Paratuberculosis (also called Johne’s disease) is a chronic disease caused by *Mycobacterium avium* ssp. *paratuberculosis* (MAP) that affects ruminants and other animals. The epidemiology of paratuberculosis is complex and the clinical manifestations and economic impact of the disease in cattle can be variable depending on factors such as herd management, age, infection dose, and disease prevalence, among others. Additionally, considerable challenges are faced in the control of paratuberculosis in cattle, such as the lack of accurate and reliable diagnostic tests. Nevertheless, efforts are directed toward the control of this disease because it can cause substantial economic losses to the cattle industry mainly due to increased premature culling, replacement costs, decreased milk yield, reduced feed conversion efficiency, fertility problems, reduced slaughter values, and increased susceptibility to other diseases or conditions. The variability and uncertainty surrounding the estimations of paratuberculosis prevalence and impact influence the design, implementation, and efficiency of control programs in diverse areas of the world. This review covers important aspects of the economic impact and control of paratuberculosis, including challenges related to disease detection, estimations of the prevalence and economic effects of the disease, and the implementation of control programs. The control of paratuberculosis can improve animal health and welfare, increase productivity, reduce potential market problems, and increase overall business profitability. The benefits that can derive from the control of paratuberculosis need to be communicated to all industry stakeholders to promote the implementation of control programs. Moreover, if the suspected link between Johne’s disease in ruminants and Crohn’s disease in humans was established, significant economic losses could be expected, particularly for the dairy industry, making the control of this disease a priority across dairy industries internationally.
conditions (Ott et al., 1999; Weber, 2006; Gonda et al., 2007; Richardson and More, 2009). Most infected animals show clinical disease between 2 and 6 yr of age, although clinical manifestations can range from 4 mo to 15 yr (Caldow et al., 2001). An animal in clinical stage has the potential to infect 25 more animals, although disease transmission depends on several factors such as close contact between animals (Whitlock and Buergelt, 1996). The main route of MAP transmission is the oral–fecal route but other infection routes have been proposed, such as intrauterine and aerosol transmission. The MAP bacterium has been detected in dust in cattle facilities housing infected animals, suggesting that aerosol spread of MAP might be possible (Eisenberg et al., 2010). Furthermore, MAP has been isolated from tracheobronchial lymph nodes, supporting the hypothesis of aerosol transmission (Pavlík et al., 2000b). Moreover, there is no effective treatment of cows infected with paratuberculosis (Extension, 2014; NADIS, 2014).

Animals most likely become infected with MAP during the first 6 mo of life; neonates are particularly susceptible to infection (Cocito et al., 1994) and intrauterine infection is also possible. Whittington and Windsor (2009) conducted a meta-analysis and estimated the prevalence of MAP infections in utero to be 39% among cows with clinical disease and 9% among subclinical cows. It has been suggested that MAP infection during adulthood rarely develops into clinical disease (Rankin, 1962). In fact, increased resistance to infection with age has been observed that could be explained by the more fragile immune system in younger animals, which in turn facilitates access of the bacteria to the Peyer’s patches (Sweeney, 1996). It can take a few years for animals to develop clinical disease; however, subclinical infections also hamper animal health, productivity, and farm profitability (Johnson-Ihearulundu et al., 2000). Furthermore, animals in subclinical stages may excrete MAP organisms in variable numbers; they are usually low or moderate shedders (shedding fewer than 10^3 colonies/g of feces) but they could also be super-shedders and excrete millions or billions of bacteria into the environment (Whitlock et al., 2006).

Infected bulls can excrete MAP bacteria in feces and semen (Larsen et al., 1981; EFSA, 2004; Abbas et al., 2011). Infected cows can excrete MAP in feces, milk, and colostrum. Heavy fecal shedders are more likely to shed MAP in colostrum (Streeter et al., 1995). In fact, MAP infection of young animals can happen via intrauterine transmission or consumption of infected colostrum or milk although it occurs primarily via the fecal–oral route (Clarke, 1997). The bacterium has also been detected in raw milk and therefore could be transferred to humans via milk because MAP might not be effectively inactivated by pasteurization (Corti and Stephan, 2002; Gao et al., 2002; Grant et al., 2002a,b). The disease affects primarily ruminants; however, a potential link between Johne’s disease in ruminants and Crohn’s disease in humans has raised concerns over the safety of dairy products, prioritizing the control of the disease in ruminants, particularly dairy cattle (Chamberlin et al., 2001; Ghadiali et al., 2004; Naser et al., 2004). The potential link between paratuberculosis in cattle and Crohn’s disease in humans forms part of an ongoing scientific debate (European Commission, 2000; Chacon et al., 2004; Ghadiali et al., 2004; Herrewegh et al., 2004; Shanahan and O’Mahony, 2005; Food FSAI, 2009; Juste, 2012). Although there is no definitive evidence to demonstrate that the bacteria causes or contributes to Crohn’s disease in humans, MAP has been detected more commonly in patients with Crohn’s disease (Scientific Committee on Animal Health and Animal Welfare, 2000; Bull et al., 2003; Naser et al., 2004; Feller et al., 2007). This potential link between Johne’s disease in ruminants and Crohn’s disease in humans needs to be clarified but the presence of viable MAP in pasteurized milk for human consumption (Ayele et al., 2005; Ellingson et al., 2005) has prompted public health agencies and organizations to advise the industry to prevent MAP from entering the food chain.

The potential zoonotic risk for consumers, the effect on animal health and welfare, and the large financial losses that may be caused by this disease have led to the implementation of disease control programs in many countries. This paper aims to review the most important aspects related to paratuberculosis impact and control in cattle. For this purpose, relevant epidemiological aspects are included to provide context and background information.

**DISEASE DETECTION AND PREVALENCE**

The tests most commonly used for the identification of infected animals, for estimation of prevalence, and for disease control programs are fecal culture (individual and pooled fecal samples), serum ELISA, and milk ELISA. Fecal PCR may also be used as a confirmatory test (Clark et al., 2008). Individual fecal culture of MAP is considered the reference test (Barrett et al., 2011). The apparent prevalence of MAP will partly depend on the diagnostic test used. In general, the sensitivity of fecal culture and PCR seem to be superior to that of ELISA for the identification of MAP-infected cattle. As an example, a study conducted by Smith et al. (2009) found a prevalence varying from 0 to 4.9% when using serum ELISA and a prevalence of 0 to 13.6% when using liquid fecal culture. The sensitivity and specificity of diverse diagnostic tests for the detec-
tion of paratuberculosis can be very variable (Nielsen and Toft, 2008), which represents one of the main challenges for the control of this disease. The sensitivity of the diagnostic tests can vary widely: milk ELISA from 21 to 61%, serum ELISA from 7 to 94% (Nielsen and Toft, 2008), and PCR from 4 to 100% (Gilardoni et al., 2012), whereas the sensitivity of individual fecal culture may range from 20 to 74% (Whitlock et al., 2000; Nielsen et al., 2002; Nielsen and Toft, 2008; OIE, 2014). The sensitivity of fecal culture may increase significantly when samples are strategically pooled (Kalis et al., 2000; Wolf et al., 2014). Environmental samples can be taken to detect the presence of MAP in the herd (using culture). Samples can be obtained from the cattle environment such as milking parlor, holding pens, and manure pit (Lombard et al., 2005b).

Obviously, diagnostic methods play a crucial role in the correct identification of infected and disease-free animals and serve as a basis for the implementation of control strategies and disease management programs. Correctly identifying the infection status of cattle depends on the diagnostic tests but also on the stage of the infection process; in general, cattle with clinical infection are more likely to be detected (Weber, 2006). This fact and the presence of a high number of animals in subclinical stages may explain in part why the overall sensitivity of diagnostic tests for paratuberculosis is low.

