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Antibiotic resistance in wild and commercial non-enterococcal Lactic Acid Bacteria and Bifidobacteria strains of dairy origin: An update

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A B S T R A C T

Antibiotic Resistance is a growing concern for public health and global economy. Lactic acid bacteria (LAB) involved in the production of dairy products and commonly present in the agro-zootechnical environment can act as reservoirs of antibiotic resistance genes, acquiring or transferring them to other microorganisms. The review focuses on LAB group of dairy origin (*Lactobacillus*, *Lactococcus*, *Streptococcus*, *Leuconostoc*, *Pediococcus* and *Weissella)* and *Bifidobacterium* genus, considering its large use in dairy industry. We have analyzed data in the last 25 years, highlighting atypical resistance, genetic traits correlated to antibiotic resistance and their ability to be transmitted to other microorganisms; comparative analysis of resistomes was also considered. Differences were observed among wild strains isolated from different regions because of authorized antibiotic use. Commercial strains belonging to *Lactobacillus, Streptococcus* and *Bifidobacterium* currently used for industrial dairy products are frequently resistant to gentamycin, kanamycin, chloramphenicol together with tetracycline. The presence of resistant wild LAB in raw milk products has been significantly reduced as a result of worldwide restrictions on the use of antibiotics in animal husbandry. Transmissible resistances are still present in industrial cultures, despite the great effort of starter industries in the process control and the safety screening of commercial cultures.

1. General introduction

Antibiotic resistance (AR) is a growing concern for public health and global economy, with the cost of over 50,000 lives per year only in Europe and US. If the problem is not adequately addressed worldwide, it is assumed that by 2050 the presence of resistance would lead to 10 million people dying every year and it would cost trillions of USD to healthcare system (Ojha et al., 2021).

AR phenomenon is represented by the spread of bacterial strains no longer sensitive to antibiotics that has been accentuated and accelerated by the selective pressure exerted by the use and abuse of antibiotics in human and veterinary medicine as well as their use as growth promoters in animal husbandry (Flórez et al., 2016). There are many mechanisms by which the cell can resist to antibiotics (Fig. 1) that can be distinguished in intrinsic and atypical (or acquired). Atypical resistance can be acquired by chromosomal mutation, but the most common mechanisms rely on mobile genetic elements such as plasmids, transposons and integrons (Das et al., 2020) that can be horizontally acquired between different genera, including pathogenic species by conjugation, transformation and transduction.

Over the years, studies on AR have been extended to non-pathogenic microorganisms such as LAB and *Bifidobacterium*, widely used as starter and adjunct cultures to produce many fermented products, besides being naturally associated with animal and vegetable raw materials. Since LAB may also exhibit and transfer antibiotic resistance, fermented food can be a critical dissemination channel leading to the transmission of AR from non-pathogenic bacteria to consumers (Wang and Schaffner, 2011; Wang et al., 2019). Only in recent years the microbiological breakpoints of thirteen antimicrobial molecules have been defined by the EFSA FEEDAP Panel to distinguish resistant LAB and *Bifidobacterium* strains from susceptible ones (EFSA-FEEDAP, 2018). moreover, from the latest EFSA-FEEDAP guidelines (2018) it is recommended to interrogate the whole genome sequences (WGS) with *in silico* method for the presence of antibiotic resistance genes relevant to their use in humans and animals; screening of the whole genome to look for antibiotic resistance genes has the advantage of being rapid and the possibility of identifying similar, but not identical genes (unlike other classical methods such as PCR). The synergy between phenotypic and genotypic methods allows greater

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clarity on the antibiotic resistance profile because a susceptible phenotype may carry silent genes, which are observed with genotyping; despite the inhibition of their expression, these genes could be transferred to other species where they would be activated (Korhonen, 2010).

An overview of the scientific literature from the late 1990s to the present day using "antibiotic resistance" and "lactic acid bacteria" as a search term leads to obtaining a total of 2735 articles, with an increase of published articles by more than ten times from 1995 to 2021 (Fig. 2A), most of which are related to food science technology area (Fig. 2B) (Clarivate - web of science all databases).

In this review, we have summarized the current knowledge on antibiotic resistance and their mechanisms of transmission in wild type and industrial strains of LAB and Bifidobacteria of dairy origin, highlighting the changes that have occurred over time; we have excluded from the study *Enterococcus* genus because it has been extensively studied for its facility to acquire and transmit resistance therefore many species within this genus have been associated with a number of human and animal infections.

Below are reported the available data on antibiotic resistance detected among *Lactobacillus, Lactococcus, Leuconostoc, Pediococcus, Streptococcus*, *Weissella* and *Bifidobacterium* strains of dairy origin.

2. *Lactobacillus*

Lactobacillus genus, comprising more than 260 species, is the largest group among LAB and the most widespread in a variety of foods, mainly dairy products, thus studying antibiotic resistance dissemination within this genus is quite difficult due to its taxonomic complexity (Gueimonde et al., 2013; Zheng et al., 2020). Recently a reclassification of the genus *Lactobacillus* has been proposed by Zheng et al. (2020), leading to the identification of 25 genera. Nevertheless, in this paper, we decided to refer to the taxonomy used up to now for simplicity and effectiveness since all the articles we cited used the previous nomenclature.

2.1. *Antibiotic susceptibility*

Within this genus a great variability about resistance to different classes of antibiotics was observed (Table 1). Most species of *Lactobacillus* show a high level of resistance to glycopeptides (vancomycin and teicoplanin) (Ammor et al., 2007a,b), and resistance to vancomycin is the best characterized intrinsic resistance in lactobacilli (Goldstein et al., 2015; Colautti et al., 2022).

Regarding other cell wall synthesis inhibitors like β-lactam antibiotics, lactobacilli are usually sensitive to penicillins (such as penicillin G, ampicillin and oxacillin). However, several studies have shown atypical resistance to this group of antibiotics. One strain of *L. plantarum* isolated from Karst ewe's cheese by Čanžek Majhenič et al. (2007) and one strain of *L. rhamnosus* isolated from traditional Italian cheese Valtellina Casera (Morandi et al., 2015), as well as one *L. helveticus* from Chinese fermented milk (Guo et al., 2017) were resistant to Penicillin G. Moreover, one out of 46 *Lactobacillus* isolated from raw milk cheeses in Spain (Rodríguez-Alonso et al., 2009) was resistant to both penicillin G and oxacillin. It is worth highlighting that resistance to β-lactams was also observed within industrial cultures: most of the *L. bulgaricus* strains isolated from Chinese yogurts by Zhou et al. (2012) were resistant to penicillin G and ampicillin, as well as *Lactobacillus* strains isolated from both dairy and pharmaceutical Egyptian products (Gad et al., 2014). Moreover, seven strains of *L. bulgaricus* recently isolated from commercial fermented dairy products were resistant to ampicillin (Yang and Yu, 2019) and different studies highlighted resistance to both oxacillin and cephalosporins, specifically in wild strains isolated from dairy products (Danielsen and Wind, 2003; Coppola et al., 2005; Belletti et al., 2009).

Resistance to bacitracin varies greatly within the genus *Lactobacillus*; all 46 isolates of *Lactobacillus* from Galician artisanal cheeses were susceptible to bacitracin (Rodríguez-Alonso et al., 2009), as well as all *Lactobacillus* strains from fermented food analyzed by Nawaz et al.

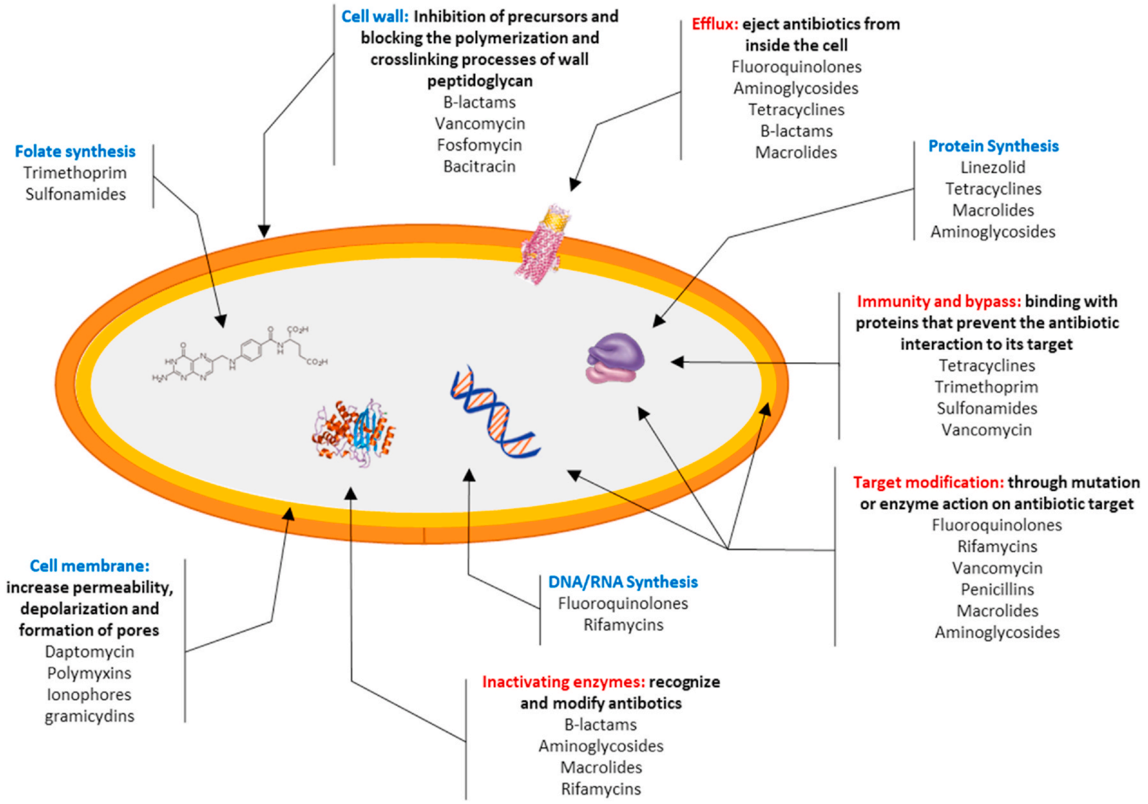

Fig. 1. Antibiotics targets (blue) and mechanisms by which the cell can resist to antibiotics (red). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

