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REVIEW

Antibiotic resistance genes in the Actinobacteria phylum

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Abstract

The Actinobacteria phylum is one of the oldest bacterial phyla that have a significant role in medicine and biotechnology. There are a lot of genera in this phylum that are causing various types of infections in humans, animals, and plants. As well as antimicrobial agents that are used in medicine for infections treatment or prevention of infections, they have been discovered of various genera in this phylum. To date, resistance to antibiotics is rising in different regions of the world and this is a global health threat. The main purpose of this review is the molecular evolution of antibiotic resistance in the Actinobacteria phylum.

Keywords Actinobacteria · Antibiotics · Antibiotics resistance · Antibiotic resistance genes · Phylum

Brief introduction about the taxonomy of Actinobacteria

One of the oldest phyla in the bacteria domain that have a significant role in medicine and biotechnology is the phylum Actinobacteria [1, 2]. In this phylum, DNA contains G + C rich about 50–70%, non-motile (*Actinosynnema pretiosum* subsp. *pretiosum* and *Actinosynnema pretiosum* subsp. *Auranticum* are motile [3]), non-spore forming and non-capsule forming. In Actinobacteria, there are different cell wall types (I-VIII) with various sugars (arabinose, xylose, galactose, 3-O-methyl-D-galactose) and amino acids (diaminopimelic acid, glycine, lysine, ornithine) in their cell wall structure. Sometimes in literature, the Actinobacteria phylum is divided into two different groups with mycolic acids and without mycolic acid compounds in their cell wall structure. The role of mycolic acids compounds in bacteria cell wall is in the pathogenesis. Some of the genera in this phylum have mycolic acids in their cell wall compositions, which include *Amycolicicoccus*, *Corynebacterium*, *Dietzia*, *Gordonia*, *Hoyosella*, *Millisia*, *Mycobacterium*, *Nocardia*, *Rhodococcus*, *Rothia*, *Segniliparus*, *Skermania*, *Smaragdicoccus*, *Tomitella*, *Tsukamurella*, and *Williamsia* [2, 4–7]. There are various methods for Actinobacteria identification and taxonomic classifications, which include (i) chemical taxonomy: in this method, analysis of cell wall and whole cell compositions such as various sugars, amino acids, lipids, menaquinones, proteins, and etc., are studied [5]. (ii) Phenotypic classification: there are various phenotypic tests such as the use of conventional and specific staining such as Gram stain, partially acid-fast, acid-fast (Ziehl-Neelsen stain or Kinyoun stain), and methenamine silver staining; morphology of colony and pigmentation; aerial mycelium formation; growth at different NaCl concentrations and pH; acid production of carbohydrates; hydrolysis of amino acids; growth at various temperatures; enzymes production [4, 8–11]; and matrix-assisted laser desorption/ionization [12–16]. (iii) Molecular classifications: (a) one of the most common molecular methods for Actinobacteria identification is genes sequence-based identification. In this method, different target genes such as *hsp70* [17], *hsp65*, *rpoB*, *rpoC*, *fusA*, *rplB*, *xfp*, *secA*, *gyrA* and *B*, *vapA* and *N*, *catA*, *choE*, *sod*, *ftsZ*, *dnaK*, *atpI*, 16S-23S rRNA, 23S rRNA (*rrl* gene), and 16S rRNA (*rrs* gene) genes are used. The 16S rRNA gene is a powerful tool for phylogenetic study and relationships between bacteria [4, 5, 8–11, 18–23]. (b) PCR-restriction fragment length polymorphism (RFLP): this method has been used for a few of the genera in Actinobacteria such as *Actinomadura*, *Corynebacterium*, *Gordonia*, *Mycobacterium*, *Nocardia*, *Rhodococcus*, *Streptomyces*, and *Tsukamurella* [8–11, 24, 25]. (c) DNA-DNA hybridization (DDH): DDH has been used for bacteria of the 1960s [26], and this method is necessary for novel species description when the similarity value of 16S rRNA gene sequence is more than 97% [27, 28]. Cut-off value for this method is 70% [29]. (d) Whole genome sequencing (WGS): there is all of the new information about

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bacterial taxonomic, prediction antibacterial susceptibility and resistance genes, virulence genes, molecular typing, prediction secondary metabolites, phages and plasmids in the complete nucleotide sequence of DNA [30–34]. This method can be used in laboratories medicine and reference [35]. Cut-off value for this method is 94% [29].

Role of Actinobacteria in human infections

There are more than 200 genera in this phylum [1, 5, 36] and many of them are soil microflora, although some of them are isolating of various clinical specimens. *Acidipropionibacterium* (formerly identified as *Propionibacterium*) [37], *Acidothermus* [38], *Actinobaculum* [39], *Actinomadura* [40], *Actinomyces* [41], *Actinotignum* [42], *Agromyces* [43], *Alloscardovia* [44], *Arcanobacterium* [45], *Arthrobacter* [46], *Atopobium* [47], *Bifidobacterium* [48], *Brachybacterium* [15], *Branchiibius* [49], *Brevibacterium* [50], *Cellulomonas* [51], *Cellulosimicrobium* [52], *Corynebacterium* [53], *Cryptobacterium* [54], *Cutibacterium* [55], *Dermabacter* [56], *Dermacoccus* [57], *Diaminobutyricimonas* [58], *Dietzia* [59], *Eggerthella* [60], *Gardnerella* [61], *Glycomyces* [62], *Gordonia* [9], *Gordonibacter* [63], *Janibacter* [15], *Kocuria* [64], *Kineococcus* [65], *Kytococcus* [66], *Lawsonella* [67], *Leifsonia* [68], *Microbacterium* [15], *Micrococcus* [69], *Mobiluncus* [70], *Mycobacterium* [71], *Nesterenkonia* [15], *Nocardia* [8], *Nocardiopsis* [72], *Olsenella* [73], *Paraeggerthella* [74], *Parascardovia* [75], *Propionibacterium* [76], *Propionimicrobium* [15], *Pseudoclavibacter* [77], *Pseudonocardia* [78, 79], *Pseudopropionibacterium* [80], *Renibacterium* [81], *Rhodococcus* [11], *Rothia* [82], *Saccharopolyspora* [83], *Scardovia* [84], *Segniliparus* [85], *Senegalimassilia* [58], *Serinicoccus* [86], *Slackia* [87], *Streptomyces* [5], *Tessaracoccus* [58], *Timonella* [58], *Tropheryma* [88], *Trueperella* [89], *Tsukamurella* [10], *Turicella* [90], *Varibaculum* [91], *Williamsia* [92], and *Zimmermannella* [15] have been isolated from human clinical specimens.

Antibacterial resistance and Actinobacteria

Microbes surviving and competing for nutrition source and living space with other microorganisms produced antimicrobial compounds [93, 94], and these compounds created resistance mechanisms to antimicrobial agents [95, 96]. One of the health-threatening factors for humans is increasing antibiotic resistance [97]. To date, antibiotic resistance is rising all over the world and the introduction of new antibacterial agents is essential for infections treatment. Due to the high utilization of antibiotic agents for infections treatment in hospitals, bacterial resistance to antibiotics firstly appeared there. Various resistance genes are causing antimicrobial resistance in bacteria. Accurate identification of resistance genes is important for three reasons: (i) the epidemiologic study, (ii) detection of resistant isolates, and (iii) detection and confirmation of isolates of non-susceptible bacteria. Molecular identification of ARG has been carried out using PCR and microarray and these methods are expensive and time-consuming [98–101]. There are various mechanisms for resistance to antibiotics in Gram-positive and Gram-negative bacteria including production extended-spectrum beta-lactamases (ESBLs), extended--spectrum cephalosporins; mutation in the drug efflux pump, DNA gyrase, and target genes; impermeability; and alteration in the cell wall or essential enzymes in metabolism [102–104]. Costa et al. reported ARGs of classical DNA from 30,000 years old that caused resistance to β-lactam, glycopeptides, and tetracycline antibiotics [95]. A large number of resistance genes originated from antibiotic-producing organisms such as *Streptomyces* spp. These bacteria are multidrug-resistant (MDR) to antibiotic agents that may reverberate two points: (1) these bacteria produce more than one antibiotic and (2) continue to survive in the vicinity to antibiotic-producing microorganisms in the environment [105–107]. A study showed a large number of *Streptomyces* strains isolated from soil were resistant to multiple antibiotics and have suggested that these resistance genes are in the environment [108]. In another study, it has been suggested that aminoglycoside, quinolone, and vancomycin resistance and CTX-M-resistant genes were acquired from environmental resistome (resistome: all of the resistant genes that is contributing to antimicrobial resistance) [106]. Multidrug-resistant bacteria were first reported in *Escherichia coli*, *Salmonella*, and *Shigella* [101]. In Actinobacteria, multiple antibiotic resistance genes were reported in *Actinoplanes* sp. (*marR* gene) [109], *Collinsella aerofaciens* (*marA* gene) [110], and *Corynebacterium ulcerans* (*marR2* gene) [111].

