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Efficacy of antibiotic treatment and test-based culling strategies for eradicating brucellosis in commercial swine herds

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ABSTRACT

Swine brucellosis caused by *Brucella suis* biovar 2 is an emerging disease in continental Europe. Without effective vaccines being available, the European Food Safety Authority (EFSA) recommends the full depopulation of infected herds as the only strategy to eradicate *B. suis* outbreaks. Using data collected from 8 herds suffering natural swine brucellosis outbreaks, we assessed the efficacy of four control strategies: (*i*) oxytetracycline treatment only, as a default scenario, (*ii*) oxytetracycline treatment combined with skin testing and removal of positive animals, (*iii*) oxytetracycline treatment combined with serological testing (Rose Bengal test—RBT—and indirect ELISA -iELISA-) and removal of seropositive animals and (*iv*) oxytetracycline treatment combined with both serological (RBT/iELISA) and skin testing and removal of positive animals. A Susceptible-Infectious-Removal model was used to estimate the reproduction ratio (R) for each strategy. According to this model, the oxytetracycline treatment alone was not effective enough to eradicate the infection. However, this antibiotic treatment combined with diagnostic testing at 4-monthly intervals plus immediate removal of positive animals showed to be effective to eradicate brucellosis independent of the diagnostic test strategy used in an acceptable time interval (1–2 years), depending on the initial number of infected animals.

1. Introduction

Swine brucellosis due to *Brucella suis* biovar 2 is an infectious disease causing long term reproductive failure in pigs and important economic losses as well as trade restrictions. *B. suis* biovar 2 is restricted to Western and Central Europe and it is considered to have a low pathogenicity for human beings but to be the major cause of swine brucellosis (EFSA, 2009; Olsen et al., 2012), especially in pigs reared in outdoor breeding systems (Garin-Bastuji et al., 2000; Cvetnic et al., 2009; Muñoz et al., 2010). Although sporadic outbreaks in domestic pigs occur likely as spill-over from wild boar—which is the main natural reservoir (Godfroid and Käsbohrer, 2002; Godfroid et al., 2005; Cvetnic et al., 2009; EFSA, 2009)—the EU countries are considered officially free from swine brucellosis. In consequence, official surveillance in the EU is only performed for trade and semen production purposes.

As no suitable vaccines are available, the full depopulation of infected holdings is the only strategy recommended to eradicate swine brucellosis outbreaks in the EU (EFSA, 2009). However, such a strategy is both economically devastating and socially undesirable if outbreaks occur in large intensive holdings or in outdoor breeding systems based on rare endangered pig breeds. In these cases, the use of alternative control strategies based on effective antibiotic treatments combined with partial culling could be a more cost-effective and socially acceptable option (Olsen et al., 2012). Oxytetracycline administered continuously in feed minimizes the clinical impact and spread of brucellosis in infected holdings, but does not eliminate the infection (Olsen et al., 2012; Dieste-Pérez et al., 2015a). However, this antibiotic treatment, combined with the removal of infected pigs might result in an effective eradication of the disease from infected herds. Infected animals can be identified using *Brucella* O-polysaccharide (O/PS)-based serological tests such as the Rose Bengal test (RBT) and the indirect enzyme-linked Immunosorbent assays (iELISA) (EFSA, 2009; OIE, 2012; Muñoz et al., 2012). However, an important proportion of pigs in brucellosis-free holdings may show false positive results in these tests (Jungersen et al., 2006; McGiven et al., 2012; Dieste-Pérez et al., 2014, 2015b) due to infections caused by other gram-negative bacteria (*Yersinia ente-*

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rocolitica O:9 being the most frequent) sharing common epitopes with *Brucella* O/PS (Thibodeau et al., 2001; EFSA, 2009). As an alternative, a skin test based on O/PS free *Brucella* cytosolic proteins can be used for diagnosing *Brucella* infection and differentiating these false positive serological reactions (Dieste-Pérez et al., 2014, 2015c). Comparison of such alternative control strategies in a quantitative way is of interest for decision-making regarding control of swine brucellosis outbreaks.

The reproduction ratio (R) is a suitable parameter to determine whether or not an infection will go extinct (De Jong and Kimman, 1994). If $R > 1$, the infection spreads resulting in either major or minor outbreaks; in contrast, if $R < 1$ the infection will fade (Diekmann et al., 1990; Velthuis et al., 2007). Thus R can be used as a measure to compare the efficacy of the various control measures implemented. Any effective strategy should result in R values below 1 (Velthuis et al., 2007). The aim of this study was to assess the efficacy, using estimates of R, of an antibiotic treatment given alone and in combination with several test-based culling strategies to eradicate *B. suis* biovar 2 outbreaks in swine herds.

2. Materials and methods

2.1. Background data for the estimation of model parameters

Data were available from 8 commercial multiplier Landrace × Large White herds suffering natural outbreaks of *B. suis* biovar 2 between 2008 and 2013. *B. suis* biovar 2 infection was confirmed in all herds by bacterial isolation from swabs of aborted material. Briefly, swabs were cultured on Farrell's and CITAís selective media under the incubating conditions described by De Miguel et al. (2011), and suspected colonies identified by standard (Alton et al., 1988) microbiological methods (oxidase, urease and agglutination with monospecific anti-A and anti-M sera). Bacterial DNA was extracted using QIAamp DNA minikit (QIAGEN, Hamburg, Germany) and Bruce-ladder multiplex PCR (García-Yoldi et al., 2006) was performed to identify *B. suis*. A multiplex PCR designed to differentiate between the five *B. suis* biovars (López-Goñi et al., 2011) was also used.

