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Invited Review

What is the global economic impact of *Neospora caninum* in cattle – The billion dollar question

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ABSTRACT

Neospora caninum is regarded as one of the most important infectious causes of abortions in cattle world-wide, yet the global economic impact of the infection has not been established. A systematic review of the economic impact of *N. caninum* infections/abortions was conducted, searching PubMed with the terms 'cattle' and '*Neospora*'. This yielded 769 publications and the abstracts were screened for economically relevant information (e.g. abortion prevalence and risk, serological prevalence). Further analysis was restricted to countries with at least five relevant publications. In total, 99 studies (12.9%) from 10 countries contained data from the beef industry (25 papers (25.3%)) and 72 papers (72.8%) from the dairy industry (with the remaining two papers (2.0%) describing general abortion statistics). The total annual cost of *N. caninum* infections/abortions was estimated to range from a median US $1.1 million in the New Zealand beef industry to an estimated median total of US $546.3 million impact per annum in the US dairy population. The estimate for the total median *N. caninum*-related losses exceeded US $1.298 billion per annum, ranging as high as US $2.380 billion. Nearly two-thirds of the losses were incurred by the dairy industry (US $842.9 million). Annual losses on individual dairy farms were estimated to reach a median of US $1,600.00, while on beef farms these costs amounted to just US $150.00. Pregnant cows and heifers were estimated to incur, on average, a loss due to *N. caninum* of less than US $20.00 for dairy and less than US $5.00 for beef. These loss estimates, however, rose to ~US $110.00 and US $40.00, respectively, for *N. caninum*-infected pregnant dairy and beef cows. This estimate of global losses due to *N. caninum*, with the identification of clear target markets (countries, as well as cattle industries), should provide an incentive to develop treatment options and/or vaccines.

1. Introduction

Neospora caninum is recognised world-wide as an important infectious cause of abortion in, primarily, cattle and of clinical disease in dogs (Dubey and Schares, 2011).

Infection with *N. caninum* is frequent in canid populations (Barber et al., 1997; Reichel, 1998; also recently reviewed by Al-Qassab et al. (2010)), yet clinical cases in dogs are rarely reported (Munday et al., 1990; Gasser et al., 1993; Ruehlmann et al., 1995; Barber and Trees, 1996; Patitucci et al., 1997; Reichel et al., 1998; McInnes et al., 2006). Clinical cases of neosporosis in dogs can be treated, although often with limited success (Reichel et al., 2007). Although there is a cost to that treatment which has to be borne by the owner, these canine cases tend to be mostly singular in nature and thus costs are usually contained.

In cattle, *N. caninum* is generally viewed as primarily an abortifacient and abortions follow three main patterns (sporadic, endemic and epidemic abortions). The epidemic, "storm-like" pattern is the most devastating, and costly, with a large proportion (>10%) of at risk ("in-calf") cows aborting over a short period of time (Dubey et al., 2007). These abortion storms are generally viewed as very costly (and sometimes devastating in the extreme) to the primary producer. Endemic abortions, however, can also be costly (Hall et al., 2005). There have also been reports of *N. caninum* infection effects on milk production; in some publications the infection is shown to be associated with a decrease in milk production (Thurmond and Hietala, 1997b); in other reports, however, milk production increases in sero-positive cows (Pfeiffer et al., 2002; Hall et al., 2005). A reduction in neonatal mortality in

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congenitally *N. caninum*-infected calves has also been reported and may be a potential benefit (Paré et al., 1996). Earlier culling of sero-positive cattle has been reported (Thurmond and Hietala, 1996), as have increased costs of veterinary medical treatment (Barling et al., 2000) and a reduction in growth rates (Barling et al., 2000, 2001a). Thus, while some of the above reported effects of *N. caninum* infection are costly to primary producers, some of the information is equivocal; the majority of reports, however, describe abortions as the main impact of infection and that will be the focus of this review. Other factors that may impact on the economic effects of *N. caninum* may include (but are not limited to) differing genetics and susceptibilities of cattle, different herd management practices across the globe, nutrition, milk production goals (kg/day), and the possibility of concurrent infection with other infectious agents that has not been fully evaluated nor is that information consistently presented in published studies.

Transmission of the parasite from dam to offspring appears to be highly efficient and is quoted as ranging as high as 75–100% (Paré et al., 1996; Anderson et al., 1997; Schares et al., 1998; Björkman et al., 2003; Hall et al., 2005). Post-natal transmission rates are often quoted as being comparatively low, generally less than 10 per 100 cow years (Paré et al., 1996, 1997; Davison et al., 1999b; Hietala and Thurmond, 1999; Hall et al., 2005). Infection (and sero-positivity) is generally assumed to persist for life (Dubey and Schares, 2006), although fluctuation in antibody responses may lead to occasional conversion back to sero-negative status in some animals (Conrad et al., 1993). Sero-positivity increases the risk of abortion, with estimates for the increased risk often quoted to range between 1.7 and 7.4-fold (Thurmond and Hietala, 1997a; Moen et al., 1998), but decreasing over time with increasing parity (Thurmond and Hietala, 1997a).