Antibiotic resistance mechanisms and prevalence resistance genes in Actinobacteria

Beta-lactams

Penicillin is the first antibiotic of this family that was reported by Alexander Flemming at St. Mary's Hospital in Paddington, London in 1928. This antibiotic is produced by *Penicillium notatum* and has been used of *Penicillium chrysogenum* for industrial production. Penicillin has two drug forms which include penicillin G (benzylpenicillin) and V (phenoxymethyl penicillin) that are labile and stable to stomach acid, respectively. In the past decades to the present, new beta-lactam antibiotics

have been generated. These antibiotics such as penicillins and derivatives (such as penicillin (natural penicillins), methicillin (beta-lactamase-resistant penicillins), ampicillin (aminopenicillins), ticarcillin (carboxypenicillins), and piperacillin (ureidopenicillins)) have a nucleus structure. Other beta-lactam antibiotics such as cephalosporin antibacterial agents have a 7-aminocephalosporanic acid nucleus. Cephalosporins contain four generations including the first generation (cephalexin and etc.), second generation (cefoxitin and etc.), third generation (cefotaxim and etc.), and fourth generation (cefepime and etc.)); ceftaroline (this agent is active against methicillin-resistant *S. aureus* [MRSA]); and carbapenems such as imipenem (thienamycin), and monobactams such as aztreonam [112–118]. β-lactam antibiotics inhibit transpeptidation (transpeptidases) and transglycosylation reactions in the bacterial cell wall synthesis. Also, one of the major targets of beta-lactam antibiotics in the cell wall is penicillin-binding proteins (PBPs). Resistance to penicillin was reported in *S. aureus* from London in 1940 [101, 117, 119, 120]. Abraham and Chain first reported bla_{AmpC} in 1940 that destroyed penicillin in *E. coli* [121]. Various mechanisms of antibacterial resistance to β-lactams reported in literature include ESBLs, bla_{AmpC}, and carbapenemases [112]. There are various classifications for β-lactamases but the best classification is molecular classification based on the protein sequence. In this classification, β-lactamases divided into four classes A, B (metallo-β-lactamases), C, and D [116, 122]. One of the ways to deal with β-lactamases producer bacteria is combination antibiotic and clavulanate (first isolated in *Streptomyces clavigulerus*) or sulbactam or tazobactam, for example, amoxicillin-clavulanate (augmentin), ticarcillin-clavulanate (timentin), ampicillin-sulbactam (unasyn), and piperacillin-tazobactam(zocin) [116]. In the genus *Streptomyces* (such as *Streptomyces cacaoi*), resistance to β-lactam antibiotics is owing to very low affinity to PBPs such as PBP2a [123, 124]. β-lactamases can be localized to genomic DNA, transposons, and plasmids [125]. PBPs were reported in *Corynebacterium resistens* (*ldt1* and *ldt2* genes) [126], *Mycobacterium tuberculosis* (penicillin-binding proteins and *ponA* gene) [127, 128], and *Leucobacter chironomi* (penicillin-binding proteins) [129]. In literature, β-lactamases gene or genes have been reported in *Actinomadura* sp. [Class D] [130]; *Nocardiopsis alba*, *Mycobacterium senegalense*, *Mycobacterium conceptionense* [class A] [131, 132]; *Streptomyces lavendulae*, *Streptomyces afghaniensis* [bla_{L} gene] [131]; *Streptomyces badius*, *Streptomyces filamentosus*, *Streptomyces rapamycinicus*, *Streptomyces violaceusnige* [bla_{U} gene] [131]; *Streptomyces cacaoi* [bla_{L} and bla_{U} genes] [131]; *L. chironomi* [class C] [129]; *Leucobacter komagatae* [bla_{TEM} gene] [133]; *Mycobacterium vulneris* [bla_{F} and $bla_{\mathrm{MFO\text{-}1}}$ genes] [131]; *Mycobacterium farcinogenes* [class A, bla_{F}, and $bla_{\mathrm{MFO\text{-}1}}$ genes] [131, 132]; *Nocardia asteroides* sensu *stricto* [$bla_{\mathrm{AST\text{-}1}}$ gene] [134]. bla_{L} gene [131]; and nitroimidazole resistance gene [135] reported in *Streptomyces avermitilis*. β-lactamase resistance genes in other bacteria of this phylum are shown in Tables 1 and 2.

Glycopeptide

Vancomycin is the first glycopeptide agent isolated from *Amycolatopsis orientalis* (formerly identified as *Streptomyces orientalis*) in 1950 [282, 283]. To date, there are four types of glycopeptides that include vancomycin, avoparcin, ristocetin, and teicoplanin types [284]. In between different types, vancomycin and teicoplanin (first isolated from *Actinoplanes teichomyceticus*) are used for infections treatment and they have bactericidal activity against bacteria [112, 116, 285]. Glycopeptide antibiotics inhibit peptidoglycan synthesis in the cell wall [115]. Antibiotic resistance to glycopeptides probably is encoding by chromosome or plasmids [285]. Transposons and mobile elements are reservoirs for the transmission of antibacterial resistance to other bacteria [286]. Vancomycin producer bacteria are protected themselves from the effect of vancomycin by the change in peptidoglycan precursor (modification D-Ala–D-Alaterminus to D-Ala–D-Lac terminus) during antibiotic production [116]. There are various resistance genes for resistance to vancomycin such as *vanA*, *vanB*, *vanD* (modification D-Ala–D-Lac in peptidoglycan precursors) and *vanC*, *vanE*, *vanG* (modification D-Ala–D-Serin peptidoglycan precursors), *vanH* (pyruvate reductase), and *vanX* (dipeptidase) [112, 116]. In literature, vancomycin resistance gene or genes have been reported in *Arcanobacterium haemolyticum*, *Oerskovia turbata*, *Rathayibacter toxicus* (*vanA* gene) [287, 288]; *Atopobium minutum* (*vanX*, *vanR*, *vanS*, *vanB*, *vanY*, and *vanH* genes) [132]; *Kocuria palustris* (*vanW* gene) [289]; *Lentzea guizhouensis*, *Nocardioides* sp., *Streptomyces silvensis*, *Streptomyces phaeopurpureus* (*vanR* gene) [132]; *A. teichomyceticus* (*vanHAX* gene cluster and *vanX*) [183]; and *Amycolatopsis orientalis* and *Streptomyces toyocaensis* (*vanHAX* gene cluster) [118], *Nonomuraea gerenzanensis* (*vanY* and *vanX*) [183]. Glycopeptide resistance genes in bacteria of this phylum are shown in Tables 1 and 2.

Aminoglycoside

Antibiotic agents of this family have been isolated from *Streptomyces* and *Micromonospora* species. Streptomycin is the first antibiotic of this family discovered of *Streptomyces griseus* by Selman Waksman and is effective against *M. tuberculosis*. Other antibiotic agents of this family such as gentamicin, neomycin, and kanamycin were isolated from *Micromonospora echinospora* (formerly identified as

Table 1 Antibacterial resistance genes in the genus and species level in the Actinobacteria phylum without mycolic acids compounds in cell wall structure

