



Q fever outbreaks

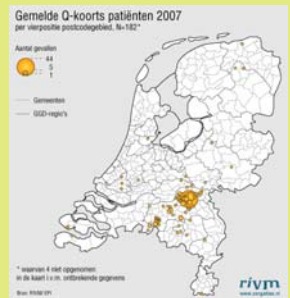
Syndromic approach for detection of hidden clusters.

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Introduction (1)

- Q fever
 - *C. burnetii*
 - Animal reservoir cattle/sheep/goats (abortion tissue)
 - Aerosol transmission to humans (also ingestion)
 - Symptoms: flu-like syndrome, pneumonia, hepatitis, endocarditis
- Netherlands: large Q fever outbreaks since 2007
 - Before 2007: 15 cases per year
 - 2007: 178 cases
 - 2008: 1000 cases
 - 2009: > 2200 cases, 6 deaths
 - 20-25% of the notified cases hospitalized
 - Rural areas in the southern part of the country



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Maps created by
Henriette Giesbers en
Ben Mom, RIVM

Introduction (2)

- Dairy goat farms putative source
 - >30 goat farms with Q fever abortion waves
 - » first farms reported in 2005



Did we detect the first human outbreak in 2007.....
or did we miss Q fever in earlier years or other areas?



Retrospective syndromic approach

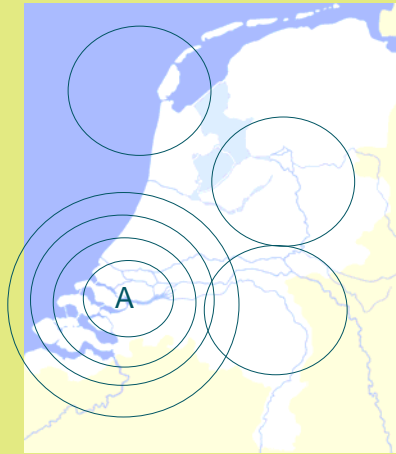
Data and analysis

- Hospitalizations 2005-2007 (>80 coverage, 16 million pop.)
 - Primary and secondary diagnoses
 - Q fever syndromes (ICD9 coded)
 - LRIs (Lower respiratory infections, 108338 included)
 - Hepatitis (3826 included)
 - Endocarditis (2130 included)
- Detect local clusters
 - Simulated prospective surveillance (retrospective data, weekly analysis)
 - Space-Time Scan Statistic
 - Satcan space-time permutation scan statistic

» Validated in earlier study → detects LRI outbreaks

Cluster detection

- in space and time
 - Space time scan statistic



- Flexible windows in time and space
- Clusterdetection based upon observed vs expected # cases in all possible circles A
- Time also varies, so circle A is actually a "cilinder"



- Satscan software: space time permutation scan statistic (www.satscan.org)
- (Expected # cases in A in week x)
= ((total # cases in A) / (total #cases)) * (total #cases in week x)

Evaluate clusters detected

- Plausibility that Q fever caused the clusters detected
 - epidemiological data (e.g. age distribution)
 - surveillance data on other pathogens (RSV/influenza)
 - geographical overlap with Q fever farms

