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Hajj pilgrims' knowledge about Middle East respiratory syndrome coronavirus, August to September 2013

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In preparation for Hajj 2013, 360 French pilgrims were interviewed regarding their knowledge about Middle East respiratory syndrome (MERS). Respondents were aged 20–85 years, male-female ratio was 1.05:1; 64.7% were aware of the MERS situation in Saudi Arabia; 35.3% knew about the Saudi Ministry of Health recommendations for at-risk pilgrims to postpone participation in the 2013 Hajj. None of 179 at-risk individuals (49.9%) decided to cancel their Hajj participation even after advice during consultation.

Background

After its emergence in June 2012 [1], most cases of Middle East respiratory syndrome coronavirus (MERS-CoV) infections were reported from Saudi Arabia (SA) [2] where the Hajj, the largest religious mass gathering takes place annually. A rapid acquisition of respiratory viruses, most notably rhinovirus was evidenced in 39% of French pilgrims suffering respiratory symptoms soon after commencing the 2012 Hajj, with 11% returning infected to France with potential spreading of these respiratory viruses [3]. No case of MERS-CoV nasal carriage was evidenced in this cohort, despite high rates of respiratory symptoms [4]. International spread of *Neisseria meningitis* infections by Hajj pilgrims has occurred in the past which prompted the requirement for meningococcal vaccination before participating in the pilgrimage [5]. The Hajj is expected to draw over three million pilgrims from within Saudi Arabia and around the world. Given the predicted population movements out of Saudi Arabia, there may be a potential for worldwide spread of MERS-CoV [6].

For the 2013 Hajj, the Saudi Ministry of Health (MoH) recommends that elderly people, above 65 years of age, and those with chronic diseases e.g. heart disease, kidney disease, respiratory disease and diabetes and pilgrims with immune deficiency such as congenital and acquired, malignancies and terminal illnesses, pregnant women and children (under 12) coming for Hajj and Umrah this year, postpone the performance of the Hajj and Umrah for their own safety [7].

Early results of the first week of 2013 mandatory meningococcal vaccination campaign for Hajj at our institution (19 to 25 August 2013) showed that 48% of pilgrims preparing for Hajj this year had at least one disorder for which the Saudi MoH recommends to postpone the performance of the Hajj [8]. These results prompted us to perform a knowledge, attitudes, and practices (KAP) survey that addressed MERS and its prevention among Hajj pilgrims presenting subsequently at our travel clinic.

Knowledge, attitudes, and practices survey among Hajj pilgrims

We conducted a KAP survey that addressed MERS and its prevention among Hajj pilgrims during four weeks, from 26 August to 22 September 2013. The study was based on a standardised questionnaire designed specifically by our team and comprising 15 items including demographics, previous participation to the Hajj, chronic conditions, pregnancy, vaccination status, knowledge about MERS and preventive measures against respiratory infections. A total of 360 persons (184 men, 176 women, ratio 1.05:1) aged 20-85 years (mean: 58 years) who attended our outpatient clinic as part of a pre-Hajj meningococcal vaccination campaign, were invited to participate in a face to- face interview during which a medical doctor completed the questionnaire. A 100% participation rate was achieved in the given period. Most pilgrims were born in North Africa (89.4%), had lived in France for more than 20 years (70.0%) and were traveling to Saudi Arabia for the first time (76.9%). A total of 49.2% had at least one condition for which the Saudi MoH recommends to postpone the performance of the 2013 Hajj (Table 1); 64.7% of the respondents were aware of an ongoing MERS epidemic in SA and 35.3% were aware of the Saudi MoH recommendations for at risk pilgrims to postpone performing the Hajj in 2013. Even though women pilgrims were statistically significantly less in the >65 years age group, there was no difference for the co-morbidities except for immune deficiency.

Table 1

Demographics and co-morbidities in Hajj pilgrims, France, August–September 2013 (n=360)

	Pilgrims in preparation for the Hajj (N = 360)	Men (n=184)	Women (n=176)	p value (men vs women)
Mean age in years (min-max) › 65 years ‹ 12 years	58.3 (20-85) 111 (30.8%) 0 (0.0%)	58.5 (20–85) 74 (40.4%) 0 (0.0%)	58.1 (22–79) 37 (21.0%) 0 (0.0%)	0.767 $<10^{-3}$ NA
Any co-morbidity	116 (32.2%)	56 (30.4%)	60 (34.1%)	0.458
Diabetes	83 (23.1%)	40 (21.7%)	43 (24.4%)	0.544
Chronic kidney disease	1 (0.3%)	0 (0%)	1 (0.6%)	0.489
Chronic heart disease	34 (9.4%)	15 (8.2%)	19 (10.8%)	0.391
Chronic lung disease	17 (4.7%)	8 (4.3%)	9 (5.1%)	0.732
Malignant disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
Immune deficiency	6 (1.7%)	0 (0.0%)	6 (3.4%)	0.013
Pregnancy	1 (0.3%)	NA	1 (0.6%)	NA
At least one condition for which the Saudi Ministry of Health recommends to postpone the performance of the Hajj	179 (49.9%)	99 (54.1%)	80 (45.5%)	0.102

NA: not applicable.

Among 179 at risk individuals (99 men, 80 women), none decided to cancel their participation to the Hajj after even after advice during consultation. However, when informed about the potential effectiveness of prevention measures against respiratory infection (use of face masks and disposable tissue, hand hygiene, social distancing and avoiding touching eyes, nose and mouth) most pilgrims (90.1%) were willing to apply such measures (Table 2).

Conclusions

Although our results cannot be extrapolated to all Hajj pilgrims, they show that pilgrims departing from southern France were unaware of the ongoing MERS epidemic and of the Saudi MoH recommendations before consulting a specialised travel clinic. However, such information was relayed by the French MoH in July 2013 to hospital healthcare providers, specialised travel agencies, and Muslim authorities, and was extensively covered in French newspapers. Moreover, despite receiving special advice about these issues during the pre-Hajj consultation in our specialised centre, at-risk pilgrims maintained their decision to participate in the 2013 Hajj. Although this was not documented in our survey, it could be that some pilgrims declined to change their plans because they had already arranged and paid for their travel before. Furthermore, it is possible that those pilgrims who come to our clinic are more health-conscious compared to pilgrims who received their mandatory vaccine from their general practitioner. Nevertheless, the latter group may also comprise a considerable number of at-risk individuals. Risk perception in the context of the Hajj is very likely influenced by cultural and religious beliefs. Identifying effective communication strategies for necessary preventive measures in the context of religious mass gatherings would be of high value for public health authorities those providing healthcare and advice to individuals. With the exception of travel restriction for at-risk individuals, a high acceptability rate towards individual preventive measures was observed among pilgrims which confirm previous results conducted in 2009 [9] and this should be noted during pre-travel advice consultations.

Conflict of interest

None declared.

Authors' contributions

Philippe Gautret: study design, result interpretation, writing manuscript; Samir Benkouiten: statistics, analysing results, reviewing manuscript; Imane Salaheddine: data collection; Khadidja Belhouchat: data collection; Tassadit Drali: data collection; Philippe Parola: reviewing manuscript; Philippe Brouqui: reviewing manuscript.

Table 2

Acceptability of preventives measures Hajj pilgrims, France, August–September 2013 (n=360)

Acceptability of preventives measures	n (%)
Use of face mask	314 (87.2%)
Hand washing	343 (95.3%)
Use of hand disinfectant	333 (92.5%)
Use of disposable tissue	337 (93.6%)
Avoiding contact with ill people	310 (86.1%)
Avoiding touching eyes, nose and mouth	310 (86.1%)

Source of preventive measures: [7].