Species	Sulfonamide and trimethoprim resistance gene or genes	MLSKO resistance and efflux gene or genes	Tetracycline resistance and efflux gene or genes	Rifampicin-resistance	Aminoglycoside resistance and efflux gene or genes	Beta-lactamase gene or genes
Acidothermus sp.	Sulfonamide resistance		Tetracycline resistance			bla_{TEM}, bla_{CTX}
Actinobaculum suis	*sul1*	*erm*(X)	*tet*(Z)			
Actinomyces sp.		*erm*(X), *erm*(B), *erm*(C), *erm*(F), *erm*(FS), *erm*(FU)	*tet*(M), *tet*(W), *tet*(L)			
Actinotignum schaalii (formerly identified as *Actinobaculum schaalii*)	*sul1*	*erm*(X)				
Agromyces sp.			*tet* genes			
Arthrobacter sp.	*sul1*, *sul2*	*erm*(A), *erm*(R)	*tet*(A), *tet*(M), Tetracycline resistance			
Bifidobacterium breve		*erm*(X)	*tet*(M), *tet*(S)			
Bifidobacterium kashiwanohense		*erm*(X)	*tet*(W)			
Bifidobacterium animalis subsp. *lactis*		*erm*(X)	*tet*(W)			
Bifidobacterium pseudocatenulatum		*erm*(X)	*tet*(W), *tet*(O), *tet*(S)		*aphE*	
Bifidobacterium longum subsp. *longum*			*tet*(W), *tet*(M), *tet*(O)			
Bifidobacterium bifidum		*erm*(X)	*tet*(A), *tet*(W), *tet*(O)		*aphE*	
Bifidobacterium sp.	*sul1*	*erm*(X), *erm*(CD), *erm*(Y)	*tet*(W), *tet*(M), *tet*(O), *tet*(Q), *tet*(L)			
Brachybacterium vulturis						β-lactamase
Catenulispora acidiphila		*rlmA*,*ere*			*aac3*, *ant2*, *aph3*	bla_A
Cellulosimicrobium sp.						Metallo-β-lactamase
Cutibacterium (formerly identified as *Propionibacterium*) *acnes*		*erm*(X)				
Dermabacter hominis	*sul1*				*aph(6)-Id*	
Eggerthella sp.		*erm*(B)	*tet*(W)		*aadE*	
Eggerthella lenta			*tet*(M)			
Gardnerella vaginalis		*mef*(A)	*tet*(M)			
Gardnerella sp.		*erm*(F), *erm*(FS), *erm*(FU), *lsa*(C)	*tet*(M), *tet*(Q)			
Ilumatobacter coccineus					*aacC*	β-lactamase
Intrasporangium calvum					*aph3, aph67, hph, ant3, ant6*	β-lactamase
Janibacter melonis						β-lactamase
Janibacter terrae						β-lactamase
Janibacter limosus						Class C
Kibdelosporangium sp.						β-lactamase
Kitasatospora cheerisanensis (formerly identified as *Streptomyces aureofaciens*)			*tcr*		Aminoglycoside resistance	bla_{AmpC}, metallo-β-lactamase, bla_L
Kocuria rhizophila		*erm*(36)			*aph6*	
Mobiluncus sp.		*erm*(F), *erm*(FS), *erm*(FU)	*tet*(O), *tet*(Q)			
Roseiflexus castenholzii		*vatB*, *macB*			*aph6*	class B
Saccharopolyspora erythraea		*erm*(E), macrolide glycosyltransferase (*mgt*)				
Slackia exigua	*dfr*, *sul2*	*erm*(A), *erm*(B), *erm*(X), *strA*, *strB*, *lsa*(A), *lsa* (C)	*tet*(M), *tet*(O), *tet* (W), *tet* (32)		*ant(6)-Ia*, *aph(3'')-II*	*cfxA3*

Table 1 (continued)

Sphaerobacter thermophilus					*adeA*, *adeB*, *adeC*	β-lactamase
Streptomyces coelicolor		*erm*(O)	*tet*(M)	*arr*		
Streptomyces lincolnensis		*erm*(U), *lmr*(A), *lmr*(B)				
Streptomyces glaucescens					*aph(6)-Ib*	bla_F
Streptomyces venezuelae		*erm*(30), *erm*(31), *pik*R1, *pik*R2		RifMO	*aph(4)-I*	
Streptomyces ambofaciens		*erm*(O), *erm*(Z), *mgtA*, *gimA*, *oleD*, *srmB*	Tetracycline_resistance			
Streptomyces rimosus			*Otr*(A), *otr*(B), *otr* (C)		*aac(3)-VIIa*, *aph(3′)-VIII*	class A, bla_L
Streptomyces sp.	*sul1*, *sul3*	*erm*(I), *carA*	*tet*(M), *tet*(W), *tet*(L)	*arr*	*aph(4)-I*, *aac(3)-X*,*aph(3″)-I*,*aph(6)-I*,*aac(3)-Ia*,*aac(3)-VIIa*	class A,B,C
Streptomyces wadayamensis						Class A
Streptomyces albus					*aac(6)-I*	Class A, bla_L
Streptomyces thermotolerans		*erm*(H), *carA*				
Streptomyces fradiae		*erm*(N), *erm*(S), *erm*(32), *tlrB*, *tlrC*			*aac(3)-VIIIa*, *aph(3′)-Va*	bla_F
Streptomyces antibioticus		*oleD*, *oleD2*, *oleI*, *oleB*, *oleC*				
Streptomyces globisporus						bla_U
Streptomyces clavuligerus						β-lactamase, bla_L
Streptomyces niveus						
Streptomyces griseus					*aac(3)-Xa*, *aph(3″)-Ia*, and *aph(6)-Ia*	β-lactamase
Streptomycess peibonae				*rgt1438*		
Thermomonospora curvata						Class D
Tropheryma whipplei						
Trueperella pyogenes (formerly identified as *Arcanobacterium pyogenes*)	*dfrB4*,*dfrA12*, *dfrB2a*	*erm*(B), *erm*(X), *tlrB*, *tlrC*, *mef*(A), *msr*(A)	*tet*(W), *tet*(Z), *tet*(33)	*arr*-2, *arr*-3	*aadA1*, *aadA2*, *aadA5*, *aadA24*, *aadB*, *aac(6′)-IIc*, *aac(6′)-Ib*, *aacA4*	bla_{OXA-10}, bla_{P1}
Turicella otitidis						
Leucobacter sp.	*sul1*, *sul2*		*tet*(B)		*aadA9*	
Thermobifida fusca		*vatb*, *macB*	*tet*(S)			

Species	Chromosomal point mutations	Vancomycin resistance gene or genes	Chloramphenicol resistance and efflux gene or genes	Quinolone resistance and efflux gene or genes	Reference
Acidothermus sp.					[136]
Actinobaculum suis					[132]
Actinomyces sp.					[112, 132, 137–139]
Actinotignum schaalii (formerly identified as *Actinobaculum schaalii*)	*gyrA*,*ParC*, rifampicin resistance-determining region (RRDR) of *rpoB*				[140–142]
Agromyces sp.		*vanR*			[132, 143]
Arthrobacter sp.	*gyrA*, *gyrB*				[112, 132, 144–146]
Bifidobacterium breve					[132, 147]
Bifidobacterium kashiwanohense					[132]
Bifidobacterium animalis subsp. *lactis*					[132, 148]
Bifidobacterium pseudocatenulatum					[132, 147, 149, 150]
Bifidobacterium longum subsp. *longum*		*vanZ*			[132, 147, 151]
Bifidobacterium bifidum					[132, 147, 149, 150]
Bifidobacterium sp.					[112, 137, 138, 152]
Brachybacterium vulturis		*vanW*			[153]

Table 1 (continued)

Catenulispora acidiphila		*vanH*, *vanA*, *vanX*, *vanR*, *vanS*			[154]
Cellulosimicrobium sp.		*vanW*			[155]
Cutibacterium (formerly identified as *Propionibacterium*) *acnes*	*gyrA*, 23S rRNA,16S rRNA				[156, 157]
Dermabacter hominis			Chloramphenicol exporter		[132]
Eggerthella sp.					[132]
Eggerthella lenta		*vanB*, *vanS*, *vanH*, *vanA*, *vanX*, *vanZ*			[132, 158–162]
Gardnerella vaginalis					[132]
Gardnerella sp.					[112, 138]
Ilumatobacter coccineus					[163, 164]
Intrasporangium calvum		*van*			[165–167]
Janibacter melonis		Vancomycin resistance		Quinolone resistance	[168]
Janibacter terrae		Vancomycin resistance		Quinolone resistance	[168]
Janibacter limosus		Vancomycin resistance		Quinolone resistance	[168]
Kibdelosporangium sp.		*vanR*			[132]
Kitasatospora cheerisanensis (formerly identified as *Streptomyces aureofaciens*)			Chloramphenicol resistance		[112, 131, 169]
Kocuria rhizophila		*van*		Quinolone resistance	[170–173]
Mobiluncus sp.					[112, 174–176]
Roseiflexus castenholzii		*vanA*, *vanD*, *vanG*			[177, 178]
Saccharopolyspora erythraea				*mfpA*	[132, 179, 180]
Slackia exigua		*van*	*cmx*		[181]
Sphaerobacter thermophilus					[182]
Streptomyces coelicolor	*rpoB*	*vanK*, *vanX*, *vanY*	Chloramphenicol exporter		[132, 183–185]
Streptomyces lincolnensis					[132, 144]
Streptomyces glaucescens					[112, 186]
Streptomyces venezuelae			Chloramphenicol exporter		[132, 144, 187, 188]
Streptomyces ambofaciens					[132, 144, 189]
Streptomyces rimosus					[112, 131, 132, 187]
Streptomyces sp.		*vanR*	*catA*, chloramphenicol exporter	*mfpA*	[112, 132, 179, 187, 190, 191]
Streptomyces wadayamensis			*catA*		[132]
Streptomyces albus			*catA*		[131, 132]
Streptomyces thermotolerans					[144]
Streptomyces fradiae					[112, 131, 144]
Streptomyces antibioticus					[144]
Streptomyces globisporus				*qepA*	[131, 192]
Streptomyces clavuligerus				*qepA*	[131, 192, 193]
Streptomyces niveus	*gyrA*				[194]
Streptomyces griseus					[112, 195]
Streptomycess peibonae					[196]
Thermomonospora curvata	23S rRNA				[197]
Tropheryma whipplei	*gyrA*, *parC*	*vanE*			[198]
Trueperella pyogenes (formerly identified as *Arcanobacterium pyogenes*)	16S rRNA, 23S rRNA		*catB3*	*cmlA6*	[132, 144, 199–205]
Turicella otitidis	23S rRNA				[206]
Leucobacter sp.					[207–210]
Thermobifida fusca					[211]

