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## Paratuberculosis control strategies in dairy cattle: A systematic review

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### Abstract

**Background:** *Mycobacterium avium* subsp. *paratuberculosis* is the causative agent of paratuberculosis (PTB), incurable enterocolitis, affecting domestic and wild ruminants. Economic losses, impacts on animal health and welfare, and public health concerns justify its herd-level control.

**Aim:** To systematically collect information to answer: What are the control and eradication strategies of PTB in dairy cattle worldwide?

**Methods:** The search procedure was carried out on October 2nd, 2019, and updated on August 3rd, 2021, using OVID®, SciELO, and Redalyc databases, and the registers from the International Colloquium on Paratuberculosis (1991–2018). The inclusion criteria considered articles published in English, Portuguese, and Spanish and in peer-reviewed journals. The exclusion criteria included irrelevant topics, species other-than bovines, and not original articles. Definitive studies were obtained through the consensus of the authors on eligibility and quality. Data extraction was performed, considering bibliographic information, control and outcome strategies, follow-up time, and results.

**Results:** Twenty-six relevant studies were found, reporting the use of three grouped control strategies: hygiene and management strategy (HMS), test-and-cull strategy (TCS), and vaccination strategy (VS). The HMS was the most common one (20/26), followed by TCS (17/26) and VS (7/26). Combined control strategies such as TCS-HMS (12/26), TCS-VS (1/26), and HMS-VS (1/26) were also described, and the consideration of the three control strategies (TCS-HMS-VS) was reported in two articles. The HMS included practices such as neonates/juvenile livestock hygiene, biosecurity, prevention of infection introduction into the herd, and environmental management. Within HMS, the most frequent practices were to remove calves from their dams as soon as possible after birth and to keep the minimal exposure of calves and heifers to adult cattle. As limitations, within the HMS, it is considered that some strategies cannot be included due to lack of compliance, or the application of the same strategy among one study and another may have a different degree of interpretation; publication bias was not controlled since the results of the control programs in endemic countries may be not available.

**Conclusion:** The main PTB control strategies in dairy cattle worldwide are HMS, TCS, and VS. The use of one or several combined strategies has been found to succeed in controlling the disease at the herd-level.

**Keywords:** Control strategy, Dairy cattle, Eradication, Johne's disease.

### Introduction

Paratuberculosis (PTB), also known as Johne's disease, is a severe slow-developing and incurable granulomatous enteritis caused by *Mycobacterium avium* subsp. *paratuberculosis* (MAP) (Clarke, 1997). This disease affects cattle and other domestic and wild ruminants (Sweeney *et al.*, 2012). A localized infection is the first stage of the disease, lately resulting in chronic granulomatous enteritis with diarrhea, weight loss, and, finally, death (Clarke, 1997).

Several tests are available for the *ante-mortem* detection of MAP-infected animals, including the detection of MAP antibodies, DNA, or live organisms by the culture. The diagnostic tests available are imperfect although useful if applied properly when a specific purpose has been identified (Nielsen and Toft, 2008).

This worldwide-extended disease affects more than 50% of herds in countries with a significant dairy industry (Manning and Collins, 2010). Economic losses are higher in PTB-infected herds, due to reduced milk yield, increased cow-heifer replacement costs, lower cull-cow revenue, and greater cow mortality (Hutchinson, 1996; Ott *et al.*, 1999; Lombard *et al.*, 2005; Gonda *et al.*, 2007; Richardson and More, 2009; Smith *et al.*, 2010). On the other hand, MAP has been associated with Crohn's disease (Feller *et al.*, 2007) and other human autoimmune diseases, such as Blau syndrome, type I diabetes, Hashimoto thyroiditis, and multiple sclerosis, reinforcing the zoonotic potential of this pathogen (Lee *et al.*, 2011; Sechi and Dow, 2015). Hence, MAP primary public health concerns are related to food and environmental contamination (Eltholth *et al.*, 2009). Therefore, due to its direct effects on

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animal health, economic losses, potential public health implications, and livestock trade, PTB is listed by the World Organization for Animal Health.

Geraghty *et al.* (2014) conducted a narrative review on PTB control programs in six endemic countries, reporting a significant heterogeneity among them. More recently, Whittington *et al.* (2019) conducted a narrative review on 48 countries (2012–2018) on the same topic. Authors reported that 20% of the herds of half of the countries of study were MAP-infected. In addition, PTB report is mandatory in most of the countries, and only 46% (22/48) had an established control program for the disease. Animal health and production losses were found to be the rationale for the control programs in these countries, and the most common objective was to reduce PTB prevalence.

PTB herd-level control is difficult due to its long incubation period, imperfect diagnostic tests, and persistent environmental survival (Kennedy and Benedictus, 2001). To reduce the risk of infection, control strategies should aim to eliminate infected animals (particularly those affected and infectious from the herd—e.g., test-and-cull strategy; TCS), to break down transmission routes of the disease, and to reduce the risk of infection, particularly to young animals (Johnson-Ifearulundu and Kaneene, 1998; Garry, 2011). One of the main interventions reported in dairy cattle is to avoid the contact of calves with feces of adult cattle (Doré *et al.*, 2012), interfering with the fecal-oral transmission. Other practices include feeding pasteurized milk or colostrum from MAP-seronegative cows and calf and heifer-hygienical raising strategies (Aly *et al.*, 2015). These last are known as hygiene and management strategies (HMS). On the other hand, vaccination strategies (VS) are reported to reduce the clinical incidence of PTB, delaying the onset of the disease and reducing fecal shedding of MAP, thus reducing the economic losses and transmission of the disease (Bastida and Juste, 2011). Nevertheless, VS are controversial due to its possible interference with tuberculosis control programs (Coad *et al.*, 2013; Serrano *et al.*, 2017).

