellites containing each type of data (clinical, epidemiologic, biologic, serologic), bound to a base containing identification data. Up to 10 successive occurrences of the same data can be included in a satellite. Groups of patients were then sorted with criteria using one or several items.

### Statistical Methods

Pearson's  $\chi^2$  test and Fisher's exact test were used to compare the frequencies of qualitative data. A difference was considered significant when  $p < 0.05$ .

In order to compare the age distribution of our Q fever patients with that of the French population, we considered the cases of our study as the incidence of the detection of the disease at the NRC, and not as the incidence of the disease in France. Since this incidence rate was very low, a group of 1,000 persons with the same age distribution as the French population could be considered as a "control group." For each age group, compared with the rest of the population, we calculated an "odds ratio," which could be considered as the relative risk (RR) of Q fever detection at the NRC, depending upon the exposure to an age group. We calculated RR-1 to enhance the visibility of risk which becomes positive, whereas the protective effect becomes negative.

### Sources of Data

Demographic data on the French population were found in an on-line computer data bank called GEODATEL. Useful items for our study were the mean French population between 1982 and 1990 (55,474,682 inhabitants), its age distribution, its sex ratio (0.96), and the number of farmers (7.5%). The population of Marseille (862,134 inhabitants) and its age distribution were available only for 1982.

Data on nationally notifiable diseases were obtained from the statistic department of the "Direction Départementale des Affaires Sanitaires et Sociales" in Marseille.

## RESULTS

### Serosurvey

old: 11 positive/299 sera (3.7%); 43 to 54 years old: 14 positive/264 sera (5.3%); 55 to 66 years old: 2 positive/95 sera (2.1%). According to this distribution, the mean age of the population was 38.5 years and that of patients with positive sera was 38.6 years.

### Serologic Data

Between January 1985 and December 1990, 22,496 sera were tested against *C. burnetii* using IFA. This number rose from 2,290 in 1985 to 4,720 in 1990. Cumulative monthly distributions show a statistically significant increase of the number of tested sera between July and October ( $p < 0.001$ ).

A total of 5,166 of these sera (23%) were positive (i.e., titer greater than or equal to 1:25) and 1,754 of them (34% of positive sera and 7.8% of all sera) had a phase II IgG titer of greater than or equal to 1:200, with numbers increasing from 99 in 1985 to 550 in 1990.

The total number of cases of acute Q fever detected at the NRC between 1982 and 1990 was 323, rising from 1 in 1982 to 107 in 1990.

Our database contained those 323 records, collected from 81 hospital wards in France. Available epidemiologic, clinical, and biologic data have been collected for 274 of them.

### Epidemiologic Data

The number of patients included in each part of the study was determined by the presence of an answer (positive or negative) to all of the considered questions.

**INCIDENCE AND LETHALITY:** Since this study was neither exhaustive nor an epidemiologic survey, we could not consider our 323 cases of acute Q fever as the incidence of the disease in France, but rather they represented the incidence of the detection of the disease at the NRC. The incidence rate of this detection was 0.58 per 100,000 inhabitants over a 9-year period.

Among 207 patients for whom the data were available, 5 died within 19 days after admission (2.4%). The first one was a 66-year-old man, who died 19 days after admission for pneumonia, with heart failure and cardiac arrhythmia. The second one was a 75-year-old man, hospitalized for pneumonia (with *Pseudomonas aeruginosa* in sputum), who died 16 days later with heart failure. The third one was a 59-year-old man, hospitalized for pneu-



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## FOR DEBATE

# *Coxiella burnetii* and milk pasteurization: an early application of the precautionary principle?

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## SUMMARY

Stringency of milk pasteurization has been established on requirements for *Coxiella burnetii* as being the most heat-resistant organisms of public health significance. This paper discusses the estimation of the efficiency of pasteurization time/temperature combinations as required in regulations for food safety. Epidemiological studies have been interpreted as *C. burnetii* being a significant pathogen causing clinical disease through ingestion of milk. The paper examines the evidence and challenges the designation of *C. burnetii* as a foodborne pathogen. Consequently it questions the need for pasteurization parameters to be established on its heat resistance characteristics.

## INTRODUCTION

Milk pasteurization was introduced to prevent the oral transmission of tuberculosis, brucellosis, and other milk-borne infectious diseases. Early in the twentieth century, it was established that the cells of the tubercle bacillus were the most heat-resistant vegetative bacterial cells in milk. Therefore, the first recommendations for time and temperature combinations for pasteurization were established on this basis. However, pasteurization of milk is defined by the Codex alimentarius Committee for Food Hygiene [1] as 'a microbiocidal heat treatment aimed at reducing the number of any pathogenic micro-organisms in milk and liquid milk products, if present, to a level at which they do not constitute a significant health hazard. Pasteurization conditions are designed to effectively destroy the organisms *Mycobacterium tuberculosis* and *Coxiella burnetii*'.

Thus the international definition points to the need for the destruction of *Coxiella burnetii* to protect the health of milk consumers.

*C. burnetii* is the cause of Q fever, recognized in 1935 as an occupational disease of workers in abattoirs in Australia and as a tick-transmitted disease in the United States [2]. After the Second World War, a high prevalence of Q fever and serological conversion was observed among the population in Europe and North America, in regions where raw milk and raw milk products were commonly consumed [3, 4]. There was a consensus that milk should not be consumed raw and, therefore, milk pasteurization was recommended. Studies were conducted in several countries to check the efficiency of heat against *C. burnetii* [3, 5–9]. Eventually time-temperature conditions for pasteurization published by US researchers in 1957 [10–12] became the international standard.

In the first part of this paper, we will indicate how these researchers used a safety factor, and will show that the recommended heating treatment not only provides at least 4·7 decimal reductions or 'log kills'

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Table. Number of decimal reductions (log kills) of *C. burnetii* demonstrated experimentally, and values calculated for internationally recommended pasteurization time/temperature combinations, assuming a linear survival curve. Calculations were done with  $z = 4.34^\circ\text{C}$

Temp. (F)	Temp. (°C)	Decimal reduction time, D	Min. time of destruction plus 2 s.d.*	Corresponding number of decimal reductions	Combinations recommended by the authors	Corresponding number of decimal reductions	Presently recommended combinations	Corresponding number of decimal reductions
145	62.8	4.14 min	25.42 min	6.1	30 min	7.2		
	63	3.72 min					30 min	8.1
161	71.7	2.21 s	15.4 s	6.9	15 s	6.8		
	72	1.88 s					15 s	7.9

\* s.d., Standard deviation.

(rather than 5 as usually reported), but plausibly even more. In the second part we will question if Q fever is a foodborne disease and if pasteurization is scientifically justified for the prevention of Q fever.

#### Heat resistance of *C. burnetii*

A number of studies conducted to measure the heat resistance of *C. burnetii* did not lead to any convincing conclusion related to the efficacy of time-temperature combinations used in pasteurizers [3, 5-9]. Enright *et al.* [11, 12] put an end to this by publishing undisputed results validated through infection studies in guinea pigs by intraperitoneal inoculation. Since the appearance of specific complement-fixing antibody was significantly induced by killed *C. burnetii*, the authors demonstrated the presence of infective viable microbial cells by two consecutive passages on guinea pigs. They used whole raw milk from an experimentally infected cow containing  $10^5$  infecting doses in 2 ml ( $5 \times 10^4$  infective doses/ml) and heated in the laboratory at temperatures from 60.6 to 66.1 °C for different lengths of time.

For the shortest heating times, viable cells were still present. For the longest heating times, no viable cells could be found. Linear regressions of  $\log_{10}(\text{time})$  against temperature were calculated to determine two lines:

- the line A below which vials were still positive (containing at least one surviving cell);
- the line B over which no vial contained survivors (corresponding to the 'minimum time of destruction' according to the authors).

Positive as well as negative vials could be found between lines A and B.

A second series of experiments conducted by a regular commercial pasteurization plant from 68.1 to 72.8 °C confirmed the validity of the first series.

The authors based their recommendations for pasteurization conditions by adding two standard deviations or 97.7% confidence interval to the minimum times of destruction estimated by the regression B. They finally recommended two time-temperature combinations that have subsequently been universally recognized: 30 min at 62.8 °C (145 F) or 15 s at 71.7 °C (161 F).

The influence of temperature is, therefore, given by  $z = 4.34^\circ\text{C}$ . These recommendations were then simplified as follows [1, 13]: 30 min at 63 °C or 15 s at 72 °C, thus providing an extra safety margin. Assuming the survival curves are straight lines, this would achieve eight decimal reductions.

If, for a given temperature  $\log_{10}(a)$  is the ordinate of line A, and  $\log_{10}(b)$  the ordinate of line B, then the most probable time  $t$  for which there is one survivor per vial is [14]:

$$\log_{10} t = 0.63 (\log_{10} b - \log_{10} a) + \log_{10} a$$

and the decimal reduction time is calculated with [14]:

$$D = t / \log_{10}(N),$$

where  $N$  is the initial number of microbial cells per vial.

The experimental data of Enright *et al.* [11] are reported in the Table together with calculated  $D$  values and numbers of decimal reductions corresponding to recommended treatments.

The experimental work of Enright *et al.* [11, 12] was performed carefully. It was the first study regarding *C. burnetii* where the results were modelled using statistical regression, and where a safety margin was

used. However, the paper was not clear as to the origin of the *C. burnetii* cells subjected to heating: whether they were from one or several animals; and whether a single strain or a mixture of strains was used? The shape of survival curves was not studied, and it was not checked if the curve was linear or biphasic, i.e. having a second part or 'tail' indicative of a slower killing rate; therefore, the addition of two standard deviations by Enright *et al.* [11] did not guarantee a larger killing effect. While there is no certainty about the actual number of decimal reductions, one can nevertheless reasonably assume that, for the studied strain(s), pasteurization achieved between 4.7 [i.e.  $\log \log_{10}(5 \times 10^4)$ ] and 8 decimal reductions of *C. burnetii*.

#### Transmission of Q fever to people

It is well documented that *C. burnetii* is transmitted to man from infected wild or domesticated mammals, including farm animals and pets, by inhalation and by bites of haematophagous arthropods. The disease affects mostly farmers, veterinarians, researchers, abattoir workers and persons exposed to aerosols in dwellings situated down wind, or being in the vicinity of infected herds [15-49]. All outbreaks and sporadic cases reported for the last 50 years in Australia, France, Germany, Italy, and the United States were attributed to inhalation and sometimes to arthropod bites [23, 24, 26, 27, 31, 34, 36, 39, 47, 50-55]. No information is given of the infective dose.

In his comprehensive review, Wegener [3] noted the widespread opinion at that time: 'Milk is the most significant source among products of animal origin. Personnel in dairies and their families with the greatest use of raw milk are heavily infected in the regions with Q fever problems in North America and Italy.' This opinion on foodborne transmission was based on a survey in the United States where 10.7% of people consuming raw milk had a positive serological test, compared to 0.7% among non-exposed people. Other authors used the same argument on the basis of observations in England [4, 17, 56] and in other countries [18, 19, 25, 57-60]. Nevertheless several reports mentioned the oral route as possible but infrequent, circumstantial, or needing a very high dose [15, 33, 44, 61-63]. According to Enright *et al.* [11], milk of naturally infected cows contained the following numbers of guinea pig infective doses (ID) per millilitre: 1 (5 animals), 10 (5 animals), 100

(5 animals) or 1000 (3 animals), while the milk of an experimentally infected cow contained 10000 guinea pig ID/ml. These microbiological loads should be compared to those of inhaled air around infected animals or herds. However, we could not find any indication of these.

A few publications that reported a correct epidemiological approach did confirm that seroconversion indicated infection, but not the clinical disease. Fishbein *et al.* [18] reported a significant association between seropositivity and drinking non-pasteurized milk products whether people were in contact with goats or not, but the article did not provide information about clinical disease. Benson *et al.* [62] indicated that 35% of prisoners drinking infected milk had a positive serological test against 4% in a non-exposed control group; yet the authors emphasized that no manifestations of disease were recorded. Hatchette *et al.* studied an outbreak affecting goats in Newfoundland (Canada):

Risk factors associated with human infection [based on people with serological conversion, but where infection was not confirmed and no indication was given in the paper about manifestation of disease] on univariate analysis included being a farmer, milking goats, assisting with kidding, handling placentas, shovelling manure, having direct contact with goats, eating cheese made from goat milk, petting goats, feeding goats, being a worker, smoking tobacco, and drinking alcohol. When only a multivariate analysis was used, the following were significant risk factors for infection with *C. burnetii*: contact with the placenta ( $P < 0.001$ ), smoking history ( $P = 0.001$ ), and eating cheese made from [pasteurized] goat milk ( $P = 0.022$ ). Consumption of goat milk itself was not associated with an increased risk of infection (OR 1.07) [30].

The authors concluded: 'The reason for the association between ingesting goat cheese and developing Q fever is not clear and suggests further study is needed. At present, this is an epidemiological association only, as *C. burnetii* has not been recovered from the goat cheese.'

There is also evidence from Australia that indicates direct contact (inhalation) with *C. burnetii* is more important in causing Q fever than other exposure including ingestion, as detected by immunological reactivity. Q fever has been a notifiable disease in Australia since 1977 with about 600 cases reported each year (range 202-870) [64, 65]. The majority of notified cases (60%) are from people employed in the meat industry as abattoir workers. About 30% of notified cases of Q fever are from the agricultural industry [64]. This would represent a Q fever

notification rate of 1240/100 000 and 164/100 000 for meat and agricultural sectors respectively. In contrast, immunological reactivity is more commonly found in the agricultural rather than the meat industry.

In Australia, immunological testing of people presenting for Q fever vaccination programmes for people at risk of infection in meat works or rural communities shows that prior to vaccination 17% of meat industry workers compared to 28% from the agricultural industries (including farm families) had positive reactions indicating previous exposure to *C. burnetii* [65]. All cows' milk sold in Australia must be pasteurized in accordance with Food Standards regulations and non-pasteurized milk is only available to farming families. It is also of interest to note that 85% of notified cases of Q fever in Australia are males and 70% of cases are between 20 and 50 years [65]. This pattern of disease is different from potential exposure through consumption of non-pasteurized milk.

Some authors accepting the foodborne transmission paradigm assumed that the form of the disease could be different according to the route of contamination: hepatitis for ingestion, pneumonia for inhalation [18, 28, 58, 66–70]. It is now recognized that this is not true [71].

## CONCLUSION

From what is reported above, it seems more than plausible that clinical disease of Q fever results only from inhalation of *C. burnetii* and sometimes arthropods bites. Ingestion of *C. burnetii*-contaminated milk or milk products may result in serological conversion potentially indicating infection but not necessarily clinical disease. In addition it is likely that seroconversion follows the ingestion of inactivated cells as well as of live cells. Therefore, one may question:

- (1) Should Q fever be still listed among the foodborne zoonoses?
- (2) Should temperature and time conditions for milk pasteurization still be based on the heat resistance of *C. burnetii*?

If the answer is 'no' to both questions, the historical decision to pasteurize milk in order to kill *C. burnetii*, made almost 50 years ago, could be considered retrospectively as an early example of the application of the precautionary principle.

## ACKNOWLEDGEMENTS

We acknowledge collaboration with A. Mimouni. Part of this work is a contribution by one of us (O.C.) to a report to the French Food Safety Agency (AFSSA).

## DECLARATION OF INTEREST

None.

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## Fièvre Q actualités

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Unité des Rickettsies  
 Centre National de Référence  
 CNRS UMR 6020  
 Faculté de Médecine  
 Marseille

## La Fièvre Q


- ✓ Décrite par DERRICK en 1935 en Australie
- ✓ Zoonose ubiquitaire
- ✓ Due à *Coxiella burnetii*
- ✓ Réservoir animal
- ✓ Maladie humaine: polymorphisme clinique
  - ↳ Fièvre Q aiguë
  - ↳ Fièvre Q chronique

### Primo- Fièvre Q aiguë : infection

- ✓ Episode fébrile isolé 13 %
- ✓ Syndrome pseudo-grippal 40 %
- ✓ Hépatite granulomateuse +++ 40 %
- ✓ Pneumopathie 17 %
- ✓ Formes rares
  - ↳ Méningo-encéphalite
  - ↳ Myocardite - Péricardite
  - ↳ Eruption

Asymptomatiques : 60%


Hospitalisation : 2 %



Tissot Dupont H et al. Am J Med 1992;93:427-434  
 Raoult D, Tissot Dupont H et al. Medicine 2000; 79:109-123

### Fièvre Q chronique

- ✓ Endocardite à hémocultures négatives
  - ↳ Fait toute la gravité de l'affection (léthargie 25 - 60 %)
  - ↳ Lésions valvulaires préexistantes
- ✓ Infection sur matériel prothétique
  - ↳ Prothèse valvulaire
  - ↳ Prothèse vasculaire
  - ↳ Prothèse articulaire



Brouqui P et al. ArchInt Med 1993;153:642-648

### Fièvre Q aiguë → chronique

38 % des valvulopathes qui présentent une fièvre Q aiguë développent une endocardite dans les 2 ans

1 à 2 % de valvulopathes dans la population générale

0,3 % à 0,6 % des patients présentant une fièvre Q aiguë développeront une endocardite

↓  
 Dépister les valvulopathies chez les patients qui présentent une fièvre Q aiguë

↓  
 Dépister la fièvre Q chez les valvulopathes fébriles

### Fièvre Q et grossesse

- ✓ Peut être asymptomatique
- ✓ Avortement ou prématurité > 50 % des cas
- ✓ Primo-infection durant une grossesse
  - ↳ Profil sérologique d'infection aiguë
- ✓ Réactivation lors d'une nouvelle grossesse
  - ↳ Profil sérologique d'infection chronique
- ✓ Problème de Santé Publique
  - ↳ 1 cas de fièvre Q pour 540 grossesses
  - ↳ Toxo : 1 - 4 p. 1 000 - Rubéole : 0,2 p. 10 000

Stein A et al. Clin Infect Dis 1998;27:592-596

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## Fièvre Q et grossesse

- ✓ Traitement systématique en cas de positivité
  - ↳ Bactrim Forte<sup>®</sup> 2 cp/j
  - ↳ Pendant toute la grossesse (non bactéricide)
  - ↳ Surveillance des effets indésirables tous les 15 jours
- ✓ A l'accouchement
  - ↳ Précautions - Culture du placenta
  - ↳ Allaitement contre-indiqué
  - ↳ Sérologie post-partum
    - Profil d'infection aiguë ou convalescent : RAS
    - Profil d'infection chronique : traitement éradicateur

## Recommandations du CNR

Population générale  
Taux d'incidence estimé : 0,5 pour 1000 / an

- ✓ Penser à la fièvre Q
- ✓ Rechercher les valvulopathies en cas de fièvre Q
- ✓ Valvulopathes : sérologie systématique devant
  - ↳ Tout épisode fébrile inexpliqué
  - ↳ Toute asthénie inexpliquée
- ✓ Femmes enceintes : sérologie systématique devant
  - ↳ Toute lésion anormale de grossesse
  - ↳ Tout épisode fébrile inexpliqué

<http://ifr48.free.fr>

## Recommandations du CNR

Population en contact avec les animaux  
Séroprévalence > 50 %

- ✓ Echographie cardiaque
  - ↳ systématique à la recherche de toute anomalie valvulaire y compris minime (Prévalence élevée surtout Bicuspidie aortique, Prolaps mitral)
  - ↳ Sérologie fièvre Q systématique en cas d'anomalie
    - Positifs
      - Prise en charge
      - Traitement
    - Négatifs
      - Surveillance
- ✓ Femmes enceintes
  - ↳ Sérologie fièvre Q systématique en début de grossesse
    - Positifs
      - Prise en charge
      - Traitement
    - Négatifs
      - Surveillance mensuelle
      - Eviter exposition