Other resistance genes include the *ileS* gene: resistance gene to mupirocin in *Bifidobacterium* [212]; *tlrC* gene: resistance gene to tylosin in *Plantactinospora* sp. [213]; *fusH* gene: resistance gene to fusidic-acid in *S. coelicolor* [132]; *tcmA* gene: resistance gene to tetracenomycin in *S. coelicolor*, *Streptomyces parvulus*, *Streptomyces pactum*, and *Streptomyces avermitili* [132]; *tlyA* gene: resistance gene to capreomycin in *M. smegmatis* [127]

Micromonospora purpurea), *Streptomyces fradiae*, and *Streptomyces kanamyceticus* in 1960, 1949, and 1957, respectively. To date, some of the antibiotics of this family are semi-synthetic and the first semi-synthetic antibiotic was reported in the 1970s. For instance, amikacin and kanamycin are derived from kanamycin and sisomicin, respectively [112, 115–118, 187, 290–293]. The role of the ribosome in bacteria is protein synthesis that is composed of the 30S and 50S subunits. Some of the antibiotics families inhibit protein synthesis with an effect on these subunits. All of the antibiotics of this family inhibit protein synthesis in gram-positive and gram-negative bacteria by connecting and preventing the activity of bacterial 30S ribosomal [115, 294, 295]. Mechanisms of aminoglycoside resistance have been reported which include (i) alteration in the ribosomal receptor (mutation or methylation in the area connected to the 16S rRNA gene in the 30S rRNA subunit); (ii) enzymatic degradation of the antibiotic; (iii) decrease permeability; (iiii) aminoglycoside-modifying enzymes (AMEs) such as acetyltransferases (AAC), kinases, nucleotidyltransferases, and phosphoryltransferase (APH); and (iiiii) Active efflux pump [112, 115, 296]. In literature, aminoglycoside resistance gene or genes have been reported in *Actinokineospora spheciospongiae* (Phosphotransferase) [297], *Actinosynnema mirum* (*hur* gene) [109], *Corynebacterium singular* (*aph*(*3′*)-*I* gene) [132], *Dietzia* sp. (*aadA9* and *aadA5* genes) [207], *Dietzia maris* (*ant*(*3″*)-*Ia*, *aph*(*3′*) and *aph*(*6*)-*1d* genes) [298], *Knoellia sinensis* (aminoglycoside resistance gene) [299], *Micromonospora chalcea* (*aac*(*3*)-*IXa* and *aph*(*3′*)-*Vc* genes) [112], *M. echinospora* and *Micromonospora rosea* (aminoglycoside resistance genes (*grm*)) [300], *Micromonospora inyoensis* (*sisA* gene) [301], *Mycobacterium nonchromogenicum*, and *Mycobacterium pseudoshottsii* (*aac*(*2′*)-*I* gene) [132], *Nocardiopsis* sp. (*rpsL* gene) [302], *Sanguibacter* sp. (*pur8* gene) [303], *Streptomyces rubrolavendulae* (*aph*(*3′*)-*V*, *aac*(*3*)-*VIII*, and viomycin phosphotransferase genes) [132], *Streptomyces griseus* subsp. *griseus* (*aph*(*3′*)-*I* and *aph*(*6*)-*I* genes) [132], *Streptomyces europaeiscabiei* and *Streptomyces anulatus* (*aac*(*3*)-*X* gene) [132], *Streptomyces hygroscopicus* (*aph*(*4*)-*Ib* and *aph*(*7″*)-*Ia* genes) [112], *Streptomyces pactum* (16S rRNA methylation/ *pct* gene) [187], and *Streptomyces netropsis* (formerly identified as *Streptomyces flavopersicus*) (*aph*(*9*)-*Ib* gene) [112]. Aminoglycoside resistance genes in other bacteria of this phylum are shown in Tables 1 and 2.

Chloramphenicol

This antibiotic was first isolated from *Streptomyces venezuelae* in 1947 and was used in infections treatment in 1950 [117]. Chloramphenicol inhibits protein synthesis with binding to the 50S subunit and it has bacteriostatic activity against a wide range of Gram-positive and Gram-negative bacteria [112, 115, 304]. Antibiotic resistance to chloramphenicol is due to inactivation of the drug by an enzyme (chloramphenicol acetyltransferases) that is controlled by plasmid [115]. Chloramphenicol acetyl transferases are coding by *catA* and *catB* genes. Also, other bacterial resistance mechanisms have been reported in the literature which include multidrug efflux pump systems, impermeable barriers, inactivation by chloramphenicol 3′-O-phosphotransferase, and target site mutations [112]. In literature, one resistance gene have been reported only in *Bifidobacterium adolescentis* (*cat* gene) and *Streptomyces setonii* (formerly identified as *Streptomyces acrimycini*) (*catA-5* gene) [112, 132]. Chloramphenicol resistance genes in other bacteria of this phylum are shown in Tables 1 and 2.

Macrolide–Lincosamide–Streptogramin

Erythromycin (chemical structure:$C_{37}H_{67}NO_{13}$) is the first macrolide isolated from *Saccharopolyspora erythraea* (formerly identified as *Streptomyces erythreus*) in 1952 [115, 174, 295]. To date, this family of antibiotics has extended and modified to the MLSKO (Macrolide–Lincosamide–Streptogramin B-Ketolides-Oxazolidinones) family [137]. In the macrolide family, erythromycin (narrow spectrum) and azithromycin or clarithromycin (expanded spectrum) are widely used for infections treatment. Also, linezolid of the oxazolidinones family is used for vancomycin-resistant enterococci (VRE) and MRSA treatment [116, 117]. Lincomycin and streptogramins were first isolated from *Streptomyces lincolnensis* and *Streptomyces halstedii* (formerly identified as *Streptomyces graminofaciens*), respectively [117, 305]. Macrolide–Lincosamide–Streptogramin (quinupristin/dalfopristin) inhibits protein synthetase in bacteria by binding to the 50S (23S rRNA gene) ribosomal subunit of bacteria [115, 119]. First antibiotic resistance to erythromycin have been reported in staphylococci [306]. Mechanisms of antibiotic resistance in this family include efflux pumps, rRNA methylases (encoded by the *erm* genes), and macrolide inactivation genes [137, 307]. In literature, three ways for self-resistance in macrolide producer streptomycetes have been reported which includes modification in 23S rRNA gene, ATP-binding cassette (ABC) type proteins (for example *oleB* gene in *Streptomyces antibiouticus*), and inactivation of antibiotic while it is still in the intracellular form [116]. In literature, MLSKO resistance genes have been reported in *Bifidobacterium thermophilum*, *Turicella* sp., *Corynebacterium coyleae*, *Corynebacterium aurimucosum*, and *Corynebacterium afermentans*, *Corynebacterium argentoratense* [*erm*(X) gene] [132, 148, 219, 308], *Micromonospor* sp. [*erm*(W) and *myr*(B) genes] [112], *Mycobacterium boenickei*, *Mycobacterium houstonense*, *Mycobacterium neworleansense*, and *Mycobacterium porcinum* [*erm*(39) gene] [236], *Mycobacterium wolinskyi* [*erm*(40) gene] [236], *Mycobacterium abscessus* subsp.

abscessus, *Mycobacterium abscessus* subsp. *Bolletii*, and *Streptomyces sviceus* [*erm*(E) gene] [132, 236], *Streptomyces viridochromogenes* [*erm*(V) gene] [112, 144], *Streptomyces caelestis* [*clr* gene] [187], *Acidipropionibacterium acidipropionici* (formerly identified as *Propionibacterium acidipropionici*) [*erm*MLgene] [309], and *Austwickia chelonae* [*rlm*A gene] [310]. Resistance genes to linezolid have been reported in *M. tuberculosis* [mutation in 23S rRNA and *rplC* genes] [128, 311], *Corynebacterium*, and *Acidothermus* [*cfr* gene] [136]. *erm*(A), *erm*(X) [132], and efflux pump [175] have been reported in *Varibaculum cambriense*. MLSKO resistance genes in other bacteria of this phylum are shown in Tables 1 and 2.

