ESGEM-AMR

ESCMID

AMRrules

Agenda

1. **Updates to rule spec (v0.5)**
2. Examples of rules for core genes and wild-type phenotypes
3. Updates from organism subgroups
4. General ESGEM-AMR updates
5. Next meeting

AMRrules | ESCMID | ESGEM-AMR

Rules Specification

AMR Rules Spec v0.5

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bit.ly/AMRrules_spec05

B15

	A	B	C	D	E	F	G	H	I	J	K	L
1	ruleID	organism	gene	nodeID	refseq accession	GenBank accession	HMM accession	ARO accession	mutation	variation type	context	drug
2	required	required	required	require AT LEAST ONE OF: nodeID (preferred) or refseq or GenBank or HMM accession				optional (recommended)	required	required	required	require ONE O class
3	KPN0001	s__Klebsiella pneumoniae	blaSHV	blaSHV	NF000285.3	-	-	ARO:3000015	-	Gene presence detected	core	-
4	KPN0002	s__Klebsiella pneumoniae	oqxA	oqxA	NF000272.1	-	-	ARO:3003922	-	Gene presence detected	core	-
5	KPN0003	s__Klebsiella pneumoniae	oqxB	oqxB	NF000037.1	-	-	ARO:3003923	-	Gene presence detected	core	-
6	KPN0004	s__Klebsiella pneumoniae	fosA5_fam	fosA5_fam	NF040540.1	-	-	-	-	Gene presence detected	core	fosfomycin
7	KPN0005	s__Klebsiella pneumoniae	fosA5	fosA5	WP_012579083.1	-	-	ARO:3003209	-	Gene presence detected	core	fosfomycin

All links at: github.com/interpretAMR/AMRrulesCuration/

If we find this gene…

in this species…

ruleID	organism	gene	drug	drug class	phenotype	clinical category
required	required	required	require ONE OF: drug or drug class		required	required
KPN0001	s__Klebsiella pneumoniae	blaSHV	-	penams	wildtype	R
KPN0002	s__Klebsiella pneumoniae	oqxA	-	fluoroquinolone	wildtype	S
KPN0003	s__Klebsiella pneumoniae	oqxB	-	fluoroquinolone	wildtype	S
KPN0004	s__Klebsiella pneumoniae	fosA5_fam	fosfomycin	-	wildtype	S

…we expect this phenotype

for this drug

Adding specificity about the genotype

These rules apply when we detect the **presence** of a **core** gene

ruleID	organism	gene	mutation	variation type	context
required	required	required	required	required	required
KPN0001	s__Klebsiella pneumoniae	blaSHV	-	Gene presence detected	core
KPN0002	s__Klebsiella pneumoniae	oqxA	-	Gene presence detected	core
KPN0003	s__Klebsiella pneumoniae	oqxB	-	Gene presence detected	core
KPN0004	s__Klebsiella pneumoniae	fosA5_fam	-	Gene presence detected	core

Adding specificity about the genotype

These rules apply when we detect the **presence** of a **core** gene

ruleID	organism	gene	mutation	variation type	context
required	required	required	required	required	required
KPN0001	s__Klebsiella pneumoniae	blaSHV	-	Gene presence detected	core
KPN0002	s__Klebsiella pneumoniae	oqxA	-	Gene presence detected	core
KPN0003	s__Klebsiella pneumoniae	oqxB	-	Gene presence detected	core
KPN0004	s__Klebsiella pneumoniae	fosA5_fam	-	Gene presence detected	core
KPN0008	s__Klebsiella pneumoniae	gyrA	p.Ser83Tyr	Protein variant detected	core

This rule applies when we detect a specific **protein variant** in a **core** gene

Adding specificity about the gene

This gene name

…maps to these identifiers in specific databases

ruleID	organism	gene	nodeID	refseq accession	GenBank accession	HMM accession	ARO accession
required	required	required	require AT LEAST ONE OF: nodeID (preferred) or refseq or GenBank or HMM accession				optional (recommended)
KPN0001	s__Klebsiella pneumoniae	blaSHV	blaSHV	NF000285.3	-	-	ARO:3000015
KPN0002	s__Klebsiella pneumoniae	oqxA	oqxA	NF000272.1	-	-	ARO:3003922
KPN0003	s__Klebsiella pneumoniae	oqxB	oqxB	NF000037.1	-	-	ARO:3003923
KPN0004	s__Klebsiella pneumoniae	fosA5_fam	fosA5_fam	NF040540.1	-	-	-

NCBI Gene Hierarchy node

RefSeq protein accession

GenBank protein accession

NCBI HMM accession

CARD accession

Adding specificity about the phenotype

This phenotype categorization

…is defined by these criteria

ruleID	organism	gene	phenotype	clinical category	breakpoint	breakpoint standard
required	required	required	required	required	required	required
KPN0001	s__Klebsiella pneumoniae	blaSHV	wildtype	R	not applicable	Expected resistant phenotypes v1.2 (13 January, 202
KPN0002	s__Klebsiella pneumoniae	oqxA	wildtype	S	not applicable	EUCAST v14.0 (2024)
KPN0003	s__Klebsiella pneumoniae	oqxB	wildtype	S	not applicable	EUCAST v14.0 (2024)
KPN0004	s__Klebsiella pneumoniae	fosA5_fam	wildtype	S	MIC >128 mg/L	ECOFF (January 2024)

Note for a rule defined for a drug class (here oqxAB -> fluoroquinolone), breakpoint is ‘not applicable’ as this applies to drugs not classes.

Summarising the evidence for the rule

What **kind** of evidence is there to support the rule?

Overall, how **strong** is this evidence?

What are we not sure about?

PMID	evidence code	evidence grade	evidence limitations
required	required	required	optional
32284385	ECO:0001091 knockout phenotypic evidence	strong	
30834112	ECO:0001103 natural variation mutant evidence	moderate	low clinical relevance, lacks evidence for this allele
30834112	ECO:0001103 natural variation mutant evidence	moderate	low clinical relevance, lacks evidence for this allele
33128341	ECO:0001103 natural variation mutant evidence	moderate	low clinical relevance

ECO:0001091 knockout phenotypic evidence	E.g. evidence that knocking out the proposed AMR gene in a phenotypically resistant strain results in loss of resistance
ECO:0000012 functional complementation evidence	E.g. evidence that, when a gene knockout results in change from R to S, the phenotype is reversed (resistance is restored) when the gene is reintroduced
ECO:0001113 point mutation phenotypic evidence	E.g. for a mutation, evidence that this specific mutation is associated with a change in susceptibility phenotype
ECO:0000024 protein-binding evidence	E.g. evidence that the gene product binds to this drug
ECO:0001034 crystallography evidence	E.g. structural evidence from crystallography that the mutated position in this gene product interacts with the drug
ECO:0000005 enzymatic activity assay evidence	E.g. evidence that the gene product has enzymatic activity against the drug
ECO:0000042 gain-of-function mutant phenotypic evidence	E.g. for a mutation, evidence that introducing this specific mutation into a wildtype background is associated with a change in susceptibility phenotype
ECO:0007000 high throughput mutant phenotypic evidence	E.g. evidence from a transposon mutant library that mutation or loss of a gene in a phenotypically resistant strain results in loss of resistance
ECO:0001103 natural variation mutant evidence	E.g. for an acquired gene or mutation, evidence that natural variation in presence vs absence is associated with susceptibility to the drug (genotype-phenotype association in a natural population)
ECO:0005027 genetic transformation evidence	E.g. evidence that transfer of the gene into a susceptible recipient strain results in resistance
ECO:0000020 protein inhibition evidence	E.g. evidence that a mutation inhibits protein function to reduce interaction the effect of the drug and confer resistance

Evidence grade	What it means	Use this when
strong	The curators have a lot of confidence that the categorisation reflects the true effect	Experimental evidence provides strong support for the interpretation of this gene/variant in this species for this drug.
moderate	The curators believe that the categorisation probably reflects the true effect	There is good evidence to support the interpretation of this gene/variant in this species for this drug, but there is some uncertainty (e.g. lack of direct evidence in this organism; or there is statistical geno/pheno evidence but no experimental evidence).
weak	The curators believe that the categorisation might not reflect the true effect	There is evidence supporting a link between this gene/variant and this drug, but the interpretation in this species is unclear and the categorical interpretation may be wrong.

Evidence limitations
lacks evidence for this species
lacks evidence for this genus
lacks evidence for this allele
lacks evidence of the degree to which MIC is affected
low clinical relevance
unknown clinical relevance
statistical geno/pheno evidence but no experimental evidence

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2. **Examples of rules for core genes and wild-type phenotypes**
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Examples from staphylococci

Table 4 Expected resistant phenotype (susceptibility not expected) in gram-positive bacteria. Gram-positive bacteria are expected to be resistant to aztreonam, temocillin, polymyxin B/colistin and nalidixic acid.

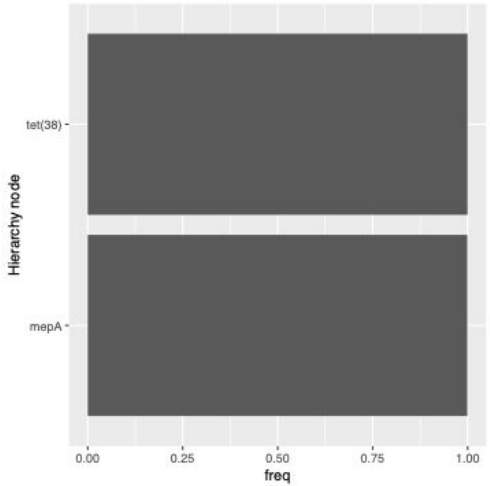
Rule	Organisms	Fusidic acid	Ceftazidime	Cephalosporins (except ceftazidime)	Aminoglycosides	Macrolides	Clindamycin	Quinupristin-dalfopristin	Vancomycin	Teicoplanin	Fosfomycin	Novobiocin	Sulfonamides
4.1	*Staphylococcus saprophyticus*	R	R								R	R	
4.2	*Staphylococcus cohnii*		R									R	
4.3	*Staphylococcus xylosus*		R									R	
4.4	*Staphylococcus capitis*		R								R		
4.5	Other coagulase-negative staphylococci and *S. aureus*		R										
4.6	*Streptococcus* spp.	R	R		R[1]								
4.7	*Enterococcus faecalis*	R	R	R	R[1]	R	R	R					R
4.8	*Enterococcus gallinarum, Enterococcus casseliflavus*	R	R	R	R[1]	R	R	R	R				R
4.9	*Enterococcus faecium*	R	R	R	R[1,2]	R							R
4.10	*Corynebacterium* spp.										R		
4.11	*Listeria monocytogenes*		R	R									
4.12	*Leuconostoc* spp., *Pediococcus* spp.								R	R			
4.13	*Lactobacillus* spp. (*L. casei, L. casei* var. *rhamnosus*)								R	R			