The likelihood of a herd infection with MAP depends on factors such as the clinical history and the management of the herd. Obviously, herds with a history of clinical paratuberculosis will be more likely to test positive (Hirst et al., 2004). Nevertheless, paratuberculosis is largely underreported although evidence suggests that it is an endemic disease in some areas of the world, particularly in areas with large dairy industries (Kennedy et al., 2001). Comparison between diverse MAP prevalence studies can be challenging due to differences in diagnostic tests, diagnostic strategies, and sampling design (Muskens et al., 2000; National Research Council, 2003). A review of MAP prevalence in farmed cattle around Europe has revealed that numerous prevalence studies have been conducted but comparable true prevalence estimates are difficult to obtain (Nielsen and Toft, 2009). Moreover, differentiation between animal-level prevalence (individual animals), within-herd prevalence (number of animals testing positive for MAP within a particular herd), and herd-level prevalence (number of herds that are MAP positive) should be made (Lombard, 2011). Examples of MAP prevalence studies (animal- and herd-level prevalences) are presented in Tables 1 and 2.

The prevalence of MAP can be underestimated when the sensitivity of the diagnostic test is low, leading to false-negative results. On the other hand, false-positive results can be obtained due to cross-reactivity to other

Table 1. Examples of Mycobacterium avium ssp. paratuberculosis (MAP) animal-level prevalence studies

<table>
<thead>
<tr>
<th>Country (state)</th>
<th>Reference</th>
<th>Cattle type</th>
<th>No. of herds; No. of cattle</th>
<th>Animal-level apparent prevalence (%)</th>
<th>Reported true prevalence (%)</th>
<th>Diagnostic method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>Boelaert et al. (2000)</td>
<td>Dairy</td>
<td>98; 4,497</td>
<td>1.16</td>
<td>NR</td>
<td>Serum ELISA</td>
</tr>
<tr>
<td>Belgium</td>
<td>Boelaert et al. (2000)</td>
<td>Beef</td>
<td>259; 4,010</td>
<td>0.52</td>
<td>NR</td>
<td>Serum ELISA</td>
</tr>
<tr>
<td>Denmark</td>
<td>Jakobsen et al. (2000)</td>
<td>Dairy</td>
<td>22; 1,155</td>
<td>8.8</td>
<td>NR</td>
<td>Milk ELISA</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>Muskens et al. (2000)</td>
<td>Dairy</td>
<td>378; 15,822</td>
<td>2.54</td>
<td>NR</td>
<td>Serum ELISA</td>
</tr>
<tr>
<td>Canada</td>
<td>Chi et al. (2002)</td>
<td>Dairy</td>
<td>90; 2,604</td>
<td>NR</td>
<td>0.8</td>
<td>Serum ELISA</td>
</tr>
<tr>
<td>Canada</td>
<td>Waldner et al. (2002)</td>
<td>Beef</td>
<td>NR; 1,799</td>
<td>0.0</td>
<td>NR</td>
<td>Serum ELISA</td>
</tr>
<tr>
<td>Canada</td>
<td>Sorensen et al. (2003)</td>
<td>Dairy</td>
<td>50; 1,500</td>
<td>7.0</td>
<td>NR</td>
<td>Serum ELISA</td>
</tr>
<tr>
<td>United States (16 states)</td>
<td>Lombard et al. (2005a)</td>
<td>Dairy</td>
<td>38; 7,879</td>
<td>3.8</td>
<td>NR</td>
<td>Serum ELISA</td>
</tr>
<tr>
<td>Austria</td>
<td>Dreier et al. (2006)</td>
<td>Mixed</td>
<td>NR; 756</td>
<td>19</td>
<td>NR</td>
<td>Several methods</td>
</tr>
<tr>
<td>Spain</td>
<td>Dieguez et al. (2007)</td>
<td>Dairy</td>
<td>1,210; 38,077</td>
<td>2.53</td>
<td>4.03</td>
<td>Serum ELISA</td>
</tr>
<tr>
<td>Spain</td>
<td>Dieguez et al. (2007)</td>
<td>Beef</td>
<td>1,497; 22,964</td>
<td>1.59</td>
<td>2.07</td>
<td>Serum ELISA</td>
</tr>
<tr>
<td>Spain</td>
<td>Dieguez et al. (2007)</td>
<td>Mixed</td>
<td>28; 84</td>
<td>2.44</td>
<td>3.84</td>
<td>Serum ELISA</td>
</tr>
<tr>
<td>Ireland</td>
<td>Mee and Richardson (2008)</td>
<td>Dairy</td>
<td>34; 949</td>
<td>1.37</td>
<td>2.88</td>
<td>Serum ELISA</td>
</tr>
<tr>
<td>Ireland</td>
<td>Good et al. (2009)</td>
<td>Dairy</td>
<td>165; NR</td>
<td>NR</td>
<td>2.74</td>
<td>Serum ELISA</td>
</tr>
<tr>
<td>Ireland</td>
<td>Good et al. (2009)</td>
<td>Beef</td>
<td>458; NR</td>
<td>NR</td>
<td>3.09</td>
<td>Serum ELISA</td>
</tr>
<tr>
<td>Germany</td>
<td>Denzin et al. (2011)</td>
<td>Dairy</td>
<td>NR; 986</td>
<td>4.24</td>
<td>0.7</td>
<td>Serum ELISA</td>
</tr>
<tr>
<td>India</td>
<td>Gupta et al. (2012)</td>
<td>Dairy</td>
<td>5; 350</td>
<td>15.14</td>
<td>15</td>
<td>Serum ELISA</td>
</tr>
<tr>
<td>Latin America and Caribbean</td>
<td>Fernández-Silva et al. (2014)</td>
<td>Systematic review (21 studies)</td>
<td></td>
<td>16.9</td>
<td>NR</td>
<td>Several methods</td>
</tr>
<tr>
<td>Germany</td>
<td>Donat et al. (2014)</td>
<td>Dairy</td>
<td>14; 1,021</td>
<td>41.43</td>
<td>NR</td>
<td>Fecal culture</td>
</tr>
<tr>
<td>Canada</td>
<td>Pruvot et al. (2014)</td>
<td>Beef</td>
<td>28; 840</td>
<td>0.8</td>
<td>NR</td>
<td>Serum ELISA</td>
</tr>
</tbody>
</table>

1NR = not reported.
Mycobacterium species. For example, common antigens are shared between MAP and *Mycobacterium bovis* (Leroy et al., 2009; Santema et al., 2009); therefore, exposure to MAP may induce low-level protection against *M. bovis* and compromise disease diagnosis (Hope et al., 2005). In fact, MAP infection can interfere with tuberculosis diagnostic tests (Aranaz et al., 2006; Alvarez et al., 2009; Lilenbaum et al., 2009) and, conversely, tuberculosis and the tuberculin test might also interfere with paratuberculosis diagnosis (Alvarez et al., 2009; Lilenbaum et al., 2009; Vargas et al., 2009). Due to the limitations of the diagnostic tests, true MAP prevalence estimations can be difficult to obtain but good study designs and the use of Bayesian approaches may help to overcome this problem (Branscum et al., 2004; Messam et al., 2008; Norton et al., 2010; Pozzato et al., 2011).

