Resistance to the tetracyclines and macrolide-lincosamide-streptogramin group of antibiotics and its genetic linkage – a review

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Abstract

An excessive use of antimicrobial agents poses a risk for the selection of resistant bacteria. Of particular interest are antibiotics that have large consumption rates in both veterinary and human medicine, such as the tetracyclines and macrolide-lincosamide-streptogramin (MLS) group of antibiotics. A high load of these agents increases the risk of transmission of resistant bacteria and/or resistance determinants to humans, leading to a subsequent therapeutic failure. An increasing incidence of bacteria resistant to both tetracyclines and MLS antibiotics has been recently observed. This review summarizes the current knowledge on different tetracycline and MLS resistance genes that can be linked together on transposable elements.

Key words

antibiotics, genetic determinants of resistance, transposons, transmission of resistance

INTRODUCTION AND BACKGROUND

An excessive use of antimicrobial agents poses a risk for the selection of resistant bacteria, which could be either causative agents of a specific disease or a reservoir of genetic determinants of resistance. The latest surveillance report on antimicrobial consumption in the community (i.e. outside hospitals) lists macrolides and tetracyclines as the third and fourth most commonly used subgroups of antibacterials in Europe [1]. Even more pronounced, however, is their use in veterinary medicine, where tetracyclines are the most frequently sold therapeutic antibiotics (37 %), and macrolides account for 8% of the total sales, and are the fourth most frequently sold antibiotic class for veterinary use within Europe [2]. Because of their wide usage in veterinary medicine, their presence in the environment and agriculture is ubiquitous. Table 1 lists the tetracycline and macrolide-lincosamine-streptomycin (MLS) antibiotics that have been approved for human or veterinary use.

Tetracyclines are broad spectrum antibiotics discovered in the late 1940s. They block the attachment of charged aminoacyl-tRNA to the ribosomal acceptor (A) site, and so interfere with the protein synthesis by preventing the introduction of new amino acids to the nascent peptide chain. They are effective against a wide range of gram-positive and gram negative bacteria, chlamydiae, mycoplasma, rickettsiae and protozoan parasites [3, 4]. Due to their low cost, they have been widely used in veterinary medicine for the treatment of various infections, such as colibacillosis, chronic respiratory disease, enteritis and many others [3]. In Europe, tetracyclines belong to the most widely used veterinary antibiotics, ranging from 12.4 up to 102.8 mg/kg of produced meat [5]. Moreover, tetracyclines have also been used in aquaculture [6] and agriculture [7].

Table 1. List of approved tetracyclines, macrolides, lincosamides and streptogramins for human or veterinary use in European Union (2011_Adriaenssens, 1999_EMEA). http://www.chemeurope.com/en/encyclopedia/ATC_code_J01. html#J01AA_Tetracyclines

<table>
<thead>
<tr>
<th>Tetracyclines</th>
<th>Macrolides</th>
<th>Lincosamides</th>
<th>Streptogramins</th>
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<tr>
<td>Chlorotetracycline</td>
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<td>Clindamycin</td>
<td>Pristinamycin</td>
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<tr>
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<td>Clarithromycin</td>
<td>Lincomycin</td>
<td>Quinupristin/ Dalfopristin</td>
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<td>Dirithromycin</td>
<td>Pirilmycin</td>
<td>Virginiamycin</td>
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<td>Oxytetracycline</td>
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<td>Rokitamycin</td>
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<td>Glycylcyclines****</td>
<td>Roitithromycin</td>
<td>Spiramycin</td>
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<tr>
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<td>Tildipirosin</td>
<td>Tilmicosin</td>
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<tr>
<td>Rolithromycin</td>
<td>Troleandomycin</td>
<td></td>
<td></td>
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<tr>
<td>Tylosin*</td>
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<td></td>
<td></td>
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<tr>
<td>Tylvalosin*</td>
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</table>

* A new class of antibiotics derived from tetracycline, with tigecycline as the only glycylcycline antibiotic approved for antibiotic use by now
** veterinary use only
*** veterinary and human use
**** human use only

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To-date, 59 tetracycline resistance genes (tet genes) have been described. They can mediate resistance to tetracyclines by three different mechanisms: ribosomal protection, efflux and enzymatic inactivation of the active compound [8, 9].