Although some reports on PTB control strategies have been published, there is great variability in control strategies reported regarding their application within control programs in PTB endemic countries and the success in controlling the disease at the herd-level. Many of these control strategies have been implemented under different field conditions and they vary depending on the prevalence of diseases, the diagnostic strategies, the control objective, and the sanctions for non-participation. A systematic review (SystRev) about the control strategies that have been implemented for the control of PTB in dairy cattle would provide a great opportunity to understand the best opportunity to learn from past and collective experiences of PTB control and to design and implement improved control programs

in the future. Therefore, we aimed to systematically collect information on the control strategies of PTB in dairy cattle worldwide.

### Materials and Methods

SystRev was designed, performed, and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, suggested by Page *et al.* (2021). An *a priori* established and pre-tested SystRev protocol was carried out, including the study question, procedure for literature search, study inclusion/exclusion criteria and checklists for conducting relevance screening, basic characterization, methodological assessment, and data extraction on relevant primary research.

#### Search strategy

The identification of relevant articles considered a specific research question: What are the control and eradication strategies of PTB in dairy cattle worldwide? The search procedure was performed on October 2, 2019 and updated on August 3, 2021. The question was divided into components and the search terms used to find relevant studies in the platforms were [(control OR management OR regulation?) AND (eradication OR elimination OR clearance) AND (paratuberculosis OR johne\* disease? OR *mycobacterium avium paratuberculosis*) AND (dairy OR cow? OR livestock OR cattle OR bovi\* OR ruminant\* OR calf OR calve? OR heifer? OR bull? OR steer?)].

Three search databases (i.e., OVID®/MEDLINE, SciELO, Redalyc). The registers from the proceedings of the 3rd (1991) to the 12th (2014) International Colloquium on Paratuberculosis (ICP), were available from the platforms explored. The 13th and 14th ICP proceedings (2016 and 2018, respectively) were available at the International Association for Paratuberculosis web site (<http://www.paratuberculosis.net/>). This last material was hand-searched for existing published primary studies. Finally, references related to the SystRev subject were hand-searched in Behr and Collins (2010) and Behr *et al.* (2020) books to track primary publications.

#### Eligibility criteria

The inclusion criteria considered only articles published in English, Portuguese, and Spanish and in peer-reviewed journals. Findings were not limited by year or country of publication.

The first selection of citations was done according to the information contained only in the title. Two of the authors completed the selection and a *kappa* coefficient was estimated. The exclusion criteria were: i) irrelevant topics (e.g., Crohn's disease, economic impact, *Mycobacterium bovis*, diagnosis, and modeling); ii) species other-than bovines (e.g., goats, sheep, human); iii) not an original article (e.g., review, book). Duplicated articles were not considered. All citations selected by at least one of the two authors were considered eligible to continue in the process.

The eligible citations were screened by two of the authors using the abstract. A *kappa* coefficient was estimated. Exclusion criteria were the same as for the title screening. Conflicts were resolved through consensus between authors and if necessary, a third author was consulted.

The full text of selected articles was reviewed by two authors to identify and extract relevant information to answer the research question. Each full text was reviewed with particular attention to the materials and methods and results sections. A *kappa* coefficient was estimated. Articles were considered eligible using the same exclusion criteria described above. Conflicts were resolved through consensus between authors and if necessary, a third author was consulted.

Two of the authors hand-searched the reference lists of relevant articles identified by the full-text screening for additional published primary articles (“snowballing” procedure). In addition, the same strategy was applied to two literature reviews on the topic (Geraghty *et al.*, 2014; Whittington *et al.*, 2019).

The ICP proceedings and other abstracts identified during the primary search were revised to identify further citations in peer-reviewed journals. In this concern, abstracts found able to answer the research question were identified and an email was sent to the corresponding author to inquire if the abstract was further published in a peer-reviewed journal. The articles obtained from this previous step, as well as those detected at the Behr and Collins (2010) and Behr *et al.* (2020) books, were screened by two of the authors.

#### **Data extraction and descriptive statistics**

After all available articles were compiled, data extraction was performed by one of the authors, considering bibliographic information, control strategies—categorized in TCS, HMS, and VS, according to Bastida and Juste (2011), outcome strategies (e.g., prevalence, incidence, test-positivity, and fecal shedding rate), follow-up time of the program, and results to the interventions. A second author reviewed data-extraction products.

### **Results**

The combined results from the search platforms yielded 371 eligible citations (after deduplication), potentially related to the subject of this SystRev. The review of the reference lists in the Behr and Collins (2010) and Behr *et al.* (2020) books provided six eligible citations. The hand searching of the ICP proceedings (3rd to 14th) delivered seven eligible citations, of which none continued in the process, since they were not further published in peer-reviewed journals (according to the email responses by the corresponding authors). Therefore, the final number of citations was 377.

After reading the titles of the articles, 302 were considered irrelevant (agreed by the two authors). The final number of citations based on title screening was 75

(retained by at least one of the authors). After reading the abstracts of the articles, 51 were excluded and 25 original articles remained for the full-text review (by both authors). Ten were excluded because of the criteria already described by title and abstract screening. The full text of 16 articles were completely reviewed and kept for data extraction. The “snowballing” strategy was then applied through the reference lists of the 16 definitive articles and six more citations were found. In addition, the same strategy was applied to two literature reviews (Geraghty *et al.*, 2014; Whittington *et al.*, 2019) and four more citations were found. The final number of articles full filling the eligibility criteria and hence included in the qualitative synthesis was 26. Figure 1 describes the review protocol and the selection of relevant articles.

Twenty-six selected articles were published in 15 different journals, all in English, except for one in Portuguese. The relevant articles were published between 1982 and 2021. Most of the articles (50%; 13/26) were published between 2008 and 2013 and the United States was the most common country of publication (50%; 13/26), followed by The Netherlands (15%; 4/26), Australia (7%; 2/26), Spain (7%; 2/26), Germany (7%; 2/26), Hungary (7%; 2/26), United Kingdom (7%; 2/26), Brazil (4%; 1/26) and Denmark (4%; 1/26).

