Drug-Resistant Infections Priority Programme

Transforming our response to drug-resistant infections

ECCMID
April 13th, 2019

Drug-resistant Infections programme aligns science and policy

- As well as investing in the best science and research, we are increasingly engaging in policy and advocacy issues that underpin the global response to drug resistance
- In doing so, we will build on our position of neutrality with industry and governments

The role of industry

As with all areas of the response to AMR, there is a key role for industry to play in improving surveillance of drug-resistant infections.

- The 'Industry Roadmap' signed by 13 leading companies at the 2016 UNGA committed to:

> iii. Continue to share the surveillance data we generate with public health bodies and healthcare professionals, and work with them to improve understanding of resistance trends, inform appropriate antibiotic and vaccine use and, over time, thereby help increase surveillance capabilities globally.

Nearly half of the companies surveyed by the Access to Medicine Foundation AMR Benchmark are active in surveillance programmes:

Surveillance contributors:
Cipla, GSK, Johnson & Johnson, Merck & Co., Inc., Pfizer, Sanofi, Shionogi, Roche, Wockhardt

OPEN DATA INITIATIVE-
to mobilise industry data to inform evidence base and policy

Barriers to using pharma data

The open data initiative was launched to overcome these barriers, creating a truly open portal with the full ‘raw’ data accessible

Data Re-use Prize WINNERS:

1st PRIZE:

A syndrome-level composite resistance index to inform the use of empiric antibiotic therapies
Antibiotic Resistance: Interdisciplinary Action team from the
London School of Hygiene & Tropical Medicine

2nd PRIZE:

Data Re-use, Dr Liam Shaw from the University of Oxford

3rd PRIZE:

AMR Surveillance Analysis with Bayesian WISCA, Dr Zafer Tandogdu from the University of Oslo

Thank you

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#StopSuperbugs

A syndrome-level composite resistance index to inform the use of empiric antibiotic therapies

