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Acquired antibiotic resistance genes: an overview

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In this review an overview is given on antibiotic resistance (AR) mechanisms with special attentions to the AR genes described so far preceded by a short introduction on the discovery and mode of action of the different classes of antibiotics. As this review is only dealing with acquired resistance, attention is also paid to mobile genetic elements such as plasmids, transposons, and integrons, which are associated with AR genes, and involved in the dispersal of antimicrobial determinants between different bacteria.

Keywords: antimicrobial resistance mechanisms, acquired, antibiotics, mobile genetic elements

INTRODUCTION

The discovery and production of (synthetic) antibiotics in the first half of the previous century has been one of medicine's greatest achievements. The use of antimicrobial agents has reduced morbidity and mortality of humans and contributed substantially to human's increased life span. Antibiotics are, either as therapeutic or as prophylactic agents, also widely used in agricultural practices.

The first discovered antimicrobial compound was penicillin (Flemming, 1929) a β-lactam antibiotic. Soon after this very important discovery, antibiotics were used to treat human infections starting with sulfonamide and followed by the aminoglycoside streptomycin and streptothricin (Domagk, 1935; Schatz and Waksman, 1944). Nowadays numerous different classes of antimicrobial agents are known and they are classified based on their mechanisms of action (Neu, 1992). Antibiotics can for instance inhibit protein synthesis, like aminoglycoside, chloramphenicol, macrolide, streptothricin, and tetracycline or interact with the synthesis of DNA and RNA, such as quinolone and rifampin. Other groups inhibit the synthesis of, or damage the bacterial cell wall as β-lactam and glycopeptide do or modify, like sulfonamide and trimethoprim, the energy metabolism of a microbial cell.

Upon the introduction of antibiotics it was assumed that the evolution of antibiotic resistance (AR) was unlikely. This was based on the assumption that the frequency of mutations generating resistant bacteria was negligible (Davies, 1994). Unfortunately, time has proven the opposite. Nobody initially anticipated that microbes would react to this assault of various chemical poisons by adapting themselves to the changed environment by developing resistance to antibiotics using such a wide variety of mechanisms. Moreover, their ability of interchanging genes, which is now well known as horizontal gene transfer (HGT) was especially unexpected. Later on it was discovered that the emergence of resistance actually began before the first antibiotic, penicillin, was characterized. The first β-lactamase was identified in *Escherichia coli* prior to the release of penicillin for use in medical practice (Abraham and Chain, 1940). Besides β-lactams, the aminoglycoside–aminocyclitol family was also one of the first groups of antibiotics to encounter the challenges of resistance (Wright, 1999; Bradford, 2001). Over the years it has been shown by numerous ecological studies that (increased) antibiotic consumption contributes to the emergence of AR in various bacterial genera (MARAN, 2005, 2007; NethMap, 2008). Some examples of the link between antibiotic dosage and resistance development are the rise of methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE). The initial appearance of MRSA was in 1960 (Jevons et al., 1963), whereas VRE were first isolated about 20 years ago (Uttley et al., 1988). Over the last decades they have remained a reason for concern, but additional public health threats in relation to resistant microorganisms have also arisen (see for example Cantón et al., 2008; Goossens, 2009; Allen et al., 2010).

Bacteria have become resistant to antimicrobials through a number of mechanisms (Spratt, 1994; McDermott et al., 2003; Magnet and Blanchard, 2005; Wright, 2005):

I. Permeability changes in the bacterial cell wall which restricts antimicrobial access to target sites,
II. Active efflux of the antibiotic from the microbial cell,
III. Enzymatic modification of the antibiotic,
IV. Degradation of the antimicrobial agent,
V. Acquisition of alternative metabolic pathways to those inhibited by the drug,
VI. Modification of antibiotic targets,
VII. Overproduction of the target enzyme.

These AR phenotypes can be achieved in microorganisms by chromosomal DNA mutations, which alter existing bacterial proteins, through transformation which can create mosaic proteins and/or as a result of transfer and acquisition of new genetic material between bacteria of the same or different species or genera (Spratt, 1994; Maiden, 1998; Ochman et al., 2000).

There are numerous examples of mutation based resistance. For example, macrolide resistance can be due to nucleotide(s) base substitutions in the 23S rRNA gene. However, a similar resistance phenotype may also result from mutations within the ribosomal proteins L4 and L22 (Vester and Douthwaite, 2001). Single nucleotide polymorphisms (SNPs) can be the cause for resistance against the synthetic drugs quinolones, sulfonamides, and trimethoprim (Huovinen et al., 1995; Hooper, 2000; Ruiz, 2003) and mutations within the *rpsL* gene, which encodes the ribosomal protein S12, can result in a high-level streptomycin resistance (Nair et al., 1993). A frame shift mutation in the chromosomal *ddl* gene, encoding a cytoplasm enzyme D-Ala–D-Ala ligase, can account for glycopeptides resistance (Casadewall and Courvalin, 1999).

ACQUIRED RESISTANCE

This review deals with the description of acquired resistance against several classes of antibiotics. For each class the development of resistance is summarized along with the mechanisms of action. Furthermore an extensive summary is given of the resistance mechanisms and resistance genes involved.

AMINOGLYCOSIDE

History and action mechanism

The aminoglycoside antibiotics initially known as aminoglycosidic aminocyclitols are over 60 years old (Siegenthaler et al., 1986; Begg and Barclay, 1995). In the early 1940s the first aminoglycoside discovered was streptomycin in *Streptomyces griseus* (Schatz and Waksman, 1944). Several years later, additional aminoglycosides were characterized from other *Streptomyces* species; neomycin and kanamycin in 1949 and 1957, respectively. Furthermore, in the 1960s gentamicin was recovered from the actinomycete *Micromonospora purpurea*. Because most aminoglycosides have been isolated from either *Streptomyces* or *Micromonospora* a nomenclature system has been set up based on their source. Aminoglycosides that are derived from bacteria of the *Streptomyces* genus are named with the suffix "-mycin," while those which are derived from *Micromonospora* are named with the suffix "-micin."

The first semi-synthetic derivatives were isolated in the 1970s. For example netilmicin is a derivative of sisomicin whereas amikacin is derived from kanamycin (Begg and Barclay, 1995; Davies and Wright, 1997).

Aminoglycosides are antimicrobials since they inhibit protein synthesis and/or alter the integrity of bacterial cell membranes (Vakulenko and Mobashery, 2003). They have a broad antimicrobial spectrum. Furthermore, they often act in synergy with other antibiotics as such it makes them valuable as anti-infectants.

Resistance mechanisms

Several aminoglycoside resistance mechanisms have been recognized; (I) Active efflux (Moore et al., 1999; Magnet et al., 2001), (II) Decreased permeability (Hancock, 1981; Taber et al., 1987), (III) Ribosome alteration (Poehlsgaard and Douthwaite, 2005), (IV) Inactivation of the drugs by aminoglycoside-modifying enzymes (Shaw et al., 1993). Intrinsic mechanisms, i.e., efflux pumps and 16S rRNA methylases but also chromosomal mutations can cause the first three resistance properties. In recent years acquired 16S rRNA methylases appear to have increased in importance (Galimand et al., 2005; Doi and Arakawa, 2007; **Table 1**). The first gene identified of a plasmid-mediated type of aminoglycoside resistance was *armA* (Galimand et al., 2003). To date five additional methylases have been reported, i.e., *npmA*, *rmt*A, *rmtB*, *rmtC*, and *rmtD* (Courvalin, 2008; Doi et al., 2008). Data regarding the 16S rRNA methylase genes are accumulated and provided at the website: www.nih.go.jp/niid/16s_database/index.html.

The major encountered aminoglycoside resistance mechanism is the modification of enzymes. These proteins are classified into three major classes according to the type of modification: AAC (acetyltransferases), ANT (nucleotidyltransferases or adenyltransferases), APH (phosphotransferases; Shaw et al., 1993; Wright and Thompson, 1999; Magnet and Blanchard, 2005; Wright, 2005; Ramirez and Tolmansky, 2010). Within these classes, an additional subdivision can be made based on the enzymes different region specificities for aminoglycoside modifications: i.e., there are four acetyltransferases: AAC(1), AAC(2′), AAC(3), and AAC(6′); five nucleotidyltransferases: ANT(2″), ANT(3″), ANT(4′), ANT(6), and ANT(9) and seven phosphotransferases: APH(2″), APH(3′), APH(3″), APH(4), APH(6), APH(7″), and APH(9). Furthermore, there also exists a bifunctional enzyme, AAC(6′)–APH(2″), that can acetylate and phosphorylate its substrates sequentially (Shaw et al., 1993; Kotra et al., 2000). **Table 1** displays the currently known aminoglycoside resistance genes. The action mechanisms of the determinants, the variety in gene lengths, accession numbers, and the distribution are all indicated. As can be deduced from the second column of **Table 1**, inconsistencies arose in the nomenclature of genes for aminoglycoside-modifying enzymes (Vakulenko and Mobashery, 2003). In some cases, genes were named according to the site of modification, followed by a number to distinguish between genes. Using a different nomenclature, for example, the genes for AAC(6′)-Ia and AAC(3)-Ia are referred to as *aacA1* and *aacC1*, respectively. The nomenclature proposed by Shaw et al. (1993), who utilize the identical names for the enzymes and the corresponding genes, but the names of genes are in lowercase letters and italicized will be used in this review (see **Table 1**). According to this more convenient nomenclature, the genes for the AAC(6′)-Ia and AAC(3)-Ia enzymes are termed *aac(6′)-Ia* and *aac(3)-Ia*, respectively.

β-LACTAM

History and action mechanism

As already mentioned before, the first antibiotic discovered was a β-lactam, i.e., penicillin. The Scottish scientist Alexander Flemming accidentally noticed the production of a substance with antimicrobial properties by the mold *Penicillium notatum* (Flemming, 1929). Over the last 30 years, many new β-lactam antibiotics have been developed. By definition, all β-lactam antibiotics have a β-lactam nucleus in their molecular structure. The β-lactam antibiotic family includes penicillins and derivatives, cephalosporins,

Table 1 | Acquired Aminoglycoside resistance genes.

Gene name	Mechanism	Length (nt)	Accession number or reference	Coding region	Genera
aac(2′)-Ia	ACT	537	L06156	264..800	*Providencia*
aac(2′)-Ib	ACT	588	U41471	265..852	*Mycobacterium*
aac(2′)-Ic	ACT	546	U72714	373..918	*Mycobacterium*
aac(2′)-Id	ACT	633	U72743	386..1018	*Mycobacterium*
aac(2′)-Ie	ACT	549	NC_011896	3039059..3039607	*Mycobacterium*
aac(3)-I	ACT	465	AJ877225	5293..5757	*Pseudomonas*
aac(3)-Ia	ACT	534	X15852	1250..1783	*Acinetobacter*, *Escherichia*, *Klebsiella*, *Salmonella*, *Serratia*, *Streptomyces*
aac(3)-Ib	ACT	531	L06157	555..1085	*Pseudomonas*
aac(3)-Ib-aac(6′)-Ib	ACT	1,005	AF355189	1435..2439	*Pseudomonas*
aac(3)-Ic	ACT	471	AJ511268	1295..1765	*Pseudomonas*
aac(3)-Id	ACT	477	AB114632	104..580	*Proteus*, *Pseudomonas*, *Salmonella*, *Vibrio*
aac(3)-Ie	ACT	477	AY463797	8583..9059	*Proteus*, *Pseudomonas*, *Salmonella*, *Vibrio*
aac(3)-If	ACT	465	AY884051	61..525	*Serratia*, *Pseudomonas*
aac(3)-Ig	ACT	477	CP000282	2333620..2334096	*Saccharophagus*
aac(3)-Ih	ACT	459	CP000490	509912..510370	*Paracoccus*
aac(3)-Ii	ACT	459	CP000356	638262..638720	*Sphingopyxis*
aac(3)-Ij	ACT		CP000155		*Hahella*
aac(3)-Ik	ACT	444	BX571856	765853..766296	*Staphylococcus*
aac(3)-IIa	ACT	861	X51534	91..951	*Acinetobacter*, *Enterobacter*, *Escherichia*, *Klebsiella*, *Pseudomonas*, *Salmonela*
aac(3)-IIb	ACT	810	M97172	656..1465	*Serratia*
aac(3)-IIc	ACT	861	X54723	819..1679	*Escherichia*
aac(3)-IId	ACT	861	EU022314	1..861	*Escherichia*
aac(3)-IIe	ACT	861	EU022315	1..861	*Escherichia*
aac(3)-IIIa	ACT	816	X55652	1124..1939	*Pseudomonas*
aac(3)-IIIb	ACT	738	L06160	984..1721	*Pseudomonas*
aac(3)-IIIc	ACT	840	L06161	106..945	*Pseudomonas*
aac(3)-IVa	ACT	786	X01385	244..1029	*Escherichia*
aac(3)-Va					
aac(3)-Vb					
aac(3)-VIa	ACT	900	M88012	193..1092	*Enterobacter*, *Escherichia*, *Salmonella*
aac(3)-VIIa	ACT	867	M22999	493..1359	*Streptomyces*
aac(3)-VIIIa	ACT	861	M55426	466..1326	*Streptomyces*
aac(3)-IXa	ACT	846	M55427	274..1119	*Micromonospora*
aac(3)-Xa	ACT	855	AB028210	2711..3565	*Streptomyces*
aac(6′)	ACT	441	AY553333	1392..1832	*Pseudomonas*
aac	ACT	555	AJ628983	1985..2539	*Pseudomonas*
aac(6′)	ACT	402	DQ302723	81..482	*Pseudomonas*
aac(6′)	ACT	555	EU912537	2092..2646	*Pseudomonas*
aac(6′)-Ia	ACT	558	M18967	757..1314	*Citrobacter*, *Escherichia*, *Klebsiella*, *Shigella*
aac(6′)-Ib	ACT	606	M21682	380..985	*Klebsiella*, *Proteus*, *Pseudomonas*
aac(6′)-Ib-cr	ACT	519	EF636461	1124..1642	*Enterobacter*, *Escherichia*, *Klebsiella*, *Pseudomonas*, *Salmonella*
aac(6′)-Ic	ACT	441	M94066	1554..1994	*Serratia*
aac(6′)-Id	ACT	450	X12618	905..1354	*Klebsiella*
aac(6′)-Ie					
aac(6′)-If	ACT	435	X55353	279..713	*Enterobacter*
aac(6′)-Ig	ACT	438	L09246	544..981	*Acinetobacter*
aac(6′)-Ih	ACT	441	L29044	352..792	*Acinetobacter*
aac(6′)-Ii	ACT	549	L12710	169..717	*Enterococcus*

