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Microbiome engineering to combat antimicrobial resistance and upsurge productivity of food animals: a systematic review

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ABSTRACT

Extensive antimicrobial usage in animal farming plays a prominent role in the antimicrobial resistance (AMR) crisis and is repeatedly highlighted as an area needing development under the 'One Health' approach. Alternative therapies such as microbiome products can be used as prophylaxis to help avoid infectious disease. However, a limited number of studies have focused on AMR-targeted microbiome products. We conducted this systematic review by using PRISMA guidelines to screen for literature that have evaluated food animals' health when administrated with microbiome products targeting antimicrobial resistance (AMR) or antibiotic-resistant genes (ARGs). We searched and examined studies from SCOPUS, Web of Science, Embase, and Science direct databases for studies published up to November 2021, restricted to the English language. The findings of this review showed that microbiome products have a promising capability to tackle specific AMR/ARGs coupled with animal's health and productivity improvement. Furthermore, our study showed that probiotics were the most favourable tested microbiome products, with the most targeted resistance being to tetracycline, macrolides, and beta-lactams. While microbiome products are promising alternatives to antibiotic prophylactics, there is a dearth of studies investigating their efficacy in targeting AMR. Thus, it is highly recommended to further investigate, develop, and improve the microbiome, to better understand their utility and circumvent their limitations.

Keywords: AMR, antimicrobials, ARG, bacteria, food animals, microbiome, microbiome products, probiotics.

Introduction

Antimicrobials are used extensively as treatments, prophylactics, and growth promoters in large-scale animal-farming systems (Kimera *et al.* 2020). According to the United Nations Report (2019), the world population is estimated to be 9.7 billion by 2050 (United Nations PD 2019). This increased population will proliferate the demand for food-producing animals and their products. To fulfil this demand, several countries are shifting to intensive livestock production systems that use antimicrobial (AM) treatments to maintain animal health and improve growth and productivity (Kober *et al.* 2022). Accordingly, the global consumption of AMs used for food animals is predicted to increase by up to 67%, from 63 151 Mg in 2010 to 105 596 Mg in 2030 (Xiong *et al.* 2018). This dependence on antimicrobials has contributed to the increase in AM resistance (AMR), which was predicted by Sir Alexander Fleming, who introduced the first antibiotic, during his Nobel prize speech in 1945 (Diarra *et al.* 2021). AMR is a natural process and a common defence mechanism in bacteria. It can lead to difficulties in treatment and increases healthcare costs, especially in the case of multidrug resistance. In 2018, it was estimated that the numbers of deaths from AMR were about 700 000 per year (Seong *et al.* 2021). An additional consequence of the long-lasting practice of subtherapeutic antibiotic doses in food animals is the selection of antibiotic-resistant bacteria (ARB), which in some cases may increase the mutation rate (Revitt-Mills and Robinson 2020; Zalewska *et al.* 2021). ARB can transfer antibiotic-resistance genes (ARGs) to other enteric bacteria in the host's intestinal tract (Zalewska *et al.* 2021).

For instance, the transfer of ciprofloxacin, azithromycin, or tigecycline resistance has been detected in *Pseudomonas aeruginosa* and *Enterococcus faecalis* (Brooks *et al.* 2021). Food-producing animal farms are ARB hotspots (Alhababi *et al.* 2020; Eltai *et al.* 2020*a*, 2020*b*; Guo *et al.* 2021). There have been many studies on the extensive use of antibiotics in livestock and aquaculture industries and the potential risks posed to animal and public health through the spread of AMR (Baquero 2012; Kimera *et al.* 2020; Kim *et al.* 2021; Yun *et al.* 2021; Lin *et al.* 2021; Pissetti *et al.* 2021).

Several efforts have been made to minimise excessive AM usage in food-producing animal farms. The European Union banned their use as growth promoters and prophylactics, and the United States significantly reduced their usage in food animals (Kogut 2017; World Health Organization 2017). Nevertheless, AMs remain necessary for limiting disease in food animals and maintaining production levels to meet global demand. An important aspect of AM stewardship is identifying alternatives to continue treating animals but limiting AMR spread (Ricker *et al.* 2020). One promising approach is microbiome engineering (Foo *et al.* 2017; Kogut 2017; Cullen *et al.* 2020; Bae *et al.* 2021; Diarra *et al.* 2021). Studies have shown that manipulation of domesticated animal microbiomes can be a powerful tool to reduce morbidity and fight infectious diseases. The most studied animal microbiome engineering products are probiotics and prebiotics; however, there are reports of the use of postbiotics and combinations of the three (synbiotics; Jin Song *et al.* 2019; Kober *et al.* 2022).

