ESGEM-AMR

ESCMID

AMRrules

Agenda

1. Introduce organisers, Subgroups & Subgroup Leads
2. Recap of ESGEM-AMR Goals
3. Where to start?
4. Data sharing
5. Work plans
    a. Outputs
    b. Meeting schedule
    c. Communications
6. Open issues
7. Any other business

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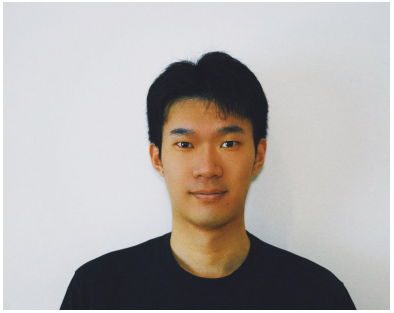
Organisers

Co-Chair
Kat Holt, LSHTM

Co-Chair
Natacha Couto, ESGEM Chair

Bioinformatics Lead
Jane Hawkey, Monash



Coordinator
Shaojie Bao, LSHTM

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Organism Subgroups

1

ESKAPEE pathogens

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

2

Other WHO Priority Pathogens

- *Salmonella*
- *Serratia*
- *Neisseria gonorrhoeae*
- *Streptococcus*
- *Campylobacter* spp.
- *Mycobacterium tuberculosis*
- *Haemophilus influenzae*

3

Others

- *Achromobacter xylosoxidans*
- *Aeromonas*
- Anaerobes
- *Bordetella*
- *Brucella*
- *Burkholderia cepacia* complex
- *Burkholderia pseudomallei*
- *Chryseobacterium indologenes*
- *Corynebacterium diphtheriae*
- *Edwardsiella*
- *Legionella*
- *Listeria*
- *Mycoplasma pneumoniae*
- *Neisseria meningitidis*
- *Pasteurella*
- *Proteus mirabilis*
- *Shewanella*
- *Stenotrophomonas maltophilia*
- *Treponema*
- *Vibrio*
- *Yersinia*

Enterococcus

Francesc Coll
Thomas Demuyser
Ana R. Freitas
Guido Werner
Precious Osadebamwen
Theo Gouliouris
Fiona Walsh
Valeria Bortolaia

Staphylococcus

Natacha Couto
Guido Werner
Birgitta Duim
Valeria Bortolaia
Sarah Baines
Sandra Reuter
Assaf Rokney
Holly Grace Espiriu
Manal AbuOun
Sankarganesh Jeyaraj
Robert Kozak

A. baumannii

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

Enterobacter

Teresa Coque
Rafael Canton
Paul Higgins
Fernando Lazaro Perona
Po-Yu Liu
Elena Martinez
Rietie Venter
Ana Budimir
Angela Novais
Patrick Harris
Valeria Bortolaia

P. aeruginosa

Antonio Oliver
Adriana Cabal Rosel
Alasdair Hubbard
Bogdan Lorga
Xena Li
Carla Lopez Causape
Juliette Severin
David Wareham
Adam Witney
Ørjan Samuelsen
Bela Kocsis
Joana Moreira da Silva
Derek Sarovich
Fernando Lazaro Perona
Valeria Bortolaia

K. pneumoniae

Kat Holt/Kara Tsang
Valeria Bortolaia
Adam Komorowski
Elisenda Miro
Jon Iredell
Ørjan Samuelsen
Sally Partridge
Manal AbuOun
Sandra Reuter
Sankarganesh Jeyaraj
Fernando Lazaro Perona
Richard Goodman
Teresa Conque
Bogdan Iorga
Clement Tsui
Margaret Lam
Priyanka Khopkar-Kale
Varum Shamanna
Adam Witney
Alasdair Hubbard
Nicole Stoesser
Sam Lipworth
Deepali Desai
+**KlebNet Geno/Pheno Consortium**