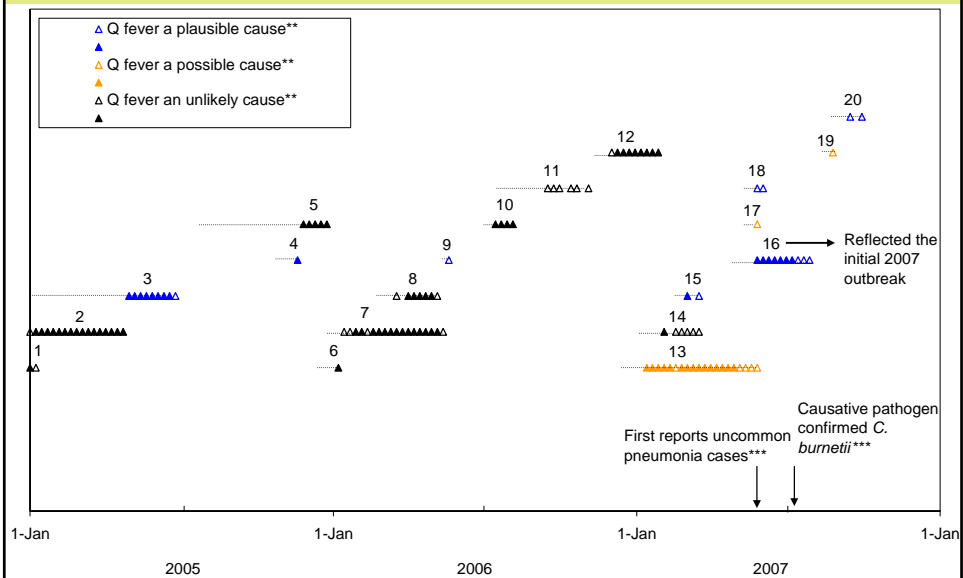
→ If detected prospectively

- detection of human Q-fever
 - before 2007?
 - in other areas?

Results

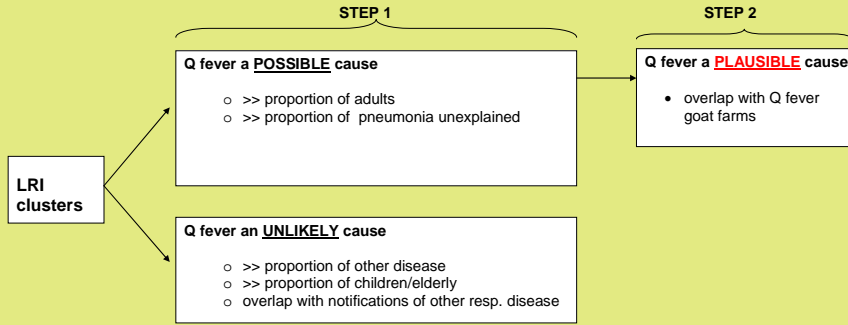
- 20 LRI clusters detected (2005-2007)
 - For 7 clusters Q fever a plausible cause
- 2 Hepatitis clusters detected (2005-2007)
 - For 1 cluster Q fever seemed a plausible cause
- No valid endocarditis clusters detected (3 with duplicates due to artifacts)

LRI clusters detected 2005-2007



Criteria: Did Q fever cause these clusters?

(two-step criteria for LRI clusters)



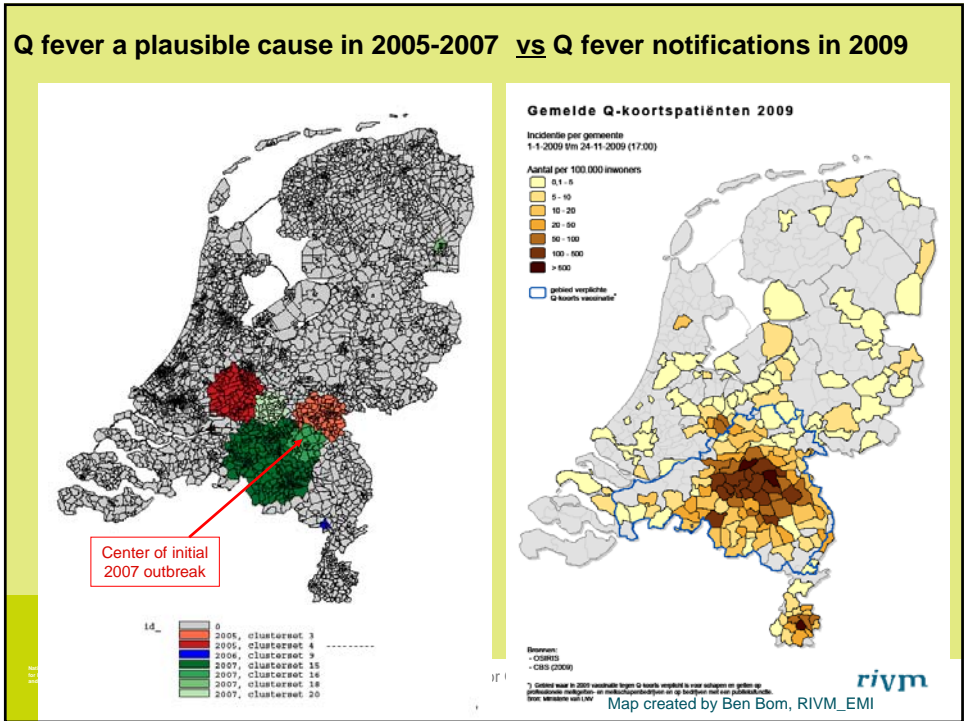
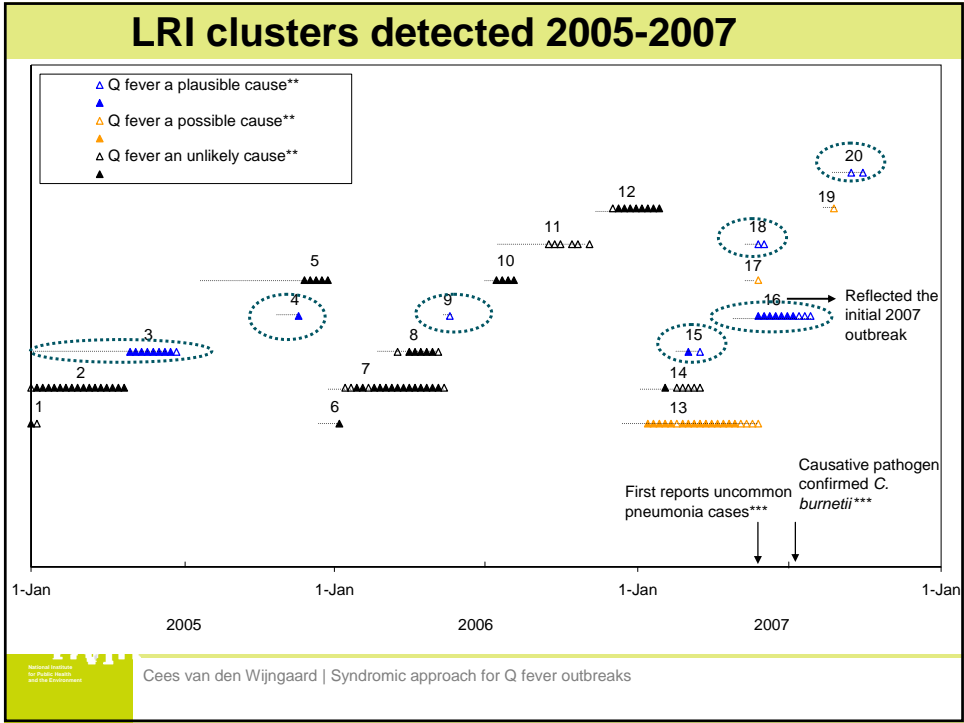
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Table B1. Detailed description of all space-time clusters in hospitalizations with LRI in 2005-2007.