Tetracycline

Chlortetracycline (trade name is Aureomycin) and oxytetracycline (trade name is Terramycin) are the first antibiotics of this family that were isolated from *Streptomyces aureofaciens* and *Streptomyces rimosus*, respectively, in 1948 [112, 138]. This family has bacteriostatic activity against a broad spectrum of Gram-positive and Gram-negative bacteria [115]. Tetracyclines inhibits protein synthetase in the 30S rRNA subunit, and they are divided into two classes which include 1- typical such as minocycline (isolated in 1972 and trade name is minocin) and etc., and 2- atypical such as 6-thiatetracycline and etc. [112, 138]. Antibiotic resistance to tetracycline was reported in 1950 [312]. Three resistance mechanisms to tetracyclines have been reported which include (i) enzymatic inactivation [*tet*(X) gene]; (ii) ribosomal protection proteins (RPPs)[*tet*(M), *tet*(O), *tet*(S), *tet*(W),*tet*(Q), *tet*(T), *otr*(A), *tet*P(B) genes]; and (iii) efflux pumps [*tet*(A), *tet*(B), *tet*(C), *tet*(D), *tet*(E), *tet*(G), *tet*(H), *tet*(I), *tet*(J), *tet*(Z), *tet*(30), *tet*(31), *tet*(K), *tet*(L), *tet*(K), *tet*(L), *otr*(*B*), *tcr3*, *tet*P(A), *tet*(V), *tet*(Y) genes] [112, 138]. In the Actinobacteria phylum, The most common resistance genes to tetracyclines are *tet*(M) and *tet*(W)(see Tables 1 and 2). In literature, tetracycline resistance gene or genes have been reported in *Actinomyces graevenitzii*, *Bifidobacterium animalis*, *Georgenia* sp., *Olsenella* sp., *Tessaracoccus* sp. [*tet*(W) gene] [132, 208]; *Atopobium deltae*, *Brachybacterium* sp., *Collinsella tanakaei*, *Mobiluncus curtisii* subsp. *holmesii*, *Mobiluncus curtisii* subsp. *curtisii* [*tet*(M) gene] [132, 152]; *Bifidobacterium thermophilum* [*tet*(M) and *tet*(W) genes] [132, 147]; *Leifsonia* sp., *Mobiluncus curtisii* [*tet*(O) gene] [138]; *Microbacterium* sp., *Streptomyces atrovirens* [*tet*(Z) gene] [132]; *Mobiluncus mulieris* [*tet*(M), *tet*(O), and *tet*(Q) genes] [132, 313, 314]; *Actinomyces viscosus* [*tet*(L) gene] [313]; *Microbacterium* sp. [*tet*(z) and *tet*(w) genes] [208, 221]; *Bifidobacterium longum* [*tet*(W), *tet*(M), *tet*(O)] [132, 147]; *Cellulosimicrobium cellulans* [*tet*(39)] [315]; *Glutamicibacter arilaitensis* [*tet*(V) gene] [316]; and *tet*(M) gene [132] and efflux pump have been reported in *Denitrobacterium detoxificans*. Tetracyclines resistance genes in bacteria of this phylum are shown in Tables 1 and 2.

Quinolone

This family of antibiotics has bactericidal activity against Gram-positive and Gram-negative bacteria in various infections. Quinolones block DNA replication and repair through inhibiting the action of topoisomerase II (DNA gyrase) and topoisomerase IV. Topoisomerases are necessary for bacteria life. For example, the role of DNA gyrase is important in replication and transcription while topoisomerase IV also has an effective role in DNA replication and decatenation at the end of the replication. Topoisomerases I–IV were encoded by *topA*, *gyrA* and *gyrB*, *topB*, and *parC* and *parE* genes [116, 138, 317]. Other antibiotic agents such as novobiocin (first isolated from *Streptomyces niveus*) and coumermycin (this is an aminocoumarin antibiotic) inhibited the action of DNA gyrase in bacteria [116]. Molecular structure of two enzymes (DNA gyrase and topoisomerase IV) are similar and includes 2 GyrA, 2 GyrB subunits (DNA gyrase) and 2 A, 2 B subunits (topoisomerase IV) [112]. Chromosomal resistance is caused by mutations and includes changes in A, B subunits; DNA gyrase; and mutation in *ParC* and *ParE* genes in topoisomerase IV. Efflux pumps are encoded by plasmid [115]. *Qnr* has various genes which includes *qnrA*, *qnrB*, *qnrC*, *qnrD*, *qnrAS*, and *qnrS* [112]. In literature, quinolone resistance genes have been reported in *Amycolatopsis mediterranei*, *Saccharopolyspora spinosa*, *Serinicoccus profundi*, *Mycobacterium colombiense*, *Mycobacterium gilvum*, *Mycobacterium chubutense*, *Mycobacterium tusciae*, *Mycobacterium parascrofulaceum*, *Mycobacterium intracellular*, *Mycobacterium rhodesiae*, *Mycobacterium phlei*, *Mycobacterium vanbaalenii*, *Rhodococcus imtechensis*, *Rhodococcus jostii* [*mfpA* gene] [179], and *Dermatophilus congolensis* [*norB* gene] [264]. Quinolone resistance genes in bacteria of this phylum are shown in Tables 1 and 2.

Sulfonamide and trimethoprim

This family was first reported in 1932 [318, 319], and sulfamethoxazole is the most common and cheap agent in this family for treating bacterial infections. To date, the use of sulfonamides is limited for various reasons including (i) introduction of novel antibacterial agents that are more effective to sulfonamides, (ii) resistance to this family in a lot of bacterial pathogens, and (iii) drug allergic reaction in patients. In 1968, the combination of trimethoprim and sulfamethoxazole has been used for bacterial infections treatment. The mechanism of antibiotic resistance to sulfamethoxazole is competitive inhibition of para-aminobenzoic acid (PABA) or dihydropteroate synthase (DHPS) while trimethoprim block dihydrofolate reductase (DHFR) in the biosynthetic folic acid

Table 2 Antibacterial resistance genes in the genus and species level in Actinobacteria phylum with mycolic acids compounds in cell wall structure

Species	Sulfonamide and trimetoprim resistance genes	MLSKO resistance and efflux gene or genes	Tetracycline resistance and efflux gene or genes	Rifampicin-resistance	Aminoglycoside resistance and efflux gene or genes	Beta-lactamase gene or genes	Chromosomal point mutations	Vancomycin resistance genes	Chloramphenicol resistance and efflux gene or genes	Quinolone resistance and efflux gene or genes	Reference
Corynebacterium sp.	*sul1*	*erm*(*A*), *erm*(C), *erm*(X), *erm*(F), *erm* (FS), *erm*(FU), *erm*(CD), *erm*(Y), *msr*(*A*,*B*,*SA*,*D*), *mef*(*A*)	Tetracycline resistance, *tet*(33)		*aac*(*3*)-*IV*	bla_{TEM}, bla_{CTX}					[112, 132, 136, 137, 214]
Corynebacterium diphtheriae	*sul1*	*erm*(X)	*tet*(M)		*aph*(*aph3ia*)				[chloramphenicol_ exporter]		[132, 215]
Corynebacterium diphtheriae biovar *mitis*	*dfrA16*								*cmlA*		[217]
Corynebacterium amycolatum		*erm*(X)	*tet*(O)			bla_{OXA2}					[218–220]
Corynebacterium glutamicum	*sul1*	*lmrB*	*tet*(A), *tet*(33), *tet* (Z)		*aadA9*				*cata1*, *cmr*		[112, 221–225]
Corynebacterium urealyticum		*erm*(X), *erm*(B), *tlrC*			*strA*(*aph33ib*), *strB* (*aph*(*6*)-*Id*), *aph*(*aph3ia*), *aph*(*3′*)-*Ic*				*cmx*, *cml_e8*		[219, 226–228]
Corynebacterium glucuronolyticum									*cmx1*/*cmx2*		[144, 229–229]
Corynebacterium striatum	*sul1*	*erm*(X), *erm*(B), *erm*(CX)	*tet*(W), *tet*(A), *tet* (B)		*aph*(*3′*)-*Ic*, *aph*(*3″*)*Ib*, *aph*(*6*)*Id*, *aac*(*3*)*XI*, *strA*(*aph33ib*), *aph*(*3′*)-*Ia*	class A, bla_{AmpC}, *dppD*	*gyrA*		*cml_e8*, *cmx1*/*cmx2*		[219, 229–234]
Corynebacterium jeikeium		*erm*(X)							*cmx1*/*cmx2*		[229, 235,]
Corynebacterium resistens		*erm*(X)	*tet*(W)		*aphA1-IAB*, *strA-strB*		*gyrA*		*cmx*		[126]
Mycobacterium abscessus		*erm*(*B*), *erm*(C), *erm*(39), *erm*(40),	*tet*(M)	*arr*	*aph*(*3′*)-*I*, *aadE*	bla_{Mab}	23S rRNA, 16S rRNA		*cat*		[132, 236–240]