Control options for *N. caninum* infection in cattle have been discussed previously (Reichel and Ellis, 2002). The costs of these control options have also been modelled, and threshold levels of *N. caninum* infection that make intervention economically preferable over living with the disease, have been defined (Reichel and Ellis, 2006). The treatment option (with toltrazuril (Kritzner et al., 2002)) has been identified as expensive in cattle and is potentially fraught with issues of milk and meat residues. Vaccines appear to be the favoured control option and the subject of a considerable body of research (Liddell et al., 1999; Miller et al., 2005). The different approaches to *N. caninum* vaccines have recently been comprehensively reviewed (Reichel and Ellis, 2009). However, after the withdrawal from world-wide sales of the only commercial *N. caninum* vaccine (Neoguard®), a vaccine which had demonstrated little more than 60% efficacy at best, and whose efficacy may have been as low as 25% (Weston et al., 2012b), there are now few management options available.

One option, apart from living with the disease, is to test and then cull *N. caninum*-infected cattle from the herd. This approach has been found to be quite efficacious (Hall et al., 2005), but is also costly and the cost of this approach needs to be put into perspective with the cost of the disease. Variations to this option might include selective breeding from only sero-negative cows, breeding of sero-positive cows only to beef, and the culling of those cows that have actually aborted. Herds with reduced or reducing sero-prevalence of *N. caninum* infection also need to be protected from subsequent infection (although in general, the published literature reports very low post-natal infection rates (Paré et al., 1996; Thurmond and Hietala, 1997a; Davison et al., 1999b), thus enhanced biosecurity measures (fencing, the exclusion of canine faeces from feed and water, and prevention of access for canids to bovine material (carcasses, placentas, aborted foetuses)) would need to be instituted, at some cost.

"Test-and-cull" would essentially incur the cost of testing all cattle, additionally incur the cost of culling all infected cattle (i.e. the replacement cost with non-infected, tested cattle) against the long-term benefit of the reduced cost of abortions. The costs of *N. caninum* abortions at farm, industry, national and world-wide levels are hitherto ill-defined and the present review is aimed at establishing these costs based on the published literature.

2. Materials and methods

2.1. Database search

A search was conducted on PubMed (http://www.ncbi.nlm.nih.gov/pubmed), using 'cattle' and '*Neospora*' as search terms. As of January 31, 2012, this search yielded 769 publications whose abstracts were individually screened, initially for the reporting of economically relevant information (abortion incidence, prevalence and risk, serological data and reproductive parameters) (Fig. 1).

2.1.1. Inclusion criteria

Papers with economically relevant information on *N. caninum* and cattle were grouped by countries and only the published literature for countries where a threshold of at least five separate relevant publications was exceeded were included in the analysis. This threshold was chosen to allow for a more robust set of data for subsequent economic modelling. As a result of this threshold, published papers with relevant information originated from 10 countries (Australia, New Zealand, Canada, Mexico, the United States of America (US), Argentina, Brazil, the Netherlands, Spain and the United Kingdom (UK)) and were then subjected to further analysis and economic modelling.

2.1.2. Exclusion criteria

All papers that did not include economically relevant information in the abstract, and those where the country-specific sum of all relevant papers failed to exceed the threshold of five publications, were excluded from further economic modelling. A list of the 45 countries in the PubMed search that had published with keywords of 'cattle' and '*Neospora*', but were excluded from further analysis in this study, are given in Table 1.

2.2. Baseline data for abortions

Abortions occur frequently in cattle, for a variety of reasons, and not all of them are caused by infectious agents, however baseline data (i.e. the prevalence of those abortions that are not caused by *N. caninum*) are difficult to obtain. In New Zealand, the overall loss rate has been estimated to be 6.4% of pregnancies as reported by (McDougall et al., 2005), in others as high as 25% (Thornton et al., 1994), with the median value for abortion losses being 2.9%. In Australia, the median value for abortions is 2.5% (ranging from 2.4% to 21.3% in some reports (Atkinson et al., 2000; Quinn et al., 2004; Hall et al., 2005)) (for further details, see Table 2). Where baseline data for a specific cattle industry were unobtainable, a baseline figure of 3% of pregnant cattle aborting was assumed.

2.3. Cost of abortion

The cost of abortion in each country that qualified for further economic evaluation (i.e. where at least five peer-reviewed publications with economically relevant data were available) was calculated from the number of cows at risk (i.e. pregnant), the accepted "normal" abortion rate, their increased risk of abortion (odds ratio) specific to *N. caninum* multiplied by the sero-prevalence of *N. caninum* in the cattle population at risk (i.e. pregnant) and the loss/cost incurred by that abortion, largely as previously described (Reichel and Ellis, 2006).

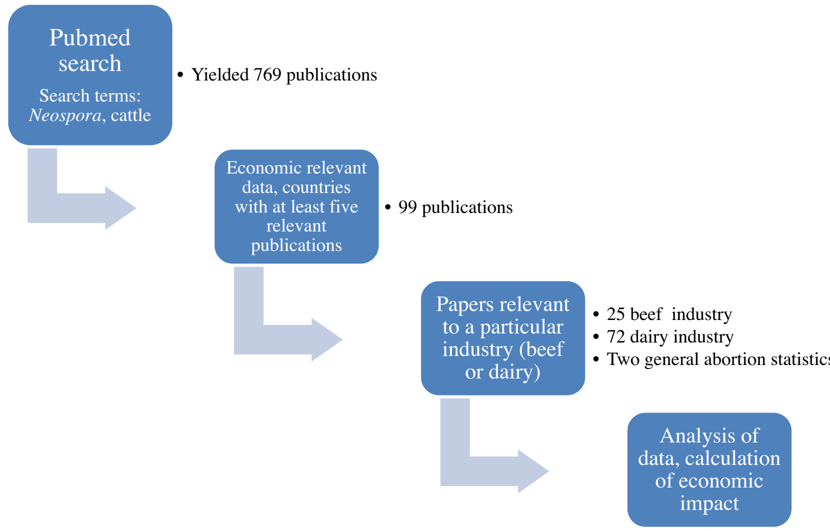

Fig. 1. Schematic representation of a PubMed search (using '*Neospora*' and 'cattle' as search terms) and inclusion/exclusion process for further economic analysis/modelling.