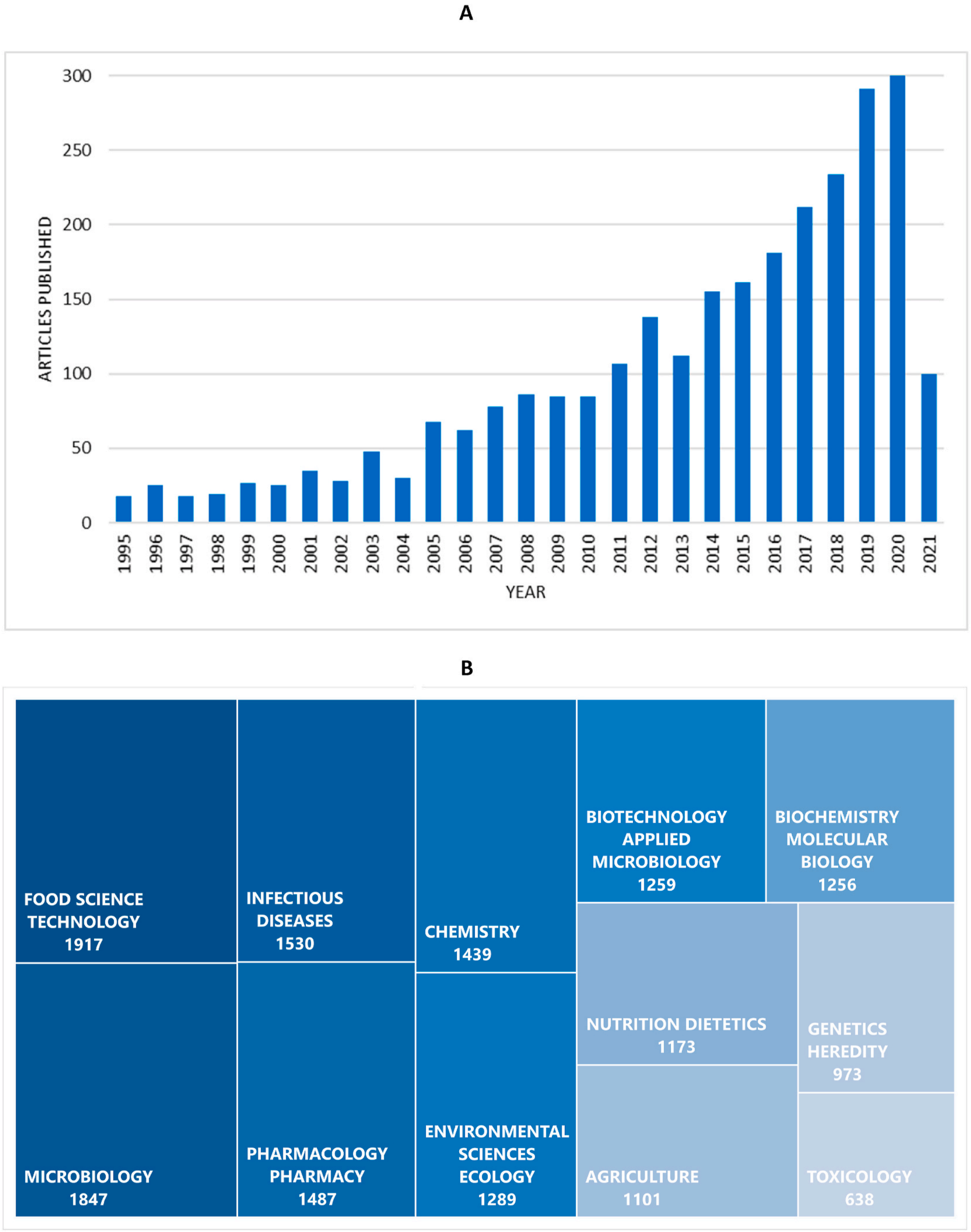

Fig. 2. A Articles on antibiotic resistance (Source: web science all databases, 1995–2021; update to June 25, 2021). Fig. 2B Articles published about antibiotic resistance within LAB (A) and related distribution in the main research areas (B) (Source: web science, 1995–2021; update to June 25, 2021).

(2011), nevertheless, two *L. plantarum* strains highly resistant to bacitracin have been identified in marketed foods and drug additives in China (Liu et al., 2009).

Concerning antibiotics inhibiting the synthesis of proteins, *Lactobacillus* genus tends to be resistant to aminoglycoside like kanamycin, streptomycin and gentamycin, but a great variability among lactobacilli species has been observed (Table 1). Resistance to gentamycin was occasionally detected in many species. Some studies reported a high prevalence of *L. casei* and *L. plantarum* strains resistant to gentamycin (Zhou et al., 2005; Liu et al., 2009; Nawaz et al., 2011; Anisimova and Yarullina, 2019; Yang and Yu, 2019). In contrast, other authors found that all *L. casei* and *L. plantarum* strains were susceptible to gentamycin (Hummel et al., 2007; Basbülbül et al., 2015; Guo et al., 2017). Resistance to kanamycin and streptomycin were identified also in new probiotic *L. plantarum, L. rhamnosus* and *L. acidophilus* strains (Zhou et al., 2005), as well as in *Lactobacillus* isolated from Spanish artisanal raw milk cheeses (Rodríguez-Alonso et al., 2009), along with *L. casei, L. plantarum* and *L. helveticus* strains from traditional dairy products in China (Guo et al., 2017), in *Lactobacillus* strains isolated from an Italian traditional raw milk cheese (Morandi et al., 2015) and in *L. casei* and *L. fermentum* strains isolated from Mozzarella cheese (de Souza et al., 2019). All species (*L. acidophilus, L. rhanmosus, L. casei, L. johnsonii, L. reuteri*, *L. delbrueckii* subsp. *bulgaricus)* except for *L. plantarum*, isolated from fermented milk and yogurt by Temmerman et al. (2003), showed resistance to kanamycin as well as all the 22 strains from probiotics, dairy products and fermented plants tested by Anisimova and Yarullina

Table 1
Overview of studies considering both antibiotic resistance phenotypes and resistance determinants within LAB group.

Microorganism		Antibiotic resistance		References
Genus	Species	Phenotypic resistance	Detected genes	
Lactobacillus	*acidophilus*	GEN, KAN, NEO, STR, FUS, NAD	–	Zhou et al. (2005)
	brevis	VAN, TET, CLI	–	Coton et al. (2018)
	buchneri	VAN, TET, CHL	*tetK*	Coton et al. (2018) Anisimova & Yarullina (2019)
	bulgaricus	AMP, PENG, TET, CHL, GEN, KAN, NEO, STR, VAN, STR, CIP, SMX	*tetM, ant(6), aph(3′)-IIIa, sulI, aac(6′)-aph(2″)*	Zhou et al. (2012) Yang and Yu (2019)
	casei	VAN, TET, RIF, KAN, CIP, TMP	*vanX, gyrA, ermB, vanE, rpoB*	Guo et al. (2017)
	helveticus	CHL, RIF, AMP, VAN, TET, CHL, KAN, STR, CIP, TMP, ERY, VAN, TET	*aph(3″)-III, gyrA, dfrD, vanX, ermB, tetW*	Fortina et al. (1998) Guo et al. (2017) Cho et al. (2018)
	paracasei	ERY, TET	*tetM, tetW, ermB*	Comunian et al. (2010)
	plantarum	PENG, VAN, AMK, GEN, CIP, SMX/TMP, RIF, KAN, STR, CIP	*vanX, tetL, parC, aadE, mefA*	Canžek Majhenic et al., 2007 Anisimova & Yarullina (2019)
	reuteri	PENG, VAN, TET, CHL, KAN	*tetM* *cat*	Lin et al. (1996) Temmerman et al. (2003)
	rhamnosus	CEP, VAN, GEN, NEO, SMX/TMP	–	Coppola et al. (2005)
	salivarius	ERY, STR; CIP	–	Hummel et al. (2007)
Lactococcus	*garvieae*	VAN, KAN, TET, OX	*tetM, tetS*	Fortina et al. (2007) Morandi et al. (2015)
	lactis	ERY, TET, CLI, NIT, AMP, STR	*aac(6′)-Ie-aph(2′)-Ia* *tetM, ermB* *tetS, strA, strB*	Wang et al. (2006) Walther et al. (2008) Devirgiliis et al. (2009) Vahabzadeh and Özpinar, 2018 Morandi et al. (2015)
	lactis subs. *cremoris*	TET, GEN, KAN, STR, TMP	*tetM, tetS*	Fernández et al. (2011) Zycka-Krzesinska et al. (2015)
Leuconostoc	*citreum*	OX, VAN, CIP, NIT	*tetL, tetM*	Morandi et al. (2013)
	lactis	OX, VAN, CHL, STR, CIP, NIT	*tetM, tetS*	Morandi et al. (2013)
	mesenteroides	VAN, TET, CLI, PENG, OX, ERY, CHL, RIF, STR, CIP, NIT	*tetL, tetM, tetS*	Flórez et al. (2005) Morandi et al. (2013) Morandi et al. (2015)
	mesenteroides subsp. *mesenteroides*	VAN, NAD, SMX, TMP	–	de Paula et al., 2015
	pseudomesenteroides	OX, VAN, CHL, RIF, STR, CIP, NIT	*tetM*	Morandi et al. (2013)
	mesenteroides	NAD, CM, TET, NEO, NO, STR, OX	–	Akpinar and Yerlikaya (2021)
	Leuconosto spp.	PENG, OX, VAN, SPE, KAN, STR	–	Rodríguez-Alonso et al., 2009
Pediococcus	*acidilactici*	PEN, VAN, TET, CHL, OX, VAN, GEN, STR, CIP	*tetM* *ermA*	Temmerman et al. (2003) de Sant’Anna et al. (2017) Lüdin et al. (2018)
	pentosaceus	VAN, STR, CIP, OX, SMX/TMP	*tetM, vanA, vanC1, tetO, vatE*	Morandi et al. (2015) Cavicchioli et al. (2019)
Streptococcus	*thermophilus*	AMK, GEN, SMX, TMP, PEN, ERY, TET, CHL, KAN, CLI, CIP, NAD, OX, VAN, STR, AMP	*dfrA, tetM, tetS, ermB, sul, sulII*	Wang et al. (2006) Liu et al. (2009) Nawaz et al. (2011) Morandi and Brasca (2012) Morandi et al. (2015) Flórez and Mayo, 2017 Yang and Yu (2019)
Weissella	*confusa*	ERY, VAN, TET, CHL	*vanA*	Basbülbül et al. (2015)
	hellenica	VAN, CHL, TMP	–	Flórez et al. (2016)
	paramesenteroides	AMP, CEP, PENG, ERY, VAN, TET, SMX, TMP	–	Shi et al. (2019)
Bifidobacterium	*animalis subsp. animalis*	TET, GEN, CLI, CIP	–	Xu et al. (2018) Rozman et al. (2020)
	animalis subsp. lactis	TET, GEN, KAN, STR, CIP	*tetW* *ermX*	Van Hoek et al. (2008a) Georgieva et al. (2015) Raeisi et al. (2018) Rozman et al. (2020)
	bifidum	ERY, TET, CHL, GEN, STR, CLI, CIP	*tetW*	Delgado et al. (2005) Moubareck et al. (2005) Georgieva et al. (2015) Raeisi et al. (2018) Xu et al. (2018) Sirichoat et al. (2020)
	breve	TET, GEN, CIP,	–	Raeisi et al. (2018) Xu et al. (2018)
	infantis	ERY, TET	–	Xu et al. (2018)
	lactis	VAN, GEN, KAN, STR, FUS	*tetW*	Zhou et al. (2005) Kastner et al. (2006)
	longum	ERY, VAN, TET, CHL, GEN, CLI, CIP, SMX/TMP	*ermX* *tetW*	Scott et al. (2000) Delgado et al. (2005) Kazimierczak et al. (2006) Liu et al. (2009) Georgieva et al., 2015

