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A systematic review to assess the effectiveness of pre-harvest meat safety interventions to control foodborne pathogens in beef

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ABSTRACT

Safe beef is a priority for consumers, policy makers, official veterinarians, and producers. This systematic review aims to update the recent knowledge on pre-harvest interventions to control main foodborne pathogens in beef and to assess their effectiveness. Only controlled trials in beef or dairy cattle were included. A total of 1514 studies were retrieved from PubMed® and Web of Science™ for 13 selected pathogens in particular *Salmonella* and Shiga toxin-producing *Escherichia coli* (STEC). After the screening, 28 papers remained for *Campylobacter* (n = 1), *Clostridium botulinum* (n = 1), *Clostridium perfringens* (n = 1), Extended spectrum-lactamase AmpC gene-carrying bacteria (ESBL/AmpC) (n = 1), *Salmonella* (n = 11), and STEC (n = 13). Results were synthesised narratively using tables as support. Research on pre-harvest interventions to control foodborne zoonoses in bovines was mostly focused on *Salmonella* spp. and STEC. The studies retained on *Salmonella* and STEC showed that vaccination, and cleaning, disinfection, management, and biosecurity were the most tested and effective interventions, denoting their potential to control or reduce detection and shedding of these pathogens. The correct implementation of such measures is crucial for their efficacy. While vaccination can be implemented to prevent severe outcomes of disease and reduce shedding; cleaning, disinfection, and biosecurity can prevent the introduction and/or the spread of pathogens to/within farms. The use of feed additives and treatments had mixed results but seemed to be effective for *Salmonella*. The criteria for paper selection excluded observational studies which document effective practices like depopulation and repopulation with healthy animals. Overall, high herd health status coupled with good management and biosecurity were effective to control or prevent the important foodborne pathogens in cattle at pre-harvest level.

1. Introduction

Cattle, as one of the most important domestic livestock animals and as an important source of red meat, are associated with a proportion of foodborne zoonotic diseases in humans (McDaniel et al., 2014). Indeed, in 2013, the European Food Safety Authority (EFSA) issued a scientific opinion on the public health hazards to be covered by the inspection of meat from bovine animals. This document contained a list of 13 biological hazards (Table 1) that can be transmitted to humans through the handling, preparation and/or consumption of beef and products thereof (EFSA, 2013). In the risk ranking process, EFSA (2013) identified *Salmonella* spp. and pathogenic Shiga toxin-producing *Escherichia coli* (STEC, also called Verocytotoxin-producing *Escherichia coli* (VTEC)) as "current high-priority biological hazards for meat inspection of bovine animals".

Due to their relevance to public health, and because these hazards are not detected by traditional meat inspection, control options using a farm-to-fork approach are needed to minimise the risk and spread of these 13 pathogens by consumption of beef. Pre-harvest interventions take place on-farm and/or during transport of animals to slaughter and aim to minimise the introduction, persistence, and transmission of foodborne pathogens into beef and dairy cattle herds. Though beef cattle are reared with the purpose of producing meat, dairy herds are also an important source of beef entering the food chain.

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In cattle production, key concepts for interventions at herd level are the control of the purchase of animals, the use of vaccination, and cleaning and disinfection of specific farm areas to minimise the prevalence of disease. In-feed interventions are also described. Many of these measures are described in the literature but their effectiveness to control the different foodborne pathogens transmitted through the consumption of beef has not been addressed. This systematic review of literature aims to update the knowledge on pre-harvest interventions to control 13 public health hazards enlisted in EFSA's report (EFSA, 2013), and to assess their effectiveness.

2. Materials and methods

The present work focused on the pre-harvest interventions to control foodborne zoonoses caused by the consumption of meat from bovine animals (both beef and dairy cattle were included in this study). The methods followed in this review are similar to those described by Pessoa et al. (2021), and Rodrigues da Costa et al. (2021) who reviewed pre-harvest interventions to control foodborne zoonoses in poultry and pork, respectively. The methods employed were based on the EFSA guidelines issued for "those carrying out systematic reviews" for food and feed safety assessments (EFSA, 2010), and on the methodology proposed in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (Moher, 2009; Page et al., 2021). PRIMA's checklist for systematic reviews and for PRISMA abstracts were completed and are available as supplementary material (S1).

2.1. Search structure and strings used

Literature searches were carried out on PubMed® and Web of Science™ on the 23rd of March 2021. Only peer-reviewed studies written in English and published until December 31st, 2020 were included in this analysis. The foodborne pathogens selected were those short listed by EFSA (2013): *Bacillus anthracis*; *B. cereus*; *Campylobacter* spp.; *Clostridium botulinum*; *C. perfringens*; *Listeria monocytogenes*; *Pathogenic* VTEC (now called STEC); ESBL/AmpC gene-carrying bacteria; *Salmonella* spp.; *Staphylococcus aureus*; *Sarcocystis hominis*; *Taenia saginata*; and *Toxoplasma gondii*. Searches were restricted to title and abstract. No time restrictions were imposed. The structure of the search strings is shown in Fig. 1.

Each search had pathogen-specific keywords, as shown in Table 1. The detailed search strings used for each database can be assessed in the supplementary material (S2).

2.2. Screening process

All records were imported into EndNote® and duplicates were removed. One co-author screened abstracts using a defined set of inclusion and exclusion criteria (Table 2).

In a second phase, full texts of all remaining references were retrieved and screened by two co-authors independently, using the same eligibility criteria (Table 2). For any record to be removed, both co-authors had to agree on its exclusion. When an agreement was not attained, a third co-author reviewed the full text and made the final decision – three studies had to be reviewed by a third co-author. The flow of information through the systematic review process is shown in Table 1.

The risk of bias was not formally assessed in studies included in this review. Despite that, the quality of the studies selected and retained was checked through the following steps: 1) this systematic review selected exclusively peer-review publications, 2) the screening steps were designed to reduce the bias of selection and to ensure assessors were in agreement during the full-text screening phase. To better illustrate the qualitative results obtained, a narrative description supported by tables was the preferred method of synthesis.