The control strategies were grouped into HMS, TCS, and VS. The HMS were the most common (77%; 20/26), followed by TCS (65%; 17/26), and VS (27%; 7/26). Combined control strategies such as TCS-HMS (46%; 12/26), TCS-VS (4%; 1/26), and HMS-VS (4%; 1/26) were also described, and the consideration of the three control strategies (TCS-HMS-VS) was reported by two articles.

The 77% (20/26) of the reported studies considered a range of 1–1,261 herds. A 26% (5/26) reported animal-level control strategies (ranging from 85 to 866 animals). Selected articles reported a follow-up time of 2.5 months to 20 years, mainly a 5-year follow-up (35%; 9/26). All selected articles found a reduction in their outcome strategies or expected results (e.g. prevalence, incidence, test-positivity, fecal shedding rate).

The HMS were grouped into practices used in control programs for PTB as reported by Whittington *et al.* (2019): hygienic rearing of neonates/juvenile livestock (if hygiene actions were indicated in the calving area, management of new-borns, calves and heifers), herd-level biosecurity, prevention of infection introduction (related to actions to identify infected and infectious animals and the purchase of external animals), and environmental and pasture management (related to actions to avoid contamination by MAP). Within HMS, the most common practices were to remove calves from their dams as soon as possible after birth (14/20) and to limit the exposure of calves and heifers to adult cattle manure (14/20). Detailed information extracted

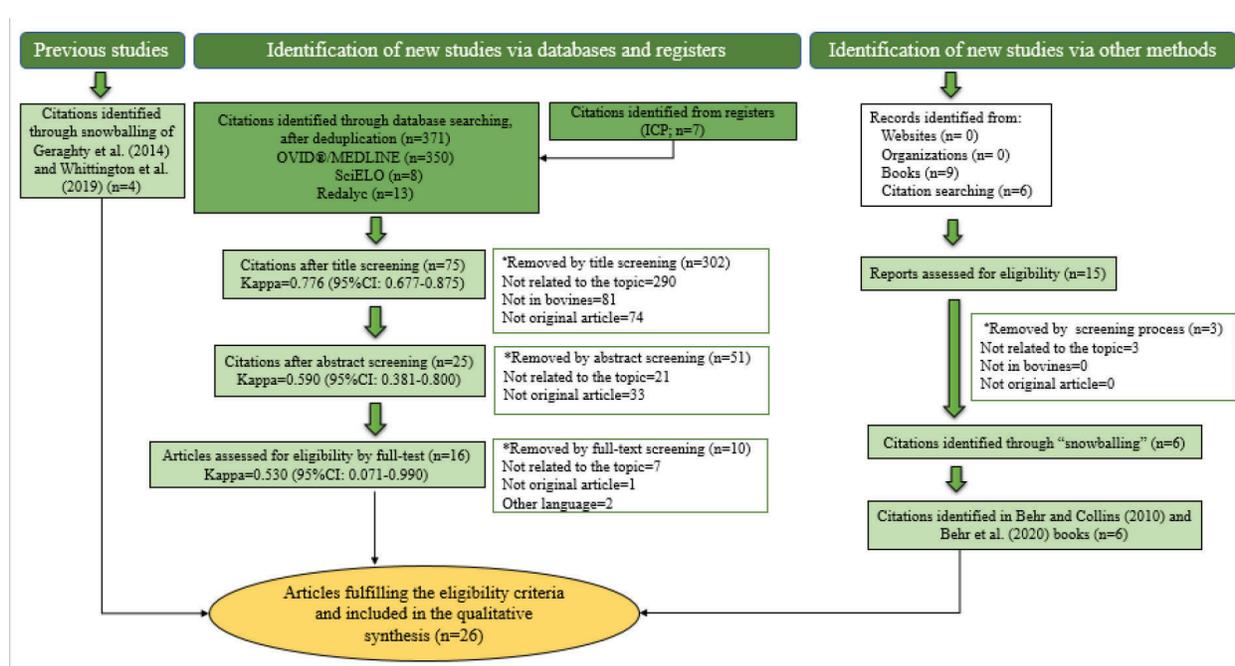


Fig. 1. Flow-chart of selection of relevant articles (PRISMA), describing the progress of the studies through the SystRev.

from the 26 relevant articles describing the PTB control strategies in dairy cattle is shown in Table 1. Table 2 describes the HMS reported in the selected articles and the corresponding management practice.

Within TCS, enzyme-linked immunosorbent assay (ELISA) was used in 13/17 selected publications on this specific strategy, fecal culture was reported in three articles. Other practices included culling positive animals (13/17) and culling clinical ones (6/17), and culling decisions included to cull offspring and fecal shedders. All tests were performed in animals > 24 months of age, except for one article, which considered animals > 3 years (Yamasaki *et al.*, 2010). No testing-frequency was found, but it was reported that most of the tests were carried out on a year-basis (5/17). Table 3 describes the TCS reported in the selected articles.

Articles on VS reported animals of all ages, but mostly >1-month-old. Three studies reporting this strategy used one commercial vaccine (SILIRUM Paratuberculosis®. CZ Veterinaria S.A., Pol. La Relva, Torneiros, Spain) and four experimental approaches, all used heat-inactivated bacterin of MAP. According to all reports, the VS is important for reducing the fecal excretion of MAP and the clinical presentation of PTB. Table 4 describes seven references reporting VS.

### Discussion

Studies about PTB control strategies in dairy cattle were reviewed using a systematic methodology for the first time. Our purpose was to compile all published available evidence about control strategies for the disease, considering different practices and strategies applied along the reviewed studies. Our findings

allowed us, not only to answer the specific research question, but to present other elements of the control programs, such as frequency strategies, follow-up times, and outcomes.