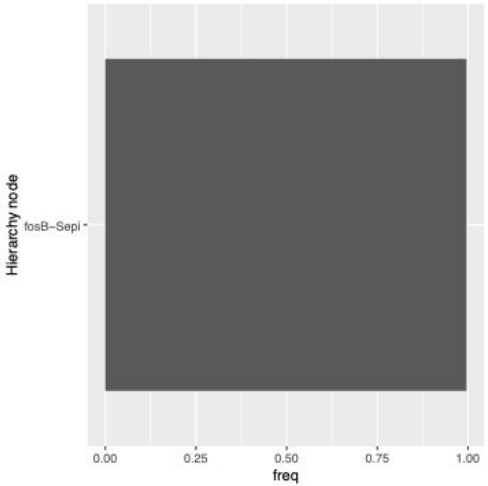
[1] Low-level resistance (LLR) to aminoglycosides. Combinations of aminoglycosides with cell wall inhibitors (penicillins and glycopeptides) are synergistic and bactericidal against isolates that are susceptible to cell wall inhibitors and do not display high-level resistance to aminoglycosides

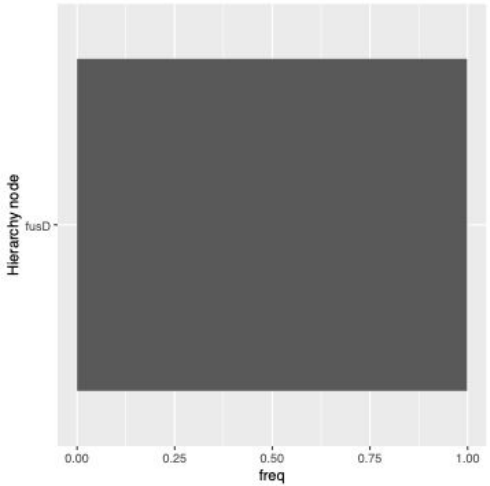
[2] In addition to LLR to aminoglycosides, *Enterococcus faecium* produces a chromosomal AAC(6')-I enzyme that is responsible for the loss of synergism between aminoglycosides (except gentamicin, amikacin and streptomycin) and penicillins or glycopeptides

https://docs.google.com/spreadsheets/d/1A7luG7hi9u2tOAbNn4jGAQSnpRAZ94-OUdsDkxHjsKM/edit?gid=0#gid=0

Examples from staphylococci







https://docs.google.com/spreadsheets/d/1A7luG7hi9u2tOAbNn4jGAQSnpRAZ94-OUdsDkxHjsKM/edit?gid=0#gid=0

AMRFinderPlus from AllTheBacteria genomes

Example: core gene *oqxA* in *Klebsiella pneumoniae*

ruleID	organism	gene	nodeID	refseq	GenBank	HMM	ARO	mutation	variation type	context	drug	drug class	phenotype	clinical category	breakpoint	breakpoint standard
KPN0002	s__Klebsiella pneumoniae	oqxA	oqxA	NF000272.1	-	-	ARO:3003922	-	Gene presence detected	core	-	fluoroquinolone	wildtype	S	not applicable	EUCAST v14.0 (2024)

PMID	evidence code	evidence grade	evidence limitations	rule curation note
30834112	ECO:0001103 natural variation mutant evidence	moderate	low clinical relevance, lacks evidence for this allele	Wildtype core gene encoding an efflux pump. This efflux pump likely contributes to some MIC distributions in K. pneumoniae being shifted upwards compared to other Enterobacteriaceae, but it is not associated with clinical resistance in this species unless efflux activity is upregulated. (The specific alleles or mutations associated with upregulation of the efflux pump in K. pneumoniae are not well described.)

Example: core gene *fosA* in *Klebsiella pneumoniae*

ruleID	organism	gene	nodeID	refseq	GenBank	HMM	ARO	mutation	variation type	context	drug	drug class	phenotype	clinical category	breakpoint	breakpoint standard
KPN0004	s__Klebsiella pneumoniae	fosA5_fam	fosA5_fam	NF040540.1	-	-	-	-	Gene presence detected	core	fosfomycin	-	wildtype	S	MIC >128 mg/L	ECOFF (January 2024)

PMID	evidence code	evidence grade	evidence limitations	rule curation note
33128341	ECO:0001103 natural variation mutant evidence, ECO:0001091 knockout phenotypic evidence	moderate	low clinical relevance	Wildtype core gene encoding a fosfomycin-modifying enzyme. This gene likely contributes to the fosfomycin MIC distribution in K. pneumoniae being shifted upwards compared to other Enterobacteriaceae, but it is not associated with clinical resistance in this species unless activity is upregulated or modified. (The specific alleles or mutations associated with these changes in K. pneumoniae are not well described.)

Example: acquired gene *qnrB1* in *Klebsiella pneumoniae*

ruleID	organism	gene	nodeID	refseq	GenBank	HMM	ARO	mutation	variation type	context	drug	drug class	phenotype	clinical category	breakpoint	breakpoint standard
KPN0012	s__Klebsiella pneumoniae	qnrB1	qnrB1	WP_014386481.1	-	-	-	-	Gene presence detected	acquired	ciprofloxacin	-	nonwildtype	I	MIC >0.25 and <= 0.5 mg/L	EUCAST v14.0 (2024), ECOFF (January 2024)

PMID	evidence code	evidence grade	evidence limitations	rule curation note
16569827	ECO:0005027 genetic transformation evidence, ECO:0000020 protein inhibition evidence, ECO:0001103 natural variation mutant evidence, ECO:0000012 functional complementation evidence	moderate	lacks evidence of the degree to which MIC is affected	Encoded protein QnrB1 provides concentration-dependent protection of DNA gyrase from ciprofloxacin inhibition of DNA supercoiling, partially restoring DNA replication efficiency in the presence of ciprofloxacin. The initial report described qnrB1 as associated with 'low-level ciprofloxacin resistance' in K. pneumoniae (n=2 isolates with MIC 0.5 mg/L, n=1 with MIC=0.25 mg/L), and KlebNET data shows solo PPV for I/R=123/148=83%; solo PPV for R=64/148=43%, hence the expected category is annotated here as I but many strains are likely to be R.

Example: mutation in core gene *gyrA* in *Klebsiella pneumoniae*

ruleID	organism	gene	nodeID	refseq	GenBank	HMM	ARO	mutation	variation type	context	drug	drug class	phenotype	clinical category	breakpoint	breakpoint standard
KPN0010	s__Klebsiella pneumoniae	gyrA	gyrA	WP_117036963.1	-	-	-	p.Ser83Tyr	Protein variant detected	core	ciprofloxacin	-	nonwildtype	R	MIC >0.5 mg/L	EUCAST v14.0 (2024), ECOFF (January 2024)

PMID	evidence code	evidence grade	evidence limitations	rule curation note
KlebNET	ECO:0001103 natural variation mutant evidence	moderate	lacks evidence for this species, lacks evidence of the degree to which MIC is affected, statistical geno/pheno evidence but no experimental evidence	Experimental evidence in other species shows the mutation directly affects binding of gyrA with ciprofloxacin. In K. pneumoniae the mutation is associated with an upward shift in MIC that typically results in exceeding the S breakpoint, but not always the R breakpoint (KlebNET: solo PPV for I/R=37/37=100%; solo PPV for R=32/37=78%).

Example: mutation in core gene *glpT* in *Escherichia coli*

ruleID	organism	gene	nodeID	refseq	GenBank	HMM	ARO	mutation	variation type	context	drug	drug class	phenotype	clinical category	breakpoint	breakpoint standard
ECO0003	s__Escherichia coli	glpT	glpT	WP_000948731	-	-	-	p.Glu448Lys	Protein variant detected	core	fosfomycin	-	wildtype	S	MIC <=8 mg/L	EUCAST v14.0 (2024)

PMID	evidence code	evidence grade	evidence limitations	rule curation note
32847131	ECO:0001103 natural variation mutant evidence	strong	low clinical relevance	Natural polymorphism, not associated with resistance. Very common (>90%) in Clermont clades B1 (54952/5513), B2 (34361/36252), C (5448/5552), D (15151/15207), E (21826/21893), F (4159/4171), G (3297/3307) and Shigella sonnei (13751/13849), Shigella flexneri (9959/9964), Shigella boydii (815/818), Shigella dysenteriae (934/934); common (57%) in Clermont clade A (28543/49862); based on Enterobase as at October 2024.

Example: core gene *bla*SHV in *Klebsiella pneumoniae*

ruleID	organism	gene	nodeID	refseq	GenBank	HMM	ARO	mutation	variation type	context	drug	drug class	phenotype	clinical category	breakpoint	breakpoint standard
KPN0001	s__Klebsiella pneumoniae	blaSHV	blaSHV	NF000285.3	-	-	ARO:3000015	-	Gene presence detected	core	-	penams	wildtype	R	not applicable	Expected resistant phenotypes v1.2 (13 January, 2023)

PMID	evidence code	evidence grade	evidence limitations	rule curation note
32284385	ECO:0001091 knockout phenotypic evidence, ECO:0000024 protein-binding evidence, ECO:0001034 crystallography evidence, ECO:0000012 functional complementation evidence, ECO:0000005 enzymatic activity assay evidence	strong		Wildtype core gene, all SHV alleles are expected to confer resistance to penicillins (penams), explaining the expected resistant to ampicillin. (Certain SHV alleles can also have expanded enzyme activity, and confer resistance to third-generation cephalosporins.)