Prebiotics are non-digestible food ingredients that stimulate the growth and/or activity of beneficial gut microbiota (Mountzouris 2022). These authors demonstrated an improvement in the abundance of beneficial bacteria such as *Bifidobacterium* and/or *Lactobacillus* spp., which help in digestion, defence against pathogens, constipation relief, and shift the microbial populations reducing pathogen numbers (Cullen *et al.* 2020). Probiotics are viable ingestible microorganisms obtained from a healthy donor. They are used to restore or enhance gut microbiota. The best-studied probiotics include members of the genera *Bacillus*, *Lactobacillus*, *Bifidobacterium*, *Enterococcus*, *Lactococcus*, *Megasphaera*, *Pediococcus*, and *Propionibacterium* (Wideman *et al.* 2015; Jin Song *et al.* 2019). These bacteria aid in fibre fermentation, regulate inflammatory responses, help amino acid and vitamin production, and support the maintenance of gut–brain axis (Yan and Polk 2020).

Additionally, these organisms play a crucial role in improving host immunity against pathogens by preventing colonisation or proliferation through competition, releasing antimicrobial molecules, and improving the intestinal barrier function and immunomodulation (Wan *et al.* 2019; Cullen *et al.* 2020). Most notably, probiotics can fight infectious diseases in animals, thus reducing the pressure on antibiotic use (Jin Song *et al.* 2019). The most frequently used probiotics in livestock are the lactic acid bacteria and *Bifidobacterium* strains (Kober *et al.* 2022). Postbiotics, are products or metabolic by-products secreted by bacteria or released after bacterial lysis (Aguilar-Toalá *et al.* 2018; Wan *et al.* 2019). An example of postbiotics are short-chain fatty acids (SCFAs), enzymes, peptides, and organic acids. Notably, organic acids were found to have an AM effect against ARB (Roth *et al.* 2017).

Several studies have investigated microbiome products as substitutes for AMs for improving food-producing animal production and animal health (Han *et al.* 2017; Ayala *et al.* 2019; González-Ortiz *et al.* 2020; Helmy *et al.* 2020; Bae *et al.* 2021; Zhe *et al.* 2021; Pham *et al.* 2022). Yet, data on their effects on AMR are limited. Therefore, reviewing major literature databases and selecting original studies from a set of criteria may help identify the missing gap in the impact of microbiome products in fighting AMR in food animals. Herein, we present a systematic review that may unify the assessment of microbiome products in combating antimicrobial resistance in food animals. The main objectives extended to investigate the common type and composition of the products used for food animals and evaluate their effects on animals' state of health and productivity.

Materials and methods

Database searches

This systematic review was performed following the PRISMA checklist for standards for systematic reviews (Moher *et al.* 2009). Three databases were screened on 28 November 2021, no date limits were applied. The filtered databases were ScienceDirect, SCOPUS, and Web of Science. The search was updated on 14 March 2022, by adding a fourth database (Embase), with date restrictions for the articles published before 28 November 2021. Additional articles were identified by searching the references of the included studies and the first 100 results of Google Scholar.

The search strategy included terms on the topics of animal, microbiome, antimicrobial resistance, and antibiotics, consistent with the eligibility criteria. One example of the exact search string was ('(animal)' AND '(microbiome)' AND '(antimicrobial resistance)' AND '(antibiotics)'). Only studies published in English were included.

Study screening

All studies were imported into Zotero, and duplicates were removed using the built-in 'Find Duplicates' feature. The titles and abstracts were independently screened by two independent reviewers (LA and A-RJ). The following three questions were used to determine whether the study met the eligibility criteria:

1. Does the paper describe a primary research study?

2. Does the paper describe the use of microbiome products (prebiotics, probiotics, postbiotics, or synbiotics) and have they been tested on food animals?
3. Does the paper include the outcome of using the microbiome products on the antimicrobial-resistant bacteria and animals' productivity?

Full-text review using the same criteria was performed for (1) studies that met all of the inclusion criteria and (2) studies for which this could not be conclusively determined. Studies that did not meet all eligibility criteria were excluded. Full-text review was similarly performed by two independent reviewers (LA and A-RJ). A third independent reviewer (HA) resolved disputes between the two reviewers during the title/abstract screening and full-text review stages. The reviewers screened the references in the included papers after completing data extraction. The titles and abstracts of the references were screened by the reviewer (LA), following the same criteria as in the original search and then double-checked by the reviewer (A-R J). The full texts of these articles were reviewed following the same process as above.