(Continued)

Table 1 | Continued

Gene name	Mechanism	Length (nt)	Accession number or reference	Coding region	Genera
aac(6′)-Ij	ACT	441	L29045	260..700	*Acinetobacter*
aac(6′)-Ik	ACT	438	L29510	369..806	*Acinetobacter*
aac(6′)-Il	ACT	522	Z54241	530..1051	*Acinetobacter*, *Citrobacter*
aac(6′)-Im	ACT	537	AF337947	1215..1751	*Escherichia*
aac(6′)-In	ACT	573	Wu et al. (1997)		*Citrobacter*
aac(6′)-Iq	ACT	552	AF047556	127..678	*Klebsiella*, *Salmonella*
aac(6′)-Ir	ACT	441	AF031326	1..441	*Acinetobacter*
aac(6′)-Is	ACT	441	AF031327	1..441	*Acinetobacter*
aac(6′)-It	ACT	441	AF031328	1..441	*Acinetobacter*
aac(6′)-Iu	ACT	441	AF031329	1..441	*Acinetobacter*
aac(6′)-Iv	ACT	441	AF031330	1..441	*Acinetobacter*
aac(6′)-Iw	ACT	441	AF031331	1..441	*Acinetobacter*
aac(6′)-Ix	ACT	441	AF031332	1..441	*Acinetobacter*
aac(6′)-Iy	ACT	438	AF144880	3452..3979	*Salmonella*
aac(6′)-Iz	ACT	462	AF140221	390..851	*Stenotrophomonas*
aac(6′)-Iaa	ACT	438	NC_003197	1707358..1707795	*Salmonella*
aac(6′)-Iad	ACT	435	AB119105	1..435	*Acinetobacter*
aac(6′)-Iae	ACT	552	AB104852	1935..2486	*Pseudomonas*, *Salmonella*
aac(6′)-Iaf	ACT	552	AB462903	1200..1751	*Pseudomonas*
aac(6′)-Iai	ACT	567	EU886977	544..1110	*Pseudomonas*
aac(6′)-I30	ACT	555	AY289608	1524..2078	*Salmonella*
aac(6′)-31	ACT	519	AJ640197	2474..2992	*Acinetobacter*
aac(6′)-32	ACT	555	EF614235	2247..2801	*Pseudomonas*
aac(6′)-33	ACT	555	GQ337064	1203..1757	*Pseudomonas*
aac(6′)-IIa	ACT	555	M29695	707..1261	*Aeromonas*, *Klebsiella*, *Pseudomonas*, *Salmonella*
aac(6′)-IIb	ACT	543	L06163	532..1074	*Pseudomonas*
aac(6′)-IIc	ACT	582	AF162771	62..643	*Enterobacter*, *Klebsiella*, *Pseudomonas*
aac(6′)-IId					
aac(6′)-III					
aac(6′)-IV	ACT	435	X55353	279..713	*Enterobacter*
aac(6′)-aph(2″)	NUT	1,440	M13771	304..1743	*Enterococcus*, *Lactobacillus*, *Staphylococcus*, *Streptococcus*
aacA29	ACT	381	AY139599	768..1148	Unknown
aacA43	ACT	564	HQ247816	639..1202	*Klebsiella*
aadA1	NUT	972	X02340	223..1194	*Acinetobacter*, *Aeromonas*, *Enterobacter*, *Escherichia*, *Klebsiella*, *Proteus*, *Pseudomonas*, *Salmonella*, *Shigella*, *Vibrio*
aadA1b	NUT	792	M95287	3320..4111	*Pseudomonas*, *Serratia*
aadA2	NUT	780	X68227	166..945	*Acinetobacter*, *Aeromonas*, *Citrobacter*, *Enterobacter*, *Escherichia*, *Klebsiella*, *Proteus*, *Pseudomonas*, *Salmonella*, *Shigella*, *Staphylococcus*, *Vibrio*, *Yersinia*
aadA3	NUT	792	AF047479	1296..2087	*Escherichia*
aadA4	NUT	789	Z50802	1306..2094	*Acinetobacter*, *Aeromonas*, *Escherichia*, *Pseudomonas*,
aadA5	NUT	789	AF137361	64..852	*Acinetobacter*, *Aeromonas*, *Escherichia*, *Pseudomonas*, *Salmonella*, *Shigella*, *Staphylococcus*, *Vibrio*
aadA6	NUT	846	AF140629	61..906	*Pseudomonas*
aadA7	NUT	798	AF224733	32..829	*Escherichia*, *Salmonella*, *Vibrio*
aadA8	NUT	792	AF326210	1..792	*Klebsiella*, *Vibrio*
aadA8b	NUT	792	AM040708	1174..1965	*Escherichia*
aadA9	NUT	837	AJ420072	26773..27609	*Corynebacterium*
aadA10	NUT	834	U37105	2807..3640	*Pseudomonas*

(Continued)

Table 1 | Continued

Gene name	Mechanism	Length (nt)	Accession number or reference	Coding region	Genera
aadA11	NUT	846	AY144590	1..846	*Pseudomonas*, *Riemerella*
aadA12	NUT	792	AY665771	1..792	*Escherichia*, *Salmonella*, *Yersinia*
aadA13	NUT	798	AY713504	1..798	*Escherichia*, *Pseudomonas*, *Yersinia*
aadA14	NUT	786	AJ884726	540..1325	*Pasteurella*
aadA15	NUT	792	DQ393783	1800..2591	*Pseudomonas*
aadA16	NUT	846	EU675686	3197..4042	*Escherichia*, *Klebsiella*, *Vibrio*
aadA17	NUT	792	FJ460181	774..1565	*Aeromonas*
aadA21	NUT	792	AY171244	47..838	*Salmonella*
aadA22	NUT	792	AM261837	74..865	*Escherichia*, *Salmonella*
aadA23	NUT	780	AJ809407	119..898	*Salmonella*
aadA24	NUT	780	AM711129	1264..2043	*Escherichia*, *Salmonella*
aadC	NUT	477	V01282	225..701	*Staphylococcus*
aadD	NUT	771	AF181950	3176..3946	*Staphylococcus*
ant(2″)-Ia	NUT	543	X04555	1296..1829	*Acinetobacter*, *Enterobacter*, *Escherichia*, *Klebsiella*, *Proteus*, *Pseudomonas*, *Salmonella*, *Serratia*, *Shigella*, *Vibrio*
ant(3″)-Ih-aac(6′)-IId	NUT-ACT	1,392	AF453998	3555..4946	*Serratia*
ant(4′)-Ib	NUT	771	AJ506108	209..979	*Bacillus*
ant(4′)-IIa	NUT	759	M98270	145..903	*Pseudomonas*
ant(4′)-IIb	NUT	756	AY114142	1061..1816	*Pseudomonas*
ant(6)-Ia	NUT	909	AF330699	22..930	*Enterococcus*, *Staphylococcus*
ant(6)-Ib	NUT	858	FN594949	27482..28339	*Campylobacter*
ant(9)-Ia	NUT	783	X02588	331..1113	*Enterococcus*, *Staphylococcus*
ant(9)-Ib	NUT	768	M69221	271..1038	*Enterococcus*, *Staphylococcus*
aph(2″)-Ia					
aph(2″)-Ib	PHT	900	AF337947	272..1171	*Enterococcus*, *Escherichia*
aph(2″)-Ic	PHT	921	U51479	196..1116	*Enterococcus*
aph(2″)-Id	PHT	906	AF016483	131..1036	*Enterococcus*
aph(2″)-Ie	PHT	906	AY743255	131..1036	*Enterococcus*
aph(3′)-Ia	PHT	816	J01839	1162..1977	*Escherichia*, *Klebsiella*, *Pseudomonas*, *Salmonella*
aph(3′)-Ib	PHT	816	M20305	779..1594	*Escherichia*
aph(3′)-Ic	PHT	816	X625115	410..1225	*Acinetobacter*, *Citrobacter*, *Escherichia*, *Klebsiella*, *Salmonella*, *Serratia*, *Yersinia*
aph(3′)-Id	PHT	816	Z48231	820..1635	*Escherichia*
aph(3′)-IIa	PHT	795	X57709	1..795	*Escherichia*, *Pseudomonas*, *Salmonella*
aph(3′)-IIb	PHT	807	X90856	388..1194	*Pseudomonas*
aph(3′)-IIc	PHT	813	AM743169	2377498..2378310	*Stenotrophomonas*
aph(3′)-III	PHT	795	M26832	604..1398	*Bacillus*, *Campylobacter*, *Enterococcus*, *Staphylococcus*, *Streptococcus*
aph(3′)-IV	PHT	789	X03364	277..1065	*Bacillus*
aph(3′)-Va	PHT	807	K00432	307..1113	*Streptomyces*
aph(3′)-Vb	PHT	792	M22126	373..1164	*Streptomyces*
aph(3′)-Vc	PHT	795	S81599	282..1076	*Micromonospora*
aph(3′)-Va	PHT	780	X07753	103..882	*Acinetobacter*, *Pseudomonas*
aph(3′)-VIb	PHT	780	AJ627643	4934..5713	*Alcaligenes*
aph(3′)-VIIa	PHT	753	M29953	131..1036	*Campylobacter*
aph(3′)-VIII	PHT	804	AF182845	1..804	*Streptomyces*
aph(3′)-XV	PHT	795	Y18050	4758..5552	*Achromobacter*, *Citrobacter*, *Pseudomonas*
aph(3″)-Ia	PHT	819	M16482	501..1319	*Streptomyces*
aph(3″)-Ib	PHT	801	AB366441	11310..12110	*Enterobacter*, *Escherichia*, *Klebsiella*, *Pasteurella*, *Pseudomonas*, *Salmonella*, *Shigella*, *Yersinia*, *Vibrio*
aph(4)-Ia	PHT	1,026	V01499	231..1256	*Escherichia*

(Continued)

Table 1 | Continued

Gene name	Mechanism	Length (nt)	Accession number or reference	Coding region	Genera
aph(4)-Ib	PHT	999	X03615	232..1230	*Streptomyces*
aph(6)-Ia	PHT	924	AY971801	1..924	*Streptomyces*
aph(6)-Ib	PHT	924	X05648	382..1305	*Streptomyces*
aph(6)-Ic	PHT	801	X01702	485..1285	*Escherichia*, *Pseudomonas*, *Salmonella*
aph(6)-Id	PHT	837	M28829	866..1702	*Enterobacter*, *Escherichia*, *Klebsiella*, *Pasteurella*, *Pseudomonas*, *Salmonella*, *Shigella*, *Yersinia*, *Vibrio*
aph(7″)-Ia	PHT	999	X03615	232..1230	*Streptomyces*
aph(9)-Ia	PHT	996	U94857	151..1146	*Legionella*
aph(9)-Ib	PHT	993	U70376	7526..8518	*Streptomyces*
apmA	ACT	822	FN806789	2858..3682	*Staphylococcus*
armA	MET	774	AY220558	1978..2751	*Acinetobacter*, *Citrobacter*, *Enterobacter*, *Escherichia*, *Klebsiella*, *Salmonella*, *Serratia*
npmA	MET	660	AB261016	3069..3728	*Escherichia*
rmtA	MET	756	AB120321	6677..7432	*Pseudomonas*
rmtB	MET	756	AB103506	1410..2165	*Enterobacter*, *Escherichia*, *Klebsiella*, *Pseudomonas*, *Serratia*
rmtC	MET	846	AB194779	6903..7748	*Proteus*, *Salmonella*
rmtD	MET	744	DQ914960	8889..9632	*Klebsiella*, *Pseudomonas*
rmtD2	MET	744	HQ401565	14139..14882	*Citrobacter*, *Enterobacter*
rmtE	MET	822	GU201947	55..876	*Escherichia*
spc	MET	783	X02588	331..1113	*Enterococcus*, *Staphylococcus*
sph	NUT	801	X64335	6557..7354	*Escherichia*, *Pseudomonas*, *Salmonella*
str	NUT	849	X92946	18060..18908	*Enterococcus*, *Staphylococcus*, *Lactococcus*
sat2[A]	ACT	525	X51546	518..1042	*Acinetobacter*, *Enterobacter*, *Escherichia*, *Klebsiella*, *Proteus*, *Pseudomonas*, *Salmonella*, *Shigella*, *Vibrio*
sat3[A]	ACT	543	Z48231	221..763	*Escherichia*
sat4[A]	ACT	543	X92945	38870..39412	*Campylobacter*, *Enterococcus*, *Staphylococcus*, *Streptococcus*

This table was adapted from: Elbourne and Hall (2006), Magnet and Blanchard (2005), Partridge et al. (2009), Ramirez and Tolmansky (2010), Shaw et al. (1993), Vakulenko and Mobashery (2003), and data provided by B. Guerra, B. Aranda, D. Avsaroglu, B. Ruiz del Castillo, and R. Helmuth, on behalf of the Med-Vet Net (EU Network of Excellence) WP29 Project Group. The data were collected within the subproject "AME's," with following participants representing their Institutions: Agnes Perry Guyomard (ANSES), Dik Mevius (CVI), Yvonne Agerso (DTU), Katie Hopkins (HPA), Silvia Herrera (ISCIII), Alessandra Carattoli (ISS), Antonio Battisti (IZS-Rome), Stefano Lollai (IZS-Sardegna), Lotte Jacobsen (SSI), Béla Nagy (VMRI), M. Rosario Rodicio and M. C. Mendoza (University of Oviedo, UO), Luis Martínez-Martínez (University Hospital of Valdecilla, HUV), and Bruno Gonzalez-Zorn (UCM).