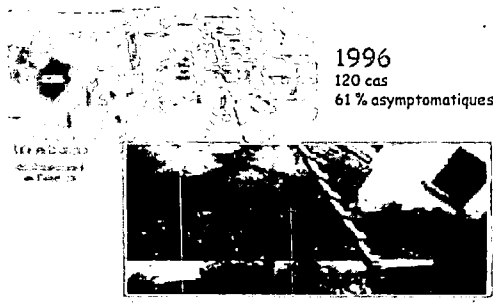
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## Fièvre Q : épidémiologie

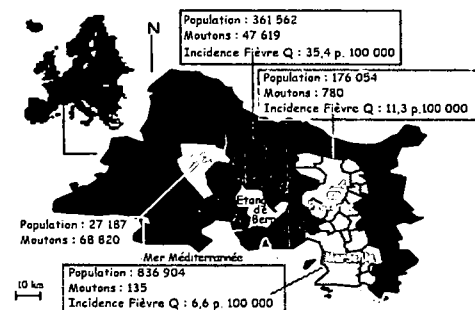
Retrouvée dans toutes les régions où elle a été recherchée

Sa distribution suit celle des rickettsiologues  
N'a pas été retrouvée en Nouvelle Zélande  
Exposition multifactorielle lors des épidémies

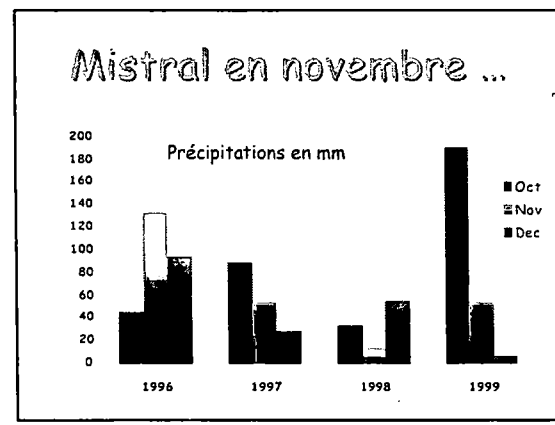
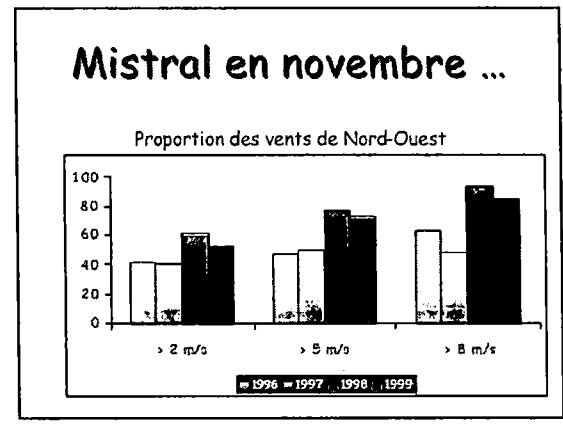
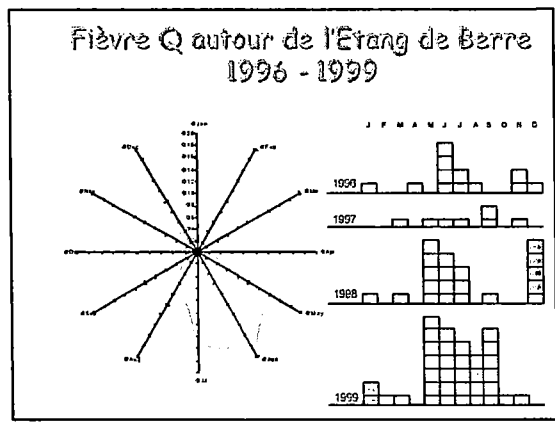
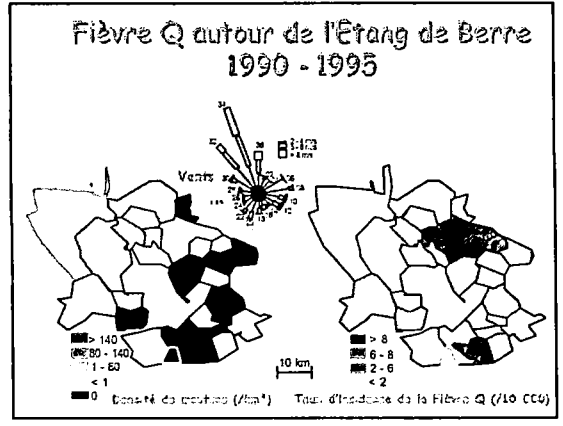
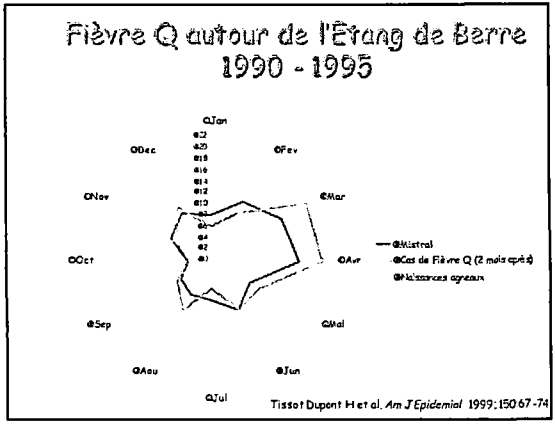
## Epidémie de Fièvre Q à Briançon



## Fièvre Q autour de l'Étang de Berre 1990 - 1995







### ...Fièvre Q en décembre !

- ✓ Confirmation du rôle du vent
  - ✗ Non contrôlable - Surveillance
- ✓ Facteurs d'exposition individuelle
  - ✗ Enquête cas-témoins
    - Ovins : OR = 3,1
    - Animaux nés : OR = 4
  - ✗ Ferme pédagogique
    - Cas : 4,7%
    - Témoins : 0

H et al. Emerg Infect Dis 2004; 10:1263-4

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## Perspectives de travail

Outils de détection  
et de veille  
épidémiologique  
Réseaux (InVS - OMS - MSA)  
Déclaration obligatoire

Information  
des médecins  
et des vétérinaires  
Zones d'élevage  
et de transit de bétail

Réflexion sur les  
cibles vaccinales  
Q-Vax - AMM  
Professions exposées  
Extension d'indications

Réflexion sur les  
terrains à risque  
Valvulopathes  
Femmes enceintes  
Immunodéprimés

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ORIGINAL ARTICLES  
Surveillance report

# CASE-CONTROL STUDY FOR RISK FACTORS FOR Q FEVER IN SOUTHWEST ENGLAND AND NORTHERN IRELAND

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Q fever (*Coxiella burnetii*) is thought to account for 1% (700 cases) of community acquired pneumonia in the United Kingdom each year, and can result in serious complications such as endocarditis. Although outbreaks have frequently been reported worldwide, the causes are often not clearly identified and there have been few studies of risk factors in sporadic cases.

We conducted a matched case-control study. Cases of acute Q fever in people aged over 15 years in southwest England and Northern Ireland were identified from January 2002 to December 2004. Controls were matched for age, sex and the general practice at which they were registered. Questionnaires asking about contact with animals, and leisure and work activities, were posted to cases and controls.

Questionnaires were completed by 39/50 (78%) of the cases and 90/180 (50%) of the controls. In the single variable analysis, occupational exposure to animals or animal products was the only risk factor associated with cases at the 5% level (P=0.05, odds ratio (OR) 3.4). Long term illness appeared to be significantly protective (P=0.03, OR 0.3). In multivariable analysis the strength of association between occupational exposure and illness remained high (OR 3.6, 95% confidence interval (CI) 0.9 to 14.8) and smoking emerged as a possible risk factor.

This is the first case-control study to identify occupational exposure to animals or animal products as the most likely route of infection in sporadic cases as opposed to outbreaks.

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**Key words:** Coxiella, Q fever, occupational exposure, case-control studies.

### Introduction

Q fever is a zoonotic infection caused by the rickettsial organism *Coxiella burnetii*. In the United Kingdom it is most commonly carried, often asymptotically, in sheep, cattle and goats, and is transmitted to humans by inhalation of aerosols. High concentrations of the organism are found in the placenta/placental fluids. *Coxiellae* can remain viable for months in the environment. The disease occurs most frequently in humans exposed to farm animals or in areas where animal products are handled [1]. Retrospective serological studies have shown evidence of high rates of past infection in farm workers, which suggests that many cases are often not identified at the time of illness [2].

The major clinical manifestations of Q fever are respiratory, cardiac and hepatic, although symptoms are often non-specific. *C. burnetii* is thought to account for 1% (700 cases) of community-acquired pneumonia in the UK each year, and although more serious complications such as endocarditis are rare, they do represent a significant burden of disease [3].

Although outbreaks have frequently been reported worldwide, the causes have often not been identified [4] and we have only been able to

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find one previous case-control study in the literature determining risk factors in sporadic cases [5]. The highest incidence of cases in England is consistently reported from the southwest and in an epidemiological review this rural region reported one third of all cases in England and Wales [3]. Northern Ireland reports even higher rates of Q fever per 100 000 population, with between 21 and 75 cases per year since 1990 [6].

### Methods

We collaborated with laboratories in southwest England and Northern Ireland to identify cases of Q fever for a matched case-control study to determine risk factors for sporadic infection. A required sample size of 43 cases was estimated using Epi Info. This size was based on a case-control ratio of 1:3, with 95% confidence and 80% power to detect an OR of 3.

Cases in patients resident in southwest England and Northern Ireland aged 16 years and over between 1 January 2002 and 31 December 2004 were identified by local laboratories and confirmed as acute by the Health Protection Agency Regional Laboratory in Bristol on the basis of a history of acute illness and the detection of specific immunoglobulins to *C. burnetii* phase 2 antigens in human sera (Coxiella burnetii-Spot IF; bioMerieux<sup>®</sup> sa, France, using sheep anti-human IgG and IgM conjugates supplied by The Binding Site Ltd, UK), to detect either a fourfold rise in IgM and/or IgG on paired sera, or IgM and IgG titres  $\geq 640$ .

Initially, three controls of the nearest age, same sex and registered with the same general practice were selected for each case (general practices in the UK cover an average population of 6000 people in the same geographical area). In 2003, the study duration was extended from two to three years and the number of controls per case increased to five, because case numbers had been lower than expected and there had been poor response rates, especially from controls.

Postal questionnaires, including questions about contact with animals, consumption of pasteurised/unpasteurised milk, and leisure and work activities within the four weeks before illness (past four weeks for controls), were sent to cases and controls. Non-responders

were sent one reminder after four weeks. Data were entered onto a Microsoft Access database. Where responses were not received and there was evidence of individuals only responding where the answer was 'yes', a 'no' response was entered for data that were missing. 'Don't know' responses were excluded from the analysis. Single variable conditional logistic regression was carried out using Stata (v8.2). Variables with  $P < 0.2$  in the single variable analysis were then included in a multivariable conditional logistic regression analysis. The study received approval from the appropriate local ethics committees.

### Results

Questionnaires were returned by 39/50 (78%) of the cases identified with acute Q fever and 90/180 (50%) of the controls. After excluding records without case or control matches, data from 34 cases and 77 controls were available for analysis, a ratio of 1:2.3. The age range for both cases and controls was 20-73 years (mean 47 and 48 years respectively). Twenty five (73.5%) of the case patients were men, and 9 (26.5%) were women. Over the three year study period, the majority of cases (63.6%) were reported between the months of March and June and were from a rural location (29/34 cases lived on a farm or within 3 miles of farmland). There was a clustering of four cases within a 10 mile (16 km) radius in one rural area. Further investigation did not identify any specific exposure common to these cases.

All cases reported sweating and/or a fever, 28 (82.4%) had a headache, 27 (79.4%) had respiratory symptoms (shortness of breath and/or cough), 27 (79.4%) experienced weight loss, 23 (67.7%) had joint pain and 20 (58.8%) had chest pain. Three (8.8%) had jaundice and 8 (28.6%) patients experienced other symptoms including vomiting, blurred vision, dizziness, extreme thirst, 'sore kidneys' and increased sensitivity of senses (taste and smell). The median duration of illness was 21 days. Twelve patients (35.2%) said they were still unwell at the time of completing the questionnaire.

In the single variable analysis, occupational exposure to animals or animal products was the only risk factor associated with cases at the 5% level ( $P = 0.05$ , OR 3.4, 95% CI 1.0 to 11.8) [TABLE 1]. Long term illness

TABLE 1

Single variable analysis of risk factors for Q fever, southwest England and Northern Ireland, January 2002 - December 2004

Risk factor	Cases exposed (%) (n=34)	Controls exposed (%) (n=77)	Matched OR (95% CI)	P value
Close contact with sheep	4 (11.8)	10 (13.0)	0.8 (0.2 to 2.7)	0.66
Close contact with cows <sup>1</sup>	2 (6.1)	4 (5.3)	1.5 (0.3 to 8.4)	0.63
Close contact with pigs	3 (8.8)	1 (1.3)	6.9 (0.7 to 70.9)	0.11
Close contact with goats	2 (5.9)	2 (2.6)	2.8 (0.4 to 20.4)	0.32
Contact with pets (Cats, dogs, birds and other animals)	31 (91.2)	65 (84.4)	1.6 (0.4 to 6.1)	0.50
Occupational exposure to animals/animal products (e.g. veterinarian, butcher, arable farmer)	9 (26.5)	8 (10.4)	3.4 (1.0 to 11.8)	0.05
Consumption of unpasteurised dairy products (milk or cheese)	1 (2.9)	5 (6.5)	0.5 (0.1 to 4.2)	0.51
Proximity to nearest farmland <sup>2</sup>	0	5 (7.9)		
	0 - 1.6 km	18 (62.1)	0.6 (0.2 to 1.7)*	0.38
	1.6 - 5 km	6 (20.7)	9 (14.3)	
Handling/use of organic matter (Straw, hay, manure and/or compost)	15 (44.1)	24 (31.2)	1.8 (0.8 to 4.1)	0.18
All river/lake water contact (Swimming, water sport and other contact in a river/lake water)	9 (26.5)	15 (19.5)	1.6 (0.6 to 4.7)	0.36
Other outdoors activities (Country walking, horseriding, gardening and other outdoors activities)	27 (79.4)	56 (72.7)	1.4 (0.6 to 3.7)	0.46
Long-standing illness/medical condition <sup>3</sup>	8 (24.2)	34 (46.6)	0.3 (0.1 to 0.9)	0.03
Smoking status	Never smoked	7 (20.6)	35 (45.5)	1
	Ex-smoker	17 (50.0)	27 (35.1)	2.6 (1.0 to 7.1)
	Smoker	10 (29.4)	15 (19.5)	2.4 (0.7 to 7.7)

\* For each additional increase in category

<sup>1</sup> Case n = 33; Control n = 76

<sup>2</sup> Case n = 29; Control n = 63

<sup>3</sup> Case n = 33; Control n = 73

TABLE 2

Multivariable analysis of risk factors for Q fever, southwest England and Northern Ireland, January 2002 – December 2004

Risk factor		Matched OR (95% CI)	P value
Long-standing illness/medical condition		0.2 (0.05 to 0.7)	0.006
Smoking status	Never smoked	1	0.03
	Ex-smoker	4.5 (1.3 to 15.2)	
	Smoker	2.5 (0.7 to 9.6)	
Occupational exposure		3.6 (0.9 to 14.8)	0.06

appeared to be significantly protective ( $P=0.03$ , OR 0.3, CI 0.1 to 0.9). In the multivariable analysis, long term illness remained significantly protective, and smoking emerged as a possible risk factor [TABLE 2]. Although the  $P$  value increased from 0.05 to 0.06 when added to the multivariable model, the strength of association between occupational exposure and illness remained high (OR 3.6, 95% CI 0.9 to 14.8).

### Discussion

Occupational exposure has been documented as a risk for Q fever in case series and outbreaks since the organism was first discovered in 1937 [7]. As far as we are aware, this is the first case-control study to identify it as the most likely route of exposure in sporadic cases. The temporal distribution of Q fever cases between March and June is similar to that seen in other studies in the UK and Spain, consistent with increased exposure to *C. burnetii* after animal births in spring [3, 8].

As expected, the majority of cases reported non-specific symptoms such as fever and sweating. However, cough and shortness of breath were consistent with respiratory tract involvement, the most common manifestation of Q fever in the UK. The low proportion of cases with jaundice supports the observation that hepatitis is not a common presentation in the UK [3], although patients with mild or granulomatous hepatitis would not necessarily have been jaundiced. Other countries have reported a higher proportion of cases with hepatitis, up to 40% of acute cases in one study in France [9].

The incidence of Q fever in the study regions fell almost as soon as the study started. It is possible that this was due to the effects of foot and mouth disease that occurred in England in 2001, just before the study commenced. Also, a low response rate, especially among controls, resulted in some variables being dropped from the analysis, and misclassification bias may have been introduced into the analysis by assigning missing values to 'no'. It is also possible that other risk factors

were not included in the study, such as exposure to rats, which have been identified as an important reservoir for *C. burnetii* in the UK [10].

The apparent protective effect of long term illness was surprising, but could reflect lower outdoor exposure to rural environments in people with long term illness. Apart from occupational exposure and a possible link with smoking, other risk factors studied did not reach statistical significance at the 5% level. Occupational exposure could explain at most a quarter of cases, but we did not expect to have sufficient statistical power to identify risk factors below an odds ratio of 3. Further studies to elucidate risk factors for sporadic Q fever should plan for a larger sample size. In the meantime, prevention and control measures should be directed at reducing the risk of occupational exposure [11].

### \* Members of the South West Q Fever Project Group:

David Dance (chairman), David Carrington, John Hartley, Simon Hill, Graham Lloyd, Conall McCaughey, Marina Morgan, Isabel Oliver, Hilary Orr, Mike Smith, Robert Smith, Brian Smyth, James Stuart

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# Een uitbraak van Q-koorts in Nederland – mogelijk verband met geiten

J.E.van Steenberg, G.Morroy, C.A.R.Groot, F.G.H.Ruikes, J.H.Marcelis en P.Speelman\*

Door melding en retrospectief onderzoek werden 73 patiënten met Q-koorts in 2007 bekend afkomstig uit een regio die zich uitstrekt van Tilburg in het zuidwesten tot Arnhem in het noordoosten. De infecties stamden uit de late lente, met name mei en juni. Er waren in deze regio 4 melkgeitenbedrijven met veel spontane abortussen door Q-koorts. Voor heel Nederland waren dit er in 2006 6 en in 2007 7. De maand april was in deze zuidelijke regio in 2007 uitzonderlijk droog. Zwangeren uit een klein gebied met de hoogste incidentie in het noordoosten van Noord-Brabant werden opgeroepen voor diagnostiek. Alle bevestigde patiënten werden gevolgd voor klachten en zondig echocardiografie. Een bron voor de infectie werd tot nu toe niet met zekerheid vastgesteld. Gedacht werd aan een combinatie van brede verspreiding onder geiten en verspreiding naar de mens door daarvoor gunstige klimatologische omstandigheden.