As expected, the HMS were the most reported strategies throughout the selected studies, showing a wide variety of corrective actions, which are supported in the different observational studies on MAP-transmission risk factors (Obasanjo *et al.*, 1997; Johnson-Ifearelundu and Kaneene, 1999; Wells and Wagner, 2000; Caldow *et al.*, 2001, Doré *et al.*, 2012; Puerto-Parada *et al.*, 2018). This may explain that most of the HMS applied in bovines are related to the protection against infection at susceptible ages (new-borns and calves under 12 months), such as the elimination/control of infection sources as feces, milk, and colostrum (Stabel, 2008; Pithua *et al.*, 2009). Fourteen management strategies in this regard were found, representing the greatest control actions against PTB in dairy cattle. The purchase of external animals without history of MAP diagnosis has also been identified as a risk factor for the disease entry in a herd, even under control programs (Pillars *et al.*, 2009; Correia- Gomes *et al.*, 2010; Künzler *et al.*, 2014; Pieper *et al.*, 2015, Puerto-Parada *et al.*, 2018); therefore, the management of closed herds, and the purchase of animals from farms with a known MAP-status is a recommended practice for dairy farmers.

Although the application of all HMS is not mandatory, the risk assessment and management plans (Garry, 2011) —considered as the best methodology for PTB control programs, was reported in some of the relevant studies, with the disadvantage of hindering the structuring of comparable strategies and units of

**Table 1.** Information on control strategies for paratuberculosis in dairy cattle, extracted from the selected studies ( $n=26$ ) of the SystRev.

Authors (year of publication)	Country of study	Unit of analysis (n)	Outcome strategy <sup>a</sup>	Follow-up time (in years)	Control strategies: features	Results
Wilesmith (1982)	Great Britain	Herd (231; 172 dairies)	Frequency	8 years	<b>VS:</b> calves > 1 month	Mean annual herd incidence of clinical disease reduced from 10.6% before vaccination to 0.1% 7 years later.
Wentink et al. (1994)	The Netherlands	Animal (380)	Frequency	6 years	<b>VS:</b> 30-days-old calves, bimonthly <b>HMS:</b> hygienic rearing of neonates/juvenile livestock.	Animals culled for clinical PTB decreased from 7.8% to 1.8%.
Körmendy (1994)	Hungary	Animal (866)	Frequency	5 years	<b>VS:</b> 30-days-old female calves	Fecal shedding was reduced by annual fecal microscopic tests.
Jubb and Galvin (2000)	Australia	Herd (36)	Frequency	<i>n/s</i>	<b>TCS:</b> ELISA, animals > 24 months of age, annually	ELISA reactor prevalence decreased from 2.7% to 2.2%.
Kalis et al. (2001)	The Netherlands	Herd (58)	Frequency	<i>n/s</i>	<b>VS:</b> 0 to 4-weeks-old calves <b>TCS:</b> ELISA and/or fecal culture, cull positive animals. <b>HMS:</b> hygienic rearing of neonates/juvenile livestock, environmental and pasture management.	Positive results on culture decreased from 10.9 and 5.7% to 3.5% and 0%, respectively in the two vaccinated herds.
Jubb and Galvin (2004)	Australia	Herd (542)	Frequency	10 years	<b>TCS:</b> animals > 24 months of age, annually, ELISA, cull clinical cases and offspring. <b>HMS:</b> hygienic rearing of neonates/juvenile livestock, environmental and pasture management.	Prevalence had a slow decline with a marked peak occurring at the fourth herd test. No homebred reactors born after the start of the program.
Ridge et al. (2005)	Australia	Herd (54)	Clinical presentation and frequency	<i>n/s</i>	<b>HMS:</b> hygienic rearing of neonate/juvenile livestock. <b>TCS:</b> animals > 24 months of age, annually, ELISA, cull clinical animals, cull offspring.	Seropositivity in herds reduced from 1.43% to 1.07%.
Benedictus et al. (2008)	United States	Herd (1)	Frequency	20 years	<b>HMS:</b> hygienic rearing of neonates/juvenile livestock. <b>TCS:</b> whole-herd fecal-samples taken twice a year.	Prevalence decreased from 60% to less than 20%