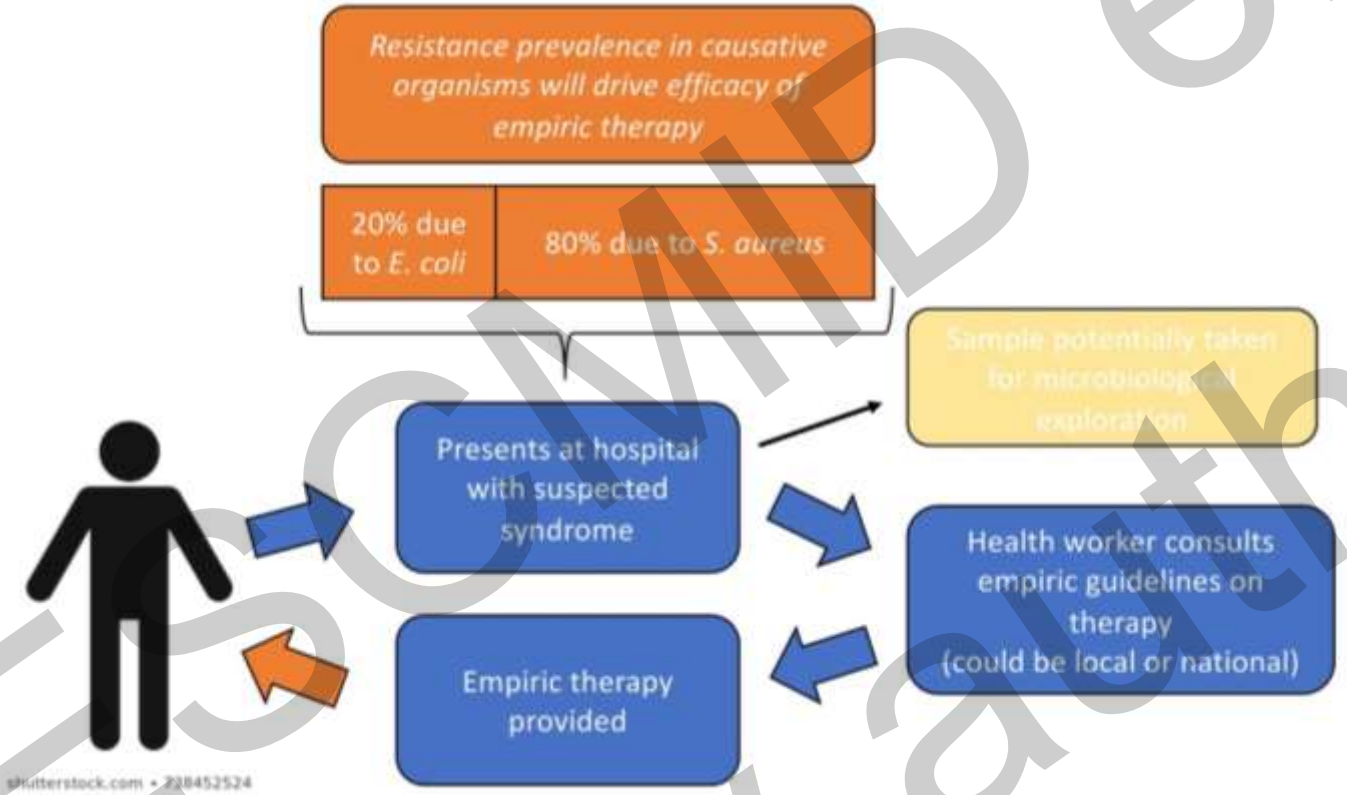
Data Re-use prize: AMR Surveillance

Date: 13/04/2019

Dr Francesc Coll presenting on behalf of the
AR.IA (Antibiotic Resistance: Interdisciplinary Action) team from the
London School of Hygiene & Tropical Medicine

Introduction

Most bacterial infections are treated empirically, wherein antibiotics are prescribed before the infectious agent and its susceptibilities to antibiotics are known.



Surveillance data on antibiotic susceptibilities for infectious → design of empirical antibiotic guidelines [1, 2] → make sure they remain effective to treat the majority of infections.

[1] J. F. Hindler, J. Stelling, Analysis and Presentation of Cumulative Antibiograms: A New Consensus Guideline from the Clinical and Laboratory Standards Institute. Medical Microbiology. 44, 867–873 (2007). [2] T. H. Dellit et al., Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship. Clinical Infectious Diseases. 44, 159–177 (2007).

Surveillance to clinical relevance

What does the "percentage of *E. coli* resistant to drug X" really mean?

