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Adverse events and association with age, sex and immunological parameters of Q fever vaccination in patients at risk for chronic Q fever in the Netherlands 2011

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ABSTRACT

Background: Following a large Q fever outbreak in the Netherlands, patients at risk for chronic Q fever received a whole-cell Q fever vaccine. Sensitized people were excluded based on pre-vaccination screening with skin test (ST) and serology. An investigational IFN-γ-production assay was added. No previous experience existed for Q fever vaccination in this patient risk-group with predefined cardiac valvular anomalies or aortic aneurysm/prosthesis and many co-morbidities. We studied the adverse events (AE) and their association with patient characteristics and immunological parameters.
Methods: AE registration covered the week after skin test and 90 days following vaccination, with the use of diaries, interviews and spontaneous reports. Serious (S)AE were assessed immediately to ensure safety. We coded AE according to reported severity. Univariate and multivariate analysis addressed associations.
Results: Pre-vaccination screening led to exclusion of 182 patients with positive serology and 207 patients with positive skin test-reading. The skin test did not lead to any causally related SAE. Subsequent vaccination of 1370 patients did not reveal unexpected AE; however, 80% of vaccinees reported local AE (in 26% of these pronounced or extensive). The two causally related SAE (0.1%) both concerned a persistent subcutaneous injection site mass. AE were more frequent in women, younger patients, and those without immunosuppressive co-morbidity/medication. The occurrence of local AE after skin test was associated with pre-vaccination positive serology and high IFN-γ production. This was also true for local AE following vaccination, with a strong association with local AE after skin test as well. The proportion of vaccinees with positive serology and positive IFN-γ values 6 months after vaccination was higher in those with local AE after skin test or after vaccination (non-significant, probably due to small numbers).
Conclusion: Q fever vaccination was safe but reactogenic in this high-risk patient-group. Rates of local AE were higher in women, younger age groups and in those with positive immunological parameters. Vaccinees with local AE after skin test or after vaccination appear to have more pronounced post-vaccination immune responses.

Abbreviations: *C. burnetii*, *Coxiella burnetii*; HC, health council; AE, adverse events; AEFI, adverse events following immunization; SAE, serious adverse events; ST, skin test; IFN-γ, interferon-gamma; ST-locAE, local adverse event following skin test; ST-systAE, systemic adverse event following skin test; Vac-locAE, local adverse event following vaccination; Vac-systAE, systemic adverse event following vaccination; AE grade 3-4, adverse event with size or severity grade 3 or 4.

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1. Introduction

Human acute Q fever infection, caused by *Coxiella burnetii*, is asymptomatic in over 50% of cases. In symptomatic cases, clinical presentation ranges from self-limiting febrile illness to pneumonia or hepatitis for which prompt treatment with antibiotics shortens duration [1,2]. Chronic Q fever develops in about 5% of patients, often resulting in endocarditis and vascular infection [3]. In contrast to acute infection, chronic Q fever has high lethality if untreated. Long-term antibiotic therapy, and often surgical intervention, are necessary [4].

In spring 2007, an attentive rural family general practitioner (GP) noticed several cases of atypical community-acquired pneumonia in young adults [5,6]. This proved to be one of the first signals of the largest Q fever outbreak ever [7]. Nearby goat farms were the sources of human infections. Retrospectively, this livestock epidemic started in 2005, following years of intensive goat farming [8]. From 2007 to 2011, 4107 acute Q fever patients were reported, with peak incidence in 2009. Numbers of infected people are estimated to have been ten times as high [9]. Numbers of chronic Q fever increased thereafter, amounting to over 200 cases identified until 2011 with a 13% lethality [10,11]. From 2009 onwards, consecutive measures to curtail the livestock epidemic included mandatory vaccination and culling of carrying animals on infected farms [8]. Some preventive measures, like avoiding human proximity to infected farms, were not feasible due to the dense population.

Several risk-groups for chronic Q fever have been identified, notably those with structural cardiac (valvular) anomalies, prosthetic valves or aortic aneurysms/prostheses [12,13]. The value of antibiotic prophylaxis after initial infection for the prevention of chronic Q fever in these patients has been debated [14,15]. An effective Q fever vaccine is registered in Australia, where – mostly healthy young – people at occupational risk are vaccinated [16].