To estimate transmission parameters, information about herd structure, swine brucellosis apparent prevalence and diagnostic tests results were needed. Data on herd structure, i.e. average herd size, age distribution, annual replacement rate and farrowing interval, were obtained from the farmer's breeding records. Data on apparent within-herd prevalence and diagnostic tests results were obtained from veterinarianís surveillance records; surveillance was performed at different time intervals (i.e., some herds were sampled every month, others less frequently). The specific time intervals applied at each farm were taken into account in the data analysis. The main characteristics of the herds, the outbreaks as well as the control measures applied are shown in Table 1.

Briefly, after confirmation of infection an antibiotic treatment based on oxytetracycline administration to all animals as pelleted feed (2000 ppm), at approximately 20 mg/kg body weight daily (Dieste-Pérez et al., 2015a), was applied until eradication was achieved. This treatment was combined with various diagnostic tests and removal measures. In some herds (herds 1–4), a skin test with O/PS free *Brucella* cytosolic extracts (Dieste-Pérez et al., 2014, 2015c) was used to identify infected animals. In herd 8, only serological tests (RBT and iELISA, Ingezim Brucella Porcine. INGENASA S.L, Madrid, Spain) were used as described previously (Muñoz et al., 2012). In the remaining herds (herds 5–7), both serological and skin tests were used to identify infected animals. According to previous studies in similarly infected herds, diagnostic sensitivity (Se) of these tests were estimated as 100% (95% confidence interval (CI) 92.8–100) for skin test, 93.2% (95% CI 88.2–96.6) for RBT and 95.1% (95% CI 90.5–97.8) for the iELISA, while the specificities (Sp.) were 100% (95% CI 98.5–100), 98.5% (95% CI 96.8–99.5) and 99.8% (95% CI 98.6–100), respectively (Dieste-Pérez et al., 2014, 2015b). If initial prevalence within a herd was higher than 10%, only the aborting, infertile and old (after 4–5th farrowing cycle, depending on the farm) positive sows were removed at weaning. The other animals were kept and removed gradually when meeting the previous requirements. Once within-herd prevalence reached 10% or less, all positive animals in any test were removed. In herds 6 and 7 all positive animals were removed irrespective of prevalence, since within-herd prevalence in these herds was close to 10% at the beginning of the outbreak.

2.2. Modelling

2.2.1. Control strategies modelled

Four control strategies were evaluated:

(*i*) *Oxytetracycline treatment only*. This strategy did not include any further testing and it was assumed that infected sows were removed exclusively on the basis of the normal average annual replacement rates (ARR) as estimated over the 8 farms included in the study (48.7%, Table 1). This intervention was considered as a default scenario for comparison, but note that this strategy was not applied in any of the study herds.

(*ii*) *Oxytetracycline treatment combined with the removal of skin test positive animals*. This strategy was modelled with an increasing testing interval from 1 to 25 months. It was assumed that skin test positive animals were removed immediately after testing.

(*iii*) *Oxytetracycline treatment combined with the removal of RBT and/or iELISA (RBT/iELISA) positive animals.* In this strategy, both serological tests were applied in parallel and positive animals to either RBT or iELISA were removed immediately after testing. Removal rate was modelled as described in *ii.*

(*iv*) *Oxytetracycline treatment combined with the removal of RBT and/or iELISA and/or skin test positive animals (RBT/iELISA/skin test).* In this strategy, the three diagnostic tests were applied in parallel and positive animals to at least one of the tests were removed immediately after testing. Removal rate was modelled as described in *ii.*

2.2.2. Data analysis

A deterministic susceptible-infected-removed (SIR) model (Velthuis et al., 2007) was used to estimate the transmission rate of *B. suis* biovar 2 infection within the herds. In this model, susceptible sows become infected with a rate of $\beta \times S \times I/N$, where β is the transmission rate parameter, S and I are the number of susceptible and infectious sows respectively, N the herd size and thus I/N is the prevalence within a herd. Animals were classified as I when reacting positive to at least one of the tests applied. Sows were considered S if the test(s) applied showed negative results. According to previous studies and experience (Olsen et al., 2012), infected sows in intensive multiplication farms were deemed to be infectious until removal or death.

The expected number of new cases ($E(C)$) per time interval (Δt) depends directly on β, S and I/N as follows (Velthuis et al., 2003):

$$E(C) = S \times \left(1 - e^{-\beta \times \frac{I}{N} \times \Delta t}\right)$$

Based on the replacement rate in each cycle, new cases (C) were estimated as the difference between the number of infected sows observed at the end and the start of each time interval. If this difference was negative, C was set to zero. The number of infected sows that caused these new infections was estimated on the basis of within-herd prevalence at the previous time interval. Underlying assumption was that there is no age-dependent susceptibility.