(*continued on next page*)

Table 1 (*continued*)

Microorganism		Antibiotic resistance		References
Genus	Species	Phenotypic resistance	Detected genes	
	Bifidobacterium spp.	ERY, VAN, GEN, CIP, SMX/TMP	*tetM* *tetW* *tetL*	Raeisi et al. (2018) Xu et al. (2018) Cao et al. (2020) Flórez et al. (2006) Milazzo et al. (2006) Van Hoek et al. (2008b) Erginkaya et al. (2018) Yasmin et al. (2020) Chopra & Roberts (2001)

Note. Antibiotics abbreviation: AMK, amikacin; CEP, cephalexin; CHL, chloramphenicol; CIP, ciprofloxacin; CM, clindamycin; ERY, erythromycin; FUS, fusidic acid; GEN, gentamycin; NAD, nalidixid acid; NEO, neomycin; NIT, nitrofurantoin; OX, NO, novobiocin; oxacillin; PENG, penicillin G; RIF, rifampicin; SMX, sulfamethoxazole; SMX/TMP, sulfamethoxazole/trimethoprim; STR, streptomycin; TET, tetracycline; TMP, trimethoprim; VAN, vancomycin.

(2019).

Recently, Shani et al. (2021) showed as 37 *L. delbrueckii* subsp. *lactis* out 71 (52.1%) displayed MICs higher than the FEEDAP microbiological cut-off for kanamycin and one (1.4%) streptomycin (EFSA-FEEDAP, 2018).

Resistance to other aminoglycosides like neomycin, spectinomycin and amikacin has been investigated to a less extent than the previous antibiotics. Resistance to amikacin was found in strains from Chinese dairy and pharmacological products by (Liu et al., 2009); almost all strains (16/17) of *L. delbrueckii* subsp. *bulgaricus* from Chinese yogurt showed resistance to neomycin as well as all 63 *L. rhamnosus* strains analyzed by (Zhou et al., 2005). On the other hand, all *L. casei* (n. 11), *L. delbrueckii* (n. 17), *L. helveticus* (n. 13) and *L. plantarum* (n. 11) tested by (Hajimohammadi Farimani et al., 2016) and (Guo et al., 2017), isolated respectively from Iranian and Chinese dairy products, were sensitive to neomycin.

Lactobacillus species are generally susceptible to chloramphenicol, erythromycin, clindamycin, and tetracycline, however, strains resistant to these antibiotics were found. In particular, high-level resistance to chloramphenicol was identified in *L. delbrueckii* subsp. *bulgaricus* and *lactis* from Chinese yogurt (Zhou et al., 2012) and different dairy products (Shani et al., 2021), and resistance to erythromycine was highlighted in *L. paracasei* (Čanžek Majhenič et al., 2007; Holmes et al., 2016), and in *L. casei* from Mozzarella cheese (de Souza et al., 2019). *Lactobacillus* strains resistant to tetracycline were detected in several dairy products (Čanžek Majhenič et al., 2007; Zhou et al., 2012; Morandi et al., 2015; Shani et al., 2021). Resistance to erythromycin among *Lactobacillus* strains was frequently detected in the past, but over the years it seems to have declined and in recent years it has been found only in a few regions (Table 2).

Resistance to tetracycline was found in strains of *L. crispatus*, *L. johnsonii* and *L. plantarum* (Danielsen and Wind, 2003), in *Lactobacillus* spp. isolated from dairy and no-dairy food (Nawaz et al., 2011; Gad et al., 2014; Colautti et al., 2022), in *L. acidophilus*, *L. casei* and *L. reuteri*/*L. fermentum* groups (Klein, 2011), and also in strains isolated from Chinese fermented milk (Guo et al., 2017). Resistance to quinolones in Lactobacilli is related to cell wall structure, permeability, or due to an efflux mechanism (Abriouel et al., 2015a); in addition, other mechanisms have been shown to be involved in the development of resistance to fluoroquinolones in Gram-positive bacteria, like mutations

Table 2
Phenotypic resistance to erythromycin over the years within *Lactobacillus* genus.

Species	n° strains	N° resistant to erythromycin (%)	Food	Origin	Reference
L. acidophilus	13	1 (8%)	Probiotic products	Europe	Temmerman et al. (2003)
L. rhamnosus	24	1 (4%)			
L. casei	29	3 (10%)			
L. plantarum	6	2 (33,3%)			
L. paracasei	8	1 (12,5%)	Raw milk cheese	Slovenia	Canžek Majhenic et al., 2007
L. rhamnosus	1	1 (100%)			
L. salivarius	1	1 (100%)	probiotics	Germany	Hummel et al. (2007)
L. helveticus	35	1 (2,9%)	whey starter coltures	Italy	Belletti et al. (2009)
L. delbrueckii subsp. *lactis*	85	2 (20%)			
L. casei	11	1 (9,1%)	cheese		
L. paracasei	121	7 (5,8%)	cheese, dairy and meat	Italy	Comunian et al. (2010)
L. fermentum	6	0	dairy	Turkey	Basbülbül et al., 2015
L. plantarum	6	0			
L. casei	13	0			
L. delbrueckii subsp. *bulgaricus*	5	0	traditional yogurt	Iran	Hajimohammadi Farimani et al. (2016)
L. delbrueckii subsp. *lactis*	12	0			
L. helveticus	2	0			
Lactobacillus spp.	46	5 (10,9%)	dairy	Turkey	Erginkaya et al. (2018)
L. helveticus	11	0	fermented milk	China	Guo et al. (2017)
L. casei	11	0			
L. plantarum	11	0			
L. plantarum	4	0	fermented goat's milk	Tajikistan	Cho et al. (2018)
L. helveticus	6	1 (16,7%)			
L. delbrueckii	11	0			
L. pentosus	1	0			
L. paracasei	1	0			
L. bulgaricus	31	0	fermented dairy	China	Yang &Yu (2019)
L. plantarum	6	0			
L. paracasei	4	0			
L. acidophilus	2	0			

involving genes encoding DNA gyrase and topoisomerase IV, essential type II topoisomerases necessary for DNA replication, chromosome segregation and DNA compaction in the cell (Anisimova and Yarullina, 2019), explaining the high variability observed within the genus. All the 6 strains of *Lactobacillus* isolated from dairy products by Zhou et al. (2005) where resistant to nalidixic acid (30 μg/disk), differently to what reported by Gad et al. (2014), who found 46 isolates out of a total of 96 highly resistant to this antibiotic (>512 μg/mL). None of the 14 *Lactobacillus* strains isolated from a traditional Italian cheese were resistant to levofloxacin and ciprofloxacin (with one exception for this latter antibiotic for one *L. paracasei* subsp. *paracasei*) (Morandi et al., 2015) whereas about 30% of *Lactobacillus* strains isolated from Turkish fermented dairy products were resistant to ciprofloxacin (Erginkaya et al., 2018); high-resistance to ciprofloxacin (>64 mg/L) has also been detected in *Lactobacillus* species isolated from fermented food by Nawaz et al. (2011), in 22/22 *L. helveticus* and *L. plantarum* from fermented milk analyzed by Guo et al. (2017) and in 19/19 strains from probiotics, commercial dairy products and fermented plant material (except for *L. rhamnosus*) by Anisimova and Yarullina (2019).

2.2. Antibiotic resistance genes

Even though intrinsic resistance to quinolone is related to characteristics such as cell wall structure, permeability and efflux mechanism (Abriouel et al., 2015a; Ojha et al., 2021), *parC* resistance determinants codifying for ciprofloxacin resistance were identified by Anisimova and Yarullina (2019) in strains of *L. plantarum*, *L. brevis* and *L. buchneri*, meanwhile *gyrA* was found by (Guo et al., 2017) in ciprofloxacin-resistant lactobacilli (Table 1), but this gene was not able to be transferred between the donor strains and the recipient *E. faecalis* by filter mating (Guo et al., 2017).

The occurrence of resistance genes within *Lactobacillus* strains was not always associated with phenotypic resistance (Table 3).