2.3. Data extraction

The data within the 28 records included in this work was extracted to a spreadsheet (stored in Microsoft Office Excel®). Studies (i.e., original research, peer-reviewed, in which data were collected, analysed, and reported) were grouped by type of pre-harvest intervention tested. For each study, the following information was recorded: year of publication, country of study, population, study setting, type of experiment, intervention type, sample type, outcome measured, and results reported with a brief description. Some studies assessed the efficacy of multiple interventions. In *Salmonella* and STEC studies, the comparison of each intervention (or treatment) with the control was recorded as a trial and,

Table 1
Keyword search and flow of information through the systematic review for 13 foodborne pathogens (EFSA, 2013) transmitted through the consumption of beef.

Pathogen	Keyword searched	Records identified	Records after duplicate removal	Records retained after abstract screening	Records retained after full text screening
Bacillus anthracis	*Bacillus anthracis* OR anthrax	48	42	3	0
Bacillus cereus	*Bacillus cereus*	30	30	0	0
***Campylobacter* spp.**	*Campylobacter** OR "*Campylobacter jejuni*" OR "*Campylobacter coli*"	244	211	9	1[a]
Clostridium botulinum	*Clostridium botulinum* OR botulism	31	27	5	1
Clostridium perfringens	*Clostridium perfringens* OR *c. perfringens* OR clostridial diarrh*	40	38	3	1
ESBL/AmpC [b] gene-carrying bacteria	Extended spectrum beta lactamase OR ESBL* OR AmpC	107	90	2	1
Listeria monocytogenes	*Listeria monocytogenes* OR listeriosis	94	84	3	0
Methicillin Resistant *Staphylococcus aureus* (MRSA)	Methicillin resistant *staphylococcus aureus* OR MRSA OR resistant *S. aureus*	108	100	0	0
***Salmonella* spp.**	Salmone*	541	456	43	11 [a]
Sarcocytis hominis	*Sarcocystis*	9	8	0	0
Shiga toxin-producing *Escherichia coli* (STEC) also called Verocytotoxigenic *Escherichia coli* (VTEC)	VTEC OR STEC OR *E. coli* O157 OR verotoxigenic *E. coli* OR verocytotoxigenic *E. coli* OR shiga toxin-producing *E. coli*	363	323	32	13 [a]
Taenia saginata	*Taenia saginata* OR beef tapeworm OR taeniasis OR cysticercosis	41	37	4	0
Toxoplasma gondii	*Toxoplasma gondii* OR toxoplasmosis	77	68	0	0
TOTAL	-	1733	1514	104	28

[a] In total, four records were retained after title and abstract screening but not screened in the full text step because we were unable to retrieve them. These records belonged to the following pathogens: *Campylobacter* spp. (n = 1), *Salmonella* spp. (n = 1), and Shiga toxin-producing *Escherichia coli* (STEC; n = 4).
[b] Extended spectrum-lactamase (ESBL) bacteria carrying th AmpC genes.

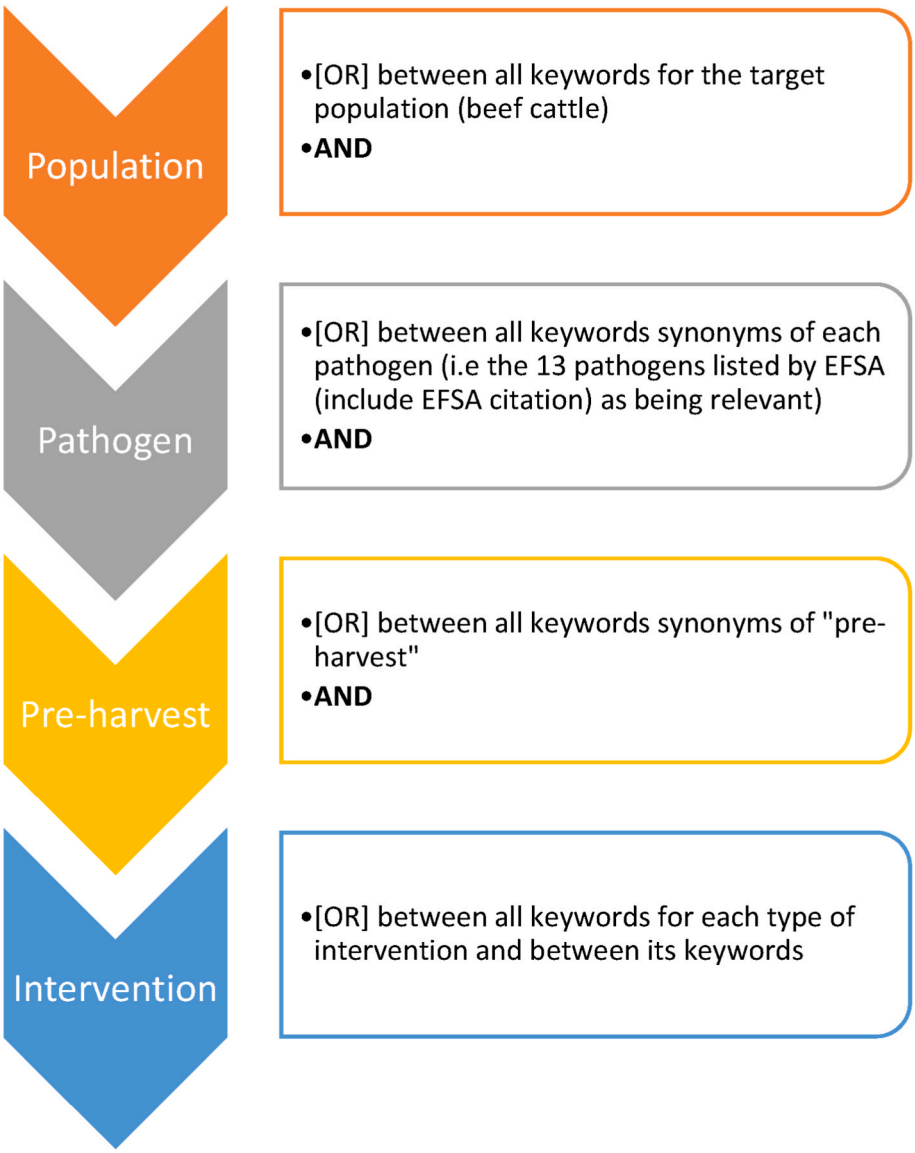

Fig. 1. Structure of the text strings used for the searches conducted in PubMed® and the Web of Science™ databases on March 23rd, 2021, reproduced and adapted from Pessoa et al. (2021) and Rodrigues da Costa et al. (2021) which employed similar methods.