ACT, Acetyltransferase; MET, Methyltransferase; NUT, Nucleotidyltransferase; PHT, Phosphotransferase.

[A]*Although the sat genes are not aminoglycoside resistance determinants, they encode streptothricin acetyltransferases, for convenience they are included in this table.*

carbapenems, monobactams, and β-lactam inhibitors (Williams, 1987; Bush, 1989; Petri, 2006; Queenan and Bush, 2007).

The core compound of penicillin, 6-aminopenicillanic acid (6-APA) is used as the main starting point for the preparation of numerous semi-synthetic derivatives. Although the cephalosporins are often thought of as new and improved derivatives of penicillin, they were actually discovered as naturally occurring substances (Petri, 2006). They can be grouped in first, second, third, and forth generation cephalosporins according to their spectrum of activity and timing of the agent's introduction. In general, first generation agents have good Gram-positive activity and relatively modest coverage for Gram-negative organisms; second generation cephalosporins have increased Gram-negative and somewhat less Gram-positive activity; third generation antimicrobials have improved Gram-negative and variable Gram-positive activity; forth generation β-lactams have good true broad spectrum activity against both Gram-negatives and Gram-positives (Williams, 1987; Marshall et al., 2006). The second generation cephamycins are sometimes also grouped among the cephalosporins.

Because carbapenems diffuse easily in bacteria they are considered as broad spectrum β-lactam antibiotic. Imipenem and meropenem are well known representative. Even though monobactams do not contain a nucleus with a fused ring attached, they still belong to the β-lactam antibiotics. The β-lactamase inhibitors, like clavulanic acid, do contain the β-lactam ring, but they exhibit negligible antimicrobial activity and are used in combination with β-lactam antibiotics to overcome resistance in

bacteria that secrete β-lactamase, which otherwise inactivates most penicillins.

The β-lactam antibiotics work by inhibiting the cell wall synthesis by binding to so-called penicillin-binding proteins (PBPs) in bacteria and interfering with the structural cross linking of peptidoglycans and as such preventing terminal transpeptidation in the bacterial cell wall. As a consequence it weakens the cell wall of the bacterium and finally results in cytolysis or death due to osmotic pressure (Kotra and Mobashery, 1998; Andes and Craig, 2005).

The β-lactamase inhibitors can be classified as either reversible or irreversible and the latter are considered more effective in that they eventually result in the destruction of enzymatic activity. Not surprisingly the inhibitors in clinical use, i.e., clavulanic acid, sulbactam, and tazobactam are all examples of irreversible β-lactamase inhibitors (Bush, 1988; Drawz and Bonomo, 2010).

Resistance mechanisms

The first bacterial enzyme reported to destroy penicillin was an AmpC β-lactamase of *E. coli* (Abraham and Chain, 1940). Nowadays, bacterial resistance against β-lactam antibiotics is increasing at a significant rate and has become a common problem. There are several mechanisms of antimicrobial resistance to β-lactam antibiotics. The most common and important mechanism through which bacteria can become resistant against β-lactams is by expressing β-lactamases, for example extended-spectrum β-lactamases (ESBLs), plasmid-mediated AmpC enzymes, and carbapenem-hydrolyzing β-lactamases (carbapenemases; Bradford, 2001; Jacoby and Munoz-Price, 2005; Paterson and Bonomo, 2005; Poirel et al., 2007; Queenan and Bush, 2007; Jacoby, 2009).

The β-lactamase family has been subdivided either based on functionality or molecular characteristics. Initially, before genes were routinely sequenced various biochemical parameters were determined of the different β-lactamases which allowed classification of this AR determinants family into four groups (Bush et al., 1995; Wright, 2005). Groups 1, 2, and 4 are serine-β-lactamases, while members of group 3 are metallo-β-lactamases. Classification based on molecular characteristics, i.e., amino acid homology has also resulted in four major groups, the so-called Ambler classes A–D, which correlate well with the functional scheme but lack details concerning the enzymatic activity. Ambler classes A, C, and D include the β-lactamases with serine at their active site, whereas Ambler class B β-lactamases are all metallo-enzymes who require zinc as a metal cofactor for their catalytic activities (Ambler, 1980; Bradford, 2001; Paterson and Bonomo, 2005; Wright, 2005; Poirel et al., 2007, 2010; Bush and Jacoby, 2010; Drawz and Bonomo, 2010). In this review the Ambler classification will be used (**Table 2**).

In addition to the production of β-lactamases resistance can also be due to possession of altered PBPs. Since β-lactams cannot bind as effectively to these altered PBPs, the antibiotic is less effective at disrupting cell wall synthesis. The PBPs are thought to be the ancestors of the naturally occurring chromosomally mediated β-lactamase in many bacterial genera (Bradford, 2001).

Although plasmid-encoded penicillinase arose much earlier in Gram-positives in *Staphylococcus aureus*, due to the use of penicillin (Aarestrup and Jensen, 1998), the first plasmid-mediated β-lactamase, TEM-1, was described in the early 1960s in Gram-negatives (Datta and Kontomichalou, 1965). Currently over 1,150 chromosomal, plasmid, and transposon located β-lactamases are currently known (Bush and Jacoby, 2010; Drawz and Bonomo, 2010; **Table 2**).

Based on their activity to hydrolyze a small number or a variety of β-lactams the enzymes can be subdivided into narrow-, moderate-, broad-, and ESBLs. A commonly used definition specifies that broad spectrum β-lactamases are capable to provide resistance to the penicillins and cephalosporins and are not inhibited by inhibitors such as clavulanic acid and tazobactam. The ESBLs confer resistance to the penicillins, first-, second-, and third-generation cephalosporins and aztreonam, but not to carbapenems and are inhibited by β-lactamase inhibitors. In recent years acquired AR genes encoding ESBLs have become a major concern (Bradford, 2001). In time the parent enzymes $bla_{\text{TEM-1}}$, $bla_{\text{TEM-2}}$, and $bla_{\text{SHV-1}}$ have undergone amino acid substitutions (point mutations) evolving to the ESBLs, starting with $bla_{\text{TEM-3}}$ and $bla_{\text{SHV-2}}$ (Bradford, 2001). Additional mutations at critical amino acids important for catalysis resulted in over 140 currently known SHV and TEM ESBL variants. In addition, plasmid-encoded class C β-lactamases or AmpC determinants, like bla_{CMY} have also caught people's awareness (Jacoby, 2009). Furthermore, in the past decade CTX-M enzymes have become very prevalent ESBLs, both in nosocomial and in community settings (Cantón and Coque, 2006).

Table 2 illustrates the size and diversity of the group of β-lactamases and ESBLs. The vast and still increasing number of (broad spectrum) β-lactamases and ESBLs has become a problem for the nomenclature for novel genes. Names have been assigned according to individual preference rather than according to systematic procedures (Bush, 1989). Fortunately, an authoritative website has been constructed on the nomenclature of ESBLs hosted by Jacoby and Bush[1].

CHLORAMPHENICOL

History and action mechanism

In 1947, the first chloramphenicol, originally referred to as chloromycetin, was isolated from *Streptomyces venezuelae* (Ehrlich et al., 1947). Probably because chloramphenicol is a molecule with a rather simple structure only a small number of synthetic derivates have been synthesized without adverse effects on antimicrobial activity (Schwarz et al., 2004). In azidamfenicol two chlorine atoms ($-Cl_2$) are replaced by an azide group. Substitution of the nitro group ($-NO_2$), by a methyl–sulfonyl residue ($-SO_2CH_3$) resulted in the synthesis of thiamphenicol, whereas in the fluorinated thiamphenicol derivative florfenicol the hydroxyl group ($-OH$) is replaced with fluorine ($-F$).

Chloramphenicol is a highly specific and potent inhibitor of protein synthesis through its affinity for the peptidyltransferase of the 50S ribosomal subunit of 70S ribosomes (Schwarz et al., 2004). Due to its binding to this enzyme the antibiotic prevents peptide chain elongation. The substrate spectrum of chloramphenicol includes Gram-positive and Gram-negative, aerobic and anaerobic bacteria. Chloramphenicol analogs including

[1] www.lahey.org/Studies

Table 2 | β-Lactamases and ESBLs families.

Amber class A β-lactamases and ESBLs	Number of variants*	Amber class B β-lactamases and MBLs	Number of variants*	Amber class C β-lactamases and ESBLs	Number of variants*	Amber class D β-lactamases and ESBLs	Number of variants*
bla_{ACI}	1	bla_{B}	13	bla_{ACC}[a]	4	*ampH*	1
bla_{AER}	1	bla_{CGB}	2	bla_{ACT}[a]	9	*ampS*	1
bla_{AST}	1	bla_{DIM}	1	bla_{BIL}	1	bla_{LCR}	1
bla_{BEL}	3	bla_{EBR}	1	bla_{BUT}	2	bla_{NPS}	1
bla_{BES}	1	bla_{GIM}	1	bla_{CFE}[a]	1	bla_{OXA}[a]	219
bla_{BIC}	1	bla_{GOB}	18	bla_{CMG}	1	*loxA*	1
bla_{BPS}	5	bla_{IMP}[a]	30	bla_{CMY}[a]	72		
bla_{CARB}	8	bla_{IND}[a]	7	bla_{DHA}[a]	8		
bla_{CKO}	5	bla_{JOHN}	1	bla_{FOX}[a]	10		
bla_{CME}	2	bla_{MUS}	1	bla_{LAT}[a]	1		
bla_{CTX-M}[a]	119	bla_{NDM}	6	bla_{LEN}[c]	24		
bla_{DES}	1	bla_{SPM}	1	bla_{MIR}[a]	5		
bla_{ERP}	1	bla_{TUS}	1	bla_{MOR}	1		
bla_{FAR}	2	bla_{VIM}[a]	30	bla_{MOX}[a]	8		
bla_{FONA}	6	*cepA*	7	bla_{OCH}	7		
bla_{GES}[a,b]	17	*cfiA*	16	bla_{OKP-A}[c]	16		
bla_{HERA}	8	*cphA*	8	bla_{OKP-B}[c]	20		
bla_{IMI}	3	*imiH*	1	bla_{OXY}[c]	23		
bla_{KLUA}[d]	12	*imiS*	1	bla_{TRU}	1		
bla_{KLUC}[d]	2			bla_{ZEG}	1		
bla_{KLUG}	1			*cepH*	1		
bla_{KLUY}	4						
bla_{KPC}[a]	11						
bla_{LUT}	6						
bla_{MAL}	2						
bla_{MOR}	1						
bla_{NMC-A}	1						
bla_{PER}[a]	7						
bla_{PME}	1						
bla_{PSE}	4						
bla_{RAHN}	2						
bla_{ROB}	1						
bla_{SED}	1						
bla_{SFC}	1						
bla_{SFO}	1						
bla_{SHV}[a]	141						
bla_{SME}[a]	3						
bla_{TEM}[a]	187						
bla_{TLA}	1						
bla_{TOHO}	1						
bla_{VEB}[a]	7						
bla_{Z}	1						
cdiA	1						
cfxA	6						
cumA	1						
hugA	1						
penA	1						

**Last update: June 17th, 2011.*

[a]*According to http://www.lahey.org/Studies.*

[b]*GES and IBC-type ESBLs have all been renamed as* bla_{GES} *according to Weldhagen et al. (2006).*

[c]*According to http://www.pasteur.fr/ip/easysite/go/03b-00002u-03q/beta-lactamase-enzyme-variants.*

[d]bla_{KLUA}, bla_{KLUC}, bla_{KLUG}, *and* bla_{KLUY} *seem to be the chromosomal progenitors of acquired CTX-M group 2, 1, 8, and 9 genes, respectively (Saladin et al., 2002; Olson et al., 2005).*

the fluorinated derivative florfenicol have a similar spectrum of activity.

Resistance mechanism

The first and still most frequently encountered mechanism of bacterial resistance to chloramphenicol is enzymatic inactivation by acetylation of the drug via different types of chloramphenicol acetyltransferases (CATs; Murray and Shaw, 1997; Schwarz et al., 2004; Wright, 2005). CATs are able to inactivate chloramphenicol as well as thiamphenicol and azidamfenicol, however, due to its structural modification florfenicol is resistant to inactivation by these enzymes. Consequently, chloramphenicol resistant strains, in which resistance is exclusively based on the activity of CAT, are susceptible to florfenicol. There are two defined types of genes coding CATs which distinctly differ in their structure: i.e., the classical *catA* determinants and the novel, also known as xenobiotic CATs, encoded by *catB* variants (**Table 3**). Besides the inactivating enzymes, there are also reports on other chloramphenicol resistance systems, such as inactivation by phosphotransferases, mutations of the target site, permeability barriers, and efflux systems (Schwarz et al., 2004). Of the latter mechanism, *cmlA* and *floR* are the most commonly known (Bissonnette et al., 1991; Briggs and Fratamico, 1999). The presence of a *cmlA* gene will result in resistance to chloramphenicol, but susceptibility to florfenicol. In contrast, *floR* will give rise to a chloramphenicol and florfenicol resistance phenotype. Inconsistencies in the nomenclature arose, like with many other AR genes, due to the increasing number of chloramphenicol resistance determinants. Schwarz et al. (2004) suggested a unified nomenclature. **Table 3** represents the currently known chloramphenicol/florfenicol resistance genes. Some characteristics which are mentioned in **Table 3** are mechanism of action, diverse gene lengths, accession numbers, and the distribution.