Cluster	Center province	1 st signal	Total # signals	Total episode	Observed cases-#exceedance		Rat diti in km	Cluster characteristics and/or circumstantial evidence	Spatial overlap* with positive tested goat/sheep farms,**	Might the cluster have been caused by Q fever?	
					min	max					
1	ZH/NH	30oct2004	3	8	1994	6513	33	<ul style="list-style-type: none"> All cluster-signals had >> proportions (p <= 0.01) of bronchitis/bronchiolitis cases and 0-4 yrs of age 1 cluster-signal >> proportions of unexplained pneumonia 7 cluster-signals overlapped with regional influenza-like-illness elevations 	n/a	Q fever seems unlikely. Likely other causes: RSV/influenza	
2***	NB	01jan2005	1	16	26dec2004-23apr2005	244-151 = 70	10-14	<p>Q fever possible cause</p> <ul style="list-style-type: none"> 2 cluster-signals had >> proportions (p <= 0.01) of bronchitis and 0-4 yrs of age All cluster-signals overlapped with regional influenza-like-illness elevations, however the cluster only contains a relatively small area, whereas the regional influenza-like-illness elevations are measured by dividing the Netherlands in 4 widespread areas <p>Overlap infected farms</p>	4 goat farms: 1 firstly tested positive in 2006, 1 in 2007 and 2 in 2008	Q fever seems unlikely. Other causes: RSV/influenza	
3***	GLD	30apr2005	1	8	26dec2004-25jun2005	244-151 = 70	10-14	<ul style="list-style-type: none"> 2 cluster-signals had >> proportions (p <= 0.05) of 20-49 yrs of age All cluster-signals overlapped with regional influenza-like-illness elevations, however the cluster only contains a relatively small area, whereas the regional influenza-like-illness elevations are measured by dividing the Netherlands in 4 widespread areas 	4 goat farms: 1 firstly tested positive in 2006, 1 in 2007 and 2 in 2008	Q fever plausible cause	
4****	ZH	19nov2005	0	1	23oct2005-	n/a	149-93 = 17	<ul style="list-style-type: none"> The cluster-signal overlapped with regional influenza-like-illness elevations, however the cluster only contains a relatively small area, whereas the regional influenza-like-illness elevations are measured by dividing the Netherlands in 4 widespread areas 	2 goat farms and 1 sheep farm: 1 goat farm firstly tested positive in 2001, the other in 2007 and the sheep farm in 2008.	Q fever seems a plausible cause.	
5****	NH	26nov2005	0	5	24jan2005-24dec2005	2766-2502 = 264	3708-3388 = 320	51-53	<ul style="list-style-type: none"> 2 cluster-signals had >> proportions (p <= 0.05) of hospitalizations with legionellosis as discharge diagnosis 5 cluster-signals had >> proportions (p <= 0.01) of 0-4 yrs of age All cluster-signals overlapped with regional influenza-like-illness elevations, however the national influenza-like-illness incidence was below 3/10,000 pop. 	n/a	Q fever seems unlikely. Likely other causes: RSV/influenza, possibly Legionella as well.
6	NB	07jan2006	0	1	18dec2005-07jan2006	n/a	432-325 = 107	44	<ul style="list-style-type: none"> The cluster-signal had >> proportion (p <= 0.01) of bronchitis/bronchiolitis cases and 0-4 yrs of age 	n/a	Q fever seems unlikely. Likely other causes: RSV/influenza
7	OV	14jan2006	4	14	25dec2005-13may2006	220-153 = 67	2361-2130 = 231	28-59	<ul style="list-style-type: none"> 8 cluster-signals had >> proportions (p <= 0.05) of bronchitis/bronchiolitis cases (5 of these also at p <= 0.01) 16 cluster-signals had >> proportions (p <= 0.01) of 0-4 yrs of age 1 cluster-signal had >> proportions (p <= 0.05) of 0-4 and 5-19 yrs of age all cluster-signals overlapped with regional influenza-like-illness elevations a space-time cluster of 4 LD notifications overlapped with the cluster, however due to the large radius and time window of the LRI cluster this is possibly a coincidence (the LD cluster only had a window of 3 weeks). 	n/a	Q fever seems unlikely. Likely other causes: RSV/influenza
8	ZH	18mar2006	2	5	19feb2006-06may2006	31-11 = 20	1771-1574 = 197	4-28	<ul style="list-style-type: none"> 4 cluster-signals had >> proportions of bronchitis/bronchiolitis cases (p <= 0.01) and 5 cluster-signals >> proportions of 0-4 yrs of age (p <= 0.05, 3 of these cluster-signals also at p <= 0.01) 	n/a	Q fever seems unlikely. Likely other causes: RSV/influenza
9	LI	20may2006	1	0	14may2006-20may2006	n/a	5-0 = 5	3	<ul style="list-style-type: none"> no special cluster-signal characteristics 	2 goat farms (just next to the cluster area at the west-side); both firstly tested positive in 2007.	Q fever seems a plausible cause.