MLS antibiotics are three chemically distinct, but functionally similar antibiotic classes. Macrolides with mycarose sugars on the fifth carbon in the lactone ring, lincosamides and streptogramin A inhibit the peptidyl transferase reaction [10], whereas macrolides of the erythromycin group prevent the early events of peptide elongation, and streptogramin B blocks the exit tunnel through which the nascent peptide chains exit the ribosome, resulting in the release of incomplete peptides [10, 11].
The first described macrolide erythromycin has a moderately broad spectrum of activity, while newer semi-synthetic derivatives (e.g. clarithromycin and azithromycin) have a broader spectrum and are used in human medicine for the treatment of upper and lower respiratory tract infections, infections of the skin and soft tissue, sexually transmitted diseases, community-acquired pneumonia and atypical Mycobacterium infections. Together with lincosamides, macrolides are also used for the treatment of group B streptocoocal infections, or for the intrapartum prevention of Streptococcus agalactiae neonatal infections in penicillin hypersensitive patients [12, 13]. In combination with fluoroquinolones, erythromycin is commonly used in the therapy of severe infections caused by Campylobacter spp. [5]. In veterinary medicine, macrolides (e.g. tylosin) are recommended for the treatment of respiratory infections in cattle, swine and poultry. Further indications include treatment of proliferative enteropathy, enteritis and arthritis in swine, necrotic enteritis in poultry, and mastitis in cattle caused by Gram-positive bacteria.

A total of 92 genes that confer resistance to MLS antibiotics have been described to-date [14]. They can be roughly divided into three groups, depending on the mechanisms by which they confer resistance to one or all of these groups of antibiotics. Three main mechanisms of resistance to MLS antibiotics have been described: methylation of RNA (target modification), active efflux and inactivation of the antibiotic. Target modification is achieved via the action of the protein product of one of more than 42 different erm (erythromycin rRNA methylase) genes. They confer crossresistance between macrolides, lincosamides and streptogramin B (so-called MLS, resistance) and evoke most concerns. Active efflux and inactivating enzymes represent two additional mechanisms of resistance that are targeted only to particular antibiotics or antibiotic classes. For example, mef genes encode for macrolide efflux, msr genes for efflux of macrolides and streptogramin B, and the lsa gene for efflux of lincosamides and streptogramin A.

There is a vast body of information overseen by traditional microbiologist on the non-antimicrobial use of tetracyclines and macrolides in clinic and research, as recently reviewed by Aminov [15]. This type of therapy often includes low-dose, long-term exposure to antibiotics, which promotes dissemination of antibiotic resistances among commensal and pathogenic microbiota. Some progress has been made in developing compounds that retain their immunomodulatory activities, while abolishing antimicrobial activities [15], but continuous efforts are necessary in order to completely circumvent the selective pressure exhibited on the microbiota through this type of therapy.

The occurrence of bacteria resistant to both tetracyclines and MLS antibiotics has been observed [16, 17, 18]. This review will summarize the current knowledge on the topic of genetic linkage of different tetracycline and MLS resistance genes, and possible risks coupled with it for public health.

**TETRACYCLINE AND MLS RESISTANCE GENES AND TRANSPONS**

Identification of antibiotic resistance genes provides valuable information; however, knowledge about their association with mobile genetic elements is crucial for assessment of the risk for acquisition and dissemination of antimicrobial resistance. Transposable elements are by definition ‘specific DNA segments that can repeatedly insert into one or more sites in one or more genomes’ [19]. They can be distributed on both chromosomes and plasmids, and are able to interact by recombination between elements and/or by transposition into other elements, forming all kinds of novel chimeric structures [20, 21]. Their complex nomenclature has been revised, and since 2008 all newly-discovered, fully sequenced and/or functional autonomously transposable elements that show <100 % sequence identity with the closest relative, were designated with a new Tn number. The acronyms ICE (integrative conjugative elements) and IME (integrative mobilizable element) are retained, but now interchangeable with CTn or MTn for conjugative transposon or mobilizable transposon, respectively, if conjugation or mobilization can be proved [22]. The first conjugative transposon identified in bacteria was Tn916 from E. faecalis [23], and was carrying the tetracycline resistance. Since then, a vast amount of different transposable elements have been identified, including those that carried several resistance and virulence genes [24]. Under the pressure of any of antibiotics to which the element confers resistance, the whole transposon is retained and, accordingly, multiple antibiotic resistance genes remain in the population. They can persist for decades in animal husbandry due to co-selection, fitness and other phenomena [25]. An overview of transposons and selected mobile genetic elements conferring resistance to tetracyclines and/or MLS antibiotics discussed in this review is given in Table 2 and Figure 1.

