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Effect of a phase I *Coxiella burnetii* inactivated vaccine on body temperature and milk yield in dairy cows

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ABSTRACT

Q fever is a zoonotic disease caused by *Coxiella burnetii*. The pathogen is prevalent in ruminants (goats, sheep, cows), which are the main sources of human infection. In the cattle industry around the world, animal (15 to 20%) and herd (38 to 72%) level prevalences of *C. burnetii* are high. Vaccination of ruminants against Q fever is considered important to prevent spreading of the disease and risk of infection in humans. However, published information on side effects of the Q fever vaccination under field conditions is limited for cows. The objective of this study was to investigate the effect of the phase I *C. burnetii* inactivated vaccine Coxevac on body temperature and milk yield in dairy cows. In 2 experiments, a total of 508 cows were randomly divided into 2 groups to determine the effect of first vaccination on body temperature and milk yield. The *C. burnetii* serostatus of all cows was tested before vaccination with an indirect ELISA. The first experiment took place in the teaching and research barn of the Clinic of Animal Reproduction at the Freie Universität Berlin. Temperature was measured vaginally in 10 cows in a crossover design. The second experiment was conducted on a commercial dairy farm. Milk yield of 498 cows was measured 1 wk before and 1 wk after vaccination. In a subset of 41 cows, temperature was measured rectally. In both experiments, body temperature increased significantly after vaccination (1.0 ± 0.9°C and 0.7 ± 0.8°C). A significant difference was also found in body temperature between vaccinated and control cows. Thirty percent of the vaccinated animals in experiment 1 showed reversible swelling at the injection site as a reaction to the vaccination. The results indicate that vaccination against Q fever causes a transient increase of body temperature that peaks in the first 12 to 24 h and declines after that. In experiment 2, vaccinated cows (26.8 ± 0.39 kg/d) produced significantly less milk than did control cows (28.2 ± 0.44 kg/d) 7 d after first vaccination. The cumulative milk loss after first vaccination was influenced by an interaction between *C. burnetii* serostatus and average milk yield 7 d before first vaccination. This was considered as part of the physiological immune response. Three out of 10 vaccinated animals in experiment 1 showed painful swelling of the skin at the injection site, which had a maximum size of 14.0 × 14.0 × 1.1 cm. In conclusion, a transient increase of body temperature and a decrease in milk yield is prevalent after Coxevac vaccination.
Key words: *Coxiella burnetii*, Q fever, vaccination, body temperature

INTRODUCTION

Q fever is a zoonotic disease prevalent worldwide that is caused by the gram-negative bacterium *Coxiella burnetii*. *Coxiella burnetii* has the capacity to produce spores that are exceptionally resistant to physicochemical factors (Bielawska-Drózd et al., 2013), thus surviving well in the environment. It is well known that domestic ruminants are the major reservoirs of *C. burnetii*. Human infections are primarily attributed to sheep and goats (Delsing and Kullberg, 2008) but rarely to cattle (Hellenbrand et al., 2001). In 6 out of 40 Q fever outbreaks in humans between 1944 and 1999 in Germany, the suspected source was cattle (Hellenbrand et al., 2001). The effect of an animal species on the transmission of Q fever to humans presumably depends on the main types of exposure to an animal species in a population, and the infection rate of these animals (Bernard et al., 2012). Risk factors associated with seropositivity include veterinarian procedures such as cattle obstetrics (Bernard et al., 2012), breeding cattle, and any job contact with waste from beef cattle or goats (Whitney et al., 2013). Cattle are frequently persistently infected, and persistent infection is associated with elevated seroactivity (Guatteo et al., 2007).

In most species, Q fever infection is asymptomatic and can last for a lifetime (Garcia-Ispierto et al., 2014).

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In humans, symptoms are usually flu-like, thus often leading to delayed or misdiagnoses and underestimation of cases (Taurel et al., 2014). In more severe cases, Q fever causes abortion, endocarditis, hepatitis, and osteoarticular infection (Parker et al., 2006). In cattle around the world, animal (15 to 20%) and herd (38 to 72%) level prevalence of *C. burnetii* is high (Guatteo et al., 2011). In a German study intensively screening dairy farms in Bavaria, sero- and herd prevalences of *C. burnetii* were 14.8 ± 0.48% and 72.3 ± 3.6%, respectively (Böttcher et al., 2011). Yet, Q fever symptoms described in the literature have so far been inconsistent (Guatteo et al., 2011). Infertility, abortion (Bildfell et al., 2000), metritis, and mastitis (Arricau-Bouvery and Rodolakis, 2005; Barlow et al., 2008) were commonly reported. The presence of *C. burnetii* in dairy herds has not been clearly demonstrated to negatively affect reproductive performance, and the infection mechanism remains unknown (López-Gatius et al., 2012; Garcia-Ispierto et al., 2013, 2014).