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2. Examples of rules for core genes and wild-type phenotypes
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Updates from organism subgroups

Acinetobacter	(Paul Higgins/Bogdan Iorga)
Staphylococcus	(Natacha Couto)
Klebsiella & E. coli	(Kara Tsang/Kat Holt)
Neisseria gonorrhoeae	(Leonor Sánchez Busó)
Bordetella	(Laurence Luu)
Enterococcus	(Francesc Coll)
Campylobacter	(Birgitta Duim/Bogdan Iorga)
Enterobacter	(Teresa Coque)

Apologies from:

- *Pseudomonas*
- *Salmonella*
- *Burkholderia pseudomallei*

Acinetobacter subgroup

Paul Higgins, Rahul Garg, Mehrad Hamidian, Bogdan Iorga, Priyanka Khopkar-Kale, Margaret Lam, Bruno Silvester Lopes, Ignasi Roca, Varun Shamanna, Clement Tsui, David Wareham, Valeria Bortolaia

- 983 genomes with AST data
- 186 rules defined for all acquired beta-lactamases found in *A. baumannii* (specs version 0.5)
- 49 of them submitted for review (strong experimental support, validated by at least 2 persons with clinical experience) – some others need more discussion
- intrinsic genes will follow

ESGEM-AMR *Acinetobacter baumannii* subgroup

Acinetobacter baumannii

EUCAST Clinical Breakpoint Tables v. 14.0, valid from 2024-01-01

Breakpoints available for a limited amount of antibiotics, need to also use ECOFF values.

Carbapenems	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
Doripenem	0.001	2		10	50	22	
Ertapenem	-	-			-	-	
Imipenem	2	4		10	24	21	
Imipenem-relebactam[1]	Note[1]	Note[1]			Note[A]	Note[A]	
Meropenem (indications other than meningitis)	2	8		10	21	15	
Meropenem (meningitis)	2	2		10	21	21	
Meropenem-vaborbactam[1]	Note[1]	Note[1]			Note[A]	Note[A]	

Aminoglycosides[1]	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
Amikacin (systemic infections)	(8)[1]	(8)[1]		30	(19)[A]	(19)[A]	
Amikacin (infections originating from the urinary tract)	8	8		30	19	19	
Gentamicin (systemic infections)	(4)[1]	(4)[1]		10	(17)[A]	(17)[A]	
Gentamicin (infections originating from the urinary tract)	4	4		10	17	17	
Netilmicin	IE	IE			IE	IE	
Tobramycin (systemic infections)	(4)[1]	(4)[1]		10	(17)[A]	(17)[A]	
Tobramycin (infections originating from the urinary tract)	4	4		10	17	17	

Fluoroquinolones	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
Ciprofloxacin	0.001	1		5	50	21	
Delafloxacin	IE	IE			IE	IE	
Levofloxacin	0.5	1		5	23	20	
Moxifloxacin	-	-			-	-	
Nalidixic acid (screen only)	NA	NA			NA	NA	
Norfloxacin (uncomplicated UTI only)	-	-			-	-	
Ofloxacin	-	-			-	-	

Miscellaneous agents	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
Chloramphenicol	-	-			-	-	
Colistin[1]	(2)[2]	(2)[2]			Note[A]	Note[A]	
Daptomycin	-	-			-	-	
Fosfomycin iv	Note[3]	Note[3]			Note[B]	Note[B]	
Fosfomycin oral	-	-			-	-	
Fusidic acid	-	-			-	-	
Lefamulin	-	-			-	-	
Metronidazole	-	-			-	-	
Nitrofurantoin (uncomplicated UTI only)	-	-			-	-	
Nitroxoline (uncomplicated UTI only)	-	-			-	-	
Rifampicin	-	-			-	-	
Spectinomycin	-	-			-	-	
Trimethoprim (uncomplicated UTI only)	-	-			-	-	
Trimethoprim-sulfamethoxazole[4]	2	4		1.25-23.75	14	11	

Acinetobacter subgroup

ESCMID | ESGEM-AMR

ruleID	organism	gene	nodeID	refseq accession	GenBank accessio	HMM accession	ARO accession	mutation	variation type	context	drug	drug class	phenotype
required	required	required	require AT LEAST ONE OF: nodeID (preferred) or refseq or GenBank or HMM acces:				optional (recommenc	required	required	required	require ONE OF: drug or drug class		required
ACI0001	s__Acinetobacter baumannii	blaOXA-23_fam	blaOXA-23_fam	-	-	NF000266.2	ARO:3007710	-	Gene presence detected	acquired	-	carbapenems	nonwildtype
ACI0002	s__Acinetobacter baumannii	blaOXA-23	blaOXA-23_fam	WP_001046004.1	-	-	ARO:3001418	-	Gene presence detected	acquired	-	carbapenems	nonwildtype
ACI0003	s__Acinetobacter baumannii	blaOXA-27	blaOXA-23_fam	WP_063862443.1	-	-	ARO:3001422	-	Gene presence detected	acquired	-	carbapenems	nonwildtype
ACI0004	s__Acinetobacter baumannii	blaOXA-49	blaOXA-23_fam	WP_063864111.1	-	-	ARO:3001671	-	Gene presence detected	acquired	-	carbapenems	nonwildtype
ACI0005	s__Acinetobacter baumannii	blaOXA-146	blaOXA-23_fam	WP_063861044.1	-	-	ARO:3001779	-	Gene presence detected	acquired	-	carbapenems	nonwildtype
ACI0006	s__Acinetobacter baumannii	blaOXA-165	blaOXA-23_fam	WP_063861123.1	-	-	ARO:3001465	-	Gene presence detected	acquired	-	carbapenems	nonwildtype
ACI0007	s__Acinetobacter baumannii	blaOXA-166	blaOXA-23_fam	WP_063861129.1	-	-	ARO:3001466	-	Gene presence detected	acquired	-	carbapenems	nonwildtype
ACI0008	s__Acinetobacter baumannii	blaOXA-167	blaOXA-23_fam	WP_063861133.1	-	-	ARO:3001467	-	Gene presence detected	acquired	-	carbapenems	nonwildtype

phenotype	clinical c...	breakpoint	breakpoint standard	PMID	evidence code	evidence...	evidence limitations	rule curation note	Approved by	submitted date
required	required	required	required	required	required	required	optional	optional (recommended)		
nonwildtype	R	MIC > 4 mg/L (imipenem) ; MIC > 8 g/L (meropenem)	EUCAST v14.0 (2024)	10602749	ECO:0001103 natural variation mutant evidence	moderate		blaOXA-23 is a core gene in *Acinetobacter radioresistens*, acquired in all other organisms.	BSL, PGH, MH	11/12/2024
nonwildtype	R	MIC > 4 mg/L (imipenem) ; MIC > 8 g/L (meropenem)	EUCAST v14.0 (2024)	10602749	ECO:0001103 natural variation mutant evidence	strong		blaOXA-23 is a core gene in *Acinetobacter radioresistens* and does not confer carbapenem resistance unless there is an IS element upstream that leads to overexpression. *blaOXA-23* can be acquired by other *Acinetobacter* species and is associated with IS*Aba1*, and carbapenem resistance.	BSL, PGH, MH	11/12/2024
nonwildtype	R	MIC > 4 mg/L (imipenem) ; MIC > 8 g/L (meropenem)	EUCAST v14.0 (2024)	11158758	ECO:0001103 natural variation mutant evidence	strong		blaOXA-23 is a core gene in *Acinetobacter radioresistens*, acquired in all other organisms.	BSL, PGH, MH	11/12/2024
nonwildtype	R	MIC > 4 mg/L (imipenem) ; MIC > 8 g/L (meropenem)	EUCAST v14.0 (2024)	22842601	ECO:0001103 natural variation mutant evidence	moderate		No specific MIC is described in the associated paper.	BSL, PGH, MH	11/12/2024
nonwildtype	R	MIC > 4 mg/L (imipenem) ; MIC > 8 g/L (meropenem)	EUCAST v14.0 (2024)	23877677	ECO:0001103 natural variation mutant evidence	strong			BSL, PGH	11/12/2024
nonwildtype	R	MIC > 4 mg/L (imipenem) ; MIC > 8 g/L (meropenem)	EUCAST v14.0 (2024)			moderate	lacks evidence for this allele	No associated paper available specifically for this allele. Phenotype inferred from the family.	BSL, PGH	11/12/2024
nonwildtype	R	MIC > 4 mg/L (imipenem) ; MIC > 8 g/L (meropenem)	EUCAST v14.0 (2024)			moderate	lacks evidence for this allele	No associated paper available specifically for this allele. Phenotype inferred from the family.	BSL, PGH	11/12/2024
nonwildtype	R	MIC > 4 mg/L (imipenem) ; MIC > 8 g/L (meropenem)	EUCAST v14.0 (2024)			moderate	lacks evidence for this allele	No associated paper available specifically for this allele. Phenotype inferred from the family.	BSL, PGH	11/12/2024

ruleID	organism	gene	nodeID	refseq accession	GenBank accession	HMM accession	ARO accession	mutation	variation type	context	drug	drug class	phenotype
required	required	required	require AT LEAST ONE OF: nodeID (preferred) or refseq or GenBank or HMM acces:				optional (recommenc	required	required	required	require ONE OF: drug or drug class		required
AClxxxx	s__Acinetobacter baumannii	blaOXA-48_fam	blaOXA-48_fam	-	-	NF000387.2	ARO:3007721	-	Gene presence detected	acquired	-	carbapenems	nonwildtype
AClxxxx	s__Acinetobacter baumannii	blaOXA-48	blaOXA-48_fam	WP_015059991.1	-	-	ARO:3001782	-	Gene presence detected	acquired	-	carbapenems	nonwildtype
AClxxxx	s__Acinetobacter baumannii	blaOXA-232	blaOXA-48_fam	WP_043907054.1	-	-	ARO:3001778	-	Gene presence detected	acquired	-	carbapenems	nonwildtype
AClxxxx	s__Acinetobacter baumannii	blaOXA-252	blaOXA-48_fam	WP_037428895.1	-	-	ARO:3001501	-	Gene presence detected	acquired	-	carbapenems	nonwildtype
ACI0032	s__Acinetobacter baumannii	blaOXA-58_fam	blaOXA-58_fam	-	-	NF000500.2	ARO:3007728	-	Gene presence detected	acquired	-	carbapenems	nonwildtype
ACI0033	s__Acinetobacter baumannii	blaOXA-58	blaOXA-58_fam	WP_002002480.1	-	-	ARO:3001611	-	Gene presence detected	acquired	-	carbapenems	nonwildtype
ACI0034	s__Acinetobacter baumannii	blaOXA-96	blaOXA-58_fam	WP_063864543.1	-	-	ARO:3001631	-	Gene presence detected	acquired	-	carbapenems	nonwildtype
ACI0035	s__Acinetobacter baumannii	blaOXA-97	blaOXA-58_fam	WP_063864544.1	-	-	ARO:3001647	-	Gene presence detected	acquired	-	carbapenems	nonwildtype
ACI0036	s__Acinetobacter baumannii	blaOXA-164	blaOXA-58_fam	WP_063861121.1	-	-	ARO:3001662	-	Gene presence detected	acquired	-	carbapenems	nonwildtype
AClxxxx	s__Acinetobacter baumannii	blaOXA-397	blaOXA-58_fam	WP_063862756.1	-	-	ARO:3001583	-	Gene presence detected	acquired	-	carbapenems	nonwildtype
AClxxxx	s__Acinetobacter baumannii	blaOXA-420	blaOXA-58_fam	WP_063862810.1	-	-	ARO:3003116	-	Gene presence detected	acquired	-	carbapenems	nonwildtype
AClxxxx	s__Acinetobacter baumannii	blaOXA-512	blaOXA-58_fam	WP_063864184.1	-	-	ARO:3005742	-	Gene presence detected	acquired	-	carbapenems	nonwildtype
AClxxxx	s__Acinetobacter baumannii	blaOXA-1178	blaOXA-58_fam	WP_268871882.1	-	-	-	-	Gene presence detected	acquired	-	carbapenems	nonwildtype