if possible, detailed information was collected for each trial. For these two pathogens, the results of the interventions tested were summarised according to whether there was a reduction of *Salmonella* or STEC shedding or a reduction of *Salmonella* or STEC counts. Whenever the outcome of an intervention was measured through several time-points, data collected at the end of the study (i.e., closer to the slaughter date) were preferred. In studies looking at the effect of transport on the detection or shedding of *Salmonella* or STEC, an outcome was considered positive if the detection or shedding of *Salmonella* or STEC did not increase (i.e., no differences found between control – before transport – and treatment – after transport) or if it decreased. This was decided as transport and the stress associated with it may increase shedding of zoonotic *Enterobacteriaceae* in general (Dewell et al., 2008a; 2008b) and if this could not be shown, a positive effect of the intervention can be assumed.

3. Results and discussion

A total of 1514 studies were retrieved from PubMed® and Web of Science™ for the 13 selected pathogens. After the screening, 28 papers for six pathogens remained. These were: *Campylobacter* spp. (n = 1), *Clostridium botulinum* (n = 1), *Clostridium perfringens* (n = 1), Extended spectrum–lactamase AmpC gene-carrying bacteria (ESBL/AmpC)) (n = 1), *Salmonella* (n = 11), and STEC (n = 13). No studies were retrieved for *Bacillus anthracis*, *Bacillus cereus*, *Listeria monocytogenes*, MRSA, *Sarcocystis hominis*, *Taenia saginata*, and *Toxoplasma gondii*. Out of the studies retained in this systematic review, the first study was published in 2001, while the most recent study retained was published in 2020. No obvious temporal pattern was identified regarding the publication of these studies. A figure showing the number of publications per year from 2001 to 2020 is available as supplementary material (S3), together with a list of all papers retained (n = 28) in the review by pathogen. A list of all studies excluded in the full text screening and reasons for their exclusion, are provided as supplementary material (S4).

3.1. *Salmonella spp.*

There were 11 papers retained for *Salmonella*, reporting a total of 16 trials. All trials tested single interventions. All studies were performed in the USA, with the exception of Mohammed (2016) which was performed in Switzerland. Table 3 summarises the characteristics of these trials and the results obtained.

Table 2
Eligibility (inclusion and exclusion) criteria used for the screening of title/abstracts and full texts.

PICO[a]	Inclusion	Exclusion
Population	Animal species being evaluated: must include (but not limited to) cattle	Does not include actual or theoretical <pathogen> infection/contamination in cattle
	Unit of study [animal, batch, herd] and [surfaces, food, water, environment, drinkers, feeder, other animals]	Others
Intervention	Interventions to control/ reduce/eradicate <pathogen> in cattle	Studies/trials not mentioning control/reduce/eradicate interventions for <pathogen> in cattle
	Interventions on-farm or during transport (pre-harvest)	Interventions on lairage, at slaughter and post-harvest
	Field/experimental studies	Lab/bench studies
Comparison	Control group present [group subjected to no intervention]	Control group absent
Outcomes	Provides some measure of the efficacy of the intervention (i.e., lower detection or lower shedding of <pathogen>)	Efficacy of the intervention not measured; efficacy of intervention measured through immune function outcomes
Others	Language: English	Other languages
	Peer-reviews	Grey literature

[a] PICO (participants, interventions, comparisons, and outcome(s)) constitutes the framework in which research questions are formulated, as proposed in the PRISMA statement (Moher, 2009; Page et al., 2021).

Table 3
Interventions tested and number of positive results reported in the trials described by the 11 studies investigating pre-harvest interventions to control *Salmonella* spp. in cattle, and by the 13 studies investigating pre-harvest interventions to control Shiga toxin-producing *E. coli* (STEC) in cattle. Effectiveness is given by the proportion of trials with positive results out of all trials for each intervention.

Intervention type	*Salmonella* spp. (N = 16)		STEC (N = 34)	
	N (% out of all Salmonella trials)	Effectiveness N (%)	*N (% out of all STEC trials)*	Effectiveness N (%)
Vaccination	5 (31.3%)	2 (40%)	10 (29.4%)	8 (80%)
In-feed treatments, additives or supplementation	4 (25.0%)	2 (50%)	4 (11.8%)	0 (0%)
Cleaning, disinfection, management, and biosecurity	3 (18.8%)	2 (66%)	10 (29.4%)	5 (50%)
Antimicrobial treatment	2 (12.5%)	0 (0%)	NA	NA
Other	2 (12.5%)	2 (100%)	NA	NA
Mixed	NA	NA	3 (0.9%)	1 (33.3%)
• Mixed with transport	NA	NA	7 (20.6%)	2 (28.6%)

Note: trials were considered to have positive results when the intervention tested resulted in the decrease of detection or shedding of *Salmonella* spp or STEC. In the case of vaccination, results showing improved immunity were not considered positive unless accompanied with a reduction of detection or shedding of *Salmonella* or STEC. *In studies looking at the effect of transport on detection or shedding of *Salmonella* or STEC, an outcome was considered positive if the detection or shedding of these pathogens did not increase (i.e., no differences found between control – before transport – and treatment – after transport) or if eventually it decreased.

The vast majority of the studies retained focused on dairy calves (n = 5), followed by beef cattle (n = 3), while two studies took place in dairy farms and one study focused on dairy cattle and cattle breeders. Most of these studies were performed in a commercial setting (n = 7), with three studies being performed in a research facility. One study reported trials done in both settings.

Overall, eight of the 16 included trials (50%) reported positive results (Edrington et al., 2009, 2020; Mohammed, 2016; Patton et al., 2009; Vipham et al., 2015), meaning that the interventions tested successfully reduced *Salmonella* spp. detection or shedding.