Data extraction

The author (LA) reviewed all full-text studies meeting the initial criteria and extracted data from included papers using a data-collection form. The following information was recorded for each manuscript where applicable: the author, publication year, country, food animal and the number of animals, type of microbiome products (prebiotics, probiotics, postbiotics, or synbiotics), proposed mode of administration, targeted ARB, effect on or ARG abundance, outcome measures evaluated (effect on animal health/production), and the authors' conclusions. The data were then reviewed by the author (A-R J) for final inclusion in the review, duplicate screening, eligibility, and quality assurance. Any disagreements were resolved by consensus.

Data synthesis

The primary outcome was the effect of the product on the abundance of ARB or the ARGs. We also assessed the studies according to the frequently studied food animals and the most investigated AM-resistant bacteria or genes. Likewise, we examined the the effects of the product on animals' health. We stratified the microbiome products according to their components (prebiotics, probiotics, postbiotics, or synbiotics) to find the rate of its effect on the AMR/ARGs in animals. In each study, ARB or gene results were then sorted as showing an increase, decrease, or no change in resistance.

All study results were compared in regard to the efficiency of the applied products on AMR abundance and the outcomes.

Results

The search and selection processes are shown in Fig. 1. In total, 925 records were identified from the databases and manual searches. Removing duplicates resulted in 755 records for the initial title and abstract screening. From which, only 49 papers were retained. After reviewing the full texts, eight studies were included from the search, and two were abstracts only (Hofacre *et al*. 2002; Sommer-Lassa *et al*. 2019). In total, 402 references were retrieved from the eight included studies. Their titles and abstracts were screened, and only three studies met the inclusion criteria. The full texts of these were assessed, and all were included.

Information on the year of publication, country of the study, animal species studied, microbiome studied, investigated resistance, targeted bacteria, and other general characteristics are described in Tables 1–3. The earliest article was published in 2002, while all the remaining 10 papers were published from 2014 onward, with 63.6% of them published between 2014 and 2019. Only 27.3% were published in the last 2 years (i.e. 2020–2021). The United States was the most represented country (36.4%), followed by the Netherlands (18.2%). The five remaining studies were conducted in the United Kingdom, Ireland, Austria, Spain, and Colombia. It is worth mentioning that the study location in three of the included studies was not specified but was inferred from the first author's primary affiliation (Hofacre *et al*. 2002; Delgado *et al*. 2014; Ceccarelli *et al*. 2017).

The most investigated food animals were chickens (63.6%), followed by bovines (e.g. steers, bulls, and heifers, at 36.4%). Pigs were investigated only in one study (9.1%). The average age of the food animals studied ranged from 1 day to 218.6 days. Most of the studied animals were young; all chickens investigated were chicks, and most of the studied bovines and pigs were weaned. Only two studies used adult animals for their investigation (e.g. bulls and heifers).

Information about the microbiome products and the targeted bacteria addressed in the included studies are summarised in Table 2. In general, most of the included studies investigated the effect of probiotics on AMR (54.5%). Postbiotics were tested in three studies, synbiotics in two studies, and prebiotics were evaluated only in one study. Many probiotic products contained *Lactobacillaceae* species or the products of *Saccharomycetaceae* species. Multiple routes of dietary product administration were used in all the studies, except one study in which a direct administration challenge was employed. *Escherichia coli* was the most frequently targeted bacteria in the included studies (45.5%), followed by *Salmonella Enteritidis* (18.2%). The targeted bacteria were not specified in four of the included studies.

The abundance of different AMR or ARGs in food animals was investigated in the included studies, to evaluate the efficacy of microbiome products in tackling AMR. Briefly,