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E. coli/Shigella

Kate Baker
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
Florence Crombe

Salmonella

Kristy Horan
Pieter-Jan Ceyssans
Anthony Smith
Gültekin Ünal
Abdurrahman Hassan Jibril
Manal AbuOun
Jelalu Kemal Birmeka
Varun Shamanna
Assaf Rokney
Malgorzata Ligowska-Marzeta
Megan Carey

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N. gonorrhoeae

Leonor Sanchez Buso
Yonatan Grad
Sheeba Manoharan-Basil
Martin McHugh
Tatum Mortimer
Anna Roditscheff
Faina Wehrli
Adam Witney

Streptococcus

Mario Ramirez
Assaf Rokney
Holly Grace Espiriu

Campylobacter

Birgitta Duim
Bruno Silvester Lopes
Malgorzata Ligowska-Marzeta
Assaf Rokney
Jelalu Kemal Birmeka

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H. influenzae

Assaf Rokney
Charlotte Michel
Priyanka Khopkar-Kale
Derek Sarovich

Anaerobes

Trefor Morris
Ulrik Stenz Justesen
Marcela Krutova
Linda Veloo
Kathleen Boiten

S. maltophilia

Jane Hawkey
Derek Sarovich
David Wareham
Fiona Walsh
Rietie Venter
Kat Holt

Serratia

Sandra Reuter
Teresa Coque
Adam Komorowski

Achromobacter xylosoxidans

Charlotte Michel

Aeromonas, Shewanella

Po-Yu Liu

Bordetella

Laurence Luu
Carla Rodrigues

Burkholderia cepacia complex

Charlotte Michel
David Wareham

Burkholderia pseudomallei

Claire Chewapreecha
Derek Sarovich
Jessica Webb

Chryseobacterium indologenes

Rietie Venter

Brucella, Listeria, Edwardsiella, Pasteurella

Jelalu Kemal Birmeka

Corynebacterium diphtheriae

Sylvain Brisse

Legionella

Charlotte Michel
Ghislaine Descours

Mycoplasma pneumoniae

Mike Beeton

Neisseria meningitidis

Célia Bettencourt
Leonor Sanchez Buso

Proteus mirabilis

Axel Hamprecht
Janko Sattler
Elisenda Miro
Rémy Bonnin
Stephan Goettig

Treponema

Brian Alcock

Vibrio

Assaf Rokney

Yersinia

Pieter-Jan Ceyssens
Cyril Savin

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M. tuberculosis

Leonid Chindelevitch
Iñaki Comas
Philip Fowler
Kristy Horan
Priyanka Khopkar-Kale
Mariana López
Conor Meehan
Adam Witney
Brian Alcock

Data & Tools subgroup

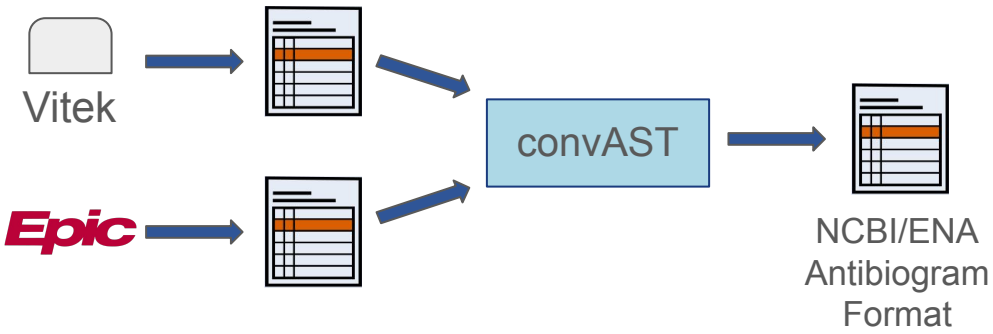
Jane	**Hawkey***	**Co-lead**
Kat	**Holt***	**Co-lead**
Kristy	Horan*	AbritAMR
Torsten	Seemann*	AbritAMR
Derek	Sarovich	ARDAP
Romain	Pogorelcnik	BioMerieux
Bogdan	Iorga	BLDB
Brody	Duncan*	CARD
Amogelang	Raphenya	CARD
Andrew	McArthur*	CARD
Emily	Bordeleau	CARD
Kara	Tsang	Kleborate
Michael	Feldgarden*	NCBI Pathogens
Finlay	Maguire*	PHA4GE, hAMRonization
Dag	Harmsen	Rhidom Seqsphere
Mackenzie	Wilke	StarAMR
Zoe	Dyson	Typhi Mykrobe
Leonid	Chindelevitch*	WHO TB Catalog
Yu	Wan	