Recently, the importance of Q fever prevention and control were emphasized by outbreaks in the Netherlands between 2007 and 2010 that infected more than 3,500 humans and led to 7 deaths (van der Hoek et al., 2010). Two main strategies can be used to control and prevent the disease: nonmedical and medical strategies. Nonmedical strategies are mostly hygiene related and focus on the time around parturition as ruminants have been reported to shed large loads of the bacteria at that time (Berri et al., 2002). Their efficiency is poorly documented in the literature (Taurel et al., 2014). Medical strategies include antibiotic therapy and vaccination. Antibiotic therapy is mainly based on the use of tetracyclines. However, the efficacy of tetracycline to reduce shedding is inconsistent (Durand, 1993; Taurel et al., 2012; Taurel et al., 2014), and a blanket treatment is not in accordance with a prudent use of antibiotics. It has been demonstrated, however, that a phase I vaccine is effective to prevent shedding at calving when administered to noninfected animals such as nulliparous animals (Guatteo et al., 2008) and to reduce shedding in infected animals at calving (Arricau-Bouvery et al., 2005). Most recently, it has been reported that a phase I vaccine is effective to reduce the prevalence of animal shedding the bacteria, bacterial load shed in cows (Taurel et al., 2014), and abortion (Arricau-Bouvery et al., 2005). Vaccination also may increase the likelihood of pregnancy by 1.25 (López-Helguera et al., 2013).

Phase I *C. burnetii* inactivated vaccine (Coxevac, Ceva Santé Animale, Libourne, France) against Q fever has been conditionally licensed in the European Union since 2010 and was granted full registration in 2015. Vaccines prepared from phase I *C. burnetii* organisms (virulent phase) are more protective against Q fever in laboratory animals than those prepared from phase II bacteria (Arricau-Bouvery et al., 2005). For goats, swelling at the injection site, increased body temperature, and decreased milk production after vaccination are described by the manufacturer (Ceva, 2012). For cows, only swelling at the injection site was reported by the manufacturer. Although anecdotal evidence is available of fever and decreased milk yield in some dairy cows after vaccination, science-based information is not available. Therefore, the objective of this study was to determine the effect of the vaccine on body temperature, milk yield, and injection site reactions in dairy cows.

MATERIALS AND METHODS

Two experiments were conducted to evaluate the effect of an inactivated phase I vaccine against *C. burnetii* on body temperature and milk yield after first vaccination. In both experiments, a commercial vaccine was used (Coxevac, Ceva Santé Animale, Libourne, France). Each vaccinal dose of 4 mL contained purified corpuscular antigens of phase I *C. burnetii* (100 g/mL) inactivated by formaldehyde. Components of the vaccine are thiomersal, sodium chloride, disodium hydrogen phosphate, potassium dihydrogen phosphate, and water for injections. Coxevac does not contain any adjuvants.

The first experiment was conducted in August and September 2014 at the Clinic of Animal Reproduction, Freie Universität Berlin, Germany (52°25′37″N, 13°14′14″E). A total of 10 clinically healthy Holstein dairy cows were used. They were housed in a freestall barn with cubicles, bedded with a mix of chopped straw and lime. Animals were fed twice daily with grass, silage, concentrate, and hay. Serostatus of all cows was determined using an indirect ELISA (LSIVet Ruminant Q Fever, Life Technologies Corporation, Carlsbad, CA). A serum sample was considered as negative for antibodies against *C. burnetii* when the optical density as a percentage of a positive control (% optical density, **OD%**) was ≤40. A serum sample was considered as positive for antibodies against *C. burnetii* when OD% was >40. All cows were negative except one that was questionable.

The cows were randomly divided into 2 groups by use of a random treatment allocation plan generated before initiation of the trial with the random number function of Excel (version 2013, Microsoft Corp., Redmond, WA). Group I (n = 5) was vaccinated and group II (n = 5) served as the control. Two weeks later, group II was vaccinated and group I served as the control group.