Tetracycline resistance genes are the most common and studied in *Lactobacillus* genus (Gueimonde et al., 2013; Das et al., 2020; Colautti et al., 2022); there are several tetracycline resistance determinants, sometimes found in combination (Tables 1 and 3). Tetracycline efflux gene *tetK* was identified in *L. buchneri* (Anisimova and Yarullina, 2019), *tetW* in three strains of *L. helveticus* (Guo et al., 2017) while *tetM* gene was present in several species of *Lactobacillus* (Zhou et al., 2012; Gad et al., 2014). It is worth to underline that *tetM* can potentially be transferred, because this gene was identified by Devirgiliis et al. (2009) in *L. paracasei* within the *Tn916* transposon (Table 4), a conjugative element originally detected in a strain of *E. faecalis*, but its transfer might also occur through others mobile elements as suggested by Morandi et al. (2015). In confirmation of this, Yang and Yu (2019) successfully transferred the *tetM* and *tetS* genes, respectively from a strain of *L. delbrueckii* subsp. *bulgaricus* and one *L. plantarum* to a strain of *Listeria monocytogenes* in a filter mating experiment. Erythromycin resistance transfer from *Lactobacillus* strains to *Listeria* spp. was observed at high frequencies by Toomey et al. (2009a,b) and Transfer of *erm*(B) and multiple *tet* genes from *Lactobacillus* spp. to bacterial pathogens in animal gut was also observed by other authors (Thumu and Halami, 2019).

The *cat* gene, responsible for chloramphenicol resistance, is often located on plasmid associated with *Lactobacillus* (Lin et al., 1996), even though Abriouel et al. (2015) searching for this AR determinant through an *in silico* genome analysis found out the presence of *cat* gene on the chromosome of *L. plantarum* and *L. fermentum* isolated from dairy products. Also, Abriouel et al. (2015a) analyzing the sequences of this resistant trait has come to the conclusion that *cat* genes do not seem to be able to be horizontally transmitted among lactobacilli (from food and non-food) and other bacteria, since no homology was detected between the chromosomally and plasmid encoded *cat* genes. Always Abriouel et al. (2015) searched for *vanZ* gene in genomic DNA sequences of different lactobacilli and showed the presence of this glycopeptide resistance trait in different species isolated from dairy products (Table 4); also in this case the presence of resistant gene for glycopeptides was not due to horizontal transfer.

3. *Lactococcus*

In this context, we have focused on *Lactococcus lactis* because it is the only species involved in technological food processing (Devirgiliis et al., 2013) and on *Lc. garvieae,* which is a zoonotic pathogen (Teuber et al., 1999; Devriese and Pot., 1995; Mofredj et al., 2000; Pitkälä et al., 2004) that can be one of the prevalent species in animal-based products like raw milk cheeses (Lafarge et al., 2004).

3.1. Antibiotic susceptibility

The genus *Lactococcus* is reported to be susceptible to β-lactams (penicillin, ampicillin, amoxicillin, piperacillin, ticarcillin and imipenem), to antibiotics with spectrum on Gram-positive (macrolides, bacitracin, lincomycin, novobiocin, teicoplanin and vancomycin) and to the

Table 3

Detection of resistance genes in susceptible LAB strains.

Species	Food	Origin	Reference	Susceptibilty	Genes detected
L. casei	Fermented milk	China	Guo et al. (2017)	ciprofloxacin	*gyrA*
L. casei				erytromycin	*ermB*
L. casei				rifampicin	*rpoB*
L. helveticus				kanamycin, neomycin	*aph(3″)-III*
L. helveticus				trimethoprim	*dfrD*
L. helveticus				vancomycin	*vanX*
L. helveticus				erytromycin	*ermB*
L. helveticus				tetracycline	*tetW*
L. plantarum				erytromycin	*ermB*
L. plantarum	dairy products		Anisimova and Yarullina (2019)	erytromycin	*ermB*
Lc. garvieae	cow milk	Switzerland	Walther et al. (2008)	erytromycin	*mdtA*
Lc. lactis				gentamycin	*aac(6′)-Ie-aph(2′)-Ia*
Lc. lactis	raw milk curd	Italy	Morandi et al. (2015)	tetracycline	*tetM*
Ln. citreum	raw milk cheese	Italy	Morandi et al. (2013)	tetracycline	*tetL, tetM*
Ln. lactis					*tetM, tetS*
Ln. mesenteroides					*tetL, tetM, tetS*
Ln. pseudomesenteroides					*tetM*
Ln. mesenteroides	raw milk cheese	Italy	Morandi et al. (2015)	tetracycline	*tetM, tetS*
P. pentosaceus	curd	Italy	Morandi et al. (2015)	tetracycline	*tetM*
P. pentosaceus	artisanal cheese		Cavicchioli et al. (2019)	tetracycline	*tetO*
S. thermophilus	starter	unknow	Zarzecka et al. (2022)	tetracycline, chloramphenicol	*tetO, cat*
S. thermophilus	starter	unknow	Zarzecka et al. (2022)	tetracycline, chloramphenicol	*tetM, cat*

Table 4
Genes encoding for antibiotic resistance and their localization.

Species	Genes	Localization	Reference
B. animalis	*tetW*	genomic island	Rozman et al. (2020)
B. longum	*tetQ*	plasmid	Cao et al. (2020)
L. casei	*vanZ*	chromosome	Abriouel et al., 2015a
L. delbrueckii subsp. *bulgaricus*			
L. fermentum			
L. fermentum	*cat*	chromosome	Abriouel et al., 2015a
L. fermentum	*ermB*	Conjugative plasmid	Nawaz et al. (2011)
L. helveticus	*vanZ*	chromosome	Abriouel et al., 2015a
L. paracasei	*tetM*	*Tn916* transposon	Devirgiliis et al. (2009)
L. paracasei	*tetM*	conjugative transposon Tn916	Comunian et al. (2010)
L. plantarum	*cat*	chromosome	Abriouel et al., 2015a
L. plantarum	*vanZ*	chromosome	Abriouel et al., 2015a
L. salivarius	*ermB*	Conjugative plasmid	Nawaz et al. (2011)
L. reuteri	*cat*	plasmid	Lin et al. (1996)
Lc. garvieae	*tetM, Int-Tn*	conjugative transposons Tn1545- Tn916 family	Fortina et al. (2007)
Lc. garvieae	*mdtA*	chromosome	Walther et al. (2008)
Lc. lactis	*tetM*	plasmid	Flórez et al. (2008)
Lc. lactis	*dfrA*	transposon Tn4003 in *St. aureus*	Liu et al. (2009)
Lc. lactis	*tetM*	conjugative transposon Tn916	Zycka-Krzesinska et al. (2015)
Lc. lactis	*tetM*	Plasmid and chromosome	Zycka-Krzesinska et al. (2015)
Lc. lactis	*tetS*	plasmids	Zycka-Krzesinska et al. (2015)
Lc. lactis subsp. *cremoris*	*tetM-tetW, blaZ, cat*	plasmids	Zarzecka et al. (2022)
Lc. lactis	*tetM-tetO*	plasmids	Zarzecka et al. (2022)
Lc. lactis	*tetK, cat*	plasmids	Zarzecka et al. (2022)
Lc. lactis	*tetO, tetW, cat*	plasmids	Zarzecka et al. (2022)
Ln. pseudomesenteroides	*tetM*	conjugative transposon Tn916	Morandi et al. (2013)
Ln. mesenteroides	*tetS ermB*	plasmid	Flórez et al. (2016)
Ln. mesenteroides	*aadE–sat4–aphA-3, (cluster)*	plasmid	Flórez et al. (2016)
P. acidilactici	*tetM, ermA*	conjugative transposon Tn916	Lüdin et al. (2018)
S. thermophilus	*dfrA*	transposon Tn4003 in *St. aureus*	Liu et al. (2009)
S. thermophilus	*ermB*	plasmid	Toomey et al. (2009)
S. thermophilus	*tetS, tetL*	unknown	Morandi et al. (2015)

broad-spectrum antibiotics (rifampicin, spectinomycin and chloramphenicol) (Ammor et al., 2007a,b; Khemariya et al., 2013), but atypical resistance in *Lc. lactis* has been seen to ampicillin in five strains from Turkish cow milk (Vahabzadeh and Özpinar, 2018) and to penicillin G in one strain from Turkish cheese (Kazancıgil et al., 2019); also, *Lc. lactis* shows variability in terms of resistance about erythromycin (Vahabzadeh and Özpinar, 2018).

Concerning antibiotics like tetracycline, cephalothin and nitrofurantoin, resistance is highly variable (Ammor et al., 2007a,b). Resistance to tetracycline was found in six strains of *Lc. lactis* from Swiss milk (Walther et al., 2008), in 43 strains from Italian PDO Mozzarella di Bufala Campana (Devirgiliis et al., 2010) and more recently in strains from Turkish dairy products (Vahabzadeh and Özpinar, 2018), but differently, other studies carried out in recent years showed the absence of this resistance (da Silva et al., 2019; Kazancıgil et al., 2019; Caro et al., 2020). Concerning others aminoglycosides, resistance to amikacin was observed in Chinese fermented milk (Liu et al., 2009) and resistance to streptomycin was identified in strains isolated from several dairy products in the last years (Rasovic et al., 2017; Vahabzadeh and Özpinar, 2018; Caro et al., 2020), whereas all strains from Norwegian dairy products and starters (Katla et al., 2001), Swiss milk (Walther et al., 2008), Italian curd (Morandi et al., 2015) and Polish artisanal products (Zycka-Krzesinska et al., 2015) were susceptible to streptomycin.

Lc. garvieae's antibiotic resistance profile is similar to that of *Lc. lactis*, with exception for two circumstantial studies highlighting a high percentage of strains isolated from Kosovo raw milk that were resistant to vancomycin and chloramphenicol (Mehmeti et al., 2015) and 31 strains from Swiss milk that were resistant to clindamycin (Walther et al., 2008). Given the still low number of studies for this species, it is difficult to overviewing antibiotic resistance changes over the years, and the observed differences appear to be mainly related to the antibiotics allowed in different states.