Table 1
Countries with reports on 'cattle' and '*Neospora*' derived from a PubMed search conducted on 31 January 2012 but excluded from further analysis.

Africa	Americas	Asia	Europe
Algeria	Costa Rica	China	Andorra
Senegal	Paraguay	India	Austria
South Africa	Peru	Indonesia	Belgium
Sudan	Uruguay	Iran	Czech Republic
Zimbabwe	Venezuela	Israel	Denmark
		Japan	France
		Jordan[a]	Germany
		Korea	Greece
		Malaysia	Hungary
		Pakistan	Ireland
		Taiwan	Italy
		Thailand	Norway
		Turkey	Poland
		Vietnam	Portugal
			Romania
			Slovakia
			Sweden
			Switzerland

[a] One country record published in 2012 after the original PubMed deadline of 31 January 2012.

Only female *N. caninum*-infected and pregnant cattle (generally, annual pregnancy rates (*PR*) of 90% of all breeding-age dairy female cattle and 75% of all breeding-age female beef cattle ($n(c+h)$) were assumed, unless country-specific data were available) are at risk of aborting, thus median sero-prevalence (*SP*) data for *N. caninum* for pregnant cattle (see above), multiplied by the specific *N. caninum* risk of abortion (NcsprA), will result in the average expected number of *N. caninum* abortions (NcA (n)) to be calculated as:

$$\mathrm{NcA}(n) = (n(c+h) \times PR \times SP \times \mathrm{NcsprA})$$

Neospora caninum abortions usually occur between 5–7 months of gestation (Dubey et al., 2006), and aborted cows can be expected to miss one lactation, thus the cost of a *N. caninum* abortion (in dairy cattle) is essentially the cost of replacing that cow with an identical cow at a similar stage of lactation that will go on to produce a calf and milk. In beef cattle, the cost of *N. caninum* abortions is the cost of a replacement calf.

As an example, the cost of *N. caninum* in Argentina was calculated as the cost of a replacement pregnant dairy cow (US $2,400.00) from which the slaughter (salvage) value of an empty cow (US $900.00) was subtracted to arrive at an estimate of the loss from one abortion (US $1,500.00). In beef cattle, the cost was calculated as the loss of a calf and the differential between replacement and slaughter value (US $830.00). These respective values were multiplied by the number of cows and heifers at risk of abortion (total number of beef (75%) cows and dairy (80%) cows pregnant, times the overall risk of abortion (4.5% or 8%, respectively) multiplied by the specific median contribution of *N. caninum* to abortions in Argentina from available abortion statistics (Table 2).

Where sero-prevalence and *N. caninum*-specific increased risk (odds ratio) of abortion data were available, the cost of *N. caninum* abortions was calculated as follows: total number of cows at risk (as above; $(n(c+h) \times PR)$), times the median sero-prevalence for *N. caninum* (*SP*), multiplied by *N. caninum*-specific abortion risk ("background" abortion risk (rA) times the odds of abortion increased by *N. caninum* infection (NcRR)), as in the case of the calculation for the New Zealand dairy situation (Table 2) which arrives at the number of abortions estimated to be caused by *N. caninum*, multiplied by the cost of an abortion .

$$\text{Cost of abortion x} \quad \mathrm{NcA}(n) = (n(c+h) \times PR \times SP \times \mathrm{rA} \times \mathrm{NcRR})$$

Cattle population statistics and values for cattle in the respective countries were procured from publicly available databases and sources. Results were converted to US dollars at the prevailing exchange rates in early May 2012 (www.xe.com).

3. Results

3.1. Literature cited

The initial PubMed search for the search terms 'cattle' and '*Neospora*' yielded 769 publications. Of that total, 99 studies (12.9%) contributed to this review, containing data that pertained to a total of 221,713 head of cattle, of which 45,863 (20.7%) resided in the beef industry (25 papers (25.3%)) and 175,850 (79.3%) in the dairy industry (72 papers (72.8%)) with the remaining two papers (2.0%) describing general abortion statistics.

3.2. Sero-prevalence and N. caninum abortion risk

An overview of the sero-prevalence data for the 10 countries and their industries, i.e. where the numbers of peer-reviewed

Table 2
Median background and *Neospora caninum* (*Nc*)-specific abortion risk (and range), odds ratios (and range) and median (and range) of *N. caninum* sero-prevalence in dairy and beef cattle in the cattle industries of 10 countries (ND = no data).