3.1.1. Vaccination

Vaccination and in-feed treatments, additives or supplements (including probiotics) were the most tested interventions. Regarding the vaccination trials (n = 5), all but one tested active vaccination schemes in dairy calves or steers (beef cattle), and only one (Foster et al., 2019) tested passive immunity (i.e., vaccination of cows and administration of colostrum from these cows to calves) as an intervention to protect dairy calves against a *Salmonella* challenge. Three vaccination trials used *Salmonella* spp. challenges to test the efficacy of the proposed vaccine and vaccination scheme, and two of these trials reported a reduction in the detection or shedding of *Salmonella* spp. The exception was described by Foster et al. (2019), which tested the effect of passive vaccination. The two trials performed by Heider et al. (2008) and Habing et al. (2011) did not challenge animals. Heider et al. (2008) aimed to evaluate the effectiveness of a commercially available subunit vaccine against *Salmonella* enterica in reducing subclinical shedding of the bacteria in dairy cattle. The authors reported no evidence that the vaccine used reduced shedding of *S. enterica* in sub-clinically infected dairy cows in the herds in study. Habing et al. (2011) looked at the efficacy of a modified-live *Salmonella* Dublin vaccine in calves administered orally, and concluded it was not effective in reducing the incidence of disease. However, the authors refer that the study had limited power due to the low incidence of clinical salmonellosis.

3.1.2. In-feed treatments, additives or supplementation

The trials testing in-feed treatments, additives or supplementation were reported in the studies by Edrington et al. (2012); Edrington et al. (2018), and Vipham et al. (2015). Two trials from two studies by the same author (Edrington et al., 2012, 2018) focused on the effect of pasteurising waste milk before feeding it to dairy calves on the faecal shedding of *Salmonella.* The first study aimed to examine the effect of pasteurisation of waste milk on the bacterial diversity of the lower guts of dairy calves, and the authors reported a reduction in *Salmonella* detection but linked with age and not associated with treatment, with exception for the first sampling in one week old calves. The authors speculated that the differences found between treatments could be also due to the commercial farms in study, and suggest that there may be recontamination of milk following pasteurisation once the *Salmonella* populations in faeces were similar between treatments. In the subsequent study, the objective was to determine if the pasteurisation of waste milk influenced faecal concentrations and prevalence of *Salmonella*, and the serotype of the cultured isolates. The results were aligned with the first study and the authors noted that based on the data "milk borne *Salmonella* is not an important vector of transmission in dairy neonates, nor does pasteurisation of waste milk influence faecal shedding of this pathogen". The two trials (two reps) by Vipham et al. (2015) looked at the efficacy of using a direct-fed microbial (DFM; *Lactobacillus animalis* - NP51, and *Propionibacterium freudenreichii* - NP24 - at 10^9 cfu/head/day) in feedlot cattle diets to control *Salmonella* in peripheral lymph nodes. Cattle were assigned randomly to either control or DFM treatment groups. At abattoirs, subiliac lymph nodes (SLNs) were collected and cultured to estimate the concentration and presence of *Salmonella*. In the first trial, the effects of DFM supplementation varied across slaughter days, whereas in the second trial, *Salmonella* presence was reduced by 82% in SLNs of cattle fed DFMs. A significant decrease in the concentration of *Salmonella* in SLNs on both a cfu/g and cfu/node basis was observed in cattle given NP51 and NP24 in the first trial. However, in the second trial, there were insufficient quantifiable SLNs to

enable meaningful comparisons. Based on the results, Vipham et al. (2015) concluded that NP51 and NP24 supplementation could potentially help in decreasing the occurrence and concentration of *Salmonella* in SLNs.

3.1.3. Cleaning, disinfection, management, and biosecurity

Three trials looked at the efficacy of cleaning, disinfection, management and biosecurity interventions to control *Salmonella* on cattle farms (Edrington et al., 2009; Mohammed, 2016). The study by Edrington et al. (2009) performed two trials to study the effect of sprinklers in the feedbunk (treatment A) or in the holding pen before the milking parlour (treatment B) on faecal shedding of *Salmonella* and *E. coli* O157:H7 in lactating dairy cattle. Results showed that *Salmonella* spp. was lower in both treatments in day-7 (positive effect) when compared to control, whereas on day-28 the feedbunk sprinklers increased the number of *Salmonella* positive cows (treatment A, negative effect). *Salmonella* prevalence "decreased on day-5 and when examined across days in cows exposed to sprinklers prior to milking" (treatment B, positive effect). The authors concluded that having sprinklers in the holding pen before the milking parlour may be an effective intervention to decrease the faecal prevalence of *Salmonella* in lactating cattle. Another trial evaluated the effectiveness and practicality of two disinfectants for treating drinking water in small-scale cattle breeders and dairy farms in Switzerland were assessed (Mohammed, 2016). Water samples were collected from water troughs representing different water sources (tap, underground, and surface water). The bactericidal efficacy of hydrogen peroxide 50% and of Na-dichloroisocyanurate (in several doses) against indicator bacteria in these three water sources after 24 h of exposure was tested with positive effects. However, these effects were seen in the water, not in the animal.

3.1.4. Antimicrobial treatment

The study by Levent et al. (2019) looked at the effect of a single-dose of antimicrobials on the population dynamics of *Salmonella enterica* in beef cattle. Healthy cross breed cattle with initial body weights of around 340 kg were administered a dose of either ceftiofur, tulathromycin, or nothing (control). *Salmonella* population characteristics in cattle faeces, peripheral lymph nodes, and on hides were examined at day 0 (day in which cattle were administered the single dose antibiotic) and at day 99+ (slaughter age) with the authors finding no long-term effects of the antibiotic administration on *Salmonella* prevalence and antimicrobial resistance at slaughter.