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Late season interim estimates of influenza vaccine effectiveness reliably predict end of season estimates in Victoria, Australia, 2007 to 2012

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Twice each year the World Health Organization makes a recommendation for the composition of the influenza vaccine, based on circulating strains of influenza A(H3N2), A(H1N1) and B. Strain selection has always been based on immunogenicity studies with limited human data. Immunogenicity can be considered as a proxy for vaccine effectiveness (VE). However, only interim VE estimates for the target hemisphere can be considered in time for the strain selection meeting. Using surveillance data from Victoria, Australia, we retrospectively estimated and compared interim and final VE estimates for 2007 to 2012. In general, interim estimates were within five percentage points of final estimates. However, estimates made too early or in years of low influenza activity may be unreliable.

Introduction

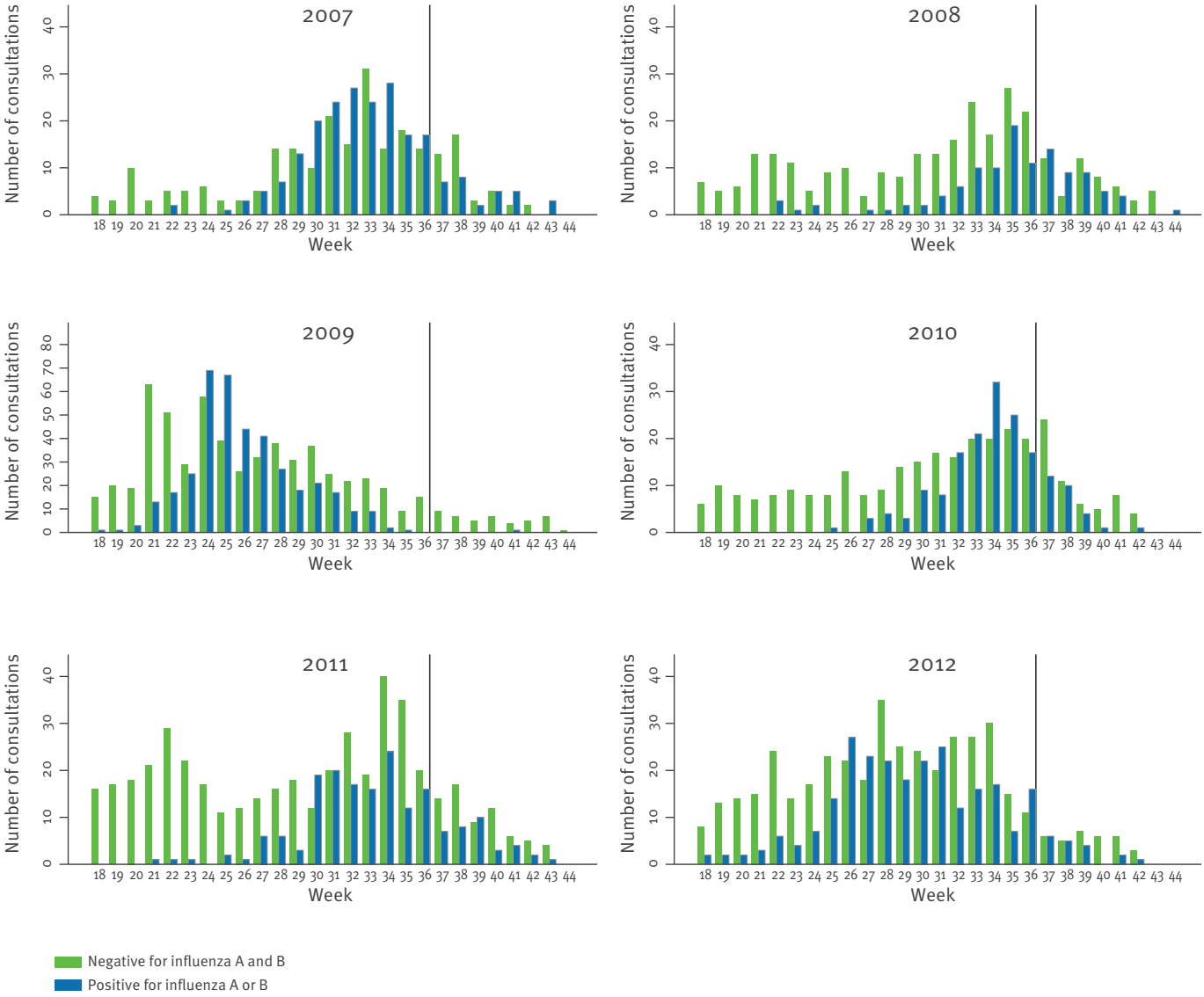
Twice every year, the World Health Organization (WHO) hosts an influenza vaccine strain selection meeting where data gathered by members of the Global Influenza Surveillance and Response System (GISRS) are reviewed and used to generate formal recommendations for the composition of seasonal influenza vaccines [1,2]. Recommendations for the northern hemisphere vaccine are made in February and for the southern hemisphere in September. Strain selection is based on serological data, with human data used to estimate immunogenicity, generally considered as a proxy for vaccine effectiveness (VE). At the February 2013 meeting, epidemiological data were submitted reporting interim VE estimates from surveillance systems in Canada, Europe and the United States (US). These estimates were published [3-8] and included for the first time with the package reviewed by GISRS meeting members. Final season estimates for the northern hemisphere were recently presented at the September 2013 meeting, as well as interim estimates for the southern hemisphere.

Interim estimates are vulnerable to change. First, as the season reaches its peak more data become available. For example, early US interim estimates released for the period from 3 December to 2 January 2013 [9] suggested a crude VE of 62% (95% confidence interval (CI): 51 to 71), while a second, lower interim estimate of 51% (95% CI: 43 to 58) was released later in February, with an adjusted estimate of 56% (95% CI: 47 to 63) [6]. The second interim estimate was made after the peak of influenza circulation had been reached, included more than double the sample size and had more complete information on covariates for adjustment and/or exclusion. Interim and final season estimates might also be expected to differ when the predominant type or subtype shifts within a season. For example, the early adjusted VE estimate from pooled European Influenza Monitoring Vaccine Effectiveness (I-MOVE) data in 2010/11 was 42% (95% CI: –7 to 69) [10] while the final estimate was 52% (95% CI: 30 to 67) [11]. In the interim analysis, 77% of viruses were influenza A(H1)pdm09 and 21% were influenza B, whereas the final analysis included 58% influenza A(H1)pdm09 and 38% influenza B viruses [10,11]. In the 2011/12 season final European estimates against influenza A(H3) were all revised down [12-14]. This was attributed to waning immunity against A(H3), a phenomenon that is being further investigated.

In the 2007/08 season, Belongia and colleagues compared interim and final estimates from US data, observing a difference of about seven percentage points (44%; 95% CI: 11 to 65 versus 37%; 95% CI: 22 to 49) [15]. They concluded that interim estimates were a useful indicator of VE mid-season. Systematic comparison of interim and final estimates has not been done since and has not been done for multiple seasons. To assess whether interim estimates reliably predicted final estimates, we compared retrospective interim and final VE estimates against influenza A and B for six influenza seasons, from 2007 to 2012, in Victoria, Australia.

Figure 1

Number of influenza-like-illness consultations per week by case status for the Victorian general practice sentinel surveillance network, Victoria, Australia, 2007–2012



Only patients from whom a swab was taken are included. The black vertical lines indicate the end of the interim period for the principle analysis (week 36). Note different y-axis scale used for 2009.

Methods

We used data collected as part of the Victorian General Practice Sentinel Surveillance network for the years 2007 to 2012 to calculate retrospective interim and final estimates. This network has been described in detail elsewhere [16]. Briefly, recruitment follows the case test-negative design [17-19]: a subset of patients seeing their general practitioner (GP) for influenza-like-illness (ILI; combination fever (measured or history of), cough and fatigue [20]) during the southern hemisphere influenza surveillance period are recruited at the GP's discretion, swabbed and tested for influenza by real-time reverse transcription-polymerase chain reaction (RT-PCR). Those testing positive for influenza A or B are cases and those testing negative are non-cases. The GPs collect demographic data (age, sex), symptom onset date, vaccination status, vaccination date and, since 2011, the presence of conditions predisposing the patient to severe influenza (chronic heart disease, chronic respiratory disease, diabetes, impaired immunity, obesity, pregnancy). Surveillance generally begins in epidemiological week 18 in April/May and ends in week 44 in October/November.