There is a variety of transposons conferring tetracycline resistance. They are most often associated with tetracycline resistance, carry the tet(M) gene and belong to the Tn916 transposon family. An excellent review on this topic was recently published and is recommended for more information on the subject [19]; however the main focus of this study are transposons carrying both resistance determinants, against tetracycline and MLS antibiotics, some of which belong to the Tn916 transposon family and will be discussed in detail. Elements associated with MLS resistance are the Tn917 transposon that carries the erm(B) gene [26] or MEGA element (macrolide efflux genetic assembly, 5.5kb) that carries the mef(E)-msr(D)operon [27]. The Tn916 transposon family has a broad host range and transfer readily to a wide variety of Gram-positive and Gram-negative bacteria [19]. The integrate (int) and excisase (xis) genes used for identification of this group of transposons are indistinguishable by PCR methods from the int and xis genes of the Tn1545 transposon [28]. They differ by only one nucleotide over approximately 2 kb. Moreover, the tet(M)genes from these two different transposons exhibit 94.5 % nucleotide identity. Nevertheless,
Resistance to the tetracyclines and macrolide-lincosamide-streptogramin group of antibiotics and its genetic determinants are discussed in this review. Several transposons and mobile genetic elements contribute to resistance, including Tn5253, Tn3872, Tn917, Tn2009, Tn2010, Tn2017, Tn6002, Tn6003, Tn1545, Tn6079, and Tn5253 family. These elements contain genes encoding resistance to tetracyclines and MLS antibiotics, such as the mefE and msrD genes. The schema shows the structural organization of these elements and their insertion sites.

**Figure 1.** Schematic drawing of transposons and selected mobile genetic elements conferring resistance to tetracyclines and/or MLS antibiotics discussed in this review. Tn5253 transposon family is shown as a Tn5252 element (LT, left terminal region; CTR, conjugal-transfer related region; RT, right terminal region) with indicated (arrows) insertion sites of Tn5251 or other Tn916-like transposons (A, Tn6002; B, Tn5251/Tn916 or SpnRi3ermB-like element; C, Tn916 or Tn6002; D, Tn916, Tn6002, Tn2009 or Tn3872).
Table 2. Summary of transposons conferring resistance to tetracycline and/or MLS discussed in this review

<table>
<thead>
<tr>
<th>Transposon</th>
<th>tet gen</th>
<th>Comments</th>
<th>Size</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tn916*</td>
<td>tet(M)</td>
<td></td>
<td>18 kb</td>
<td>(Franke and Clewell, 1981)</td>
</tr>
<tr>
<td>Tn917</td>
<td>erm(B)</td>
<td></td>
<td>7 kb</td>
<td>(Shaw and Clewell, 1985)</td>
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<tr>
<td>MEGA</td>
<td>mef(A)-msr(D) operon</td>
<td>5.5 kb</td>
<td>(Del Grosso et al. 2006)</td>
<td></td>
</tr>
<tr>
<td>Tn1545*</td>
<td>tet(M)</td>
<td>MAS and erm(B) elements inserted into Tn916-like structure</td>
<td>26.5 kb</td>
<td>(Cochetti et al. 2008)</td>
</tr>
<tr>
<td>CTnDOT</td>
<td>tet(Q) or tet(X)</td>
<td>erm(F), erm(B) and aad</td>
<td>65-100 kb</td>
<td>(Gupta et al. 2003; Shoemaker et al. 2001)</td>
</tr>
<tr>
<td>Tn2009*</td>
<td>tet(M)</td>
<td>MEGA element inserted into Tn916-like structure</td>
<td>23.5 kb</td>
<td>(Del Grosso et al. 2004)</td>
</tr>
<tr>
<td>Tn2010*</td>
<td>tet(M)</td>
<td>erm(B) element inserted into Tn2009</td>
<td>26 kb</td>
<td>(Del Grosso et al. 2006; Li et al. 2011)</td>
</tr>
<tr>
<td>Tn2017*</td>
<td>tet(M)</td>
<td>Tn917 inserted into Tn2009</td>
<td>28.5 kb</td>
<td>(Del Grosso et al. 2009)</td>
</tr>
<tr>
<td>Tn3872*</td>
<td>tet(M)</td>
<td>Tn917 inserted into Tn916</td>
<td>24 kb</td>
<td>(Cochetti et al. 2007; McDougal et al. 1998)</td>
</tr>
<tr>
<td>Tn5253</td>
<td>tet(M)</td>
<td>Tn916-like transposon inserted into Tn5252 carrying the cat gene</td>
<td>40-65 kb</td>
<td>(Ayudhya et al. 1991; Mingoia et al. 2011)</td>
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<td>Tn6002*</td>
<td>tet(M)</td>
<td>MAS element inserted into Tn6002</td>
<td>21 kb</td>
<td>(Warburton et al. 2007)</td>
</tr>
<tr>
<td>Tn6003*</td>
<td>tet(M)</td>
<td>Tn6002</td>
<td>25 kb</td>
<td>(Cochetti et al. 2007)</td>
</tr>
<tr>
<td>Tn5385</td>
<td>tet(M)</td>
<td>tet(M) (Tn381): aac(6')-aph(2&quot;) (Tn4001); erm(B) and merRAB (Tn3384); bla (Tn552); aadE</td>
<td>65 kb</td>
<td>(Rice and Carias, 1998)</td>
</tr>
<tr>
<td>Tn6079*</td>
<td>tet(M) and tet(L)</td>
<td>Tn16/Tn1545-like transposon carrying the erm(T) gene</td>
<td>26 kb</td>
<td>(de Vries et al. 2011)</td>
</tr>
<tr>
<td>ICESp2905*</td>
<td>tet(O)</td>
<td>Icesp2907 integrated into Icesp2906</td>
<td>65 kb</td>
<td>(Bencirciani et al. 2011; Giovannetti et al. 2012)</td>
</tr>
</tbody>
</table>