3.2. *Antibiotic resistance genes*

Several resistance determinants have been found in *Lc. lactis* (Table 1), indeed both *L. lactis* IPLA 31008 and IPLA 31009 were positive for a plasmid associated with a *tetM* gene (Flórez et al., 2008), which was identical to the *tetM* encoded by the conjugative transposon *Tn916*, i.e. a conjugative transposon that has showed the possibility of being transferred between Gram-positive and Gram-negative organisms (Bertram et al., 1991); also Zycka-Krzesinska et al. (2015) found *tetM* gene within the *Tn916* transposon, whereas *tetS* gene was found to be located on plasmids in *Lc. lactis* (Table 4). Moreover, two isolates of *Lc. lactis* from cheese samples possessed the *tetS* and *tetM* genes and the multidrug-resistant plasmid pK214 from *Lc. lactis* K214 was also successfully transformed into *S. mutans* (Wang et al., 2006). Concerning other *tet* determinants, Zarzecka et al. (2022) found *tetK*, *tetW* and *tetO* in different starter coltures belonging to *Lc. lactis* species (Table 4). (2008) suggested that the higher diffusion of *tetM* and *tetS* genes in *Lactococcus* within dairy sector may be related to the fact that tetracycline is frequently used to treat metritis (tetracycline accounts for about 73% of the antibiotic used in utero treatment in Switzerland).

Other antibiotic resistance determinants identified within this species are *strA*, *strB* and *ermB* (Table 1), which confer resistance respectively to streptomycin and erythromycin (Devirgiliis et al., 2010; Vahabzadeh and Özpinar, 2018). Moreover, different *Lc. lactis* strains commonly used as starters harboured genes encoding for aminoglycoside, β-lactams and chloramphenicol resistance (*aph(3′)-IIIa; aac(6′)-Ie-aph(2′)-Ia; blaZ* and *cat*) (Zarzecka et al., 2022) (Table 4). A further potential horizontal gene transfer has been identified by Liu et al. (2009), regarding a gene homologous to *dfrA* of *St. aureus* (associated with trimethoprim resistance), which was carried by one strain of *Lc. lactis*.

A chromosomal inversion underlying genomic plasticity has been shown to confer resistance to high concentrations of spectinomycin in *Lc. lactis* S50 (Kojic et al., 2008) while Alexa (Oniciuc) et al. (2020), considering an approach based on *in silico* screening of antibiotic resistance determinants, found out a large proportion of multidrug-resistant *Lc. lactis* in raw milk samples, due to the presence of the MsbA efflux protein capable to confer resistance to several antibiotics, like erythromycin.

4. *Streptococcus*

Regarding the genus *Streptococcus* we focused on the only species of technological relevance, namely *Streptococcus thermophilus,* which is considered one of the most important starter for the dairy industry.

4.1. Antibiotic susceptibility

Ammor et al. (2007) reported variability in resistance to penicillin G, ampicillin and vancomycin, but in most of the studies analyzed all the strains were sensitive to these antibiotics (Dong et al., 2014; Morandi et al., 2015; Hajimohammadi Farimani et al., 2016; Flórez and Mayo, 2017; Tarrah et al., 2018a, 2018b; Hu et al., 2020). Although in the past *S. thermophilus* was considered sensitive to antibiotics such as chloramphenicol, tetracycline, erythromycin, cephalothin, quinupristin/dalfopristin and ciprofloxacin (Ammor et al., 2007a,b), Tosi et al., (2007) examining 64 strains of *S. thermophilus* isolated from 1948 to 2005 observed abnormal resistance to tetracycline, erythromycin, streptomycin and clindamycin limited to strains isolated after 2004.

Moreover, several strains resistant to these antimicrobials have been recently identified in different countries, i.e., in raw milk cheese from Italy (Morandi and Brasca, 2012; Morandi et al., 2015) and from Spain (Flórez and Mayo, 2017) as well as in commercial yogurt and fermented milk from China (Yang and Yu, 2019).

Furthermore, 31 strains out of the 39 isolated by Yang and Yu (2019) showed resistance to ciprofloxacin, and several among them were also resistant to vancomycin.

4.2. Antibiotic resistance genes

Concerning genes for antibiotic resistance, the *ermB* gene, responsible for erythromycin resistance (Tables 1 and 4), was identified in *S. thermophilus* by Nawaz et al. (2011), whereas none of the common genetic determinants for erythromycin (*ermB* and *ermC*) and vancomycin (*vanA, vanB, vanC1, vanC2, vanC3, vanD, vanE, vanG*) were found by Morandi and Brasca (2012), which instead linked the resistance to tetracycline to *tetS, tetL* and *tetM* genes; it is interesting to note that all isolated strains of *S. thermophilus* from Italian DOP cheeses harbored tetracycline resistance genes (Morandi et al., 2015). Moreover, a substantial percentage of *S. thermophilus* identified as tetracycline and erythromycin resistant from cheese samples were positive for *tetS, tetM and ermB* (Wang et al., 2006).

On the contrary, the occurrence of resistance genes (*tetM*, *tetO* and *cat*) within *S. thermophilus* strains was not always associated with tetracycline and chloramphenicol phenotypic resistance (Zarzecka et al., 2022) (Table 3).

Even if the susceptibility to sulfonamides is not often investigated, traits for resistance to sulfamethoxazole were found in several *S. thermophilus* from yogurt in China (Yang and Yu, 2019).

With regard to horizontal transmission, the concern arises from the fact that plasmids are common within *S. thermophilus* species (Janzen et al., 1992; Mercenier et al., 1994), and a correlation between plasmids and antibiotic resistance was highlighted by Aslim and Beyatli (2004); also, Wang et al. (2006) successfully transferred AR genes to oral pathogen *S. mutans* by natural transformation. Indeed, a good capacity to transfer *ermB* gene (located on plasmid) from *S. thermophilus* to *E. faecalis* was observed *in vitro* using the filter mating method (Toomey et al., 2009a,b) and a gene homologous to *dfrA* located in the transposon *Tn4003* of *St. aureus*, which is associated with trimethoprim resistance, was identified in a strain highly resistant to trimethoprim/sulphamethoxazole by Liu et al. (2009).

5. *Leuconostoc*

5.1. Antibiotic susceptibility

Regarding β-lactams, different species of *Leuconostoc* are sensitive to ampicillin e penicillin G, but several strains resistant to oxacillin belonging to *Ln. citreum*, *Ln. lactis*, *Ln. mesenteroides* and *Ln. pseudomesenteroides* were identified by Morandi et al. (2013) in Italian cheese (Table 1); also, Rodríguez-Alonso et al. (2009) found resistant strains to this antimicrobial from Spanish cheese.

Susceptibility to rifampicin, erythromycin, clindamycin and tetracycline was frequently reported in the past (Swenson et al., 1990; Flórez et al., 2005), but afterwards resistance to these antimicrobials were also found (Table 1): for example Morandi et al. (2013) identified strains of *Ln. mesenteroides* resistant to erythromycin, chloramphenicol and rifampicin; Flórez et al. (2005) found one strain of *Ln. citreum* and one of *Ln. mesenteroides* resistant respectively to chloramphenicol and tetracycline, and five strains of *Ln. mesenteroides* were found resistant by Basbülbül et al. (2015).

Resistance to aminoglycosides results variable. *Leuconostoc* is generally susceptible to ciprofloxacin, but atypical resistance to this antimicrobial was found in one strain of *Ln. citreum* from Spanish cheese (Alegría et al., 2013) and in several strains from Italian cheese by Morandi et al. (2013).

Recently, Akpinar and Yerlikaya (2021) detected in raw milk and kefir grains different *Ln. mesenteroides* strains that were resistant to nalidixic acid, clindamycin, tetracycline, novobiocin, neomycin, streptomycin and polymyxin B (Table 1).

5.2. Antibiotic resistance genes

Concerning the possible dissemination of resistance traits, the transferability of the *ermB* gene from one resistant strain of *Leuconostoc* to *E. faecalis* was demonstrated both *in vitro* and in cheese (Flórez et al., 2016). Also, Morandi et al. (2013) have identified for the first time the presence of the transposon integrase gene (*int* gene) of the *Tn916/Tn1545* family within *Leuconostoc* species, particularly in one strain of *Ln. pseudomesenteroides* (Table 4).

The genome analysis of the flanking regions of AR genes in two strains of *Ln. mesenteroides* was performed by Flórez et al. (2016), observing in one strain the presence of two *orfs* encoding plasmid-replication proteins nearby *ermB* genes, suggesting the association of the resistance gene with a plasmid, and identifying in the second strain a cluster of AR genes (*aadE–sat4–aphA-3*) with an high homology sequence to a cluster previously detected in other microorganisms; moreover nearby this three AR genes it was identified an *orf* which encoded a plasmid-associated replication proteins, suggesting its localization on the plasmid (Flórez et al., 2016).

6. *Weissella*

Weissella genus was recently recognized because previously it was classified under *Leuconostoc* (Fessard and Remize, 2017).

6.1. Antibiotic susceptibility

The knowledge regarding antibiotic resistance is very poor and breakpoints values have not yet been established (Ayeni et al., 2011; EFSA-FEEDAP, 2018). Patel et al. (2012) observed resistance to gentamicin, kanamycin, and norfloxacin in *Weissella* strains of food origin, while Yadav and Shukla (2022) detected kanamycin, tetracycline, ceftazidime, nalidixic acid, vancomycin and penicillin G resistance in *W. paramesenteroides* MYPS5.1 isolated from dairy products.

For other antimicrobial little information is available and often discordant to each other.

6.2. Antibiotic resistance genes

Antibiotic resistance-encoding genes in *Weissella* species were revealed by *in silico* screening of 13 annotated genome sequences by Abriouel et al. (2015b) with regard to daunorubicin, fosfomycin, methicillin, glycopeptide, sulfonamide and tetracycline. It is worthwhile to note that these resistance genes were not present on mobile genetic elements.

7. *Pediococcus*

7.1. Antibiotic susceptibility

Studies on antibiotic resistance profiles in pediococci isolated from dairy products are very limited (Tables 1, 3–5).

Data about rifampicin and clindamycin are too scarce to establish an antibiotic resistance profile.