Table 2 (continued)

	erm(41), *lsa*								
Mycobacterium tuberculosis[1–5]	*erm*(E), *erm*(37)			*aac(2′)-I*, *rpsL*, *gidB*	bla_C-bla_{NDM-1}, class A	*katG*, *rpoA*, *rpoB*, *rpoC*, 16S rRNA, *gidB*, *gyrA*, *gyrB*,*tlyA*	*cat*	*mfpA*	[127, 128, 132, 236, 241–252]
Mycobacterium bovis	*erm*(E), *erm*(37)			*aac(2′)-I*	bla_C	*katG*		*mfpA*	[127, 131, 132, 244]
Mycobacterium tuberculosis complex sp.	*erm*(37)			*aac(2′)-I*					[132, 144]
Mycobacterium smegmatis	*erm*(38)	*tet*(V)	*arr*, *mspA*, *mspC*	*aac(2′)-Id*	bla_S, bla_E, $bla_{F/MFO-1}$, class A			*mfpA*, *lfrA*	[112, 127, 131, 132, 179, 239, 253–257]
Mycobacterium goodii	*erm*(38)	*tet*(V)	*arr*						[132, 236]
Mycobacterium microti						*katG*		*mfpA*	[132, 244]
Mycobacterium canettii					bla_C			*mfpA*	[131, 132]
Mycobacterium africanum						*katG*		*mfpA*	[132, 244]
Mycobacterium fortuitum subsp. *fortuitum*	*erm*(39)			*aac(2′)-Ib*, *aph(3″)-I*	class A				[132]
Mycobacterium sp.	*erm*(MT)	*tet*(M), *tet*(O), *tet*(K), *tet*(L), *tet*(V)			bla_{AmpC}	23S rRNA		*mfpA*	[112, 132, 137, 138, 179, 258]
Mycobacterium leprae				*aac(2′)-Ie*		*rpoB*, *gyrA*			[259]
Mycobacterium marinum				*aac(2′)-I*	bla_C	*rpoB*		*mfpA*	[128, 131, 132]
Mycobacterium fortuitum	*erm*(39), *erm*(K), *erm* (38),	*otrA*, *otrB*		*aph(3′)-I*, *aac(2′)-I*, *aph(3″)-Ic*	classA, $bla_{F/MFO-1}$	23S rRNA			[131, 132, 179, 236, 260–262]
Mycobacterium fortuitum subsp. *acetamidolyticum*	*erm*(39)			*aph(3″)-I*	class A				[132]
Mycobacterium massiliense	*erm*(41)							*mfpA*	[179, 263]
Mycobacterium kansasii[1]					bla_C			*mfpA*	[128, 131, 179, 236]

Table 2 (continued)

							rpoB, *gyrA*, *gyrB*, 23S rRNA				
Mycobacterium peregrinum		*erm*(38), *erm*(39)	*otrA*, *otrB*, *tet*(K), *tet* (L)								[238, 260]
Mycobacterium chelonae		*erm*(38), *erm*(39), *erm*(40)					23S rRNA				[238, 239]
Mycobacterium avium							23S rRNA				[265]
Mycobacterium ulcerans					*aac(2′)-I*	bla_{C}	*rpoB*			*mfpA*	[131, 132, 179, 236]
Mycobacterium mageritense		*erm*(40)				$bla_{F/MFO-1}$					[131, 236]
Mycobacterium leprae							*rpoB*				[236]
Nocardia farcinica	*sul1*, *sul2*	*erm*(A), *msr*(D), *mef*(A)		RifMO	*aph(3′)*, *aph(6)*, *aph(2″)*	bla_{TEM-1}, bla_{VIM-2}, bla_{FAR-1}	*gyrA*, *rpoB2*	*vanR*		*qepA*	[132, 192, 266–270]
Nocardia nova						bla_{TEM-1}	*gyrA*				[266]
Nocardia veterana						bla_{Z}	*gyrA*				[266]
Nocardia flavorosea		*msr*(D), *mef*(A)				bla_{Z}	*gyrA*				[266]
Nocardia cyriacigeorgica						bla_{FAR-1}	*gyrA*				[131, 266]
Nocardia carnea		*mef*(A)					*gyrA*				[266]
Nocardia transvalensis		*erm*(A), *msr*(D), *mef*(A)					*gyrA*				[266]
Nocardia sp.		*mef*(A)	*tet*(K), *tet*(L)								[112, 138, 266]
Nocardia seriolae	*dfrA26*	*macB*, *vat*(B), *vat*(C), *srmB*, *carA*	*otrB*, *tcr3*		*aac(6′)-Ic*	bla_{2a}		*vanRB*, *vanRC*	*catB1*	*mfpA*	[266, 271]
Nocardia brasiliensis				Rifampin glucosylation		bla_{AST-1}					[131, 272]
Nocardia asteroides							*rpoB2*				[268]
Rhodococcus opacus			*tet*(A)		*hygR*					*mfpA*	[132, 179, 273]
Rhodococcus erythropolis				RifMO							[132]
Rhodococcus sp.				RifMO						*mfpA*	[132, 179]

Table 2 (continued)

prescottella equi	*erm*(46)	RifMO	*iri*	*gyrA*, *gyrB*, 23S rRNA, *rpoB*	*vanO*		[274–278]
Rhodococcus fascians				bla_F	*cmr*		[279, 280]
Rothia sp.	*erm*(B), *erm*(X)	*tet*(W)					[112, 132, 139, 281]

Other resistance genes include 1- *eis* and 16S rRNA genes: resistance genes to amikacin/kanamycin [128]; 2- *thyA*, *folC*, and *ribD* genes: resistance genes to para-aminosalicylic acid [128]; 3- *rv0678*, *atpE*, and *pepQ* genes: resistance genes to bedaquiline [128, 245]; 4- *fgd1*, *fbiC*, *fbiA*, *fbiB*, and *ddn* genes: resistance genes to delamanid/pretonamid [245]; and 5- 16S rRNA, *tylA*, and *eis* genes: resistance genes to capreomycin/viomycin [128]

pathway [112, 115–117]. One of the resistance mechanisms that are encoded by chromosomal is the mutation in the *folP* gene. Also, other resistance genes that were carried with plasmid include *sul* (*sul1*, *sul2*, *sul3*) genes. These genes have an important role in resistance to sulfonamides. *dfrA* and *dfrB* genes and mutation in the *folA* (is encoding dihydrofolate reductase) gene are causing resistance to trimethoprim [112, 117]. In literature, sulfonamide and trimethoprim resistance gene or genes have been reported in *Brevibacterium* sp. [*sul* genes] [190], *Collinsella* sp., *Kocuria* sp., and *Ornithinibacter* sp. [*sul1* gene] [145, 208]. Sulfonamide and trimethoprim resistance genes in bacteria of this phylum are shown in Tables 1 and 2.

Rifampicin

Rifampicin (also known as Rifampin) was first isolated from *Amycolatopsis mediterranei* (formerly identified as *Streptomyces mediterranei*), and it is the first-line treatment for mycobacterial infections specially *M. tuberculosis*. This antibiotic inhibits RNA synthesis (transcription) in microorganisms [115, 295]. The RNA polymerase structure in bacteria contains α2ββ'ω and σ subunits (α2ββ' and σ subunits are encoding *rpoA*, *rpoB*, *rpoC*, and *rpoD* genes, respectively). Expression of different σ factors are under various growth conditions [116, 241]. Resistance mechanisms to rifampicin include (a) mutation in the *rpoA*, *rpoB*, and *rpoC* genes [241, 320]; (b) phosphotransferase [321]; (c) ADP ribosyl transferase (*arr* genes) [322]; (d) efflux systems [323]; (e) glucosylation [272], phosphorylation [324], decomposition [274, 324, 325], and ribosilation [326]; (f) monooxygenases (Rox) [188]; and (g) inactivation of rifampin (*iri* gene) [274]. Rifampin inactivation by ribosilation was reported in a large number of *Mycobacterium* spp. such as *Mycobacterium smegmatis*, also in closely related species *Gordona* and *Tsukamurella* [327, 328]. In literature, only resistance to rifampicin (rifampin_monooxygenase) has been reported in *prescottella hoagie* (formerly identified as *Rhodococcus hoagie*) and *Rhodococcus enclensis* [132]. Rifampin resistance genes in other bacteria of this phylum are shown in Tables 1 and 2.