+ PHA4GE DS AMR Subgroup

- AST data converter (convAST)
- Universal AMR gene ID
- Standardising variant names

*Members of PHA4GE Data Structures

AST data converter (convAST) - PHA4GE AMR group



Examples needed!

AST output files exported from

AST Devices:

- **Vitek**
- Microscan
- Kiestra
- **Phoenix**
- Sensititre

EMR/LIMs exports:

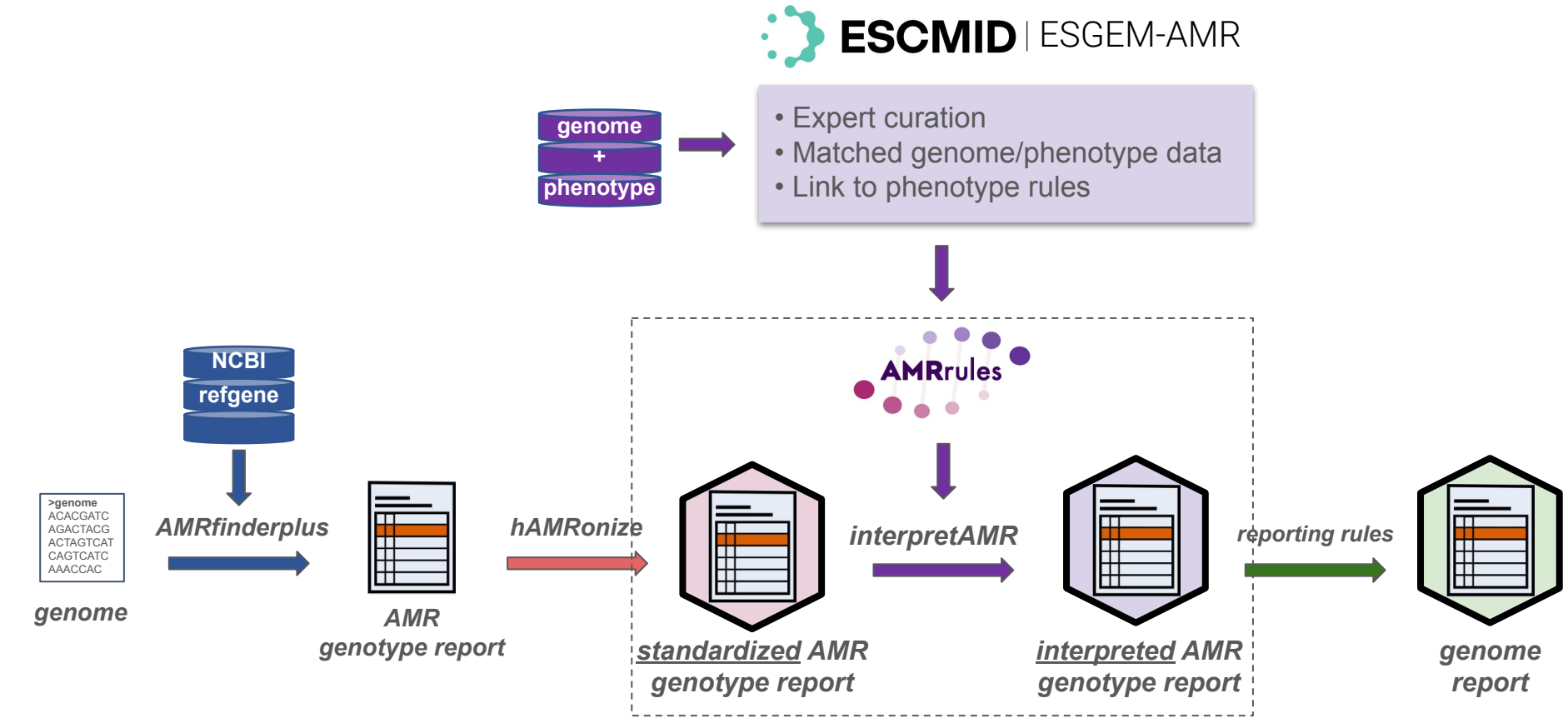
- **EPIC**
- Cerner
- Meditech
- Other LIMS?