phenotype	clinical c...	breakpoint	breakpoint standard	PMID	evidence code	evidence...	evidence limitations	rule curation note	Approved by	submitted date
required	required	required	required	required	required	required	optional	optional (recommended)		
nonwildtype	R	MIC > 4 mg/L (imipenem) ; MIC > 8 g/L (meropenem)	EUCAST v14.0 (2024)			moderate		Phenotype of this gene family inferred from MICs of several members.		
nonwildtype	R	MIC > 4 mg/L (imipenem) ; MIC > 8 g/L (meropenem)	EUCAST v14.0 (2024)	14693513		moderate		MIC 64 mg/L (imipenem) ; MIC 64 mg/L (meropenem) in a *K. pneumoniae* strain		
nonwildtype	R	MIC > 4 mg/L (imipenem) ; MIC > 8 g/L (meropenem)	EUCAST v14.0 (2024)	23305656		moderate		MIC >32 mg/L (imipenem) ; MIC >32 mg/L (meropenem) in a *K. pneumoniae* strain		
nonwildtype	R	MIC > 4 mg/L (imipenem) ; MIC > 8 g/L (meropenem)	EUCAST v14.0 (2024)			moderate		Phenotype of this gene in *Acinetobacter baumannii* inferred from the other members of the family.		
nonwildtype	R	MIC > 4 mg/L (imipenem) ; MIC > 8 g/L (meropenem)	EUCAST v14.0 (2024)		ECO:0001103 natural variation mutant evidence	strong		Phenotype of this gene family inferred from MICs of several members.	PGH, BSL, MH	11/12/2024
nonwildtype	R	MIC > 4 mg/L (imipenem) ; MIC > 8 g/L (meropenem)	EUCAST v14.0 (2024)	15616297	ECO:0001103 natural variation mutant evidence	strong		MIC 32 mg/L (imipenem) ; MIC >64 mg/L (meropenem)	PGH, BSL, MH	11/12/2024
nonwildtype	R	MIC > 4 mg/L (imipenem) ; MIC > 8 g/L (meropenem)	EUCAST v14.0 (2024)	17284537	ECO:0001103 natural variation mutant evidence	strong		MIC 16 mg/L (imipenem)	PGH, BSL, MH	11/12/2024
nonwildtype	R	MIC > 4 mg/L (imipenem) ; MIC > 8 g/L (meropenem)	EUCAST v14.0 (2024)	18299404	ECO:0001103 natural variation mutant evidence	strong		MIC 32 mg/L (imipenem) ; MIC 16 mg/L (meropenem)	PGH, BSL, MH	11/12/2024
nonwildtype	R	MIC > 4 mg/L (imipenem) ; MIC > 8 g/L (meropenem)	EUCAST v14.0 (2024)	20921306	ECO:0001103 natural variation mutant evidence	strong		MIC 8...>=16 mg/L (imipenem) ; MIC 2...8 mg/L (meropenem) (Vitek2) MIC 32 mg/L (imipenem) ; MIC 8...32 mg/L (meropenem) (Etest)	PGH, BSL, MH	11/12/2024
nonwildtype	R	MIC > 4 mg/L (imipenem) ; MIC > 8 g/L (meropenem)	EUCAST v14.0 (2024)			moderate		Phenotype of this gene in *Acinetobacter baumannii* inferred from the other members of the family.		
nonwildtype	R	MIC > 4 mg/L (imipenem) ; MIC > 8 g/L (meropenem)	EUCAST v14.0 (2024)			moderate		Phenotype of this gene in *Acinetobacter baumannii* inferred from the other members of the family.		
nonwildtype	R	MIC > 4 mg/L (imipenem) ; MIC > 8 g/L (meropenem)	EUCAST v14.0 (2024)			moderate		Phenotype of this gene in *Acinetobacter baumannii* inferred from the other members of the family.		
nonwildtype	R	MIC > 4 mg/L (imipenem) ; MIC > 8 g/L (meropenem)	EUCAST v14.0 (2024)			moderate		Phenotype of this gene in *Acinetobacter baumannii* inferred from the other members of the family.		

Staphylococcus subgroup

Natacha Couto, Birgitta Duim, Valeria Bortolaia, Sarah Baines, Sandra Reuter, Assaf Rokney, Holly Grace Espiriu, Manal AbuOun, Sankarganesh Jeyaraj, Robert Kozak, Basil Britto Xavier, Nick Duggett, Birgit Strommenger

- So far we had 3 online meetings
- 6696 matched AST+AFP observations = From AlltheBacteria + AMRFinderPlus + NCBI AST
- First define rules for expected resistance phenotypes (STA, STS, STE, STH, STP)

Staphylococcus subgroup

ruleID	organism	gene	nodeID	refseq accession	GenBank accession	HMM accession	ARO accession	mutation	variation type	context	drug
required	required	required	require AT LEAST ONE OF: nodeID (preferred) or refseq or GenBank or HMM accession				optional (recommended)	required	required	required	require ONE C class
STS0001	s__Staphylococcus saprophyticus	unknown			-	-		-		core	ceftazidime
STS0002	s__Staphylococcus saprophyticus	fusD	fusD	WP_011303797.1	-	-	ARO:3003731	-	Gene presence detected	core	fusidic acid
STS0003	s__Staphylococcus saprophyticus	fosB			-	-	-	-	Gene presence detected	core	fosfomycin
STS0004	s__Staphylococcus saprophyticus	gyrB	gyrB	WP_172606401.1	-	-	-	p.Gly85Asp	Protein variant detected	core	novobiocin
STS0005	s__Staphylococcus saprophyticus	gyrB	gyrB	WP_172606401.1	-	-	-	p.Lys140Arg	Protein variant detected	core	novobiocin
STS0006	s__Staphylococcus saprophyticus	STS0005 & STS0006	-	WP_172606401.1	-	-	-	-	Combination	core	novobiocin

Missing

Search for intrinsic *fosB* gene in STS genomes using BLAST to confirm association.
Search for *gyrB* protein variants in STS genomes using BLAST to confirm association.

AMRrules

KlebNET-GSP
AMR Genotype-Phenotype Group

ESCMID | ESGEM-AMR

- Organized two meetings
  - 14,000+ KpSC genomes with matched antibiograms (1000+ since merging both groups)
  - Ciprofloxacin resistance prediction manuscript shared with co-authors

- Curation using AMR Rules Spec v0.5
  - Core gene curation *blaSHV*, *oqxAB*, *fos* genes
  - Acquired gene/mutation curation test based on ciprofloxacin geno/pheno study (GyrA-S83F, *qnrA1, qnrB1)*

- Learnings so far
  - Must work through examples for defining rules, and be very clear
  - Some genotype-phenotype relationships thought to be well-established have little direct experimental evidence on the impact of MIC in *Klebsiella pneumoniae*
    - ➢ Having matched genome-antibiogram data is very helpful in this case

AMRrules

ESCMID | ESGEM-AMR

Next tasks

- Add AMRFinderPlus *Klebsiella* specific mutations
  - looking at geno/pheno data for evidence to define AMRrules (or recommend to remove)
- Add ESBL/BLI *blaSHV* alleles
  - from our recent publication using geno/pheno data
  - check additional evidence for other alleles in newly contributed data
- Review core beta-lactamases in *K. variicola, K. quasipneumoniae*
  - but low numbers / evidence
- Tackle acquired genes by class? Next: aminoglycosides

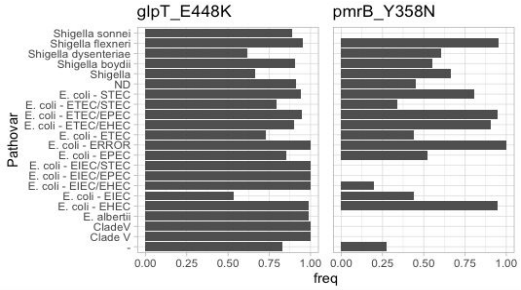
E. coli subgroup

Ebenezer Foster-Nyarko, Pieter-Jan Ceyssens, Fiona Walsh, Carolina Silva Nodari, Soe Yu Naing, Richard Goodman, Abdurrahman Hassan Jibril, Jelalu Kemal Birmeka, Elena Martinez, Teresa Coque, Ramon Maluping, Ana Vale, Gultekin Unal, Axel Hamprecht, Valeria Bortolaia, Bogdan Lorga, Alasdair Hubbard, Manal AbuOun, Jon Iredell, Sally Partridge, Nicole Stoesser, Sam Lipworth, Etienne Rupée, Gherard Batisti Biffignandi, Kate Baker, Kat Holt

- 3-4 meetings
- Enterobase data (n=276,784) with AMRfinderplus v3.11.26 to review **core genes**
- Focusing on collating geno/pheno data (n=15,274 so far)
    - Combining AlltheBacteria/AMRFinderPlus + NCBI data
    - Published data
    - Gathering contributions from the group
- Defined **core genes** and rules for these

AMRrules

Enterobase data
(276,784 genomes)



E. coli subgroup

gene	refseq accession	mutation	variation type	context	drug	drug class	category	PMID	rule curation note	breakpoint	breakpoint_standard
blaEC	WP_063610930.1	-	Gene presence detected	core	ampicillin	-	wt S	-	Core gene, not associated with resistance. Very common in E. coli (96.5%, n=199920/207180), including all Clermont clades and Shigella spp; based on Enterobase as at October 2024.	MIC <=8 mg/L	EUCAST v14.0 (2024)
pmrB	WP_001300761.1	p.Tyr358Asn	Protein variant detected	core	-	polymyxins	wt S	-	Natural polymorphism, not associated with resistance. Very common (>90%) in Clermont clade B1 (n=53783/55130) and C (n=5496/5552), Shigella dysenteriae (n=916/934), Shigella flexneri (n=9953/9964); based on Enterobase as at October 2024.	MIC <=4 mg/L	EUCAST v14.0 (2024)
glpT	WP_000948731	p.Glu448Lys	Protein variant detected	core	fosfomycin	-	wt S	32847131	Natural polymorphism, not associated with resistance. Very common (>90%) in Clermont clades B1 (54952/5513), B2 (34361/36252), C (5448/5552), D (15151/15207), E (21826/21893), F (4159/4171), G (3297/3307) and Shigella sonnei (13751/13849), Shigella flexneri (9959/9964), Shigella boydii (815/818), Shigella dysenteriae (934/934); common (57%) in Clermont clade A (28543/49862); based on Enterobase as at October 2024.	MIC <=8 mg/L	EUCAST v14.0 (2024)
mdf(A)	Y08743.1	-	Gene presence detected	core	azithromycin	-	wt S	9079913	Gene tagged as confering resistance to macrolides in some databases, it shows no effect on azithromycin.	MIC >16 mg/L	EUCAST v14.0 (2024)

Neisseria gonorrhoeae subgroup

- ~100 rules in **AMR rules** spec v0.4
- Run AMRfinderplus + hAMRonize summarize on ~20k *N. gonorrhoeae* genome assemblies.
  - Issues identified:
    - *N. gonorrhoeae* database in AMRfinderplus: multiple nomenclatures for the same mutation.