Also, sensibility to tetracycline is not defined and variable, in fact the 38% of *P. acidilactici* studied by Temmerman et al. (2003) from food supplements and the 80% of the *Pediococcus* species isolated by Basbülbül et al. (2015) from Turkish fermented dairy products were resistant to tetracycline, but other authors did not find any resistance in isolates from dairy products (Abbasiliasi et al., 2012; Morandi et al., 2015; Fguiri et al., 2016; de Sant'Anna et al., 2017; Cui et al., 2018; Cavicchioli et al., 2019). Regarding aminoglycosides, some authors reported full resistance to this class (Tankovic et al., 1993; Temmerman et al., 2003; Hummel et al., 2007), but strains of *P. acidilactici* and *P. pentosaceus* from different dairy sources were susceptible to amikacin, gentamycin, kanamycin, streptomycin and neomycin (Ge et al., 2007; Abbasiliasi et al., 2012; Barbosa et al., 2015; Morandi et al., 2015). *Pediococcus* species are generally susceptible to penicillin G, chloramphenicol and erythromycin (Danielsen et al., 2007), but some exceptions were found: eight out of 10 *P. acidilactici* isolated from Turkish cheese were resistant to chloramphenicol (Basbülbül et al., 2015) and two and three strains of *P. acidilactici* were respectively resistant to penicillin G and chloramphenicol (Temmerman et al., 2003); moreover, one strain of *P. pentosaceus* from Chinese artisanal raw cheese was found resistant to erythromycin (Shi et al., 2019). Recently, *P. acidilactici* resistant to vancomycin and trimethoprim/sulphamethoxazole were isolated from Brazilian artisanal cheese (Todorov et al., 2021). Vancomycin resistance in *Pediococcus* spp. is an intrinsic resistance and should not be compared with plasmid-mediated acquired resistance, met in enterococci or in other lactic acid bacteria species (Zarzecka et al., 2022).

7.2. Antibiotic resistance genes

Genetic markers related to antibiotic resistance need to be investigated more in depth within this genus because information is limited (Tables 1 and 3). However, *tetM* gene was detected in one strain of *P. pentosaceus* isolated from an Italian raw milk cheese (Morandi et al., 2015), while *vanA* and *vanC1*, *vatE* (streptogramin resistance) and *tet*O were amplified for the first time in one *P. pentosaceus* from raw milk cheese (Cavicchioli et al., 2019). Moreover, vancomycin (*vanC1* and *vanC2*), erythromycin (*ermB* and *ermC*), tetracycline (*tetL* and *tetO*) and bacitracin (*bcrB*) determinants were detected in *P. acidilactici* from Brazilian artisanal cheese (Todorov et al., 2021).

An *in silico* analysis made by Lüdin et al. (2018) allowed to identify in one strain of *P. acidilactici* isolated from Swiss Emmental cheese both *tetM* and *ermA* genes. The analysis of the whole genome was particularly useful in this case because it allowed confirming and explaining the phenotypic susceptibility test for this strain, in addition to identifying for the first time in a strain of *P. acidilactici* the co-presence of *tet* and *erm* resistance genes, often found together on transposons of the *Tn916* family.

8. *Bifidobacterium*

8.1. Antibiotic susceptibility

Bifidobacteria are Gram-positive bacteria grouped within the Actinobacteria phylum and although not included in lactic acid bacteria group we have considered this genus given its broad use in dairy industry.

Bifidobacteria are generally considered susceptible to low concentration of β-lactams, Gram positive spectrum antibiotics (macrolides, bacitracin, erythromycin, lincomycin, novobiocin and teicoplanin) and to broad-spectrum antibiotics like rifampicin, spectinomycin and chloramphenicol (Delgado et al., 2005; Moubareck et al., 2005; Zhou et al., 2005; Masco et al., 2006). However, exceptions were found by Xu et al. (2018) that identified three strains of *B. longum* and one of *B. bifidum* resistant to chloramphenicol and one of *B. infantis* resistance to erythromycin; also Erginkaya et al. (2018) identified one strain of *Bifidobacterium* from Turkish dairy products resistant to erythromycin, whereas resistance to clindamycin and rifampicin were reported respectively in two strains of *B. animalis* subsp. *animalis* (Rozman et al., 2020) and in one strains of *Bifidobacterium* from camel milk (Yasmin et al., 2020).

However, some authors reported susceptibility for aminoglycosides: none of the strains analyzed by Georgieva et al. (2015) were resistant to gentamycin and streptomycin and only three out of 15 strains of *Bifidobacterium* studied by Erginkaya et al. (2018) and only few strains isolated by Xu et al. (2018) were resistant to gentamycin. Furthermore, Bifidobacteria are resistant to metronidazole and Gram-negative spectrum antibiotics, such as fusidic acid, nalidixic acid and polymyxin B (Charteris et al., 1998; Delgado et al., 2005; Moubareck et al., 2005; Zhou et al., 2005; Masco et al., 2006). Concerning quinolones and fluorochinolones several authors reported, over the years, high resistance to this class of antimicrobials for different *Bifidobacterium* species (Zhou et al., 2005; Moubareck et al., 2005; Milazzo et al., 2006; Raeisi et al., 2018; Yasmin et al., 2020).

Bifidobacterium species seem to be susceptible to vancomycin with some exceptions: nine strains out of 15 isolated from traditional Turkish dairy products were resistant to vancomycin (Erginkaya et al., 2018), as well as one strain of *B. longum* isolated from nutritional health food and dairy products from Japan (Xu et al., 2018) and one strain of probiotic *B. lactis* from China (Zhou et al., 2005). Furthermore, species-related variability was reported by many, especially for resistance to tetracycline (Matteuzzi et al., 1983; Delgado et al., 2005; Masco et al., 2006; D'Aimmo et al., 2007); in fact all strains of *B. animalis* subsp. *lactis* isolated from fermented milk products in UK were resistant to tetracycline (Raeisi et al., 2018) and also several isolates found by Delgado et al. (2005), Xu et al. (2018) and Rozman et al. (2020), but none of the eight *Bifidobacterium* isolated by Yasmin et al. (2020) showed resistance to this antibiotic, as well as the 15 strains analyzed by Erginkaya et al. (2018). Milazzo et al. (2006) identified three strains of *Bifidobacterium* highly resistant to trimethroprim/sulfametoxazole, but bifidobacteria were generally reported to be susceptible to these antibiotics (Erginkaya et al., 2018; Raeisi et al., 2018; Xu et al., 2018).

8.2. Antibiotic resistance genes

The spread of resistance genes has not been deepened in Bifidobacteria and information are limited to tetracycline and macrolides (Gueimonde et al., 2013); specifically, the tetracycline resistance traits (*tet* genes), which protect ribosomes from the action of this antibiotic, have been frequently found in *Bifidobacterium* genus (Scott et al., 2000; Ammor et al., 2007; Gueimonde et al., 2010). The common genes identified are *tetW* (Scott et al., 2000; Moubareck et al., 2005; Flórez et al., 2006; Kastner et al., 2006; Kazimierczak et al., 2006; Masco et al., 2006; Raeisi et al., 2018; Sirichoat et al., 2020) and *tetM* (Lacroix and Walker, 1995; Chopra and Roberts, 2001), but also *ermX* and *tetL* were

Table 5
Studies reporting phenotypic resistance to the antimicrobials most relevant to their use in humans and animals according to EFSA-FEEDAP, 2018.

Genus	Ampicillin	Vancomycin	Gentamicin	Kanamycin	Streptomycin	Erythromycin	Clindamycin	Tetracycline	Chloramphenicol	Ciprofloxacin
Lactobacillus	China (Zhou et al., 2012) Egypt (Gad et al., 2014) China (Guo et al., 2017) China (Yang and Yu, 2019)	IR	Zhou et al. (2005) Italy (Coppola et al., 2005) Hummel et al. (2007) China (Liu et al., 2009) Italy (Belletti et al., 2009) China (Zhou et al., 2012) China (Dong et al., 2014) Egypt (Gad et al., 2014) Turkey (Erginkaya et al., 2018) China (Yang and Yu, 2019) most Russia (Anisimova and Yarullina, 2019)	Italy (Fortina et al., 1998) Europe (Temmerman et al., 2003) Zhou et al. (2005) China (Zhou et al., 2012) Bulgaria (Georgieva et al., 2015) Iran (Hajimohammadi Farimani et al., 2016) China (Guo et al., 2017) Coton et al. (2018) most Russia (Anisimova and Yarullina, 2019)	Italy (Fortina et al., 1998) Zhou et al. (2005) Hummel et al. (2007) China (Zhou et al., 2012) Egypt (Gad et al., 2014) Iran (Hajimohammadi Farimani et al., 2016) China (Guo et al., 2017) Tajikistan (Cho et al., 2018) Coton et al. (2018) most Russia (Anisimova and Yarullina, 2019) China (Yang and Yu, 2019)	Europe (Temmerman et al., 2003) Slovenia (Canžek Majhenic et al., 2007) Italy (Belletti et al., 2009) Italy (Comunian et al., 2010) Egypt (Gad et al., 2014) Coton et al. (2018) Turkey (Erginkaya et al., 2018)	Italy (Belletti et al., 2009) Bulgaria (Georgieva et al., 2015) Egypt (Gad et al., 2014) Coton et al. (2018)	Europe (Temmerman et al., 2003) Slovenia (Canžek Majhenic et al., 2007) Italy (Comunian et al., 2010) China (Zhou et al., 2012) Egypt (Gad et al., 2014) Turkey (Basbülbül et al., 2015) Iran (Hajimohammadi Farimani et al., 2016) China (Guo et al., 2017) Turkey (Erginkaya et al., 2018) Tajikistan (Cho et al., 2018) Coton et al. (2018) China (Yang and Yu, 2019)	Italy (Fortina et al., 1998) Europe (Temmerman et al., 2003) China (Zhou et al., 2012) Bulgaria (Georgieva et al., 2015) Turkey (Basbülbül et al., 2015) China (Guo et al., 2017) Coton et al. (2018) China (Yang and Yu, 2019)	Hummel et al. (2007) China (Liu et al., 2009) Egypt (Gad et al., 2014) China (Guo et al., 2017) Turkey (Erginkaya et al., 2018) most Russia (Anisimova and Yarullina, 2019) China (Yang and Yu, 2019)
Lactococcus lactis	Turkey (Vahabzadeh and Özpinar, 2018)		IR	IR	Rasovic et al. (2017) Turkey (Vahabzadeh and Özpinar, 2018) Mexico (Caro et al., 2020)	Walther et al. (2008) Italy (Devirgiliis et al., 2010) Rasovic et al. (2017) Turkey (Vahabzadeh and Özpinar, 2018) Mexico (Caro et al., 2020)	Walther et al. (2008) Mexico (Caro et al., 2020)	Spain (Flórez et al., 2005) Walther et al. (2008) Italy (Devirgiliis et al., 2010) Poland Zycka-Krzesinska et al. (2015) Turkey (Vahabzadeh and Özpinar, 2018)		Mexico (Caro et al., 2020)
Streptococcus thermophilus	China (Zhou et al., 2012) China (Yang and Yu, 2019)	Europe (Temmerman et al., 2003) Italy (Morandi and Brasca, 2012)	IR	IR	IR	Europe (Temmerman et al., 2003) Most in Italy (Tosi et al., 2007)	Most in Italy (Tosi et al., 2007) China Nawaz et al. (2011)	Europe (Temmerman et al., 2003) Most in Italy (Tosi et al., 2007)	Europe (Temmerman et al., 2003) China (Nawaz et al., 2011)	China (Nawaz et al., 2011) China (Yang and Yu, 2019)