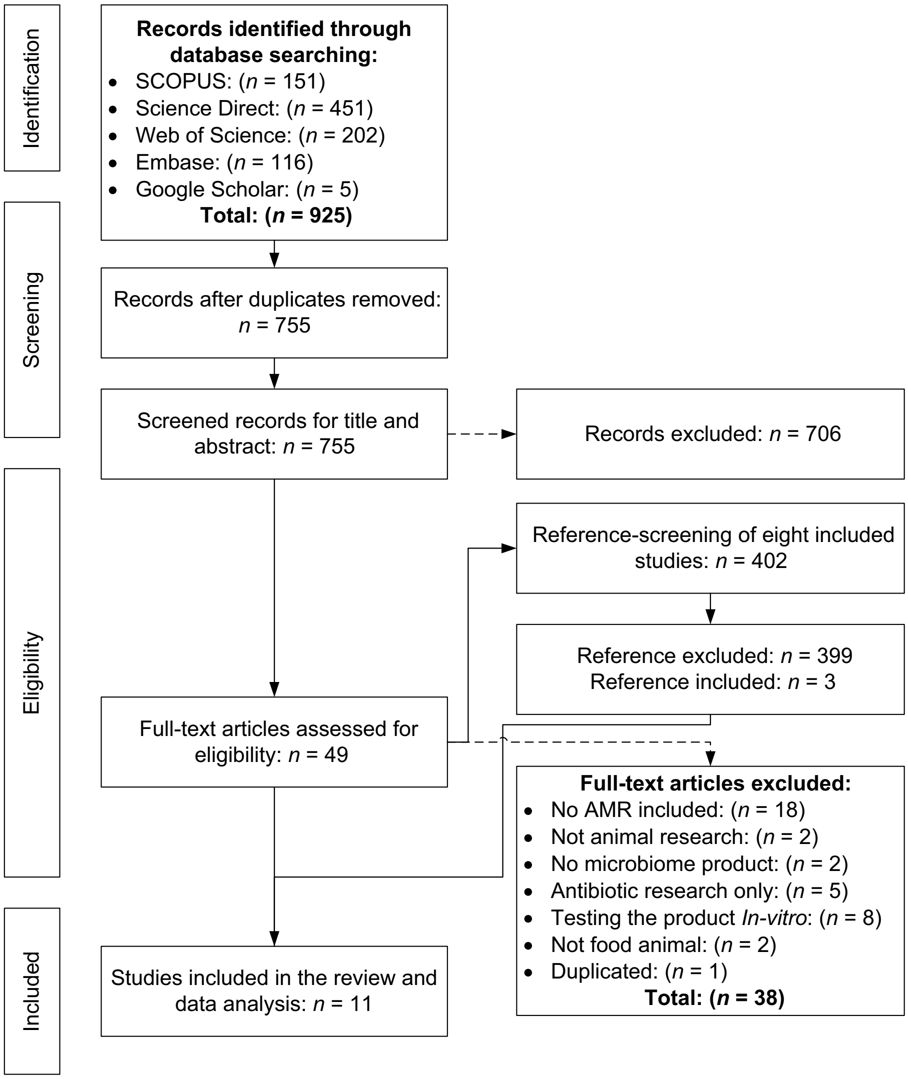

Fig. 1. PRISMA schematic selection process of the included studies at each stage of the screening process.

three included studies analysed resistance in both AMR and ARG, five studies targeted AMR only, and three studies targeted ARGs only. Only one study did not specify the AMR or ARGs of the investigated resistance. Interestingly, tetracycline resistance was the most frequently investigated in the included studies, followed by beta-lactam and macrolide resistance. Other investigated AMR and ARGs are shown in Table 3. Overall, 90.9% of the samples were from the gastrointestinal tract (GIT), including rumen, colon, small intestine, large intestine, whole intestine, duodenal and faecal swabs (Table 3). Alternatively, 9.1% of the collected samples were taken from organs other than the GIT, such as the yolk sac.

The effectiveness of the microbiome products on animal health and on AMR/ARG abundance was also evaluated. Generally, product effectiveness varied according to the type and composition of the microbiome product. In the case of probiotics, 50% of the studies described an increase in animal health, 25% reported no increase, and 25% did not specify the product effectiveness. All other types of microbiome products included in the review (prebiotic, postbiotic, and synbiotic) showed increased animal health and productivity. In terms of the effectiveness of the tested product on AMR and ARGs, varying results were observed in the included studies. A significant decrease in the AMR or ARG abundance was reported in 62.5% of the studies that examined probiotics, whereas the remaining 37.5% showed no effect. Likewise, precise results varying between an increase and a decrease and no impact on the AMR or ARGs abundance were reported while using the prebiotic product. The remaining products (postbiotic and synbiotic) reported a reduction in the number of the AMR or ARGs.

Table 1. Characteristics (publication year, country, and animal studied) of the 11 included studies.

Reference	Publication year	Country	Animal	Animal category	Number	Age
Casanovas-Massana *et al.* (2014)	2014	Spain[A]	Bovine	Holstein bulls	40	218.6 ± 2.62 (mean ± s.e.)
			Pigs	Weaned	30	21 days
Lee *et al.* (2021)	2021	United Kingdom	Chicken	Chicks	220	14 days
Huebner *et al.* (2019)	2019	United States	Bovine	Yearling steers	4689	N/S
Sommer-Lassa *et al.* (2019)	2019	United States[A]	Bovine	Weaned steers	32	N/S
Delaney *et al.* (2021)	2021	Ireland	Chicken	Chicks	16	1-day old
Ceccarelli *et al.* (2017)	2017	Netherlands	Chicken	Chicks	24	1-day old
Dame-Korevaar *et al.* (2020)	2020	Netherlands	Chicken	Chicks	100	1-day old
Hofacre *et al.* (2002)	2002	United States	Chicken	Chicks	N/S	1 and 2 days
Feye *et al.* (2016)	2016	United States	Bovine	Heifers	1495	N/S
Roth *et al.* (2017)	2017	Austria	Chicken	Chicks	480	1-day old
Delgado *et al.* (2014)	2014	Colombia[A]	Chicken	Chicks	60	1-day old

[A]The country was inferred from the author's affiliation.
N/S, not stated.