### Table 2. Examples of *Mycobacterium avium* ssp. *paratuberculosis* (MAP) herd-level prevalence studies

<table>
<thead>
<tr>
<th>Country (state)</th>
<th>Reference</th>
<th>Cattle type</th>
<th>No. of herds; No. of cattle</th>
<th>Herd-level apparent prevalence (%)</th>
<th>Reported true herd prevalence (%)</th>
<th>Diagnostic method</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Netherlands</td>
<td>Muskens et al. (2000)</td>
<td>Dairy</td>
<td>378; 15,822</td>
<td>54.7^2</td>
<td>NR</td>
<td>Serum ELISA</td>
</tr>
<tr>
<td>Belgium</td>
<td>Boelaert et al. (2000)</td>
<td>Dairy</td>
<td>98; 4,497</td>
<td>32</td>
<td>10^3</td>
<td>Serum ELISA</td>
</tr>
<tr>
<td>Belgium</td>
<td>Boelaert et al. (2000)</td>
<td>Beef</td>
<td>259; 4,010</td>
<td>7</td>
<td>3^2</td>
<td>Serum ELISA</td>
</tr>
<tr>
<td>United States</td>
<td>Dargatz et al. (2001)</td>
<td>Beef</td>
<td>380; 10,371</td>
<td>7.9^4</td>
<td>NR</td>
<td>Serum ELISA</td>
</tr>
<tr>
<td>Canada</td>
<td>Waldner et al. (2002)</td>
<td>Beef</td>
<td>NR; 1,799</td>
<td>15,1 3^2</td>
<td>NR</td>
<td>Serum ELISA</td>
</tr>
<tr>
<td>Switzerland</td>
<td>Corti and Stephan (2002)</td>
<td>Dairy</td>
<td>1,384</td>
<td>19.7</td>
<td>NR</td>
<td>Bulk-tank milk PCR</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Grant et al. (2002b)</td>
<td>Dairy</td>
<td>244</td>
<td>7.8</td>
<td>NR</td>
<td>Bulk-tank milk PCR</td>
</tr>
<tr>
<td>United States (CA)</td>
<td>Adaska and Anderson (2003)</td>
<td>Dairy</td>
<td>65; 1,950</td>
<td>68,4 35^3</td>
<td>NR</td>
<td>Serum ELISA</td>
</tr>
<tr>
<td>Canada</td>
<td>Sorensen et al. (2003)</td>
<td>Dairy</td>
<td>50; 1,500</td>
<td>40.0^3</td>
<td>26.8</td>
<td>Serum ELISA</td>
</tr>
<tr>
<td>Austria</td>
<td>Dreier et al. (2006)</td>
<td>Mixed</td>
<td>NR; 756</td>
<td>19</td>
<td>NR</td>
<td>Several methods</td>
</tr>
<tr>
<td>United States (APHIS)</td>
<td>(2007)</td>
<td>Dairy</td>
<td>524; NR</td>
<td>68.1</td>
<td>NR</td>
<td>Composite fecal culture</td>
</tr>
<tr>
<td>Spain</td>
<td>Dieguez et al. (2007)</td>
<td>Dairy</td>
<td>1,210; 38,077</td>
<td>35.95,4 14.96^3</td>
<td>27.77,4 18.79^3</td>
<td>Serum ELISA</td>
</tr>
<tr>
<td>Spain</td>
<td>Dieguez et al. (2007)</td>
<td>Beef</td>
<td>1,497; 22,964</td>
<td>10.68,4 2.47^3</td>
<td>2.78,4 2.40^3</td>
<td>Serum ELISA</td>
</tr>
<tr>
<td>Spain</td>
<td>Dieguez et al. (2007)</td>
<td>Mixed</td>
<td>28; 84</td>
<td>7.14,4 3.57^3</td>
<td>5.70,4 12.24^3</td>
<td>Serum ELISA</td>
</tr>
<tr>
<td>Ireland</td>
<td>Mee and Richardson (2008)</td>
<td>Dairy</td>
<td>34; 949</td>
<td>50,4 25^3</td>
<td>NR</td>
<td>Serum ELISA</td>
</tr>
<tr>
<td>Ireland</td>
<td>Good et al. (2009)</td>
<td>Dairy</td>
<td>165; NR</td>
<td>31.5</td>
<td>20.6</td>
<td>Serum ELISA</td>
</tr>
<tr>
<td>Ireland</td>
<td>Good et al. (2009)</td>
<td>Beef</td>
<td>458; NR</td>
<td>17.9</td>
<td>7.6</td>
<td>Serum ELISA</td>
</tr>
<tr>
<td>United States</td>
<td>Lombard et al. (2013)</td>
<td>Dairy</td>
<td>524 herds</td>
<td>70.4</td>
<td>91.1</td>
<td>Composite fecal culture</td>
</tr>
<tr>
<td>United States</td>
<td>Toth et al. (2013)</td>
<td>Dairy</td>
<td>13 farms</td>
<td>76.92</td>
<td>NR</td>
<td>Composite fecal culture</td>
</tr>
<tr>
<td>Latin America and</td>
<td>Fernández-Silva et al.</td>
<td>Mixed</td>
<td>Systematic review (21 studies)</td>
<td>75.8</td>
<td>NR</td>
<td>Several methods</td>
</tr>
<tr>
<td>Caribbean</td>
<td>(2014)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New Zealand</td>
<td>Verdugo et al. (2014)</td>
<td>Beef</td>
<td>116; NR</td>
<td>29</td>
<td>42</td>
<td>Pooled fecal culture + individual serum ELISA</td>
</tr>
<tr>
<td>Switzerland</td>
<td>Keller et al. (2014)</td>
<td>Dairy</td>
<td>12; 855</td>
<td>83.3</td>
<td>NR</td>
<td>Pooled fecal culture + PCR</td>
</tr>
<tr>
<td>Switzerland</td>
<td>Keller et al. (2014)</td>
<td>Beef</td>
<td>11; 484</td>
<td>72.7</td>
<td>NR</td>
<td>Pooled fecal culture + PCR</td>
</tr>
<tr>
<td>Canada</td>
<td>Pruvot et al. (2014)</td>
<td>Beef</td>
<td>28; 840</td>
<td>21</td>
<td>20</td>
<td>Serum ELISA</td>
</tr>
</tbody>
</table>

^1NR = not reported.

^2Adjusted cut-off level upward to increase specificity.

^3Based on 2 or more animals testing positive.

^4Based on 1 or more animals testing positive.
MAP SURVIVAL AND DISEASE RISK FACTORS

*Mycobacterium avium* ssp. *paratuberculosis* bacteria are considered to be resistant to cold, drying, acidic conditions, and UV radiation (Whittington et al., 2004; Donaghy et al., 2009). They seem to be also heat resistant, raising concerns over the effectiveness of heating milk on the inactivation of MAP. High-temperature, short-time (HTST) pasteurization (at least at 71.7°C for 15 s or any equivalent combination) does not seem to inactive all viable MAP (Grant et al., 2001, 2002a). Results from studies investigating log reductions of MAP bacteria after HTST treatment are inconsistent and estimates range from 1.3 to 7.0 logs (Lewis, 2010). It has been suggested that MAP can survive in soil up to 47 mo (Caldow et al., 2001). Moreover, MAP bacteria might survive in water environments for up to 48 wk and therefore contaminated water might be an important reservoir for infections (Whittington et al., 2004, 2005). In addition, MAP can survive and replicate inside free-living amoeba in aquatic environments (Whan et al., 2006). Those authors also reported that MAP living inside amoeba might become more resistant to the effect of chlorine, which could have an effect on MAP-control measures on farms.

The fact that MAP bacteria can survive in fecal material for up to 55 wk (Whittington et al., 2004) and in soil supports the risk associated with bringing in slurry, which is considered a significant biosecurity risk (AHI, 2013). The purchase of new animals has also been found to be a considerable biosecurity risk and to be significantly associated with an increased seroprevalence of paratuberculosis (Wells and Wagner, 2000; Tiwari et al., 2009; AHI, 2013). Additionally, the presence of “super-shedders” represents the greatest source of MAP infections in the herd (Whittlock et al., 2005). Parasites such as nematodes could also act as a vector for MAP transmission (Lloyd et al., 2001).

Diverse factors will influence the prevalence, maintenance, detection, spread of infection, and effect of paratuberculosis in cattle herds. The age of the animals tested for paratuberculosis has been found to be an important factor for the detection of test-positive animals (Kostoulas et al., 2013; Nielsen et al., 2013). In a study conducted by Good et al. (2009), most of the positive animals identified (75%) were 4 yr of age and over. Herd size has been identified as a significant factor for the spread and prevalence of paratuberculosis (Ott et al., 1999; Caldow et al., 2001; Muskens et al., 2003; Groenendaal, 2005; Sayers and Cook, 2009; Barrett et al., 2011). Cattle residing in larger herds (>100 animals) and in herds where new animals have been acquired are at higher risk and more likely to test positive to paratuberculosis (Wells and Wagner, 2000; Hirst et al., 2004; Mee and Richardson, 2008). Several risk factors associated with increased exposure of calves to fecal matter contaminated with MAP have been reported, such as close contact with adult infected cows and group housing for periparturient cows and preweaned calves (Obasanjo et al., 1997; Johnson-Ifeearulundu and Kaneene, 1999; Wells and Wagner, 2000; Caldow et al., 2001). The presence of MAP in feces contaminating the udders and the calving environment can be a primary risk factor for MAP infection of very young calves (National Research Council, 2003). In a study conducted by Johnson-Ifeearulundu and Kaneene (1998), cleaning maternity pens was associated with a reduced risk of MAP infection. A study conducted in Ireland found risk factors such as feeding waste milk to calves, large herds, absence of individual calving pens, and herd depopulations due to notifiable diseases to be significantly associated with paratuberculosis in cattle (Mee and Richardson, 2008). Another Irish study found cattle importation, herd size, and herd depopulation as significant risk factors for paratuberculosis, whereas obtaining colostrum from off-farm sources seemed to be a protective factor in this particular study (Barrett et al., 2011). This last finding seems surprising because MAP can be present in colostrum when colostrum is acquired from MAP-positive cows. However, in the study conducted by Barrett et al. (2011), colostrum from off-farm sources seemed to be a protective factor, possibly because it had been acquired from MAP-negative animals. The association of paratuberculosis with larger herds could be due to depopulation and restocking practices, particularly after removal of animals for disease control purposes (Mee and Richardson, 2008).