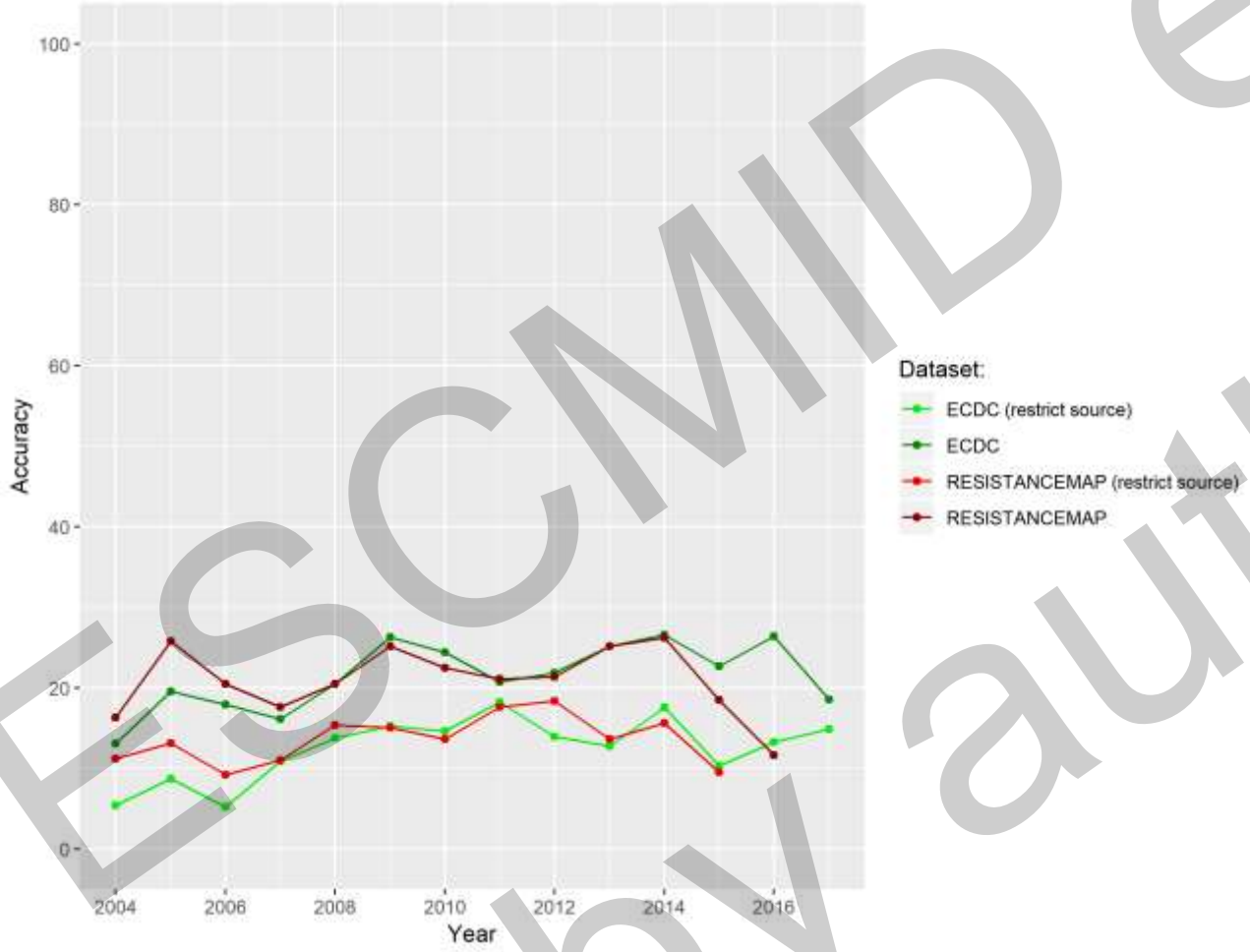
Aim: to translate increasing amounts of surveillance data, such as ATLAS, to clinically meaningful index

To do this focus on

- relevant infection syndromes for empiric therapy
- their bacterial aetiology
- the combination of aetiology and resistance levels to give *probability* of empiric therapy success at a national level

Objective 1: comparison of antibiotic resistance rates

We calculated a resistance rate for each country/year/species/antibiotic and compare them to those estimated from ECDC and ResistanceMap datasets.