* Tn916-like elements

Tn916 and Tn1545 differ in size (18 vs. 25.2 kb) and genetic content. In addition to the tet(M) gene, Tn1545 also harbours other determinants of resistance, i.e. the MEGA (macrolide-aminoglycoside-streptothricin) element and the erm(B) element [29]. Thus the co-selection of tetracycline and MLS resistance may occur via the Tn1545 transposon, and might be underestimated if isolates were screened only with int/xis specific primers [18, 30]. A new Tn6079 conjugative transposon of the Tn916/Tn1545-like family that harbours two tetracycline resistance genes [tet(M)and tet(L)], and one gene conferring MLS resistance (erm(T1)) was recently identified in samples from an infant faecal fosmid library [31]. The presence of genetic determinants of resistance to both tetracyclines and MLS antibiotics was also described for other large transposons, such as the CTnDOT family, Tn2009, Tn2010, Tn2017, Tn3872, Tn5253, Tn6058, Tn5385, Tn6002 and Tn6003 that arose as a combination of smaller transposons [20, 27, 32, 33, 34].

CTnDOT family transposons are large conjugative transposons from Bacteroides spp. that carry resistance genes against tetracycline (tet(X), tet(Q)) and MLS antibiotics (erm(B), erm(F), erm(G)) [35]. Their excision and conjugative transfer is dependent on tetracycline, although CTnDOT-positive Bacteroidetes spp. are not always tetracycline resistant due to their anaerobic nature and the fact that tetracycline resistance mediated by the tet(X) gene is oxygen dependent [4, 34], they can serve as resistance reservoir for other pathogenic bacteria. Dissemination of tet(X) resistance genes is of special concern because it may contribute to resistance also against third generation tetracycline tigecycline[36]. Although the use of this antibiotic is strictly regulated, tet(X) has already been observed among pathogenic bacteria [37], and sequence similarity of flanking regions around tet(X) suggest that its spread is most likely due to horizontal transfer of transposons from the CTnDOT family [38].

Tn3872 is a composite element resulting from the insertion of the erm(B)-containing Tn917 transposon into orf9 of Tn916. The association between mef/EmrS/R and tet(M) was found in 2009 transposons that have the MEGA element inserted into a Tn916-like structure [20]. In addition to that, Tn2010 and Tn2017 carry the erm(B) gene due to the insertion of the erm(B) element or Tn917, respectively, into a Tn916-like structure [27, 39]. Tn6002 is an element resulting from the insertion of an erm(B)-containing DNA fragment (the erm(B) element) into Tn916[33, 40]. Tn6003 carries determinants of resistance to aminoglycosides and streptothricin due to the MAS element, which can circularise, excise and turn back Tn6003 into Tn6002[32, 41].