10	NH	15jul2006	0	4	2jul2006-5aug2006	19-4 = 15	98-53 = 45	6-19	<ul style="list-style-type: none"> All cluster-signals had >> proportions ($p \leq 0.01$) of hospitalizations with legionellosis as discharge diagnosis (ICD9 4828). All LRI cluster-signals strongly overlapped both in space and time with a cluster in legionnaires' disease notifications (max 50 cases). All cluster-signals occur in the already known episode and area of an LD outbreak in Amsterdam in 2006. 	n/a	Q fever seems unlikely . Certainly another cause: Legionella
11	ZH	16sep2006	6	0	16jul2006-4nov2006	102-60 = 42	160-105 = 55	6	<ul style="list-style-type: none"> All cluster-signals had >> proportions ($p \leq 0.01$) of bronchitis/bronchiolitis cases and 0-4 yrs of age All cluster-signals overlapped with regional influenza-like-illness elevations, however the national influenza-like-illness incidence was below 3/10,000 pop. 	n/a	Q fever seems unlikely . Likely another cause: RSV
12	GLD	2dec2006	1	8	12nov2006-27jan2007	932-790 = 142	2776-2512 = 264	34-55	<ul style="list-style-type: none"> The 9 consecutive cluster-signals move from the east to the center of the Netherlands 2 cluster-signals had >> proportions of bronchitis/bronchiolitis cases ($p \leq 0.01$) 4 cluster-signals had >> proportions of ≥ 65 yrs of age ($p \leq 0.05$, 1 signal $p \leq 0.01$) a space-time cluster of 15 LD notifications overlapped in time and slightly in space with the cluster, however due to the large radius of the LRI cluster this is possibly a coincidence (the LD cluster only had a window of 3 weeks). 	n/a	Q fever seems unlikely . Likely another cause: RSV/Influenza or possibly to some extent Legionella
13	NH	13jan2007	5	15	17dec2006-26may2007	28-8 = 20	127-78 = 49	3-5	<ul style="list-style-type: none"> All cluster-signals had >> proportions ($p \leq 0.01$) of unexplained pneumonia cases 3 cluster-signals had >> proportions of ≥ 65 yrs of age and 1 signal 5-19 yrs of age ($p \leq 0.05$) 1 hospitalization was diagnosed with pottacosis pneumonia and 2 with aspergillosis (which was significant different from the rest of the Netherlands at $p < 0.01$ and 0.05 in that order) 5 cluster-signals overlapped with regional influenza-like-illness elevations, however the national influenza-like-illness incidence was below 3/10,000 pop. 	No overlap with positive tested farms	Although this cluster did not exactly match the criteria for Q fever as a possible cause, we still decided to assess whether it overlapped with reported Q fever abortion waves because of the consistently high proportion of unexplained pneumonia cases.
14	DR/GR	3feb2007	5	1	14jan2007-17mar2007	71-36 = 35	653-330 = 123	20-60	<ul style="list-style-type: none"> All cluster-signals had >> proportions ($p \leq 0.01$) of bronchitis/bronchiolitis cases and 0-4 yrs of age 	n/a	Q fever seems unlikely . Likely another cause: RSV/Influenza
15	NB	3mar2007	1	1	18feb-17mar2007	182-120 = 62	550-440 = 110	19-29	<ul style="list-style-type: none"> 1 cluster-signal had >> proportions ($p \leq 0.05$) of unexplained pneumonia cases Both cluster-signals overlapped with regional influenza-like-illness elevations 	9 goat farms: 2 goat farms firstly tested positive in 2005, 3 goat farms in 2006, 2 in 2007 and 2 in 2008	Q fever seems a plausible cause (but regional influenza activity as well)
16	NB	26may2007	3	7	29apr2007-26jul2007	15-3 = 12	110-64 = 46	4-11	<ul style="list-style-type: none"> All cluster-signals had >> proportions of unexplained pneumonia cases ($p \leq 0.05$, 8 cluster-signals also at $p \leq 0.01$) 7 cluster-signals had >> proportions of 50-64 yrs of age ($p \leq 0.05$, 2 cluster-signals also at $p \leq 0.01$) and 9 cluster-signals 20-49 yrs of age ($p \leq 0.05$, 7 cluster-signals also at $p \leq 0.01$) All cluster-signals overlapped in space and time with a cluster of 31 Q fever notifications The cluster-signals occurred in the known 2007 Q fever outbreak area and episode, although in a slightly more widespread area. The cluster-signal had >> proportion of 50-64 yrs of age ($p \leq 0.05$) The cluster-signal overlapped with regional influenza-like-illness elevations, however the national influenza-like-illness incidence was below 3/10,000 pop. 	4 goat farms: 1 goat farm firstly tested positive in 2006 and 2 in 2007.	Q fever seems a plausible cause (or even certainly the cause as the cluster reflects the known 2007 outbreak)
17	NH	26may2007	1	0	13may2007-26may2007	n/a	11-1 = 10	6	<ul style="list-style-type: none"> The cluster-signal had >> proportion of 50-64 yrs of age ($p \leq 0.05$) The cluster-signal overlapped with regional influenza-like-illness elevations, however the national influenza-like-illness incidence was below 3/10,000 pop. 	No overlap with positive tested farms	Q fever seems possible .