Dapsone

This antibiotic was discovered by Eric Fromm and J. Wittmann from Germany in 1908 [329]. Dapsone structure is similar to sulfanilamides and this antibiotic is effective against leprosy infections [115], although the gold standard treatment for this disease is the use of clofazimine, dapsone, and rifampin [330]. The *folP1* gene encodes the DHPS enzyme that is causing resistance to dapsone (point mutations in this gene) in *Mycobacterium leprae* [259, 330, 331].

Cycloserine

This antibiotic was first discovered by Kurosawa in 1952 and has been isolated from *Streptomyces* species such as *Streptomyces* K-300 and *Streptomyces lavendulae* [332]. The antibacterial mechanism of cycloserine is interference with bacterial cell wall synthesis (peptidoglycan synthesis) with inactivation of D-Ala-D-Ala ligase (DDL) and alanine racemase (ALR) [128, 333, 334]. This antibiotic is used in the second-line treatment for tuberculosis [335]. Antibiotic resistance genes to cycloserine have been reported in *M. tuberculosis* (*alr*, *ddl*, *cycA*, *ald*, *betP*, *gabD2*, *sugI*, *hisC2*, *rv0059*, *rv0221*, *rv1403c*, *rv1683*, *rv1726*, and *rv2749* genes) [128, 336].

Ethionamide

This antibiotic has activity against a narrow spectrum of bacteria specially mycobacteria [337]. Ethionamide structure is similar to isoniazid and both antibiotics inhibit mycolic acid synthesis in the cell wall. This antibiotic is used for tuberculosis treatment as second-line antitubercular antibiotics [338]. Also, ethionamide is effective against *Mycobacterium avium* complex and *M. leprae* infections [339]. Antibiotic resistance genes to ethionamide have been reported from *M. tuberculosis* (mutation in the *ethA*, *inhA*, *ethR*, *ndh*, *katG*, and *mshA* genes) [128, 339], *M. smegmatis*, and *Mycobacterium bovis* (mutation in the *inhA* gene) [339–341].

Ethambutol

Ethambutol (EMB) is an antimycobacterial compound that firstly has been described in 1961 [342]. The target site of the antibiotic is the mycobacterial cell wall [343] and inhibits the synthesis of cell wall arabinogalactan/arabinomannan components or inhibits the transfer of arabinosyl [236, 342]. Resistance mechanisms to EMB include mutation in various genes and efflux genes. Antibiotic resistance genes to ethambutol have been reported from *M. tuberculosis* (mutation in the *ubiA*, *embC*, *embA*, *embB*, and *embR* genes) [127, 128]; *M. smegmatis* and *M. leprae* (mutation in the *embC*, *embA*, and *embB* genes) [344, 345]; *M. avium* (mutation in the *embA* and *embB* genes) [342]; *Mycobacterium abscessus*, *Mycobacterium peregrinum*, *Mycobacterium kansasii*, *Mycobacterium fortuitum*, and *Mycobacterium chelonae* (mutation in the *embB* gene) [345]. The presence of the efflux gene *jefA* in *M. tuberculosis* caused resistance to EMB and isoniazid [242].

Clofazimine

This antibiotic is a dye compound originally and discovered in 1957. Clofazimine has antibacterial activity against mycobacteria infections such as *M. tuberculosis* and atypical mycobacteria [346, 347]. Target position for clofazimine is NADH dehydrogenase in bacteria [128]. Resistance genes to clofazimine have been reported from *M. tuberculosis* (*rv0678*, *rv1979c*, mutation in the *ndh*, and *pepQ* genes) [128, 348], and *M. abscessus* (*MAB-2299c*, *MAB-1483*, and *MAB-0540*) [349].

Isoniazid

This antibiotic is the most important and efficient antituberculosis drug that is used as a first-line treatment. Isoniazid blocks the synthesis of mycolic acids in the bacteria cell-wall and catalase-peroxidase (KatG) enzymes [115, 350, 351]. Resistance mechanisms to isoniazid include mutations in various genes and active efflux pump. Resistance genes to isoniazid have been reported from *M. tuberculosis* (mutation in the *kasA*, *katG*, *ahpC*, *iniA*, *iniB*, *iniC*, *inhA*, *fabG*, *fadE24*, *furA-katG*, *fabG1-inhA*, *ahpC-oxyR*, *efpA*, *nat*, *srmR*, and *Ndh* genes or presence of the *mmpL7* efflux gene) [128, 352–354], *M. bovis* (mutation in the *inhA* gene) [341], *M. smegmatis*, *Mycobacterium aurum* (mutation in the *katG* gene) [355], and *M. avium* (mutation in the *KatG* gene) [356].

Pyrazinamide

This antibiotic has bactericidal activity and is used for tuberculosis treatment as first-line drugs. Pyrazinamide (PZA) enters the bacilli via passive transport and is an analogue of nicotinamide [241, 357]. Resistance genes to pyrazinamide have been reported from *M. tuberculosis* (mutation in the *clpC1*, *pncA*, *panD*, *mas*, *rspA*, *rpsA*, and *ppsA-E* genes and lack of pyrazinamidase activity) [127, 128, 241, 358–360], *M. smegmatis* (due to active efflux system) [357], *M. kansassi* (reduce pyrazinamidase activity) [357, 361], *M. bovis* (lack pyrazinamidase activity and mutations in the *rpsA* and *pncA* genes) [357, 362], *Mycobacterium canettii* (mutations in the *rpsA* and *pncA* genes) [362], *Mycobacterium caprae* (mutations in the *rpsA* gene), and *M. avium* (due to absence of uptake of PZA and mutation in the *pncA* gene) [357, 363, 364].

Nitroimidazole

This antibiotic is used for various infections treatment in human and animals. This antibiotic is effective against a variety of Gram-positive and Gram-negative anaerobe bacteria and protozoa (*Trichomonas vaginalis*, *Giardia*, and *Entamoeba histolytica*). Mechanisms of action of this antibiotic are free radicals formation and DNA damage. *nim* genes such as *nimA-D* are causing antibiotic resistance to nitroimidazole with change in the structure of the antibiotic (nitro group change into a non-bactericidal amine with reductases). These

genes carried on the chromosome (*nimB* gene) or plasmids (*nimA*, *nimC*, and *nimD* genes) [119, 135]. A few of genera in the Actinobacteria phylum are carrying nitroimidazole resistance genes that include *C. aerofaciens* (*nimB* gene) [365], *S. avermitilis* (*nim* homologs) [135], *Cutibacterium* (formerly identified as *Propionibacterium*) *acnes* (*nimA* gene) [366], *Actinomyces odontolyticus* (*nimA* gene) [366], and *Gardnerella vaginalis* (*nim* gene) [367]. Also, resistance genes to nitroimidazole have been reported from *M. tuberculosis* (*rv0407* and *rv3547* genes) [128].