Very young calves are considered to be at greater risk of infection particularly during the first 24 h of life and therefore management practices should be considered to decrease the exposure of very young calves to MAP infection (AHI, 2012). Aly et al. (2015) conducted a cohort study recording MAP status of heifers over time and observed that heifers that had been separated from the farm of origin and reared offsite were associated with a lower risk of MAP infection. Those authors concluded that rearing heifer calves away from infected adult cows might have a protecting effect against MAP infection.

**ECONOMIC IMPACT**

Paratuberculosis is of increased concern for the cattle industry as it is considered a threat to efficiency and profitability (Spackman, 2011). The economic impact of paratuberculosis in a cattle herd will depend on the number of animals affected, infected, infectious (shedding bacteria), showing clinical signs, or in the sub-
clinical stage. Disease impact will also be influenced by factors such as the production system, herd size, and herd management (Dufour et al., 2004). The economic consequences of MAP infection can be difficult to assess due to the lack of accurate data related to disease prevalence and the fact that most MAP infections are subclinical (Johnson-Iheurulundu and Kaneene, 1997; National Research Council, 2003). Nevertheless, losses due to MAP infections can be substantial and the economic impact of paratuberculosis is of increasing concern due to the apparent increase in the global prevalence, associated economic losses, and potential consequences for trade (Rideout et al., 2003). In the UK, the average cost of paratuberculosis per animal per year has been calculated as £26.00 for dairy cattle (approximately $47 based on the average exchange rate in 2004) and £17.00 for beef cattle (approximately $31 based on the average exchange rate in 2004; Gunn et al., 2004). In the United States, a MAP-related estimated average cost of $22 to $27 per cow per year has been reported (Ott et al., 1999). However, the cost of the disease in positive herds was estimated to be $100 per cow compared with negative herds, and in herds with clinical cases the disease-associated losses may exceed $200 per cow (Ott et al., 1999). In fact, the net economic impact of paratuberculosis in the US dairy industry has been estimated to vary from $200 to $1,500 million annually (Jones, 1989; Ott et al., 1999). A French study estimated paratuberculosis associated costs as €1,940 for a clinical case (approximately $2,386 based on the average exchange rate in 2004) and €461 for a subclinical case (approximately $567 based on the average exchange rate in 2004), considering an average dairy herd in France (Dufour et al., 2004). Those authors estimated the costs associated with a clinical paratuberculosis case, including the loss of the cow and its calf, costs of replacements, costs associated with loss of milk production, costs related to veterinary treatment, and costs of testing. The estimate for a subclinical paratuberculosis case was based on the expected reduced milk yield due to the disease. In Ireland, information based on data from one case study over a 10-yr period indicated that the annual average gross margin in this herd decreased between €130 and €155 (approximately $163 and $194 based on the average exchange rate in 2012) per cow during the study period (AHI, 2012), whereas Barrett et al. (2006) reported significant reductions in profit margin of between €168 and €253 (approximately $210 and $316 based on the average exchange rate in 2006) per cow in an Irish herd affected with paratuberculosis.

The economic impact might be difficult to measure in herds with a very low prevalence or with a small number of animals in the subclinical stage (Lombard, 2011). Nevertheless, the economic impact is likely to increase over time in infected herds if control measures are not implemented to prevent the spread of the disease. Although significant negative economic impacts have been reported in association with clinical paratuberculosis (Harris and Barletta, 2001), the economic impact of subclinical paratuberculosis (test-positive only) seems less clear and variable results have been obtained (Hasonova and Pavlik, 2006). On the other hand, it has been suggested that the economic impact of subclinical cases can be significant when the disease affects a large number of animals (Tiwari et al., 2008). Animals infected with MAP in subclinical stages may show reduced general performance, reduced production, reduced fertility, and increased susceptibility to other diseases before more obvious clinical signs appear (AHI, 2012). The impact of the subclinical stage is likely to vary between individual animals (genetic variation) and herds (Nordlund et al., 1996; Koets et al., 2000; Johnson et al., 2001; Gonda et al., 2007) and therefore the quantification of the economic impact might be challenging. Furthermore, the reported economic impact of this disease can vary depending on factors such as the geographical area, production systems, data included in the studies, animal disease status, and disease prevalence to mention a few. Simulation models have estimated annual losses due to subclinical MAP infections of $35 per cow (increasing to $72 per cow per year after 20 yr) for a typical 100-head US dairy herd (Groenendaal and Galligan, 2003). Higher economic annual losses (mean loss of $2,992; 95% CI: $143 to $9,741) were estimated in a study using data from an average Canadian dairy herd with 12.7% of cows seropositive for MAP (Tiwari et al., 2008). A recent US study conducted by Bhattacharai et al. (2013a) reported an economic annual loss of $1,644 ($625–$3,250) due to paratuberculosis in a herd with 100 animals and a 7% true prevalence based on information obtained from producers. The same study reports a very similar estimation based on information collected from veterinarians of $1747 ($575–$3,375).

**Economic Impact Related to Milk Production**

Studies have estimated the economic impact of paratuberculosis in relation to milk production, reporting reductions of mean milk yield between 500 and 1,400 kg/cow in the lactation when the infection was detected (Johnson et al., 2001; Kudahl et al., 2004; Beaudet et al., 2007; Gonda et al., 2007; Richardson and More, 2009). A correlation between the prevalence of paratuberculosis within herds and milk yield reductions has been reported (Ott et al., 1999). Reductions in milk production are sometimes noticed in first lactation but
in general they are more pronounced in older cows and as infection is more advanced (Johnson et al., 2001). Chi et al. (2002) reported milk yield reductions of 19.5 and 15%, respectively, among cows clinically and sub-clinically MAP infected. A significant milk yield reduction of 24% (1,528 L) was observed in an Irish herd affected with paratuberculosis between the years 1997 and 2002 (Barrett et al., 2006). General farm performance was substantially reduced in this farm between 1993 and 2003. A study conducted by Raizman et al. (2009) evaluated the differences in net income per lactation of cows shedding MAP before calving compared with fecal test-negative cows. The authors estimated that fecal-culture-positive (FCP) cows produced 1,355 kg less milk than fecal-culture-negative (FCN) cows, although this effect was more evident in first-lactation cows (when FCP cows produced 1,803 kg less milk than FCN cows). The reduction in milk production translated in a loss of $276 related to milk income from FCP cows compared with cows that were FCN. Richardson and More (2009) conducted a retrospective case study collecting data over 11 yr from paratuberculosis cases and control animals belonging to a commercial dairy herd in Ireland. Cattle with clinical signs of the disease produced significantly lower milk yield (approximately 1,260 kg/lactation). Gonda et al. (2007) reported decreased milk production in MAP-infected cows (7.89% of cows included in the study), which produced 303.9 kg less milk/lactation, 11.46 kg less fat/lactation, and 9.49 kg less protein/lactation. In addition, MAP-infected animals had a significantly lower productive life (2.85 mo less). Interestingly in that study, consistently larger effects on all studied traits were found in FCP cows compared with ELISA-positive animals, reflecting that the impact of paratuberculosis on milk production can also be influenced by disease status. Lombard et al. (2005a) observed that cows with strong positive serum ELISA results showed significantly lower milk production traits (mature-equivalent 305-d milk production, mature-equivalent 305-d maximum milk production, and total lifetime milk production) than animals in the other 3 categories (ELISA negative, inconclusive, or positive).