3.1.5. Other

Finally, the study by Patton et al. (2009) evaluated "other" types of interventions by looking at the efficacy of inoculating an anti-*Salmonella* bacterium (an *E. coli* strain which possessed bacteriocin-like activity and was proven to be able to decrease viability of *Salmonella* organisms *in vitro* and *in vivo*) to reduce *Salmonella* detection and/or shedding in a cattle herd with persistent *Salmonella* infection. Patton et al. (2009) performed two trials, one in which the anti-*Salmonella* bacterium was orally administered before challenge, and another in which it was administered after challenge. Both trials had positive results, reporting a decrease in the shedding of *Salmonella.* This study highlights the potential of competitive exclusion as an intervention useful in the context of safeguarding public health.

3.1.6. Overview of interventions to control Salmonella

Although mixed results were reported, the studies retained show there are effective interventions to reduce *Salmonella* detection and shedding in cattle. The feasibility and costs associated with these interventions (i.e. rigorous and detailed cleaning and disinfection protocols) varies from herd to herd, meaning that a cost-benefit analysis tailored to each farm is necessary. In addition to the control of *Salmonella* at herd level, countries such as Finland, Norway and Sweden have documented that the successful control of *Salmonella* at national level in cattle, pigs and poultry through pre-harvest interventions is possible (Maijala et al., 2005; Norwegian Veterinary Institute, 2021; Plym Forshell et al., 2006). This success story can be attributed to a combination of factors, including strong government regulations, effective surveillance programmes, and collaboration between the different sectors involved in the production and processing of beef, including *Salmonella* control programmes in primary production. These programmes involve biosecurity measures, and testing of animals and feed to detect the presence of *Salmonella*. The most effective measures are likely to include heat-treatment of feed, and starting with breeding animals free from *Salmonella* at the top of the health and breeding pyramid (Blagojevic et al., 2021). These measures controlled at regional or national level also require feasibility studies and cost-benefit analysis. One good example is the evaluation of the *Salmonella* control programme of Pig Feeds in Finland (Niemi et al., 2019). The food safety authorities have an important role in following up positive herds to prevent transmission to other herds, humans and food, by prohibiting the purchase and transport of animals and foods from infected farms. This highlights that prevention rather than control is a feasible pre-harvest intervention when targeting this hazard in beef.

3.2. Shiga toxin-producing Escherichia coli (STEC)

There were 13 studies retained for STEC, reporting a total of 34 trials. Seven papers were carried out in the USA, three in Canada, and one in Argentina, Germany, and the UK. Table 3 summarises the characteristics and the results of the studies and trials reported. The vast majority of the studies focused on beef cattle (n = 7), followed by dairy calves (n = 4), while two studies took place in dairy farms. Most of these studies were performed in a commercial setting (n = 8), with five studies being performed in a research facility.

Overall, 16 trials (45.7%) reported positive results (Alonso et al., 2007; Eicher et al., 2010; Ellis-Iversen et al., 2008; Martorelli et al., 2018; Peterson et al., 2007; Schmidt et al., 2018; Sharma et al., 2011; Zhao et al., 2006).

3.2.1. Vaccination

Vaccination and cleaning, disinfection, management, and biosecurity were the most tested interventions, accounting for 59% of the trials. Interventions testing only vaccination had an efficacy rate of 80%. All vaccination trials were performed in calves. Five trials challenged the animals to test the efficacy of the vaccine or vaccination scheme in the study. Martorelli et al. (2018) examined the effect of two vaccines (two trials) against STEC (carboxy-terminal fraction of Intimin gamma (IntC280) and EspB, with EspB + IntC280 + BLS-Stx2B) and its effect on faecal shedding after experimental challenge was evaluated. Both vaccines reduced *E. coli* 0157:H7 shedding compared to the control group. Schmidt et al. (2018) looked at the effect of a vaccination scheme including passive (colostrum from vaccinated cows) together with active immunisation (vaccination), and the supplementation with moderate or high vitamin E concentrations. The trials included in this study were: vaccination and high vitamin E intake; sham vaccination and high vitamin E intake; vaccination, and moderate intake of vitamin E. A treatment with no vaccination and moderate vitamin E supplementation served as control. Overall, less faecal samples from vaccinated calves were stx1 and/or stx2 positive than samples from control animals when calves were fed a moderate amount of vitamin E, suggesting that this vaccination scheme may be used to prevent foodborne zoonoses caused by STEC.

Peterson et al. (2007) reported several trials studying the efficacy of dose regimen and observation of herd immunity from a vaccine against *E. coli* O157:H7 for feedlot cattle. The treatments observed were 1) no vaccination (control), 2) one dose, vaccinated once at reimplant (which corresponds to the re-administration or insertion of a growth stimulant implant which was and still is allowed in beef cattle in the USA (Beck et al., 2022); day 42); 3) two doses, vaccinated on arrival (day 0) and

again at reimplant (day 42); and 4) three doses, vaccinated on arrival (day 0), on day 21, and again at reimplant (day 42). All vaccination schemes had positive effects. Treatment efficacy (2, 3 and 4) was 68, 66, and 73%, respectively, compared with cattle in pens not receiving the vaccine. Cattle administered treatment 4 were significantly less likely to shed *E. coli* O157:H7 than controls within the same pen. Controls housed with vaccinated cattle were 59% less likely to shed *E. coli* O157:H7 than cattle in pens not in study, which the authors discuss is likely due to herd immunity. Sharma et al. (2011) tested the use of two mutant strains of *E. coli* O157:H7 (hha and hha sepB) as bacterins for reducing *E. coli* O157:H7 shedding in cattle. Weaned calves were injected intramuscularly with a sham vaccine (control) or with bacterins containing 109 heat-killed cells of the hha + wild-type (treatment 1), 109 heat-killed cells of the hha isogenic mutants (treatment 2), or 109 heat-killed cells of the hha sepB isogenic mutants (treatment 3). Calves were boosted with the same doses 2- and 4-weeks later, were challenged with wild-type *E. coli* O157:H7 and the shedding was evaluated. Positive effects were reported in treatments 2 and 3. Following oral inoculations, the group of calves vaccinated with either the hha or hha sepB mutant bacterins showed a higher number of individuals that stopped shedding the inoculum strain shortly after vaccination, as compared to the group of calves vaccinated with the hha + wild-type bacterin or PBS sham vaccine. Finally, Stanford et al. (2014) studied the effect of direct-fed microbials and a type III secreted proteins' vaccine to control *E. coli* O157:H7 in faeces and hides of feedlot cattle. Only the treatment with the vaccine is summarised here, please see below the section on in-feed treatment, additives and supplementation for a description on the other trial. Though the vaccine treatment had positive effects throughout the trial, it failed to reduce the detection or shedding of *E. coli* O157:H7 at slaughter.