ESGEM-AMR Goals

The overall purpose of the group is to **capture expert knowledge** on the relationship between antimicrobial resistance (AMR) genotypes and antimicrobial susceptibility testing (AST) phenotypes in bacterial pathogens, in a manner that:

i. Recognises and accounts for differences between species (is organism-specific);
ii. Connects with EUCAST Expert Rules, Expected Phenotypes, and other standards as far as practicable;
iii. Uses standardised data structures to capture expert knowledge, which are interoperable with a range of informatics tools and databases (i.e. not platform-specific).

The initial focus of the ESGEM-AMR working group will be expert curation of interpretive standards for AMR genotypes in the AMRrules format, but may expand in future to include other activities/projects.



github.com/interpretAMR/AMRrules

Organism-specific interpretation of genotype report

***Standardized* AMR genotype report**

Gene symbol	Class	Subclass
blaSHV-11	BETA-LACTAM	BETA-LACTAM
fosA	FOSFOMYCIN	FOSFOMYCIN
oqxA	PHENICOL/QUINOLONE	PHENICOL/QUINOLONE
oqxB19	PHENICOL/QUINOLONE	PHENICOL/QUINOLONE
blaCTX-M-15	BETA-LACTAM	CEPHALOSPORIN

(example NCBI AMRfinderplus output)

***Interpreted* genotype report**

Context	Drug	Interpretation
core	penicillins	wt R
core	fosfomycin	wt S
core	ciprofloxacin	wt S
core	ciprofloxacin	wt S
acquired	ceftriaxone	nwt R

Specification of interpretive rules

Google sheet:
bit.ly/AMRrules_Spec02

organism	GTDB taxonomy
gene	NCBI AMR reference gene hierarchy
refseq accession	*Optional: NCBI RefSeq accession*
ARO accession	*Optional: CARD ARO accession*
mutation	*Optional: Mutation within gene*
context	Core or acquired
drug	Drug *OR* drug class *(WHO ATC Index)*
drug class	
category	**Expected phenotype category (wt/nwt and S/I/R)**
PMID	PubMed ID for supporting literature
rule curation note	*Optional: brief description of rule logic/mechanism*
breakpoint	Definition used to define category
breakpoint_standard	AST standard used (e.g. EUCAST 2024)

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

Specification of interpretive rules

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PMID	PubMed ID for supporting literature
rule curation note	*Optional: brief description of rule logic/mechanism*
breakpoint	Definition used to define category
breakpoint_standard	AST standard used (e.g. EUCAST 2024)
evidence level	*To be defined*
explanatory note	*To be defined*