VE estimates from the sentinel network have been reported for all years from 2007 to 2012 [21-24]. The

present analysis compared interim with end-of-surveillance period estimates, where the interim period ended to coincide with the WHO vaccine strain selection meeting in September. This meeting usually falls around week 38, so the interim period was restricted to weeks 18 to 36, to hypothetically allow two weeks to generate estimates and submit the report to the WHO. Final estimates were calculated using the entire surveillance period (weeks 18–44). For simplicity, we used all available data for weeks 18 to 36 or weeks 18 to 44, without considering other markers for influenza activity (such as ILI or laboratory indicators), which we have previously shown can influence VE estimates in seasons when the VE estimates are not robust [25].

VE was estimated as (1 – OR) using logistic regression. Patients were considered vaccinated if they had received the vaccine ≥14 days prior to the onset of symptoms and excluded if vaccination took place <14 days. Patients were considered influenza-positive if they tested positive to any of influenza A(H1), A(H3) or influenza B viruses by real-time RT-PCR, but no separate analyses were conducted for type or subtype. Models were adjusted for age group (<18, 18–64, ≥65 years) and week of presentation. The sensitivity of the estimates was tested in four ways: (i) the end of the interim period was brought forward by one and two weeks; (ii) final estimates excluded patients presenting more than eight days after symptom onset to reduce the possibility of false negative results, an exclusion which may not be possible in an interim analysis; (iii) estimates were restricted to people in a target group for vaccination (people with predisposing conditions or aged ≥65 years); and (iv) different variables for adjustment were used in the interim and final models. The fourth sensitivity analysis was based on the likely scenario where some information would be missing for the interim analysis, such as complete data on the presence of a condition predisposing to severe influenza and the date of onset, and where a decision was made to change the age groups used to increase comparability with other studies. Thus, the model for the final VE estimate included a variable representing the presence of at least one comorbid condition and a variable indicating the time between onset and consultation, an additional age group was added (<18, 18–44, 45–64, ≥65 years) and month was used instead of week to denote calendar time. The third and fourth sensitivity analyses were restricted to the years 2011 and 2012 because data on predisposing conditions were only available for these two years.

Results

The data available for each year are shown in Figure 1 with lines indicating the end of the interim period. For all years, the peak of the season preceded the end of the interim period. The characteristics of participants were not different for interim and final estimates (Table).

Interim and final estimates were determined using the same model adjusting only for age group and week. There were no statistical differences between estimates, with point estimates varying by up to five percentage points (Figure 2). For 2007, 2008, 2010 and 2011 interim point estimates were lower than final estimates, while for other years interim estimates were higher. In the first sensitivity analysis, when the interim period was shortened by one week, there continued to be little difference in estimates for all years except 2008, where estimates differed by more than 10 percentage points. Shortened by a further week, estimates for 2008 continued to show great variability, and the direction of effect was reversed.

The second sensitivity analysis excluded people presenting more than eight days since symptoms onset (or for whom the onset date was not recorded), resulting in the exclusion of 437 people from the analysis (Table). VE estimates with this exclusion criterion were 61% (95% CI: 30 to 79) for 2007, –7% (95% CI: –123 to 49) for 2008, –2% (95% CI: –49 to 30) for 2009, 69% (95% CI: 41 to 84) for 2010, 48% (95% CI: –2 to 74) for 2011, and 44% (95% CI: 12 to 64) for 2012. VE estimates were within four percentage points of those made without the exclusion criterion, with the exception of 2009; The 2009 estimates differed by nine percentage points and this year had the most exclusions (n=197).

The third and fourth sensitivity analyses were restricted to 2011 and 2012, the only two years for which data on comorbidity were collected. When interim and final estimates were compared for only those people in a target group for vaccination, the interim estimate was 61% (95% CI: –149 to 94) for 2011, while the final estimate was 48% (95% CI: –110 to 87). For 2012, the interim estimate was 30% (95% CI: -60 to 69), while the final estimate was 32% (95% CI: –52 to 70). Interim and final estimates were also compared when using different models for the estimates. The interim model adjusted for age group (<18, 18–64, ≥65 years) and week, while the final model included presence of a predisposing condition, days between symptom onset and consultation, an additional age group (<18, 18–44, 45–64, ≥65 years) and month. The interim and final estimates for 2011 were 44% (95% CI: –26 to 75) and 43% (95% CI: –20 to 73) respectively, and for 2012 were 49% (95% CI: 21 to 68) and 44% (95% CI: 13 to 69).

Discussion

We found that interim VE estimates over six influenza seasons closely approximated final estimates when the interim period was limited to week 36. When the interim period was shortened, estimates for 2008 were different by more than ten percentage points. Estimates for 2008 showed the greatest instability, which may be explained by that year's smaller sample size and the timing of the season, the peak of which fell later than in other years in week 35 (Figure 1). Only one interim estimate has previously been reported for this surveillance network, for the 2009 pandemic [26], a season

Table

Characteristics of patients with influenza-like-illness, Victoria, Australia, 2007–2012