GLYCOPEPTIDE

History and action mechanism

In the late 1950s, the first glycopeptide, vancomycin was introduced in a clinical setting. Vancomycin was isolated as a fermentation product from a soil bacterium, *Streptomyces orientalis*, displaying antimicrobial activity (McCormick et al., 1956). Nearly 30 years later followed another glycopeptide antibiotic, teicoplanin (Parenti et al., 1978). Currently, four groups of glycopeptides are recognized, i.e., vancomycin type, avoparcin type, ristocetin type, and teicoplanin type. (Yao and Crandall, 1994). Among them, vancomycin and teicoplanin are the only two therapeutics currently used against Gram-positive microorganisms. During the 1990s, an association between the use of avoparcin and the occurrence of glycopeptide-resistant enterococci (GRE), more commonly designated VRE, in farm animals was demonstrated (Aarestrup, 1995; Klare et al., 1995). As a consequence avoparcin was banned as a growth promoter in all European Union countries in 1997.

Glycopeptides have an unusual mode of action. Instead of inhibiting an enzyme, they bind to a substrate. To be more specific, the molecular target of these glycopeptide antibiotics is the D-alanyl–D-alanine (D-Ala–D-Ala) terminus of the cell wall peptidoglycan precursor. After the glycopeptides are bound to their target, they inhibit the subsequent transglycosylation reaction by steric hindrance. (Gao, 2002; Klare et al., 2003).

Resistance mechanism

The introduction of antibiotics into clinical setting is usually followed by the fairly rapid emergence of resistant bacteria. In this respect, vancomycin was somewhat atypical, because for almost 30 years following its introduction, resistance to this glycopeptide was reported only rarely and appeared to have little clinical significance. However, in the late 1980s, the emergence of acquired glycopeptides resistance was recognized for the first time (Leclercq et al., 1988; Johnson et al., 1990). This vancomycin resistance resulted from the production of modified peptidoglycan precursors ending in D-Ala–D-Lac (VanA, VanB, and VanD) or D-Ala–D-Ser (VanC, VanE, and VanG), to which glycopeptides exhibit low binding affinities. Classification of glycopeptide resistance is based on the primary sequence of the structural genes for the resistance-mediating ligases. The *van*A and *vanB* operons are located on plasmids or on the chromosome, whereas the *vanC1*, *vanC2/3*, *vanD*, *vanE,* and *vanG* have so far been found exclusively on the chromosome (Gao, 2002; Klare et al., 2003; Depardieu et al., 2007). Currently, resistance to the glycopeptides, vancomycin, and teicoplanin or both, has been detected in six, all Gram-positive bacterial genera: *Enterococcus*, *Erysipelothrix*, *Lactobacillus*, *Leuconostoc*, *Pediococcus,* and *Staphylococcus* (Woodford et al., 1995).

MACROLIDE–LINCOSAMIDE–STREPTOGRAMIN B

History and action mechanism

The first macrolide, erythromycin A, was discovered in the early 1950s (McGuire et al., 1952). The main structural component of this molecule is a large lactone ring to which amino and/or neutral sugars are attached by glycosidic bonds. To address the limitations of erythromycin, like chemical instability, poor absorbance, and bitter taste, newer 14-, 15-, and 16-membered ring macrolides such as clarithromycin and the azalide, azithromycin, have been developed (Kirst, 2002; Roberts, 2002).

Macrolides have a similar mode of antibacterial action and comparable antibacterial spectra as two other antibiotic classes, i.e., lincosamides and streptogramins B. Consequently, these antibiotics, although chemically distinct, have been clustered together as Macrolide–Lincosamide–Streptogramin B (MLS) antibiotics (Roberts, 2002). Nowadays this class of antibiotics should even be extended due to the development of various synthetic drugs. The ketolides (Zhanel et al., 2002; Ackermann and Rodloff, 2003) and oxazolidinones (Diekema and Jones, 2000) can be grouped together with the MLS antimicrobial agents which results in the MLSKO family of antibiotics (Roberts, 2008).

Macrolides, lincosamides, and streptogramins B all inhibit protein synthesis by binding to the 50S ribosomal subunit of bacteria (Weisblum, 1995; Roberts, 2002).

Resistance mechanism

Shortly after the introduction of erythromycin into clinical setting in the 1950s, bacterial resistance to this antibiotic was reported for the first time in staphylococci (Weisblum, 1995). Since then a large number of bacteria have been identified that are resistant to MLS

Table 3 | Acquired chloramphenicol resistance genes.

Group	Gene	Gene(s) included	Mechanism	Length (nt)	Accession number	Coding region	Genera
Type A-1	*catA1*	*cat*, *catI*, *pp-cat*	Inactivating enzyme	660	V00622	244..903	*Acinetobacter*, *Escherichia*, *Klebsiella*, *Salmonella*, *Serratia*, *Shigella*
Type A-2	*catA2*	*cat*, *catII*	Inactivating enzyme	642	X53796	187..828	*Aeromonas*, *Agrobacterium*, *Escherichia*, *Haemophilus*, *Photobacterium*, *Salmonella*
Type A-3	*catA3*	*cat*, *catIII*	Inactivating enzyme	642	X07848	272..913	*Actinobacillus*, *Edwardsiella*, *Klebsiella*, *Mannheimia*, *Pasteurella*, *Shigella*
Type A-4	*Cat*		Inactivating enzyme	654	M11587	880..1533	*Proteus*
Type A-5	*Cat*		Inactivating enzyme	663	P20074*	1002758..1003420	*Streptomyces*
Type A-6	*cat86*		Inactivating enzyme	663	K00544	145..807	*Bacillus*
Type A-7	*cat(pC221)*	*cat*, *catC*	Inactivating enzyme	648	X02529	2267..2914	*Bacillus*, *Enterococcus*, *Lactobacillus*, *Staphylococcus*, *Streptococcus*
Type A-8	*cat(pC223)*	*cat*	Inactivating enzyme	648	AY355285	1000..1647	*Enterococcus*, *Lactococcus*, *Listeria*, *Staphylococcus*, *Streptococcus*
Type A-9	*cat(pC194)*	*cat*, *cat-TC*	Inactivating enzyme	651	NC_002013	1260..1910	*Bacillus*, *Enterococcus*, *Lactobacillus*, *Staphylococcus*, *Streptococcus*
Type A-10	*Cat*		Inactivating enzyme	687	AY238971	1055..1741	*Bacillus*
Type A-11	*catP*	*catD*	Inactivating enzyme	624	U15027	2953..3576	*Clostridium*, *Neisseria*
Type A-12	*catS*		Inactivating enzyme	492[§]	X74948	1..492	*Streptococcus*
Type A-13	*Cat*		Inactivating enzyme	624	M35190	309..932	*Aeromonas*, *Campylobacter*
Type A-14	*Cat*		Inactivating enzyme	651	S48276	479..1129	*Listonella*, *Photobacterium*, *Proteus*
Type A-15	*catB*		Inactivating enzyme	660	M93113	145..804	*Clostridium*
Type A-16	*catQ*		Inactivating enzyme	660	M55620	459..1118	*Clostridium*, *Streptococcus*
Type B-1	*catB1*	*cat*	Inactivating enzyme	630	M58472	148..777	*Agrobacterium*
Type B-2	*catB2*		Inactivating enzyme	633	AF047479	5957..6589	*Acinetobacter*, *Aeromonas*, *Bordetella*, *Escherichia*, *Klebsiella*, *Pasteurella*, *Pseudomonas*, *Salmonella*
Type B-3	*catB3*	*catB4*, *catB5*, *catB6*, *catB8*	Inactivating enzyme	633	AJ009818	883..1515	*Acinetobacter*, *Aeromonas*, *Bordetella*, *Enterobacter*, *Escherichia*, *Klebsiella*, *Kluyvera*, *Morganella*, *Pseudomonas*, *Salmonella*, *Serratia*, *Shigella*

(Continued)

Table 3 | Continued

Group	Gene	Gene(s) included	Mechanism	Length (nt)	Accession number	Coding region	Genera
Type B-4	*catB7*		Inactivating enzyme	639	AF036933	177..815	*Pseudomonas*
Type B-5	*catB9*		Inactivating enzyme	630	AF462019	27..656	*Vibrio*
Type B-6	*catB10*		Inactivating enzyme	633	AF878850	1197..1829	*Pseudomonas*
Type E-1	*cmlA1*	*cmlA, cmlA2, cmlA4, cmlA5, cmlA6, cmlA7, cmlA8, cmlA10, cmlB*	Efflux	1,260	M64556	601..1860	*Acinetobacter, Aeromonas, Arcanobacterium, Enterobacter, Escherichia, Klebsiella, Pseudomonas, Salmonella, Serratia, Staphylococcus*
Type E-2	*cml*		Efflux	903	M22614	427..1335	*Escherichia*
Type E-3	*floR*	*cmlA*-like, *flo, pp-flo, cmlA9*	Efflux	1,215	AF071555	4445..5659	*Acinetobacter, Aeromonas, Bordetella, Pasteurella, Salmonella, Stenotrophomonas, Vibrio*
Type E-4	*fexA*		Efflux	1,428	AJ549214	177..1604	*Bacillus, Staphylococcus*
Type E-5	*cml*		Efflux	1,179	X59968	508..1686	*Corynebacterium, Pseudomonas*
Type E-6	*cmlv*		Efflux	1,311	U09991	28..1338	*Staphylococcus*
Type E-7	*cmrA*	*cmr*	Efflux	1,176	Z12001	993..2168	Uncultured
Type E-8	*cmr*	*cmx*	Efflux	1,176	U85507	3518..4693	*Acinetobacter, Escherichia, Klebsiella, Salmonella, Serratia, Shigella*
	cfr		Inactivating enzyme	1,050	AJ579365	6290..7339	*Aeromonas, Agrobacterium, Escherichia, Haemophilus, Photobacterium, Salmonella*
	pexA		Efflux	1,248	HM537013	24055..25302	*Actinobacillus, Edwardsiella, Klebsiella, Mannheimia, Pasteurella, Shigella*

Adapted from Partridge et al. (2009), Schwarz et al. (2004). ***§*** *Partial sequence.* ******* *Protein accession number, nucleotide sequence not available in DNA library.*

due to the presence of various different genes. The AR determinants responsible include rRNA methylases, efflux, and inactivating genes (Roberts et al., 1999; Roberts, 2008). The latter group can be further subdivided in esterases, lyases, phosphorylases, and transferases (**Table 4**).

The most common mechanism of MLS resistance is due to the presence of rRNA methylases, encoded by the *erm* genes. These enzymes methylate the adenine residue(s) resulting in MLS resistance. The methylated adenine prevents the binding of the drugs from binding to the 50S ribosomal subunit. The other two mechanisms efflux pumps and inactivating genes are encoded by *msr* and *ere* determinants, respectively.

Because currently over 60 MLS resistance genes are recognized a nomenclature for naming these genes has been proposed that considers the same rules developed for identifying and naming new tetracycline resistance genes (see below; Roberts et al., 1999; Roberts, 2008). **Table 4** represents the MLS acquired resistance genes. The genes included, the resistance mechanism, diverse gene lengths and accession number, and their distribution are displayed in this table.

QUINOLONE

History and action mechanism

In 1962, during the process of synthesis and purification of chloroquine (an antimalarial agent), a quinolone derivative, nalidixic acid, was discovered which possessed bactericidal activity against Gram-negatives (Lescher et al., 1962). The second generation quinolones arose when it became clear that the addition of a fluoride atom at position 6 of a quinolone molecule, creating a fluoroquinolone, greatly enhanced its biological activity. During the 1980s, various fluoroquinolones were developed, e.g., ciprofloxacin, norfloxacin, and ofloxacin. These fluoroquinolones demonstrated a broadened antimicrobial spectrum, including some Gram-positives (Wolfson and Hooper, 1989; Hooper, 2000; King et al., 2000).

In the 1990s, further alterations resulted in the third-generation (fluoro)quinolones, e.g., levofloxacin and sparfloxacin, showing potent activity against both Gram-negative and Gram-positive microbes. The new compounds, such as trovafloxacin, also show promising activity against anaerobic bacteria (Hooper, 2000; King et al., 2000).

Table 4 | Acquired macrolide–lincosamide–streptogramin B (MLS) resistance genes.