18	DR	26may2007	2	0	13may2007-2jun2007	18-4 = 14	22-6 = 16	3	<ul style="list-style-type: none"> The cluster-signals had >> proportions of bronchitis/bronchiolitis cases ($p \leq 0.01$) The cluster-signals had >> proportions of 50-64 yrs of age ($p \leq 0.01$ and $p \leq 0.05$ in that order). Abortion waves were reported at 1 sheep farm within close range of the cluster area in 2005-2008. 	1 sheep farm (approximately 14 km south-west of the cluster center) firstly tested positive in 2006	Q fever seems a plausible cause.
19	ZH	25aug2007	1	0	12aug2007-25aug2007	n/a	24-7 = 17	4	<ul style="list-style-type: none"> The cluster-signals overlapped with regional influenza-like-illness elevations, however the national influenza-like-illness incidence was below 3/10,000 pop. The cluster-signal overlapped in space and time with a cluster of 5 pottacosis patients between June 24th and Sept 15th 2007, but with a much wider radius (22km). However, none of the pottacosis patients lived in the area that directly overlapped with the LRI cluster. 	No overlap with positive tested farms	Q fever seems possible .
20	GLD	15sep2007	2	0	19aug2007-19sep2007	44-19 = 25	62-31 = 31	10	<ul style="list-style-type: none"> Both cluster-signals had >> proportions ($p \leq 0.05$) of unexplained pneumonia cases. The cluster-signals overlapped in space and time with cluster-signals of 6 Q fever patients between sep2nd and dec 29th 2007, however no Q fever cases were notified that lived in postal codes areas that actually overlapped with the LRI cluster Abortion waves were reported at 1 goat farm within or at close range of the cluster area in 2005-2008. 	1 goat farm, that firstly tested positive in 2006	Q fever seems a plausible cause.