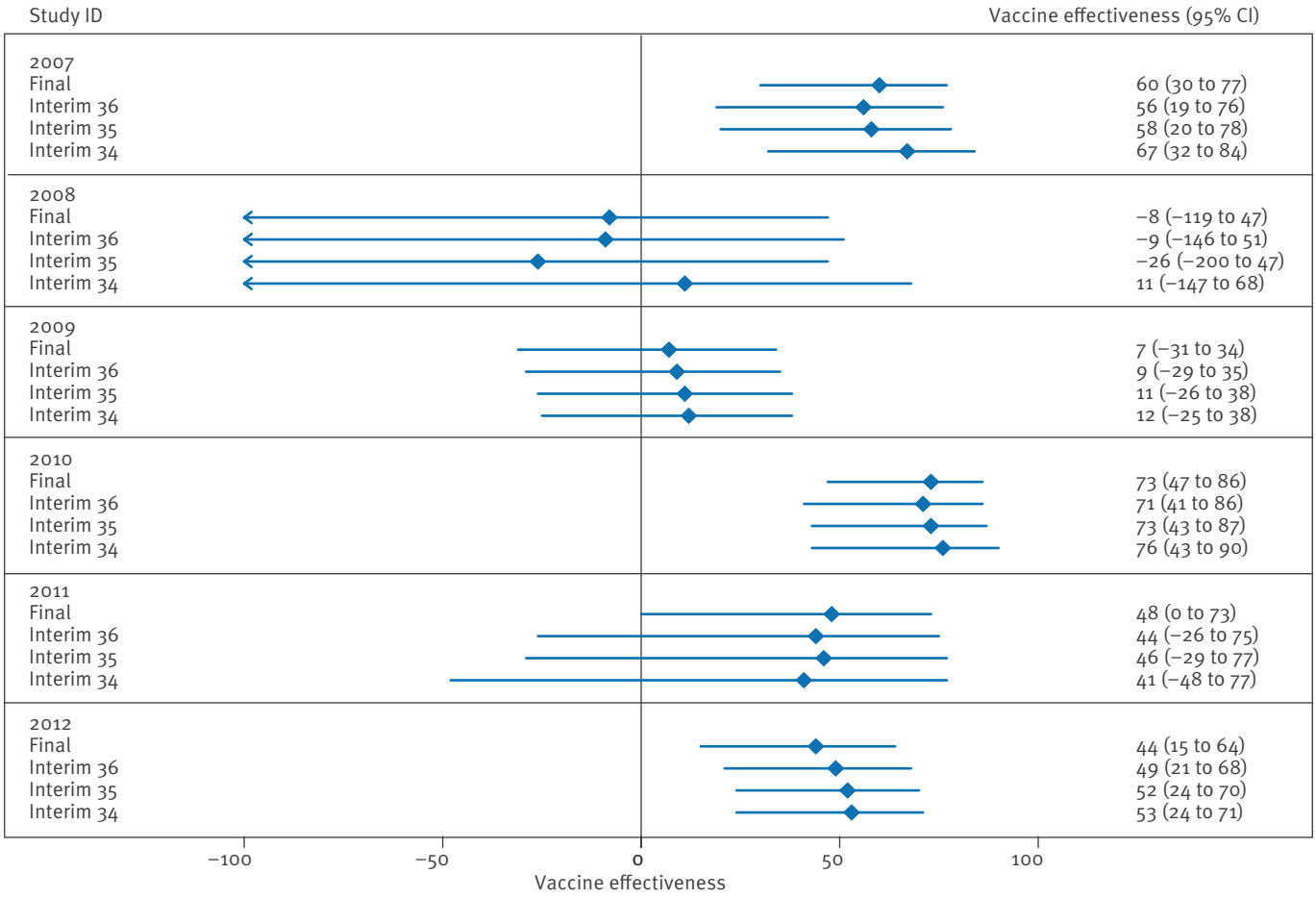
	2007			2008			2009			2010			2011			2012		
	Interim n (%)	Final n (%)	p-value[a]	Interim n (%)	Final n (%)	p-value[a]	Interim n (%)	Final n (%)	p-value[a]	Interim n (%)	Final n (%)	p-value[a]	Interim n (%)	Final n (%)	p-value[a]	Interim n (%)	Final n (%)	p-value[a]
Total swabbed	392	466	ND	310	404	ND	1,010	1,060	ND	391	478	ND	551	665	ND	653	710	ND
Total included[b]	386	458	ND	304	396	ND	955	1,003	ND	378	464	ND	530	632	ND	627	678	ND
Sex[c]																		
Female	182 (47)	217 (47)	0.9	151 (50)	192 (48)	0.8	452 (48)	474 (48)	1	169 (49)	208 (50)	0.8	266 (50)	317 (50)	1	326 (52)	356 (53)	0.9
Male	204 (53)	241 (53)		153 (50)	204 (52)		493 (52)	519 (52)		179 (51)	212 (50)		263 (50)	313 (50)		301 (48)	322 (47)	
Age group																		
<18 years	64 (17)	73 (16)	1	44 (14)	62 (16)	0.8	264 (28)	273 (27)	1	77 (20)	98 (21)	0.9	172 (32)	200 (32)	0.9	162 (26)	172 (25)	0.9
18–64 years	298 (77)	357 (78)		235 (77)	306 (77)		653 (68)	691 (69)		289 (76)	353 (76)		337 (64)	409 (65)		415 (66)	455 (67)	
≥65 years	24 (6)	28 (6)		25 (8)	28 (7)		38 (4)	39 (4)		12 (3)	13 (3)		21 (4)	23 (4)		50 (8)	51 (8)	
Vaccination status																		
Unvaccinated	316 (82)	370 (81)	0.7	244 (80)	326 (82)	0.5	760 (80)	798 (80)	1	300 (79)	372 (80)	0.8	467 (88)	548 (87)	0.5	475 (76)	516 (76)	0.9
Vaccinated	70 (18)	88 (19)		60 (20)	70 (18)		195 (20)	205 (20)		78 (21)	92 (20)		63 (12)	84 (13)		152 (24)	162 (24)	
Influenza A or B																		
Negative	198 (51)	240 (52)	0.7	232 (76)	282 (71)	0.1	570 (60)	617 (62)	0.4	238 (63)	296 (64)	0.8	385 (73)	452 (72)	0.7	382 (61)	415 (61)	0.9
Positive	188 (49)	218 (48)		72 (24)	114 (29)		385 (40)	386 (38)		140 (37)	168 (36)		145 (27)	180 (28)		245 (39)	263 (39)	
Influenza type/subtype																		
A(H1)	46 (24)	48 (22)	0.5	4 (6)	4 (4)	0.4	343 (89)	343 (89)	1	121 (86)	146 (87)	1	26 (18)	27 (15)	0.6	23 (9)	23 (9)	0.5
A(H3)	115 (61)	127 (58)		22 (31)	41 (36)		7 (2)	7 (2)		7 (5)	7 (4)		46 (32)	64 (36)		198 (80)	205 (78)	
A(mixed)	1 (1)	1 (0)		0(0)	0(0)		0(0)	0(0)		0(0)	0(0)		0(0)	0(0)		0(0)	0(0)	
A(NS)	7 (4)	7 (3)		1 (1)	6 (5)		35 (9)	36 (9)		8 (6)	11 (7)		4 (3)	9 (5)		0(0)	0(0)	
B	19 (10)	35 (16)		45 (63)	63 (55)		0(0)	0(0)		4 (3)	4 (2)		69 (48)	80 (44)		24 (10)	35 (14)	
Presentation after time of symptoms onset (exclusion of > 8days or date of symptom unknown made for final estimates only in sensitivity analysis 2)[d]																		
≤8 days	NA	412 (90)	NA	NA	359 (91)	NA	NA	806 (80)	NA	NA	425 (92)	NA	NA	588 (93)	NA	NA	604 (89)	NA
>8 days or onset date unknown	NA	46 (10)		NA	37 (9)		NA	197 (20)		NA	39 (8)		NA	44 (7)		NA	74 (11)	
In a target group for vaccination (for sensitivity analysis 3)[e]																		
No	ND	ND	NA	ND	ND	NA	ND	ND	NA	ND	ND	NA	462 (87)	550 (87)	0.9	498 (79)	542 (80)	0.8
Yes	ND	ND		ND	ND		ND	ND		ND	ND		68 (13)	82 (13)		129 (21)	136 (20)	
Has a condition predisposing to severe influenza (for sensitivity analysis 3 and 4)[f]																		
No	ND	ND	NA	ND	ND	NA	ND	ND	NA	ND	ND	NA	411 (88)	483 (88)	0.9	473 (82)	512 (82)	0.9
Yes	ND	ND		ND	ND		ND	ND		ND	ND		55 (12)	67 (12)		103 (18)	109 (18)	

A(NS): Influenza A (not subtyped); NA: not applicable; ND: not determined.

[a] p-values are for the chi-squared test comparing characteristics of patients used in the interim versus final estimates.
[b] Patients were excluded if missing vaccination status or age.
[c] Figures may not sum to 'Total included' due to missing data. Complete information on sex was not a criterion for inclusion in the analysis.
[d] Data not provided for interim columns because this exclusion was only made for final estimates in sensitivity analysis 2.
[e] Target group for vaccination includes people aged >65years or with a condition predisposing them to severe influenza (not collected in 2007–2010).
[f] Data on predisposing conditions not collected in 2007–2010.

Figure 2

Interim and final vaccine effectiveness estimates against influenza A and B for six influenza seasons, Victoria, Australia, 2007–2012



CI: confidence interval; ID: identity.

All models adjusted for age group (‹18, 18–64, ≥65 years) and week of presentation. Oldest age group dropped from all models in 2010 due to perfect prediction (no unvaccinated cases). Final refers to the period defined by weeks 18–44; interim 36 is weeks 18–36; interim 35 is weeks 18–35; interim 34 is weeks 18–34.

which started and peaked earlier than in other years. The final estimate for that year used a more complete model with data collected over a much longer period but the VE point estimate was the same, and differed by only four percentage points when the analysis was restricted to the weeks of maximum influenza activity [22]. Thus, interim estimates may be their most reliable when made after the peak, which is more likely in seasons which start early. For weeks 18 to 36 of the 2013 season, our interim estimate at the time of writing was 43% (95% CI: −30 to 75). However, like 2008, the 2013 season has been characterised by a late start and relatively low activity. In addition the VE estimate was unusually sensitive to the model used. Consequently, we expect the interim estimate for 2013 to be less reliable than in other years.