Gene	Gene(s) included	Mechanism	Length (nt)	Accession number	Coding region	Genera
car(A)		Efflux	1,656	M80346	411..2066	*Streptomyces*
cfr		rRNA methylase	1,050	AM408573	10028..11077	*Staphylococcus*
cmr		Other	1,380	U43535	646..2025	*Corynebacterium*
ere(A)		Inactivating enzyme[A]	1,221	AY183453	2730..3950	*Citrobacter*, *Enterobacter*, *Escherichia*, *Klebsiella*, *Pantoea*, *Providencia*, *Pseudomonas*, *Serratia*, *Staphylococcus*, *Stenotrophomonas*, *Vibrio*
ere(B)		Inactivating enzyme[A]	1,260	X03988	383..1642	*Acinetobacter*, *Citrobacter*, *Enterobacter*, *Escherichia*, *Klebsiella*, *Proteus*, *Pseudomonas*, *Staphylococcus*
ere(C)		Inactivating enzyme[A]	1,257	FN396877	943..2199	*Klebsiella*
erm(A)	*erm*(TR)	rRNA methylase	732	X03216	4551..5282	*Aggregatibacter*, *Bacteroides*, *Enterococcus*, *Helcococcus*, *Peptostreptococcus*, *Prevotella*, *Staphylococcus*, *Streptococcus*
erm(B)	*erm*(2), *erm*(AM), *erm*(AMR), *erm*(BC), *erm*(BP), *erm*(BZ), *erm*(IP), *erm*(P)	rRNA methylase	738	M36722	714..1451	*Aggregatibacter*, *Acinetobacter*, *Aerococcus*, *Arcanobacterium*, *Bacillus*, *Bacteroides*, *Citrobacter*, *Corynebacterium*, *Clostridium*, *Enterobacter*, *Escherichia*, *Eubacterium*, *Enterococcus*, *Fusobacterium*, *Gemella*, *Haemophilus*, *Klebsiella*, *Lactobacillus*, *Micrococcus*, *Neisseria*, *Pantoea*, *Pediococcus*, *Peptostreptococcus*, *Porphyromonas*, *Proteus*, *Pseudomonas*, *Ruminococcus*, *Rothia*, *Serratia*, *Staphylococcus*, *Streptococcus*, *Treponema*, *Wolinella*
erm(C)	*erm*(IM), *erm*(M)	rRNA methylase	735	M19652	988..1722	*Aggregatibacter*, *Actinomyces*, *Bacillus*, *Bacteroides*, *Corynebacterium*, *Eubacterium*, *Enterococcus*, *Haemophilus*, *Lactobacillus*, *Micrococcus*, *Neisseria*, *Prevotella*, *Peptostreptococcus*, *Staphylococcus*, *Streptococcus*, *Wolinella*
erm(D)	*erm*(J), *erm*(K)	rRNA methylase	864	M29832	430..1293	*Bacillus*, *Salmonella*
erm(E)	*erm*(E2)	rRNA methylase	1,146	X51891	190..1335	*Bacteroides*, *Eubacterium*, *Fusobacterium*, *Ruminococcus*, *Shigella*, *Streptomyces*
erm(F)	*erm*(FS), *erm*(FU)	rRNA methylase	801	M14730	241..1041	*Aggregatibacter*, *Actinomyces*, *Bacteroides*, *Clostridium*, *Corynebacterium*, *Eubacterium*, *Enterococcus*, *Fusobacterium*, *Gardnerella*, *Haemophilus*, *Lactobacillus*, *Mobiluncus*, *Neisseria*, *Porphyromonas*, *Prevotella*, *Peptostreptococcus*, *Ruminococcus*, *Shigella*, *Selenomonas*, *Staphylococcus*, *Streptococcus*, *Treponema*, *Veillonella*, *Wolinella*
erm(G)		rRNA methylase	735	M15332	672..1406	*Bacillus*, *Bacteroides*, *Catenibacterium*, *Lactobacillus*, *Prevotella*, *Porphyromonas*, *Staphylococcus*
erm(H)	*car*(B)	rRNA methylase	900	M16503	244..1143	*Streptomyces*
erm(I)	*mdm*(A)	rRNA methylase		–		*Streptomyces*
erm(N)	*tlr*(D)	rRNA methylase	876	X97721	160..1035	*Streptomyces*
erm(O)	*lrm*, *srm*(A)	rRNA methylase	783	M74717	40..822	*Streptomyces*
erm(Q)		rRNA methylase	774	L22689	262..1035	*Aggregatibacter*, *Bacteroides*, *Clostridium*, *Staphylococcus*, *Streptococcus*, *Wolinella*

(Continued)

Table 4 | Continued

Gene	Gene(s) included	Mechanism	Length (nt)	Accession number	Coding region	Genera
erm(R)		rRNA methylase	1,023	M11276	333..1355	*Arthrobacter*
erm(S)	*erm*(SF), *tlr*(D)	rRNA methylase	960	M19269	460..1419	*Streptomyces*
erm(T)	*erm*(GT), *erm*(LF)	rRNA methylase	735	M64090	168..902	*Enterococcus*, *Lactobacillus*, *Streptococcus*
erm(U)	*lrm*(B)	rRNA methylase	837	X62867	361..1197	*Streptomyces*
erm(V)	*erm*(SV)	rRNA methylase	780	U59450	397..1176	*Eubacterium*, *Fusobacterium*, *Streptomyces*
erm(W)	*myr*(B)	rRNA methylase	936	D14532	1039..1974	*Micromonospora*
erm(X)	*erm*(CD) *erm*(Y)	rRNA methylase	855	M36726	296..1150	*Arcanobacterium*, *Bifidobacterium*, *Corynebacterium*, *Propionibacterium*
erm(Y)	*erm*(GM)	rRNA methylase	735	AB014481	556..1290	*Staphylococcus*
erm(Z)	*srm*(D)	rRNA methylase	849	AM709783	2817..3665	*Streptomyces*
erm(30)	*pikR1*	rRNA methylase	1,011	AF079138	1283..2293	*Streptomyces*
erm(31)	*pikR2*	rRNA methylase	969	AF079138	154..1122	*Streptomyces*
erm(32)	*tlr*(B)	rRNA methylase	843	AJ009971	1790..2632	*Streptomyces*
erm(33)		rRNA methylase	732	AJ313523	163..894	*Staphylococcus*
erm(34)		rRNA methylase	846	AY234334	355..1200	*Bacillus*
erm(35)		rRNA methylase	801	AF319779	33..833	*Bacteroides*
erm(36)		rRNA methylase	846	AF462611	186..1031	*Micrococcus*
erm(37)	*erm*(MT)	rRNA methylase	540	AE000516	2229013.. 2229552	*Mycobacterium*
erm(38)		rRNA methylase	1,161	AY154657	63..1223	*Mycobacterium*
erm(39)		rRNA methylase	741	AY487229	2153..2893	*Mycobacterium*
erm(40)		rRNA methylase	756	AY570506	2035..2790	*Mycobacterium*
erm(41)		rRNA methylase	522	EU590124	258..779	*Mycobacterium*
erm(42)	*erm*(MI)	rRNA methylase	906	FR734406	1..906	*Pasteurella, Photobacterium*
lmr(A)		Efflux	1,446	X59926	318..1763	*Streptomyces*
lnu(A)	*lin*(A)	Inactivating enzyme[C]	486	M14039	413..898	*Clostridium*, *Lactobacillus*, *Staphylococcus*
lnu(B)	*lin*(B)	Inactivating enzyme[C]	804	AJ238249	127..930	*Clostridium*, *Enterococcus*, *Staphylococcus*, *Streptococcus*
lnu(C)		Inactivating enzyme[C]	495	AY928180	1150..1644	*Streptococcus*

(Continued)

Table 4 | Continued

Gene	Gene(s) included	Mechanism	Length (nt)	Accession number	Coding region	Genera
lnu(D)		Inactivating enzyme[C]	495	EF452177	19..513	*Streptococcus*
lnu(F)	*lin*(F), *lin*(G)	Inactivating enzyme[C]	822	EU118119	1030..1851	*Escherichia, Salmonella*
lsa(A)	*abc-23*	Efflux	1,497	AY225127	41..1537	*Enterococcus*
lsa(B)	*orf3*	Efflux	1,479	AJ579365	4150..5628	*Staphylococcus*
lsa(C)		Efflux	1,479	HM990671	5193..6671	*Gardnerella, Streptococcus*
mdf(A)		Other	1,233	Y08743	1..1233	*Escherichia, Shigella*
mdt(A)		Other	1,257	X92946	10534..11790	*Lactococcus*
mef(A)		Efflux	1,218	U70055	314..1531	*Acinetobacter, Bacteroides, Citrobacter, Clostridium, Corynebacterium, Enterococcus, Enterobacter, Escherichia, Fusobacterium, Gemella, Klebsiella, Lactobacillus, Micrococcus, Morganella, Neisseria, Pantoea, Providencia, Proteus, Ralstonia, Pseudomonas, Salmonella, Serratia, Staphylococcus, Streptococcus, Stenotrophomonas*
mef(B)		Efflux	1,230	FJ196385	11084..12313	*Escherichia*
mef(E)		Efflux	1,218	U83667	1..1218	*Enterococcus, Fusobacterium, Gemella, Granulicatella, Staphylococcus, Streptococcus*
mef(G)		Efflux	1,218	DQ445270	1..1218	*Streptococcus*
mph(A)	*mph*(K)	Inactivating enzyme[D]	906	D16251	1626..2531	*Aeromonas, Escherichia, Citrobacter, Enterobacter, Klebsiella, Pantoea, Pseudomonas, Proteus, Serratia, Shigella, Stenotrophomonas*
mph(B)	*mph*(B)	Inactivating enzyme[D]	909	D85892	1159..2067	*Escherichia, Enterobacter, Proteus, Pseudomonas*
mph(C)	*mph*(BM)	Inactivating enzyme[D]	900	AF167161	5665..6564	*Staphylococcus, Stenotrophomonas*
mph(D)		Inactivating enzyme[D]	840[§]	AB048591	1..840	*Escherichia, Klebsiella, Pantoea, Proteus, Pseudomonas, Stenotrophomonas*
mph(E)	*mph, mph1, mph2*	Inactivating enzyme[D]	884	AY522431 AF550415 DQ839391	22181..23064	*Citrobacter, Escherichia*
mre(A)		Efflux	936	U92073	119..1054	*Streptococcus*
msr(A)	*msr*(B), *msr*(SA)	Efflux	1,467	X52085	343..1809	*Corynebacterium, Enterobacter, Enterococcus, Gemella, Pseudomonas, Staphylococcus, Streptococcus*
msr(C)		Efflux	1,479	AY004350	496..1974	*Enterococcus*
msr(D)	*mel, orf5*	Efflux	1,464	AF274302	2462..3925	*Acinetobacter, Bacteroides, Citrobacter, Clostridium, Corynebacterium, Enterococcus, Enterobacter, Escherichia, Gemella, Fusobacterium, Klebsiella, Morganella, Neisseria, Proteus, Providencia, Pseudomonas, Ralstonia, Staphylococcus, Streptococcus, Serratia, Stenotrophomonas*
msr(E)	*mel*	Efflux	1,476	AY522431	20650..22125	*Citrobacter, Escherichia*
ole(B)		Efflux	1,710	L36601	1421..3130	*Streptomyces*
ole(C)		Efflux	978	L06249	1528..2505	*Streptomyces*
srm(B)		Efflux	1,653	X63451	558..2210	*Streptomyces*
tlc(C)		Efflux	1,647	M57437	277..1923	*Streptomyces*
vat(A)		Inactivating enzyme[C]	660	L07778	258..917	*Staphylococcus*

(Continued)

Table 4 | Continued

Gene	Gene(s) included	Mechanism	Length (nt)	Accession number	Coding region	Genera
vat(B)		Inactivating enzyme[C]	639	U19459	67..705	*Enterococcus, Staphylococcus*
vat(C)		Inactivating enzyme[C]	639	AF015628	1307..1945	*Staphylococcus*
vat(D)	*sat*(A)	Inactivating enzyme[C]	630	L12033	162..791	*Enterococcus*
vat(E)	*sat*(G), *vat*(E-3)–*vat*(E-8)	Inactivating enzyme[C]	645	AF139725	63..707	*Enterococcus, Lactobacillus*
vat(F)		Inactivating enzyme[C]	666	AF170730	70..735	*Yersinia*
vat(G)		Inactivating enzyme[C]	651	GQ205627	3037..3687	*Enterococcus*
vga(A)	*vga*	Efflux	1,569	M90056	909..2477	*Staphylococcus*
$vga(A)_{LC}$	*vga*	Efflux	1,569	DQ823382	1..1569	*Staphylococcus*
vga(B)		Efflux	1,659	U82085	629..2287	*Enterococcus, Staphylococcus*
vga(C)	*vga*(D)	Efflux	1,578	GQ205627	1394..2971	*Enterococcus*
vgb(A)	*vgb*	Inactivating enzyme[B]	900	M20129	641..1540	*Enterococcus, Staphylococcus*
vgb(B)		Inactivating enzyme[B]	888	AF015628	399..1286	*Staphylococcus*

Adapted from http://faculty.washington.edu/marilynr/. [§]Partial sequence. [A]Esterase, [B]Lyase, [C]Transferase, [D]Phosphorylase.

Quinolones inhibit the action of DNA gyrase and topoisomerase IV, two enzymes essential for bacterial DNA replication and as a result the microbes are killed. (Hooper, 1995, 2000). DNA gyrase is a tetrameric enzyme composed of 2 GyrA and 2 GyrB subunits. The topoisomerase IV has a similar structure, comprised of 2 A and 2 B subunits, encoded by *parC* and *parE*, respectively. The four genes coding for the subunits of these enzymes are the targets for resistance mutations (see below).

Resistance mechanism

For decades, the mechanisms of resistance to quinolones were believed to be only chromosome-encoded, however, recently three plasmid-mediated resistance mechanisms have been reported (Robicsek et al., 2006a; Courvalin, 2008; Martínez-Martínez et al., 2008). The chromosome-encoded resistance result in either a decreased outer-membrane permeability related to porin loss, to the (over)expression of naturally occurring efflux pumps or mutations of the molecular targets DNA gyrase and topoisomerase IV (Hooper, 2000; Ruiz, 2003; Jacoby, 2005). In the latter case mutations occur at specific "quinolone resistance determining regions" (QRDR) in the genes *gyrA*, *gyrB*, *parC,* and *parE* encoding the subunits of DNA gyrase and topoisomerase IV. Not surprisingly this QRDR is situated on the DNA-binding surface of the enzymes (Jacoby, 2005).

Although the possibility of the existence of plasmid-mediated resistance was already suggested in 1990 (Courvalin, 1990), the first actually identified plasmid-mediated quinolone resistance gene, a *qnr* determinant, which encodes for a protein that protects DNA gyrase and type IV topoisomerase from quinolone inhibition, was reported nearly a decade later (Martínez-Martínez et al., 1998).

Currently five families of *qnr* genes have been reported; *qnrA* (7), *qnrB* (39), *qnrC* (1), *qnrD* (1), and *qnrS* (4). The number in between brackets indicates the variants known of each type (Jacoby et al., 2008; Cattoir and Nordmann, 2009; Cavaco et al., 2009; Strahilevitz et al., 2009; Torpdahl et al., 2009). Because of the increasing number of *qnr* genes a database has been constructed and will be maintained to assign further allele numbers to novel variants[2]. Very recently an additional family has been described, qnrAS in the fish pathogen *Aliivibrio salmonicida* (Sun et al., 2010). **Table 5** describes all known *qnr* families and their variants, together with the gene lengths, accession numbers, and in which bacterial genera they have been identified so far.