Continued

Authors (year of publication)	Country of study	Unit of analysis (n)	Outcome strategy <sup>a</sup>	Follow-up time (in years)	Control strategies: features	Results
Pillars <i>et al.</i> (2009)	United States	Herd (6)	Frequency	5 years	<b>TCS:</b> ELISA and/or fecal culture	Average prevalence of herds reduced from 12% (2003) to 8.5% (2007).
Ferrouillet <i>et al.</i> (2009)	United States	Herd (6)	Frequency and fecal shedding	5 years	<b>TCS:</b> ELISA and/or fecal culture annually, prior calving, cull clinical cases, and heavy fecal shedding cows. <b>HMS:</b> hygienic rearing of neonates/juvenile livestock, farm-level biosecurity to prevent the introduction of infection, environmental and pasture management.	ELISA-positive reduced from 8% to 3.1%; fecal-positivity reduced from 10.4% to 5.6%; and fecal shedding, from 3.1% to 1.5%.
Juste <i>et al.</i> (2009)	Spain	Herd (6)	Fecal shedding	4 years 1 year	<b>VS:</b> all animals of all ages on the farm. <b>TCS:</b> cull of positive ELISA or fecal PCR positive-result animals.	The total amount of MAP shed was reduced by 77% in the vaccinated and 94% in the control herds.
Collins <i>et al.</i> (2010)	United States	Herd (9)	Frequency	6 years	<b>HMS:</b> hygienic rearing of neonates/juvenile livestock, environmental and pasture management. <b>TCS:</b> adult, ELISA, cull repeated positive.	Reduction in ELISA-positive cows, from 11.6% to 5.6%. Apparent prevalence decline among first-lactation cows was greater and was evident by ELISA (10.4% vs. 3.0%) and by fecal culture (17.0% vs. 9.5%).
Yamasaki <i>et al.</i> (2010)	Brazil	Animal (298)	Frequency	3 years	<b>TCS:</b> animals > 3 years of age ELISA, cull clinical cases. <b>HMS:</b> hygienic rearing of neonates/juvenile livestock.	Seropositivity reduced from 44% (2006) to 40% (2009). The only one-clinical case was observed.
Click <i>et al.</i> (2011)	United States	Animal (85)	Frequency	60,5 months	<b>HMS:</b> hygienic rearing of neonates/juvenile livestock (research program using <i>Dietzia</i> ).	<i>Dietzia</i> treatment and HMS prevent the development of PTB. No heifer was test-positive.
Eisenberg <i>et al.</i> (2011)	The Netherlands	Barn (2)	Frequency	10 weeks	<b>HMS:</b> environmental and pasture management.	Experimental barn reduced positive MAP qPCR and viable MAP DNA after depopulation, high-pressure cleaning, and disinfection to zero.
Nielsen and Toft (2011)	Denmark	Herd (1,261)	Frequency	4,25 years	<b>TCS:</b> four annual milk-ELISA, repeated positive cows culled. <b>HMS:</b> Hygienic rearing of neonates/juvenile livestock.	The proportion of purchased animals, culling of repeated test-positive animals, and use of waste milk from specific cow groups influenced the decrease in prevalence.

Continued

Authors (year of publication)	Country of study	Unit of analysis (n)	Outcome strategy <sup>a</sup>	Follow-up time (in years)	Control strategies: features	Results
Pillars <i>et al.</i> (2011)	United States	Herd (7)	Frequency	5 years	<b>HMS:</b> hygiene rearing of neonates/juvenile livestock. <b>TCS:</b> animals > 24 months of age, ELISA, and/or fecal culture.	Seven cows exposed to the control program were infected, while 20% of cows not exposed were infected.
Espejo <i>et al.</i> (2012)	United States	Herd (8)	Frequency	5-10 years	<b>TCS:</b> animals > 24 months of age, annually, ELISA and/or fecal culture, cull clinical animals, cull MAP shedders. <b>HMS:</b> hygienic rearing of neonates/juvenile livestock, farm-level biosecurity to prevent the introduction of infection, environmental and pasture management.	Reduction of disease transmission and that reduction were associated with herd-level management practices implemented.
Alonso-Hearn <i>et al.</i> (2012)	Spain	Animal (88)	Clinical presentation and age at culling	n/s	<b>VS:</b> calves > 1 month of age, a cow at the time of joining the trial, and all new calves. <b>HMS:</b> hygienic rearing of neonates/juvenile livestock, farm-level biosecurity to prevent introduction of infection, environmental and pasture management. <b>TCS:</b> cull positive animals.	Therapeutic effect of the vaccine and a significant attenuation of pre-existing infection in cows naturally infected with PTB that were adults at the time of vaccination.
Pithua <i>et al.</i> (2013)	United States	Herd (3)	Frequency	5 years	<b>HMS:</b> hygienic rearing of neonates/juvenile livestock.	Cows born in the individual calving pen had a hazard ratio of 0.37 for testing MAP serum ELISA positive, compared with cows born in group calving pen.
Donat (2016)	Germany	Herd (76 dairies, 29 beef-cattle)	Frequency	7 years	<b>HMS:</b> hygienic rearing of neonates/juvenile livestock, farm-level biosecurity to prevent introduction of infection. <b>TCS:</b> fecal culture, animals > 24 months of age, annually, cull positive animals and clinical animals	Cumulative Incidence decreased significantly from 14.0% (2008) to 5.6% (2014)
Donat <i>et al.</i> (2016)	Germany	Herd 28	Frequency	5 years	<b>HMS:</b> hygienic rearing of neonates/juvenile livestock	Cumulative incidence of MAP shedders in the herds reduced from 8.1% (2008) to 3.6% (2012)

*Continued*

Authors (year of publication)	Country of study	Unit of analysis (n)	Outcome strategy <sup>a</sup>	Follow-up time (in years)	Control strategies: features	Results
Arango-Sabogal et al. (2017)	Canada	Herd (18)	Frequency	5 years	<b>HMS:</b> hygienic rearing of neonates/juvenile livestock, environmental and pasture management.	The individual prevalence by fecal culture decreased from 2% (2011) to 1.3% (2015). The within-herd prevalence decreased from 2.9% (2011) to 2% (2015)
Fox et al. (2018)	United Kingdom	Herd (15)	Frequency	3 years	<b>TCS:</b> ELISA, animals > 24 months of age, annually, cull positive animals, cull offsprings. <b>HMS:</b> hygienic rearing of neonates/juvenile livestock.	Prevalence reduced from 16% (2008) to 7.2% (2011).  The maximum difference was observed at the 2–3 years interval with a 33.9% mortality reduction in the calf vaccinated group, corresponding to the maximum non-specific effect on PTB incidence (24.5% to 9.5%).
Juste et al. (2021)	Spain	Herd (30)	Frequency	1-13 years	<b>VS:</b> two groups' calves (< 3 months) and animals vaccinated at any other age.	Vaccination afforded to calves a 26.5% yearly mortality protection, split between 11.1% PTB-specific and 15.4% non-specific effect.  Results support a non-specific effect on total mortality associated with PTB vaccination that appeared to persist for up to 6–7 years.
Klopfstein et al. (2021)	Switzerland	Herd 17 (10 dairies, 7 beef-cattle)	Frequency	3 years	<b>TCS:</b> fecal culture, animals > 12 months of age, two times per year, cull positive animals and clinical animals, cull offsprings. <b>HMS:</b> hygienic rearing of neonates/juvenile livestock, farm-level biosecurity to prevent introduction of infection, environmental and pasture management	The apparent within-herd prevalence remained constant despite limited implementation of control strategies, and no group of control strategies was found to be associated with changes in prevalence. Prevalence reduced from 5.8% (2011) to 4.6% (2015)