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

Specification of interpretive rules

organism	gene	refseq	ARO	mut.	context	drug	drug class	category	PMID	rule curation note	breakpoint	breakpoint_standard
s__Klebsiella pneumoniae	blaSHV	NF000285.3	ARO:3000015	-	core	-	penicillins	**wt R**	32284385	Specific alleles can be ESBL, these are mostly mobile	not applicable	Expected resistant phenotypes v1.2 (13 January, 2023)
s__Klebsiella pneumoniae	oqxA	NF000272.1	ARO:3003922	-	core	--	fluoroquinolones	**wt S**	30834112	Wildtype core gene, not expected to confer multiple drug resistance unless mobilised under strong promoter	MIC <=0.25 mg/L	EUCAST v14.0 (2024)
s__Klebsiella pneumoniae	oqxB	NF000037.1	ARO:3003923	-	core	-	fluoroquinolones	**wt S**	30834112	Wildtype core gene, not expected to confer multiple drug resistance unless mobilised under strong promoter	MIC <=0.25 mg/L	EUCAST v14.0 (2024)
s__Klebsiella pneumoniae	fosA5_fam	NF040540.1	-	-	core	fosfomycin	-	**wt S**	33128341	Wildtype core gene, not expected to confer multiple drug resistance unless mobilised under strong promoter (fosA5_family is the parent node for K. pneumoniae chromosomal fosA)	MIC >128 mg/L	ECOFF (January 2024)
s__Klebsiella pneumoniae	fosA5	WP_012579083.1	ARO:3003209	-	core	fosfomycin	-	**wt S**	25441705	Wildtype core gene, not expected to confer multiple drug resistance unless mobilised under strong promoter	MIC >128 mg/L	ECOFF (January 2024)
s__Klebsiella pneumoniae	fosA6	WP_069174570.1	ARO:3004111	-	core	fosfomycin	-	**wt S**	27261267	Wildtype core gene, not expected to confer multiple drug resistance unless mobilised under strong promoter	MIC >128 mg/L	ECOFF (January 2024)
s__Klebsiella pneumoniae	fosA10	WP_004214174.1	-	-	core	fosfomycin	-	**wt S**	32431524	Wildtype core gene, not expected to confer multiple drug resistance unless mobilised under strong promoter	MIC >128 mg/L	ECOFF (January 2024)

Example - *Klebsiella pneumoniae*, covering core genes and wildtype phenotypes

ESGEM-AMR: Initial (Phase 1) Priorities

Create AMRrules that clearly delineate **core genes** associated with **‘wildtype’** phenotypes for each species (**wt S** or **wt R**)

- Use expert knowledge, literature, and matched genome/AST data where available
- Focus on EUCAST breakpoints/ECOFFs as the target for definition
- Aim to explain all Expected Resistances with core genes

EUCAST Expected Resistance Rules

Susceptibility testing is best avoided. A result which goes against the expected phenotype should be viewed with suspicion.

Rule	Organisms	Ampicillin/Amoxicillin	Amoxicillin-clavulanic acid	Ampicillin-sulbactam	Ticarcillin	Cefazolin, Cephalothin Cefalexin, Cefadroxil	Cefoxitin[2]	Cefuroxime	Tetracyclines	Tigecycline	Polymyxin B, Colistin	Fosfomycin	Nitrofurantoin
1.1	*Citrobacter koseri, Citrobacter amalonaticus*[3]	R			R								
1.2	*Citrobacter freundii*[4]	R	R	R		R	R						
1.3	*Enterobacter cloacae* complex	R	R	R		R	R						
1.4	*Escherichia hermannii*	R			R								
1.5	*Hafnia alvei*	R	R								R		
1.6	*Klebsiella aerogenes*	R	R	R		R	R						
1.7	*Klebsiella pneumoniae* complex	R			R								
1.8	*Klebsiella oxytoca*	R			R								

www.eucast.org/expert_rules_and_expected_phenotypes/expected_phenotypes

Specification of interpretive rules

organism	gene	refseq	ARO	mut.	context	drug	drug class	category	PMID	rule curation note	breakpoint	breakpoint_standard
s__Klebsiella pneumoniae	blaSHV	NF000285.3	ARO:3000015	-	core	-	penicillins	**wt R**	32284385	Specific alleles can be ESBL, these are mostly mobile	not applicable	Expected resistant phenotypes v1.2 (13 January, 2023)
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s__Klebsiella pneumoniae	fosA10	WP_004214174.1	-	-	core	fosfomycin	-	**wt S**	32431524	Wildtype core gene, not expected to confer multiple drug resistance unless mobilised under strong promoter	MIC >128 mg/L	ECOFF (January 2024)

Example - *Klebsiella pneumoniae*, covering core genes and wildtype phenotypes

ESGEM-AMR: Secondary/Phase 2 goals

Develop the specification

- Outstanding issues, including coding complex variants
- Evidence standards
- Incorporate quantitative estimates (e.g. OR [95% interval] for association with R)

Define rules for acquired resistance

- Depends on sufficient high-quality matched genome/AST data
- Ultimate goal to automate this as much as possible to reduce curation burden

Clinical reporting rules?