The second type of plasmid located quinolone resistant gene is a cr variant of *aac(6′)-Ib*, *aac(6′)-Ib-cr*, responsible for low-level ciprofloxacin resistance. It encodes an aminoglycoside acetyltransferase, called AAC(6′)-Ib-cr which has two amino acid changes, Trp102Arg and Asp179Tyr. These substitutions are responsible for the enzyme's ability to acetylate ciprofloxacin (Park et al., 2006; Robicsek et al., 2006b; Strahilevitz et al., 2009).

The third mechanism is *qepA*, a plasmid-mediated efflux pump which can extrude hydrophilic fluoroquinolones, e.g., ciprofloxacin and enrofloxacin (Périchon et al., 2007; Yamane et al., 2007). A variant of this resistance pump, QepA2, was identified in an *E. coli* isolate from France (Cattoir et al., 2008).

[2]www.lahey.org/qnrstudies

Table 5 | Acquired quinolone resistance genes.

Gene*	Length (nt)	Accession number	Coding region	Genera
qepA	1,536	AB263754	7052..8587	*Escherichia*
qepA2	1,536	EU847537	1672..3207	*Escherichia*
qnrA1	657	AY070235	303..959	*Citrobacter*, *Enterobacter*, *Escherichia*, *Klebsiella*, *Shigella*
qnrA2	657	AY675584	1..657	*Klebsiella*, *Shewanella*
qnrA3	657	DQ058661	1..657	*Shewanella*
qnrA4	657	DQ058662	1..657	*Shewanella*
qnrA5	657	DQ058663	1..657	*Shewanella*
qnrA6	657	DQ151889	1..657	*Proteus*
qnrA7	657	GQ463707	1..657	*Shewanella*
qnrAS	657	FM178379	1699484..1700140	*Aliivibrio*
qnrB1	645	DQ351241	37..681	*Enterobacter*, *Escherichia*, *Klebsiella*
qnrB2	645	DQ351242	1..645	*Citrobacter*, *Enterobacter*,, *Klebsiella*, *Salmonella*
qnrB3	645	DQ303920	37..681	*Escherichia*
qnrB4	645	DQ303921	4..648	*Citrobacter*, *Enterobacter*, *Escherichia*, *Klebsiella*
qnrB5	645	DQ303919	37..681	*Enterobacter*, *Salmonella*
qnrB6	645	EF520349	37..681	*Enterobacter*, *Escherichia*, *Klebsiella*, *Pantoea*
qnrB7	645	EU043311	1..645	*Enterobacter*, *Klebsiella*
qnrB8	645	EU043312	1..645	*Citrobacter*, *Enterobacter*
qnrB9	645	EF526508	1..645	*Citrobacter*
qnrB10	645	DQ631414	37..681	*Citrobacter*, *Enterobacter*, *Escherichia*, *Klebsiella*
qnrB11	645	EF653270	4..648	*Citrobacter*
qnrB12	645	AM774474	2435..3079	*Citrobacter*
qnrB13	645	EU273756	37..681	*Citrobacter*
qnrB14	645	EU273757	37..681	*Citrobacter*
qnrB15	645	EU302865	37..681	*Citrobacter*
qnrB16	645	EU136183	37..681	*Citrobacter*
qnrB17	645	AM919398	37..681	*Citrobacter*
qnrB18	645	AM919399	37..681	*Citrobacter*
qnrB19	645	EU432277	1..645	*Escherichia*, *Klebsiella*, *Salmonella*
qnrB20	645	AB379831	37..681	*Escherichia*, *Klebsiella*
qnrB21	645	FJ611948	1..645	*Escherichia*
qnrB22	645	FJ981621	37..681	*Citrobacter*
qnrB23	645	FJ981622	37..681	*Citrobacter*
qnrB24	645	HM192542	37..681	*Citrobacter*
qnrB25	645	HQ172108	1..645	*Citrobacter*
qnrB26	645	HM439644	1..645	*Citrobacter*
qnrB27	645	HM439641	1..645	*Citrobacter*
qnrB28	645	HM439643	1..645	*Citrobacter*
qnrB29	645	HM439649	37..681	*Citrobacter*
qnrB30	645	HM439650	37..681	*Citrobacter*
qnrB31	645	HQ418999	1..681	*Klebsiella*
***qnrB32*– *qnrB39* not public yet**				
qnrC	666	EU917444	1717..2382	*Proteus*
qnrD	645	EU692908	1..645	*Salmonella*
qnrS1	657	AB187515	9737..10393	*Enterobacter*, *Escherichia*, *Klebsiella*, *Proteus*, *Salmonella*, *Shigella*
qnrS2	657	DQ485530	1..657	*Aeromonas*, *Salmonella*
qnrS3	657	EU077611	1..656	*Escherichia*
qnrS4	657	FJ418153	1..657	*Salmonella*

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STREPTOTHRICIN

History and action mechanism

In the early days of the antibiotics era screening for new compound resulted in the discovery of a *Streptomyces lavendulae* isolate which inhibited growth of Gram-negative as well as Gram-positive bacteria. Isolation of the active antimicrobial substance resulted in the identification of streptothricin (Waksman and Woodruff, 1942). Delayed toxicity prevents streptothricin's use in man, but it is effective in preventing animal infections.

Streptothricins consist of three moieties: gulosamine, streptolidin, and a β-lysine peptide chain. Since, the discovery of the streptothricin, six analogs have been reported, streptothricin A–F. The analogs differ from the parent molecule in the number of β-lysine residues (Keeratipibul et al., 1983; Tschäpe et al., 1984).

The streptothricins are potent inhibitors of bacterial protein synthesis, via direct binding to ribosomes. They also cause misreading of mRNA codons, although they are unrelated to other drugs that cause translational ambiguity, like the aminoglycosides (Tschäpe et al., 1984).

Resistance mechanism

Since streptothricin is inactivated by acetylation in its producer it is not surprising that the identified resistance mechanisms are acetyltransferases. The first streptothricin resistant bacterium identified was an *E. coli* isolate from a rectal swab of pigs under streptothricin F treatment. The AR gene was localized on a transferable plasmid (Tschäpe et al., 1984). Currently three different streptothricin acetyltransferases are recognized, *sat2–sat4* (Partridge and Hall, 2005; see **Table 1**).

SULFONAMIDE

History and action mechanism

Sulfonamides belong to the oldest introduced synthetic drugs. They were first used in 1932 (Domagk, 1935; Sköld, 2001). A number of different sulfonamides have been developed of which the most commonly used nowadays is sulfamethoxazole. Moreover, since 1968, the combination of trimethoprim and sulfamethoxazole (called co-trimoxazole) has been used extensively because a combination of both drugs at certain concentrations has a synergetic bactericidal effect, it reduces selection of AR to either drug and associated costs (Roberts, 2002; Grape, 2006).

A sulfonamide, with its structural analogy to *p*-aminobenzoic acid, which is involved in the biosynthetic pathway leading to folic acid, competitively inhibits the enzyme dihydropteroate synthase (DHPS). This protein is part of the next to last step of the folate biosynthetic pathway that is required for thymine production and bacterial cell growth (Sköld, 2000, 2001; Roberts, 2002).

Resistance mechanism

Resistance to sulfonamide among pathogenic bacteria appeared quite soon after its introduction into clinical practice in the 1930s (Sköld, 2001). Since sulfonamides are synthetic antibacterial agents, naturally occurring enzymes degrading, or modifying this drug were not to be expected. However, chromosomal sulfonamide resistance occurs, mostly low level, by mutations in the *folP* gene encoding DHPS (Huovinen et al., 1995; Sköld, 2000, 2001; Grape, 2006).

Acquired sulfonamide resistance was discovered in the 1960s, but the plasmid-mediated genes were characterized later on in the 1980s as *sul1* and *sul2* (Swedberg and Sköld, 1983; Rådström and Swedberg, 1988; Sundström et al., 1988). Currently three plasmid-borne drug-resistant variants of the DHPS enzymes are known; besides the two genes mentioned above also *sul3* has been identified (Perreten and Boerlin, 2003).

TETRACYCLINE

History and action mechanism

The first tetracycline antibiotic was characterized in 1948 as chlortetracycline from *Streptomyces aureofaciens* (Chopra et al., 1992; Chopra and Roberts, 2001). In consecutive decades additional tetracyclines were identified either as naturally occurring molecules mostly in *Streptomyces* species (e.g., oxytetracycline, tetracycline) or products of semi-synthetic approaches (e.g., doxycycline, minocycline; Chopra et al., 1992; Hunter and Hill, 1997; Chopra and Roberts, 2001).

Tetracyclines were the first major group to which the term "broad spectrum" was applied (Chopra and Roberts, 2001). Because of this spectrum of activity, their relative safety, and low cost, tetracyclines have been used widely throughout the world and are second after penicillin in world consumption. This class of antibiotic can be separated into two groups, typical, (e.g., chlortetracycline, doxycycline, minocycline, oxytetracycline, and tetracycline) and atypical tetracyclines (e.g., anhydrotetracycline and 6-thiatetracycline), see below (Rasmussen et al., 1991; Oliva and Chopra, 1992; Chopra and Roberts, 2001).

Initially, it was thought that tetracyclines and most of its derivatives are antimicrobial agents only because they inhibit the growth of microbes by entering the bacterial cell, interacting with the ribosomes, and consequently blocking protein synthesis, the so-called typical tetracyclines (Speer et al., 1992; Roberts, 2002). However, Oliva and Chopra (1992) suggested an additional mode of action. Certain tetracycline derivatives are poor inhibitors of protein synthesis and appear to bind ribosomes inefficiently or not at all, in stead they interact with the bacterial membrane (Rasmussen et al., 1991; Chopra, 1994).

Resistance mechanism

Prior to the mid-1950s, the majority of commensals and pathogens were susceptible to tetracycline. However, in 1953 the first tetracycline resistant bacteria were isolated (Watanabe, 1963). The resistance mechanisms for the tetracycline class of antibiotics fall in three categories; energy-dependent efflux pumps, ribosomal protection proteins (RPPs), or enzymatic inactivation.

A novel tetracycline resistance determinant is identified as unique if it shares <79% amino sequence identity with all previously described genes. Initially, letters of the Roman alphabet have been used to name tetracycline resistance determinants. However, the number of *tet* genes has reached the end of the alphabet and to accommodate new genes, a nomenclature employing numerals for future determinants was introduced (Levy et al., 1999). Moreover, also naturally occurring hybrid tetracycline resistance genes exist. A simple, descriptive nomenclature for these mosaic *tet* determinants has been proposed incorporating the designations of the known tet genes classes forming the hybrid, e.g., *tet*(O/W) and

tet(O/W/O; Levy et al., 2005; Stanton et al., 2005; van Hoek et al., 2008).

There are currently over 40 different acquired tetracycline resistance determinants recognized, i.e., 38 *tet* (tetracycline resistance) and 3 *otr* (oxytetracycline resistance) genes, additionally 1 *tcr* gene has been identified (Roberts, 1996, 2005; Brown et al., 2008; see **Table 6**). Among these 25 of the *tet*, 2 of the *otr* genes and the only *tcr* determinant code for efflux pumps, whereas 10 *tet* and 1 *otr* code for a RPP. The enzymatic inactivation mechanism can be attributed to 3 *tet* genes. The *tet*(U) determinant represents an unknown tetracycline resistance mechanism since its sequence does not appear to be related to either efflux or RPPs, nor to the inactivation enzymes (**Table 6**). The efflux and RPP encoding genes are found in members of Gram-positive, Gram-negative, aerobic, as well as anaerobic bacterial species. In contrast the enzymatic tetracycline inactivation mechanism has so far only been identified in Gram-negatives (**Table 6**). The *tet*(M) has the broadest host range of all tetracycline resistance genes, whereas *tet*(B) gene has the widest range among the Gram-negative microbes. In recent years published data indicate that there are increasing numbers of Gram-negative bacteria that carry "Gram-positive *tet* genes" (Roberts, 2002).

TRIMETHOPRIM

History and action mechanism

Trimethoprim has been available since 1962 and is considered the last truly new antibacterial agent introduced into clinical practice (Roth et al., 1962). All later developed agents have been variations of older antibiotics, that is, belonging to families of agents, within which cross-resistance is common (Sköld, 2001; Roberts, 2002). Trimethoprim is a completely synthetic drug, belonging to the diaminopyrimidine group of compounds, i.e., 5-benzyl-2,4-diamino-pyrimidine (Huovinen, 1987).

Trimethoprim inhibits the enzyme dihydrofolate reductase (DHFR) by competitively binding to its active site. DHFR catalysis the NAHPH-dependent reduction of dihydrofolate acid to the active co-enzyme tetrahydrofolate. As such trimethoprim can be regarded as an antifolate, a structural analog of folic acid. DHFR, like DHPS is part of the folate biosynthetic pathway (Sköld, 2001; Grape, 2006; see section Sulfonamides).

Resistance mechanism

Because trimethoprim like sulfonamide is a synthetic antibacterial agent, naturally occurring enzymes degrading, or modifying it are unlikely. However, resistance, mostly low level, can for example occur via non-allelic and drug-resistant variants of the chromosomal *folA* gene encoding the bacterial DHFR (Huovinen et al., 1995; Sköld, 2001; Grape, 2006).

High-level resistance is generally achieved by a bypass mechanism through the action of an acquired gene which is a non-allelic and drug-insusceptible variant of a chromosomal DHFR. These plasmid-mediated DHFRs emerged in Gram-negative bacteria within several years of the clinical introduction of the drug (Fleming et al., 1972; Huovinen and Toivanen, 1980; Amyes and Towner, 1990).