We expected interim estimates would be their least reliable when made for specific, smaller groups, such as people in a target group for vaccination. Moreover in the presence of waning VE within a season, it would be expected that the distribution of vaccinated cases would be skewed towards the end of the season, resulting in a lower final VE estimate. For example, in the 2011/12 European season, pooled estimates against A(H3) for people in a target group for vaccination were 43% (95% CI: −0.4 to 68) in the interim [27] and 25% (95% CI: −6 to 46) at the end of the season [12]. Similarly, our final estimates for people in a target group for vaccination in 2011 declined 13 percentage points, from 61% to 48%. Conversely, estimates increased two percentage points in 2012 but the sample size was larger in 2012 and the season peaked earlier. Meaningful differences between interim and final estimates might also be expected when making estimates separately for each type/subtype, as the distribution of cases may be skewed or the number of exposed cases may be small.

Estimates varied little when the model used for final estimates was altered, as was done in the second and fourth sensitivity analyses. The restriction of patients to include only those presenting within eight days was done to reduce the possibility of false negatives. However, this modification to the model may not be expected to alter estimates, as imperfect, nondifferential sensitivity in the presence of perfect specificity will not usually bias estimates [19, 28]. In contrast, modifying the covariates in the model might be expected to have a greater impact on both point estimates (by removing or introducing bias) and precision. By comparison with the principle analysis, we observed modest changes using a larger model, suggesting the more parsimonious model would have sufficed for these data. However, this may not always be the case. In some circumstances, larger models can reduce the effective sample size used due to complete or quasi-complete separation (also known as perfect prediction), which can inflate estimates and reduce precision [29]. For the data reported here, perfect prediction led to the loss of the oldest age group in the 2010 analyses. This problem has also been reported by the I-MOVE investigators when including calendar time (week) as a categorical variable, due to perfect prediction within a week or weeks [11]. In such cases, it may be preferable to employ methods such as exact logistic regression or penalised likelihood estimation to avoid generating biased estimates [29].

The relatively recent adoption of the test-negative study design [17-19] has permitted rapid dissemination of VE estimates on a yearly and interim basis, and consideration of these estimates in vaccine strain selection meetings has been suggested for some time [30]. However at this early stage, VE estimates are unlikely to influence strain selection; VE studies are less developed than the immunogenicity studies that have been used for decades to guide strain selection and should not yet be expected to provide reliable estimates of VE by type, sub-type, age-group and target group. However, our results illustrate the likely range of protection afforded by trivalent influenza vaccines (the only vaccines licensed in Australia) and support the use of late interim estimates as a proxy for final estimates. As VE studies evolve, their usefulness for strain selection should improve. The results presented here are hypothetical comparisons using cleaned data. It would be instructive to see a similar retrospective comparison for countries in the northern hemisphere.

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Conflict of interest

None declared.

Authors' contributions

SGS conceptualised the study, undertook analysis and interpretation of the data, and participated in writing the manuscript. HK conceptualised the study, undertook interpretation of the data and participated in writing the manuscript.

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A dynamic case definition is warranted for adequate notification in an extended epidemic setting: the Dutch Q fever outbreak 2007–2009 as exemplar

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Q fever is a notifiable disease in the Netherlands: laboratories are obliged to notify possible cases to the Municipal Health Services. These services then try to reconfirm cases with additional clinical and epidemiological data and provide anonymised reports to the national case register of notifiable diseases. Since the start of the 2007–2009 Dutch Q fever outbreak, notification rules remained unchanged, despite new laboratory insights and altered epidemiology. In this study, we retrospectively analysed how these changes influenced the proportion of laboratory-defined acute Q fever cases (confirmed, probable and possible) that were included in the national case register, during (2009) and after the outbreak (2010 and 2011). The number of laboratory-defined cases notified to the Municipal Health Services was 377 in2009, 96 in 2010 and 50 in 2011. Of these, 186 (49.3%) in 2009, 12 (12.5%) in 2010 and 9 (18.0%) in 2011 were confirmed as acute infection by laboratory interpretation. The proportion of laboratory-defined acute Q fever cases that was reconfirmed by the Municipal Health Services and that were included in the national case register decreased from 90% in 2009, to 22% and 24% in 2010 and 2011, respectively. The decrease was observed in all categories of cases, including those considered to be confirmed by laboratory criteria. Continued use of a pre-outbreak case definition led to over-reporting of cases to the Municipal Health Services in the post-epidemic years. Therefore we recommend dynamic laboratory notification rules, by reviewing case definitions periodically in an ongoing epidemic, as in the Dutch Q fever outbreak.