Further research necessary

- Serology on historical blood samples
 - to confirm that Q fever did cause these clusters
- no samples available from specific patients in 2005-2007....
 - Possibly blood donor samples from cluster areas?

Conclusion

- Substantial support Q fever outbreaks in 2005-2007
 - before detection of the known 2007 outbreak
 - in a wider geographical area (corresponding with 2008/09 outbreaks)
- Prospective syndromic surveillance could have detected these clusters
 - prompting further investigations and laboratory testing
 - possibly detection of Q fever outbreaks up to 2 years earlier and in a wider area

Acknowledgements

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Hepatis cluster for which Q fever seemed plausible cause



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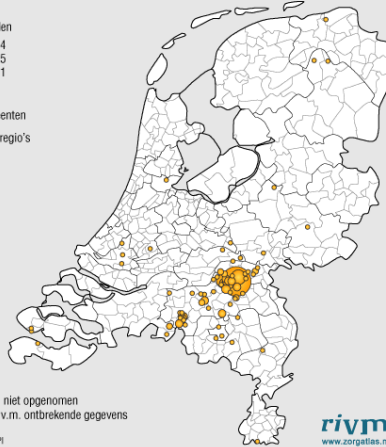
Hepatitis clusters

Set	Center province	1 st signal	Total # signals		Total episode	#observed-#expected = #exceedance		Radii in km	Cluster characteristics and/or circumstantial evidence	Spatial overlap* with positive tested goat/sheep farms,**	Might the cluster have been caused by Q fever?
			yr	Sy		min	max				
1	UT	10feb2007	1	0	7jun2007-10feb2007	n/a	28-11=17	19	* The cluster-signal overlaps in space and time with a cluster of 4 hepatitis C notifications.	n/a	Q fever seems unlikely , possible cause is hepatitis C
2	LI	12may2007	1	0	29apr2007-12may2007	n/a	10-2=8	26	-	2 goat farms, both firstly tested positive in 2007	Q fever seems a plausible cause

Gemelde Q-koorts patiënten 2007 per vierposities postcodegebied, N=182*

Aantal gevallen

— Gemeenten
 — GGD-regio's



* waarvan 4 niet opgenomen in de kaart i.v.m. ontbrekende gegevens

Bron: RIVM EPI

Q fever notifications 1 January - 31 December 2008 by four-position postal code areas, n = 994 (6 missing)

per 10,000 inhabitants

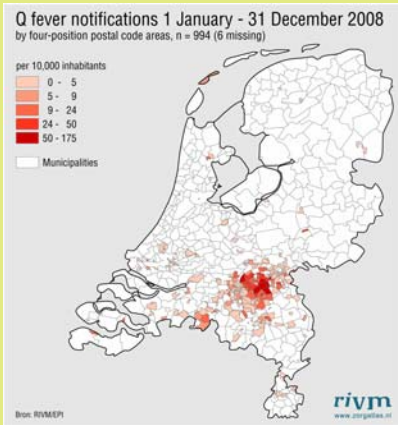
0 - 5
 5 - 9
 9 - 24
 24 - 50
 50 - 175

— Municipalities



Bron: RIVMEPI

Maps created by Henriette Giesbers and Cindy Deuning, RIVM-VTV



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