Initially, the acquired DHFRs fell into two quite distinct families, *dfrA* and *dfrB* genes (Howell, 2005). Members of the *dfrA* group are at least 474 nucleotides (nt) long (157 amino acids, aa), whereas the *dfrB* genes are 237 nt in length (78 aa). Currently six plasmid-mediated families can be distinguished with relatively few *dfr* determinants originating from Gram-positive bacteria. (**Table 7**). The *dfrK* gene is the newest addition to the trimethoprim resistance determinant family (Kadlec and Schwarz, 2009). In contrast to the latest reported DHFRs, the oldest families, *dfrA* and *dfrB*, each contain several members (Roberts, 2002; Levings et al., 2006). For example, the *dfrA* group accommodates over 30 genes. Determinant *dfrA27* is the newest reported DHFR gene among Gram-negatives (Wei et al., 2009), although a newer, however unpublished, *dfrA* variant is present in the public DNA library and some genes apparently have changed nomenclature (**Table 7**). Among this family two sub-families can be distinguished (Adrian et al., 2000). The *dfrA1*-group with 12 different genes share 64–90% identity on amino acids level. The *dfrA12*-group, with five members, display 84% amino acid identity and similar trimethoprim-inhibition profiles. The additional *dfrA* genes are less related to each other, some have even less than 25% amino acid sequence identity. In contrast to the *dfrA* family, the *dfrB* group is somewhat smaller, with only eight reported genes (Levings et al., 2006; Partridge et al., 2009).

MOBILE GENETIC ELEMENTS

Acquired AR genes are frequently contained within mobile DNA which can be loosely defined as any segment of DNA that is capable of translocation from one part of a genome to another or between genomes. This definition includes a wide range of distinct mobile elements. The major players in HGT are the conjugative and mobilizable elements, the former contain all the genetic information required to transfer from one bacterium to another whilst the latter use the conjugation functions of co-resident conjugative elements (conjugative plasmids or conjugative transposons) to transfer to another host. Bacteriophages also play a role in the spread of DNA between bacteria, they do this by a process called transduction in which bacterial DNA, rather than phage DNA, is packaged into the phage head and injected into the recipient bacterium. There are also elements which are capable of translocation to new sites in the genome but are not themselves capable of transfer to a new host (of course if they transpose to a conjugative element they can be moved to new hosts). These include the transposons and the mobile introns.

Bacteria can also acquire AR genes by transformation. The process occurs in both Gram-positive and Gram-negative bacteria. Bacteria capable of taking up DNA from the environment are termed "competent." Some microorganisms, such as many streptococci, are competent at a specific stage in their growth whilst others have no obvious competence window. Some bacteria have specific sequence requirements to successfully take up DNA such as *Neisseria* (Smith et al., 1999), while others like *Bacillus subtilis* have no obvious such requirements. In this process naked DNA is taken up by the recipient bacteria and either incorporated into the host genome by homologous recombination or transposition. Alternatively the DNA molecule may be able to replicate autonomously, e.g., plasmids. Mobile genetic elements are often acquired by transformation as well as by conjugation. For a recent review of the mechanisms of transformation see (Kovács

Table 6 | Acquired tetracycline resistance genes.

Gene	Mechanism	Length (nt)	Accession number	Coding region	Genera
otr(A)	Ribosomal protection	1,992	X53401	349..2340	*Mycobacterium*, *Streptomyces*
otr(B)	Efflux	1,692	AF079900	40..1731	*Mycobacterium*, *Streptomyces*
otr(C)	Efflux	1,056	AY509111	324..1379	*Streptomyces*
tcr	Efflux	1,539	D38215	516..2054	*Streptomyces*
tet(A)	Efflux	1,200	X00006	1328..2527	*Acinetobacter*, *Aeromonas*, *Bordetella*, *Chryseobacterium*, *Citrobacter*, *Edwardsiella*, *Enterobacter*, *Escherichia*, *Flavobacterium*, *Klebsiella*, *Laribacter*, *Plesiomonas*, *Proteus*, *Pseudomonas*, *Salmonella*, *Serratia*, *Shigella*, *Variovorax*, *Veillonella*, *Vibrio*
tetA(P)	Efflux	1,263	L20800	1063..2325	*Clostridium*
tet(B)	Efflux	1,206	J01830	1608..2813	*Acinetobacter*, *Actinobacillus*, *Aeromonas*, *Aggregatibacter*, *Brevundimonas*, *Citrobacter*, *Enterobacter*, *Erwinia*, *Escherichia*, *Haemophilus*, *Klebsiella*, *Mannheimia*, *Moraxella*, *Neisseria*, *Pantoea*, *Pasteurella*, *Photobacterium*, *Plesiomonas*, *Proteus*, *Providencia*, *Pseudomonas*, *Roseobacter*, *Salmonella*, *Serratia*, *Shigella*, *Treponema*, *Vibrio*, *Yersinia*
*tet*B(P)	Ribosomal protection	1,959	L20800	2309..4267	*Clostridium*
tet(C)	Efflux	1,191	X01654	86..1276	*Aeromonas*, *Bordetella*, *Chlamydia*, *Citrobacter*, *Enterobacter*, *Escherichia*, *Francisella*, *Halomonas*, *Klebsiella*, *Proteus*, *Pseudomonas*, *Roseobacter*, *Salmonella*, *Serratia*, *Shigella*, *Vibrio*
tet(D)	Efflux	1,185	X65876	1521..2705	*Aeromonas*, *Alteromonas*, *Citrobacter*, *Edwardsiella*, *Enterobacter*, *Escherichia*, *Halomonas*, *Klebsiella*, *Morganella*, *Pasteurella*, *Photobacterium*, *Proteus*, *Salmonella*, *Shewanella*, *Shigella*, *Vibrio*, *Yersinia*
tet(E)	Efflux	1,218	L06940	21..1238	*Aeromonas*, *Alcaligenes*, *Escherichia*, *Flavobacterium*, *Plesiomonas*, *Proteus*, *Providencia*, *Pseudomonas*, *Roseobacter*, *Serratia*, *Vibrio*
tet(G)	Efflux	1,128	AF071555	6644..7771	*Acinetobacter*, *Brevundimonas*, *Escherichia*, *Fusobacterium*, *Mannheimia*, *Ochrobactrum*, *Pasteurella*, *Proteus*, *Providencia*, *Pseudomonas*, *Roseobacter*, *Salmonella*, *Shewanella*, *Vibrio*
tet(H)	Efflux	1,203	U00792	716..1918	*Acinetobacter*, *Actinobacillus*, *Mannheimia*, *Moraxella*, *Pasteurella*
tet(J)	Efflux	1,197	AF038993	1084..2280	*Escherichia*, *Morganella*, *Proteus*
tet(K)	Efflux	1,380	M16217	305..1684	*Bacillus*, *Clostridium*, *Enterococcus*, *Eubacterium*, *Haemophilus*, *Lactobacillus*, *Listeria*, *Mycobacterium*, *Nocardia*, *Nocardia*, *Peptostreptococcus*, *Staphylococcus*, *Streptococcus*, *Streptomyces*
tet(L)	Efflux	1,377	D00006	189..1565	*Acinetobacter*, *Actinobacillus*, *Actinomyces*, *Bacillus*, *Bifidobacterium*, *Citrobacter*, *Clostridium*, *Enterobacter*, *Enterococcus*, *Escherichia*, *Flavobacterium*, *Fusobacterium*, *Geobacillus*, *Kurthia*, *Lactobacillus*, *Listeria*, *Mannheimia*, *Morganella*, *Mycobacterium*, *Nocardia*, *Ochrobactrum*, *Oceanobacillus*, *Paenibacillus*, *Pasteurella*, *Pediococcus*, *Peptostreptococcus*, *Proteus*, *Pseudomonas*, *Rahnella*, *Salmonella*, *Sporosarcina*, *Staphylococcus*, *Streptococcus*, *Streptomyces*, *Variovorax*, *Veillonella*, *Virgibacillus*
tet(M)	Ribosomal protection	1,920	U08812	1981..3900	*Abiotrophia*, *Acinetobacter*, *Actinomyces*, *Aerococcus*, *Aeromonas*, *Afipia*, *Arthrobacter*, *Bacillus*, *Bacterionema*, *Bacteroides*, *Bifidobacterium*, *Brachybacterium*, *Catenibacterium*, *Clostridium*, *Corynebacterium*, *Edwardsiella*, *Eikenella*, *Enterobacter*, *Enterococcus*, *Erysipelothrix*, *Escherichia*, *Eubacterium*, *Flavobacterium*, *Fusobacterium*, *Gardnerella*, *Gemella*, *Granulicatella*, *Haemophilus*, *Kingella*, *Klebsiella*, *Kurthia*, *Lactobacillus*, *Lactococcus*, *Listeria*, *Microbacterium*, *Mycoplasma*, *Neisseria*, *Paenibacillus*, *Pantoea*, *Pasteurella*, *Peptostreptococcus*, *Photobacterium*, *Prevotella*, *Pseudoalteromonas*, *Pseudomonas*, *Ralstonia*, *Selenomonas*, *Serratia*, *Shewanella*, *Staphylococcus*, *Streptococcus*, *Streptomyces*, *Ureaplasma*, *Veillonella*, *Vibrio*

(Continued)

Table 6 | Continued

Gene	Mechanism	Length (nt)	Accession number	Coding region	Genera
tet(O)	Ribosomal protection	1,920	M18896	207..2126	*Actinobacillus*, *Aerococcus*, *Anaerovibrio*, *Bifidobacterium*, *Butyrivibrio*, *Campylobacter*, *Clostridium*, *Enterococcus*, *Eubacterium*, *Fusobacterium*, *Gemella*, *Lactobacillus*, *Megasphaera*, *Mobiluncus*, *Neisseria*, *Peptostreptococcus*, *Psychrobacter*, *Staphylococcus*, *Streptococcus*
tet(Q)	Ribosomal protection	1,926	Z21523	362..2287	*Anaerovibrio*, *Bacteroides*, *Capnocytophaga*, *Clostridium*, *Eubacterium*, *Fusobacterium*, *Gardnerella*, *Lactobacillus*, *Mitsuokella*, *Mobiluncus*, *Neisseria*, *Peptostreptococcus*, *Porphyromonas*, *Prevotella*, *Ruminococcus*, *Selenomonas*, *Streptococcus*, *Subdoligranulum*, *Veillonella*
tet(S)	Ribosomal protection	1,926	L09756	447..2372	*Enterococcus*, *Lactobacillus*, *Lactococcus*, *Listeria*, *Staphylococcus*, *Streptococcus*, *Veillonella*
tet(T)	Ribosomal protection	1,956	L42544	478..2433	*Lactobacillus*, *Streptococcus*
tet(U)	Unknown	318	U01917	413..730	*Enterococcus*, *Staphylococcus*, *Streptococcus*
tet(V)	Efflux	1,260	AF030344	462..1721	*Mycobacterium*
tet(W)	Ribosomal protection	1,920	AJ222769	3687..5606	*Acidaminococcus*, *Actinomyces*, *Arcanobacterium*, *Bacillus*, *Bacteroides*, *Bifidobacterium*, *Butyrivibrio*, *Clostridium*, *Fusobacterium*, *Lactobacillus*, *Megasphaera*, *Mitsuokella*, *Neisseria*, *Porphyromonas*, *Prevotella*, *Roseburia*, *Selenomonas*, *Staphylococcus*, *Streptococcus*, *Streptomyces*, *Subdoligranulum*, *Veillonella*
tet(X)	Enzymatic	1,167	M37699	586..1752	*Bacteroides*, *Sphingobacterium*
tet(Y)	Efflux	1,176	AF070999	1680..2855	*Aeromonas*, *Escherichia*, *Photobacterium*
tet(Z)	Efflux	1,155	AF121000	11880..13034	*Corynebacterium*, *Lactobacillus*
tet(30)	Efflux	1,185	AF090987	1130..2314	*Agrobacterium*
tet(31)	Efflux	1,233	AJ250203	1651..2883	*Aeromonas*
tet(32)	Ribosomal protection	1,920	DQ647324	181..2100	*Enterococcus*, *Eubacterium*, *Clostridium*, *Streptococcus*
tet(33)	Efflux	1,224	AJ420072	22940..24163	*Corynebacterium*
tet(34)	Enzymatic	465	AB061440	306..770	*Aeromonas*, *Pseudomonas*, *Serratia*, *Vibrio*
tet(35)	Efflux	1,110	AF353562	2213..3322	*Stenotrophomonas*, *Vibrio*
tet(36)	Ribosomal protection	1,923	AJ514254	2534..4456	*Bacteroides*, *Clostridium*, *Lactobacillus*
tet(37)	Enzymatic	327	AF540889	1..327	Uncultured
tet(38)	Efflux	1,353	AY825285	1..1353	*Staphylococcus*
tet(39)	Efflux	1,188	AY743590	749..1936	*Acinetobacter*
tet(40)	Efflux	1,221	AM419751	14211..15431	*Clostridium*
tet(41)	Efflux	1,182	AY264780	1825..3006	*Serratia*
tet(42)	Efflux	1,287	EU523697	687..1973	*Bacillus*, *Microbacterium*, *Micrococcus*, *Paenibacillus*, *Pseudomonas*, *Staphylococcus*
tet(43)	Efflux	1,560	GQ244501	60..1619	Uncultured
tet(44)	Ribosomal protection	1,923	FN594949	25245..27167	*Campylobacter*

Adapted from http://faculty.washington.edu/marilynr/

et al., 2009; Aune and Aachmann, 2010; Burton and Dubnau, 2010).

CONJUGATIVE ELEMENTS (PLASMIDS)

Typically plasmids are extra chromosomal elements that contain their own origin of replication. They have been found in almost all bacterial genera and the simplest of these elements just contain an origin of replication and genes encoding replication functions, e.g., see Chambers et al. (1988). Plasmids also commonly contain an origin of transfer and genes encoding functions that allow them to transfer to new hosts via conjugation (Smillie et al., 2010). Plasmids that harbor conjugation genes are called conjugative and plasmids that only contain an origin of transfer (*oriT*) but no conjugation genes are called mobilizable as they can make use of the conjugation functions of conjugative plasmids to transfer to a new host.