Tn5253-like transposons are large composite transposons that consist of a Tn916-like element (originally designated as Tn5251) conferring tetracycline/MLS resistance, which is inserted into the Tn5252 element that harbours the cat (chloramphenicol) resistance gene [42]. Members of this diverse transposon family are often referred to as ICE elements, followed by an acronym of the species where they were discovered, and a unique number (i.e. ICESp2905) [43]. Tn5385 is a composite 65 kb large transposon comprising several smaller mobile elements, including an 18-kb conjugative transposon (Tn5381) conferring resistance to tetracycline [tet(M)], a 26-kb transposon (Tn5384) conferring MLSR resistance (originally named erm(AM)), but now renamed as erm(B), as well as resistance to gentamicin (aac(6')-aph(2'")) and mercuric chloride (merRAB), and a 552-kb staphylococcal beta-lactamase transposon conferring resistance to penicillins (bla). The transposon further confers resistance to streptomycin via the aadE gene [29]. ICESp2905 is a widespread erm(A)- and tet(O)-carrying genetic element of S. pyogenes, resulting from one ICE (ICESp2907) being integrated into another ICE (ICESp2906) of clostridial origin [44]. Originally, the MLS resistance determinant was named erm(TR), but it has been renamed to erm(A).

Giovanetti et al. [45] genotyped clinical isolates of S.pyogenes, and in addition to the erm(B) and tet(M) genes, they identified a new genetic linkage between the tet(O) and erm(A) or mef(A) genes. The authors demonstrated that the tet(O) gene moved in conjugation experiments with and without the erm(A) gene, but always with the mef(A) gene.
This association of tet(O) and mef(A) is due to the prophage Φm46.1 identified in S. pyogenes[46]. The association of tet(O) with the erm(B) gene was further described by Martel et al. [47]. All in all, as more sequence information is revealed, and new functional metagenomics approaches are applied in the research of the resistosome, it is reasonable to expect that new transposable elements will continue to be discovered. Nevertheless, their functionality has to be proved in order to be designated by a new Tn number [22, 31].

TRANSMISSION OF TETRACYCLINE AND MLS RESISTANCE

In vitro transfer of antimicrobial resistance has been studied by many authors. Vignaroli et al. [48] investigated isolates of enterococci co-resistant to tetracycline and erythromycin originating from meat and faeces of chickens and pigs. They found that under in vitro conditions the isolates from faeces more readily transferred the resistance to enterococci of human origin. Jasni et al. [49] demonstrated reciprocal genetic exchange between E. faecalis and C. difficile, where the Tn5397 transposon carrying the tet(M) gene was incorporated at a single specific target site. Wæsel et al. [50] demonstrated the transfer of Tn6194 that carries the erm(B) gene between C. difficile and E. faecalis. Florez et al. [51] identified a Tn916-like transposon carrying the tet(M) gene in plasmids from two Lactococcus lactis strains isolated from raw milk starter-free cheese. Conjugation experiments have shown that only the transposon, but not the whole plasmid, could have been transferred from L. lactis to E. faecalis. Enterococci originating from a total production chain of swine meat commodities were shown to successfully transfer the Tn916/1545 transposon family carrying the tet(M) gene to other enterococci and L. innocua in both filter mating experiments and mating trials performed in meat matrices [52]. Transfer of tetracycline and erythromycin resistances from a human E. faecalis isolate was also demonstrated in a sausage fermentation model, even without antibiotic pressure and as early as within two days of fermentation [53]. In this model, transconjugant bacterial strains were identified among enterococci, pediococci, lactobacilli and staphylococci. In another study, a higher transfer rate for both vancomycin and tetracycline resistance was observed in fermented sausages compared to cheese [54]. Transfer of tetracycline resistance (i.e. the tet(M) gene) from Lactobacillus isolates originating from fermented dry sausages to E. faecalis and L. lactis was demonstrated in conjugation experiments by Gevers et al. [55]. Although the transposon Tn2009 was originally identified in S. pneumoniae as non-mobile [20], in a later study, however, its conjugation was proved between a variety of bacteria, such as Acinetobacter junii, Citrobacter spp., E. coli, Enterobacter cloacae, Klebsiella spp., Pantoeaagglomerans, Proteus spp., Pseudomonas spp., Rhodobacter Sphaeroides, Stenotrophomonas maltophilia, E. faecalis, Neisseria mucosa and Neisseria perflava[56]. Even the large Tn5253 transposon or its related variants were conjugal transferred under laboratory conditions from S. pneumoniae to S. pyogenes and other streptococci, as documented in previous reports [42, 57].