Country		Median abortion risk in % (range)		Odds ratio	Seroprevalence in % (range)	References
		Background	*Nc*-specific abortion risk			
Argentina	Dairy	ND	ND	2.1 (1.8–2.4)	22.2 (16.6–64.5)	Venturini et al. (1999) and Moore et al. (2002, 2009)
	Beef	ND	ND	12.0 (6.2–23.3)	11.2 (4.7–20.3)	Moore et al. (2002, 2003, 2009)
Australia	Dairy	2.5	9.8 (5.4–23.5)	6.9 (2.6–13.0)	10.9 (3.8–23.7)	Boulton et al. (1995), Obendorf et al. (1995), Atkinson et al. (2000), Quinn et al. (2004), Hall et al. (2005, 2006) and Nasir et al. (2012)
	Beef	ND	ND	ND	8.7 (2.5–14.9)	Stoessel et al. (2003) and Nasir et al. (2012)
Brazil	Dairy	ND	ND	ND	16.1 (14.1–34.8)	Gondim et al. (1999), Locatelli-Dittrich et al. (2001), Guimaraes et al. (2004), Aguiar et al. (2006), Corbellini et al. (2006) and Minervino et al. (2008)
	Beef	ND	ND	ND	15.1 (9.5–16.7)	Aguiar et al. (2006), Minervino et al. (2008) and Marques et al. (2011)
Canada	Dairy	2.1	15.8 (7.1–18.8)	ND	12.0 (5.5–22.5)	Bildfell et al. (1994), Paré et al. (1998), Keefe and VanLeeuwen (2000), Chi et al. (2002), Cramer et al. (2002), Pan et al. (2004), Hobson et al. (2005), VanLeeuwen et al. (2005), Peregrine et al. (2006) and Tiwari et al. (2009)
	Beef	1.2	ND	6.0 (5.7–6.2)	11.3 (5.9–81.3)	Rogers et al. (1985), Waldner et al. (1998, 1999, 2001) and Waldner (2005)
Mexico	Dairy	ND	ND	1.7 (1.3–10)	55.9 (42.0–59.0)	Morales et al. (2001a,b) and Garcia-Vazquez et al. (2002, 2005)
	Beef	ND	ND	ND	11.6 (11.6–11.6)	Garcia-Vazquez et al. (2009)
Netherlands	Dairy	ND	ND	2.4 (1.7–3.1)	10.4 (9.9–10.8)	Moen et al. (1998), Wouda et al. (1998), Dijkstra et al. (2003) and Bartels et al. (2006a,b)
New Zealand	Dairy	2.9	6.4 (2.6–25.9)	4.2 (1.7–26)	30.4 (6.8–73.0)	Thornton et al. (1991, 1994), Cox et al. (1998), Reichel (1998), Patitucci et al. (1999), Schares et al. (1999), Pfeiffer et al. (2002), Reichel and Pfeiffer (2002), Thobokwe and Heuer (2004), McDougall et al. (2005) and Weston et al. (2005, 2012a) and Heuer et al. (2007)
	Beef	ND	ND	ND	2.8 (2.8–2.8)	Tennent-Brown et al. (2000)
Spain	Dairy	ND	ND	6.2 (3.3–9.1)	19.1 (15.7–35.9)	Mainar-Jaime et al. (1999), Quintanilla-Gozalo et al. (1999), Bartels et al. (2006a), Gonzalez-Warleta et al. (2008, 2011) and Eiras et al. (2011)
	Beef	ND	ND	ND	15.8 (7.4–25.1)	Quintanilla-Gozalo et al. (1999), Bartels et al. (2006a), Armengol et al. (2007) and Eiras et al. (2011)
UK	Dairy	ND	14.3 (5.0–43.0)	3.5 (2.2–5.7)	15.0 (6.0–37.7)	Trees et al. (1994), Davison et al. (1999a,b,c), Williams et al. (1999), Crawshaw and Brocklehurst (2003), Woodbine et al. (2008) and Brickell et al. (2010)
USA	Dairy	ND	18.6 (0.6–39.4)	7.2 (1.7–40.0)	49.2 (16.1–89.2)	Anderson et al. (1995), McAllister et al. (1996), Dubey et al. (1997), Paré et al. (1997), Thurmond and Hietala (1997a,b),Thurmond et al. (1997), Hietala and Thurmond (1999), Dyer et al. (2000), Jenkins et al. (2000), Hernandez et al. (2002) and Rodriguez et al. (2002)
	Beef	ND	9.1 (9.1–9.1)	ND	13.0 (7.5–81.7)	Thurmond et al. (1997), Barling et al. (2000), McAllister et al. (2000), Sanderson et al. (2000) and Barling et al. (2001a,b)
Total	Dairy	2.5	14.3 (0.6–39.4)	3.5 (1.3–40.0)	16.1 (3.8–89.2)	
	Beef	1.2	9.1 (9.1–9.1)	9.0 (5.7–23.3)	11.5 (2.5–81.7)	

publications reached the threshold, suggests that the level of *N. caninum* infection is generally approximately 50% higher in dairy cattle (median sero-prevalence 16.1%) than in beef cattle (median sero-prevalence 11.5%). The *N. caninum*-specific risk of abortion in dairy cattle reached a median of 14.3% across all 10 countries, with a wide range from 0.6% to 39.4% being reported. The increase in risk (odds) of *N. caninum* causing abortions reached a median value of 3.5 (ranging from 1.3 to 40.0) in dairy cattle, while in beef cattle the median value was 9.0 (5.7 to 23.3) (which, however, could only be calculated from two countries).

3.3. Country-specific literature search statistics

3.3.1. Argentina

The PubMed search and subsequent evaluation revealed that there were five publications from Argentina with economically relevant information; three covering the dairy industry (Venturini et al., 1999; Moore et al., 2002, 2009) reporting on studies that included in excess of 4,000 cattle (n = 4,280) and three from the beef industry (Moore et al., 2002, 2003, 2009) (n = 3,241), with one publication reporting on abortion statistics with specific reference to *N. caninum* (Moore et al., 2008) (n = 666).