(*continued on next page*)

Table 5 (*continued*)

Genus	Ampicillin	Vancomycin	Gentamicin	Kanamycin	Streptomycin	Erythromycin	Clindamycin	Tetracycline	Chloramphenicol	Ciprofloxacin
		China (Yang and Yu, 2019)				Italy (Morandi and Brasca, 2012) China (Dong et al., 2014) Spain (Flórez and Mayo, 2017) China (Yang and Yu, 2019)	China (Dong et al., 2014) Spain (Flórez and Mayo, 2017)	China (Nawaz et al., 2011) China (Zhou et al., 2012) Italy (Morandi and Brasca, 2012) Spain (Flórez and Mayo, 2017) China (Yang and Yu, 2019)	China (Zhou et al., 2012) Italy (Morandi and Brasca, 2012) Spain (Flórez and Mayo, 2017) China (Yang and Yu, 2019)	
Leuconostoc	Coton et al. (2018)	IR	Hummel et al. (2007)	Spain (Rodríguez-Alonso et al., 2009) Italy (Flórez et al., 2016) Coton et al. (2018)	Norway (Katla et al., 2001) Hummel et al. (2007) Spain (Rodríguez-Alonso et al., 2009) Italy (Morandi et al., 2013) Italy (Flórez et al., 2016)	Italy (Morandi et al., 2013) Italy (Flórez et al., 2016)	Spain (Flórez et al., 2005) Italy (Flórez et al., 2016)	Spain (Flórez et al., 2005) Italy (Flórez et al., 2016)	Spain (Flórez et al., 2005) Italy (Morandi et al., 2013) Turkey (Basbülbül et al., 2015) Italy (Flórez et al., 2016)	Norway (Katla et al., 2001) Hummel et al. (2007) Italy (Morandi et al., 2013) Spain (Alegría et al., 2013) Italy (Flórez et al., 2016)
Weissella	China (Shi et al., 2019)	IR		Nigeria Ayeni et al. (2011)	Nigeria Ayeni et al. (2011)	Turkey (Basbülbül et al., 2015) China (Shi et al., 2019)		Turkey (Basbülbül et al., 2015) China (Shi et al., 2019)	IR	
Pediococcus		IR	Brasil de Sant'Anna et al. (2017) China Cui et al. (2018)		Italy (Morandi et al., 2015) Brasil de Sant'Anna et al. (2017)	China (Shi et al., 2019)	China (Shi et al., 2019)	Europe (Temmerman et al., 2003) Barbosa et al. (2015) Turkey (Basbülbül et al., 2015) China (Shi et al., 2019)	Europe (Temmerman et al., 2003) Turkey (Basbülbül et al., 2015)	IR
Bifidobacterium		Zhou et al. (2005) China (Xu et al., 2018) Turkey (Erginkaya et al., 2018)	Zhou et al. (2005) China (Liu et al., 2009) Turkey (Erginkaya et al., 2018) UK (Raeisi et al., 2018) China (Xu et al., 2018) UK (Raeisi et al., 2018) Pakistan (Yasmin et al., 2020)	Zhou et al. (2005) UK (Raeisi et al., 2018) Pakistan (Yasmin et al., 2020)	Zhou et al. (2005) UK (Raeisi et al., 2018) Pakistan (Yasmin et al., 2020) Thailand (Sirichoat et al., 2020)	Spain (Delgado et al., 2005) China (Xu et al., 2018) Turkey (Erginkaya et al., 2018)	Spain (Delgado et al., 2005) Rozman et al. (2020)	Spain (Delgado et al., 2005) China (Xu et al., 2018) UK (Raeisi et al., 2018) Rozman et al. (2020)	China (Xu et al., 2018)	Turkey (Erginkaya et al., 2018) UK (Raeisi et al., 2018) Rozman et al. (2020)

Note. Industrial strains = dark grey, wild strains = white, both wild and industrial strains = light grey.
IR=Intrinsic Resistance.

identified by van Hoek et al. (2008a; 2008b). Although conjugative plasmids are rare in *Bifidobacterium* (Ammor et al., 2007a,b), attention must be paid to other mobile genetic elements, such as transposon, in fact the *tetW* gene, which was found in *B. longum* and *B. animalis* subsp. *lactis,* seems to be located in the chromosome and surrounded by transposase target sequences or genes coding for transposases (Kazimierczak et al., 2006; Gueimonde et al., 2010, 2013). Despite Raeisi et al. (2018) have seen that *tetW* did not transfer from *B. animalis* subsp. *lactis* to *Enterococcus* species, the possibility to transfer tetracycline resistance traits from *Bifidobacterium* to non-GRAS microorganisms requires further investigation.

An *in silico* screening for *tetW* gene performed by Rozman et al. (2020) on 430 bifidobacteria's genomes has shown the presence of this gene higher than 30%, moreover all the genomes available of *B. animalis* subsp. *lactis* were positive for *tetW* (Table 4). Tetracycline resistance is so widespread among bifidobacteria because of its consumption in animals and human, in fact the average consumption of tetracycline in 2014 in Europe was 3,6 and 50,6 mg/kg respectively for humans and food-producing animals (ECDC/EFSA/EMA, 2017). Also, in almost all of the strains of *B. animalis* subsp. *lactis* and *B. animalis* not designated to subspecies (*lactis* or *animalis*) the same study identified a homologous genomic island associated with the *tetW* gene and a transposase. This means, a probably ancient co-evolution between the genomic island and the ancestral bacterial host (Guo et al., 2012), and even though it was not proved the horizontal transferability of the *tetW* between *B. animalis* subsp. *lactis* and other species, it can not be excluded (Rozman et al., 2020).

Another *in silico* genotype investigation made by Cao et al. (2020) has led to the identification of *tetW* and *ermX* as the most prevalent resistance genes in *Bifidobacterium* genus, particularly in *B. animals* and *B. longum,* respectively. The scattered distribution of *tetW* and *ermX* from the phylogenetic tree analysis may explain the diffusion of *tetW* genes among different genera, whereas *ermX* genes were mainly clustered into two groups far apart, suggesting that *ermX* genes seem to have a relatively more limited host range.

9. Discussion

Food and food production may be a vehicle of antibiotic resistant bacteria and antibiotic resistance genes to humans resulting in a public health impact.

LAB are naturally present on dairy farm environment and wild type strains are found in high numbers in raw milk fermented products. Therefore, they may colonize host gastrointestinal tract becoming a potential vehicle of antibiotic resistant bacteria to humans. In addition, they can transmit genes encoding antibiotic resistance to pathogenic microorganisms present in the human gut.

The transmission of antibiotic resistance genes between foodborne LAB strains and pathogenic microorganisms has been well documented (Feld et al., 2009; Nawaz et al., 2011; Zarzecka et al., 2022).

In addition, they can transmit genes encoding antibiotic resistance to pathogenic microorganisms present in the human gut since the gastrointestinal tract may comprise a more favourable environment for antibiotic resistance exchange than conditions provided *in vitro* (Feld et al., 2008). Confirming this, Jacobsen et al. (2007) showed *in vivo* transfer of wild-type antibiotic resistance plasmids (tetracycline and erythromycin) from *L. plantarum* isolated from Belgian fermented dry sausages to *E. faecalis* JH2-2, which represents a natural inhabitant of the human gut and a pathogenic species (Jacobsen et al., 2007).

On the other hand, at industrial level, selected LAB strains are intentionally inoculated to produce milk-based fermented products such as fermented milk, yogurt and cheese, thus they are consumed in significant numbers by consumers. Moreover, their use as bioprotective cultures is considered a worthwhile alternative to antibiotics in livestock production since they can be useful to inhibit zoonotic pathogens thanks to their effects on pH values, their production of bacteriocin or other inhibitory substances (Gálvez et al., 2010; Castellano et al., 2017).

Antibiotic resistance genes in these bacteria intended for beneficial applications for both human and animal consumption thus represent a significant avenue for AR dissemination. So, to monitoring the prevalence of antibiotic resistance strains among both wild type LAB of dairy origin and selected cultures intentionally used in dairy productions becomes essential.

The traits of resistance started to be researched within dairy LAB only from the first decade of the 21st century, probably due to lack of analytical procedures and because the problem of the spread of antibiotic resistance was not as urgent as it is today. Moreover, LAB have been considered for a long time just for their beneficial traits, and only in 2005 Luo et al., for the first time, illustrated the potentially key role of commercial starter culture in the spread of antibiotic resistance genes through the food chain. It is more and more frequently reported that strains generally recognized as safe like microorganisms intentionally added to food (starters) or probiotics may acquire antibiotic resistance determinants and transfer them horizontally to other strains (Rozman et al., 2020). Actually, a recent study confirmed the possibility of resistance genes transfer from commercially available starter and protective cultures under both *in vitro* and *in situ* conditions (Zarzecka et al., 2022). Thus, although these bacteria are not pathogenic and do not directly constitute a risk to consumers, they can act as environmental reservoirs of antibiotic resistance genes, making the food chain one of the main routes of transmission of antibiotic resistance across bacterial populations. In addition, during food production and storage starter cultures are exposed to different stress factors, which may extend the profile of antibiotic resistance (Zarzecka et al., 2020).