23S_A2045G	23S	Neisseria_gonorrhoeae	23S ribosom	core	AMR	POINT	MACROLIDE	AZITHROMYCIN	NC_002946.2		AE004969.1
23S_A2057G	23S	Neisseria_gonorrhoeae	23S ribosom	core	AMR	POINT	MACROLIDE	AZITHROMYCIN	NC_002946.2		AE004969.1
23S_A2062G	23S	Neisseria_gonorrhoeae	23S ribosom	core	AMR	POINT	MACROLIDE	AZITHROMYCIN	NC_002946.2		AE004969.1
23S_A2145G	23S	Neisseria_gonorrhoeae	23S ribosom	core	AMR	POINT	MACROLIDE	AZITHROMYCIN	NC_002946.2		AE004969.1
23S_C2597T	23S	Neisseria_gonorrhoeae	23S ribosom	core	AMR	POINT	MACROLIDE	AZITHROMYCIN	NC_002946.2		AE004969.1
23S_C2617T	23S	Neisseria_gonorrhoeae	23S ribosom	core	AMR	POINT	MACROLIDE	AZITHROMYCIN	NC_002946.2		AE004969.1

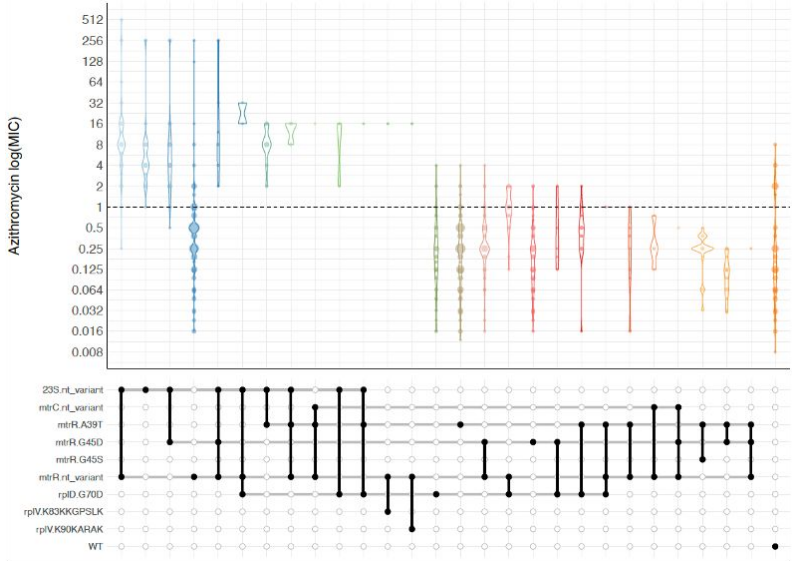
mtrC_C-120T	mtrC	Neisseria_gonorrhoeae	multidrug ef	core	AMR	POINT	MACROLIDE/	AZITHROMYCIN/BETA-LA(	NZ_CP012026.1		CP012026.1
mtrR_G-131A	mtrR	Neisseria_gonorrhoeae	multidrug ef	core	AMR	POINT	MACROLIDE/	AZITHROMYCIN/BETA-LA(	NZ_CP043871.1		CP043871.1

- Mutations in rRNA or gene promoters (`nucleotide_variant_detected`) are lost in the hAMRonize summary.

G-23-102	23S	Neisseria go	NCBI Refere	2024-07-22.:	NC_002946.2	amrfinderplu	3.12.8	nucleotide_variant_detected	
G-23-125	23S	Neisseria go	NCBI Refere	2024-07-22.:	NC_002946.2	amrfinderplu	3.12.8	nucleotide_variant_detected	
G-23-250	23S	Neisseria go	NCBI Refere	2024-07-22.:	NC_002946.2	amrfinderplu	3.12.8	nucleotide_variant_detected	
G-23-001	gyrA	Neisseria go	NCBI Refere	2024-07-22.:	WP_0036888	amrfinderplu	3.12.8	protein_variant_detected	p.D95A
G-23-001	gyrA	Neisseria go	NCBI Refere	2024-07-22.:	WP_0036888	amrfinderplu	3.12.8	protein_variant_detected	p.S91F
G-23-002	gyrA	Neisseria go	NCBI Refere	2024-07-22.:	WP_0036888	amrfinderplu	3.12.8	protein_variant_detected	p.D95G
G-23-002	gyrA	Neisseria go	NCBI Refere	2024-07-22.:	WP_0036888	amrfinderplu	3.12.8	protein_variant_detected	p.S91F

- Working on more rules, including combinatorial rules.
- Internal curation among members of the subgroup.
- Need to work on evidence codes/grades. -> v0.5.

- Run AMRfinderplus + hAMRonize summarize on ~20k *N. gonorrhoeae* genome assemblies.
  - Issues identified:
    - 23S rDNA mutated copy number: OK for reference genomes, not for Illumina assemblies.
    - Cannot properly identify mosaics (better for *penA,* not so much for *mtrR*).
      - Possibility of including *penA* and *mtrR* mosaic alleles in the database?
- Genotype (AMRfinderplus) vs phenotype (MIC)



- Study the distribution of MICs per combination of mutations.
- Define the clinical category (majority of the MIC distribution as S/I/R).
- Evaluate the MIC distribution of isolated mutations.
- Check mutations that always appear as combinations – evaluate impact on MIC.
- Integrate the experimental evidence.

Bordetella subgroup

- Focused on 5 species – *B. perussis, B. parapertussis, B. bronchiseptica, B. holmesii, B. hinzii*
  - Screened 2300 *B. pertussis* genomes and all complete genome assemblies from NCBI in AMRfinder
  - Checking evidence for hits
  - No EUCAST breakpoint, limited ECOFFs
  - Primarily based on literature
- Completed AMR rules spec v0.3 – need to update to latest version

ruleID	organism	gene	refseq accession	ARO accession	mutation	variation type	context	drug	drug class	categor	PMID	rule curation note	breakpoint	breakpoint_standard
required	required	required	optional	optional	required IF rule applies to a mutation rather than gene presence/absence	required	required	optional (need drug or drug class)	optional (need drug or drug class)	required	required	optional [recommended for all core genes]	required	required
BOR0001	s__Bordetella pertussis	23s rDNA	NC_002929.2	ARO:3004125	c.[2047A>G]3	Nucleotide variant detected in multi-copy gene	acquired	-	macrolides	nwt R	12624047	Acquired mutation in 23s rRNA confers resistance to macrolides. Bordetella pertussis has 3 copies of 23s rRNA. Mutation in all 3 copies is required to confer resistance. Mutation in one or two copies leads to heterogeneous pattern of resistance. Mutation is equivalent to 23s_A2058G (NC_000431.1) in E. coli	MIC > 256 mg/L	PMID:2624047
BOR0002	s__Bordetella bronchiseptica	blaBOR	WP_010926363.1			Gene presence detected	core	Amoxicillin/Ampicillin	-	wt R	15917575	Wildtype core gene expected to confer resistance to penicillins	Not applicable	Expected resistant phenotype (PMID:15917575)
BOR0003	s__Bordetella bronchiseptica	blaTEM	WP_080699425.1			Gene presence detected	acquired							
BOR0004	s__Bordetella bronchiseptica	floR2	WP_000214125.1			Gene presence detected	acquired	Chloramphenicol/florfenicol	-	nwt R	17224413		MIC > 8 mg/L	ECOFF (August 2024)
BOR0005	s__Bordetella bronchiseptica	sul1	WP_000259031.1			Gene presence detected	acquired	Sulfonamide	-	nwt R	16046466			
BOR0006	s__Bordetella bronchiseptica	sul2	WP_001043260.1			Gene presence detected	acquired	Sulfonamide	-	nwt R	26275219			
BOR0007	s__Bordetella bronchiseptica	aph(3'')-Ib	WP_001082319.1			Gene presence detected	acquired	Streptomycin/neomycin	-	nwt R	26275219			
BOR0008	s__Bordetella bronchiseptica	aph(6)-Id	WP_000480968.1			Gene presence detected	acquired	Streptomycin/neomycin	-	nwt R	26275219			
BOR0009	s__Bordetella bronchiseptica	tet(G)				Gene presence detected	acquired							
BOR0010	s__Bordetella parapertussis	blaBOR	WP_010926363.1			Gene presence detected	core	Amoxicillin/Ampicillin	-	wt R	15917575	Wildtype core gene expected to confer resistance to penicillins	Not applicable	Expected resistant phenotype (PMID:15917575)
BOR0011	s__Bordetella holmesii	blaHBL	WP_080700357.1			Gene presence detected	core	Amoxicillin/Ampicillin	-	wt R	35318919	Wildtype core gene expected to confer resistance to penicillins	Not applicable	Expected resistant phenotype (PMID:15917575)
BOR0012	s__Bordetella hinzii	blaHBL	WP_080700357.1			Gene presence detected	core	Amoxicillin/Ampicillin	-	wt R	35318919	Wildtype core gene expected to confer resistance to penicillins	Not applicable	Expected resistant phenotype (PMID:15917575)
BOR0013	s__Bordetella hinzii	aac(6')	WP_026868862.1			Gene presence detected								

Enterococcus subgroup

Initial subgroup discussion:

- We decided (as recommended by the general ESGEM-AMR group) that we will first need to define expected/intrinsic resistances in *E. faecium* and *E. faecalis*.
- Towards this end, on the one hand, we should aim to explain all expected resistances as defined by EUCAST, although we concluded that this may not be possible for all of them (e.g. cephalosporins) due to complex or incomplete understanding of the genetic bases of these.
- On the other hand, we should aim to assign a phenotypic effect (wt S or wt R) to all AMR core/chromosomal genes in both organisms, as defined by AMR genes detected by CARD, AMRFinder or ResFinder in most strains (>90%). We identified such genes using existing WGS collections of Efm (*aac(6')-Ii, efrA, msr(C)* and *efmA*) and Efc (*lsa(A), dfrE, IreK, efrB, emeA* and *efrA*).
- In the absence of a clear indication on what antibiotics to focus on (for the moment), we may want to aim to define rules for antibiotics of both clinical and epidemiological interest, keeping in mind we may need to prioritise the former in the future.