3.3.2. Australia

The database search recovered eight relevant publications for Australia, with six describing the dairy situation in relation to *N. caninum* (Boulton et al., 1995; Obendorf et al., 1995; Atkinson et al., 2000; Quinn et al., 2004; Hall et al., 2005, 2006; Nasir et al., 2012) (n = 1,246) and only two for the beef situation (Stoessel et al., 2003; Nasir et al., 2012) (n = 2,483).

3.3.3. Brazil

In Brazil, six publications contained relevant data on *N. caninum* in the dairy industry (Gondim et al., 1999; Locatelli-Dittrich et al., 2001; Guimaraes et al., 2004; Aguiar et al., 2006; Corbellini et al., 2006; Minervino et al., 2008) (n = 3,842), three in the beef industry

(Aguiar et al., 2006; Minervino et al., 2008; Marques et al., 2011) (*n* = 863) and one abortion statistics in general (Pescador et al., 2007) (*n* = 258).

3.3.4. Canada

From Canada, 11 publications described mostly sero-prevalence data from 36,072 dairy cattle (Bildfell et al., 1994; Paré et al., 1998; Keefe and VanLeeuwen, 2000; Chi et al., 2002; Cramer et al., 2002; Pan et al., 2004; Hobson et al., 2005; VanLeeuwen et al., 2005; Peregrine et al., 2006; Wapenaar et al., 2007; Tiwari et al., 2009) and in five publications study data from beef cattle (Waldner et al., 1998, 1999, 2001, 2004; Waldner, 2005) (*n* = 7,324).

3.3.5. Mexico

Three publications described *N. caninum* in dairy cattle (Morales et al., 2001b; Garcia-Vazquez et al., 2002, 2005) (*n* = 2,003) and one study for the beef situation (Garcia-Vazquez et al., 2009) (*n* = 596), as well as one study that described abortion statistics in the dairy industry (Morales et al., 2001a) (*n* = 211).

3.3.6. Netherlands

Five publications from the Netherlands described the impact in dairy cattle (*n* = 11,767) (Moen et al., 1998; Wouda et al., 1998; Dijkstra et al., 2003; Bartels et al., 2006a,b).

3.3.7. New Zealand

For New Zealand, reports with relevant information were obtained from 12 publications, 11 for dairy cattle (Thornton et al., 1991, 1994; Cox et al., 1998; Reichel, 1998; Patitucci et al., 1999; Schares et al., 1999; Pfeiffer et al., 2002; Reichel and Pfeiffer, 2002; Thobokwe and Heuer, 2004; Weston et al., 2005, 2012a) (*n* = 6,636) and one for the beef industry (Tennent-Brown et al., 2000) (*n* = 499).

3.3.8. Spain

From Spain there were six publications describing the situation in the dairy industry (Mainar-Jaime et al., 1999; Quintanilla-Gozalo et al., 1999; Bartels et al., 2006a; Gonzalez-Warleta et al., 2008, 2011; Eiras et al., 2011) (*n* = 48,790) and four publications describing contribution of *N. caninum* to economic losses in the beef industry (Quintanilla-Gozalo et al., 1999; Bartels et al., 2006a; Armengol et al., 2007; Eiras et al., 2011) (*n* = 26,083).

3.3.9. UK

Seven studies from the British dairy industry reported *N. caninum* related information (Trees et al., 1994; Davison et al., 1999a,c; Williams et al., 1999; Crawshaw and Brocklehurst, 2003; Woodbine et al., 2008; Brickell et al., 2010) (*n* = 23,007).

3.3.10. US

For the US, 11 published papers described the situation in the dairy industry (Anderson et al., 1995; McAllister et al., 1996; Dubey et al., 1997; Paré et al., 1997; Thurmond and Hietala, 1997a; Thurmond et al., 1997; Hietala and Thurmond, 1999; Dyer et al., 2000; Jenkins et al., 2000; Hernandez et al., 2002; Rodriguez et al., 2002) (*n* = 38,207) and five papers described the impact of *N. caninum* in beef cattle (Thurmond et al., 1997; Barling et al., 2000, 2001b; McAllister et al., 2000; Sanderson et al., 2000) (*n* = 4,774).

3.4. Economic impact calculation

Once the specific contribution of *N. caninum* to abortion in these 10 countries had been ascertained (i.e. the number of abortions that were likely to be caused by *N. caninum* calculated for each country), the cost of abortion could be calculated per industry and country (Table 3). Where several publications reported differing figures for *N. caninum* abortion risk or sero-prevalence, median values were calculated, and the estimates ranged through the lowest and highest estimate for either or both (odds of abortion or prevalence, as available).

3.5. Global economic impact assessment

Globally, the estimated median losses due to *N. caninum*-induced abortions were estimated to be in excess of US $1,298.3 million (range US $633.4 million to US $2,380.1 million). Approximately two-thirds of the losses, US $842.9 million (range US $341.1 million to US $1,739.3 million) were incurred by the national dairy industries in the 10 countries included and over one-third, at US $455,4 million (range US $292.3 million to US $640.8 million) in

Table 3
Number of pregnant cows and heifers at potential risk of abortion, estimated median and range of specific *Neospora caninum* abortion costs (in US$ at May 2012 exchange rates) at national and herd levels in 10 countries and their cattle industries.