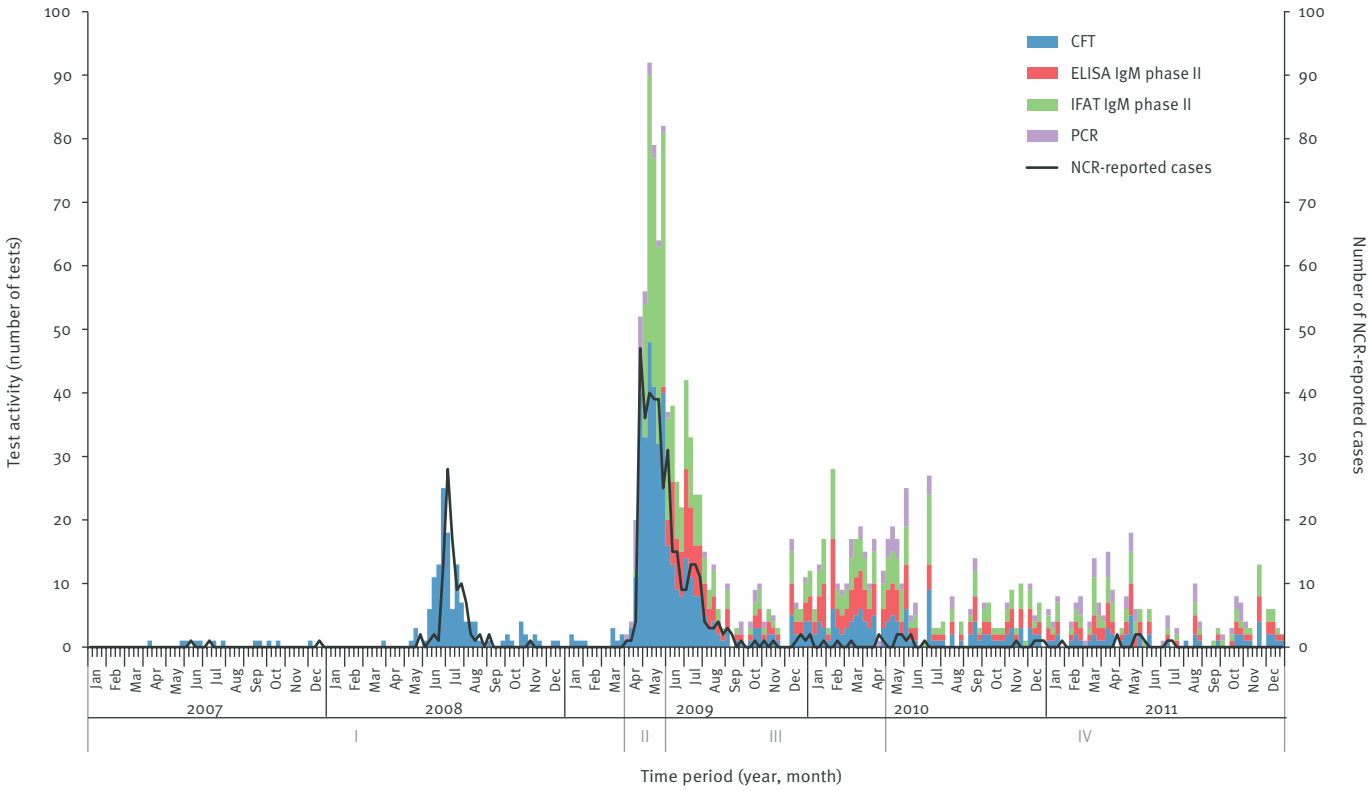
Introduction

Q fever is a zoonotic disease and human infections result mainly from inhalation of *Coxiella burnetii*-contaminated aerosols [1-3]. Domestic ruminants are the main reservoir of the causative pathogen. Infected animals can shed *C. burnetii* in their milk or faecal excretions. Infections in humans can occur after contact with infected animals or contaminated dust [1-3]. Acute Q fever is mostly self-limiting, but antibiotic treatment can reduce the duration of symptoms [1-3]. Early detection of Q fever cases is hampered by the atypical polymorphic presentation of symptoms, ranging from asymptomatic to influenza-like illness, fever and pneumonia in acute infections. Therefore under-reporting is quite substantial, especially in the beginning of an outbreak or if there is no knowledge of possible animal contact history [1-3]. The incubation period for *C. burnetii* infections is generally 9–40 days. About 1–5% of all Q fever cases may progress to chronic infection, often leading to a life-threatening endocarditis or vascular infection [1,2].

Q fever has been a notifiable disease since 1976 in the Netherlands. The head of diagnostic microbiology laboratories and the treating physicians are obliged to notify the local public health authorities (the Municipal Health Services, MHS) of possible cases [4]. In accordance with the Public Health Act, the MHS provides anonymised reports to the national case register (NCR) of notifiable diseases [4]. The decision of the MHS to report acute Q fever cases to the NCR is based on the combination of laboratory supporting evidence together with clinical information. Soon after a patient is notified to the MHS, clinical information is acquired by a MHS infectious disease specialist by consulting

Figure

Epidemic curve of 2007–2009 regional Q fever outbreak and post-outbreak years (2010–2011) combined with test activity by time period, south-east Brabant, the Netherlands (n=622)[a,b]



CFT: complement fixation test, ELISA: enzyme-linked immunosorbent assay; IFAT: indirect fluorescent antibody test; NCR: national case register; PCR: polymerase chain reaction.

Time periods: before April 2009 (I), between April and May 2009 (II), between June 2009 and April 2010 (III), from May2010 to December 2011 (IV).

Each bar represents all tests performed at that time for notified patients.

[a] In 2007, n=3; in 2008, n=96; in 2009–2011, n=523.

[b] Data from Laboratory for Pathology and Medical Microbiology (PAMM), Veldhoven, the Netherlands, including occasional PCR results before April 2010 from an external laboratory.

the physician and by questioning the patient using a questionnaire. Whenever a patient presents with at least one of three parameters (fever, pneumonia or hepatitis), a case is reconfirmed and reported to the NCR.

Q fever diagnosis is based on DNA detection by polymerase chain reaction (PCR) and serology [5,6]. The presence or absence of four different types of antibodies determines different stages of the infection. IgM and IgG antibodies against *C. burnetii* phase II antigen have been associated with early stages of illness, whereas IgM phase I and especially IgG phase I antibodies are indicative of ongoing (chronic)Q fever [2].

Various serological tests are available for acute Q fever, including indirect fluorescent antibody tests (IFATs), enzyme-linked immunosorbent assays (ELISAs) and complement fixation tests (CFTs). Recently, it was shown that the performances of these tests, in terms of confirming acute Q fever, were comparable [7]. In our laboratory in the south-east of Brabant (Laboratory for Pathology and Medical Microbiology (PAMM), Veldhoven), all three serological tests listed, together with PCR, are used for the diagnosis of acute Q fever. An algorithm was developed that supports the choice of PCR and/or serology based on the time between the first day of symptom onset and serum collection [8].

The south of the Netherlands experienced a large-scale outbreak of Q fever over three consecutive years (2007–2009), with the highest peak in 2009 [9,10]. At the beginning of the outbreak, a national case definition, including laboratory diagnostics, was established

and used for mandatory notification [11]. This case definition was not modified during the outbreak, and was based on the knowledge available in the Netherlands about Q fever diagnostics at that time, which was quite limited. As this outbreak constitutes one of the largest outbreaks ever recorded, with more than 4,000 acute Q fever cases notified, comparative laboratory-based studies yielded new insights on diagnostic markers for acute Q fever. Most importantly, it was shown that the serological response after infection is long-lasting and that IgG phase II as well as IgM phase II antibodies are detected in more than half of acute Q fever cases a year after symptom onset [7]. This implies that the serological diagnosis of acute Q fever based on a single serum sample – which was part of the case definition – can be inaccurate.

In the study presented here, we evaluated the specificity of the laboratory-defined acute Q fever cases during (2009) and after the epidemic (2010 and 2011). We also wanted to illustrate that interactions between the laboratory, physician and public health staff become more complex during an ongoing epidemic. Adaptation of the interpretation of laboratory results is warranted more and more in such a situation, especially when the laboratory techniques change over time.

Methods

Case definition

The current Dutch case definition for acute Q fever, based on clinical parameters and laboratory results, was used [11], i.e. any personwho presents with at least one of three symptoms: fever, pneumonia and/or hepatitis, combined with positive laboratory results from any of the following three tests:

- detection of *C. burnetii* DNA in serum of patients without signs of chronic Q fever;
- serum conversion or fourfold rise in IgG-specific phase II antibody titre by IFAT or CFT;
- single serum detection of IgM phase II antibodiesby IFAT or ELISA with or without IgG phase II antibodies.

Diagnostic tests and outcomes

During the study period (January 2009 to December 2011), new tests were implemented in our laboratory, situated in the south-east of the province of Brabant. The evolution of the outbreak challenged the diagnostic capacities in the affected regions (Figure). Firstly, ELISA IgM phase II was introduced, to improve throughput time by automation. Secondly, IFAT was introduced, to improve specificity. Finally, PCR was introduced, to improve early diagnosis (Table 1). A detailed description of the different test methods has been published [9]. Due to the introduction of new techniques throughout the years, seven different outcomes lead to case notification to the MHS (Table 2). On the basis of the laboratory criteria, whenever PCR was positive or a fourfold rise in IgG phase II antibodies was measured using CFT (outcomes 1 and 2, Table 2), the patient was considered to be a confirmed acute Q fever case. Whenever IgG phase II antibodies using CFT and IgM phase II antibodies using ELISA and/or IFAT were measured in a single serum sample, the patient was considered a probable case of acute Q fever (outcomes 3, 4 and 5). When only IgM phase II antibodies using ELISA and IFAT were detected, cases were considered to be possible acute cases (outcomes 6 and 7).

Table 1

Test methods used during (2009) and after (2010–2011) the 2007–2009 Q fever outbreak, the Netherlands[a]

Time period	Duration of symptoms[b]	Methods
I January 2009– March 2009	Not applicable	CFT PCR[c]
II April 2009– May 2009	Not applicable	IFAT IgM phase II CFT PCR[c]
III June 2009– April 2010	Not applicable	ELISA IgM phase II confirmed by IFAT IgM phase II[d] CFT PCR[c]
IV April 2010– December 2011	≥21 days or unknown	ELISA IgM phase II confirmed by IFAT IgM phase II[d] CFT
	<21 days	PCR[e]

CFT: complement fixation test; ELISA: enzyme-linked immunosorbent assay; IFAT: indirect fluorescent antibody test; PCR: polymerase chain reaction.