When considering both EUCAST expected resistances and core AMR genes, all draft rules can be split into the following categories, which we have split among subgroup members to work on:

1. Efm cephalosporins.
2. Efm aminoglycosides (also consider core AMR genes aac(6')-Ii and efmM).
3. Efm macrolides (also consider genes ermB, msr(C), efrA, efmA).
4. Efc cephalosporins (also consider core AMR gene IreK).
5. Efc aminoglycosides.
6. Efc macrolides, streptogramins and sulfonamides (also consider genes lsa(A), efrA and efrB).
7. Others: Efm and Efc expected fusidic acid resistance, effect of other core AMR genes (emeA, dfrE)

Study	Galimand M, Schmitt E, Panvert M, et al. Intrinsic resistance to aminoglycosides in Enterococcus faecium is conferred by the 16S rRNA m5C1404-specific methyltransferase EfmM. *Rna*. 2011;17(2):251-262. doi:10.1261/rna.2233511
PubMed ID:	21159796
Strain(s) tested	*E. faecium* strain CIP 54-32, *E. coli* TOP10
Drugs(s) tested:	Kanamycin, tobramycin, amikacin, gentamicin, netilmicin (**streptomycin not tested**)
Evidence codes	ECO:0001091 knockout phenotypic evidence; ECO:0000154 heterologous protein expression evidence; ECO:0001065 in vitro methylation assay evidence

TABLE 1. Susceptibility of strains to aminoglycosides

	MIC (μg/mL)				
Strain	Kanamycin	Tobramycin	Amikacin	Gentamicin	Netilmicin
E. faecium CIP54-32					
Wild type	128	64	32	4	24
BM4681 (Δ*aac(6′)-Ii*)	12	8	24	4	2
BM4682 (Δ*efmM*)	64	32	32	4	24
BM4683 (Δ*aac(6′)-Ii/efmM*)	6	6	24	4	2
E. coli TOP10					
pBAD/His	2	0.25	1.5	0.5	0.5
pAT855 (pBAD/HisΩ*aac(6′)-Ii*)	256	128	128	1	128
pAT854 (pBAD/HisΩ*efmM*)	24	4	2	0.5	0.5

Intrinsic/expected resistance in *E. faecium*: aminoglycosides

Study	Galimand M, Schmitt E, Panvert M, et al. Intrinsic resistance to aminoglycosides in Enterococcus faecium is conferred by the 16S rRNA m5C1404-specific methyltransferase EfmM. *Rna*. 2011;17(2):251-262. doi:10.1261/rna.2233511
PubMed ID:	21159796
Strain(s) tested	*E. faecium* strain CIP 54-32, *E. coli* TOP10
Drugs(s) tested:	Kanamycin, tobramycin, amikacin, gentamicin, netilmicin (**streptomycin not tested**)
Evidence codes	ECO:0001091 knockout phenotypic evidence; ECO:0000154 heterologous protein expression evidence
Conclusions	ECO:0001091 knockout phenotypic evidence 1. Large decrease in the MICs of aminoglycosides that are substrates for AAC(6')-Ii [> 2-fold reduction in kanamycin, tobramycin and netilmicin MICs] was observed for the *Δaac(6')-Ii* strain (BM4681). 2. Smaller decreases in the MICs [only 1-fold reduction] of kanamycin and tobramycin were observed for the *ΔefmM* strain (BM4682). 3. The lowest kanamycin and tobramycin MICs were observed for the double mutant *E. faecium* BM4683 [*Δaac(6')-Ii*/*efmM*].

Study	Galimand M, Schmitt E, Panvert M, et al. Intrinsic resistance to aminoglycosides in Enterococcus faecium is conferred by the 16S rRNA m5C1404-specific methyltransferase EfmM. *Rna*. 2011;17(2):251-262. doi:10.1261/rna.2233511
PubMed ID:	21159796
Strain(s) tested	*E. faecium* strain CIP 54-32, *E. coli* TOP10
Drugs(s) tested:	Kanamycin, tobramycin, amikacin, gentamicin, netilmicin (**streptomycin not tested**)
Evidence codes	ECO:0001091 knockout phenotypic evidence; ECO:0000154 heterologous protein expression evidence
Conclusions	ECO:0000154 heterologous protein expression evidence 4. The recombinant plasmid [pAT854 (pBADΩ*efmM*)] conferred on *E. coli* a 4-fold or greater increase in resistance to kanamycin and tobramycin; the MICs of amikacin, gentamicin, and netilmicin remained unchanged (Table 1). 5. The recombinant plasmid [pAT855 (pBADΩ*aac(6')-Ii*)] conferred on *E. coli* > 4-fold increase in MIC to kanamycin, tobramycin, amikacin, and netilmicin, while gentamicin only changed 1-fold (Table 1).

Study	Galimand M, Schmitt E, Panvert M, et al. Intrinsic resistance to aminoglycosides in Enterococcus faecium is conferred by the 16S rRNA m5C1404-specific methyltransferase EfmM. *Rna*. 2011;17(2):251-262. doi:10.1261/rna.2233511
PubMed ID:	21159796
Strain(s) tested	*E. faecium* strain CIP 54-32, *E. coli* TOP10
Drugs(s) tested:	Kanamycin, tobramycin, amikacin, gentamicin, netilmicin (**streptomycin not tested**)
Evidence codes	ECO:0001091 knockout phenotypic evidence; ECO:0000154 heterologous protein expression evidence
Conclusions	ECO:0001065 in vitro methylation assay evidence 6. in vitro methylation assays with the recombinant EfmM: EfmM methylates nucleotide the C5-position of C1404 of the 16S rRNA on the 30S ribosomal subunit.

Proposed rules (see latest version of file “AMR Rules Spec v0.X.enterococci.xlsx” for latest rule):

	A	B	C	D	H	I	J	K	L	M	N	O	P
1	ruleID	rule	organism	gene	variation type	context	drug	drug class	category	PMID	rule curation note	breakpoint	breakpoint_standard
9	EFM0007	draft	s__Enterococcus faecium	efmM	Gene presence detected	core	kanamycin	aminoglycosides	wt R	21159796	Smaller decreases in kanamycin and tobramycin MIC [only 1-fold reduction] were observed for the ΔefmM strain (BM4682). The lowest kanamycin and tobramycin MICs were observed for the double mutant E. faecium BM4683 [Δaac(6′)-Ii/efmM]. The recombinant plasmid [pAT854 (pBADΩefmM)] conferred on E. coli a 4-fold or greater increase in resistance to kanamycin and tobramycin; the MICs of amikacin, gentamicin, and netilmicin remained unchanged (Table 1).	*Low level resistance*	Expected resistant phenotypes v1.2 (
10	EFMXXX	draft	s__Enterococcus faecium	efmM	Gene presence detected	core	tobramycin	aminoglycosides	wt R	21159796	Smaller decreases in kanamycin and tobramycin MIC [only 1-fold reduction] were observed for the ΔefmM strain (BM4682). The lowest kanamycin and tobramycin MICs were observed for the double mutant E. faecium BM4683 [Δaac(6′)-Ii/efmM]. The recombinant plasmid [pAT854 (pBADΩefmM)] conferred on E. coli a 4-fold or greater increase in resistance to kanamycin and tobramycin; the MICs of amikacin, gentamicin, and netilmicin remained unchanged (Table 1).	*Low level resistance*	Expected resistant phenotypes v1.2 (

NOTES/CONSIDERATIONS:

- **Question**: no gene identifier found for efmM gene in the NCBI Reference Gene Catalogue: https://www.ncbi.nlm.nih.gov/pathogens/refgene/#efmM and CARD https://card.mcmaster.ca/ontology/. **How can be define a gene that is not present in the NCBI Reference Gene Catalogue and CARD?**
- **Question**: consider using category **“wt (R)”?** as according to Table 1, *aac(6')-Ii* seems to be the main determinant (based on MIC reduction in knockout strains), although efmM also seems to contribute (only 1-fold reduction in MIC)

Proposed rules (see latest version of file “AMR Rules Spec v0.X.enterococci.xlsx” for latest rule):