Estimates of losses related to milk production found in the literature are inconsistent. A decrease in milk production due to MAP infection would be expected; however, some studies found no effect or even higher milk production from animals testing positive for MAP (McNab et al., 1991; Johnson et al., 2001). In fact, a US study conducted by Smith et al. (2009) observed that MAP-positive animals produced more milk than negative animals before they began shedding the bacteria. However, infected animals that were shedding MAP experienced monthly milk production decreases of 0.05 to 1 kg, with the reduction in milk production being more evident in animals within progressive disease categories. A significant reduction in milk production was observed in animals with fecal culture results of >30 cfu/g. Smith et al. (2009) concluded that MAP status had a significant effect on milk production but that the effect varied depending on disease status categories; they suggested that the definition of the categories and the classification of animals played an important role in the results. In fact, these researchers proposed that in their study the higher milk production observed from animals belonging to the latent MAP-infected (but not shedding) group balanced out the lower milk production in high-shedding animals, which could explain the lack of a significant difference in milk production between MAP-uninfected and MAP-infected animals found in other studies (Johnson et al., 2001).

**Economic Impact Related to Weight Loss and Meat Production**

Paratuberculosis produces inflammation and malfunc-
tion of the intestinal tract, malabsorption syndrome, and protein-losing enteropathy, which negatively affects feed conversion and weight gain. Moreover, calves from cows that test positive for MAP and produce less milk are more likely to weigh less than calves from MAP-negative cows. A study conducted by Bhattacharai et al. (2013b) supports this hypothesis. Those authors found that the 205-d adjusted weaning weight of suckler calves from cows with strongly positive ELISA results was 21.48 kg (47.26 lb) less than that of calves from cows testing MAP negative. Furthermore, when looking at MAP-culture results, the adjusted weaning weight of calves from cows classified as heavy or moderate MAP shedders was 58.51 kg (128.72 lb) and 40.81 kg (89.78 lb) less, respectively, than that of calves from MAP-culture-negative cows. The associated economic losses were estimated as $156.60/calf and $109.23/calf for cows classified as heavy and moderate MAP shedders, respectively, and $57.49/calf for cows with strongly positive ELISA results. The results from the study conducted by Bhattacharai et al. (2013b) indicate that the economic losses of paratuberculosis related to weight loss of calves in cattle production systems can be considerable. Similarly, the effect of MAP infections on slaughter weight and slaughter value of cows can be significant in terms of economic losses and animal welfare. On occasions, carcasses with severe pathologies and postmortem findings may not enter the food chain. In the United States, the slaughter value of paratuberculosis-infected cows with clinical pathology
has been estimated to be 20 to 30% less than that of noninfected cows or animals with no clinical pathology (Chi et al., 2002; National Research Council, 2003). A study conducted in Michigan reported that a 10% increase in MAP apparent prevalence was associated with a decrease in mean weight (culled cows) of 33.4 kg (Johnson-Ifearulundu et al., 1999). The losses in terms of reduced weight of culled cows were estimated to be approximately $1,150 annually for each 10% increase in herd prevalence of paratuberculosis. Kudahl and Nielsen (2009) evaluated the effects of paratuberculosis on the slaughter weight and slaughter value of dairy cows and estimated weight losses of up to 31% and slaughter value losses up to 48% compared with MAP-negative cows (with at least 2 ELISA-negative tests). The results also depended on the diagnostic tests, with higher losses estimated when animals were classified as positive using fecal culture. It was also reported that the reduction in slaughter value was more noticeable when cattle presented enteritis or edema at postmortem examination.

**Economic Impact Related to Premature Culling, Increased Mortality, and Replacement-Associated Costs**

Infection with MAP induces a granulomatous inflammation of the intestines that is associated with a decrease in feed efficiency, with reproduction losses and premature culling (Alonso-Hearn et al., 2009). Barrett et al. (2006) observed a significant increase in culling rates due to infertility in an Irish herd with paratuberculosis. Smith et al. (2010) found that animals that were not shedding MAP were significantly less likely to be culled compared with animals in the low-shedding or ELISA-positive categories. Similarly, Raizman et al. (2009) reported that FCP animals were 3 times (95% CI: 1.6–5.8) more likely to be culled than FCN cows. Buergelt and Duncan (1978) investigated the main reasons for culling animals and classified them into 2 groups: clinical disease and MAP-infected animals with no clinical symptoms. The main reasons for culling animals in the clinical disease group were MAP-positive fecal culture (50% of animals), significant weight loss (33%), and reduced milk yield (17%), whereas the primary reasons for culling animals from the group of MAP-infected animals with no clinical symptoms were decreased milk production (46%), mastitis (27%), MAP-positive fecal culture (9%), infertility (9%), and positive complement fixation test (5%). Johnson-Ifearulundu et al. (1999) reported that mortality rate was 3% higher among herds that tested positive for paratuberculosis and estimated that the increased mortality rate could translate into losses between $1,607 and $4,400 for an average herd due to lost slaughter value and the cost of replacement animals.

Premature culling and mortality due to paratuberculosis incur costs associated with increased replacements, the loss of animals, and the loss of the potential from genetics in the herds (Sorge et al., 2010). The time at which MAP-positive cows should be culled has been a matter for discussion. Kudahl et al. (2011) investigated the effect of time of culling MAP-positive cows on prevalence and profitability using simulation models. They observed that in the long term (>7 yr from implementation of a strategy), culling cows as soon as possible after they tested positive for MAP was the most profitable strategy. However, a case scenario assuming an increased market price (20%) of replacement heifers made culling based on milk production criteria the most profitable strategy for a longer period (11 to 13 yr). Kudahl et al. (2011) concluded that the ideal culling strategy in every case will depend on factors such as the time horizon, the productive and reproductive capabilities, and the costs related to replacement animals.

**Economic Impact Related to Infertility and Predisposition to Other Diseases**

Chronic diseases in animals will cause a reduced immune system response (Kreeger et al., 1991, 1992) to a disease challenge. An association between MAP infection and reduced immune competence has been suggested, which may explain the generally observed increased rate of culling due to loss of productivity, infertility, mastitis, and other health problems (Johnson-Ifearulundu and Kaneene, 1997). Several studies have tried to estimate the impact of paratuberculosis infection on herd fertility with variable results, from significantly reduced fertility in infected cows (Johnson-Ifearulundu et al., 2000) to better fertility in MAP-infected animals (Lombard et al., 2005a; Gonda et al., 2007); McNab et al. (1991) observed no significant effect. Smith et al. (2010) observed that high-shedding animals had lower calving rates than low-shedding or ELISA-positive animals; however, animals in the latter 2 categories (low-shedding and ELISA-positive) seemed to have higher calving rates than test-negative animals.

The effect of paratuberculosis on SCC, mastitis, or both has been investigated, with some studies showing no significant effect of paratuberculosis on SCC (Lombard et al., 2005a; Gonda et al., 2007) and some studies finding an increase in SCC (McNab et al., 1991; VanLeeuwen et al., 2006; Diéguez et al., 2008) or mastitis (Buergelt and Duncan, 1978; Abbas et al., 1983;
Considerations Related to the Cost of Diagnostic Testing, Veterinary Costs, Animal Welfare Impact, Marketing, and Public Health-Related Issues

The cost of diagnostic testing (and diagnostic regimens or intervals) can be substantial and therefore should be taken into account in the cost-benefit analyses of control programs. Veterinary costs can be significant in clinical cases and outbreaks of paratuberculosis, and there could also be indirect veterinary costs associated with paratuberculosis when infected animals are more prone to other diseases such as mastitis and lameness. Moreover, chronic clinical cases of paratuberculosis can be considered an animal welfare issue, which could have negative implications for the farmer. Furthermore, a producer’s reputation can be negatively affected by the establishment of a MAP-positive status, which in turn may imply adverse marketing effects over a protracted period.