Transfer of antimicrobial resistance, however, is highly influenced by the complexity of microflora and its interactions with the host. Moreover, it is presumed that in vitro models underestimate the potential risk for resistance transfer compared to in vivo models [58, 59]. Therefore, to appropriately assess the risk for horizontal spread of antimicrobial resistance, many authors have recently performed experimental studies under in vivo conditions. Moubareck et al. [60] carried out experiments on gnotobiotic mice, and demonstrated the transfer of vanA (vancomycin resistance) and erm(B) among enterococci colonising the intestine. Although tylosin did not significantly increase the transfer of vancomycin resistance under in vitro conditions, it significantly increased intestinal colonization of the treated mice by vancomycin-transconjugants. A similar observation was reported by Doucet-Populaire et al. [61], who found that administration of tetracycline to gnotobiotic mice increased by 20-fold the transfer of Tn1545 from E. faecalis to L. monocytogenes. On a model of gnotobiotic mice, Jacobsen et al. [62] demonstrated that the tet(M) and erm(B) genes may transfer from Lactobacillus plantarum originating from fermented sausages to human isolates of E. faecalis. This finding supports the hypothesis that microorganisms of food origin may represent an important source of genetic determinants of resistance for microflora colonising human intestines. However, it should be kept in mind that experiments in gnotobiotic animals are performed under artificial conditions, i.e. in the presence of relatively high numbers of potential recipients and in the absence of competitive microflora. A recent in vivo study performed on commercial chickens has shown that the spread of a plasmid-carried erm(B) gene occurs not only within the faecal microbiota under both specific (tylosin and lincomycin) and non-specific (chlorotetacycline) antibiotic pressure, but also in the absence of any antimicrobial pressure [63]. Moreover, all isolates of enterococci and streptococci that acquired the erm(B) gene were also resistant to tetracycline, which indicates that tetracycline may co-select for MLS resistance.

De Leener et al. [64] compared enterococci of human and porcine origin for their resistance profile against erythromycin and tetracycline. The erm(B) gene was found in 85% of porcine isolates and in all human isolates. The tet(M) gene was found in 98 and 89% of the erm(B) positive isolates from pigs and humans, respectively. Among the erm(B)/tet(M) positive isolates, 77 and 70% isolates of porcine and human origin, respectively, carried a transposon of the Tn916/Tn1545 family. The authors therefore suggested either a mutual spread of resistant enterococci between humans and pigs, or the existence of a common reservoir of resistant enterococci. The hypothesis that animals can be a source of resistant enterococci for humans could be supported by the findings of Sorensen et al. [65]. In the latter study, the survival of animal derived enterococcal strains in the human intestine was investigated in 18 volunteers. Transient intestinal carriage of resistant E. faecium of animal origin was detected up to 14 days after ingesting, suggesting that enterococci of animal origin can survive the gastric passage and multiply in the human intestine. This transient colonisation increases the risk for transfer of resistance determinants within human intestinal microbiota. De Vries et al. [31] investigated the diversity of microorganisms conferring tetracycline resistance in faecal samples from a healthy mother-infant pair one month after childbirth, and evaluated potential horizontal transfer of tetracycline resistance genes. For that purpose, faecal fosmid libraries were functionally screened for tetracycline resistance genes. In the mother library, identical tetracycline resistance gene
sequences (predominantly tet(O), followed by tet(W) and tet(X)) were present in different bacterial families and even phyla, which may indicate horizontal transfer within the maternal gastrointestinal tract. Although tet genes other than those observed in the mother dominated in the infant library, tet(O) and tet(W) could also be detected in the infant faecal samples. Moreover, tet(M), tet(L) and erm(T) were identified within a novel composite transposon Tn6079 in the infant library, which indicates a potential for the joint spread of tetracycline and erythromycin resistance within the infant’s gut.

CONCLUSIONS

The antibiotic classes discussed in this review have been used for over 50 years, and still today have large consumption rates in human, but even more in veterinary medicine. They are listed by the World Health Organization as highly or even critically important in the case of macrolides. Rates of bacteria resistant to these classes of antibiotics depend on the source of isolation and history of antibiotic usage. Co-resistance between tetracyclines and MLS antibiotics is often due to the occurrence of genetic determinants for tetracycline and MLS resistance on very promiscuous transposons that can interact, recombine and form all sorts of novel chimeric elements. This type of genetic linkage on transposons is of a very great concern. It increases the risk for transfer of resistances to pathogenic species, and enables the co-selection of all genes and their retention in the population, leading to therapeutic failure and severe consequences.

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