	A	B	C	D	H	I	J	K	L	M	N	O	P
1	ruleID	rule	organism	gene	variation type	context	drug	drug class	category	PMID	rule curation note	breakpoint	breakpoint_standard
6	EFM0004	draft	s__Enterococcus faecium	aac(6')-Ii	Gene presence detected	core	kanamycin	aminoglycosides	wt R	21159796	Large decrease in the MICs of aminoglycosides that are substrates for AAC(6')-Ii [> 2-fold reduction in kanamycin, tobramycin and netilmicin MICs] was observed for the Δaac(6')-Ii strain (BM4681). The lowest kanamycin and tobramycin MICs were observed for the double mutant E. faecium BM4683 [Δaac(6')-Ii/efmM]. The recombinant plasmid [pAT855 (pBADΩaac(6')-Ii)] conferred on E. coli > 4-fold increase in MIC to kanamycin, tobramycin, amikacin, and netilmicin, while gentamicin only changed 1-fold (Table 1).	*Low level resistance*	Expected resistant phenotypes v1.2
7	EFMXXX	draft	s__Enterococcus faecium	aac(6')-Ii	Gene presence detected	core	tobramycin	aminoglycosides	wt R	21159796	Large decrease in the MICs of aminoglycosides that are substrates for AAC(6')-Ii [> 2-fold reduction in kanamycin, tobramycin and netilmicin MICs] was observed for the Δaac(6')-Ii strain (BM4681). The lowest kanamycin and tobramycin MICs were observed for the double mutant E. faecium BM4683 [Δaac(6')-Ii/efmM]. The recombinant plasmid [pAT855 (pBADΩaac(6')-Ii)] conferred on E. coli > 4-fold increase in MIC to kanamycin, tobramycin, amikacin, and netilmicin, while gentamicin only changed 1-fold (Table 1).	*Low level resistance*	Expected resistant phenotypes v1.2
8	EFMXXX	draft	s__Enterococcus faecium	aac(6')-Ii	Gene presence detected	core	netilmicin	aminoglycosides	wt R	21159796	Large decrease in the MICs of aminoglycosides that are substrates for AAC(6')-Ii [> 2-fold reduction in kanamycin, tobramycin and netilmicin MICs] was observed for the Δaac(6')-Ii strain (BM4681). The recombinant plasmid [pAT855 (pBADΩaac(6')-Ii)] conferred on E. coli > 4-fold increase in MIC to kanamycin, tobramycin, amikacin, and netilmicin, while gentamicin only changed 1-fold (Table 1).	*Low level resistance*	Expected resistant phenotypes v1.2
9	EFMXXX	draft	s__Enterococcus faecium	aac(6')-Ii	Gene presence detected	core	amikacin	aminoglycosides	wt R	21159796	Large decrease in the MICs of aminoglycosides that are substrates for AAC(6')-Ii was observed for the Δaac(6')-Ii strain (BM4681). Amikacin MIC reduced from 32 in wildtype to 24 in Δaac(6')-Ii strain, see Table 1]. The recombinant plasmid [pAT855 (pBADΩaac(6')-Ii)] conferred on *E. coli* > 4-fold increase in MIC to kanamycin, tobramycin, amikacin, and netilmicin, while gentamicin only changed 1-fold (Table 1).	*Low level resistance*	Expected resistant phenotypes v1.2

- **Question**: what ‘breakpoint’ should we indicate here when defining wt R (i.e. expected resistance)? In these cases, core chromosomal genes are expected to contribute to intrinsic low levels of resistance which ideally need to be defined with an MIC breakpoint (< ECOFF?).

Intrinsic/expected resistance in *E. faecium*: aminoglycosides

Study: Costa Y, Galimand M, Leclercq R, Duval J, Courvalin P. Characterization of the chromosomal aac(6')-Ii gene specific for Enterococcus faecium. Antimicrob Agents Chemother. 1993 Sep;37(9):1896-903. doi: 10.1128/AAC.37.9.1896.

PubMed ID: 8239603

Strain(s) tested: *E. faecium* strain CIP 54-32, *E. coli* BM694

Drugs(s) tested: Kanamycin, tobramycin, amikacin, gentamicin, netilmicin, sisomicin

TABLE 2. Susceptibilities of enterococcal and *E. coli* strains to selected aminoglycosides

Species (no. of strains)	MIC[a] (μg/ml) of:					
	Amikacin	Gentamicin	Kanamycin	Netilmicin	Sisomicin	Tobramycin
E. faecium CIP 54-32	32	4	128	32	32	64
E. faecium[b] (8)	16–32	4–16	128–1,024	16–128	16–128	64–256
E. faecium[c] (6)	32–128	4–8	>4,096	32–64	32–64	64–128
E. faecium[d] (11)	128–2,048	>4,096	>4,096	128–>4,096	>4,096	>4,096
Enterococcus spp.[e] (28)	16–256	1–32	8–128	1–64	1–64	1–32
Enterococcus spp.[f] (5)	32–512	2–16	>4,096	2–8	4–8	8–16
Enterococcus spp.[g] (11)	512–>4,096	512–>4,096	>4,096	16–512	512–>4,096	2,048–>4,096
E. coli BM694	1	0.5	2	0.5	0.5	1
E. coli BM694/pAT432	128	1	>256	128	128	128
E. faecium BM4229	NT	NT	NT	2	2	4

[a] Determined on Mueller-Hinton agar. NT, not tested; this strain contains insertionally inactivated *aac(6')-Ii* but also the *aphA-3* gene from pAT114.
[b] Strains resistant to low levels of aminoglycosides.
[c] Strains resistant to high levels of kanamycin.
[d] Strains resistant to high levels of gentamicin.
[e] Enterococci resistant to low levels of aminoglycosides (2 *E. avium*, 3 *E. casseliflavus*, 2 *E. cecorum*, 1 *E. columbae*, 3 *E. durans*, 4 *E. faecalis*, 4 *E. gallinarum*, 5 *E. hirae*, 1 *E. malodoratus*, 1 *E. mundtii*, 1 *E. pseudoavium*, and 1 *E. solitarius*).
[f] Enterococci resistant to high levels of kanamycin (1 *E. durans*, 2 *E. faecalis*, 1 *E. raffinosus*, and 1 *E. hirae*).
[g] Enterococci resistant to high levels of gentamicin (10 *E. faecalis* and 1 *E. gallinarum*).

Study	Costa Y, Galimand M, Leclercq R, Duval J, Courvalin P. Characterization of the chromosomal aac(6')-Ii gene specific for Enterococcus faecium. Antimicrob Agents Chemother. 1993 Sep;37(9):1896-903. doi: 10.1128/AAC.37.9.1896.
PubMed ID:	8239603
Strain(s) tested	*E. faecium* strain CIP 54-32, *E. coli* BM694
Drugs(s) tested:	Kanamycin, tobramycin, amikacin, gentamicin, netilmicin, sisomicin
Evidence codes	ECO:0000154 heterologous protein expression evidence - “Cloning of the plasmid pAT432 (containg gene aac(6')-Ii) into E. coli BM694 strain conferred resistance to amikacin, kanamycin, 2'-N-ethyl-netilmicin, netilmicin, sisomicin, and tobramycin and susceptible to gentamicin and 6'-N-ethyl-netilmicin.” ECO:0001091 knockout phenotypic evidence - “Determination of aminoglycoside MICs for CIP 54-32 [*E. faecium* wildtype strain] and BM4229 [*E. faecium* strain with inactivated *aac(6')-Ii*] (Table2) indicated that insertional inactivation of *aac(6')-Ii* abolished resistance to aminoglycosides that are substrates for AAC(6')-Ii [*Δaac(6')-Ii* strain only tested for netilmicin, sisomicin, tobramycin, see Table 2]”

Study	Costa Y, Galimand M, Leclercq R, Duval J, Courvalin P. Characterization of the chromosomal aac(6')-Ii gene specific for Enterococcus faecium. Antimicrob Agents Chemother. 1993 Sep;37(9):1896-903. doi: 10.1128/AAC.37.9.1896.
PubMed ID:	8239603
Strain(s) tested	*E. faecium* strain CIP 54-32, *E. coli* BM694
Drugs(s) tested:	Kanamycin, tobramycin, amikacin, gentamicin, netilmicin, sisomicin
Evidence codes	Biochemical evidence of aminoglycoside inactivation by phosphocellulose paper-binding assay: "We could not, however, detect enzyme activity in cell lysates prepared from this strain. This is in agreement with the notion that E. faecium strains generally produce low levels of AAC(6')-I that are barely detectable unless highly productive variants are selected."

- Evidence from this paper (PubMed ID 8239603) added to existing *aac(6')-Ii* aminoglycoside rules based on 21159796. If evidence from "best paper" had to be chosen, then keep 21159796. **Question: should be choose the "the best paper" or include more than one?**
- Both papers (8239603 and 21159796) show no role of *aac(6')-Ii* or *efmM* on gentamicin MICs, despite *E. faecium* displaying a rather high wildtype gentamicin MICs (ECOFF 32).
- No paper tested strains for streptomycin. Wildtype streptomycin MICs are known to be high (ECOFF 128), so evidence for the genetic basis of streptomycin intrinsic resistance needs to be found.

What about intrinsic resistance to gentamicin and streptomycin?

"Due to the above issues, only two aminoglycosides (gentamicin and streptomycin) are reliably used in clinical practice (for synergism with β-lactams) due to the fact that these compounds are **not readily affected by intrinsic enzymes produced by enterococci**." Miller *et al.* 2015 [review paper on resistance mechanisms in enterococci]
 From the evidence extracted (the two papers identified) this is true for gentamicin, but knockout mutants were not tested for streptomycin.

MIC distribution	No MIC distributions by EUCAST: https://mic.eucast.org/search/
MIC distributions reported in the literature	See next slide
Resistances breakpoint	No ECOFF or clinical breakpoint by EUCAST (https://mic.eucast.org/search/, v_14.0_Breakpoint_Tables.xlsx)
Other reported resistances breakpoint	The susceptibility criteria were those of the National Committee for Clinical Laboratory Standards. The breakpoints for resistance were: FSA >= 2.0 ug/ml Collignon *et al.* 1999 (PMID: 10528786). “For MIC, testing a breakpoint of 2 mg/l has been used to determine resistance. For disc testing, an inhibition zone diameter of <25 mm with a disc containing 10 μg sodium fusidate indicates resistance.”

Intrinsic/expected resistance in *E. faecium* & *E. faecalis*: fusidic acid

Table 2
In vitro inhibitory activity of fusidic acid against other aerobic bacteria [2,26,27,32,34–36,47,48,50–56,58,64–67,63,61,62,68]

Organism–species (comment)	Number of strains	Country	Year(s) of testing	MIC_{50} (mg/l)	MIC_{90} (mg/l)	MIC range (mg/l)	% Resistant	Ref.
Enterococcus spp.								
E. faecalis	25	USA	4	8				[32]
E. faecalis	8	UK	62	4	4	1.0–4.0		[27]
E. faecalis	117	Germany	76	25	25	3.12–25	100	[50]
E. faecalis	103	Poland	76	12.5	25	3.12–25	100	[50]
E. faecalis	9	Germany	86	16	16	16		[51]
E. faecalis	15	USA	87	4	8			[34]
E. faecalis	24	USA	87	3.12	6.25	1.56–6.25		[36]
E. faecalis	152	Canada	95	4	8	1.0–32	99	[26]
E. faecalis (VRE)	7	USA	95	4	4	4	100	[52]
E. faecium (VRE)	35	USA	95	4	4	2–16	100	[52]
E. gallinarum	4	USA	95			1–8		[52]
E. hirae	2	USA	95			8		[52]
Enterococcus spp. (not *E. faecalis*)	16	USA	86	2	4			[32]
Enterococcus spp. (not *E. faecalis*)	16	USA	87	2	4			[34]

“Activity against enterococci is also relatively poor , 26, 27, 32, 34, 36, 50, 51, 52and is similar for both vancomycin-sensitive isolates and vancomycin-resistant enterococci (VRE) isolates that have been studied. There may be some place for its use against VRE if no other alternative is available, although this does not appear to have been explored clinically. Fusidic acid was not bactericidal against enterococci [52].”