Groenendaal and Zagmutt (2008) evaluated the effects that a link between paratuberculosis in cattle and Crohn’s disease in humans could have on milk demand and the milk industry in general. Input data were acquired from the USDA National Agricultural Statistics Service. Three scenarios were considered: the first assumed that there was an effective strategy in place for risk mitigation, the second scenario considered that although there was a risk-mitigation strategy, there was also a small decrease on milk demand, and the third scenario assumed that there was no risk-mitigation strategy in place, resulting in a considerable demand reduction (of 1 or 5%), which translated into “a reduction in consumer surplus of between $600 million and $2.9 billion, and a reduction in dairy farm income of $270 million and $1.3 billion, respectively.” From those results, it seems that the milk industry should be concerned about the establishment of such a link and implement control and risk-mitigation strategies, particularly if the consumer’s perception of a public health risk is likely to be significant whether the risk is real or not.

MAP CONTROL PROGRAMS AND MODELS

Paratuberculosis control programs or voluntary pilot programs have been implemented in countries such as the Netherlands, Denmark, United States, Canada, and Australia, among others. Control programs are diverse and follow different objectives, guidelines, and control measures with variable acceptance between producers. In Sweden, MAP is included in the Swedish Epizootic Act (SFS 1999:657), which states that suspected clinical cases are notifiable and need to be investigated. Paratuberculosis control measures (including herd depopulation) have been followed in Sweden, and the last known case (an imported bull) was identified in 2004 (Frössling et al., 2013). In Sweden, MAP has never been detected in wildlife, dairy cattle, or other ruminants, and the surveillance and control program in place aims to prove freedom from disease (SVA, 2014). In Austria, clinical paratuberculosis has been notifiable since 2006, and the control program is based on testing and implementing controls on farms with MAP-positive animals (Baumgartner, 2013).

The potentially significant negative economic effects of the disease in many aspects of cattle production make producers more proactive in terms of its control. Efforts are directed toward the implementation of control programs and toward the evaluation of their effectiveness. Effective paratuberculosis control programs aim to prevent entry of infection into “MAP-free” herds and to reduce the infection pressure on susceptible animals in already infected herds. To reduce infection pressure, control strategies should be directed to eliminate infected animals (particularly affected and infectious animals) from the herds (test-and-cull strategies), to break disease transmission routes, and to reduce the risk of animals, particularly youngstock, becoming infected (Johnson-Ifearulundu and Kaneene, 1998). Control programs based on risk management require a definition of “acceptable level of risk” or “acceptable level of associated losses” due to paratuberculosis to inform control strategies (Weber, 2006).

The use of vaccination for the control of paratuberculosis in cattle seems promising but it is controversial mainly due to the potential interference with tuberculosis control programs. In some countries such as Sweden, the use of vaccines against paratuberculosis in cattle is prohibited (SVA, 2014). On the other hand, the use of vaccines has been successfully implemented for the control of paratuberculosis in small ruminants (Saxegaard and Fodstad, 1985; Fridriksdottir et al., 2000). In US cattle, the use of paratuberculosis vaccines is allowed only in restricted situations and following strict rules and regulations (Patton, 2011). Available commercial vaccines consist of MAP killed whole cells.
Risk-Based Strategies for the Control of Paratuberculosis

Risk-based control strategies and control programs are being implemented in several countries such as Norway, Denmark, Canada, and the United States. Whist et al. (2014) described a method to improve the selection of herds in a paratuberculosis risk-based surveillance program in Norway. The method combines risk factors with risk indicators (based on production and clinical data) from several national databases to provide a risk assessment for each herd. The results from the risk assessments were included in the 2014 national surveillance program.

A Danish voluntary MAP control program based on risk assessment named “Operation Paratuberculosis” was initiated in February 2006. Kudahl et al. (2008) evaluated the potential long-term effects of the risk-based program compared with non-risk-based “classical disease control measures” using the PTB-Simherd herd-simulation model (Kudahl et al., 2007). Those authors observed that the results obtained from the risk-based control strategies were very efficient in reducing the prevalence of paratuberculosis in cattle using less labor than non-risk-based control strategies (such as optimized management of all cows). It was observed that closing infection routes was crucial to the control of paratuberculosis and estimated that the prevalence of paratuberculosis could be reduced by at least 10% of the initial prevalence within 5 to 7 yr if infection routes were closed. In fact, the authors concluded that test-and-cull strategies were not cost effective if infection routes were not efficiently closed (Kudahl et al., 2008).

In Canada, the voluntary Ontario Johne’s Education and Management Assistance Program was initiated in 2010. Pieper et al. (2015) analyzed the results after 4 yr of program implementation. Investigations into the obtained Risk Assessment and Management Plan (RAMP) scores revealed that high variability was observed in relation to levels of participation among different areas, veterinary clinics, and practitioners. The results showed that RAMP scores were higher for MAP ELISA-positive herds than for negative herds but there was high variability between veterinarians. Therefore, those authors recommended that farm assessments be performed by the same veterinarians to increase consistency of results.

The US Voluntary Bovine Johne’s Disease Control Program (VBJDCP) provides participant producers with guidelines for the control of Johne’s disease and classifies herds based on risk assessment (Carter, 2012). A similar program for the control of paratuberculosis in Italy (iRAMP) was initiated in 2012. The control
program in Italy is based on education of veterinarians and producers, on the use of online risk-assessment tools, and on management plans for the control of paratuberculosis on farms (McDonald et al., 2014). In the United States, the number of herds enrolled in the control program between 2000 and 2010 was variable: 1,952 herds in the year 2000, 1,925 herds in the year 2001, 3,254 herds in the year 2002, 4,722 herds in the year 2003, 5,732 herds in the year 2004, 8,046 herds in the year 2005, 8,736 herds in the year 2006, 8,818 herds in the year 2007, 7,273 herds in the year 2008, 5,675 herds in the year 2009, and 4,611 herds in the year 2010 (Carter, 2012). Producers can select their level of involvement in the VBJDCP program, which can include education, management, and testing with and without herd classification. The program includes a RAMP to assist producers in the prevention of the disease by identifying and correcting risky practices. On-farm risk assessments are conducted by Johne’s certified veterinarians or animal health officials to identify facility characteristics and management practices that are likely to increase the risk of introduction or spread of MAP in the herd. Subsequently, a management plan is produced to minimize the introduction and spread of MAP in specific herd(s) taking into account facilities and resources. Every RAMP needs to be reviewed and updated at least every 3 yr after enrollment, and appropriate changes have to be made when necessary. The education and management parts of the program do not require testing. Herd testing for classification assists producers in the identification of the risk of Johne’s disease within their herds based on the level of infection identified by testing. In this program with 6 levels, the higher the classification level, the lower the risk for the spread or transmission of Johne’s disease. Benjamin et al. (2009) obtained surveys from 39 beef producers included in the test-negative level 4 of the VBJDCP program to describe perceived benefits of attaining level 4 status. Increased benefits and marketing opportunities were perceived by more than one-third of producers classified at test-negative level 4 status in the VBDJCP program. Benjamin et al. (2009) suggested that the success of the VBJDCP program could increase by raising awareness of producers.