Moreover, it should be considered that analytical protocols for the evaluation of the antibiotic resistance of LAB have been indicated at European and international level only in the last 10 years. The International Standard ISO10932:2010 IDF223:2010 focuses on the determination of the MIC of antibiotics applicable to Bifidobacteria and non-enterococcal LAB and considers all the factors that may affect the results, primarily the composition of the growth medium, but also the inoculum size, growth conditions (i.e., temperature, time and composition of the atmosphere). Moreover, recently EFSA (2013) has published a document with reference cut-off values to discriminate a resistant strain from a sensitive one, periodically updated (EFSA-FEEDAP, 2018). It is further important to mention that strains prone to horizontal gene transfer, even susceptible to antibiotics during screening, can still be involved in transmitting antibiotic resistance genes as intermediate and even facilitator (Luo et al., 2005).

In addition, the importance of the surveillance of antibiotic resistance in strains deliberately used as feed additives or as production organisms has been brought to the attention of European countries by the EFSA document of 2018, which recommends the analysis of the WGS in addition to the phenotypic profile of resistance to check the presence of AMR genes.

The studies examined in this paper indicate in the last two decades a substantial stability and in some cases an improvement (i.e., erythromycin) in the spread of antibiotic resistance among wild LAB of dairy origin, but it is worth making some considerations.

The reported resistance trend over time confirms the usefulness of the actions taken in recent years by many states to reduce the use of antibiotics in animal husbandry. In fact, in EU countries the level of antibiotic use has changed significantly since 2006 when the European Commission has banned the use of antibiotics on farms for non-therapeutic purposes and has recently drawn up guidelines for their proper use (EMA Committee for Medicinal Products for Veterinary Use and EFSA Panel on Biological Hazards, 2017).

Likewise, the World Health Organization (WHO) has recommended the "complete restriction of the use of antibiotics in animals to promote growth or prevent disease in the absence of diagnosis" and the Food and Drug Administration (Food and Drug Administration, U. S., 2012) has approved antibiotics in food animals only for disease treatment, control and prevention; more recently also China, the world's leading consumer of antibiotics in livestock animals, in 2017 adopted a national plan to reduce antibiotics use in animal feed (Xiao and Li, 2016). In addition, it is important to highlight that the major starter culture companies have been implemented a systematic screening and removal of antibiotic resistant strains from commercial starter cultures from their product line.

Considering the antimicrobials most relevant to their use in humans and animals (EFSA-FEEDAP, 2018), we can summarize that most of the resistances have been found in commercial strains belonging to *Lactobacillus*, *Streptococcus* and *Bifidobacterium* used for the manufacturing of products such as yogurt and fermented milk, as well as in probiotic microorganisms (Table 5); specifically, regardless of genus, the strains of industrial interest are frequently resistant to gentamycin, kanamycin, chloramphenicol together with tetracycline. Even in the last five years acquired resistances have been found in lactobacilli to all 10 antibiotics indicated by EFSA except for clindamycin (Table 5). Similarly, *S. thermophilus* strains resistant to ampicillin, vancomycin, erythromycin, tetracycline, chloramphenicol and ciprofloxacin and currently used as starter in dairy industry have been observed as well as bifidobacteria resistant to antibiotics normally effective on this genus such as vancomycin, chloramphenicol and erythromycin. No acquired resistance was pointed out for *Lc. lactis.* Most of the resistant strains have been isolated from products commercialized in countries that only recently have implemented policies to combat antibiotic resistance, unlike European countries where most phenotypic resistances have been identified in wild type strains isolated from artisanal products, often confined to a specific geographical area, thus representing a lower risk for the spread of antibiotic resistance compared to industrial products.

With regard to *Lactobacillus* genus there has been a gradual decrease in the presence of erythromycin-resistant strains over the years, and it was only rarely found after 2010 in specific geographical regions (Table 2), highlighting that the restrictions in the use of antibiotics in animal husbandry are different at the national level (Carlet et al., 2014). Anyway, data confirm the effectiveness of the efforts made at the international level and specifically the limitation for the use of antibiotics in livestock farms and the development of a list of critically important antibiotics (World Health Organization, 2017) including erythromycin.

In some cases, the target antibiotic gene was not detectable even if the MICs values were higher than the reference cut-off values. On the other hand, it is frequent to find resistance determinants within strains that have been reported susceptible to an antibiotic (Table 3). These conflicting results could be the consequence of the lack of standardization in testing methods for LAB or lack of expression for the resistance genes by the strain under examination (Morandi et al., 2015; Guo et al., 2017).

As previously described, plasmids, transposons and integrons are responsible for transfer of resistance traits within LAB group and among LAB and other bacteria. Thus, it is particularly useful to search for insertion sequences (IS) which are an indicator of horizontal gene transfer (Abriouel et al., 2015a). Considering LAB of dairy origin, it is not uncommon to find resistance genes derived from other microorganisms, but several studies have shown the ability *in vitro* to transfer these traits among different species, including pathogenic bacteria (Nawaz et al., 2011; Flórez et al., 2016).

The conjugative transposon *Tn916*, which was first found in *E. faecalis* DS16 (Clewell et al., 1995), is the most widespread in several LAB genera (Table 4) and contributes to the spread of tetracycline resistance among Gram-positive and Gram-negative bacteria (Bertram et al., 1991; Rice, 1998), i.e., the *dfrA* gene located in the transposon *Tn4003* from *St. aureus* (Liu et al., 2009) was detected in *Lc. lactis* and *S. thermophilus* strains (Table 4). Moreover, horizontal gene transmission results do not necessary match real world incidences, as undestimation and overestimation are all possible. However, even where transferability is not proven, the presence of mobile elements like plasmids or transposon raises serious doubts and further investigations are essential (Table 4).

Table 6
Number of papers found that reported the detection of the resistance genes.

Antibiotic resistance genes	Antibiotic	Studies (n°)
tetW, tetS, tetM, tetO, tetK, tetL	tetracycline	39
ermA, ermB	macrolide, lincosamide and streptogramin B	13
vanA, vanE, vanX, vanC1	vancomycin	6
cat	chloramphenicol	2
aac(6′)-aph(2″)	gentamycin	2
aph(3′)-IIIa	kanamycin, neomycin	2
ant(6)	streptomycin	2
dfrA, dfrD	trimethoprim	2
sulII, sul	sulfamethoxazole	1
strB, strA	streptomycin	1
parC	ciprofloxacin	1
aadE, aadA	streptomycin	1
gyrA	ciprofloxacin	1
mdtA	macrolides, lincosamides, streptogramins and tetracycline	1
vatE	streptogramin	1
rpoB	rifampicin	1

The *tet* genes are the most frequent resistance determinants detected within LAB group and Bifidobacteria, representing most of the resistance traits identified (Table 6). These genes confer resistance to tetracycline through different mechanisms of action: synthesis of a ribosomal protection protein (*tetW*, *tetS*, *tetM* and *tetO*) or expression for an efflux protein (*tetK* and *tetL*); others like *tetX* can lead to inactivation of the antibiotic, but to date this resistance gene has not been detected in LABs (Chopra and Roberts, 2001). The great spread of resistance to tetracycline, together with the erythromycin, is due to its great transmission capacity, being *tetM* and *ermB* genes often associated with conjugative transposon *Tn916* (Roberts and Mullany, 2011).

With regard to Bifidobacteria, there seem to be no variations in resistance phenotype in the last decades for strains of dairy origin. Information about resistance traits of wild strains is scarce, but *tetW* is frequently reported within *Bifidobacterium* in accord to Gueimonde et al. (2013). *tetW* was also detected in one strain of *B. animalis* subsp. *lactis*, with a transposase located upstream it, thus a potential transmission can not be excluded (Raeisi et al., 2018).

10. Conclusions

Available data provide the evidence that consumption of raw milk cheeses does not represent a real health risk in terms of antibiotic resistance spread to human pathogens. It is important to mention that the safety screening made by major companies has led to obtain commercial starter cultures free of AR genes (Li et al., 2011). Meanwhile is clearly highlighting that in certain areas of the world starter cultures potentially capable of transmitting resistance to antibiotics are currently used in industrial dairy products. It is therefore necessary to adopt internationally recognized and shared protocols for the evaluation of the phenotypic profile of resistance in lactic acid bacteria and also a search of the WGS for the presence of known antimicrobial resistance genes. Moreover, according to a study published in 2009 (Rodriguez-Alonso et al.), strains, including *Lc. lactis, L. paracasei* and *Leuconostoc* spp., displaying technological properties of interest for the food industry (acidifying and proteolytic/lipolytic activities, lactic odors in milk, and diacetyl production) corresponded to those with a low antibiotic resistance phenotype). It would appear that the presence of antibiotic resistance may interfere with the metabolic traits, but no explanation of this correlation has been provided so far.

Up to now, data concerning *in silico* analysis for LAB from dairy products are very few, probably due both to the fact that resistome analysis is a relatively recent approach and to the low number complete genomes sequences available within LAB species. The *in silico* genome analysis represents an innovative and particularly useful approach, enabling targeted detection of resistance traits in both phenotypical susceptible and resistant strains and identify their location on the genome (chromosome or plasmid encoded); moreover, this approach allows to analyze the homology of AR genes among strains of the same species or between different species and genera, facilitating the identification of genes which exhibit an horizontal transferability.

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Author contributions

L. Nunziata designed the study, collected and analyzed data and drafted the manuscript. **M. Brasca** designed the work, analyzed data and revised the manuscript. **S. Morandi** revised the study critically. **T. Silvetti** revised the study critically.

Declaration of competing interest

We declare we have no conflicts of interests.

The authors declare no conflict of interest.

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