Table 2. Summary on characteristics of microbiome products and the targeted bacterial species in the included studies.

Reference	Product type	Name or composition	Targeted bacteria
Casanovas-Massana *et al.* (2014)	Probiotic	Toyocerin® (*Bacillus toyonensis BCT-7112T*)	N/S
Lee *et al.* (2021)	Probiotic	Yeast (*Candida famata*) Bacterium (*Lactobacillus plantarum*)	*Escherichia coli*
Huebner *et al.* (2019)	Postbiotic	*Saccharomyces cerevisiae* fermentation product (SCFP)	N/S
Sommer-Lassa *et al.* (2019)	Probiotic	*Saccharomyces cerevisiae* feed additive	N/S
Delaney *et al.* (2021)	Prebiotic	Mannan-rich fraction (MRF)	*Escherichia coli*
Ceccarelli *et al.* (2017)	Probiotic	Intestinal microflora (Aviguard)	Extended-spectrum cephalosporin (ESC)-resistant *Escherichia coli*
Dame-Korevaar *et al.* (2020)	Probiotic Synbiotic	Unselected fermented intestinal bacteria (CEP) Aviguard Fucto-oligosaccharides and *Enterococcus faecium*, *Bifidobacterium animalis*, *Lactobacillus salivarius* (PoultryStar sol; Biomin Holding GmbH, Getzersdorf, Austria)	ESBL/pAmpC-producing *Escherichia coli*
Hofacre *et al.* (2002)	Probiotic	Commercial competitive exclusion	*Escherichia coli* O78:K8 multidrug resistance
Feye *et al.* (2016)	Postbiotic	Novel *Saccharomyces cerevisiae* fermentation prototype (PRT; NaturSafeTM)	*Salmonella Enteritidis*
Roth *et al.* (2017)	Postbiotic	Feed additive (FA) based on formic acid, acetic acid and propionic acid	*Escherichia coli*
Delgado *et al.* (2014)	Synbiotic	Glycerol with FloraMax-B11	*Salmonella Enteritidis*

N/S, not stated.

Discussion

To our knowledge, this study is the first systematic review providing an overview of the different microbiome products targeting antimicrobial resistance in food animals. Unfortunately, only a few studies have been concerned with fighting a specific AMR. Through the systematic search in four screened databases, only 11 studies fit our eligibility criteria. A possible reason is the established inclusion/exclusion criteria of this review. Many of the previously published studies were aimed to find alternatives for the AMs without specifying a certain AMR or focusing on a targeted ARG (Foo *et al.* 2017; Kogut 2017; Cullen *et al.* 2020; Bae *et al.* 2021; Diarra *et al.* 2021). Also, some investigated products fighting certain AMR in bacteria isolated from food animals but were tested *in vitro*, not on food animals. In addition, the English language restriction had been a debatable topic in terms of affecting the search strategies while conducting systematic reviews. Dobrescu *et al.* (2021) reported that English language restriction can

Table 3. Summary of investigated resistance and product effectiveness of microbiome products on animal's health and AMR or ARGs abundance.