Q-koorts is een zoonose, veroorzaakt door *Coxiella burnetii*, een micro-organisme dat in grote hoeveelheden in de omgeving vrijkomt bij de partus van een geïnfecteerd dier. *C. burnetii* is bijzonder resistent tegen chemische en fysische invloeden en verwaait in droge klimatologische omstandigheden over grote afstanden.

Bij infecties van de lagere luchtwegen en in zeldzame gevallen bij hepatitis moet ook in Nederland Q-koorts in overweging worden genomen. Het is verstandig om clusters van atypische pneumonie aan de GGD te melden. De GGD heeft contact met de Gezondheidsdienst voor Dieren die weet welke dierziekten op dat moment heersen. Gericht zoeken kan de bron identificeren en uitschakelen. Bredere bekendmaking voorkomt vervolgens vertraging bij diagnostiek en therapie en helpt chronische vormen vroeg op te sporen of te voorkomen.

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Op vrijdag 25 mei 2007 deed dr.G.Weers-Pothoff, arts-microbioloog, na overleg met de internisten van Ziekenhuis Bernhoven, locatie Oss, een melding bij GGD Hart voor Brabant dat er een toegenomen activiteit was van ernstige pneumonieën die niet goed reageerden op antibiotica. Nog

geen 4 dagen later belde, onafhankelijk daarvan, een huisarts uit Herpen, R.Besselink, met de mededeling dat hij en zijn collegae huisartsen-in-opleiding in de praktijk opvallend veel patiënten met een atypische pneumonie hadden gezien. Hij vroeg of dit elders in de regio ook zo was. Dit bleek op dat moment niet het geval te zijn. Hierop besloten zij in overleg met de betrokken longarts de behandeling te richten op atypische verwekkers middels moxifloxacine. In samenwerking met een arts-microbioloog van het Canisius-Wilhelmina Ziekenhuis te Nijmegen werd gestart met retrospectief serologisch onderzoek onder 48 patiënten naar mogelijke verwekkers.

\* Namens het responsteam, waarvan de leden aan het einde van dit artikel worden vermeld.

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  - Hr.dr.C.A.R.Groot, longarts.
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  - Mw.F.G.H.Ruikes, arts in opleiding tot huisarts.
  - St. Elisabeth Ziekenhuis, afd. Medische Microbiologie, Tilburg.
  - Hr.dr.J.H.Marcelis, arts-microbioloog.
  - Academisch Medisch Centrum/Universiteit van Amsterdam, afd. Inwendige Geneeskunde, onderafd. Infectieziekten, Tropische Geneeskunde en Aids, Amsterdam.
  - Hr.prof.dr.P.Speelman, internist-infectioloog.
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Twee weken later kreeg de GGD een vergelijkbare vraag van een huisarts uit een naburige gemeente. Omdat de uitslag van IgM tegen *Mycoplasma pneumoniae* bij 7 van de eerste 19 serummonsters positief was, werd als werkhypothese aanvankelijk gedacht aan een lokale epidemie van *M. pneumoniae*-pneumonie. Sera van 3 in het ziekenhuis opgenomen patiënten uit Herpen waren in de immunofluorescentietest (IFT) positief voor antistoffen tegen *Coxiella burnetii*, de verwekker van Q-koorts. Uit meldingsgegevens van alle GGD's, waarvan een centrale registratie wordt gevoerd door het Centrum Infectieziektebestrijding van het Rijksinstituut voor Volksgezondheid en Milieu (RIVM), was al gebleken dat in mei-juni 2007 het aantal gemelde gevallen

van Q-koorts in zuidelijk Nederland hoger was dan gebruikelijk, namelijk 8 meldingen tegen normaliter jaarlijks 0-5 uit die regio.

Daarop volgde gericht onderzoek van de 48 sera met een complementbindingsreactie (CBR) op antistoffen tegen *C. burnetii*, waarbij bij 13 sera dergelijke antistoffen werden aangetoond. Met deze bevinding werd de werkhypothese over de vermoedelijke verwekker veranderd van *Mycoplasma* naar *Coxiella*.

Door passieve melding en actieve opsporing werden in deze epidemie in zuidelijk Gelderland en Noord-Brabant (van Tilburg tot Arnhem) sedert 1 januari 2007 tot 17 augustus 2007 retrospectief 73 gevallen van Q-koorts vastgesteld met een 4-voudige titerstijging of met een éénmalige hoge titer. Van 14 personen hiervan is het klinisch beeld nog niet volledig bekend. In de rest van Nederland werden in dezelfde periode via het passieve meldingssysteem slechts 5 gevallen gemeld (www.isis.rivm.nl; doorklikken op 'GGD surveillance', 'GGD Openbaar', 'Diagnose index', 'Q-koorts', selecteren 'Absoluut aantal meldingen per week') (figuur 1).

Navraag bij de Gezondheidsdienst voor Dieren (GD) leerde dat in 2006 en 2007 bij melkgeitenbedrijven in de

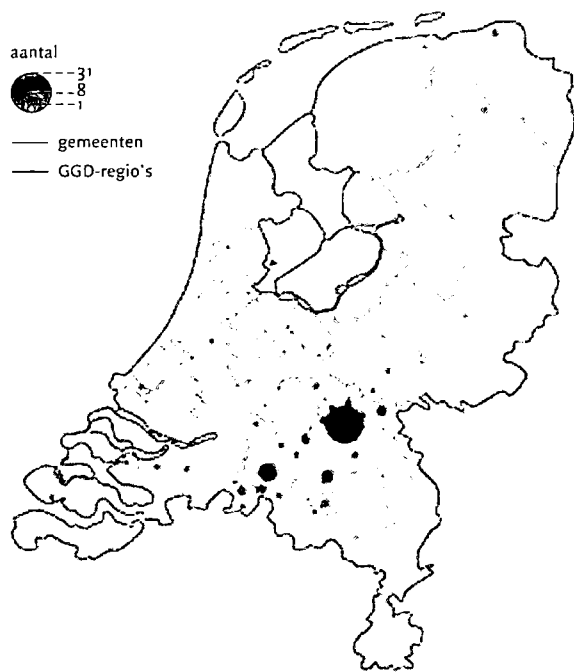
zelfde regio Q-koorts was aangetroffen. Q-koorts is weliswaar geen meldingsplichtige dierziekte, maar de verspreiding bij geiten is redelijk goed bekend. *Coxiella* leidt bij geiten, in tegenstelling tot bij de meeste andere diersoorten, tot klinische verschijnselen, met name spontane abortus ('verwerpen') en vroeggeboorte van niet-levensvatbare lammeren. Veehouders die met een dergelijk probleem geconfronteerd worden, zijn geneigd om via de eigen praktiserend dierenarts de GD in te schakelen voor diagnostiek.

#### COXIELLA BIJ KLEINE HERKAUWERS EN DE OVERDRACHT NAAR DE MENS

Q-koorts wordt, zoals gezegd, veroorzaakt door *C. burnetii*, een obligaat intracellulair groeiend micro-organisme uit de orde der *Protobacteria* (voorheen *Rickettsiales*; LCI-protocol Q-koorts, mei 2007. www.rivm.nl/cib/infectieziekten/Q\_koorts/Q\_koorts.jsp).<sup>1</sup> Q-koorts is een zoönose: runderen, schapen en geiten (herkauwers) zijn de primaire reservoirs van *C. burnetii*, maar ook huisdieren en vogels kunnen besmet raken. *C. burnetii* kan zich in teken handhaven en deze ectoparasieten zorgen waarschijnlijk voor overdracht tussen landbouwhuisdieren en andere dieren, maar slechts sporadisch naar de mens.<sup>2</sup> Dieren kunnen chronisch geïnfecteerd zijn zonder klinische symptomen en de bacterie uitscheiden in urine, feces, placentair weefsel en vruchtwater. Vooral bij de partus komen grote hoeveelheden *Coxiella* vrij in de omgeving. Na indrogen van deze uitscheidingsproducten wordt het micro-organisme verspreid via fijne stofpartikels afkomstig van bijvoorbeeld stallen, weilanden, ruwe wol en huiden.

De mens wordt met *C. burnetii* geïnfecteerd door inhalatie van deze gecontamineerde stof. Ook door consumptie van besmette, rauwe geitenmelk of geitenmelkproducten is besmetting mogelijk. Mens-op-mensoverdracht is nooit goed gedocumenteerd. Aangezien *C. burnetii* bijzonder resistent is tegen chemische en fysische invloeden, de infectie via inhalatie plaatsvindt en één organisme al ziekte bij de mens kan veroorzaken, is het soms erg moeilijk om de precieze bron van iedere infectie te achterhalen. Q-koorts bij mensen kwam in het verleden vooral voor in de buurt van Franse en Spaanse schapenhouderijen, en dan met name op windafwaarts gelegen plaatsen. De laatste jaren is humane Q-koorts ook meer gezien in Duitsland,<sup>3</sup> het Verenigd Koninkrijk,<sup>4</sup> Canada,<sup>5</sup> en in enkele landen waar de populaties van kleine herkauwers, dat wil zeggen schapen en geiten, toenemen, zoals in Bulgarije<sup>6</sup> en Slovenië.<sup>7</sup>

**Geiten.** Het laatste decennium worden in Nederland steeds meer melkgeiten gehouden, niet alleen door meer bedrijven, maar de bedrijven worden ook steeds groter, met name in Noord-Brabant. De stallen herbergen tegenwoordig tot 2000 geiten.<sup>8</sup> Er bestaat geen systematische monitoring van Q-koorts op geiten-, noch op schapenbedrijven.



FIGUUR 1. Geografische verspreiding van bevestigde gevallen van Q-koorts, bij de mens, waarbij de postcode bekend was (drie postcodes onbekend), in Nederland 1 januari-17 augustus 2007; totaal: n = 73; (bron: Rijksinstituut voor Volksgezondheid en Milieu, Centrum Infectieziektebestrijding).



Wel is bekend uit een deels retrospectief onderzoek dat er tot 2005 weinig Q-koorts onder geiten werd vastgesteld. In 2006 waren 6 bedrijven positief en in 2007 waren dit er 7. Beide jaren waren er 4 positieve bedrijven in de regio waar nu in 2007 de meeste patiënten gemeld zijn (figuur 2).

**Schapen en rundvee.** Door de GD worden jaarlijks ongeveer 2 maal zoveel verworpen schapenlammeren als geitenlammeren onderzocht. Tot nu toe is er slechts één besmet schapenbedrijf gevonden. De rundveesector heeft onlangs een eerste prevalentiestudie verricht, waarbij bleek dat in de tankmelk van 40% van de Nederlandse rundveebedrijven antistoffen tegen *Coxiella* kunnen worden gevonden (bron: Voedsel en Waren Autoriteit). Infectie bij rundvee verloopt over het algemeen asymptomatisch, hoewel in de literatuur tot 7% spontane abortus bij geïnfecteerde koeien wordt gemeld. In Nederland zijn nog geen rundveebedrijven met dergelijke problemen bekend. Bij een Nederlandse steekproef van 688 honden en 441 katten waren in het verleden bij 13 respectievelijk 11% antistoffen aantoonbaar.<sup>9</sup>

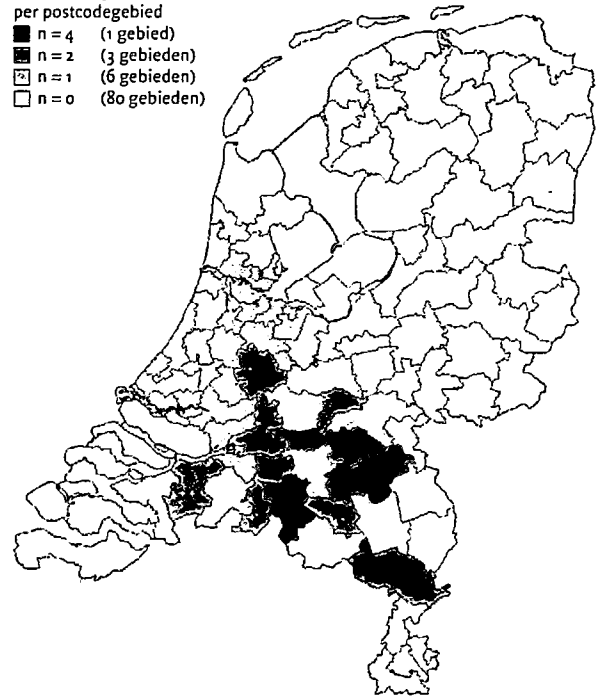
#### Q-KOORTS BIJ DE MENS

In Nederland zijn *Coxiella*-infecties bij de mens niet nieuw. In 1983 is middels IFT met een lage afkapwaarde vastgesteld dat 24% van de 359 bloeddonoren en 84% van de 221 dierenartsen tekenen had van een eerder doorgemaakte infectie.<sup>10</sup> Vrijwilligers op een kinderboerderij in Midden-Holland hadden even vaak antistoffen (80%) als een kleine controlegroep uit dezelfde regio.<sup>11</sup> In eerdere artikelen in dit tijdschrift werd terecht gesteld dat ziekte door *Coxiella* in Nederland weinig voorkomt.<sup>12-14</sup> Raoult et al. hebben berekend dat slechts 2 à 3% van de infecties leidt tot ziekenhuisopname.<sup>1</sup> In Ziekenhuis Bernhoven waren in april, mei en juni 2007 10 patiënten met een pneumonie opgenomen geweest afkomstig uit de eerdergenoemde huisartsenpraktijk te Herpen. Er werd destijds geen onderzoek verricht naar Q-koorts. De patiënten reageerden weliswaar slecht op initiële behandeling met amoxicilline of amoxicilline-clavulaanzuur, maar herstelden zonder dat een definitieve diagnose werd gesteld onder een andere antibiotische behandeling (moxifloxacin). Op dit ogenblik [17 augustus] is retrospectief bij 7 van hen *Coxiella* als verwekker vastgesteld. Uitgaande van het feit dat 2 à 3% van de infecties tot ziekenhuisopnamen leidt, zou dit overeen kunnen komen met 230 à 350 infecties in deze huisartsenpraktijk.

**Kliniek.** De incubatieperiode van Q-koorts bedraagt meestal 2-4 weken, maar varieert van 3-30 dagen. De meeste infecties verlopen zonder verschijnselen (60%), of met lichte griepachtige verschijnselen (20%). Bij ongeveer 20% van de geïnfecteerden ontstaat een ernstiger ziektebeeld met hoge koorts, soms koude rillingen, niet-productief hoesten, pijn op de borst, hevige hoofdpijn, spierpijn, misselijk-

aantal bedrijven met Q-koorts per postcodegebied

- n = 4 (1 gebied)
- n = 2 (3 gebieden)
- ▣ n = 1 (6 gebieden)
- n = 0 (80 gebieden)



FIGUUR 2. Aantal geitenbedrijven in Nederland waarvan bekend is dat er Q-koorts heeft geheerst (2001-2007), per 2-cijferig postcodegebied (bron: Gezondheidsdienst voor Dieren, Deventer).

heid, braken en diarree. Vaak ontwikkelt zich het beeld van een atypische pneumonie met weinig fysisch-diagnostische verschijnselen, maar met een duidelijk infiltraat op de thoraxfoto. Ook kan Q-koorts zich manifesteren als een acute hepatitis; sporadische infectiegevallen in Nederland betreffen vaker een pneumonie. Elders zijn ook pericarditis, myocarditis en meningo-encefalitis beschreven als manifestaties van Q-koorts.<sup>15</sup>

Mannen hebben vaker ziekteverschijnselen dan vrouwen en de ziekte verloopt ernstiger bij patiënten ouder dan 40 jaar. Bij kinderen verloopt de infectie overwegend zonder verschijnselen.

Bij 3 à 5% van de geïnfecteerden kan een chronische infectie ontstaan, met name bij personen met een al dan niet verborgen klepgebrek en bij zwangeren. Infectie tijdens de zwangerschap geeft ook bij de mens een verhoogde kans op spontane abortus of vroeggeboorte.<sup>16</sup> De belangrijkste klinische manifestatie van chronische Q-koorts is een endocarditis, vaak – maar niet uitsluitend – bij mensen met klepgebreken en soms bij zwangeren. Bij kweeknegatieve endocarditis moet men altijd denken aan de mogelijkheid van Q-koorts en dient men serologisch onderzoek te verrichten.<sup>17</sup>

In de eerste ziekte week kan men, als men Q-koorts over-

weegt, het organisme met PCR bij een kwart van de patiënten in serum aantonen.<sup>18</sup> Daarna is men aangewezen op onderzoek naar antistoffen. Afhankelijk van het laboratorium wordt een CBR of een IFT gebruikt. IFT is sensitiever en bij kleine aantallen minder tijdrovend dan CBR. Belangrijk is dat er altijd een tweede serum na minstens 2, maar liever na 3 weken wordt afgenomen. Op basis van het klinische beeld en een hoge CBR-titer in het eerste serum kan echter vaak al een voldoende sterk vermoeden worden uitgesproken om behandeling te kunnen starten. Bij IFT wordt het stadium van de infectie bepaald door detectie van IgG- en IgM-antistoffen tegen fase I- dan wel fase II-eiwitten van het micro-organisme. Bij acute Q-koorts staan de anti-fase-II-antilichamen op de voorgrond.<sup>18</sup> Er zijn serologische kruisreacties met *Legionella* mogelijk. Dit micro-organisme dient dus als verwekker te worden uitgesloten.

**Behandeling.** *Coxiella* is goed gevoelig voor doxycycline en de voorkeursbehandeling van een acute infectie bestaat uit doxycycline 200 mg 1 dd gedurende 2 tot 3 weken. De moderne fluorochinolonen zijn een goed alternatief. Zwangeren dient men te behandelen met trimethoprim-sulfamethoxazol 160 mg-800 mg 2 dd.

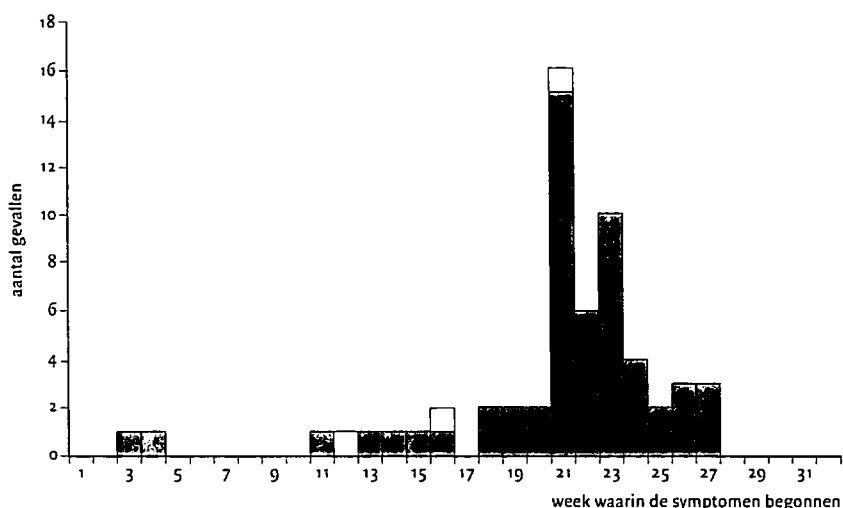
Therapie bij chronische infecties bestaat uit langdurige behandeling, dat wil zeggen tot 24 maanden, bijvoorbeeld met een combinatie van doxycycline en hydroxychloroquine of met een fluorochinolon en bij zwangeren trimethoprim-sulfamethoxazol.