Country	Industry	Cows at risk (mill)	National cost (mill US$)	(range) mill US$	Herd cost ('000s US$)	Range
Argentina	Dairy	8.8	38.5	29.2–85.3	4.0	3.0–8.7
	Beef	1.8	48.9	22.6–57.6	0.6	0.3–0.7
Australia	Dairy	1.8	26.6	7.1–54.0	9.3	2.5–18.8
	Beef	9.7	74.1	27.7–139.5	1.5	0.6–2.8
Brazil	Dairy	14.2	51.3	35.8–111.3	0.0	0.0–0.0
	Beef	29.7	101.0	63.6–111.7	0.0	0.0–0.0
Canada	Dairy	1.3	17.1	10.0–32.1	1.3	0.8–2.5
	Beef	4.3	14.3	13.6–14.8	0.2	0.2–0.2
Mexico	Dairy	2.7	68.5	52.4–403.2	0.1	0.1–0.5
	Beef	30.3	94.8	94.8–94.8	0.1	0.1–0.1
Netherlands	Dairy	1.7	12.1	8.3–20.2	0.7	0.5–0.9
New Zealand	Dairy	4.8	35.7	14.5–221.0	11.0	4.5–68.0
	Beef	1.1	1.1	1.1–1.1	0.1	0.1–0.1
Spain	Dairy	0.9	19.8	7.2–57.9	0.5	0.2–1.6
	Beef	1.7	9.8	4.6–15.6	0.2	0.1–0.2
UK	Dairy	2.0	27.0	10.8–32.4	1.8	0.7–2.1
USA	Dairy	8.2	546.3	165.8–721.9	12.2	3.7–16.1
	Beef	23.6	111.4	64.3–205.7	0.1	0.1–0.3
Total per industry	Dairy	46.3	842.9	341.1–1739.3	1.6	0.0–68.0
	Beef	102.2	455.4	292.3–640.8	0.15	0.0–2.8
Total (all cattle)		148.6	1298.3	633.4–2380.1	0.5	0.0–68.0

Mill, million.

the respective eight beef industries (summarised in Table 3). Close to two thirds of the global costs of US $1,298 million per annum are estimated to occur in North America (US $852.4 million (65.7%)), followed by South America (US $239.7 million (18.5%)) and Australasia, which incurs 10.6% of the global losses at a median value of US $137.5 million annually. Losses due to *N. caninum* abortions in Europe only accounted for 5.3% of the global losses or an estimated US $68.7 million.

As 46.4 million cows were at annual risk of abortion (i.e. pregnant) in the 10 countries included in the calculation for the dairy cattle industry, the cost per individual cow can be estimated to be, on average, US $18.16 (range US $7.35 to US $37.48). For the 102.2 million beef cattle at risk (i.e. pregnant) in eight countries the average loss per cow was estimated to be just US $4.46 (ranging from US $2.86 to US $6.27).

At the farm level, the median loss per farm was estimated to be US $1,600.00 (range <US $100 to US $ 68,000.00) in the dairy industry, and just US $150.00 for the beef industry (range <US $100 to US $2,800.00).

3.6. Country and industry-specific economic impact assessment

3.6.1. Argentina

In Argentina, the economic impact for the whole country was estimated to be US $87.4 million per annum, with US $38.5 million incurred by the dairy industry (ranging in estimates from US $29.2 million to US $85.3 million) and US $48.9 million (range US $22.6 million to US $57.6 million) by the beef industry. At the farm level, dairy farmers were likely to incur a median *N. caninum* loss of close to US $4,000 (ranging from close to US $2,993.41 to US $8,740.75) and beef farmers of approximately US $550.00 (ranging from US $256.66 to US $654.06).

3.6.2. Australia

Australian dairy farmers were calculated to incur a median annual loss of US $26.6 million (range US $7.1 million to US $54.0 million) at the national level, and US $9,300 (range US $2,500 to US $18,800) at the herd level. The beef industry was estimated to lose an annual median US $74.1 million (range US $27.7 million to US $139.5 million), with the losses at the herd level amounting to a median US $1,500 (range US $600 to US $2,800).

3.6.3. Brazil

In Brazil, dairy farmers were estimated to incur *N. caninum*-associated losses at the national level of US $51.3 million per annum (ranging in estimates from US $35.8 million to US $111.3 million), while the losses at the farm level were less than US $100.00. In the Brazilian beef industry *N. caninum* losses amounted to, nationally, US $101.0 million (ranging from US $63.6 million to US $111.7 million), while at the average dairy farm level they did not exceed US $100.00.

3.6.4. Canada

In Canada, the dairy industry was estimated to experience losses related to *N. caninum* at the national level amounting to a median US $17.1 million (ranging from US $10.0 to US $32.1 million), while losses at the individual, average farm level were estimated to be median US $1,300 (range US $800 to US $2,500). In the beef industry, losses were estimated to amount to a median annual US $14.3 million (range (US $13.6 million to US $14.8 million). At the farm level, beef losses were estimated to reach an annual US $200 only.

3.6.5. Mexico

The Mexican dairy industry was expected to incur losses due to *N. caninum* infection/abortion approaching US $68.5 million (ranging from US $52.4 million to US $403.2 million). Annual losses in the beef industry in Mexico were estimated to be US $94.8 million. At the average farm level, the losses did not exceed US $100.00 for both beef and dairy farms.

3.6.6. Netherlands

The Dutch dairy industry was estimated to incur annual median losses due to *N. caninum* infection/abortion of US $12.1 million (ranging from US $8.3 million to US $20.2 million). At the dairy farm level, losses were estimated to attain a median of US $700.00 (range from US $480.00 to US $950.00).

3.6.7. New Zealand

New Zealand dairy farmers were estimated to incur *N. caninum*-related median annual losses of US $35.7 million nationally (range US $14.5 to US $221 million), while the average dairy farm was expected to incur losses of US $11,000 (range US $4,500 to US $68,000). The national beef industry was thought to lose a median US $1.1 million only, with the average farm incurring losses of just US $100 annually.