Reference	Investigated resistance		Samples intended to evaluate the effects of the products	Outcome measures evaluated	AMR/ARG abundance	Author's conclusions
	Targeted AMR	Targeted ARG				
Casanovas-Massana *et al.* (2014)	Tetracycline Chloramphenicol	*tetM* *cat*	Rumen Colon	N/S	No effect	'The use of the feed additive Toyocerin® did not increase the levels of tetracycline and chloramphenicol-resistant bacteria in the intestinal tracts of piglets and Holstein bulls beyond the contribution directly associated with the introduction of *Bacillus. toyonensis* spores through diet'.
Lee *et al.* (2021)	Ampicillin Chloramphenicol Nalidixic acid Tetracycline	N/S	Whole intestine Yolk Salk Caecal digesta Duodenal Ileal	No effect	No effect	'The accumulation of iron and the genetic element conferring tetracycline resistance may be intertwined.'
Huebner *et al.* (2019)	Aminoglycoside Beta-lactamases Macrolide Tetracycline	*ctx*	Faecal swab	No effect	No effect	'There were no differences in the resistome by treatment group.'
Sommer-Lassa *et al.* (2019)	N/S	*Mef* (EN2) *Lnu* (AN2)	Faecal swab	N/S	Decreased	'Feeding with Saccharomyces cerevisiae feed additive significantly reduced AMR gene read abundances.'
Delaney *et al.* (2021)	N/S	ARGs corresponding to: 1. efflux pumps 2. porins 3. tetracycline 4. glycopeptide 5. beta-lactam 6. aminoglycoside 7. peptide 8. MLSB 9. nucleoside 10. fluoroquinolone 11. diaminopyrimidine	Caecum	Increased	Variable[A]	'The presence of high ARGs in food animals could adversely affect both animal and human health.'
Ceccarelli *et al.* (2017)	Cefotaxime Ciprofloxacin	$bla_{CTX\text{-}M\text{-}1}$	Faecal swab Manure	Increased	Decreased	'The use of competitive exclusion as an intervention strategy to control ESC-resistant *E. coli* in the field.'
Dame-Korevaar *et al.* (2020)	N/S	$bla_{CTX\text{-}M\text{-}1}$	Faecal swab Caecal content	Increased	Decreased	'A prolonged supply of competitive exclusion products, provided shortly after hatch, may be applied as an intervention to reduce the prevalence of *ESBL/pAmpC*-producing bacteria in the broiler production chain.'
Hofacre *et al.* (2002)	N/S	N/S	Small intestine Large intestine Caeca	Increased	Decreased	'The least amount of reduction of colonisation of the challenge *E. coli* by the competitive commercial exclusion was by the direct oral gavage at 2 days of age.'
Feye *et al.* (2016)	Ceftiofur Enrofloxacin Florfenicol	N/S	Faecal swab	Increased	Decreased	'This study revealed that a proprietary Saccharomyces cerevisiae fermentation prototype inhibits the shedding, lymph node carriage, downstream virulence, and antibiotic resistance of *Salmonella* residing in cattle.'
Roth *et al.* (2017)	Ampicillin Cefotaxime Ciprofloxacin Streptomycin	N/S	Caecal	Increased	Decreased	'A significant reduction in total *E. coli* count was not observed in the present study. Therefore, a possible selective effect of a feed additive on resistant *E. coli* should be investigated further.'

(*Continued on next page*)

Table 3. (*Continued*).

Reference	Investigated resistance		Samples intended to evaluate the effects of the products	Outcome measures evaluated	AMR/ARG abundance	Author's conclusions
	Targeted AMR	Targeted ARG				
	Sulfamethoxazol Tetracycline					
Delgado *et al.* (2014)	Nalidixic acid Novobiocin	N/S	Caeca–caecal tonsils (CCT)	Increased	Decreased	'Synergistic effect on dietary supplementation of 5% glycerol combined with FloraMax-B11 in reducing the amount and incidence of *Salmonella* from neonate broiler chickens.'

[A]Different AMR/ARG abundance was reported in the study, varying among an increase, a decrease, and no effects.
N/S, not stated.

slightly affect the estimations and conclusions for most medical topics.

Additionally, there are inconsistent definitions of the term 'food-producing animals'. The WHO defined this term as 'all terrestrial and aquatic animals (that is, includes aquaculture) used to produce food' (World Health Organization 2017). Yet, distinct definitions are used by different countries or regions. For instance, cats, dogs, rats and other wild animals were considered food animals in China before the pandemic of COVID-19 (CMOA 2020). Therefore, more animal species were expected to be in the searching process.

The majority of the included studies were published from 2014 onward. This outcome emphasises how an investigation of the effect of microbiome products on fighting AMR of ARGs is still at a preliminary stage. Therefore, studying the impact of different microbiome products on the AMR or ARGs found in food animals needs further exploration. The United Nations Food and Agriculture Organization (FAO) classified the United States as one of the top food-animal producers (FAO 2021). As such, the findings of this review meet the expectation since most of the included studies were conducted in the USA (36.4%). Moreover, chickens were the most investigated animals in the included studies. Indeed, poultry production is among the widespread industries worldwide (Ma *et al.* 2021*a*). Chicken is one of the most commonly farmed species, with over 90 billion Mg of chicken meat produced yearly (Agyare *et al.* 2018). According to the FAO, more than 10 billion chickens were farmed by China in 2018 alone, and poultry meat production reached more than 100 million chickens globally (FAOSTAT 2018). Thus, special attention has been dedicated by researchers to studying chicken as a food animal.