<sup>a</sup>According to the authors of each study;

PTB: Paratuberculosis; MAP: *Mycobacterium avium* subsp. *paratuberculosis*; VS: Vaccination strategy; HMS: Hygienical management strategy; n/s: Not specified; TCS: Test-and-cull strategy; ELISA: Enzyme-linked immunosorbent assay.

analysis (herd/animal-level) among studies. On the other hand, the different production systems (e.g. tie-stall, free-stall, grazing-based) represent a variety of production practices and models that make it difficult

to standardize risk factors among herds in different regions or countries. Although many of the HMS have greater application to tie- or free-stall dairy systems, some strategies —such as fertilization with synthetic

**Table 2.** Description of HMS for paratuberculosis control in dairy cattle, extracted from the selected studies ( $n=26$ ) of the SystRev.

Hygiene and management strategy	Description	References
Hygienic rearing of neonates/juvenile livestock	Clean, dry maternity area protected from manure from other adult cattle	Kalis <i>et al.</i> , 2001; Benedictus <i>et al.</i> , 2008; Ferrouillet <i>et al.</i> , 2009; Pillars <i>et al.</i> , 2011; Espejo <i>et al.</i> , 2012; Donat, 2016; Donat <i>et al.</i> , 2016; Arango-Sabogal <i>et al.</i> , 2017; Fox <i>et al.</i> , 2018; Klopstein <i>et al.</i> , 2021.
	Calving in a paddock	Ridge <i>et al.</i> , 2005.
	Calving in an exclusive parlor/pen	Kalis <i>et al.</i> , 2001; Donat, 2016; Donat <i>et al.</i> , 2016; Klopstein <i>et al.</i> , 2021.
	Individual calving pen	Pithua <i>et al.</i> , 2013; Klopstein <i>et al.</i> , 2021.
	Cleaning teats, skin at calving	Wentink <i>et al.</i> , 1994; Donat, 2016; Donat <i>et al.</i> , 2016; Arango-Sabogal <i>et al.</i> , 2017; Fox <i>et al.</i> , 2018.
	Remove from the dam as soon as possible after birth (Cow-calf separation)	Wentink <i>et al.</i> , 1994; Jubb and Galvin, 2004; Ridge <i>et al.</i> , 2005; Ferrouillet <i>et al.</i> , 2009; Yamasaki <i>et al.</i> , 2010; Click, 2011; Nielsen and Toft, 2011; Pillars <i>et al.</i> , 2011; Alonso-Hearn <i>et al.</i> , 2012; Espejo <i>et al.</i> , 2012; Donat, 2016; Donat <i>et al.</i> , 2016; Arango-Sabogal <i>et al.</i> , 2017; Klopstein <i>et al.</i> , 2021.
	Low-risk colostrum feeding	Kalis <i>et al.</i> , 2001; Jubb and Galvin, 2004; Ferrouillet <i>et al.</i> , 2009; Collins <i>et al.</i> , 2010; Alonso-Hearn <i>et al.</i> , 2012; Click, 2011; Espejo <i>et al.</i> , 2012; Donat, 2016; Donat <i>et al.</i> , 2016; Arango-Sabogal <i>et al.</i> , 2017; Klopstein <i>et al.</i> , 2021.
	No use of pooled colostrums	Ferrouillet <i>et al.</i> , 2009; Collins <i>et al.</i> , 2010; Pillars <i>et al.</i> , 2011; Espejo <i>et al.</i> , 2012; Klopstein <i>et al.</i> , 2021.
	Milk replacer feeding	Kalis <i>et al.</i> , 2001; Benedictus <i>et al.</i> , 2008; Ferrouillet <i>et al.</i> , 2009; Collins <i>et al.</i> , 2010; Click, 2011; Espejo <i>et al.</i> , 2012; Klopstein <i>et al.</i> , 2021.
	On-farm pasteurized milk until weaning	Pillars <i>et al.</i> , 2011; Espejo <i>et al.</i> , 2012.
	Feeding waste milk of low-risk cows	Nielsen and Toft, 2011.
	Minimal exposure of calves and heifers to manure of adult cattle	Wentink <i>et al.</i> , 1994; Kalis <i>et al.</i> , 2001; Jubb and Galvin, 2004; Ridge <i>et al.</i> , 2005; Benedictus <i>et al.</i> , 2008; Ferrouillet <i>et al.</i> , 2009; Collins <i>et al.</i> , 2010; Click, 2011; Espejo <i>et al.</i> , 2012; Donat, 2016; Donat <i>et al.</i> , 2016; Arango-Sabogal <i>et al.</i> , 2017; Fox <i>et al.</i> , 2018; Klopstein <i>et al.</i> , 2021.
	Avoid exposure to fecally-contaminated food	Ridge <i>et al.</i> , 2005; Ferrouillet <i>et al.</i> , 2009; Alonso-Hearn <i>et al.</i> , 2012; Espejo <i>et al.</i> , 2012; Arango-Sabogal <i>et al.</i> , 2017; Klopstein <i>et al.</i> , 2021.
	Avoid calf-to-calf exposure	Benedictus <i>et al.</i> , 2008.
Farm-level biosecurity and prevent introduction of infection	Identification and separate of adult cattle through sampling and clinical observation	Ferrouillet <i>et al.</i> , 2009; Collins <i>et al.</i> , 2010; Nielsen and Toft, 2011; Espejo <i>et al.</i> , 2012.
	Acquisition of animal from low-risk herds	Benedictus <i>et al.</i> , 2008; Ferrouillet <i>et al.</i> , 2009; Nielsen and Toft, 2011; Alonso-Hearn <i>et al.</i> , 2012; Klopstein <i>et al.</i> , 2021.
	Avoid exposure to fecally contaminated water sources	Ridge <i>et al.</i> , 2005; Alonso-Hearn <i>et al.</i> , 2012; Espejo <i>et al.</i> , 2012; Arango-Sabogal <i>et al.</i> , 2017; Klopstein <i>et al.</i> , 2021.
Environmental and pasture management	Depopulation and cleaning dairy barns	Eisenberg <i>et al.</i> , 2011.
	Fertilized exclusively with synthetic fertilizer	Kalis <i>et al.</i> , 2001.
	Use of separate equipment for manure cleaning and feed handling	Ferrouillet <i>et al.</i> , 2009; Espejo <i>et al.</i> , 2012; Klopstein <i>et al.</i> , 2021.