[a] Data from Laboratory for Pathology and Medical Microbiology (PAMM), Veldhoven.

[b] An algorithm, based on the time between the first day of symptom onset and serum collection, comprises the use of PCR and serology tests. For patients sampled within the first two weeks of illness, it is recommended to perform PCR. For patients having first contact with a physician later than two weeks post-symptom onset or for patients for whom the date of symptom onset is not known, serology is recommended as the initial test.

[c] Before April 2010, PCR was occasionally performed in an external laboratory. Whenever PCR was negative, IgM phase II testing was performed (ELISA IgM phase II confirmed by IFAT IgM phase II).

[d] ELISA IgM phase II positive samples were confirmed using IFAT.

[e] From April 2010, PCR was implemented in routine Q fever testing in our laboratory. Whenever PCR was negative, IgM phase II testing was performed (ELISA IgM phase II confirmed by IFAT IgM phase II).

Reporting to the national case register

The notification system in the Netherlands works like a funnel: firstly, all laboratory-defined acute Q fever patients (confirmed, probable and possible) were notified by the laboratory to the MHS. Secondly, the MHS infectious disease specialist reviewed all cases. If the case also met the clinical criteria, notification was reconfirmed and reported to the NCR. If the case did not meet these criteria, it was registered as not notifiable.

Table 2

Laboratory-defined acute Q fever patients based on test methods used, the Netherlands, 2007–2011

PCR positive	CFT IgG phase II increase[a]	CFT IgG phase II positive[b]	ELISA IgM phase II positive	IFAT IgM phase II positive[c]	Outcome	Laboratory interpretation
X					1	Confirmed case
	X				2[d]	Confirmed case
		X	X	X	3	Probable case
		X		X	4	Probable case
		X			5	Probable case
			X	X	6	Possible case
				X	7	Possible case

CFT: complement fixation test; ELISA: enzyme-linked immunosorbent assay; IFAT: indirect fluorescent antibody test; PCR: polymerase chain reaction.

[a] IgG phase II increase defined as a fourfold titre increase or seroconversion, measured by CFT.

[b] Cut-off titre >1:4.

[c] Cut-off titre ≥1:32.

[d] A serum pair for one episode of Q fever was defined whenever these sera were collected within 90 days.

Data analysis

The dataset with the reconfirmed and not-notifiable acute Q fever cases from MHS Brabant-South-East was merged with the laboratory test results, based on the patients' six-digit postal code and date of birth. After merging, retrospective analysis of the acute Q fever cases during 1 January 2009 to 31 December 2011 was conducted. Descriptive analysis included age and sex. Cases were grouped according to the laboratory interpretations (1–7) and reviewed to assess what proportion was finally included in the NCR.

Statistical analysis included computations of laboratory-outcome frequencies per year and the percentage of reconfirmed notified and not-notifiable cases per year. Significance in these groups computed using one-sided Mann–Whitney test and Fisher's exact test, respectively.

Results

Patients' characteristics

From 1 January 2009 to 31 December 2011, 658 Q fever patients were reported by laboratories in south-east Brabant to the MHS, of which 523 were from our laboratory. The remaining 135 patients were reported by other laboratories in the region and were not included in the analysis. The mean age of the 523 patients was 49 years (standard deviation (SD): 16), and 320 (61.2%) were male.

Diagnostic tests and outcomes

Of the 523 laboratory-defined cases notified to the MHS by our laboratory, 377 occurred in 2009, 96 in 2010 and 50 in 2011. During these three years, the distribution of laboratory outcomes changed substantially (Table 3): in 2009, 49.3% (186/377) of the patients in the MHS database were considered confirmed cases, mainly based on IgG seroconversion. Although PCR was indicated for most of the cases, it was seldom performed because this technique was not implemented in our laboratory before April 2010. Only 17.2% (65/377) of the notified patients in 2009 were considered possible cases, based on single IgM phase II response. The distribution changed over the years, with far fewer patients belonging to the confirmed category based on laboratory criteria in 2010 and 2011. The category of patients considered to be least certain (possible), based on laboratory criteria, increased over time, constituting almost half of the patients diagnosed in 2011. These differences in distribution were significant when comparing 2010 vs 2011 and 2009 vs 2011 (Table 3).

Reporting to the national case register

In 2009, all laboratory-confirmed cases, except two, were reconfirmed by MHS and reported to the NCR (184/186) (Table 4). In 2010 and 2011, the proportion of reconfirmed cases dropped: only 7/12 and 4/9 of the cases considered to be confirmed by laboratory criteria in 2010 and 2011 respectively were reported to the NCR. Interestingly, six of the 10 cases reported in 2010 and 2011 not reconfirmed were PCR positive in the

Table 3

Laboratory-defined Q fever cases notified to the Municipal Health Service of south-east Brabant, the Netherlands, 2009–2011 (n=523)

Year (number of cases)	Confirmed cases n (%)			Probable cases n (%)		Possible cases n (%)		P value[a] between years
	Outcome							
	1	2[b]	3	4	5	6	7	
2009 (n=377)	30 (8.0)	156 (41.4)	42 (11.1)	59 (15.6)	25 (6.6)	0 (0)	65 (17.2)	0.17 2009 vs 2010
	186 (49.3)		126 (33.4)			65 (17.2)		
2010 (n=96)	8 (8.3)	4 (4.2)	72 (75.0)	0 (0)	0 (0)	12 (12.5)	0 (0)	<0.01 2010 vs 2011
	12 (12.5)		72 (75.0)			12 (12.5)		
2011 (n=50)	8 (16.0)	1 (2.0)	17 (34.0)	0 (0)	1 (2.0)	23 (46.0)	0 (0)	0.01 2009 vs 2011
	9 (18.0)		18 (36.0)			23 (46.0)		

[a] Determined using one-sided Mann–Whitney test.

[b] A serum pair for one episode of Q fever was defined whenever these sera were collected within 90 days.

initial serum sample, and therefore in laboratory terms would be considered true positives. Follow-up serology was performed in four of these six cases: IgM phase II as well as IgG phase II antibodies against *C. burnetii* were not detected.

The proportion of the reconfirmed cases significantly decreased with the degree of certainty of the laboratory diagnosis and over the three-year period. Only a small minority of the laboratory-defined probable acute Q fever cases in 2010 and 2011 were reconfirmed by the MHS and reported to the NCR (14/72 and 5/18 respectively). This proportion was even lower for the possible cases, where almost no cases were reported to the NCR (Table 4). In contrast, the probable and possible cases in 2009 were still mainly reconfirmed (100/126 and 54/65respectively). The differences were significant between 2009/1010 and 2009/2011 for all three laboratory interpretations. No differences were observed between 2010 and 2011.

Discussion

In this study, we showed that the continued use of a pre-outbreak case definition lead to over-reporting of acute Q fever to the MHS in the post-epidemic years. This was caused by the increasing seroprevalence in the population and the observed persistence of IgM antibody titres, both influencing the interpretation of serological test results. Therefore, a test result that was diagnostic for acute disease at the start of the outbreak became almost useless later on. For instance, the specificity of single IgM phase II positive results, in terms of inclusion in the NCR, was 83.1% in 2009, whereas in 2010 and 2011,the specificity dropped to 0% and 13% respectively. According to national law, all notifications of laboratories and physicians should be investigated by the MHS infectious disease specialist in order to track down (new) sources, the principal reason for notification of Q fever. The over-reporting observed here in the course of a large outbreak does not aid such source finding.