3.6.8. Spain

The Spanish dairy industry, nationally, was estimated to incur losses specific to *N. caninum* of a median US $19.8 million (range US $7.2 million to US $57.9 million), with individual farms incurring annual losses of US $500 (range US $200 to US $1,600). The beef industry was expected to incur losses amounting to a median annual figure of US $9.8 million (range US $4.6 million to US $15.6 million), while individual farmers might incur costs of a median US $200 (range US $100 to US $200).

3.6.9. UK

In the UK, figures were only available for the dairy industry. Nationally, *N. caninum* abortions were estimated to cost an annual median of US $27 million (range US $10.8 million to US $32.4 million), which translated into an annual median cost to the average farm of US $1,800 (range US $700 to US $2,100).

3.6.10. US

In the US, annual median losses due to *N. caninum* were estimated to be approximately US $546.3 million in the dairy industry (range US $165.8 million to US $721.9 million), while on the farm the average costs were US $12,200 (range US $3,700 to US $16,100). In the beef industry, annual median losses were estimated to be US $111.4 million (range US $64.3 million to US $205.7 million) nationally, with US $100 only (range US $100 to US $300) being incurred on average by an individual farm.

4. Discussion

The peer-reviewed literature related to *N. caninum*-associated abortions in cattle from the 10 countries included in this review, suggests that the median specific risk of abortion due to *N. caninum* infection is higher in dairy cattle at 14.3% (range: 0.6–39.4%) than it is in beef cattle at 9.1%. Also, the median sero-prevalence of *N. caninum* world-wide, at 16.1% (range 3.8–89.2%), was higher in dairy cattle compared with that prevailing in the beef industries at 11.5% (range 2.5–81.7%). The odds of abortion in *N. caninum*-infected animals, however, were almost triple (at 9.0 times) in the beef industry than in the dairy industry (3.5 times higher). To our knowledge, these figures give a first global assessment of the risk of infection and abortion of *N. caninum*. The background level of abortions that are not *N. caninum*-associated appears to be higher in dairy cattle at 2.5%, compared with beef cattle at 1.2%.

The total losses in the cattle industries of the 10 countries surveyed exceeded US $1,298 million per annum, with approximately two-thirds of these losses incurred by dairy industries (US $842.9 million; 64.9%) and one third by the beef industries (US $455.4 million; 35.1%). The upper limit of assumptions for abortion risk and sero-prevalence for the total cattle industries estimated the annual global loss due to *N. caninum* abortions as at least US $2,380 million (US $1,739 million in the dairy industries and US $641 million in the beef industries, respectively), while the lower estimates suggested that costs are at least approaching US $633 million in the combined cattle industries (with a minimum of US $341.1 million (53.9%) incurred by the dairy industries and US $292.3 (46.1%) incurred by the beef industries). As the review and thus the estimate of losses was restricted to the 10 countries that each contributed more than five relevant publications to the analysis, this first estimate is likely to be at the lower end of the total global losses caused by *N. caninum* infection in cattle.

The global costs of *N. caninum* clearly exceed those presented here, and likely even the upper range of estimates, as only publications and cost estimates from 10 countries were included in the review. Forty-five other countries had reported on 'cattle' and '*Neospora*', the search terms, but had published less than the threshold of five publications or non-economically relevant information, and could not be included in the current analysis. Even for the countries that made the threshold, the number of publications rarely exceeded 10. The calculated costs show evidence of non-normal distribution (relative position of the median within the range suggesting non-symmetry), and more studies that are representative of the target population are required to give greater robustness to our assessment. Additional publications with relevant information that allow further countries to be added to our global assessment will no doubt increase the total assessed cost.

The 10 countries where relevant publications exceeded the threshold, however, include a number of the important cattle industries of the world and thus provide an initial indication of the impact of *N. caninum* in those countries. They also cover geographical areas with economically important and influential cattle populations, such as the Americas, Australasia and Europe. This, however, may also reflect a publication bias, with industries in these countries having better reporting systems or providing researchers with greater access to *N. caninum* research funds.

Two-thirds of the global costs of US $1,298 million per annum are estimated to be incurred in North America (US $852.4 million (65.7%)), followed by South America (US $239.7 million (18.5%)) and Australasia US $137.5 million (10.6%). Losses in the three countries from Europe included in the analysis only accounted for 5.3% of the global losses or US $68.7 million.

At the national level, the total annual costs of *N. caninum* abortions for the cattle industries exceeded US $100 million per annum in Australia (which is close to the estimate provided 15 years earlier by Ellis (1997)), Brazil, Mexico and the US, which hence appear to be primary target markets for any control or vaccination effort. In addition, the individual farm losses on Argentinean and New Zealand farms reach an estimated median of US $4,000 and US $11,000, respectively, thus these two countries (in addition to the aforementioned four) also seem to be potential target markets for control methods. At the individual farm level, losses in both beef and dairy sectors rarely exceeded the US $2,000 mark. Only on the average dairy farm in Argentina, Australia, New Zealand and in the US did the losses exceed an annual estimate of US $2,000 and only in the case of the latter two countries did the estimate, per farm, exceed US $10,000 per annum. On the average beef farm, only in Argentina (US $600) and Australia (US $1,500) did the annual, *N. caninum*-associated losses exceed US $500.00. The median global loss incurred at the farm level was only US $1,800 for dairy and US $150.00 for the beef industry.