**Table 3.** Description of TCS for paratuberculosis control in dairy cattle, extracted from the selected studies ( $n = 26$ ) of the SystRev.

Test	References
ELISA	Kalis <i>et al.</i> , 2001; Jubb and Galvin, 2004; Ridge <i>et al.</i> , 2005; Ferrouillet <i>et al.</i> , 2009; Juste <i>et al.</i> , 2009; Pillars <i>et al.</i> , 2009; Collins <i>et al.</i> , 2010; Yamasaki <i>et al.</i> , 2010; Nielsen and Toft, 2011; Pillars <i>et al.</i> , 2011; Alonso-Hearn <i>et al.</i> , 2012; Espejo <i>et al.</i> , 2012; Fox <i>et al.</i> , 2018
Fecal culture	Benedictus <i>et al.</i> , 2008; Donat, 2016; Klopstein <i>et al.</i> , 2021
<b>Culling decision</b>	
Positive animals	Kalis <i>et al.</i> , 2001; Jubb and Galvin, 2004; Ridge <i>et al.</i> , 2005; Ferrouillet <i>et al.</i> , 2009; Juste <i>et al.</i> , 2009; Pillars <i>et al.</i> , 2009; Collins <i>et al.</i> , 2010; Yamasaki <i>et al.</i> , 2010; Nielsen and Toft, 2011; Pillars <i>et al.</i> , 2011; Alonso-Hearn <i>et al.</i> , 2012; Espejo <i>et al.</i> , 2012; Fox <i>et al.</i> , 2018; Donat, 2016; Klopstein <i>et al.</i> , 2021
Clinical animals	Kalis <i>et al.</i> , 2001; Jubb and Galvin, 2004; Ridge <i>et al.</i> , 2005; Ferrouillet <i>et al.</i> , 2009; Yamasaki <i>et al.</i> , 2010; Espejo <i>et al.</i> , 2012; Donat, 2016; Klopstein <i>et al.</i> , 2021
<b>Test-eligible animals</b>	
>12 months-old	Klopstein <i>et al.</i> , 2021
>24 months-old	Kalis <i>et al.</i> , 2001; Jubb and Galvin, 2004; Ridge <i>et al.</i> , 2005; Ferrouillet <i>et al.</i> , 2009; Juste <i>et al.</i> , 2009; Pillars <i>et al.</i> , 2009; Collins <i>et al.</i> , 2010; Nielsen and Toft, 2011; Pillars <i>et al.</i> , 2011; Alonso-Hearn <i>et al.</i> , 2012; Espejo <i>et al.</i> , 2012; Fox <i>et al.</i> , 2018; Donat, 2016
>36 months-old	Yamasaki <i>et al.</i> , 2010

**Table 4.** Description of VS for paratuberculosis control in dairy cattle, extracted from the selected studies ( $n = 26$ ) of the SystRev.

References	Age	Type of vaccine
Wilesmith, 1982	1 month	Experimental (Central veterinary Laboratory, Weybridge)
Wentink <i>et al.</i> , 1994	1 month	Experimental
Körmendy, 1994	1 month	Experimental
Kalis <i>et al.</i> , 2001	0-4 months	Experimental
Juste <i>et al.</i> , 2009	All ages	Commercial (SILIRUM®)
Alonso-Hearn <i>et al.</i> , 2012	1 month	Commercial (SILIRUM®)
Juste <i>et al.</i> , 2020	3 months Any age	Commercial (SILIRUM®)

fertilizer-only, calving in a paddock, and the use of separate equipment for manure cleaning and feed handling, are of interest in dairy production systems such as grazing-based one.

The commitment of owners and herd managers during the long implementation time that demands PTB control, represents an important limitation. The participation of the producers and the perception of the importance of PTB in dairy production must be considered, since the first results can only be observed 1 to 2 years after the implementation of control strategies. Roche *et al.* (2019) carried out a study on the reasons why many Canadian producers did not want to continue in the PTB control programs. These authors found that producers tended to prioritize control of the disease on their farms based on previous experiences with the disease, in addition to limited visualization of benefits or the existence of official sanctions or regulations.

The TCS of high-risk animals (*e.g.* affected, infectious animals) was also found as a control strategy for PTB. Culling positive animals that may develop clinical

disease in the future —acting as a source of infection for the herd, is considered as a critical-point for the success of control programs. It is important to mention that no homogeneity was found among the studies for the definition of a test-positive case with respect to each diagnostic test used. ELISA is reported as the most widely used one (mainly because of its cost, ease, and time to perform), with a main disadvantage in terms of low sensitivity ( $Se$ ) in subclinical animals (7%–15%) (Gilardoni *et al.*, 2012). This fact can be controlled when serial screenings are performed, and decisions are made regarding the results of the diagnostic tests. A more sensitive test must be considered, aiming to detect most of the infected dams before drying-off. This practice could allow the infected dams to be managed separately and their colostrum and milk to be classed as high risk, reducing the chances of their calves (and others born in the calving pen) from becoming infected. We hypothesized that, despite the low  $Se$  of ELISA for the diagnosis of MAP, when the diagnostic purpose is considered (detection of infected, infectious, affected

animals; Nielsen and Toft, 2008), and combined with HMS in a long-term control program, the success of the control program is expected to be greater.