3.2.2. In-feed treatments, additives or supplementation

The four trials testing in-feed treatment, additives or supplementation reported negative outcomes. Stanford et al. (2014) also reported one trial testing the effect of a direct-fed microbial (DFM) on feedlot cattle finishing diets containing Bovamine® Culture Complex (Nutrition Physiology Company, LLC) with 109 CFU *L. acidophilus* and *Propionibacterium freudenreichii* fed/animal/d. No positive results were obtained, with the treatment even increasing detection of *E. coli* O157:H7 in some time-points of the trial. Stanford et al. (2013) tested another DFM to control *E. coli* O157 in commercial feedlot cattle. The authors reported that when comparing hide swabs collected at the beginning of feeding with DFM to those collected at shipping for slaughter, the prevalence of *E. coli* O157 decreased significantly ($p < 0.05$) in cattle fed DFM. However, there was no significant difference in the prevalence of *E. coli* O157 in hide swabs between the control group and the DFM-treated group at any time. Additionally, there were no significant differences in the numbers of *E. coli* O157 or the prevalence of the organism in faecal pats among the different treatments. One intervention tested the use of competing *E. coli* on water contaminated by rumen contents or faeces and it reported negative results (see the study by Zhao et al. (2006) in the cleaning, disinfection, management, and biosecurity section). Finally, the last trial testing in-feed treatments, additives or supplementation analysed the effect of a package of interventions for improved water and feed hygiene. The setting of this trial is explained below (see section cleaning, disinfection, management, and biosecurity) when describing the trials by Ellis-Iversen et al. (2008). There was no reduction of STEC in this treatment when compared to the control group.

3.2.3. Cleaning, disinfection, management, and biosecurity

The trials testing cleaning, disinfection, management, and biosecurity interventions were reported in the studies by Ellis-Iversen et al. (2008), Beauvais et al. (2018), Shepherd et al. (2007), and Zhao et al. (2006). Ellis-Iversen et al. (2008) performed a study in England and Wales looking at the effect of three management intervention packages to reduce the burden of *E. coli* O157 in groups of young-stock on cattle farms. This study reported three trials, one of which corresponds to cleaning, disinfection, management and biosecurity interventions. In this trial, seven farms were asked to change their practices in order to keep a clean environment and closed groups of young-stock, while 26 farms served as control (practices not altered). The practices implemented were: no new animals brought in, no contact with other cattle, no shared water sources, keep bedding dry, keep animals clean, maintain closed group, use boot-dip, and use overcoat. Farms testing this intervention showed a 48% reduction in *E. coli* O157 burden over the 4.5 months of observation, compared to 18% on the control farms. According to the authors, the effect of this intervention compared to the control farms, as analysed using a crude intention-to-treat model, resulted in a relative risk (RR) of 0.26 ($p = 0.122$).

Beauvais et al. (2018) studied the effect of the water-to-cattle ration in automatically refilling water troughs on the prevalence of *E. coli* O157:H7 faecal shedding in feedlot pens. Faecal samples were collected before the start of the intervention and three weeks after, and tested for the presence of *E. coli* O157:H7. The authors reported a strong association between positive faecal samples to *E. coli* O157:H7 and the sampling date (before and after intervention). Despite accounting for a high level of clustering (pen was also associated with higher detection of *E. coli*), a statistically significant association between reduced water levels in the trough and increased prevalence of *E. coli* O157:H7 in the faeces was reported. Though the authors did not expect this result, they suggested that increasing water trough levels may be effective in reducing shedding of *E. coli* O157:H7 in cattle faeces, although further work is needed to test this hypothesis. In another study, Shepherd et al. (2007) looked at the effect of manure composting on a dairy farm on *E. coli* O157:H7 concentrations. Two trials were performed involving compost heaps in duplicate, built at an outside farm location. Samples of the composting mixture were inoculated with stx-negative *E. coli* O157:H7 B6914 at two initial concentrations (trials 1 and 2, respectively). In both trials, the pathogen was inactivated below the surface, but survived at the heap's surface for up to four months. In spite of these less positive results, the authors note that composting with periodic heap turning may be a practical approach to inactivating *E. coli* O157:H7 in cattle manure. Finally, the study by Zhao et al. (2006) tested six disinfectants or combination of disinfectants (chemical treatments), and competing *E. coli* for the inactivation of *E. coli* O157:H7 in drinking water for cattle. The treatments tested were: chlorine (5 ppm), ozone (22–24 ppm at 5 °C), competing *E. coli*, and four disinfectant combinations. The first three treatments had minimal effects. Whereas the four desinfectant combinations were highly effective in killing *E. coli* O157:H7, O26:H11, and O111:NM at 21 °C in water heavily contaminated with rumen content or faeces. The combination treatments used in the study were as follows: (i) Treatment A, consisting of 0.1% lactic acid, 0.9% acidic calcium sulfate, and 0.05% caprylic acid; (ii) Treatment B, consisting of 0.1% lactic acid, 0.9% acidic calcium sulfate, and 0.1% sodium benzoate; (iii) Treatment C, consisting of 0.1% lactic acid, 0.9% acidic calcium sulfate, and 0.5% butyric acid; and (iv) Treatment D, consisting of 0.1% lactic acid, 0.9% acidic calcium sulfate, and 100 ppm chlorine dioxide. Despite the highly positive results, the authors note that the amounts of water consumed for all water treatments were significantly different from that of the control, concluding that it may be more beneficial to apply these treatments periodically to drinking water troughs and then flush them, rather than adding them continuously. This approach could help avoid potential decreases in water consumption by cattle. It is important to mention that these results were observed in water, and STEC reduction in cattle was not tested.