#### BELOOP VAN DE EPIDEMIE

De voorjaarsepidemie van 2007 in Noord-Brabant en de verspreiding onder geiten in 2006 en 2007 laten zien dat acute

Q-koorts geen ongewone diagnose meer is in Nederland. Desondanks is *C. burnetii* slechts bij een minderheid van alle patiënten met pneumonie als verwekker aangetoond. In Ziekenhuis Bernhoven waren in de eerste helft van dit jaar 256 patiënten opgenomen geweest met een pneumonie, terwijl dit er in voorgaande jaren gemiddeld 170 waren. Het ziekenhuis zoekt nu retrospectief uit welk deel veroorzaakt zou kunnen zijn door *Coxiella*. Vooralsnog is er geen reden om in andere delen van het land het beleid voor diagnostiek en therapie van thuis opgelopen pneumonie te wijzigen.<sup>19</sup> In gebieden waarvan bekend is dat er Q-koorts voorkomt, verdient het aanbeveling om bij patiënten met een al dan niet atypische pneumonie ook onderzoek naar *Coxiella*-infectie in te zetten; in 2007 was dit een gebied dat loopt van Tilburg tot Arnhem. In het epidemische gebied met de hoogste incidentie, dat wil zeggen het noordoosten van Noord-Brabant, werd alle zwangeren onderzoek aangeboden op een mogelijk onopgemerkte infectie, om met antibiotische therapie abortus te voorkomen en hygiënemaatregelen bij de bevalling te kunnen nemen. Hierbij is inmiddels bij 1 zwangere een asymptomatische, acute infectie met *C. burnetii* aangetoond. Personen met een bewezen acute infectie worden gescreend op al dan niet verborgen klep-gebreken door middel van echocardiografie.

**Beleid bij geïnfecteerden.** Bij alle personen met Q-koorts neemt de GGD een brede vragenlijst af, gericht op contact met dieren en verblijf in de buitenlucht. Er werd tot op heden geen specifieke bron gevonden. Geografisch lijken de gevallen zich te concentreren rond geïnfecteerde melkgeitenbedrijven. Het lammerseizoen van geiten loopt in Nederland hoofdzakelijk van december tot in april. Op de meeste bedrijven blijven de bokken langdurig aanwezig,



FIGUUR 3. Verdeling van gevallen van Q-koorts, passief gemeld en actief opgespoord, in 2007 naar week van eerste ziekteverschijnselen van patiënten met een bekende eerste ziektedag (n = 59): (■) Noord-Brabant en Gelderland; (□) de rest van Nederland.

waardoor soms tot zelfs in augustus nog lammeren kunnen worden geboren. De uitzonderlijk warme en droge aprilmaand van 2007 heeft wellicht, in combinatie met de grote aantallen spontane abortus in open geitenstallen, voor een uitzonderlijk hoge blootstelling in mei en juni in het noordoosten van Noord-Brabant gezorgd.

**Verder beloop.** Het daaropvolgende natte seizoen heeft mogelijk de grootste hoeveelheden *Coxiella* van het land gespoeld en aëroge verspreiding verminderd. Tot 17 augustus was 5 juli de laatste ziektedag van de recentst bekend geworden patiënt (figuur 3). Het is onduidelijk of de humane epidemie van 2007 hiermee volledig voorbij is. Wat 2008 zal brengen, is afhankelijk van de dan heersende weersomstandigheden en verspreiding onder kleine herkauwers in het lammerseizoen. Omdat kleine herkauwers in heel Nederland worden gehouden, is het goed om in 2008 de les van Noord-Brabant ter harte te nemen en in het hele land bijzondere aantallen pneumonïeën direct aan de regionale GGD te melden. De GGD heeft contact met de Gezondheidsdienst voor Dieren en weet daardoor of en in hoeverre verspreiding van Q-koorts reëel is. Een snelle actie en gericht zoeken naar deze verwekker kunnen vertraging bij diagnostiek en therapie voorkomen en zorgen dat de chronische vormen bijtijds worden opgespoord. De GGD en de Gezondheidsdienst voor Dieren doen met het Centrum Infectieziektebestrijding onderzoek naar de specifieke omstandigheden die de epidemie van 2007 kunnen verklaren. De bevindingen zullen kunnen leiden tot overdrachtbepalende maatregelen in 2008.

Deze casus illustreert eens te meer het belang van alertheid op en het melden van bijzondere clusters van onverklaarbare ziekten door behandelaren voor een effectieve infectieziektebestrijding.

Een eerste stand van zaken van deze epidemie is gepubliceerd in het elektronisch epidemiologisch bulletin van het European Center for Disease Control (Eurosurveillance Weekly; 9 augustus 2007 ([www.eurosurveillance.org/iew/2007/070809.asp#2](http://www.eurosurveillance.org/iew/2007/070809.asp#2))).

Dr.A.Horrevorts, arts-microbioloog, Canisius-Wilhelmina Ziekenhuis, Nijmegen, verrichtte de serologische bepalingen bij de 48 patiënten uit de indexp praktijk. A.Leenders en dr.G.Weers-Pothoff, artsen-microbiologen, Jeroen Bosch Ziekenhuis, Den Bosch, tevens Ziekenhuis Bernhoven, locatie Oss, verrichtten de bepalingen bij de in de kliniek opgenomen patiënten. B.Schimmer en I.Karagiannis, epidemiologen, Centrum Infectieziektebestrijding RIVM, maakten de epidemiologische curve. Dr.P.Vellema en dr.P.Francken, dierenartsen van GD, faciliteerden het brononderzoek. C.Swaan verwerkte het commentaar van de auteurs.

Voor het onderzoek naar en de bestrijding van de beschreven epidemie werd een responsteam samengesteld, waarin naast bovenstaande personen en de auteurs zitting hadden: M.Hamans en R.van Oosterom (Voedsel en Waren Autoriteit), A.Rietveld en C.Wijkmans (GGD Hart voor Brabant), P.Schneeberger (Jeroen Bosch Ziekenhuis, Den Bosch), R.ter Schegget (GGD Zuid-Oost Brabant), M.Nabuurs (Canisius-Wilhelmina Ziekenhuis, Nijmegen) en A.Timen, T.Oomen, D.Notermans, T.Kortbeek, M.Langelaar en L.Wijngergangs (Centrum Infectieziektebestrijding RIVM).

Belangenconflict: geen gemeld. Financiële ondersteuning: geen gemeld.

Aanvaard op 13 augustus 2007

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Abstract

An outbreak of Q fever in the Netherlands – possible link to goats. – In 2007, 73 cases of Q fever were identified through reports and retrospective analyses; the affected region extended from Tilburg in the southwest to Arnhem in the northeast. The infections arose in late spring, particularly in May and June. Several spontaneous abortions due to Q fever occurred on 4 dairy goat farms in the same region. The national incidence of spontaneous abortion due to Q fever was 6 cases in 2006 and 7 in 2007. Climatically, this southern region was extraordinarily dry during April 2007. All pregnant women from a small region with the highest incidence in northeast North Brabant were called for diagnostic testing. Infected patients were followed for symptoms and ultrasound was performed as indicated. A definitive source of the infection could not yet be identified. Favourable climatic conditions were suspected as the cause for

the combination of widespread dissemination among goats and transmission to humans.

Q fever is a zoonosis caused by *Coxiella burnetii*, a microorganism dispersed in great numbers in the area in which an infected animal gives birth. *C. burnetii* is particularly resistant to chemical and physical factors and can disperse by air across large distances under dry climatic conditions.

Q fever should be considered in patients in the Netherlands who present with lower airway infection and, in rare cases, hepatitis. Reporting atypical clusters of pneumonia to the Municipal Health Service (GGD) is advisable. The GGD maintains close contact with Animal Health Services, which is aware of current infectious animal diseases. Targeted investigation can identify the source of infection and eliminate it. Greater awareness can prevent delays in diagnosis and treatment and help identify chronic forms at an early stage or prevent them. Ned Tijdschr Geneesk. 2007;151:1998-2003

## Geitenrijke gemeenten

*Tussen 1 april 2000 en 1 april 2001 is het aantal boeren dat melkgeiten houdt met enkele tientallen toegenomen tot 865. Het aantal melkgeiten nam toe tot 116 duizend dieren. In 1993 waren dit er nog geen 35 duizend en in 1984 telde het CBS er nog maar 3,3 duizend. De melkgeitenhouderij is een van de weinige sectoren in de landbouw waar groei in zit.*

Het merendeel van de 865 boerenbedrijven met melkgeiten hebben deze dieren uit pure liefhebberij naast andere landbouwactiviteiten. Ongeveer 60 procent van deze bedrijven houdt niet meer dan 19 melkgeiten, de meeste hebben er slechts een, twee of drie. Op deze bedrijven is ruim een procent van onze nationale melkgeitenstapel te vinden.

### Geitenmelkproducten

Verreweg de meest melkgeiten in ons land (96 procent) verblijven op een boerderij waar ze meer dan honderd soortgenoten hebben. De groei van de Nederlandse geitenstapel voltrekt zich dan ook voornamelijk op deze grotere bedrijven. In 1993 waren er in ons land nog 114 bedrijven met meer dan honderd melkgeiten. In 2001 zijn 310 boeren die dagelijks meer dan honderd melkgeiten verzorgen. Op deze bedrijven worden gemiddeld zelfs 360 melkgeiten gehouden. Op de grootste geitenbedrijven worden dagelijks circa zevenhonderd geiten gemolken. Het gaat op

deze grootste geitenbedrijven al lang niet meer om een hobby. De hoeveelheid melk die deze bedrijven produceren kan zich goed meten met die van een doorsnee melkkoeienbedrijf van grofweg vijftig melkkoeien. De melkgeit wint aan populariteit doordat de vraag naar zuivelproducten uit geitenmelk groeit. Dat laatste heeft wellicht ook te maken met de toename van enkele koemelkallergieën, waardoor meer consumenten aangewezen zijn op geitenmelkproducten.

### Meeste geiten in Brabant

Verreweg de meeste boeren die in het laatste jaar zijn overgeschakeld op melkgeiten wonen in Friesland, Gelderland of Utrecht. Overigens huisvest Noord-Brabant nog steeds de meeste melkgeiten. In deze provincie bevindt zich bijna veertig procent van de Nederlandse melkgeiten. Dit aandeel loopt overigens wel terug. In 1993 ging het hier nog om een aandeel van 45 procent. In Friesland, Overijssel, Flevoland, Gelderland, Utrecht en

Limburg neemt het aantal melkgeiten sinds 1993 sneller toe dan in de rest van het land. In Limburg en Overijssel is de groei het sterkst. Hier lopen inmiddels negenmaal, respectievelijk zesmaal zoveel melkgeiten rond als in 1993.

### Geitenrijkste gemeenten

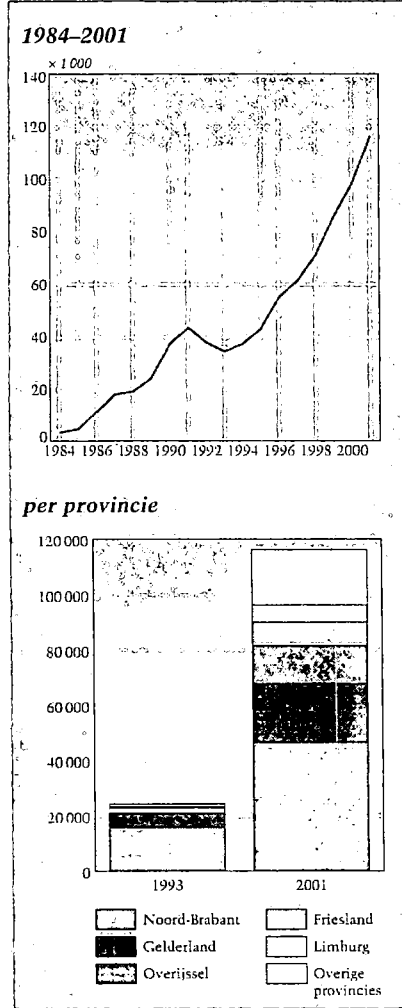
In de toptien van de geitenrijkste gemeenten bevinden zich maar liefst zes gemeenten uit Brabant. Alphen-Chaam en Oirschot voeren de lijst aan met respectievelijk 4,0 duizend en 3,5 duizend melkgeiten. Verder staan de Brabantse gemeenten Tilburg, Haaren, Lith en Maasdonk in de geitenrijkste toptien. Ook de Overijsselse gemeenten Hardenberg en Raalte scoren hoog met een paar duizend melkgeiten. Op de plaatsen 4 en 9 in de toptien staan de Gelderse gemeenten Ede en West Maas en Waal. ◀

Cor Pierik

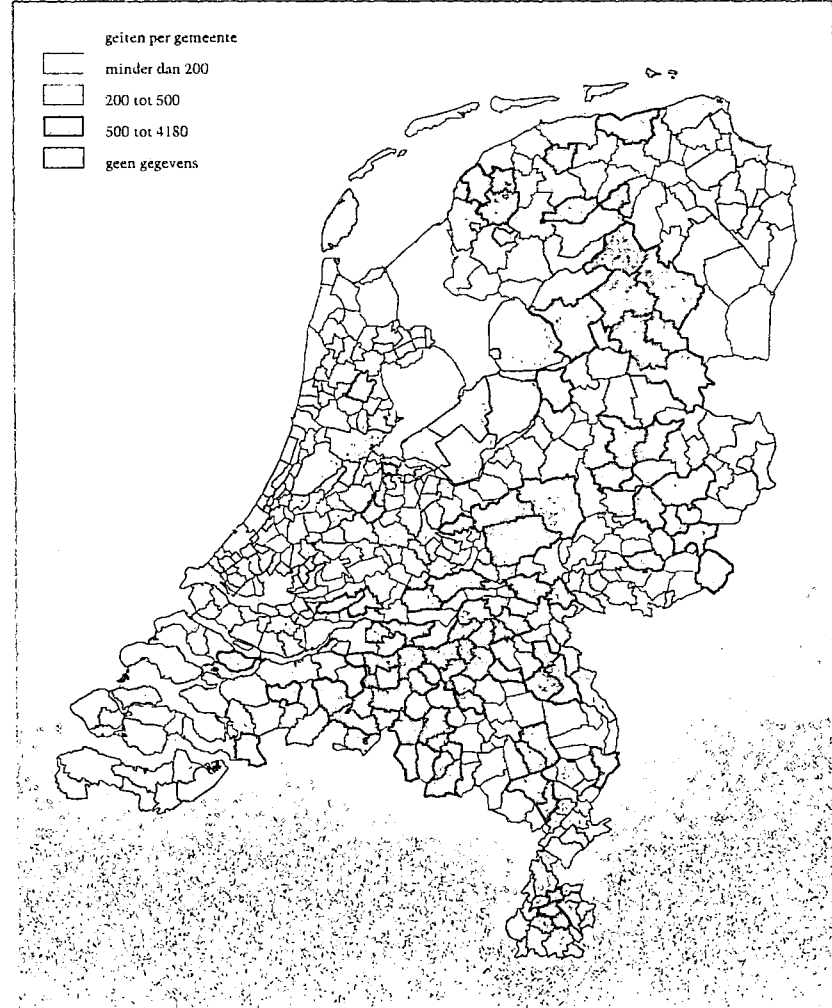
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**Melkgeiten**

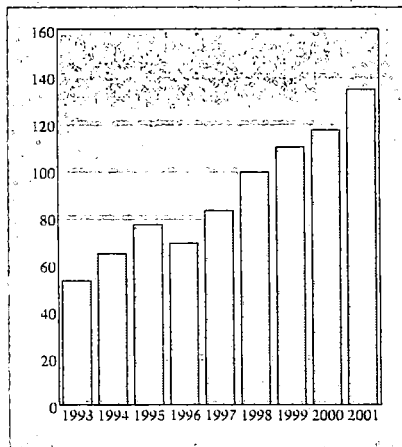


**Melkgeiten, 2001**

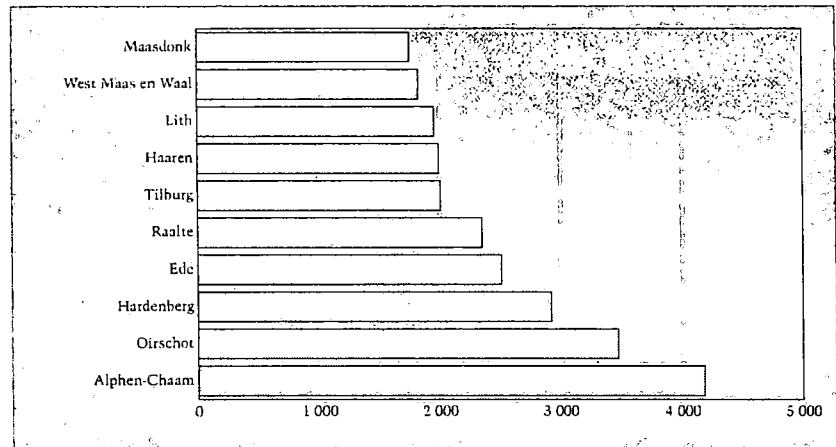


Actueel

**Gemiddeld aantal melkgeiten per bedrijf**



**Tien geitenrijkste gemeenten, 2001**



70C

Research

# Goat-Associated Q Fever: A New Disease in Newfoundland

Todd F. Hatchette,\* Robert C. Hudson,† Walter F. Schlech,\*  
Nancy A. Campbell,\* Jill E. Hatchette,\* Sam Ratnam,‡ Didier Raoult,§  
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In the spring of 1999 in rural Newfoundland, abortions in goats were associated with illness in goat workers. An epidemiologic investigation and a serologic survey were conducted in April 1999 to determine the number of infections, nature of illness, and risk factors for infection. Thirty-seven percent of the outbreak cohort had antibody titers to phase II *Coxiella burnetii* antigen >1:64, suggesting recent infection. The predominant clinical manifestation of Q fever was an acute febrile illness. Independent risk factors for infection included contact with goat placenta, smoking tobacco, and eating cheese made from pasteurized goat milk. This outbreak raises questions about management of such outbreaks, interprovincial sale and movement of domestic ungulates, and the need for discussion between public health practitioners and the dairy industry on control of this highly infectious organism.

*Coxiella burnetii* is an obligate intracellular pathogen known to be the causative agent of Q fever, a zoonosis with a worldwide occurrence (1). The organism has been found in many wild and domestic animals (1-3). The most common reservoirs of infection in humans are domestic farm animals such as cattle, goats, and sheep (4-6). *C. burnetii* is shed in urine, feces, and milk from infected animals and has a particularly high concentration in products of conception (7). The organism is highly infectious: Only one organism is required to produce infection under experimental conditions (8,9). Inhalation of aerosolized microorganisms is thought to be the most important route of infection in humans. However, ingestion of raw milk products has also been implicated (6).

Although *C. burnetii* can cause abortion and stillbirth, most animals have a persistent, relatively asymptomatic subclinical infection (10). Infection in humans usually manifests as a self-limiting febrile illness, pneumonia, or hepatitis (11). Most patients have an uneventful recovery; however, chronic infections such as Q-fever endocarditis and chronic hepatitis are uncommon but well-documented sequelae (12).

The diagnosis of Q fever is usually established by demonstrating seroconversion to *Coxiella* antigens in conjunction with an appropriate clinical history (13). *C. burnetii* can have two distinct antigenic presentations or phases; animals and humans develop antibody responses to both phases. In humans, phase II gives rise to the predominant antibody response in acute infection, while

response to phase I antigen is dominant during chronic infections (14).