In 2010, the Netherlands Health Council (HC) advised to vaccinate specific chronic Q fever risk-groups, focusing on the high-incidence area in south-eastern Netherlands [17]. A vaccination campaign was conducted between January and April 2011, with some catch-up vaccinations in June [18]. A centralized approach to screening and vaccination was chosen as the vaccine was not registered in the Netherlands and experience with this vaccine and the required skin test in this specific patient-group was lacking. Pre-vaccination screening was considered essential because previous *C. burnetii* infection is assumed to increase the risk of adverse events (AE) to this whole-cell vaccine [19]. If outcomes of serology or skin test were positive, no vaccination was given [20]. The skin test, however, by intradermal deposition of killed bacterial suspension, may provoke a local reaction. AE following skin test and vaccination were monitored intensively, with follow-up for 90 days. An investigational whole-blood interferon-gamma (IFN-γ) production assay, measuring cell-mediated immunity in vitro, was added to the screening [21,22]. While its outcome was irrelevant for the decision to vaccinate, it gave an opportunity to analyze AE in vaccinees with possibly pre-existing cell-mediated immunity.

This article describes vaccinees' characteristics, pre-vaccination screening outcomes, and reported AE after skin test and after vaccination in this specific patient-group. We also analyzed the association between local AE after skin test or vaccination, patient characteristics and pre- and post-vaccination immunological parameters [23].

2. Patients and methods

2.1. Target population

Q fever vaccination targeted specific risk conditions, based on the HC advice, with defined exclusion criteria (Box 1). Efforts to reach target populations were most intensive in the high-incidence area. GPs identified and referred patients [18].

Box 1: Inclusion and exclusion conditions for Q fever vaccination, and coding criteria for adverse events following Q fever skin test and vaccination

Inclusion conditions:

1 – history of bacterial endocarditis, other infections of the heart excluded
2 – heart valve disease or prosthesis, regardless of type
3 – aortic aneurysm or prosthesis, carotid stents excluded
4 – congenital heart anomalies, including coarctatio aortae, excluding spontaneous closure of VSD and ductus arteriosus Botalli

Exclusion conditions:

1 – age under 15 years, pregnancy, incapacity to fulfil requirements, too late referral, severe immunodeficiency
2 – history of Q fever infection, positive skin-test or serology, hypersensitivity for vaccine components

Coding criteria adverse events:

a – local redness, swelling	Vaccination:	Skintest:
	1 – <2.5 cm, mild	1 – <5 mm
	2 – 2.5 to <7.5 cm, moderate	2 – 5 to <10 mm
	3 – 7.5 to <15 cm, pronounced	3 – 10 to <15 mm
	4 – ≥15 cm, extensive	4 – ≥15 mm
b – local pain	1 – pain to the touch, no obstruction of use	
	2 – pain on movement, some interference with normal activity	
	3 – considerable pain in rest, obstruction of use	
c – fever	1 – 37.5 to <38.5 °C, mild	
	2 – 38.5 to <39.5 °C, moderate	
	3 – 39.5 to <40.5 °C, high	
	4 – ≥40.5 °C, extreme	
d – other systemic events	1 – easy to endure, minimal discomfort, no impediment	
fatigue, headache, chills, gastrointestinal symptoms, muscle pain, joint pain, etc.	2 – hindrance and some interference with normal activity	
	3 – considerable impediment of normal functioning, need for treatment	
e – duration	1 – start and resolve within 3 days after vaccination, early	
	2 – start within 3 days and resolve within 6 days after vaccination, long	
	3 – start and resolve day 4–6 after vaccination, late	
	4 – continuation after day 6, extended	

2.2. Screening and vaccination

Intake and screening took place at a municipal health centre in the high-incidence area, where eligible patients came for screening and subsequent vaccination.

2.2.1. Serology

Antibodies against *C. burnetii* (IgG against phase 1 and phase 2) were measured in 1:32 serum dilution, as described [21]. If positive, exact IgG and IgM titres were determined. Seropositive patients were informed and ST-reading was cancelled. GPs received the results, with interpretation and advice for referral if indicated. Weak IgG signals at 1:32 – 'equivocal' and possibly false positive – did not result in exclusion. Available six months' post-vaccination samples were measured in the same way [22].