3.2.4. Mixed interventions

On the studies reporting mixed pre-harvest interventions to control STEC, two have been described in the vaccination section together with the description of the study by Schmidt et al. (2018). The inclusion of high levels of vitamin E alone did not have an effect on the reduction of STEC, but its high supplementation in conjunction with a vaccination

scheme was effective in controlling STEC in calves. On the other hand, the study by Ellis-Iversen et al. (2008) incorporated a third treatment which consisted of the implementation of cleaning and disinfection measures as well as improved water and feed hygiene. This mixed treatment was not effective in controlling STEC. It must be noted that the authors reported poor compliance throughout the study.

Lastly, seven trials incorporated transport with other measures and were reported in the studies by Bach et al. (2004); Alonso et al. (2007); Eicher et al. (2010). Bach et al. (2004) looked at the effect of long (15h) or short (3h)-haul transport and administration of preconditioning in the faecal shedding of *E. coli* and *E. coli* O157:H7 by calves. Bach et al. (2004) account for four of the seven trials reported in this section. Preconditioned calves were vaccinated and weaned 29 and 13 days, respectively, prior to transport. Non-preconditioned calves were weaned one day before transport (long or short), held for 24h and transported again for 2h, and vaccinated on arrival at the feedlot. Results showed that in all treatments STEC was detected, whereas no calves were positive for *E. coli* O157:H7 before transport. This is the reason why we reported these trials as not effective. However, results showed that not preconditioning calves and long periods of transport were associated with increased faecal shedding of *E. coli* and *E. coli* O157:H7 compared to other treatments, with the authors concluding that preconditioning can be useful to reduce *E. coli* O157:H7 shedding by range calves on arrival at the feedlot. These seemingly positive results did not last long, with the authors reporting no differences between treatments 28 days after transport. This indicates that these interventions would not be suitable as food safety interventions. The study by Eicher et al. (2010) reported two trials where calves were fed yeast cell-derivatives that were either 1.8% beta-glucan in combination with ascorbyl-2-polyphosphate (BG2), or 1.8% beta-glucan yeast cell-wall derivative with a more purified yeast cell-wall derivative (70% beta-glucan; BG70) on the shedding of *E. coli* in neonatal calves transported for 4h. The percentage of calves positive for *E. coli* O157:H7 was greater for BG2-supplemented calves than for BG70-supplemented and control calves on day 7, however, no differences were seen across treatments on day 28. Thus, this also suggests that these interventions may not be suitable as food safety interventions. Finally, the study by Alonso et al. (2007) looked at the effect of washing trucks on the detection of STEC. In brief, *E. coli* O157:H7 was not isolated from any of the trucks washed prior to arrival. However, isolates of *E. coli* O157:H7 were isolated from trucks which were not cleaned. This trial is a good example of the efficacy of good hygiene practices on the control of STEC.

3.2.5. Overview of interventions to control STEC

Controlling STEC in cattle farms is key to mitigate the risk of foodborne zoonoses caused by contaminated beef products. However, since STEC of certain serotypes are widespread in the ruminant reservoir, and are probably established as part of the normal intestinal flora in these animals, complete elimination of STEC is probably impossible (Gyles, 2007; Karmali et al., 2010). In general, specific management strategies to successfully decrease the occurrence of STEC in the ruminant reservoir are missing. The studies retained on STEC show that vaccination, and cleaning, disinfection, management, and biosecurity were the most tested interventions and the most effective, denoting their potential to control or reduce detection and shedding of STEC. The correct implementation of such measures is crucial for its efficacy. For that reason, similar to *Salmonella* control programmes, feasibility and cost-benefit analysis tailored to each farm, region or nation need to be considered. While vaccination can be implemented to prevent severe outcomes of clinical disease and reduce shedding, cleaning, disinfection, and biosecurity can prevent the introduction and/or the spread of STEC to/within farms. In-feed treatments, additives or supplementation have been suggested to be effective as a control measure for STEC, but this systematic review did not find evidence to corroborate this. It is possible that post-harvest interventions can also reduce the prevalence of STEC in beef products (Antic et al., 2021). However, these interventions are costly and may affect the taste and texture of the meat.

3.3. Campylobacter spp.

The only study retained on *Campylobacter* spp. tested the antimicrobial effects of chestnut or mimosa extracts rich tannins when supplemented in-feed to feedlot cattle (Gutierrez-Bañuelos et al., 2011). Though the authors reported two trials, only one trial using in-feed supplementation tested its efficacy on the reduction of *Campylobacter* spp. in ruminal fluid and in faeces. The trial ran for 42 days. Faecal samples from day 0 and 7 were cultured for *Campylobacter*. The results showed that *Campylobacter* concentrations in faeces varied with treatment, day and their interaction, with concentrations measured in samples collected on day 7 being higher in both tannin-supplemented groups than those measured on day 0. Animals fed the chestnut tannin extract had the highest concentration. As *Campylobacter* was found in the ruminal fluid of only four steers in the study, no statistical analysis was performed. The authors asserted that these results were expected as *Campylobacter* depends on amino-acid fermentation for conservation of energy and tannins protect amino acids from degradation in the rumen, enhancing the availability of amino acids in the lower gut. For this reason, the authors commented that feeding rumen non-degradable protein to cattle may increase the concentration of *Campylobacter* in the lower gut.

3.4. Clostridium botulinum

Kruger et al. (2013) studied the effect of a toxoid vaccine for *Clostridium botulinum* types C and D on the immune response of dairy herds in Denmark, and on the presence of botulinum neurotoxins and *C. botulinum* spores in cows' faeces. Eight herds were enrolled in the study. Four herds vaccinated their cows subcutaneously, according to manufacturer's recommendation using two shots – with exception of one herd, which only administered one shot. In each herd, 30 cows (15 recently calved and 15 high yielding) were randomly chosen for blood and faecal sampling. *C. botulinum* types C and D antibodies were increased in vaccinated animals, and vaccination reduced botulism neurotoxins and *C. botulinum* spores in cattle faeces. This study strongly suggests that vaccination increases specific blood serum antibodies and reduces the prevalence of botulinum neurotoxins and *C. botulinum* spores in faeces, meaning that it can be an effective pre-harvest intervention to control *C. botulinum*. This is a meaningful result for the prevention of *C. botulinum* as a foodborne zoonoses.