In the spring of 1999, abortions were noted in goats on one farm belonging to a newly formed cooperative in rural Newfoundland. Aborted placenta had histologic evidence of *C. burnetii* infection. At the same time a number of farmers and their workers had a nonspecific febrile illness associated with severe headaches. Serologic testing revealed that these persons had recent infection with *C. burnetii*. No documented case of Q fever had previously been reported in Newfoundland. An epidemiologic investigation and serologic survey were started in April 1999 to determine the extent of the outbreak in animals and humans, the nature of the clinical illness, and risk factors for Q fever associated with this outbreak.

## Methods

### Identification of Cases

The cooperative consisted of eight goat farms within a 170-km<sup>2</sup> area of rural Newfoundland, with a population of approximately 8,000 people (Figure 1). In April 1999, farmers, workers, and contacts (family members of the farmers or workers and other persons who may have had contact with the farms) were interviewed by using a detailed questionnaire. Workers included persons who were involved directly with animal care as well as carpenters and other farm laborers. Serum samples were drawn to determine the presence of antibodies to *C. burnetii*. Family physicians in the area submitted serum samples from all patients in their practices who had been seen with symptoms compatible with Q fever.

The diagnosis of acute *C. burnetii* infection in participants was based solely on serologic findings as

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## Research

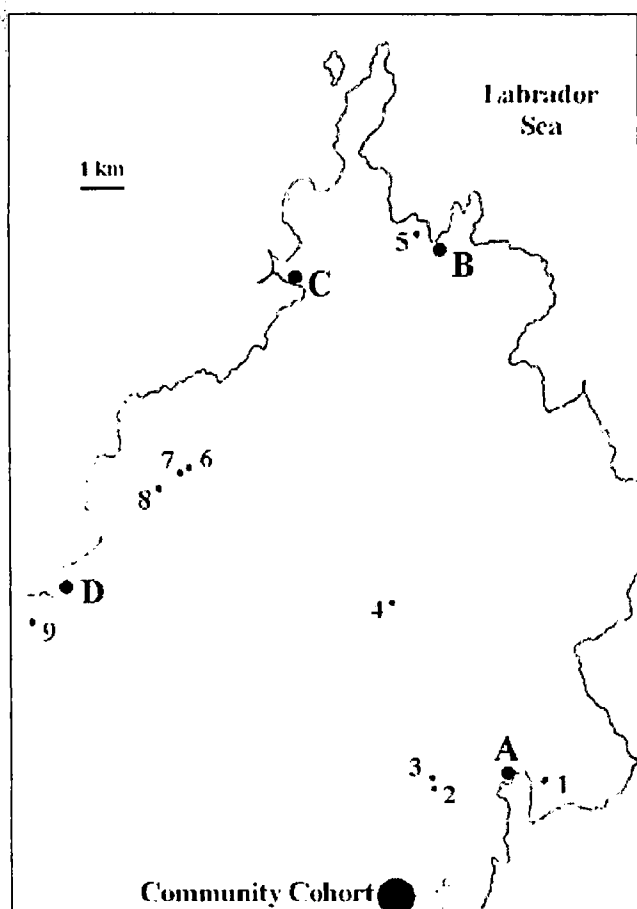


Figure 1. Map of the Newfoundland goat cooperative showing the farms (2-9) in relationship to the surrounding communities (A-D, the area from which the community cohort was derived). (Note: farm 1 is not directly involved with the cooperative.)

described below. In July 1999, follow-up serum samples were obtained to determine further evidence of seroconversion. In addition, 2 weeks earlier, serum was collected from 154 volunteers from adjacent communities (community cohort) and a questionnaire was completed for comparison with the outbreak cohort.

Serum samples were collected in May 1999 from 387 random blood donors, primarily from urban areas. These samples were used to determine the background seroprevalence of *C. burnetii* infection in Newfoundland.

### Source of Animals and Identification of *C. burnetii* Infection in Animals

Although a few locally raised goats were present in the community before the cooperative was established, the eight farms received shipments of goats from Ontario, Nova Scotia, Prince Edward Island, and Maine in the summer and fall of 1998. At the time of the outbreak, 174 goats were within the cooperative, with 10 to 38 animals per herd. Serum samples were obtained from 147 goats to determine the extent of *C. burnetii* infections in the animals.

Serum samples were collected from livestock from other farms throughout Newfoundland to determine the

background seroprevalence of Q fever in farm animals in Newfoundland.

### Laboratory Studies

Antibody titers (immunoglobulin G [IgG]) to *C. burnetii* phase I and phase II antigens were determined (15). Antibodies were detected by using indirect immunofluorescence with whole cells of the Nine-Mile strain of *C. burnetii*. An IgG antibody titer of  $\geq 1:8$  was considered seropositive, indicating prior exposure to *C. burnetii*. Acute *C. burnetii* infection was characterized by a phase II IgG titer of 1:64 or a fourfold rise in titer between two separate serum samples.

Placenta samples from goats were sent to Dr. D. Raoult in France, where they were processed for polymerase chain reaction (PCR) using established protocols (16).

### Epidemiologic Studies

A standardized questionnaire was administered to participants who submitted a serum sample. Demographic data, a detailed history of exposure to goats, clinical history, and symptoms were collected by direct interview. Where available, charts of patients were reviewed to collect additional clinical and laboratory data.

To construct epidemic curves, date of onset of symptoms was considered the date of infection. When this date was unavailable (in asymptomatic cases and participants lacking clinical data), date of infection was based on date of the first serum sample (if it had a diagnostic titer) or the halfway point in those who demonstrated a fourfold rise in antibody titer between acute- and convalescent-phase serum samples.

### Statistical Analysis

Differences between infected and uninfected participants were tested for statistical significance by using the chi-square test for proportions and Student *t* test for means. Independent risk factors for infection were determined by using a backward logistical regression analysis. Variables with a *p* value of  $<0.05$  on univariate analysis were entered into the regression analysis. All data were analyzed by using SPSS for Windows version 8.0 (SPSS Inc. 1989-1999); results were considered significant when *p* was  $<0.05$ .

## Results

### Clinical Illness in Goats and Humans

Kidding began January 6 and ended April 24, 1999. Although occasionally it was restricted to dedicated pens, most birthing took place in a communal pen on each farm. *Coxiella* was identified in placental samples examined by using electron microscopy and light microscopy (Gimenez stain), and *C. burnetii* DNA was demonstrated in all three placental samples with PCR. A total of 30 abortions were recorded at six of the eight farms. (Some farms had incomplete records.) The first abortion occurred in December before the kidding season began; the others took place between January 14 and April 24, with abortion rates of 16%-22% per farm. There was no relationship between seropositivity in goats and frequency of abortion.

The epidemic curves differed from farm to farm. Evidence of a continuous common source of infection was seen at one farm (Figure 2), while other evidence suggested a point source (Figure 3). The overall epidemic curve suggested a continuous



## Research

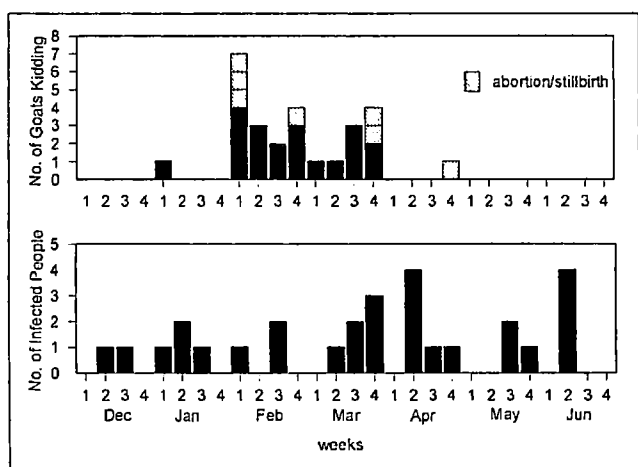


Figure 2. Epidemic curve for farm no. 4, showing the timing of human infection with kidding and abortions.

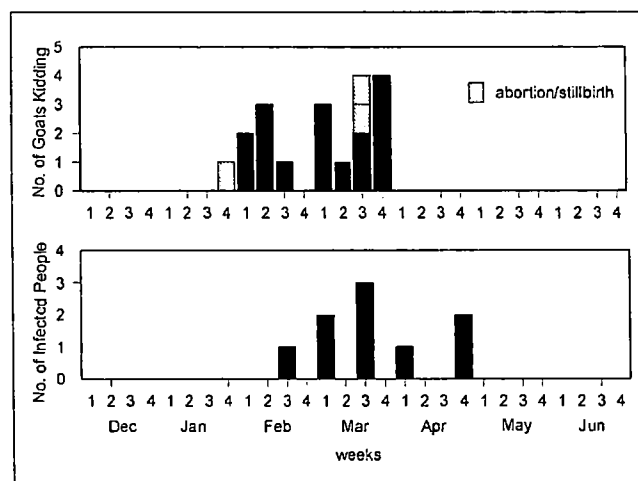


Figure 3. Epidemic curve from farm no. 6, showing the timing of human infection with kidding and abortions.

source or reservoir for infection that had a peak during the kidding season (Figure 4).

Illness in goat farmers or their workers was noted in March 1999. Serologic data were available for 179 farmers, workers, and contacts (outbreak cohort). Eighty (44.7%) outbreak cohort participants had antibodies against the phase II antigen. Sixty-six (36.9%) had phase II titers of  $\geq 1:64$  or had a fourfold rise in titer, suggesting recent infection (Figure 5). The seroprevalence of infected workers (including farmers) on each farm ranged from 0 (farm 5) to 87.5% (farm 4). In comparison, 35 (22.7%) of 154 community cohort participants were seropositive ( $p < 0.001$ ), and 2 (1.3%) had titers of antibodies to phase II antigen of  $> 1:64$  (Figure 6). Seroprevalence in blood donors (8.3%) (Table 1) was significantly lower than that of the control ( $p < 0.001$ ) and outbreak ( $p < 0.001$ ) cohorts. Five blood donors (1.3%) had titers to phase II antigen  $\geq 1:64$ .

Questionnaires were completed by 146 (81.6%) farm workers or contacts who provided blood samples. The

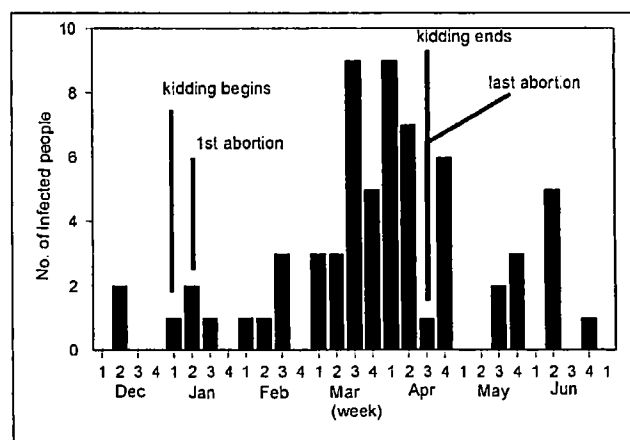


Figure 4. Overall epidemic curve for Q fever outbreak associated with Newfoundland goat cooperative.

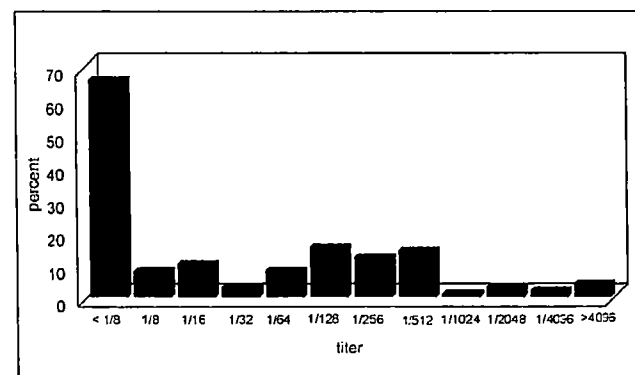


Figure 5. Antibody titers to *Coxiella burnetii* phase II antigen in the outbreak cohort. Of the infected cohort, 24/66 had a fourfold rise in antibodies to phase II (24/66 of the infected cohort had a fourfold rise in antibodies to phase II antigen)

remaining 33 could not be reached for questioning. Of the 146 participants, 9 (6.2%) were farmers, 58 (39.7%) were workers, and 79 (54.1%) were contacts. Demographic data were collected (Table 2). The infected and noninfected groups had equal numbers of men and women. Infected persons tended to be slightly older, were more likely to have been ill in the past 2 months (odds ratio [OR] 3.53), and to have visited their doctor during that time (OR 3.13). Symptoms associated with infection included sweats, chills, headache, weight loss, malaise, fever, fatigue, myalgias, dyspnea, nausea, and diarrhea (Table 2).

The incubation period for Q fever was difficult to determine as most people had many contacts with goats. However, three persons could recall the date of a specific high-risk activity such as assisting with the delivery of a stillborn kid. Incubation periods for these three persons were 21, 31, and 36 days.

A family physician performed clinical laboratory tests on 25 of the infected persons. Four (16%) of these had transaminase levels  $> 1.5x$ , the upper limit of normal. Eight had X rays; one had pneumonia.

## Research

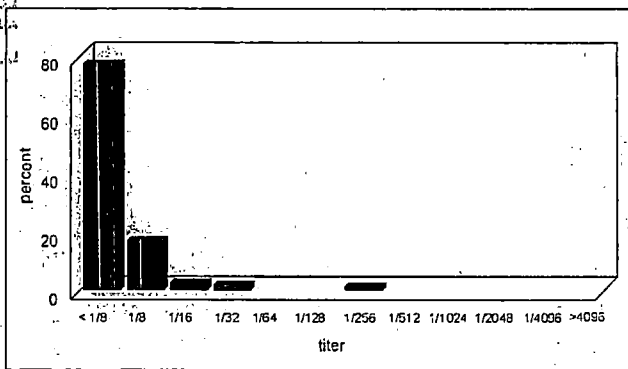


Figure 6. Antibody titers to *Coxiella burnetii* phase II antigen in the community cohort.

Table 1. Seroprevalance of antibodies to *Coxiella burnetii* phase II antigen in random blood donors from Newfoundland

Region	Seropositivity no. (%)
St. John's Center	12/155 (7.7)
Cornerbrook	1/31 (3.2)
St. John's	7/57 (12.3)
Norman's Cove	4/40 (10.0)
Foxtrap	6/71 (8.5)
Conception Bay Central	2/33 (6.1)
Total	32/387 (8.3)

Table 2. Demographic features and symptoms associated with human *Coxiella burnetii* infection in Newfoundland outbreak

Features and symptoms	Infected no. (%)	Noninfected no. (%)	Odds ratio (95% CI)
Male	31/58 (53.4)	46/88 (52.3)	1.05 (0.154-2.04)
Female	27/58 (46.6)	42/88 (47.7)	
Mean age	38.48±11.76	33.47±19.34	p=0.054
Sick in the past 2 months	49/60 (81.7)	48/86 (55.8)	3.53 (1.62-7.70)
<b>Symptoms</b>			
Sweats	11/12 (91.7)	3/9 (33.3)	22.0 (1.86-260.5)
Chills	12/14 (85.7)	4/10 (40.0)	9.00 (1.27-63.90)
Headache	43/60 (71.7)	20/78 (25.6)	7.34 (3.44-15.64)
Malaise	44/59 (74.6)	28/77 (36.4)	5.13 (2.43-10.84)
Weight loss	8/31 (25.8)	3/43 (7.0)	4.64 (1.12-19.24)
Fever	40/60 (66.7)	25/79 (31.6)	4.32 (2.11-8.84)
Fatigue	39/58 (67.2)	27/79 (34.2)	3.95 (1.93-8.11)
Myalgias	26/58 (44.8)	15/76 (19.7)	3.30 (1.54-7.11)
Dyspnea	19/60 (31.7)	12/78 (15.4)	2.55 (1.12-5.79)
Nausea	30/60 (50.0)	22/80 (27.5)	2.24 (1.30-5.34)
Diarrhea	23/60 (38.3)	18/81 (22.2)	2.18 (1.04-4.55)
Cognitive <sup>a</sup>	14/30 (46.7)	4/15 (26.7)	2.41 (0.62-9.29)
Sputum	13/46 (28.3)	11/78 (14.1)	1.72 (0.71-4.18)
EOM pain	8/15 (53.3)	4/9 (44.4)	1.43 (0.27-7.52)
Neck stiffness	16/22 (72.7)	9/14 (64.3)	1.43 (0.27-7.52)
Vomiting	12/60 (20.0)	15/81 (18.5)	1.10 (0.47-2.56)
Pleuritic pain	8/57 (14.0)	10/76 (13.2)	1.08 (0.40-2.93)
Cough	22/60 (36.7)	28/81 (34.6)	1.10 (0.55-2.20)
Loss of libido	13/32 (40.6)	5/12 (41.7)	0.96 (0.25-3.38)

<sup>a</sup>Cognitive problems, including changes in concentration, memory, or temper. EOM, extra-ocular eye movement; CI, confidence intervals.

### Risk Factors for Q Fever

Risk factors associated with human infection on univariate analysis included being a farmer, milking goats, assisting with kidding, handling placentas, shoveling manure, having direct contact with goats, eating cheese made from goat milk, petting goats, feeding goats, being a worker, smoking tobacco, and drinking alcohol (Table 3). When only a multivariate analysis was used, the following were significant risk factors for infection with *C. burnetii*: contact with the placenta ( $p < 0.001$ ), smoking history ( $p = 0.001$ ), and eating cheese made from goat milk ( $p = 0.022$ ). Both infected persons in the community cohort also had direct contact with goats.

Overall, 82 (55.8%) of the 147 goats were seropositive (range from 10% to 100%, depending on the farm); antibody titers ranged from 1:8 to >1:4,096. Although 8 (50%) of 16 goats from other areas in eastern Newfoundland had antibodies to *C. burnetii*, the highest titer was 1:16. In contrast, titers in goats in the outbreak ranged from 1:8 to >1:4,096. In the goats in the cooperative, 63 (43%) and 30 (20%), respectively, had an antibody titer of  $\geq 1:64$  to phase I and phase II antigen. Correlation between *C. burnetii* infection in goats and the geographic origin of the animals or determination of a relationship between seropositivity of goats and the number of persons infected on each farm was not feasible because of insufficient data.