- Would need to be in partnership with other groups

Where to start?

Getting started

Technical guidance v1.2:
bit.ly/AMRrules_Tech12

AMR Rules:
Interpretive Standards for AMR Genotypes

ESGEM-AMR Working Group
Technical Guidance for
Defining Interpretive Rule Sets

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

Getting started - general approach

Make a copy of the rule template for the subgroup to populate

Add a row for each drug on the EUCAST ‘Expected resistance’ list for the organism

Run AMRfinderplus on a set of genomes with known phenotypes, to identify core genes

Try to map core genes to Expected Resistances (to define **wt R rules**), otherwise explore MIC distributions and breakpoints to define **wt S rules** for them

Remember to keep track of all analyses, logic, and references that would be useful to include in an overall phase-1 paper, or in a subgroup-specific organism-focused paper

Once rules are drafted

- Add the rules (in TSV format) to the **`/draftrules`** directory in the GitHub (https://github.com/interpretAMR/AMRrulesCuration)
- These will be reviewed for format and content (including the linked supporting evidence) by someone outside the subgroup
    - *Chairs or delegates… perhaps subgroups can each review 2 others?*
- Jane (or other members of Data & Tools group) will review and test using available wildtype and non-wildtype genome data
    - *Will depend on data availability, ideally we will create a test suite of wildtype/nonwildtype genomes for each organism*
- Criteria for review and testing will be reviewed and discussed as the working group progresses.

Once rules are approved

- Approved rule sets (in TSV format) will be moved from `/draftrules` to `/rules` in the GitHub (https://github.com/interpretAMR/AMRrulesCuration)
- Versioned release including new rules plus release notes recording the addition of the organism and the names of all contributors

Goal is to have an initial ruleset covering core genes and wildtype phenotypes for as many organisms as possible, ready for release and publication in April 2025 for presentation at ESCMID Global

- Additional rules for acquired genes can be added at any time before or after this, any updates will be tested and go into versioned releases

Data Sharing

Data sharing

ESGEM-AMR

Memorandum of Understanding (v1.0, 4 April 2024)

8. Data ownership and responsibilities.

a. Working Group members retain at all times the ownership and associated rights and responsibilities of any genomic sequence data, AST data, and associated metadata that they contribute to the Working Group.

b. Members are responsible for ensuring that they comply with all relevant ethics and governance requirements in association with their data, including de-identification of patient-level information and location information.

c. Wherever possible, data (sequence, AST and metadata) should be deposited in public repositories rather than shared privately with the Working Group.

d. Where a member does share data privately with the Working Group, they must confirm in writing the intended purpose of sharing the data (e.g. for a specific analysis or paper) and clearly indicate any specific restrictions on the use of the shared data. All members must treat privately shared Working Group data as confidential, as per the “Code of Ethics and Professional Conduct”. As ESGEM-AMR is not a formal legal entity it is preferable to avoid formal Data Sharing Agreements; however if one is required, parties to the agreement will be decided on a needs basis case by case.

Data sharing

The MOU is designed to mitigate against unethical behaviour by members, ***but it is not legally enforceable.***

As ESGEM-AMR is not a legal entity, it cannot be a party to Data Sharing Agreements. Therefore any legal agreements need to be handled within the subgroups, between parties within the group who need to share data. ESGEM-AMR organisers can help advise and work through options if needed.