Interestingly, nearly all the microbiome products of the included studies were tested on animals of a young age. Jackson *et al.* (2017) reported some limitations of using older animals, such as cost and maintaining historical-data comparability. Hence, young animals helped the researcher establish a baseline or control for the experiment, since young aged animals have less microbiome mixture (Jackson *et al.* 2017). Thus, they have less contact with the surrounding environment or other animals and no sexual activities (Xu and Zhang 2021); these factors could affect the microbiome mixture and its levels. As well, younger animals may have less possible antibiotic residues in their bodies (Basulira *et al.* 2019), which can affect the activity of the proposed product tested.

It is worth noting that food animals play a significant role in spreading resistant microorganisms into the environment through their manure and to the final consumer (human) either through their products such as milk or meat or by direct contact with farmworkers (Kumar *et al.* 2021). The prevention of AMR is associated with the One Health concept, which states that human health is related to the health of animals and the environment (Mackenzie and Jeggo 2019).

Xu *et al.* (2022) investigated the most prevalent ARB and ARGs in the farm animals considered a tremendous ARB and ARGs reservoir. They found that most resistance is to β-lactams (*bla*), aminoglycosides (*aac*), tetracyclines (*tet*), sulfonamides (*sul*), macrolide–lincosamide–streptogramin B (MLSB; *erm*), FCA (fluoroquinolone, quinolone, florfenicol, chloramphenicol, and amphenicol; *fca*), vancomycin (*van*), colistin (*mcr*), and multidrugs (*mdr*) (Xu *et al.* 2022). Interestingly, the most commonly used antibiotics in poultry-intensive production are tetracyclines (Mehdi *et al.* 2018). Skarżyńska *et al.* (2020) assessed the AMR epidemiology in different animal species, including farm and wild animals, and found that tetracycline resistance was occurring in almost all tested animals, followed by the resistance to macrolides, aminoglycosides, and β-lactams. Not surprisingly, our findings are comparable with the findings of the previous studies that tetracycline resistance is most targeted, followed by macrolide and beta-lactam resistance in different food animals (Mehdi *et al.* 2018; Skarżyńska *et al.* 2020; Ma *et al.* 2021*a*, 2021*b*; Xu *et al.* 2022). This is in agreement with the most reported antimicrobials used in food-animal production systems, namely, tetracycline, sulfonamides, β-lactams aminoglycoside, and penicillin (Kimera *et al.* 2020; Ma *et al.* 2021*b*). Tetracyclines were the most widely used antimicrobial class in veterinary medicine for decades

(Skarżyńska *et al.* 2020). They represent more than two-thirds of antimicrobials administered in poultry production in the USA (Ma *et al.* 2021*b*).

Escherichia coli and *Salmonella* are the major causes of infections in poultry and other food animals such as cattle (Barrow *et al.* 2012; FDA 2020). For example, *Salmonella* is an important pathogen in chickens, causing septicaemic diseases such as fowl typhoid (FT) and pullorum disease (PD; Shivaprasad 2000). It has been found that *E. coli* and *Salmonella* have several antibiotic-resistant genes isolated from different animal meats and play a major role in AMR dissemination (Feye *et al.* 2016; Lee *et al.* 2021). Additionally, previous studies have shown that cattle and pigs are carriers of pathogenic *E. coli*, such as Shiga toxin-producing *E. coli* (STEC), and are considered pathways for introducing STEC into the environment (FDA 2020). Furthermore, these organisms have been known to acquire resistance through horizontal gene transfer (Frazão *et al.* 2019) With the emergence of AMR, the effectiveness of the AM has decreased, posing a risk to the consumer and a threat to public health (Chaudhary *et al.* 2014; Johar *et al.* 2021).

The bacteria most widely used as probiotics are *Bacillus* spp., *Lactobacillus* spp., *Enterococcus* spp. *Bifidobacterium* spp., and *Streptococcus* spp. (Abd El-Hack *et al.* 2020; Bhogoju and Nahashon 2022). In recent years, probiotic development has evolved away from bacteria and toward other species such as yeasts, such as *Saccharomyces* spp. (Elghandour *et al.* 2020; Ahiwe *et al.* 2021) and *Candida* spp. (Mokhber-Dezfouli *et al.* 2007). Our findings illustrated that *Lactobacillus* had been extensively used in the composition of the microbiome products. Dowarah *et al.* 2017 provided a review on the use of *Lactobacillus* as an alternative to antibiotic growth promoters in pigs. Their main outcomes supported the use of different species of *Lactobacillus* as an effective and safe alternative to antibiotics for swine production due to their high stability *in vivo* (Czerucka *et al.* 2007; Palma *et al.* 2015). Moreover, the present review has demonstrated that *Saccharomyces cerevisiae*, as a probiotic, is commonly used alongside the probiotic bacteria (Table 2). Its common usage is likely to be due to its natural presence in the environment, low cost and natural resistance to many antibiotics. Furthermore, its fermentation products reduced the AMR and food-safety pathogens detected in farm animals' faeces (Huebner *et al.* 2019). Another important fact is that *S. cerevisiae* may not acquire genes as the bacterial probiotics do. Bacterial probiotics are capable of acquiring genes that confer resistance to antibiotics from other bacteria in the host, and pass them on to the bacterial pathogen (Temmerman *et al.* 2003; Mathur and Singh 2005). Hence, *S. cerevisiae* usage might reduce the spread of AMR or ARGs.