Table 3. Exposure risks associated with *Coxiella burnetii* infection in the Newfoundland outbreak

Risk factors	Infected no. (%)	Noninfected no. (%)	Odds ratio (95% CI)
Visited a barn	57/60 (95.0)	63/86 (73.3)	6.94 (1.98-24.34)
Direct contact with goats	54/60 (90.0)	54/86 (62.8)	5.33 (2.06-13.79)
Milking	19/60 (31.7)	3/85 (3.5)	12.67 (3.54-45.29)
Assisting with kidding	29/60 (48.3)	6/85 (7.1)	12.32 (4.66-32.57)
Handling placenta <sup>a</sup>	31/60 (51.6)	7/86 (8.1)	12.06 (4.79-30.39)
Shoveling manure	37/60 (61.7)	19/84 (22.6)	5.50 (2.65-11.41)
Feeding	39/57 (68.4)	29/85 (34.2)	4.17 (2.06-8.43)
Petting goats <sup>a</sup>	52/60 (86.7)	51/85 (60.0)	4.33 (1.83-10.26)
Farmer	8/60 (13.3)	1/85 (1.2)	12.92 (1.57-106.32)
Farm worker	34/60 (56.7)	24/86 (27.9)	3.38 (1.67-6.77)
Household contact, visited farm	13/60 (21.7)	35/85 (41.2)	0.40 (0.19-0.84)
Household contact, no farm visit	2/60 (3.3)	23/85 (27.1)	0.09 (0.02-0.41)
Ate goat cheese <sup>a</sup>	17/60 (28.3)	6/86 (7.0)	5.27 (1.94-14.35)
Smoked <sup>a</sup>	36/58 (62.1)	28/84 (33.3)	3.27 (1.63-6.58)
Drank alcohol	37/57 (64.9)	38/84 (45.2)	2.08 (1.04-4.13)
Have liver problems	5/53 (9.4)	2/72 (2.8)	3.65 (0.68-19.57)
Have cats	25/59 (42.4)	30/86 (34.9)	1.37 (0.70-2.71)
Drink goat milk	19/60 (31.7)	27/86 (31.4)	1.01 (0.50-2.06)

<sup>a</sup>By logistic regression model, the following were statistically significant: Contact with placenta ( $p < 0.001$ ); smoking history ( $p = 0.001$ ); eating goat cheese ( $p = 0.022$ ); and petting goats ( $p = 0.055$ ).

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### Conclusion

Goats have been implicated in outbreaks of Q fever in the United States, Ontario, Bulgaria, Slovakia, Greece, and Australia, and have replaced sheep and cattle as the most common source of human infection with *C. burnetii* in Bulgaria (17-19). An estimated 20% of Ontario's dairy goat population have antibodies to *C. burnetii* (20).

The incubation period and clinical illness seen in the Newfoundland outbreak were consistent with those reported for other outbreaks (5,15,21,22). The most common manifestation of *C. burnetii* infection was an acute febrile illness. Although dyspnea was an associated feature of our outbreak, only one of eight patients with X rays had pneumonia. This is in contrast to what is typically seen in Nova Scotia, where *C. burnetii* pneumonia is common after exposure to infected parturient cats (15,23).

Although the patients reported here are the first documented cases of Q fever in Newfoundland, serologic results from blood donors suggest that infection with this organism is present elsewhere in this province but goes unrecognized. The seroprevalence of *C. burnetii* in Newfoundland blood donors (8.3%) is consistent with results from blood donors in other Atlantic Canadian provinces (24,25). The higher seroprevalence in the population from communities surrounding the outbreak area (22.7%) could be due to their close proximity to the outbreak area or may reflect a difference in prevalence, which is often higher in rural areas (11).

The eight farms in the cooperative house their goats in

aerosolization of the microorganism can persist for days after parturition, despite immediate removal of the highly infectious placenta (30), it is not surprising that exposure to the placenta was an independent risk factor for infection ( $p < 0.001$ ).

In our study, smoking tobacco was an independent risk factor for infection ( $p = 0.001$ ). This could be due to contaminated hands touching cigarettes, resulting in ingestion of *Coxiella*. Smoking does impair pulmonary host defenses and thus may have contributed to this finding (31). In addition, some barns did not have running water and washrooms until late in the spring, contributing to poor hygienic practices in some instances.

The role of drinking unpasteurized milk in *C. burnetii* infection is controversial. *C. burnetii* has been recovered from milk from infected cows and goats and from butter (17,32). Epidemiologic studies suggest that ingestion of unpasteurized milk has been a source of *Coxiella* infection for humans (6,17,33). Experimental evidence to support a causal relationship is sparse. Asymptomatic seroconversion and infection were noted in inmates fed raw milk from a Q fever infected herd (33). In another study, volunteers who drank naturally infected unpasteurized milk did not develop symptoms or an immunologic response to suggest infection (34). These authors suggest that the lack of seroconversion in their study may have been related to exposure to a different *Coxiella* strain than the one that caused infection in the inmate population (33,34). Pasteurization will effectively kill *Coxiella* in raw milk (35). However, in our study, ingestion of

which have concrete floors. The winter and spring months in

independent risk factor for infection ( $p = 0.022$ ) even though

## Research

and an environment that facilitated infection. Although exposure to goats and eating unpasteurized milk have been implicated in causing *C. burnetii* infection in the past, this is the first time that a product made from pasteurized milk has been associated epidemiologically as a risk factor. Outbreaks of Q fever in research institutions as a result of exposure to infected parturient sheep and goats has led to number of recommendations (38-41). These recommendations include using only *C. burnetii*-seronegative animals in research; vaccinating seronegative animals; using protective clothing and masks while working with animals (especially pregnant ones); restricting access to animals; properly decontaminating surfaces with formalin or bleach solutions; properly disposing of waste by incineration; and using caution, culling, confinement, or chemotherapy in herds with a rate of >20% seropositivity containing animals with titers  $\geq 1:32$ .

Some of these measures are difficult to carry out on a dairy farm; however, since data suggest that human infection can be prevented by vaccination with formalin-inactivated phase I *C. burnetii*, persons at risk from occupational exposure should be offered the vaccine (41).

Our experience raises many questions about management of *C. burnetii* outbreaks in the dairy industry, the interprovincial sale and movement of domestic ungulates, and the need for discussion between public health practitioners and the dairy industry on control of this highly

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# Atypical Q Fever in US Soldiers

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and Kimberly A. Moran\*†

Q fever is an emerging infectious disease among US soldiers serving in Iraq. Three patients have had atypical manifestations, including 2 patients with acute cholecystitis and 1 patient with acute respiratory distress syndrome. Providers must be aware of Q fever's signs and symptoms to avoid delays in treatment.

Q fever, caused by infection with *Coxiella burnetii*, is an emerging infectious disease among US soldiers deployed to Iraq and Afghanistan; >30 cases have been reported (1–3). We describe 3 cases of Q fever in soldiers treated from July through December 2006 at Walter Reed Army Medical Center (WRAMC).

## The Patients

In December 2006, 1 week after returning from Iraq, a 22-year-old white male Army National Guard member was seen at a New Hampshire hospital, with flulike symptoms, pleuritic chest pain, and mild abdominal pain. His initial examination noted temperature of 38.3°C, leukocytes 3.3×10<sup>9</sup> cells/μL (normal 4.5–10.5 × 10<sup>3</sup> cells/μL), platelets 121×10<sup>3</sup> cells/μL (normal 150–450 × 10<sup>3</sup> cells/μL), aspartate aminotransferase (AST) 144 IU/L (normal 15–46 IU/L), and alanine aminotransferase (ALT) 154 IU/L (reference 11–66 IU/L). He was admitted and treated with ceftriaxone and azithromycin. Although his fever decreased within 48 h, he had persistent abdominal pain, worsening liver function test results (AST 779, ALT 993, alkaline phosphatase 269 U/L [reference 38–126 U/L]), and increasing shortness of breath. An ultrasound examination of the right upper quadrant showed hepatosplenomegaly and a thickened gall bladder wall without evidence of cholelithiasis. Despite initially normal chest radiographic results, a repeat radiographic examination showed bilateral pulmonary infiltrates. Ceftriaxone therapy was discontinued, piperacillin/tazobactam therapy was started, and azithromycin was continued. General surgery stated that the patient had a nonsurgical abdomen. After consultation with WRAMC, the patient was given a dose of doxycycline and gentamicin before being transferred to a New Hampshire medical center. Blood

cultures and serologic tests for Epstein Barr virus and cytomegalovirus were pending. A computed tomographic (CT) examination of the chest, abdomen, and pelvis (Figure, left panel) showed gall bladder wall thickening (10 mm) without ductal dilatation, hepatosplenomegaly, and bilateral ground glass pulmonary infiltrates. Serologic tests were negative for hepatitis B and C. Thick and thin smears were negative for parasitic disease. Despite the findings on CT scan, the patient began to improve clinically and had resolution of abdominal pain and shortness of breath. He was transferred to WRAMC, where he continued to improve. Piperacillin/tazobactam was discontinued, but doxycycline was continued. A presumptive diagnosis of Q fever was made, and he was discharged to complete a 14-day course of doxycycline. Serologic tests for *C. burnetii* were positive with a phase 2 immunoglobulin M (IgM) titer of 256 (negative <1:64), phase 2 IgG titer of 128 (negative <16), and negative phase 1 serologic results. A month later he felt well and had normal liver function test results. No exposure factors were identified.

The second case occurred in December 2006, when a previously healthy 24-year-old male Army National Guard member was admitted to the 28th Combat Support Hospital (CSH) in Baghdad, Iraq, with flulike symptoms, mild nausea, and a dry, 10-day cough. At admission, his temperature was 40.2°C, but his other vital signs were normal. He had mild epigastric tenderness to palpation; otherwise, examination results were normal. Laboratory results included leukocytes 3.9×10<sup>3</sup> cells/μL, platelets of 130×10<sup>3</sup> cells/μL, alkaline phosphatase 104 U/L, AST 824 U/L, ALT 786 U/L, total bilirubin 1.2 mg/dL (reference 0.2–1.3 mg/dL), and gamma glutamyl transferase (GGT) 97 (reference 12–58). Initial erythrocyte sedimentation rate was within normal limits at 18 mm/hr (reference <20 mm/h). Results of blood cultures, monospot, and hepatitis B, C, and HIV screens were negative. A CT scan showed diffuse enhancement of the gallbladder with gallbladder wall thickening (Figure, right panel). A small amount of pericholecystic fluid was seen, but no distension of the gallbladder or gallstones were noted. These findings prompted a general surgery evaluation for acute cholecystitis, but their examination results were not consistent with this diagnosis. Given the patient's flulike symptoms and laboratory abnormalities, the diagnosis of Q fever was considered. The patient had initially been treated with doxycycline and metronidazole, but metronidazole was discontinued when his physical examination results remained benign. His fever curve decreased within 2 days of receiving doxycycline. He was transferred out of theater to Landstuhl Regional Medical Center in Germany for further evaluation. Q fever was confirmed with *C. burnetii* serum titers of 2,048 for phases 1 and 2 IgM. He improved with doxycycline, 100 mg twice a day for 14 days, and was subsequently returned to duty. No exposure factors were identified.

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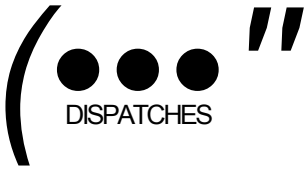


Figure. Computed tomographic scans of abdomens of 2 patients with inflammation of the gallbladder.

The third case occurred in July 2006 in a 34-year-old female active duty soldier with a history of asthma. She was seen at the troop medical clinic in Baghdad, Iraq, with flu-like symptoms. She was given symptomatic treatment and released but returned with altered mental status, shortness of breath,

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doxycycline to the treatment regimen for deployed soldiers with severe pneumonia (1).

Q fever is a Category B biologic agent and must be considered as a potential threat to deployed soldiers (13). The most likely mode of attack would be aerosolization; given the low dose required for infection (1–10 organisms), multiple cases would follow. We considered bioterrorism unlikely, given the limited number of clinically symptomatic cases and the lack of a cluster of cases.

Q fever continues to be a threat to deployed US soldiers in Southwest Asia. Lack of knowledge about it can delay diagnosis and treatment. It should be considered in the differential diagnosis of any deployed or recently deployed soldier with a febrile illness, especially when hepatitis or pneumonia is present.

Dr Hartzell is an infectious disease fellow at WRAMC in Washington, DC, and an assistant professor of medicine at the Uniformed Services University in Bethesda, Maryland. His research is focused on leishmaniasis and HIV.

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## High incidence of *Coxiella burnetii* markers in a rural population in France

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**Abstract.** Since *Coxiella burnetii*, the causative agent of Q fever, is often transmitted from goats and sheep to humans through aerosols, we examined the sera from 168 persons involved in goat breeding in the Centre region of France and 40 members of veterinary and medical staff from the same region for the presence of antibodies against *C. burnetii*. An immunofluorescence assay was used to detect the presence of antibodies of the IgG isotope against epitopes from phase II of *C. burnetii*, which are the first antibodies to appear in infected people, and from phase I, which reflect more chronic stages of the infection. Our serological survey showed that most of the tested sera were positive for *C. burnetii* markers, indicating at least an encounter with the bacterium. In the overall population of 208 subjects,

71% of the sera had antibodies against phase II epitopes (titres  $\geq$  1:40). Among the goat farmers and their immediate families, 78% had antibodies against phase II and 33% against phase I (titres  $\geq$  1:40). Considering only high titres ( $\geq$  1:320), though, only 37% of the farmers had antibodies against phase II and 15% against phase I. Only 3 out of 12 veterinarians working in the field had high titres of antibodies against phase II and phase I, while none of 28 members of veterinary and medical laboratories had significant levels of antibodies. These results emphasize the need for closer surveillance of populations at risk for Q fever, to prevent the infection by *C. burnetii* from reaching chronic stages of the disease.

**Key words:** *Coxiella burnetii*, Q Fever, Rickettsiales

### Introduction

Q fever, caused by the rickettsial species *Coxiella burnetii*, often escapes diagnosis and is not widely appreciated by many physicians [1], even though cases of the disease have been observed throughout the world [2]. In France and Spain, cases of the disease have been reported especially in areas where goats and sheep are bred [3-5], consistent with the fact that *C. burnetii* is transmitted from domestic animals to humans via the respiratory route, notably by way of aerosolized bacteria from goat and sheep litters.

In humans, Q fever is characterized, in its most common form, by a syndrome that is often mistaken for a flu. After a one- to four-week incubation, infection is often manifested by high fevers (39-40 °C), acute headaches, and muscle pains. Five to six days later, respiratory symptoms, essentially cough, often appear, and occasionally there are articular pains and digestive symptoms. In the absence of antibiotic treatment, the fever remains at a high level during fifteen days and is accompanied by profuse sweating.

The main risk of Q fever is due to transition to its chronic phase, which can become apparent years after a benign infection and results in alterations of the cardiac valves and aorta. The chronic form of Q fever thus results in an acute form of endocarditis that necessitates antibiotic treatment for several years, often requires surgical intervention, and can be fatal [6, 7].

*C. burnetii* exists in two antigenic phases, phase I and phase II. The phase I antigen appears to be a polysaccharide constituent of the lipopolysaccharide from *C. burnetii*, and the transition from antigenic phase I to phase II is probably due to the deletion of carbohydrate molecules from the lipopolysaccharide [8]. When a patient first develops an infection by *C. burnetii*, the first antibodies to appear are those against the phase II form of the bacterium [9, 10]. Ten to fifteen days after the beginning of infection, the presence of phase II antibodies are used as indicators for the acute form of Q fever. The phase II antibody titres can reach high levels (around 1:5000), persist for a while, then, without disappearing, return to levels of 1:40-1:80. During the

chronic phases of infection, antibodies against the phase I epitopes appear and become more abundant than those against phase II epitopes [7, 9-11].

*C. burnetii* is unusually resistant to physical and chemical attack and is frequently shed in the urine and feces of infected animals [12]. As the bacterium multiplies to large numbers especially in the placenta and other birth products of domestic animals, there is a high risk for human contamination among cattle, goat and sheep breeders, veterinarians, employees of slaughterhouses and veterinary laboratories, workers in the wool and meat-processing industry, and any other individuals that may come in contact with potentially contaminated aerosols. The infection often remains unnoticed in domestic animals, except in goats, in which *C. burnetii* sometimes causes abortions. Given the seriousness of the chronic stages of Q fever in humans, it would be important to identify *C. burnetii* at early stages of the infection, which are more amenable to containment by antibiotics. As a first step towards this goal, we have therefore studied the distribution of antibodies against the bacterium in populations at high risk in a goat- and sheep-breeding region of central France.

#### Material and methods

Between November 1991 and October 1992, we examined the sera from 208 individuals from the Centre region of France, comprising mostly the departments of Cher, Loiret, Indre, and Indre-et-Loire. The subjects consisted of 168 farmers involved in the breeding of goats and members of their immediate families and employees; 12 veterinarians working in the field; and 28 technicians, secretaries, veterinarians, and physicians working in veterinary laboratories or in medical centers that treat the farmers. Serum samples were collected at the Union Régionale des Groupements de Défense Sanitaire du Centre (URGDS) in Chateauroux, France, and the Mutuelle Sanitaire Agricole (MSA) and Direction Départementale des Affaires Sanitaires et Sociales (DDASS) in Bourges, France.

Antibodies against *C. burnetii* were detected in all the sera by a standard immunofluorescence assay (IFA) [9, 10, 13] using ten-well Teflon-coated glass slides. The antigens for the Nine Mile strain of *C. burnetii* in phase II and for the bacterium in phase I were obtained from the World Health Organization Collaborating Center for Rickettsiales at the Institut Pasteur (Paris, France). Twofold dilutions of each serum were prepared in phosphate buffered saline (PBS), starting at a 1:20 dilution, and the immunofluorescence tests were performed with anti-human IgG. The data were transferred to a computerized data bank and then analyzed for this retrospective study.

#### Results

Exposure to *C. burnetii* in a population of goat breeders, the farmers' families, veterinarians, and members of veterinary laboratories from the Centre region of France was determined by measuring *C. burnetii*-specific antibody levels using a standard immunofluorescence assay [9, 10, 13]. The serological analysis was performed with epitopes for both phase II antigens, indicating at least an encounter with the bacterium and possibly a past history of mild forms of Q fever; and phase I antigens, reflecting more advanced, possibly chronic, stages of the infection. The initial analysis included sera with titres as low as 1:40, as low titres may represent antibody levels normally present after the acute form of Q fever has subsided. Moreover, titres of 1:40 were reproducibly measured by immunofluorescence in our laboratory.

From the total population of 208 subjects, there was a surprisingly high proportion of sera (71%) exhibiting antibodies against either the phase I or phase II forms of *C. burnetii* at titres greater than or equal to 1:40 (not shown). Most of these subjects may have never noticed the infection, though, since only 27% of the total population had antibodies against both the phase II and the more advanced phase I forms. All subjects that had anti-phase antibodies also had anti-phase II antibodies. Among the farmers and their families, 78% had sera with antibodies against phase II and 33% against phase I (not shown). As antibody titers greater than 1:128 [14] or 1:200 [7] have been previously considered as diagnostic for Q fever, Figure 1 shows the number of subjects displaying antibodies against phase I or

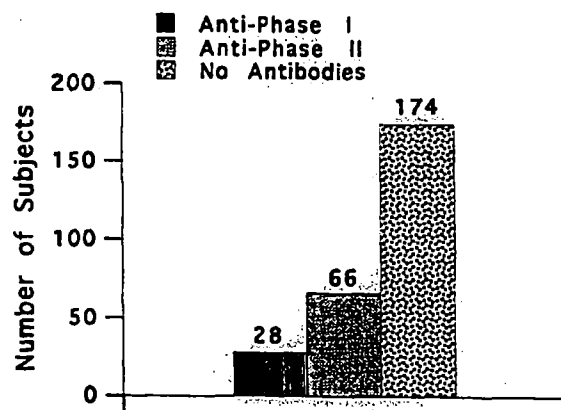


Figure 1. Histogram showing the number of individuals in the total population of 208 subjects exhibiting high levels of antibodies ( $\geq 1:320$ ) against the phase II or against the phase I epitope of *C. burnetii*, or subjects exhibiting no antibodies or low levels of antibodies (defined as those having titres  $< 1:320$ ). All subjects displaying anti-phase I antibodies also had anti-phase II antibodies. The number of subjects in each category is given above the columns.

phase II with titres equal to or above 1:320. At these titres, 32% had sera with antibodies against phase II and 13% had them against phase I.