In addition to functions involved in replication and transfer plasmids commonly encode resistance to antibiotics. If a resistance

Table 7 | Acquired trimethoprim resistance genes.

Gene	Sub-family	Gene(s) included	Length (nt)	Accession number	Coding region	Genera
dfrA1	*dfrA1*-group	*dhfrIb*, *dfr1*, *dhfrI*	474	X00926	236..709	*Actinobacter*, *Enterobacter*, *Escherichia*, *Klebsiella*, *Morganella*, *Proteus*, *Pseudomonas*, *Salmonella*, *Serratia*, *Shigella*, *Vibrio*
dfrA3			489	J03306	103..591	*Salmonella*
dfrA5	*dfrA1*-group	*dhfrV*, *dfrV*	474	X12868	1306..1779	*Aeromonas*, *Enterobacter*, *Escherichia*, *Klebsiella*, *Salmonella*, *Vibrio*
dfrA6	*dfrA1*-group	*dfrVI*	474	Z86002	336..809	*Escherichia*, *Proteus*, *Vibrio*
dfrA7	*dfrA1*-group	*dhfrVII*, *dfrVII*, *dfrA17*	474	X58425	594..1067	*Actinobacter*, *Escherichia*, *Proteus*, *Salmonella*, *Shigella*
dfrA8			510	U10186	711..1220	*Shigella*
dfrA9			534	X57730	726..1259	*Escherichia*
dfrA10			564	L06418	5494..6057	*Actinobacter*, *Escherichia*, *Klebsiella*, *Salmonella*
dfrA12	*dfrA12*-group	*dhfrXII*, *dfr12*	498	Z21672	310..807	*Actinobacter*, *Aeromonas*, *Enterobacter*, *Enterococcus*, *Citrobacter*, *Klebsiella*, *Pseudomonas*, *Serratia*, *Salmonella*, *Staphylococcus*
dfrA13	*dfrA12*-group		498	Z50802	718..1215	*Escherichia*
dfrA14	*dfrA1*-group	*dhfrIb*	474	Z50805	72..545	*Achromobacter*, *Aeromonas*, *Escherichia*, *Klebsiella*, *Salmonella*, *Vibrio*
dfrA15	*dfrA1*-group	*dhfrXVb*	474	Z83311	357..830	*Enterobacter*, *Klebsiella*, *Morganella*, *Proteus*, *Pseudomonas*, *Salmonella*, *Vibrio*
dfrA16	*dfrA1*-group	*dhfrXVI*, *dfr16*	474	AF077008	115..588	*Aeromonas*, *Escherichia*, *Salmonella*
dfrA17	*dfrA1*-group	*dhfrXVII*, *dfr17*	474	AB126604	98..571	*Actinobacter*, *Enterobacter*, *Klebsiella*, *Pseudomonas*, *Salmonella*, *Serratia*, *Shigella*, *Staphylococcus*
dfrA18		*dfrA19*	570	AJ310778	7004..7573	*Enterobacter*, *Klebsiella*, *Salmonella*
dfrA20			510	AJ605332	1304..1813	*Pasteurella*
dfrA21	*dfrA12*-group	*dfrxiii*	498	AY552589	1..498	*Klebsiella*, *Salmonella*
dfrA22	*dfrA12*-group	*dfr22*, *dfr23*	498	AJ628423	325..822	*Escherichia*, *Klebsiella*
dfrA23			561	AJ746361	6743..7303	*Salmonella*
dfrA24			558	AJ972619	83..640	*Escherichia*
dfrA25	*dfrA1*-group		459	DQ267940	54..512	*Citrobacter*, *Salmonella*
dfrA26			552	AM403715	303..854	*Escherichia*
dfrA27	*dfrA1*-group	*dfr*	474	EU675686	2543..3016	*Escherichia*
dfrA28	*dfrA1*-group		474	FM877476	116..589	*Aeromonas*
dfrA29		*dfrVII*, *dfrA7*	472	AM237806	615..1086	*Salmonella*
dfrA30		*dhfrV*	474	AM997279	705..1178	unknown
dfrA31		*dfr6*	474	AB200915	1832..2305	*Vibrio*
dfrA32	*dfrA1*-group		474	GU067642	535..1008	*Laribacter*, *Salmonella*
dfrA33	*dfrA12*-group		498	FM957884	88..585	Unknown
dfrB1		*dhfrIIa*, *dfr2a*	237	U36276	717..953	*Aeromonas*, *Bordetella*, *Escherichia*, *Klebsiella*
dfrB2		*dhfrIIb*, *dfr2b*	237	J01773	809..1045	*Escherichia*
dfrB3		*dhfrIIc*, *dfr2c*	237	X72585	5957..6193	*Aeromonas*, *Enterobacter*, *Escherichia*, *Klebsiella*
dfrB4		*dfr2d*	237	AJ429132	69..305	*Aeromonas*, *Escherichia*, *Klebsiella*
dfrB5		*dfr2e*	237	AY943084	2856..3092	*Pseudomonas*
dfrB6			237	DQ274503	394..630	*Salmonella*
dfrB7			237	DQ993182	244..480	*Aeromonas*
dfrB8			249	GU295656	1048..1296	*Aeromonas*
dfrC		*dfrA*	486	Z48233	337..822	*Staphylococcus*
dfrD			489	Z50141	94..582	*Listeria*, *Staphylococcus*
dfrG			498	AB205645	1013..1510	*Enterococcus*, *Staphylococcus*
dfrK			492	FM207105	2788..3279	*Staphylococcus*

Partly adapted from Grape (2006), Partridge et al. (2009).

gene is on a conjugative or mobilizable plasmid then it has the potential to transfer to new hosts. Some plasmids have a broad host range and can transfer between different species whereas others have a much narrower host range and are confined to one genus or species. There are also plasmids that have the capability of transferring to a particular host but cannot replicate in the new host or do not replicate well. In these circumstances the plasmid may be lost, however if it contains a resistance gene on a transposon this genetic element can translocate to the bacterial chromosome and be maintained in the absence of the plasmid. Therefore a plasmid does not necessarily need to be maintained in a particular host in order to contribute to the spread of resistance.

Both circular and linear plasmids have been described. Circular plasmids have in general been more intensively investigated then linear plasmids. This probably reflects the relative ease which they can be separated from the bacterial chromosome. Nonetheless linear plasmids have now been relatively well characterized and have been shown to convey advantageous phenotypes on the host. Like circular plasmids linear plasmids are often capable of conjugation (Meinhart et al., 1997; Chaconas and Kobryn, 2010).

Some (resistance) plasmid types cannot coexist in a microbial cell and this fact gave rise to the division into incompatibility groups (Couturier et al., 1988). Four major groups have been defined on the basis of genetic relatedness and pilus structure: IncF group (containing IncC, IncD, IncF, IncJ, and IncS), IncI group (including IncB, IncI, and IncK), IncP group (consisting of IncM, IncP, IncU, and IncW), and Ti.

CONJUGATIVE ELEMENTS (INTEGRATIVE)

The integrative conjugative elements (ICE), also called conjugative transposons (Roberts et al., 2008), like the conjugative plasmids contain an origin of transfer and the genes required to make the conjugation apparatus. Unlike plasmids these elements do not contain an origin of replication and have to integrate into a replicon in order to be maintained. This replicon can be either plasmid or chromosome. This gives them an advantage over plasmids as they do not have to have replication machinery that is compatible with the host so tend to have a larger host range than plasmids.

Integrative conjugative elements are a highly heterogeneous group of genetic elements with different properties and host ranges. However in general they do have a modular organization, i.e., a conjugation, recombination, regulation, and accessory modules. The latter commonly contains genes encoding AR.

There are also integrative elements that do not contain the conjugation region but can by mobilized by co-resident conjugative ICE or conjugative plasmids. Again these can mediate the spread of AR. There have been a number of comprehensive reviews in this area (Roberts and Mullany, 2009; Frost and Koraimann, 2010; Wozniak and Waldor, 2010).

TRANSDUCTION

There have been examples of AR genes, and even entire mobile genetic elements, being mobilized by transduction (Willi et al., 1997; Del Grosso et al., 2011). Transduction is a process in which the phage particles are packaged with bacterial DNA instead of phage. There are two type of transduction, generalized in which any segment of bacterial DNA can be packaged into the phage head, and specialized, in which the DNA adjacent to the phage insertion site is packaged.

TRANSLOCATION WITHIN GENOMES

The simplest of the mobile genetic elements are insertion sequence (IS). These elements just consist of the gene required for element mobility and the inverted repeat at the ends of the element. IS elements can be as short as 1Kb (Siguier et al., 2006). When these elements contain accessory genes not involved in element translocation they are called transposons. A simple transposon will contain an accessory gene (often encoding AR) together with the transposase (for examples of each type of element see Roberts et al., 2008). There are more complex classes of transposons that move using different mechanisms including class II transposons.

The transposons mentioned above are not capable of conjugal transfer to other bacteria and in order for them to be disseminated they need to be contained within a conjugative element. However some of ICE elements as well as being able to transfer to new hosts (see above) are also able to transpose to new genomic sites. Their ability to use different integration sites in the chromosomes depends on the type of recombinases they contain. For example Tn*916* can use a large number of different integration sites in most hosts (reviewed in Roberts and Mullany, 2009). However some elements are highly site-specific such as Tn*916* (Wozniak and Waldor, 2010). Presumably elements like Tn*916* have evolved to use different integration sites in order to increase their host range. Elements that can only use a particular number of insertion sites are limited in the hosts they can use if the site is mutated or occupied.

GENE CAPTURE ELEMENTS

Integrons are genetic elements that include components of a site-specific recombination system enabling them to capture and mobilize genes, in particular AR determinants (Stokes and Hall, 1989; Rechia and Hall, 1995; Fluit and Schmitz, 1999; Depardieu et al., 2007). They harbor an *intI* gene, encoding a site-specific integrase of the tyrosine recombinase family that carries out recombination between two distinct target sites, i.e., an attI recombination site and a 59-base element (attC site) where attI is the target site for cassette integration and a promoter (Hall and Stokes, 1993; Hall and Collis, 1995; Rechia and Hall, 1997; Mazel, 2006). In contrast to transposons integrons are not flanked by repeat sequences, in addition they do not include any genes encoding proteins that catalyze their movement. HGT of integrons to other bacteria is mostly mediated by plasmids or transposons.

The *intI* genes have been used as a basis for grouping integrons into "classes." Currently, four classes are recognized; those carrying *intI1* are defined as class 1, *intI2* as class 2, *intI3* as class 3, and *intI4* as class 4 (Carattoli, 2001; Partridge et al., 2009).

FACTORS INFLUENCING ACQUISITION OF MOBILE GENETIC ELEMENTS

The ability of mobile genetic elements containing AR genes to spread is modulated by a range of factors including, selective pressures in the environment, host factors, and properties of the genetic elements themselves. Each of these factors will be examined in turn in the next sections.

Specific host encoded factors

Bacteria have a number of systems that protect them from incoming DNA, including restriction/modification systems and CRISPR-Cas systems (Makarova et al., 2011). These systems although mechanistically very different have the same end point of identifying and destroying foreign DNA. Restriction systems work by identifying particular sequences in the incoming DNA that have not been protected by methylation and digesting them. CRISPRs act as a memory of past infection by a mobile element and can destroy that element if the bacterium encounters it again. Both these systems can be effective in stopping the spread of phage, ICE, and plasmids.

A specific host factor that attracts mobile elements has been documented in the pheromone responsive systems, in which a plasmid less recipient secrets a pheromone to which plasmids containing strains respond and transfer their plasmid to the recipients (Palmer et al., 2010).

None specific host factors

Some none specific factors that can act as barriers to HGT have been eluded to above such as not having the target site for a particular ICE or having incompatible replication systems that stop plasmids replicating in a particular host. Also the architecture of the cell surface my not allow the conjugation systems of all mobile elements to work productively. Additionally one member of a mating pair may produce inhibitory substances. Bacteria produce a number of antimicrobial products the most common being the peptide antibiotics. The best understood are the colicins produced by *E. coli*. Gram-positive bacteria also produce a diverse array of antimicrobial peptides (Riley and Wertz, 2002).

Genetic element encoded factors

Mobile genetic elements have a plethora of ways to overcome bacterial defense systems. Many plasmids and ICE encode anti-restriction proteins that as the name suggests inactivate the host restriction system allowing the element to enter the new host and survive. Also many mobile genetic elements do not have many restriction enzyme recognition sites so that they avoid the attention of the restriction enzymes. Some, including the common Tn*916*-like family of conjugative transposons, encode anti-restriction proteins which have been shown to mimic DNA and are recognized by the restriction enzyme. The anti-restriction protein ArdA from Tn*916* is one of the best characterized (McMahon et al., 2009).

Many transposons and ICE can transpose into essential genes. If this happens the host will die, to get around this some mobile elements are site-specific or preferentially target inter-genic regions (Cookson et al., 2011). Also most transposable elements (including ICE) are tightly regulated so that they only transpose at low frequency or transpose when the bacteria are stressed, such as antibiotics in their environment (reviewed in Roberts and Mullany, 2009; Wozniak and Waldor, 2010). For example members of the CTndot family of ICE transfer at a much higher frequency in the presence of tetracycline (the antibiotic to which they encode resistance). This is an advantageous response for both the element and the host bacteria (Moon et al., 2005).

Environmental factors

All the factors outlined in the previous sections are important in modulating the spread of AR but obviously if antibiotics are present in the environment there is strong selective pressure for spread of resistance and those factors that promote the spread of resistance will be selected for and those stopping the spread of mobile elements selected against.

Gene transfer is also more likely in environments where bacteria are in close proximity to each other and in relatively high density such as the gut and oral cavity. In order to control the spread of resistance it is important to have an understanding of the molecular biology of the different mobile genetic elements and of the ecology of the environments in which spread is likely.

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