It is worth mentioning that bacteriophages have great potential to act as an alternative for antimicrobials. Laird *et al.* (2022) synergised bacteriophages with AMR-free commensal bacteria. They found that this mixture is capable of reducing and possibly eliminating drug-resistant bacteria *in vitro* (Laird *et al.* 2022). This study was included with the full-text screening but failed to meet the inclusion criteria as the product should be tested on food animals (*in vivo* studies). Another similar work that has been recently published demonstrated the effectiveness of using bacteriophages to reduce drug-resistant *Salmonella* colonisation in pigs (Thanki *et al.* 2022).

The potential advantages of feeding microbiome products to food animals is to improve their state of health are of growing interest. On the basis of our findings, it has been demonstrated that an intake of specific microbiome products increases the effectiveness of animals' health. For example, a study conducted by Delaney *et al.* (2021) found that administering mannan-rich fraction (MRF), a prebiotic, to 16 broiler chickens, starting at birth and continuing to approximately 5 weeks of age, altered the microbiota balance. As a positive consequence, the treated broilers showed improvement in growth performance, indicating weight gain and a higher European production efficiency factor. These results are consistent with those of other similar studies (Feye *et al.* 2016; Ceccarelli *et al.* 2017; Roth *et al.* 2017). They may influence higher effectiveness in animal health achieved through a shift in the functional capability of the microbiota during the administration of microbiome products. This agrees with the findings of Al-Shawi *et al.* (2020) and Anee *et al.* (2021). Evidence of improved growth and feed efficiency, reduced mortality, and enhanced health was clearly shown after using probiotics. In their review, Al-Shawi *et al.* (2020) reported several studies that had shown an increase in the growth and production of animals, consequently improving health states. At the same time, Anee *et al.* (2021) discussed the general role of probiotics in poultry and ruminants. Their review showed the positive impact of probiotics in improving growth performance, reducing infection and diseases, and inducing beneficial immune response in poultry. As well as improving body weight and milk production, along with lowering infection and diarrhoea in ruminants. Another advantage of using microbiome products is that they do not leave residues, as antibiotics do, so that they can be a better choice as long-term prophylactics and growth enhancers. The continuous administering of probiotics can result in a maintained high state of the stimulated immune system (Lee *et al.* 2021).

Several studies have confirmed the capability of probiotics to improve animal health and inhibit pathogens. Even though investigations have shown that probiotic effectiveness is uncertain and can be affected by conditions (i.e. environment, sickness, diet), strain-dependent, and transient (Cameron and McAllister 2019). Likewise, probiotics can develop antimicrobial resistance, which can be taken by gene mutations or by horizontal gene transfer (Li *et al.* 2020) gained from the GIT, since it acts as a reservoir for ARGs (Daniali *et al.* 2020). Another issue that has been discussed is the poor quality of some commercial probiotic formulations that contain contamination with other microbes (Jackson *et al*. 2019; Anokyewaa *et al*. 2021). Also, the absence of standardised protocols for *in vitro* and *in vivo* investigations limits the evaluation of the potential of new species and strains, leading to an unclear correlation between the outcomes of both methods (Vinderola *et al*. 2017).

Conclusions

In conclusion, there is a global agreement that people and animal health are at high risk due to antibiotic resistance. Alternative therapies have been developed to reduce the dependence on AM in intensive animal farming. The present review illustrated that using probiotic-containing *Lactobacillus* and *S. cerevisiae* targeting specific AMR/ARGs is promising. Also, we have noticed the apparent gap in the efficacy of microbiome products to fight AMR/ARGs, since data on this topic are limited. Several investigations have targeted food-animal pathogens, but few have battled a specific AMR. Thus, further advanced studies on the effect of microbiome products for combating AMR/ARGs in food animals are needed. Experts from different fields should collaborate to improve the commercial microbiome products and develop novel therapeutics to tackle the ARB problem. Moreover, farmers should decrease or avoid the unnecessary use of antibiotics as a growth promoter in food animals to limit the spread of AMR.

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