The distribution of the antibody levels was determined on the entire population of individuals displaying antibodies (Figure 2). As expected, most of the subjects had low concentrations of the phase II antibodies. Although fewer subjects had anti-phase I antibodies, the concentrations were skewed toward higher titres and, in a small number of individuals, attained fairly high levels (one subject had an anti-phase I titre of 1:1280, two subjects had titres of 1:2560, and three subjects had titres of 1:10240).

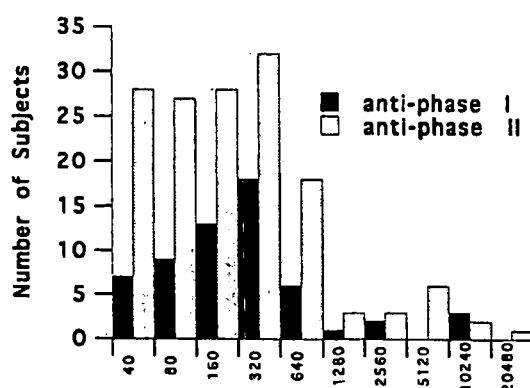


Figure 2. Levels of anti-phase I and anti-phase II IgG antibodies in the total population of subjects exhibiting anti-*C. burnetii* antibodies (107 subjects). Titres are given below the columns.

A comparative analysis of the sera from the different groups showed that, out of 168 goat breeders and their families, 132 had antibodies at titres higher than or equal to 1:40; out of 12 veterinarians, 9 had antibodies at these titres; while out of 28 members of veterinary and medical laboratories, 7 had antibodies (four subjects had titres of 1:40, two of 1:80, and one of 1:160). However, retaining only titres equal to or above 1:320 (Figure 3), only 62 farmers (37% of the group) had antibodies against phase II of *C. burnetii* (three subjects had titres of 1:1280, two of 1:2560, six of 1:5120, two of 10240, and one of 20480) and 15% had these titres against phase I (one had a titre of 1:1280, two of 1:2560, and three of 1:10240). Lower levels were detected in the other groups (Figure 3). Three veterinarians had anti-phase I antibodies (titres of 1:320, 1:320 and 1:640), but only one of them, having titres above 1:2560 for phase II and 1:640 for phase I, manifested an obvious pathology. None of the laboratory members had phase I antibodies and none had diagnostically significant levels of anti-phase II antibodies.

For the sake of comparison, over the past five years we have tested more than 1000 sera from the general population in France, and less than 5% of

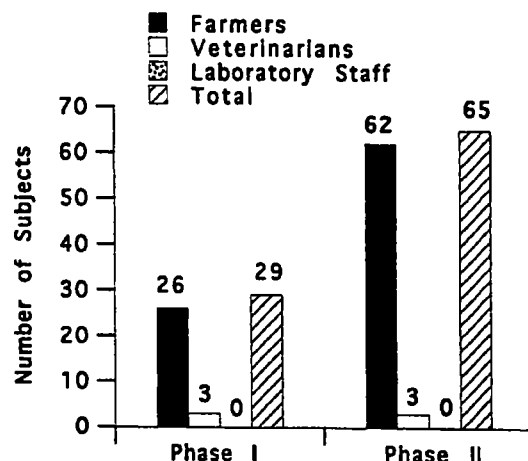


Figure 3. Histogram describing the distribution of *C. burnetii* antibodies in various segments of the rural population. Only sera with IgG titres  $\geq$  1:320 were included in the analysis.

these subjects had titres  $\geq$  1:160 for the phase II of *C. burnetii* (not shown).

## Discussion

*C. burnetii* is known to be widely distributed in the Basque country, the Alpine region of Europe, and the South of France [3-5, 15]. In sparsely populated regions of the Basque country, 38.5% of the residents were found to be infected with *C. burnetii*; which was about 50% higher than for residents of highly populated areas. Previous or current participation in agricultural activities or livestock farming were considered to be risk factors for the infection [4]. A large outbreak in an urban area in the United Kingdom was also recently reported, and windborne spread from surrounding farmlands was proposed as the route of infection [16]. In southern Sweden, 24-30% of sheep farmers and 12% of veterinarians have been exposed to *C. burnetii*; although in the non-risk groups of drafters and hospital employees, 5-7% were also sero-positive [17]. In other urban areas in Europe, the United States, and Japan, cats have been implicated as the carriers of infection to humans [2, 18, 19]. The incidence found by us for goat breeders in the Centre region of France is thus higher than reported for overall populations studied elsewhere, but are consistent with the high-risk nature of the employment of our subjects.

Most of the antibodies from the Centre region were detected in sera from goat farmers and their families. Out of 168 subjects, 132 (78% of the group) exhibited antibodies against *C. burnetii*, and 62 (37%) had titres that were greater than or equal to 1:320. As titres as low as 1:40-1:80 may correspond to antibodies remaining after the acute form of Q fever, they must be taken into account when con-

ducting studies on the exposure of a population to *C. burnetii*. The veterinarians actually working in the field were the next-most affected group, with 3 out of 12 subjects (25%) displaying high levels of anti-phase I and phase II antibodies ( $\geq 1:320$ ), although 9 of them (75%) had lower titres of antibodies against phase II. Out of 28 members of veterinary and medical laboratories, none had phase I antibodies and none had high levels of anti-phase II antibodies, suggesting that the employment of these health workers in the Centre region should not be considered as a high risk factor.

It is difficult to estimate the number of Q fever cases per year, since only the most severe cases requiring hospitalization lead to serological analysis of the patients. From 1982 to 1990, 92 cases of chronic Q fever have been reported in the South of France by the French National Center for Rickettsioses [5]; and from 1987 to 1991, we have detected 300 cases of *C. burnetii* infection by IFA, including 32 cases of *C. burnetii*-induced endocarditis [20]. However, our own experience with hospital cases allow us to estimate that there are about 1000 cases of hospitalization per year in France, including a dozen cases of endocarditis (unpublished observations). This does not include misdiagnosed cases, such as milder forms of Q fever or abortions due to infection [21]. It is currently not possible to determine whether the incidence of *C. burnetii* infections in the Centre region of France is increasing or is remaining steady, since a systematic study to detect the presence of corresponding antibodies was not attempted in the past. Follow-up studies will thus be required to evaluate what may be the tendency. However, the population of goat breeders and their families can be clearly identified as a population at high risk for contracting Q fever, and they should therefore be carefully controlled for early signs of infection, when the infection is easiest to treat with antibiotics.

Contamination of humans is due to inhalation of aerosols or dust, where *C. burnetii* can survive for long periods of time. The most dangerous dust is derived from animal litters, especially soon after birth. Placenta and by-products of abortions in domestic animals are also extremely rich in *C. burnetii*, and pregnant women are therefore strongly encouraged to avoid stables during these high-risk periods.

In preliminary studies, we have not been able to detect *C. burnetii* epitopes in milk from goats in the Centre region, consistent with the observation that 44% of the subjects studied in this work, although consuming large quantities of unpasteurized goat cheese, do not display antibodies against the bacterium. It appears more likely that the disease is spread primarily through aerosol transmission.

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## Hyperendemic Focus of Q Fever Related to Sheep and Wind

Hervé Tissot-Dupont,<sup>1</sup> Sylvie Torres,<sup>2</sup> Meyer Nezri,<sup>2</sup> and Didier Raoult<sup>1</sup>

Q fever is a worldwide zoonosis which is caused by *Coxiella burnetii* and presents as both acute or chronic cases. The disease can be transmitted from animal reservoirs to humans by the inhalation of infected aerosols. The authors investigated the epidemiology of Q fever in the Bouches-du-Rhône district of southern France. The study area was centered around the small town of Martigues near the cities of Marseille and Aix-en-Provence, where the incidence of the disease seemed higher than in neighboring areas. Epidemiologic data included sheep breeding and wind. Between 1990 and 1995, Q fever was diagnosed in 289 patients, leading to an incidence rate of 35.4 per 100,000 in the study area (range: 6–132), compared with 6.6 in the area of Marseille, and 11.4 in the area of Aix-en-Provence. There was a graphical and statistical relation between the sheep densities, the incidence of the disease, and the strong, local wind known as the Mistral, which blows from the northwest. Although *Coxiella burnetii* transmission is multifactorial, we may speculate that the high endemicity in the study area is related to a contamination by aerosols because the Mistral blows through the local steppe where 70,000 sheep are bred. This public health problem requires further studies in order to confirm this hypothesis, and to identify more individual and preventable risk factors. *Am J Epidemiol* 1999;150:67–74.

*Coxiella burnetii*; disease outbreaks; Q fever

Q fever is a worldwide zoonosis caused by *Coxiella burnetii*, an obligate intracellular organism which lives in the phagolysosomes of the host cell. The main characteristic of Q fever is its clinical polymorphism. In acute cases, the most common clinical syndromes are self-limiting, febrile illnesses of unknown origin, granulomatous hepatitis, pneumonia, and meningoen- cephalitis (1). Moreover, cases of febrile eruption, myocarditis, and pericarditis have been reported. In chronic cases, endocarditis is the main syndrome (2). Osteomyelitis, infections of vascular grafts or aneurisms (3), and infections during pregnancy (4) have also been reported. Such varied clinical presentations mean that serologic confirmation is required for the diagnosis of Q fever.

Throughout the world, the most common reservoirs for *Coxiella burnetii* are cattle, sheep, and goats (5). The bacterium is found in urine, feces, milk, and birth products of infected animals (6). Human infection occurs following inhalation of contaminated aerosols or ingestion of raw milk or fresh goat cheese. *Coxiella*

*burnetii* is ideally suited to this means of transmission, due to its ability to withstand harsh environmental conditions and to its extraordinary virulence (7). It has recently been shown that infected cats (8), rabbits (9) and dogs (10) can transmit *Coxiella burnetii* to humans, and that these animals have been sources of human outbreaks (5).

The geographic distribution of Q fever is wide and *Coxiella burnetii* is endemic in virtually every country in the world, except New Zealand (11). Due to its varied clinical presentations, the prevalence of *Coxiella burnetii* infection in humans is largely unknown and largely depends on either a local physician's interest in the disease or on the presence of a reliable diagnostic laboratory. It has been suggested that the prevalence of Q fever follows the geographic distribution of rickettsiologists (12) in that in places where the infection is extensively studied, the prevalence can be shown to be extremely high. For example, in southern Spain, 30 percent of patients hospitalized for fever that lasted more than 7 days were shown to have Q fever, and in the Basque country about 60 percent of cases of community-acquired pneumoniae were due to *Coxiella burnetii* (13, 14). Previous studies have shown a seroprevalence of 4.03 percent among apparently healthy blood donors from Marseille (phase II immunoglobulin G (IgG)  $\geq 50$ ) (1). This led us to predict that annually more than 2,000 people would become infected in Marseille. These results were consistent with other studies conducted in France: 5 percent in a previous

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Abbreviations: CI, confidence interval; IgG, immunoglobulin G; m/s, meters per second.

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study carried out in Marseille (15) and 4.4 percent in the east central France (16). A higher prevalence has been found in the Alps, where 30 percent of a village population was found to have antibodies (17).

In many countries, Q fever is not a reportable disease, and thus it is difficult to know how many cases occur. Furthermore, sporadic cases are rarely identified. France, Spain, Switzerland, Israel, and the United Kingdom have considerable Q fever activity (5), partly due to an active case finding. Two large outbreaks in Britain (18) and Switzerland (19) have been extensively studied and have provided additional information about the epidemiology of Q fever. In the British study (18), residents who lived along a road along which farm vehicles traveled developed Q fever as a result of the exposure to contaminated straw, manure, or dust from those vehicles. In the Swiss study (19), 415 residents who lived along a valley road along which sheep were herded to and from mountain pastures developed Q fever (19).

In France, from 1985 to 1995, 1,018 cases (731 acute and 287 chronic) were diagnosed at the National Reference Center (Annual Report of the Center, 1997). In the area of Marseille, where the Reference Center is located, one small town, Martigues, apparently has more cases than the surrounding towns. We therefore decided to investigate the epidemiologic situation of this town, compared with neighboring areas.

Because infectious particles containing *Coxiella burnetii* can easily be transported by the wind (5) and the fact that a large number of sheep are located windward of the study area, we wanted to determine whether wind direction and strength, as well as sheep breeding, could be significantly associated with the seasonal distribution of cases that occur in the study area.

## MATERIALS AND METHODS

### Serologic diagnosis

The serologic diagnosis was performed at the National Reference Center using the immunofluorescence reference technique as previously described (20, 21). The titers of IgG, immunoglobulin M (IgM), and immunoglobulin A (IgA) against phases I and II of *Coxiella burnetii* were determined. A serum was considered diagnostic of an evolutive Q fever (acute or chronic) when the phase II IgG titer was  $\geq 200$  and the phase II IgM titer was  $\geq 50$ . A diagnosis of chronic Q fever was made when the phase I IgG titer was  $\geq 800$  (21).

### Demographic, geographic, and meteorologic data

Marseille is a city located in Southern France with 800,000 inhabitants. About 40 km northwest of

Marseille is a large, natural lake called the "Etang de Berre." For our study, we considered all cities and villages included in a circle centered on the lake (diameter = 50 km) as the Etang de Berre area. Northwest of Etang de Berre is a semi-desert plain region called "La Crau," which is the only steppe in Western Europe. Aix-en-Provence is a city located 30 km north of Marseille with 125,000 inhabitants. For our study, the areas of Marseille and Aix-en-Provence included all towns and villages located less than 20 km from the two cities. The respective populations of the three areas were as follows: Etang de Berre area, 361,562; Marseille area, 836,904; and Aix-en-Provence area, 176,054 (figure 1).

Data on sheep breeding were obtained from the "Chambre d'Agriculture" in Aix-en-Provence. These data included the number of sheep, number of sheep breeders by area, and mean monthly number of sheep births (figure 2).

Data on medical and paramedical occupations were obtained on the Worldwide Web from the French Ministry of Health web page ([www.sante.gouv.fr](http://www.sante.gouv.fr)).

Meteorologic data were obtained from Meteo France weather stations at Istres and Salon-de-Provence in the form of monthly compass cards for 1991–1995. Wind speed and direction are measured three times an hour, leading to more than 1,400 data per month. The tables provided by Meteo France show the percent of these measures by direction, in three meters per second (m/s) speed ranges: 2–4, 5–8, and  $>8$ . The Mistral, which is the most common and strongest wind, blows from the northwest. We therefore compiled data on directions 30, 32, 34, and 36 (west-northwest, northwest, north-northwest, and north, respectively), giving a crude number of measures per month. For graphic presentation, this number of measures has been divided by the number of days in the considered month, giving a theoretical number of days per month in which the Mistral blew. The Mistral blows through La Crau before reaching the study area (figure 3). The Mistral is always characterized by the same weather conditions, i.e., a strong wind, which blows for several consecutive days, in sunny and dry conditions. As shown by figure 3, winds that blow in other conditions (rainfall, high humidity, etc.) come from other directions (mainly east and south). Therefore, we decided not to study other meteorologic factors.

### Patients

Using the serologic criteria described above, Q fever-positive patients were selected from the database of the National Reference Center from 1990 to 1995. All patients had been admitted to hospital, which mini-

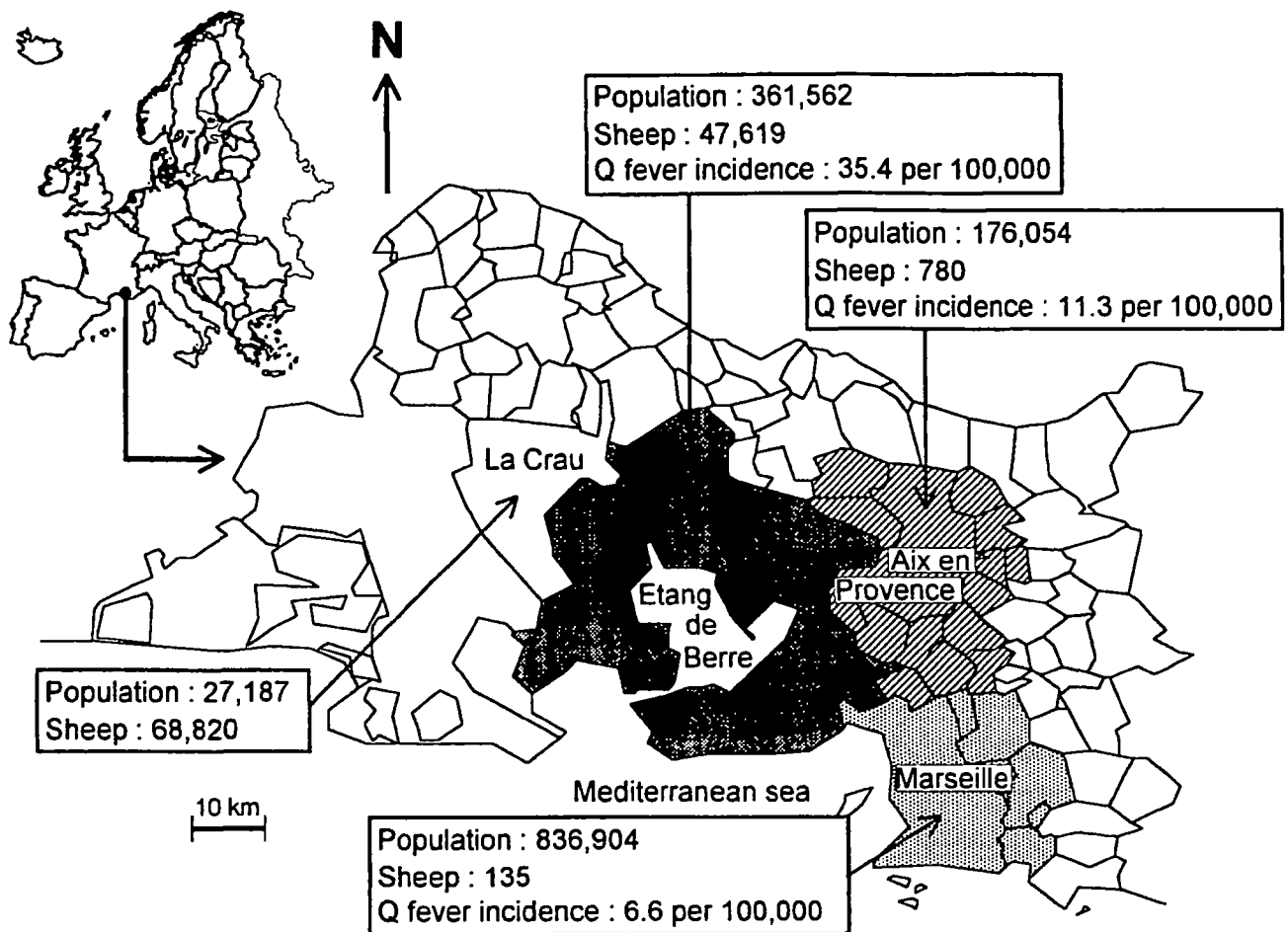


FIGURE 1. Map of the Bouches-du-Rhône district of France, comparing the global incidence rate of Q fever in the study area of Etang de Berre area, and two adjacent areas, the Marseille area and the Aix-en-Provence area, in 1990-1995.

mizes the detection bias related to physicians' awareness of the disease, although it may lower the detection. The patients were selected according to the geographic origin of their sera, which corresponded to the catchment areas for the public hospitals of Martigues, Salon-de-Provence, Aix-en-Provence, and Marseille, and the few private hospitals in the study area. Medical practice in the above centers is to send all sera for Q fever diagnosis to the National Reference Center, or to screen their sera by immunofluorescence using phase II *Coxiella burnetii* antigen provided by the National Reference Center. All positive sera are then sent to the center for confirmation, so that all diagnoses are made at the National Reference Center using the same reference technique. For each selected patient, a questionnaire was completed from the patient's files, collecting available administrative, epidemiologic, clinical, and biologic data. In regard to the retrospective patient selection, place of residence was the sole data available on their location (address in the hospital files).