Several researchers have tried to identify the most effective strategies for the control of paratuberculosis. Bennett et al. (2010) reported that control measures related to management can reduce infection routes and result in a significant decrease in herd prevalence and costs associated with the disease, whereas the strategy of test-and-cull alone did not have an effect on reducing the prevalence of the disease in agreement with other studies (Weber, 2006; Kudahl et al., 2008). Farm management practices such as providing better housing for calves, separating calves from the cows and providing more hygienic water supplies may assist in the control of paratuberculosis but they might not be justifiable from a financial perspective (Stott et al., 2005). A system of accreditation of herds “free from paratuberculosis” together with improved biosecurity could be cost effective, provided that animals from accredited farms (“MAP-free”) get a significant premium compared with animals from nonaccredited farms. The existence of accreditation programs could assist in the purchasing of animals from MAP-free accredited farms. The introduction of new animals that could be MAP infected and the fecal–oral route are considered the main transmission routes of MAP infection within a herd (Sweeney, 1996; Barrett et al., 2006; AHI, 2012; Radia et al., 2013). The importance of paratuberculosis control strategies addressing transmission routes of infection has been highlighted; in particular, the control of fecal–oral routes of transmission (e.g., by separating calves from infected adult cattle) has been considered more effective than other control measures (Radia et al., 2013). Periparturient management and calf management practices have been identified as critical factors for control of paratuberculosis in cattle (Groenendaal and Galligan, 2003; Radia et al., 2013). According to a study using the JohneSSim model (Groenendaal, 2005), the implementation of effective calf management practices could have a significant effect on the control of paratuberculosis. The minimization or prevention of a calf’s exposure to MAP-infected adult animals was found to decrease paratuberculosis prevalence significantly in modeling studies (Groenendaal et al., 2003; Groenendaal, 2005). Infected adult cows play a crucial role in the introduction, transmission, and spread of MAP (AHI, 2012; Mackenzie, 2012). The use of individual calving pens as opposed to multiple-calving sheds and outdoor calving can aid in decreasing the risk of transmission and the prevalence of paratuberculosis in the herd (Mackenzie, 2012; Radia et al., 2013). Although outdoor calving can be very desirable and cost-effective, practical considerations such as geographical areas, weather conditions, and human supervision need to be taken into account. Periparturient management and calf management are considered to be key for the control of paratuberculosis and, in fact, several MAP control programs include guidelines with specific periparturient and calf management strategies (Groenendaal and Galligan, 2003; Dorshorst et al., 2006; Kudahl et al., 2007). Interestingly, the practice of cleaning udders and legs before parturition has been associated with MAP infection; however, poor hygiene could well be a confounding factor in this case, the lack...
of hygiene on farm being a risk factor for MAP infection (Johnson-Ifearulundu and Kaneene, 1998; Wells and Wagner, 2000).

**Combination of Control Strategies with Diagnostic Testing**

The combination of various control strategies with a test-and-cull scheme has been strongly recommended (Weber, 2006; Kudahl et al., 2008, 2011). It has been suggested that the use of fecal culture for test-and-cull strategies is more effective than the use of ELISA and that positive ELISA results should be confirmed by fecal culture unless the specificity of the ELISA is very high, more than 99% (Weber, 2006). The most effective paratuberculosis control strategies seem to be based on biosecurity measures together with repeated testing (Johnson-Ifearulundu and Kaneene, 1999; Kalis et al., 2004; Rossiter et al., 2004). Targeted sampling of manure storage and alleyways has been suggested as an effective method for herd screening to determine Johne’s disease status (Raizman et al., 2004). Farm management measures such as adequate management of animal waste and improved calf management should be included in paratuberculosis control programs (Groenendaal and Galligan, 2003; Flynn et al., 2005; Dorshorst et al., 2006). The control of paratuberculosis might become more cost effective if integrated into herd health management programs for the control of several diseases. In Ireland, specific guidelines for the control of paratuberculosis on farm are available and a pilot control program is currently in place (AHI, 2012, 2013).

The voluntary paratuberculosis control programs implemented in many countries are based on different aims, control strategies, and variable acceptance. Most control programs are based on test-and-cull strategies combined with risk management. Unfortunately, farmers’ willingness to participate in such programs can be limited due to perceived high costs, long duration of programs, intensive workload, and the expectation of limited success (Khol and Baumgartner, 2012). However, although producers can, in general, be uncomfortable following disease control programs, the results in many instances indicate that producers can save time and money by implementing effective paratuberculosis control programs (Sorge et al., 2010). Khol and Baumgartner (2012) proposed a “basic paratuberculosis control program” with minimum standards that could help overcome producers’ resistance to the implementation of paratuberculosis controls. This basic control program has 3 steps: MAP testing of adult cattle with diarrhea, implementation of basic control measures on farm, and regular evaluation of herd MAP status. Khol and Baumgartner (2012) propose that this basic program could be implemented with reasonable costs and workload and could be an incentive for producers who are not willing to follow more complex control programs. Nevertheless, in any case, effective communication of the benefits associated with the implementation of paratuberculosis control programs seems crucial to increase producer compliance with recommended disease control strategies (Sorge et al., 2010). Certification programs for “MAP-free herds” have been developed and can assist in the control of paratuberculosis (Kennedy et al., 2001; Weber, 2006). Purchasing cattle from certified “MAP-free herds” is highly recommended to avoid disease introduction. In the Netherlands, herds can obtain “MAP-free” status, although the use of the term “MAP-free” has been questioned and the alternative term “low-risk” has been proposed (Benedictus et al., 1999; Weber et al., 2004; Groenendaal, 2005).

Geraghty et al. (2014) conducted a review of bovine paratuberculosis control programs in 6 endemic infected countries (Australia, Canada, Denmark, the Netherlands, United Kingdom, and United States) looking at control programs’ components, monitoring, and program evaluations. Significant heterogeneity was observed between the control programs. On the other hand, recommended biosecurity and bio-containment activities were similar across the countries included in the review. One of the greatest challenges for the implementation of paratuberculosis control programs across countries was farmers’ willingness to participate, mainly due to uncertainty regarding cost-benefit of the control programs.

Cost-Benefit Analyses of Paratuberculosis Control Programs

The evaluation of the effectiveness of paratuberculosis control programs can be time consuming and expensive and require great effort but it can have positive and productive implications. Pillars et al. (2009) evaluated the cost effectiveness of management changes implemented in infected dairy farms to control paratuberculosis. The costs of the disease control programs were estimated as $30/cow per year (average) and the losses due to the disease as $79/cow per year (average), showing that investments in paratuberculosis control programs can be worthy and cost effective. Radia et al. (2013) estimated economic losses due to paratuberculosis prevalence that could be preventable by the implementation of specific management practices. An economic model developed by the University of Wisconsin to assess the economic impact of paratuberculosis in US dairy herds was used in this study (http://www.johnes.org/handouts/files/CostofJD_IDEXX%20booklet.pdf). The results suggested that the greatest paratuberculosis-associated
preventable losses were obtained when outdoor calving was implemented and when effective management practices such as using a colostrum replacement and reducing the time that calves spent with their mothers were implemented together. In fact, significant preventable losses (of up to £11,000 (approximately $17,270 based on the average exchange rate in 2013) could be achieved (considering an average UK 200-cow herd) when implementing a management practice that addressed all of MAP transmission routes (fecal–oral, milk, colostrum, and intrauterine transmission). Pillars et al. (2009) estimated preventable losses due to the implementation of paratuberculosis control programs to be around $79/cow per year. Radia et al. (2013) applied the result from Pillars et al. (2009) to a 200-cow herd, which resulted in £10,000 (approximately $15,700 based on the average exchange rate in 2013) in preventable losses, similar to their own calculations.

Collins et al. (2010) evaluated the effectiveness of a paratuberculosis control program in reducing MAP prevalence in 9 Wisconsin dairy herds over 6 yr. The control program was based on specific management practices and diagnostic testing. The program required several control strategies to be implemented, such as separation of maternity pens for MAP-positive and MAP-negative cows, prompt removal of newborn calves from maternity pens, use of colostrum (hygienically removed) from MAP-negative cows only, feeding pasteurized milk, and minimizing contact of newborn with cows’ manure. Testing was conducted every lactation using ELISA, and cows with strong positive results (using serum ELISA) were significantly more likely to be removed from the herds. In a study conducted by Lombard et al. (2005a), cows with strong positive results (using serum ELISA) were significantly more likely to be removed from the herd 1 yr after ELISA testing. Furthermore, animals infected with other Mycobacterium spp. such as M. bovis might be removed from the herds when testing positive for tuberculosis although there are concerns related to cross-reactions and tuberculin testing (Mullowney et al., 2008). The production of false-positive reactions to the tuberculin test as a consequence of other mycobacterial infection (such as MAP) may cause problems (Balseiro et al., 2003; Garrido et al., 2013). On the other hand, false MAP-positive results could be obtained due to cross-reactions with other mycobacteria, which are a cause for concern when following test-and-cull strategies for paratuberculosis control. Furthermore, the implementation of test-and-cull strategies alone is not recommended (Weber, 2006; Kudahl et al., 2008).