The few reports regarding the use of vaccination were an expected result, since some authors have reported variable fallouts around the different studies (Patton, 2011). Nevertheless, MAP-vaccination is an important strategy in reducing contamination risks by this pathogen and reducing or delaying economic losses and clinical effects, without fully preventing infection (Bastida and Juste, 2011).

Bovine tuberculosis diagnosis-interference when using immunological tests is one of the main reasons for not vaccinating cattle. Some studies at the control program level have only reported its use in seven countries (Whittington *et al.*, 2019). It is important to note that the use of vaccination has been reported as a successful strategy in the control of PTB in small ruminants (Reddacliff *et al.*, 2006). Our findings support that VS is an interesting control strategy, specifically, to control MAP, since it shows a great advantage in preventing pathological and productive effects in dairy farms.

Combining control strategies have shown better results to specific control objectives, such as decreasing prevalence in herds (Whittington *et al.*, 2019). Specifically, TCS and HMS have been assessed in theoretical and mathematical models that simulate the transmission and control conditions of MAP in dairy farms (Marcé *et al.*, 2010). Recently, Camanes *et al.* (2018) reported the results of a study on coupling population and infection dynamics. Authors suggested that herd-level relevant control strategies mainly depend on initial prevalence. In addition, a reduced calf exposure was confirmed to be the most effective strategy, followed by test frequency and the detected-and-culled infected-animals proportion. Similarly, Konboon *et al.* (2018), suggested that a combination of test-and-cull with a frequent manure removal was the most effective strategy in reducing incidence and prevalence and the risk of MAP occurrence. Remarkably, other control strategies reported by the literature (i.e. limiting calf-adult cow contacts, raising calves in a disease-free herd or colostrum management) were less effective.

The prolonged time of application of control strategies is a fact for diseases with chronic behavior, as has been reported in other ones in cattle such as bovine tuberculosis (Palmer and Waters, 2011). Although the application of the control strategies is reported for an extensive period, it is important to mention that the complete eradication (or at least to present a low prevalence) of PTB is a scarcely reported experience, mainly followed in countries with high economic infrastructure, and, as Norway and Sweden (Whittington *et al.*, 2019), where animal health efforts are focused on disease surveillance. Disease follow-up times should be surveyed with the appropriate use of diagnostics tests that allow the success of control strategies to be reported.

Measuring the effect of control strategies based on some frequency strategies (e.g., prevalence, frequency, and positivity) was not accomplished due to lack of comparability among selected studies.

The strengths of the present SystRev are a well-defined protocol, based on a recognized one (PRISMA statement), a clearly stated and delimited research question; we performed a comprehensive search from several databases and sources to identify studies, including general-purpose databases, search engines, journals, conference proceedings, book chapters, and books from 1910 (CAB Abstracts) to the date; and we assessed the eligibility of the studies by using pre-established and explicit exclusion criteria all along the process. No geographic or temporal constraints were considered, so no biases-related results are thought to be yielded. Two of the authors independently followed selection principles, and results from each screening step were always accomplished by consensus. Agreement strategies (*kappa* coefficient) were reported all along the process to assure reliability of the results. And finally, data extracted from the original studies was clearly delineated. Since relevant studies varied in quality and in methodology, one of the authors constructed a matrix of findings, which were furtherly revised by a second author to assure consistency of the information extracted.

As limitations of the present SystRev, within the HMS it is considered that some strategies cannot be included due to lack of compliance, or the application of the same strategy among one study and another may have a different degree of compliance and interpretation. Although the strategies found are classified into three categories, it is not mandatory to follow this classification in future publications about PTB control, but we consider that the three grouped strategies found herein respond to MAP's control objectives. Publication bias was not controlled since the results of the control programs in endemic countries may be consigned in state government authorities and not as review material by a specialized public. Language bias was also considered, however, comprehensive literature searches followed by a careful assessment of study quality are required to assess the contribution of all relevant trials, independent of language of publication (Jüni *et al.*, 2002). In addition, the databases selected for the primary search of citations, responded to the ease of access from the role of research authors, also being considered by the same as the most accurate for the search of content of health and animal sciences, according to previous experience. Finally, the databases used (MEDLINE, Embase) correspond to databases reported optimal as a minimum requirement to guarantee adequate and efficient coverage in SystRev on health-related topics (Bramer *et al.*, 2017).

In conclusion, the main PTB control strategies reported in dairy cattle are HMS, TCS, and VS. Within HMS, the preventive practices of removing the calves from

its dam as soon as possible after birth and the minimal exposure of calves and heifers to adult cattle manure are the most used within the selected studies. HMS is used based on ELISA tests in animals > 2 years of age, culling different risk populations such as clinical animals, positive animals, off springs, and fecal shedders. The VS takes its importance to reduce fecal excretion of MAP and clinical presentation of PTB. The use of one or several combined strategies, considering the production and management practices, has shown to be successful in controlling the PTB in dairy cattle.

#### **Conflict of interest**

The authors declare that there is no conflict of interest.

#### **Author contributions**

All authors contributed to the study conception and design. BT had the idea of the article. The literature searches and data analysis, as well as the critical revision of the manuscript was performed by all the authors. The first draft of the manuscript was written by BT and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

#### **Availability of data, code, and other materials**

The review protocol, the template for data collection forms and data extracted from included studies are available upon request to the corresponding author.

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