### Statistical analyses

All data were managed and analyzed using EpiInfo 6 (CDC, Atlanta, Georgia) and SPSS (SPSS, Inc., Chicago, Illinois). Fisher's exact test was used to test association while mean values were compared using Student's *t* test. Prevalence odds ratios and their 95 percent confidence intervals were calculated to compare prevalences in the different areas. Correlations between wind frequencies and Q fever prevalence were tested using Spearman's rank test.

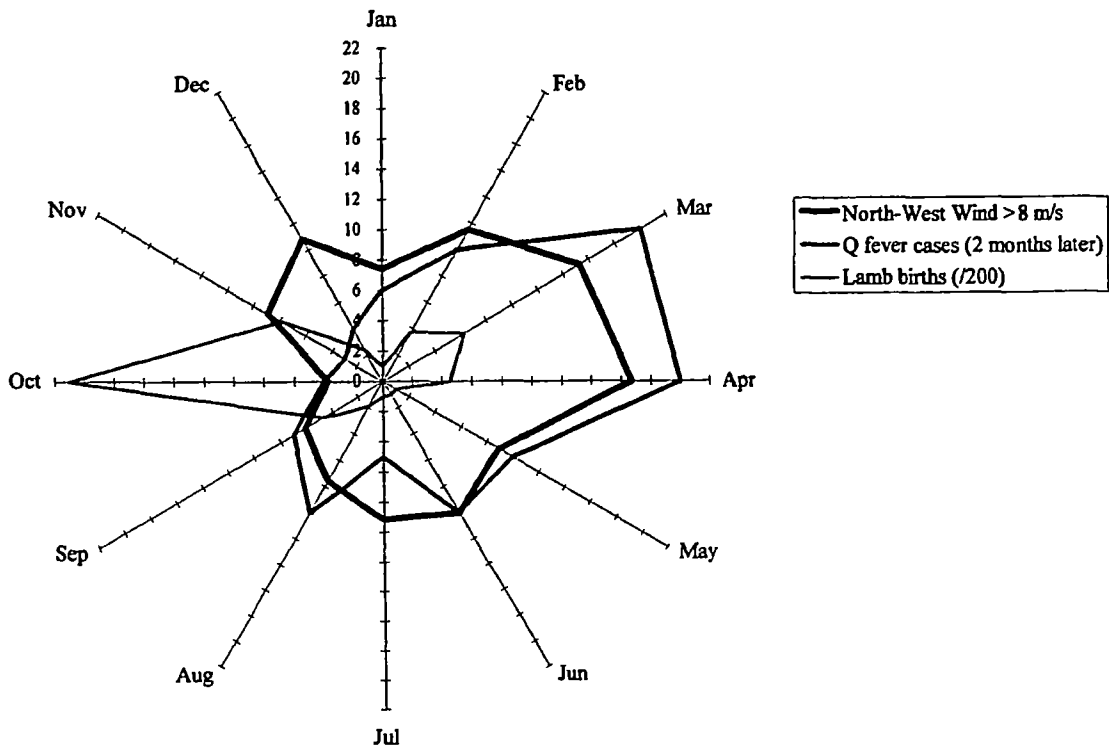
## RESULTS

### Q fever incidence

Between 1990 and 1995, 289 patients who had been admitted to hospital with an active Q fever were diagnosed in the study area. Among these 289 patients, 68 lived outside the study area, and the addresses of 18 could not be determined. As a result, 203 patients



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**FIGURE 2.** Seasonal variation of Q fever incidence, the "Mistral" wind, and sheep births in the Etang de Berre area of France. Cumulated cases for 1990–1995 are plotted 2 months before they occur (incubation and delay before diagnosis) to represent the time of infection. The northwesterly wind (directions 30, 32, 34, and 36) is represented as the mean monthly number of days with wind speed >8 meters per second (m/s).

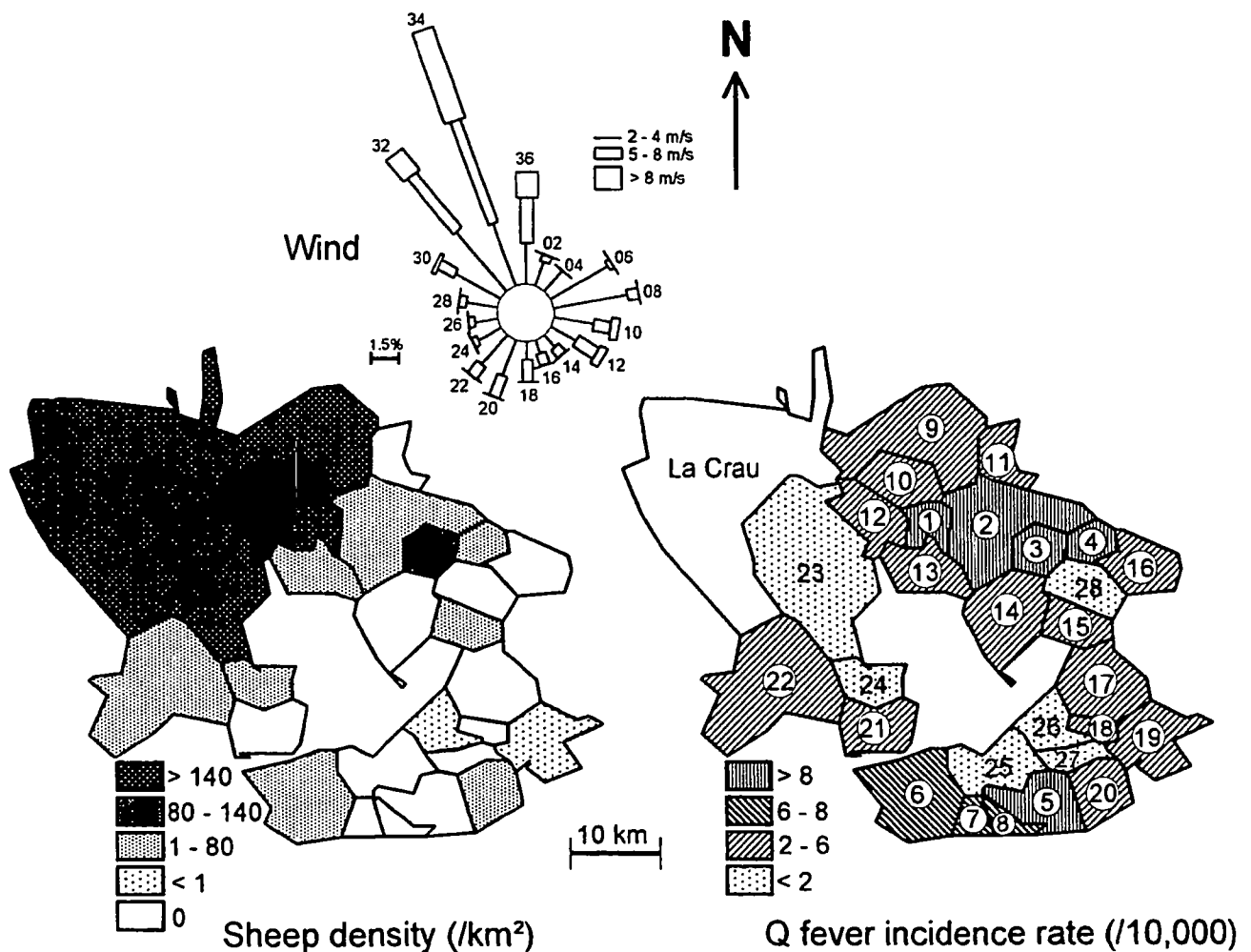
remained to be included in the study. Of these 203 patients, 128 originated from the Etang de Berre area, 55 from the Marseille area, and 20 from the Aix-en-Provence area. Under these conditions, the 5-year incidence of Q fever in the study area of Etang de Berre (35.4 per 100,000 inhabitants) was 3.0 times higher (95 percent confidence interval (CI) 1.95–4.99) than in the Aix-en-Provence area (11.3 per 100,000 inhabitants) and 5.4 times higher (95 percent CI 3.93–7.39) than in the Marseille area (6.6 per 100,000 inhabitants) ( $p < 10^{-7}$ ) (figure 1). In the Etang de Berre area, incidence of Q fever varied from 132 per 100,000 inhabitants in the city of Ensues to 6 per 100,000 in the city of Istres. The incidence by area is represented in figure 3, which shows two high prevalence areas: one to the north of the Etang de Berre (in the areas of Lançon-de-Provence, Cornillon, Coudoux, and La Fare-les-Oliviers) and one located to the south (Ensues). According to the study criteria, the semi-desert plain area of La Crau was not considered to be part of the study area. However, none of the selected patients originated from La Crau.

**Case description**

Of the 128 cases from the Etang de Berre area, five medical files could not be found. Questionnaires were

therefore completed and analyzed for 123 cases. Males represented 74.8 percent (92 of 123) of the cases admitted to hospital. This sex ratio (2.96) was significantly higher than that of the French population (0.96) ( $p < 0.001$ ) but not, however, significantly different from the sex ratio (2.3) observed in our previous study (1). The mean age of the patients was  $40 \pm 15$  years (range: 9–89 years). The yearly distribution of the 123 cases was 5 in 1990 (the selection began in July), 16 in 1991, 37 in 1992, 16 in 1993, 29 in 1994, and 20 in 1995. The seasonal distribution of the 109 acute Q fever cases from 1991 to 1995 showed a significantly increased frequency in May and June (36.7 percent of the cases) ( $p < 0.001$ ).

The epidemiologic, clinical, and biologic data are summarized in table 1. Of the 91 patients whose occupations were known, eight (8.8 percent) were considered to be exposed to *Coxiella burnetii* risk factors (farmers, stock breeders, and truck drivers who transported animals). A medical or paramedical occupation was given by eight patients (6.5 percent of the cases), which was higher than that found in the 1996 Bouches du Rhône population (2.9 percent) ( $p = 0.025$ ). A rural residence was noted for 28 of 60 patients (45.9 percent). Usual contact with animals was reported for 74 files (60 percent), which is higher than that usually



**FIGURE 3.** Maps of the Etang de Berre area of France comparing the sheep densities and the incidence rate of Q fever between 1990 and 1995. The compass card shows the frequencies of wind by speed and direction, cumulated from 1990 to 1995. The numbers indicate the administrative areas: 1, Cornillon; 2, Lançon-de-Provence; 3, La-Fare-les-Oliviers; 4, Coudoux; 5, Ensues-la-Redonne; 6, Martigues; 7, Sausset-les-Pins; 8, Carry-le-Rouet; 9, Salon-de-Provence; 10, Grans; 11, Pélissane; 12, Miramas; 13, Saint-Chamas; 14, Berre-l'Etang; 15, Rognac; 16, Ventabren; 17, Vitrolles; 18, Saint-Victoret; 19, Les-Pennes-Mirabeau; 20, Le Rove; 21, Port-de-Bouc; 22, Fos-sur-Mer; 23, Istres; 24, Saint-Mitre-les-Remparts; 25, Châteauneuf-les-Martigues; 26, Marignane; 27, Gignac-la-Nerthe.

found in Q fever cases (1). Contact with sheep was identified by seven patients (9.5 percent), with cats by six patients (8.1 percent), with dogs by 15 patients (20.3 percent), and with rabbits by two patients (2.7 percent). Presence or absence of fever was mentioned for 120 patients, 95 of whom (79.2 percent) were febrile (body temperature  $>38^{\circ}\text{C}$ ). Seventy-nine of these patients presented with hepatitis, 27 with pneumonia, and seven with a clinically isolated fever. Twenty patients had a skin eruption, and 12 had neurologic findings. Nine patients had serologic findings presumptive of chronic Q fever. Six of these patients were pregnant women who had been admitted to hospital for late abortions, of whom five had already undergone an abortion. Three patients (two males and one female) presented with an endocarditis.

#### Wind frequency

We compared the seasonal distribution of cases with the distribution of the mean monthly number of days with a northwest wind speed of  $>8$  m/s (the Mistral) on the same radar figure in the areas of Istres and Salon-de-Provence (figure 2). Cases were considered 2 months after the wind distribution. This period was chosen to account for the 3-4-week incubation period for Q fever (22), and the mean delay between the onset of the disease and serologic diagnosis (21). This figure shows the high correlation between the wind and Q fever cases (Spearman correlation coefficient = 0.57 ( $p < 0.05$ )). Strong winds ( $>8$  m/s) are twice as frequent from the northwest than from other directions (figure 3). If we consider the dominant strong winds

**TABLE 1. Epidemiologic, clinical, and laboratory findings among 123 cases of acute Q fever in the area of Martigues, Southern France, 1990-1995**

Type of findings	Cases	%
<b>Epidemiologic findings</b>		
Age (years) (SD*)	40 (15)	
Males	92	75
Exposed occupation	8	9
Medical occupation	8	9
Rural existence	28	47
Contact with animals	44	59
<b>Clinical findings</b>		
Fever (>38°C)	95	79
Chills	52	50
Sweats	64	62
Headaches	68	58
Myalgias	41	35
Arthralgias	33	28
Pulmonary syndrome	37	31
With x-ray abnormality	18	49
Cutaneous manifestations	20	17
Neurologic findings	12	10
<b>Laboratory findings</b>		
Platelets <150 giga/liter	63	53
Transaminases >50 UI/liter	85	73

\* SD, standard deviation.

that blow in this area, it may be observed that both areas with a high Q fever prevalence are in the path of the wind which blows from areas with high sheep density (figure 3). It should be noted that the areas with high Q fever prevalence (Sausset, Carry, and Ensues) are more residential, and the inhabitants have to travel daily to their place of work.

### Sheep breeding

The total numbers of sheep (and number per 1,000 inhabitants) were as follows: Marseille area, 135 (0.16/1,000); Aix-en-Provence area, 780 (4.43/1,000); Etang de Berre area, 47,619 (131.7/1,000). In La Crau, which has only 27,187 inhabitants, there were 68,820 sheep. The sheep densities for each district in the Etang de Berre area are shown in figure 3. The majority of sheep are located in the areas of Salon-de-Provence, Istres, Grans, Miramas, and Cornillon. The monthly distribution of sheep births is presented in figure 2, showing that the vast majority of these births take place in October. When we compared the maps showing sheep densities and Q fever prevalence, it was obvious that there was no correlation between the sheep density and Q fever prevalence: the highest sheep densities are in Istres (prevalence: 0.06 percent) and Salon-de-Provence (prevalence: 0.35 percent), whereas in the areas with a high Q fever prevalence ( $\geq 0.8$ ) the densities of sheep are much lower ( $< 1/\text{km}^2$ ).

### DISCUSSION

Case identification was conducted in the same way in the study area and the two comparison areas, i.e., all cases were selected from the database of the National Reference Center having fulfilled the same case definition criteria. Such a selection permitted meaningful comparisons to be made between the three areas, and thus it can be concluded that the Etang de Berre area is highly endemic for Q fever, compared with the other two areas. It is also interesting to note that the incidence rate of chronic cases (three endocarditis cases for 360,000 inhabitants in 5 years, i.e., 1.7 per million per year) also appears to be markedly higher than the national rate of 1 per million per year (5).

Data from a recent survey of the seroprevalence of Q fever in dogs from Southern France and various foreign countries (23) also showed a higher prevalence in our study area (15 positives among 57 dogs (26.3 percent) from Istres and Miramas) than in Aix-en-Provence (1 positive among 17 dogs (5.9 percent)) ( $p = 0.06$ ).

This study was not a case-control survey to identify individual behavioral risk factors, which have been previously described (5). The epidemiologic findings among the cases were very similar to those observed in our earlier study (1). Various explanations for the overrepresentation of medical and paramedical occupations may be hypothesized: 1) physicians' interest in the disease may lead to a more frequent diagnosis; 2) these occupations lead to a higher exposure to the agent; and 3) their socioeconomic conditions lead them to live in or visit more exposed areas.

Contact with animals, especially with sheep, is usually considered to be a major risk factor (5). Sheep breeding is negligible in the Marseille and Aix-en-Provence areas. However, vast numbers of sheep are located in La Crau and in towns in the Etang de Berre area, such as Istres and Salon-de-Provence, which are located near La Crau. These breeding areas were in a clear windward direction of the areas with high incidences of Q fever. It might be interesting to try to understand why areas such as Châteauneuf, Gignac, or Marignane show lower Q fever incidence, although they are located in the path of the Mistral. Châteauneuf and Gignac are mountainous areas, where a vast majority of the inhabitants live in the southern part, close to Ensues and Le Rove. Moreover, this mountain chain might create specific wind conditions (e.g., wind speed tends to increase when blowing downhill). As for Marignane, a large part of this administrative area is occupied by the International Airport of Marseille.

The seasonal distribution of Q fever, showing a peak in late spring, has already been described (1), but has not yet explained. Figure 2 compares the seasonal dis-

tribution of the cases (with a 2-month delay) with that of the Mistral in the areas of Istres and Salon-de-Provence. Figure 2 shows the clear correlation between this wind and the number of Q fever cases. The relation can be established using Spearman correlation coefficients. It is interesting to notice that in October the strong winds from the northwest are only half as frequent as during the rest of the year. Conversely, more than 80 percent of the sheep give birth in October, frequently in open fields, thus not correlating with the seasonal distribution of Q fever cases. Another explanation for this late spring peak could be the increased number of lambs slaughtered for Easter, which takes place in March or April. Among Muslim populations, increased contact with sheep occurs during the Aïd-el-Khebir religious feast, also called "the sheep feast." At this time, many uncontrolled sheep are slaughtered, in unhygienic conditions, generally at home or in open fields. It is also interesting to notice that sheep herds are moved by open trucks in June to spend the summer in the Alps. The trucks are driven through the areas of Istres and Salon-de-Provence, where the largest herds are located, then through more northern cities (e.g., Mouries and Avignon), and not through the study area. This sheep transportation in June might also provide one of the explanations for the higher Q fever incidence in late spring and summer.

This study has demonstrated a graphical and statistical association between cases and wind frequencies which blow from areas with high densities of sheep, and confirms in cases the data on clinical presentation and exposure to known risk factors, mainly contact with animals. It thus combines two factors: first, the ecologic factor of the wind, whose effects can be monitored although not controlled; and second, the individual risk factors or practices related to contact with animals, whose effects are difficult to monitor, but might be partly prevented.

In conclusion, there is a highly endemic area close to Marseille, which constitutes a significant public health threat to the population. Over a 5-year period in a population of 300,000 inhabitants, six pregnant women were infected, of whom five aborted (24), and three patients presented a potentially fatal endocarditis. Although *Coxiella burnetii* transmission is multifactorial, we speculate that the higher endemicity in the study area might be related to a contamination by aerosols, because of the Mistral which blows on the local steppe where 70,000 sheep are bred in open fields. Further analysis and epidemiologic studies in this geographic area are required in order to confirm this hypothesis and to identify and quantify more thoroughly individual and preventable risk factors. Such

future work will enable health authorities to better orientate future surveillance and possible preventive measures which could be adopted.

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