Laboratory diagnosis of acute Q fever is quite complex. Culture techniques for *C. burnetii* are not available for routine practice, and therefore diagnosis relies on pathogen detection by PCR or serology or both. Although detection of *C. burnetii* DNA in serum by PCR is highly sensitive, it is also time-dependent, with a window for detection of approximately two weeks after onset of acute Q fever symptoms [5]. Besides, not all diagnostic laboratories have *C. burnetii* PCR facilities. Therefore, serological tests will remain necessary in laboratory diagnosis of (acute) Q fever. The variety of serological techniques and the implementation of new techniques throughout recent years make the diagnostic algorithms even more challenging. In our study period, 2009–2011, procedures changed three times: IFAT was introduced April 2009 for improvement of specificity, ELISA was implemented in June 2009 to increase the throughput time, and PCR was implemented in April 2010 inour laboratory to shorten the time to diagnosis. (Table 1 and Figure) Such changes are unavoidable during a large-scale outbreak: routine methods that were in place at the start of the outbreak were not suitable for large-scale use. Changing diagnostic methods in during an outbreak may influence the case definition used. Closer interaction between laboratory diagnosticians, epidemiologists and MHS infectious disease specialists is highly recommended: it will help unravel the notifications and focus investigation on real acute Q fever cases.

The current laboratory criteria for notification contain confirmed laboratory cases (PCR positive or a four-fold

Table 4

Laboratory-defined Q fever cases reported to the national case register, the Netherlands, 2009–2011 (n=523)[a]

Year (number of cases)	Confirmed		Probable		Possible	
	Total number according to laboratory definition	Reconfirmed by MHS and reported to NCR n (%)	Total number according to laboratory definition	Reconfirmed by MHS and reported to NCR n (%)	Total number according to laboratory definition	Reconfirmed by MHS and reported to NCR n (%)
2009 (n=377)	186	184 (98.9)	126	100 (79.4)	65	54 (83.1)
2010 (n=96)	12	7 (58.3)	72	14 (19.4)	12	0 (0)
2011 (n=50)	9	4 (44.4)	18	5 (27.8)	23	3 (13.0)

MHS: Municipal Health Services; NCR: national case register.

Percentages of notified cases in all three categories of laboratory interpretations (confirmed, probable and possible) were significantly different between 2009 vs 2010 and 2009 vs 2011, with a p value <0.001. The p value was determined using two-sided Fisher's exact test.

[a] Data from Laboratory for Pathology and Medical Microbiology (PAMM), Veldhoven.

increase in IgG phase II titre) and probable and possible cases (single serum IgM phase II positive) [11]. The last criterion, applied to patients with specific clinical symptoms, had a high positive predictive value in the epidemic year (2009). After the epidemic was successfully managed at the end of 2009, the incidence of acute Q fever fell drastically from 2010 onwards [12]. However, seroprevalence was high in the affected areas, reaching up to 20% of the population in some highly affected areas in the south of the Netherlands [13]. The number of laboratory requests remained high as the diagnostic triaging changed with increasing awareness. The total number of samples tested at our laboratory for acute Q fever increased from 4,516 in 2009 to 5,138 in 2010. Two years after the epidemic, the numbers decreased to 3,116 in 2011 and 2,946 in 2012. The group of patients subjected to diagnostic testing widened, thereby changing the positive predictive value of the same test outcome. Also, in the years after the epidemic, the indication for diagnostic testing changed from acute illness to (chronic) fatigue symptoms. Microbiologists can signal such changes but only if clinical information and other relevant background information is provided by the physician requesting the tests. However, this information is often lacking. As a consequence, the laboratory kept reporting IgM phase II positive patients to the MHS. IgG phase II and IgM phase II remain detectable for a long time after initial infection. Recently, it was shown that at least until 12 months after acute Q fever IgM phase II antibodies are detectable in the majority of the patients [7]. Since most of the acute Q fever infections remain asymptomatic, IgM phase II in patients without classic symptoms represented mostly past infections instead of new acute cases in the post-epidemic period.

The need for more direct interaction between treating and notifying physicians and the laboratory was also illustrated by another finding: in our study, we found four PCR-positive cases (in 2010 and 2011) that were not included in the NCR. The reason for not reconfirming these cases was the aspecific clinical presentation together with the lack of serological response in follow-up sera from some of the cases, casting doubt on the performance of the diagnostic test. Positive PCR without serological response weeks after initial symptom onset is highly unlikely. Although it has been suggested that antibody responses may be limited when antibiotic treatment is started early, this was not observed in a recent study [14]. Therefore, finding PCR-positive patients whose infection cannot be confirmed by serology suggests that they were due to false-positive PCR tests. PCR, which is highly sensitive, has always been prone to false-positive results, requiring strict protocols. Regretfully, despite these strict protocols, positives were still found that did not match the clinical picture, and again, with widening referral of patients, the positive predictive value of the same assay decreases. The combination of diagnostic serology and PCR can be problematic, as laboratory contamination may result in antigen preparations containing high levels of *C. burnetii* DNA [15]. After this phenomenon was reported, separate samples for serological and PCR tests were taken from patients, to reduce the potential of cross-contamination.

Although serological positive results do indicate infected patients, the inability to discriminate acute, chronic and past infections based on these criteria placed a lot of emphasis on the decision-making by the MHS. Notification of past infections does not support source finding, but will give MHS staff needless

work. Therefore we recommend 'downsizing' the notification criteria, as was done in other infectious diseases [16,17]. For example, at the start of the influenza A(H1N1)pdm09 epidemic in 2009 and 2010, it was mandatory to report all new patients, but this was rapidly changed to hospitalized patients only. Notification was abandoned totally when influenza A(H1N1)pdm09 became seasonal influenza [17].

The timing of change in notification criteria is rather arbitrary, but based on our retrospective data we conclude that the criteria could have been modified in 2010 for the Q fever-endemic areas in the Netherlands. We would recommend changing the laboratory case definition to rely on more specific testing as the incidence decreases and seroprevalence increases in a previously affected region by omitting IgM phase II positive sera and only report laboratory-confirmed cases. Whenever this is based on PCR positive sera, serological confirmation is recommended to monitor false positives due to contamination. Narrowing the notification rule to confirmed cases only is likely to lead to a more meaningful epicurve; notifications that are pending would no longer be taken into account. In order to keep a close eye on an epidemic, clinicians together with laboratories should closely follow up patients after a first positive result.

This study emphasises the importance of updating diagnostic criteria during an outbreak due to emerging pathogens. New notification rules in the aftermath of an epidemic are therefore necessary. As knowledge increases and diagnostic technology improves, definitions need to be changed to reflect those trends. We suggest a case definition that includes a degree of certainty (e.g. probable or confirmed) based on the different type of laboratory results.

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Conflict of interest

None declared.

Authors' contributions

All authors were involved in the (i) conception and design and acquisition of data, or analysis and interpretation of data; (ii) drafting the article or revising it critically for important intellectual content; and (iii) final approval of the version to be published.

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EuroVaccine conference and *Eurosurveillance* scientific seminar at ESCAIDE 2013

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EuroVaccine 2013 will take place on 6 November 2013 in Stockholm, during the European Scientific Conference on Applied Infectious Disease Epidemiology (ESCAIDE).

The fifth EuroVaccine conference will cover vaccination during pregnancy, experiences from pertussis vaccination and influenza vaccination; it will also feature aspects related to the new vaccine against Meningococcus type B. EuroVaccine 2013 will be live streamed and will allow online interaction among registered participants. The conference is fully funded by the European Centre for Disease Prevention and Control (ECDC), Stockholm, and receives no financial or other support from commercial stakeholders. Both online and onsite participation are free of charge and all ESCAIDE registered participants are welcome to attend onsite.

The third *Eurosurveillance* scientific seminar will take place during the lunch break of EuroVaccine (12:00-13:30) and will also be live streamed. Professor Emmanouil Galanakis from the University of Crete (Greece) will give a presentation entitled '*Should we fire healthcare workers who decline vaccination?*' and this will be followed by an interactive panel discussion.

Details on registration for the events and live stream are available from the ESCAIDE website: www.escaide.eu.