Source: Collignon P, Turnidge J. Fusidic acid in vitro activity. Int J Antimicrob Agents. 1999 Aug;12 Suppl 2:S45-58. doi: 10.1016/s0924-8579(98)00073-9. PMID: 10528786.

Intrinsic/expected resistance in *E. faecium* & *E. faecalis*: fusidic acid

Examples of acquired fusidic acid resistance:

- Laboratory strain OG1RF was sequentially selected from OG1 for resistance to fusidic acid and rifampicin. Fusidic acid MIC > 128 according to Diaz *et al.* 2012 (PMID: 22491691) attributable to the *fusA* C1368A mutation according to Bourgogne *et al.* 2008 (PMID: 18611278)

 No papers identified that explain the genetic basis of expected/intrinsic fusidic acid resistance in enterococci.

Source: Collignon P, Turnidge J. Fusidic acid in vitro activity. Int J Antimicrob Agents. 1999 Aug;12 Suppl 2:S45-58. doi: 10.1016/s0924-8579(98)00073-9. PMID: 10528786.

Discussion point

“We had a fundamental discussion point in our last meeting, on the apparent contradictory task we have in hand of defining the genetic basis of intrinsic resistance for antibiotics that are not of clinical value for enterococci (in part because enterococci are intrinsically resistance to those antibiotics!). It would be good to know how other subgroups are prioritising antibiotics when defining intrinsic/expected resistance rules, based on this consideration.”

Next steps

- Everyone to contribute and finish drafting intrinsic/expected resistance rules
- FC to collect and normalise format of all draft rules (with latest template)
- Everyone to assess and comment on all draft rules
- To have our next meeting to discuss and “approve” final rules – mid/end January

Campylobacter subgroup

Birgitta Duim, Bruno Silvester Lopes, Malgorzata Ligowska-Marzeta, Sangeeta Banerji, Monica Oleastro, Tee Keat Teoh, Diana Costa, Bogdan Iorga

- We held 4 online meetings
- From AlltheBacteria + AMRFinderPlus, 3522 genomes with AST data
- First define rules for common beta-lactamase and tetracycline resistances in *C. jejuni, C. coli, C. fetus*
- EUCAST breakpoints, ECCOF
- Constructing a list with genomes with MIC data from group members is in progress

Campylobacter subgroup

Core genes, and variants with point mutations

organism	gene	nodeID	refseq accession	GenBank accession	mutation	variation type	context	drug
Campylobacter	23S rRNA	23S ribosomal protein		NC_002163.1		gene present	core	MACROLIDE
Campylobacter	blaOXA-61	blaOXA-61 promoter region		NZ_CP022079.1		gene present	core	BETA-LACTAM
Campylobacter	gyrA	DNA gyrase subunit A GyrA	WP_002857904.1	NC_002163.1		gene present	core	QUINOLONE
Campylobacter	porA	group 2 major outer membrane porin protein	WP_052796726.1			gene present	core	BETA-LACTAM
Campylobacter	rplD	50S ribosomal protein L4	WP_002851146.1			gene present	core	MACROLIDE
Campylobacter	rplV	50S ribosomal protein L22	WP_002779996.1	NZ_CP011015.1		gene present	core	MACROLIDE
Campylobacter	rpsL	30S ribosomal protein S12 RpsL	WP_057042458.1			gene present	core	AMINOGLYCOSIDE
Campylobacter	cmeR	multidrug efflux system transcriptional regulator	WP_002843095.1			gene present	core	MACROLIDE

Discussions

We included a G57T and supplemental mutation at A69 in *bla*$_{OXA61}$ which are associated with amoxicillin + clavulanic acid resistance in ampicillin resistant isolates

Detection of unusual genes ROB-1, TEM-116, OXA-85, might check for mobile elements to confirm the genome location

Campylobacter jejuni/coli

EUCAST Clinical Breakpoint Tables v. 14.0, valid from 2024-01-01

Fluoroquinolones	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
Ciprofloxacin	0.001	0.5		5	50	26	

Macrolides	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
Azithromycin	Note[1]	Note[1]			Note[A]	Note[A]	
Clarithromycin	Note[1]	Note[1]			Note[A]	Note[A]	
Erythromycin, *C. jejuni*	4[1]	4[1]		15	20[A]	20[A]	
Erythromycin, *C. coli*	8[1]	8[1]		15	24[A]	24[A]	

Tetracyclines	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
Doxycycline	Note[1]	Note[1]			Note[A]	Note[A]	
Tetracycline	2[1]	2[1]		30	30[A]	30[A]	

1

ESKAPEE pathogens

- *Enterococcus*
- *Staphylococcus*
- *Klebsiella pneumoniae*
- *Acinetobacter baumannii*
- *Pseudomonas aeruginosa*
- *Enterobacter cloacae* complex
- *E. coli/Shigella*

ADDED Recently

- *Klebsiella aerogenes* complex

Enterobacter

Teresa Coque
Rafael Canton
Paul Higgins
Fernando Lazaro Perona
Po-Yu Liu
Elena Martinez
Rietie Venter
Ana Budimir

Patrick Harris
Ángela Novais
Luís Martínez-Martínez
Valeria Bortolaia

Ed Feil-JukkaCorander-Davide
Saasera-Couto- **SpARK project**

Update

- Available genomes from partners
  ± 150 genomes (< 30% WT- ESBL/CRE negative)
- New sequences from partners (Ongoing)
  ± 300 genomes (+ 60% WT-ESBL/CRE negative)

Enterobacter cloacae **complex**

- Available genomes from partners
  171 genomes (SpARK project)
- New sequences from partners (Ongoing)
  XX genomes (collecting this info)

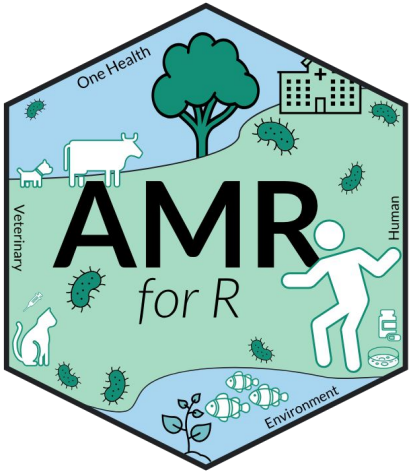
Klebsiella aerogenes **complex**

First result´s update is expected by late January 2025

Agenda

1. Updates to rule spec (v0.5)
2. Examples of rules for core genes and wild-type phenotypes
3. Updates from organism subgroups
4. **General ESGEM-AMR updates**
5. Next meeting

R Hackathon



Goal: to develop R functions for analysing AMR genotypes (genes, mutations, etc) together with antimicrobial susceptibility phenotypes (MICs, disk diffusion zones, S/I/R).

The hackathon will be led by Matthijs Berends, developer of the *'AMR'* R package, and it is envisioned the functions developed during the hackathon will form the basis for a new R package, *AMRgen*, to complement the *AMR* package.

When? January 2025: Monday 13th, 11:00 through Tuesday 14th, 16:00
Where? LSHTM, Keppel St London
Is it for me? You must be familiar with coding in R, including data wrangling with tidyverse and data visualisation with ggplot2, but you needn't have prior experience in developing functions or packages.
How to sign up? Please email esgem.amr@gmail.com by December 20 if you would like to join us.

AMRrules

Vienna, Austria, 11–15 April 2025

ESCMID | ESGEM-AMR

Join ESGEM!
https://members.escmid.org/research-projects/study-groups/join-escmid-study-groups

ESCMID Global Abstract

#06649

AMRrules: expert-curated interpretive standards for AMR genotypes

03. Bacterial susceptibility & resistance
03e. Resistance detection/prediction approaches (rapid and/or molecular assays, resistome analysis, inference methods)
Are there any research groups, study groups or consortia to acknowledge? (Do not indicate funding sources or company support) Please do not exceed 100 characters limit.
ESGEM-AMR

Background

Identifying genetic determinants of antimicrobial resistance (AMR) in bacterial genomes is a fundamental task with applications across the clinical, public health and research domains. There are well-established databases of AMR determinants, but a lack of standards for interpreting AMR genotype profiles. AMRrules aims to provide interpretive standards for AMR genotypes, akin to those available for interpreting susceptibility phenotyping results.

Methods

The AMRrules specification encodes expert rules for interpreting a specific genetic variant, in a specific organism, in terms of the expected clinical categorization (S/I/R) for a specific drug or class. It utilises reference standards and ontologies including the Antibiotic Resistance Ontology (ARO) terms to describe drugs; Human Genome Variation Society (HGVS) Nomenclature for variant specification; and Evidence & Conclusion Ontology (ECO) to record evidence. Rules are curated by organism experts, with an initial focus on encoding rules to interpret core genes (aligned with EUCAST Expected Resistances), followed by acquired genes/variants. Outputs are open-source, human and machine readable, and interoperable with a wide range of tools and pipelines.

Agenda

1. Updates to rule spec (v0.5)
2. Examples of rules for core genes and wild-type phenotypes
3. Updates from organism subgroups
4. General ESGEM-AMR updates
5. **Next ESGEM-AMR meeting**

AMRrules

ESCMID | ESGEM-AMR

What would be most useful for Jan/Feb?

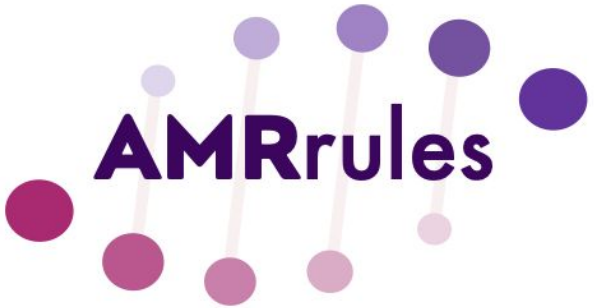
1. Natacha/Jane/Kat join subgroup meetings to work through issues?
2. Working meetings? - Weekly drop-in meeting slot, for discussion?
3. How else can we support?

Next ESGEM-AMR wide meeting late Feb

Questions? / Any other business?

ESGEM-AMR

ESCMID



https://github.com/interpretAMR/AMRrulesCuration