The four countries where the estimated costs of *N. caninum* exceed US $100 per annum are also those with rather large cattle populations. In general, when combining the cow population at risk of abortion in both the dairy and beef industry in those countries, in excess of 10 million head of cattle are potentially at risk in each of those countries, and hence flow into the cost estimations. In the case of high on-farm impacts, the countries with relatively high average herd sizes gain prominence, such as the US and Australia (countries with relatively large cattle populations as well) and Argentina and New Zealand where, particularly in the dairy industry, the number of at risk female cattle exceeds 200 head per herd.

In the 10 countries included in the calculation for the dairy cattle industry, the cost per individual cow was estimated to be less than US $20.00 (US $18.16 (range US $7.35 to US $37.48)). In the 102.2 million beef cattle at risk (i.e. pregnant) in eight countries the average loss per cow was estimated to be just under US $5.00 (US $4.46 (ranging from US $2.86 to US $6.27)).

The losses at the individual cow and farm levels for both beef and dairy cattle seem to be quite low, however they are averaged over all pregnant cows. As globally only 16.1% of dairy cows and 11.5% of beef cows are estimated to be infected with *N. caninum*, the losses incurred by *N. caninum*-infected cows can be expected to be approximately six (dairy) or nine (beef) times higher at ~US $110.00 and ~US $40.00 per animal. These estimates are not dissimilar to estimates for the impact of bovine viral diarrhoea (BVD) virus on cattle farms, which also range from US $10 to US $80 per pregnant cow (Houe, 2003; Heuer et al., 2007). BVD control and country-wide eradication receives a lot of attention, with Germany very recently commencing a BVD control campaign, and Switzerland essentially having just having completed its own eradication effort (Presi et al., 2011). In order to be able to offer a benefit to farmers with control or vaccination strategies (which might be difficult to demonstrate at an "all-cow" level), it would be important to cost-effectively identify infected properties and individual animals and target those specifically. As diagnostic assays are well developed and validated (Paré et al., 1995a,b; Ellis, 1998; Reichel and Pfeiffer, 2002), the targeted delivery of vaccines or treatment to just infected animals might not pose the problems that it might have in the past, and will deliver the benefit-to-cost ratios that primary producers desire.

While the global losses incurred by *N. caninum* in the cattle industries of 10 countries are estimated to be in excess of one billion dollars annually, it is individual farmers that need to appreciate that the parasite poses a problem and is affecting their profitability. Median losses on farms are estimated to have the potential to range as high as US $68,000 (if the highest impacting assumptions for sero-prevalence and increased risk of abortion in *N. caninum*-infected cows for that country are modelled for the cost), but in most countries individual farm losses may appear to be low to primary producers and hence go unnoticed. Losses are only likely to exceed US $2,000 per farm/year on dairy farms in four of the countries (Argentina, Australia, New Zealand and the US) included in the present review. This will continue to present a challenge to vaccine developers and marketers, as producers may choose to "live" with the disease if their perceptions of likely losses are low (Reichel and Ellis, 2006). On the other hand, this analysis may provide a starting point and target countries where the initial commercialisation of an efficacious vaccine for the prevention of *N. caninum* infections and/or abortions would be beneficial (Reichel and Ellis, 2009).

The only previously marketed commercial vaccine against *N. caninum* abortions showed low efficacy, likely because it was unable to demonstrate sufficient protection in already infected cattle (Weston et al., 2012b). Protecting naïve, uninfected cows might not need to be a priority for vaccination if post-natal infection rates are generally as low as they have been reported in the literature (Paré et al., 1996; Thurmond and Hietala, 1997a; Davison et al., 1999b; Hall et al., 2005), although others have reported post-natal transmission rates as high as 22% annually (Björkman et al., 2003). Here the benefit to cost ratio is also low, as the large majority of animals would have to be inoculated as part of an insurance policy against infection, when the actual risk of infection/abortion is low. Preventing vertical transmission and/or abortions would provide far greater benefit/cost ratios as these animals are at a demonstrably higher risk of abortion (being already infected). Expected losses at ~US $130.00 per cow are higher and more likely to occur. The efficiency of vertical transmission is reported to be high, with reported estimates ranging from 75% to 90% (Hall et al., 2005), 85%, (Björkman et al., 2003) to even 93% (Schares et al., 1998) and 100% (Anderson et al., 1997). Chronically infected cows are also at greater risk of abortion (Thurmond et al., 1997). A vaccine that could break the endogenous transmission cycle and thus prevent infection of the calf would prevent infection of the next generation of cattle, and may even be able to prevent abortions as well.

An alternative might be to have two vaccines; one for a naïve population as an insurance policy against primary infection (Williams and Trees, 2006; Innes, 2007). This vaccine would need to be very cheap to give primary producers an incentive to use it with the low average cost of *N. caninum* infection in that proportion of the cattle population. Another vaccine should be able to prevent the recrudescence of *N. caninum* and abortion in already infected animals (Williams et al., 2003; Trees and Williams, 2005). Such a vaccine could be more expensive, as *N. caninum*-associated costs in that proportion of the cattle population are estimated to be higher also. Vaccines that confer long-lasting immunity and protection could arguably be more expensive, as the economic losses presented here per cow are annual costs. A once-only applied vaccine that confers long lasting immunity may still be a better benefit-to-cost proposition in either of the above scenarios than a more traditional vaccine that requires an annual booster. Economic consideration may be just as important as drivers for research into efficacious vaccines against *N. caninum* as technical feasibility and efficacy (Reichel and Ellis, 2009).

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