Efflux pumps

Active export or active efflux systems of antibiotics is an important route in antibiotic resistance in bacteria. This resistance mechanism has been seen in various families of antibiotics such as beta-lactams, macrolides, tetracyclines, fluoroquinolones, and etc. There are two categories for system efflux pumps and category one includes Na ions, major facilitator subfamily (MFS) with Blt (resistance to quinolones), Bmr (resistance to chloramphenicol and quinolones), EmrD, NorA (resistance to chloramphenicol and quinolones), EmrB (resistance to hydrophobic quinolones), VceB (resistance to chloramphenicol, macrolides, rifampin and hydrophobic quinolones); small multidrug regulator (SMR) family with EmrE (resistance to macrolides and tetracyclines), and resistance/nodulation/cell division (RND) family with AcrB (resistance to penicillins, glycopeptides, macrolides, novobiocin, rifampin, and tetracyclines), AcrF (resistance to penicillins, glycopeptides, macrolides, novobiocin, rifampin, and tetracyclines), MexB (resistance to beta-lactams, chloramphenicol, macrolides {14 and 15 membered}, novobiocin, quinolones, sulfonamide, trimethoprim and Tetracyclines), MexD (resistance to chloramphenicol, macrolides {14 and 15 membered}, quinolones, and tetracyclines), MexF (resistance to chloramphenicol, quinolones, trimethoprim and tetracyclines), MexY (resistance to aminoglycosides, macrolides {14 membered}, and quinolones); and multidrug and toxic compound extrusion (MATE). Category two called ATP-binding cassette (ABC) family with LmrA (resistance to aminoglycosides, cephalosporins, penicillins, chloramphenicol, lincosamides, macrolides {14 and 15 membered}, quinolones, and Tetracyclines) [116, 368]. Prevalence efflux pumps in genus and species levels in Actinobacteria include Bcr/CflA (*Actinopolyspora erythraea* [369]); EmrB/QacA (*Acidipropionibacterium acidipropionici* (formerly identified as *Propionibacterium acidipropionici*) [370], *Actinokineospora auranticolor* [371], *Actinomycetospora cinnamomea* [372], *Catenulispora acidiphila* [373], *Cryptobacterium curtum* [374], *Kribbella flavida* [375], *Marmoricola scoriae* [376], *Serinicoccus* sp. [377], *Tetrasphaera japonica* [378], *Varibaculum cambriense* [175]); ABC transporter (*Arsenicicoccus* sp. [379], *Beutenbergia cavernae* [380], *Frankia alni* [381], *Hoyosella subflava* [382], *Luteipulveratus mongoliensis* [383], *Microbispora* sp. [384], *Olsenella* sp. [385], *Paenarthrobacter aurescens* [386], *S. erythraea* [387], *S. niveus* [132], *Streptomyces peucetius* [187], *Streptosporangium roseum* [388], *Leucobacter massiliensis* [389], *Roseiflexus castenholzii* [177]); MFS (*Microlunatus phosphovorus* [390], *Adlercreutzia equolifaciens* [391], *Bifidobacterium indicum* [392], *Bifidobacterium pullorum* [392], *Kibdelosporangium aridum* subsp. *aridum* (formerly identified as *Kibdelosporangium aridum*) [393], *Lechevalieria aerocolonigenes* [394], *M. abscessus* [132], *M. bovis* [243], *Rhodococcus* sp. [395], *Streptacidiphilus jiangxiensis* [396], *Streptomyces chattanoogensis* [187]); ABC transporter and MFS (*D. detoxificans* [397, 398], *Kocuria rhizophila* (formerly identified as *Micrococcus luteus*) [170], *M. smegmatis* [243]); Na^+-driven multidrug efflux pump proteins, AcrB, MFS, EmrB/QacA,Bcr/CflA, RND (*Cellulosimicrobium* sp. [155]; MATE (*Janibacter melonis*) [168]); MFS, SMR, RND, ABC (*M. tuberculosis* [128]); MFS, SMR, RND, ABC, MATE (*Rhodococcus opacus*, *Rhodococcus erythropolis*, *prescottella equi* (formerly identified as *Rhodococcus equi*), *R. jostii* [399]); MacB, EmrB/QacA, Bcr/CflA (*Rothia mucilaginosa* [400]); EmrB/QacA, ABC transporter (*ppzR1* gene) (*Thermobispora bispora* [388, 401]); Bcr/CflA, EmrB/QacA (*L. chironomi* [129]); Macb, EmrE (*Thermobifida fusca* [211]); and EmrB/ABC transporter (*Isoptericola dokdonensis* [402, 403]). In literature, the *mexB* gene (*Collinsella aerofaciens*) [404], and *mexX*, *mexY*, and *mexR* genes (*Ilumatobacter coccineus*, *Sphaerobacter thermophilus*) [163, 182] have been reported in a few of the genera in this phylum.

Integrons

One of the mobile genetic elements (MGEs) that has an important role in antibiotic resistance in bacteria are integrons that were first reported by Stokes et al. in 1989 [405]. They accumulate novel genes as a portion of gene cassettes [406, 407]. Analysis of complete or partial genome sequence in bacteria has shown presence of integrons or integrase genes [408, 409]. In literature, integrons have been identified and reported in clinical and environment bacterial isolates. Integrons were classified to three classes which include classes I, II, and III, although there is another classification for those based on their context [407]. The most common integrons in clinical isolates is class I [408] and some genes such as *qac* and *sulI* are carried by this class [410, 411]. Integrons have been reported in the Actinobacteria phylum that include class I in *Actinobaculum suis* [132], *Actinotignum schaalii* (formerly identified as *Actinobaculum schaalii*) [140], *Arthrobacter* sp. [132], *Corynebacterium*

diphtheria [132], *Kocuria* sp. [145], *Mycobacterium* sp. [412], *Nocardia nova* [266], *Trueperella pyogenes* (formerly identified as *Arcanobacterium pyogenes*) [199], *Corynebacterium diphtheria* biovar *mitis* (class I/*ereA1* gene) [218]; Class II in *A. schaalii* [140]; Class III in *A. schaalii* [140]; and *N. nova* [266].

Molecular identification and prediction of antibiotic resistance genes

One of the important things that have happened in recent decades was introduction of polymerase chain reaction (PCR) by Kary Mullis in the 1980s [413]. In the last two decades, the use of PCR is increasing in molecular diagnostics [414] especially antibiotic resistance genes identification [266]. PCR is the most common method for resistance genes' accurate identification in bacteria that use specific primers to replicate target genes. Another molecular method is real-time PCR that use fluorescent double strand DNA dyes or probes for identification. Quantitative and qualitative investigations and analysis of DNA have been done with this method [414]. To date, one of the important molecular tools is whole genome sequencing (WGS) that is used for: (1) accurate and fast identification of antibiotic resistance mechanisms in bacteria especially *M. tuberculosis*, (2) infections control, (3) survey transmission ways in bacteria, and (4) survey molecular typing such as multilocus sequence typing (MLST) or phylogenetic analysis and genetic relation between isolates in epidemiologic studies [97, 415, 416]. Also, this method can identify mutations in the RNA polymerase subunits in *M. tuberculosis* resistant to rifampin [97]. One of the servers that are used for bacterial genome annotation is rapid annotation using subsystem technology (RAST) server [417]. Although RAST forestalls the open reading frames (ORFs) and many novel proteins, it is not suitable to predict and analyze antibiotic resistance (AR) genes. Problems of analysis of whole genome sequencing and implementation include data interpretation, the absence of automated and the authors released sequences to form of contigs or short sequences and are not always complete sequences. In literature, metagenomic studies in microbial show AR have a classical origin [418]. There are various databases and software for the study of antibiotic resistance genes in WGS that include antibiotic resistance genes online (ARGO) [419], antibiotic resistance gene-annotation (ARG-ANNOT) [418], antibiotic resistance genes database (ARDB) [420], Resfinder [https://cge.cbs.dtu.dk//services/ResFinder/] [98], comprehensive antibiotic resistance database (CARD) [website: https://card.mcmaster.ca/] [421], and MvirDB [422]. ARG-ANNOT is more suitable than the others for four reasons: (i) this software in addition to the acquired AR genes identification can detect point mutations in bacterial DNA; (ii) this bioinformatic tool has superior sensitivity and specificity for AR genes identification in whole and partial gene sequences; (iii) ARG-ANNOT identified AR genes with multiple copies or closely related AR genes correctly; and (iiii) also, this software can analyze various sequence lengths of the AR genes [418]. ARG-ANNOT cannot identify single-nucleotide variants (SNVs) but CARD can [415]. Also, there are a few reports for antibiotic resistance genes with DNA microarray [423].

A hypothesis: role of antibiotic producer Actinobacteria in dissemination ARG to pathogenic bacteria

To date, a lot of antibiotics originated from this phylum and one of the most important antibiotic-producing bacteria is the genus *Streptomyces* [5, 187], and this bacterium has resistance genes clusters that are self-defense mechanism against antibacterial compounds [105, 187, 424] or they regulate the signaling activity [425]. Ogawara identified beta-lactamase classes including A, B, and C in many *Streptomyces* sp. [426]. Walker and Walker in 1970 first reported AMEs in *Streptomyces* sp. [187, 427]. Benveniste and Davies in 1973, reported aminoglycoside antibiotics inactivation enzymes in clinical isolates emanated from ARG in aminoglycoside producers gram-positive Actinobacteria (*S. kanamyceticus*: kanamycins production, *Micromonospora purpurea*: gentamicins production, *Streptomyces coelicolor*: non, *Streptomyces spectabilis*: spectinomycin, *S. fradiae*: neomycins production) via horizontal gene transfer (HGT) [428]. Pang et al. reported *otrA* and *otrB* genes in the tetracycline-resistant *Streptomyces* sp. and tetracycline-resistant *Mycobacterium fortuitum* group isolated from clinical samples [260], and their research offered that antibiotic-producing *Streptomyces* sp. are lineal source for a lot of the ARG that are found in other genera in bacteria presumably [428]. Jiang et al. in 2017 proved with bioinformatic study and experimental document that various antibiotic resistance genes in gram-negative pathogenic bacteria are closely related to antibiotic-producing Actinobacteria. Also, they reported carry-back mechanism in their article [105]. We think more studies about this topic are needed in the future.

Conclusion

The antibiotics have been used for bacterial infections treatment in different parts of the human body. Identification of molecular mechanisms for drug resistance is developing and progressing from the past decade to the present. This article showed there are various resistance genes that are causing resistance to various families of antibiotics in this phylum, and performing antibiogram susceptibility testing is necessary for treating these infections. Also, our literature review showed antibiotic-producing bacteria in this phylum are

carrying a large number of resistance genes and transferred resistant genes to Gram-negative pathogenic bacteria presumably.

Compliance with ethical standards

Conflict of interest The author declares that there is no conflict to interest.

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