Suggested model:

- **Share only what is needed - i.e. sequence + MIC**
  - There should be no need to share any personal, clinical or even source information
  - Check your local ethics/governance as you may not need formal agreements to share this kind of data as it concerns only bacterial isolates in pure culture
- **Note the suggested protocol does not require sharing of sequence reads or assemblies**, the aims could be achieved by each data-owner running the latest version of AMRfinderplus (v3.12.8) and sharing the output table with the group
  - Avoids the risk of group members running unauthorised analyses with shared data
  - Avoids issues of transferring and storing large files
- **The easiest way to share data is to make it public,** i.e. deposit/publish WGS+AST data and share accessions
  - This will be needed ultimately if subgroups want to publish details of their curation work within subgroups

Working group outputs

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1. Interpretive standards in the form of **AMRrules** rule sets

2. **InterpretAMR** code to annotate genotype reports (hAMRonize compatible)
   - NOTE: code prototype only works with AMRFinderPlus output, need to work on this to be compatible with hAMRonize format, and identifiers from input databases besides refgene

3. Publication describing initial expert curation of **AMRrules** rule sets
   - ✓ Validated rules for core genes & expected resistances in key organisms
   - ✓ Discussion of data structure and issues
   - ✓ Requirements for systematic matched genome + AST data for acquired resistance

Principles guiding WG outputs

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FAIR principles: **F**indable, **A**ccessible, **I**nteroperable, **R**eusable

- All materials freely available in GitHub repository
  - github.com/interpretAMR/AMRrules
  - github.com/interpretAMR/AMRrulesCuration
- Interoperable with NCBI refgene, hAMRonization, CARD tools and databases as far as possible
- Linked with EUCAST Expert Rules, guidance on WGS for AST prediction, and other materials as far as possible (EUCAST are partners)

Schedule for Update Meetings

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Agenda for Update Meetings

- Issues emerging related to protocols, rule specification, etc
- Updates from subgroups
- Planning for outputs, conferences, funding

Attendees

- Open to all, but not compulsory
- One spokesperson per subgroup (lead or delegate)

July 11/19 - Kickoff meeting (this one!)

September 5/6 (+ UK meetup?)

October 14/15 (+ ASM NGS meetup?)

November TBD

December TBD

January TBD

February TBD

March TBD

April 11-15 - ESCMID Global (Vienna meetup?)

Housekeeping

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Have you joined slack?

If you need the link, email esgem.amr@gmail.com

Requests to add members

- Any new additions need to be considered by the Chairs and the relevant subgroup lead
- We will consider a second call for volunteers for orphan bugs, and perhaps for more data for existing subgroups, after we see how things are progressing
- **All members need to be properly registered and sign the MOU**
- **Do not share the slack invite, or any Zoom links for ESGEM-AMR or its subgroups, with anyone who has not signed the MOU**

Open issues to consider

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- **Evidence levels** - balance mechanistic vs correlation, extrapolation from other organisms
- Genome quality
- AST data quality - most data will be from automated platforms
- Definition of core genes? - minimum number, diversity, threshold proportion?
- Which drugs should be included for a given organism?
- What if there's no breakpoint?
- What if there's multiple breakpoints?
- What if the breakpoint cuts the MIC distribution in half?
- When should we define a rule for a drug class rather than individual drugs?
- Can/should we define a rule for a taxonomic group other than species?
    - Species complex? Genus? Family?
- Can we assume some acquired genes have universal effects?
- How to define rules for combined effects of multiple genes/variants?
- How to handle combination drugs?
- How to ensure interoperability with multiple upstream databases & tools?
- Quantitative rules? OR [95% CI]

AMRrules

Questions? / Any other business?

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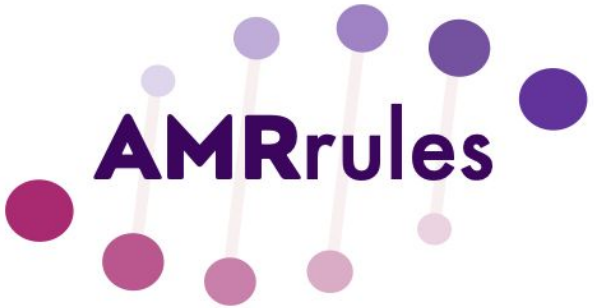

https://github.com/interpretAMR/AMRrulesCuration