Despite the lack of data in relation to some aspects of paratuberculosis epidemiology and economics, significant efforts have been conducted to estimate the economic impact of the disease and to control paratuberculosis in diverse areas of the world, and considerable challenges have been faced and identified. The economic impact can be substantial in herds with animals showing clinical signs but more difficult to measure in herds with a very low prevalence or with animals in subclinical stages of the disease (Harris and Barletta, 2001; Hasonova and Pavlik, 2006; Lombard, 2011). The lack of field studies for the estimation of disease impact...
and for the evaluation of control strategies due to the chronic nature of paratuberculosis has been recognized (Radia et al., 2013). Moreover, the lack of accurate and reliable diagnostic tests contributes to the uncertainties surrounding paratuberculosis and its control (Behr and Collins, 2010). There seems to be high variability of results in relation to disease prevalence and the effects of paratuberculosis on productivity traits, which could be attributable to individual herd characteristics, MAP exposure and infectious dose, management practices, and imperfect diagnostic tests that can lead to misclassification of animals but also due to diverse study designs and the analyses conducted in the studies. Evidence suggests that MAP infections have a significant effect on milk production, although the effect can be variable depending on disease status; therefore, classification of animals will influence observations and control programs. Furthermore, a lack of significant effects on milk production could be obtained when all MAP-infected animals are included in the same group (with latent infected animals producing more milk and high-shedding animals producing less milk), resulting in an apparent lack of effect of the disease on milk production (Johnson et al., 2001). In fact, Smith et al. (2009) reported that MAP-infected latent animals showed higher daily milk production compared with negative animals, which seemed to be a surprising result. However, this finding is in agreement with what has been observed in relation to other diseases. For example, cows with higher milk production traits seem to be more susceptible to clinical mastitis (Bar et al., 2007), supporting the hypothesis of a positive genetic correlation between higher milk production and mastitis. Similarly, there could be a genetic component related to paratuberculosis susceptibility, with animals that produce more milk being more susceptible to MAP infections.

An important aspect of the estimations of the economic impact of paratuberculosis is decision making in relation to which parameters, production traits, and potential effects of the disease should be included in the calculations of disease impact. There seems to be variability in terms of the disease effects considered in different studies. The effects of the disease on milk production are included most studies but other effects should also be considered, within reason. This review has covered most of the effects that could be included in financial studies although there are others, such as animal welfare issues and social implications, that may be difficult to quantify economically.

Disease detection and correct classification of animals for disease control purposes are important challenges that producers, researchers, and governments around the world have to face. Paratuberculosis detection can be challenging due to the lack of accurate diagnostic tests. A high number of false-negative results can be expected when using diagnostic tests with low sensitivity (sometimes as low as 4%). On the other hand, the presence of false-positive results has also been observed due to the fact that some animals might ingest the bacteria and shed it in feces without being infected (Whitlock et al., 2006; Raizman et al., 2009) and because of cross-reactivity with other mycobacteria. Furthermore, denial of the presence of MAP-positive animals in a herd could be possible due to the potential consequences of the detection of the disease, such as nonsale of milk derived from infected animals. Kalis et al. (2004) reported the detection of a small number of herds that had been considered “free from paratuberculosis” based on owners’ declarations when this was not the case. The challenges related to disease detection and the unwillingness of producers to get animals tested and to report testing results make control of the disease difficult. Nevertheless, governments in some countries are making considerable efforts to control the disease, even though producers might be reluctant to implement paratuberculosis control programs. In this respect, stating clear and realistic objectives and adequate information and education of producers highlighting the benefits of the implementation of controls can help to promote the participation of stakeholders in long-term control programs. However, the benefits that can derive from the effective implementation of paratuberculosis control programs can be many and diverse, making the quantification of benefits and the cost-benefit analyses quite challenging. Nevertheless, benefits can justify the costs. In particular, some of the control strategies that do not necessarily carry a financial cost, such as purchasing animals from low MAP-infection-risk herds, could be promoted and implemented first (Lombard, 2011). Good biosecurity and biocontainment practices are crucial for paratuberculosis control, particularly adequate housing for calves and calf management (Wells and Wagner 2000, Berghaus et al., 2005; Diéguez et al., 2008; Collins et al., 2010). To increase producers’ participation in control programs, the use of a web-based economic farm health evaluator to calculate paratuberculosis-related economic losses has been proposed (Orpin and Sibley, 2014). Similarly, a Danish project (“iCull”) is currently investigating the development of economic models (in computers or smartphones) that can assist farmers in making decisions regarding individual animals or herd management practices for the control of paratuberculosis (Kirkeby et al., 2014).

The final aim of paratuberculosis control programs is to eliminate the disease completely from the cattle population in specific areas or countries and to obtain “MAP-free” status. However, the risk of introduction
may always be present and therefore effective surveillance programs are paramount for the control and early detection of disease. Effective surveillance systems should include repeated testing to assess the absence of infection based on negative test results over time (Martin, 2008). Frössling et al. (2013) performed calculations of surveillance sensitivities and probability of freedom from MAP infection in Sweden considering the risk of MAP introduction. Proving “MAP-free” status can be challenging and for this reason the use of the alternative term “low-risk” is recommended (Benedictus et al., 1999; Weber et al., 2004; Groenendaal, 2005).

The control of paratuberculosis is very important for the cattle industry to avoid the associated economic losses, to increase the productive life of cattle, and for marketing and trade purposes. A potential link between paratuberculosis in cattle and Crohn’s disease in humans has been investigated (European Commission, 2000; FSAI, 2009; Juste, 2012) and although there is no definitive evidence, MAP has been detected in pasteurized milk for human consumption (Ayele et al., 2005; Ellingson et al., 2005), raising concerns over the safety of dairy products. If a link between Johne’s disease in ruminants and Crohn’s disease in humans is established, significant economic losses might be expected, particularly for the dairy industry, due to consumers’ fears (Groenendaal and Zagmutt, 2008). Effective communication of food safety assurance programs to consumers seems crucial to ensure and maintain trust in the safety of foods (Mazzocchi et al., 2004, 2008; Casey et al., 2010). In fact, food safety is an important concern for consumers in different areas of the world. Consumers make decisions about food consumption based on assessment of perceived associated risks and benefits (Wilcock et al., 2004; Grunert, 2005; Wang et al., 2008; Ortega et al., 2011). Following recent food scares, important lessons should be learned such as the need to follow a transparent and robust risk management approach that can be paramount to ensure consumers’ confidence in food safety.

CONCLUSIONS

Paratuberculosis is an important chronic disease affecting cattle, although the impact of the disease can be variable. Cattle showing clinical signs, high-shedding animals, and super-shedders should be removed from the herd as soon as possible. The economic impact of paratuberculosis can be considerable in herds with clinical cases but the effect of subclinical paratuberculosis (test-positive only) is less clear. Furthermore, economic estimates depend on the correct classification of animals, which in turn depends on available diagnostic tests. The lack of accurate and reliable diagnostic tests contributes to the uncertainties surrounding paratuberculosis prevalence, impact, and evaluation of effectiveness of control strategies. Due to the potentially high number of false-negative and false-positive test results, the implementation of test-and-cull strategies alone is not recommended. Most control programs combine on-farm risk assessments, testing (and culling of high-risk animals), and bioexclusion, biocontainment, and biosecurity measures. The lack of reliable diagnostic tests and farmers’ unwillingness to participate in control programs are the main hurdles for the control of paratuberculosis. Despite challenges, significant efforts are conducted to control this disease in cattle in diverse areas of the world. Furthermore, if there were a public health scare associated with paratuberculosis, the economic losses for the industry (particularly the dairy industry) could be so considerable that disease control programs would be economically justified and attractive. The implementation of reward systems based on the paratuberculosis status of cattle herds could be considered in the future, particularly if further clear evidence of a link to Crohn’s disease is established. The development of new, improved, and more reliable diagnostic methods for the correct classification of animals is very desirable for the control of paratuberculosis. In any case, improving biosecurity and the implementation of cost-effective disease prevention and control measures will have positive consequences for producers in terms of reducing the risk of introduction and spread of several infectious diseases, including paratuberculosis, which in turn will improve animal health, animal welfare, and business profitability and sustainability.

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