3.5. Clostridium perfringens

Ishihara et al. (2001) studied the effect of green tea extracts (GTE) on growth inhibition of pathogenic bacteria, including *C. perfringens*, on improving gut microflora of calves, and on preventing respiratory and gastrointestinal disease in calves. Of all three trials performed by the authors, one *in vitro* and two *in vivo*, only one trial (*in vivo*) met the inclusion criteria for this systematic review. One of the *in vivo* trials did not look at disease outcomes related with *C. perfringens,* like counts or detection. Ten female Holstein calves, individually housed, were fed GTE extracts mixed in milk replacer and 10 animals (with another 10 animals in a control group) from 1 week of age (after transport) for 30 days (weaning). Faeces were collected before GTE administration and once per week until weaning (4 sampling points). Bacteria were cultured from the faeces using different media and methods, after which bacteria colonies in each medium were counted and identified according to their characteristics. Total bacteria count decreased with growth time in both groups (control and treated calves). However, the *C. perfringens* counts decreased faster and more pronouncedly in the treated calves, showing a significantly lower number of *C. perfringens* colonies compared with control calves in sampling points (weeks) 2, 3 and 4 after the beginning of the treatment. In addition, the authors noted that bacterial counts of

Lactobacillus spp. and *Bifidobacterium* spp. were higher in treated calves compared to those in the control group, suggesting that the microflora was more balanced in treated calves. They concluded that GTE could be applied as a safe and useful feed material to control disease and disease outcomes in young calves. It is important to note that the milk replacer utilized (both in the treated and control calves) contained colistin sulfate and zinc bacitracin. These substances are antibiotics that are commonly used in animal feed to promote growth and prevent disease. Thus, the use of these substances in the milk replacer may have confounded the study results by eliminating pathogenic bacteria, such as *C. perfringens*.

Some considerations must be made about the study retained on *Clostridium perfringens*. The authors performed a trial using only 10 animals in each group, which is a very small sample size. The results suggest that GTE are useful in preventing disease in young calves, potentially reducing the pressure of infection on farm. The focus was to minimise the clinical outcome of *C. perfringens*, instead of focusing on controlling this pathogen for public health purposes. Indeed, the effect of GTE extracts in steers or animals ready to harvest is not discussed. This means that the effect of GTE to control *C. perfringens* before slaughter cannot be ascertained and more studies are necessary.

3.6. ESBL/AmpC

Smidkova and Cizek (2017) tested whether the administration of a probiotic to new-born dairy calves reduced faecal shedding of ESBL and/or AmpC-positive *E. coli* until weaning. For this, a trial was run on a dairy farm with evidence of high occurrence of AmpC-positive *E. coli* in calves. Ten randomly assigned new-born Holstein calves (five male and five female) were treated using a probiotic mix (oral administration) within 12h after birth, and nine control calves (three males and six females) were not treated. Faecal samples were collected from each calf daily on days 2 through 5, and then on days 7, 10, and 14 after birth. The faecal samples were cultured, and bacterial counts performed with the mean numbers of cefotaxime-resistant *E. coli* and confirmed enteroaggregative *E. coli* being compared between treated and untreated calves. Results suggested that probiotic treatment used (*Enterococcus faecium* M74, NCIMB 11181) failed to reduce enteroaggregative *E. coli* counts in new-born calves' faeces. The authors stated that there was no significant difference in the shedding of enteroaggregative *E. coli* between the probiotic-treated and control calves throughout the two-week study period. The trial did not obtain positive results – no differences were found in the shedding of ESBL/AmpC-positive *E. coli* in treated calves vs. control calves. However, the authors commented on the reasons for the results observed and stated that probiotics may need to be designed specifically for the target intended, instead of being used generically. Likewise, a mono or multi-strain probiotic is yet to be developed to target ESBL/AmpC-positive *E. coli*.

3.7. Limitations of this systematic review

Similar to what was reported in the studies by Rodrigues da Costa et al. (2021) and Pessoa et al. (2021), the findings of this review and the conclusions drawn from them are legitimate in light of the established inclusion and exclusion criteria. As a result, papers without a control group and those in which the intervention's causal effect could not be deduced were disregarded. This decision was made to reduce bias and to decrease possible confounding variables.

4. Conclusions

The results of this systematic review reflect that the recent research on pre-harvest interventions to control foodborne zoonoses in bovines was mostly focused on *Salmonella* spp. and STEC. Although we are missing specific management strategies to control STEC, vaccination seemed to prevent severe outcomes of disease whereas cleaning, disinfection, management and biosecurity were effective in preventing the spread of this disease. Some foodborne pathogens appear to be best or more easily controlled at a post-harvest level (Koohmaraie et al., 2005), which may justify the lack of search returns for some of the pathogens included in this review. However, pre-harvest interventions have an extra sustainable effect by avoiding recycling of zoonotic agents including ESBL/AmpC-positive bacteria via the environment. Overall, as illustrated in the studies retained for *Salmonella* and STEC, high herd health status coupled with good management and biosecurity were effective to control or prevent most foodborne pathogens in cattle at pre-harvest level. Despite not having been included in the review, the principle of starting with breeding animals free from zoonotic pathogens at the top of the health and breeding pyramid, and heat-treatment of feed have been reported as feasible and effective interventions to control foodborne pathogens like *Salmonella* spp.

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CRediT authorship contribution statement

Maria Rodrigues da Costa: Methodology, Searches and data collation, Record screening, and Data extraction, Data curation, Writing – original draft, Writing – review & editing. **Joana Pessoa:** Methodology, Searches and data collation, Record screening, and Data extraction, Data curation, Writing – review & editing, All authors have approved the final version. This statement also follows in the manuscript. **Truls Nesbakken:** Conceptualization, Methodology, Validation, Writing – review & editing, Supervision, Funding acquisition. **Diana Meemken:** Conceptualization, Methodology, Validation, Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.foodcont.2023.109944.

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