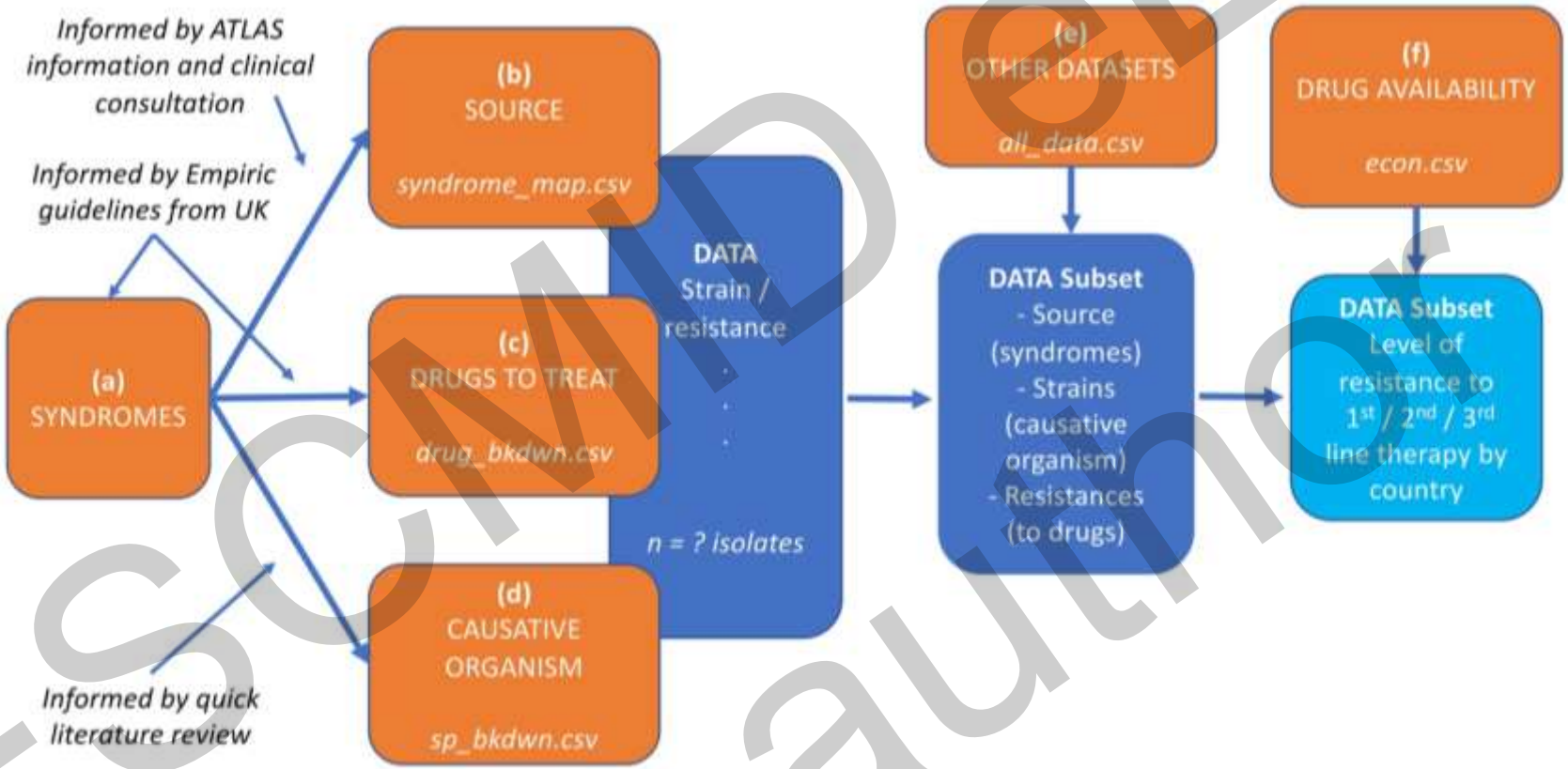
The **lack of overlap** in resistance rates
→ due to the small sample sizes for each country/year/species/antibiotic combination in the ATLAS dataset.

The ATLAS dataset:
- More bacterial species (287, compared to 8 for ECDC and 11 for ResistanceMap)
- and antibiotics (52, compared to 16 and 20)

→resulting in **smaller sample sizes** for each combination.

Objective 2: syndrome-level resistance index

We took six steps to extract and curate external sources of data (not available in the ATLAS dataset) that could be integrated with the ATLAS dataset:

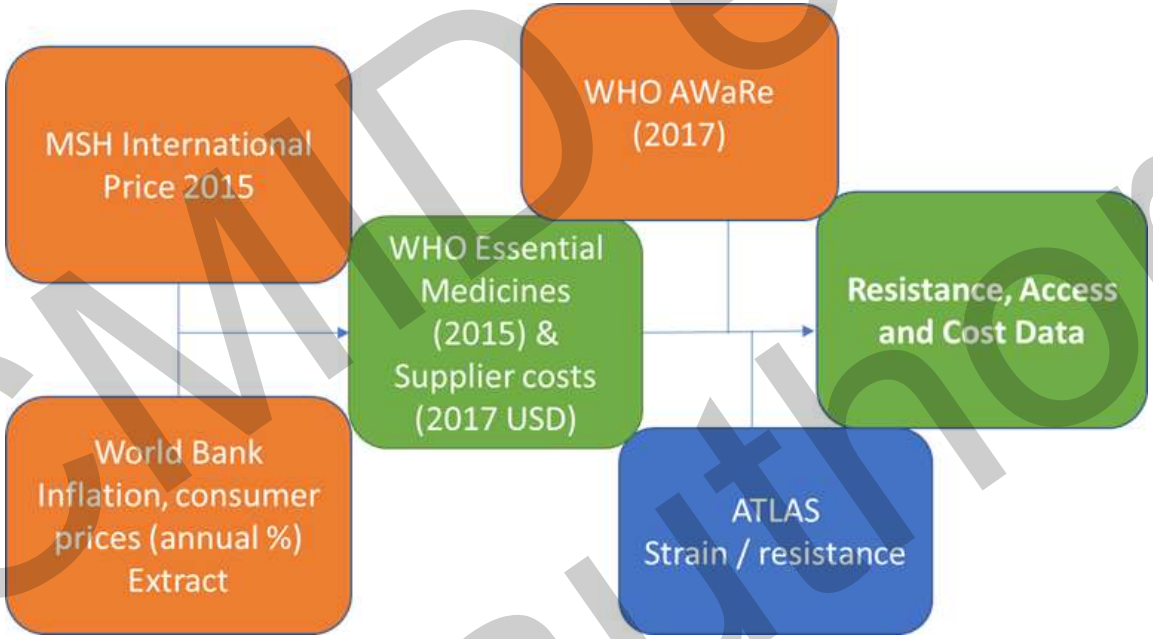


(a) And (c) The National Institute for Health and Care Excellence (NICE) and Public Health England (PHE), Summary of antimicrobial prescribing guidance - managing common infections, 1–23 (2019). (e) ECDC, ResistanceMap and GLASS (f) The International Medical Products Price Guide, World Bank inflation data, The WHO Access and The Watch and Reserve (AWaRe) list

Objective 2: syndrome-level resistance index

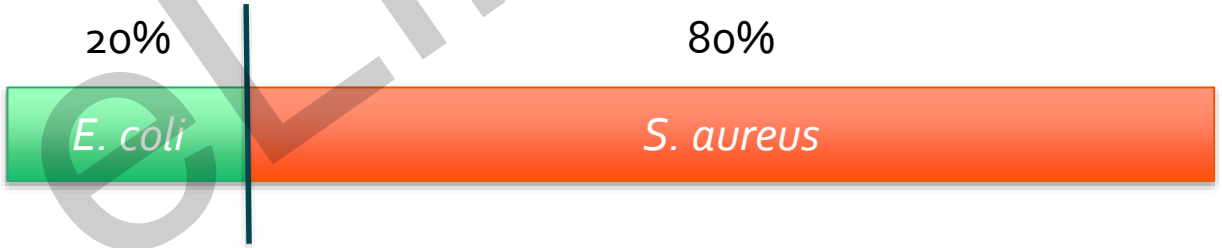
We took six steps to extract and curate external sources of data (not available in the ATLAS dataset) that could be integrated with the ATLAS dataset:

Step (f) expanded



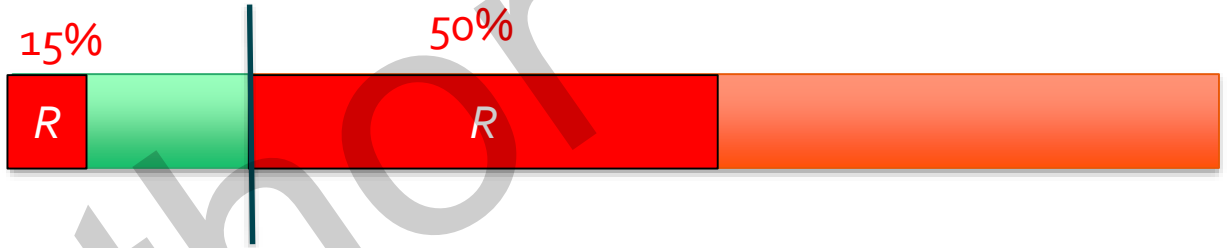
Objective 2: syndrome-level resistance index

Syndrome X =



Recommended empiric therapy = drug 1

Prevalence of resistance to drug 1 =



Composite resistance level = 20% x 15% + 80% x 50% = 3% + 40% = 43% resistant

Cut-off level = 15% 43% > 15% Recommend higher level empiric therapy

Objective 3: the AR.IA interactive web App

Inputs

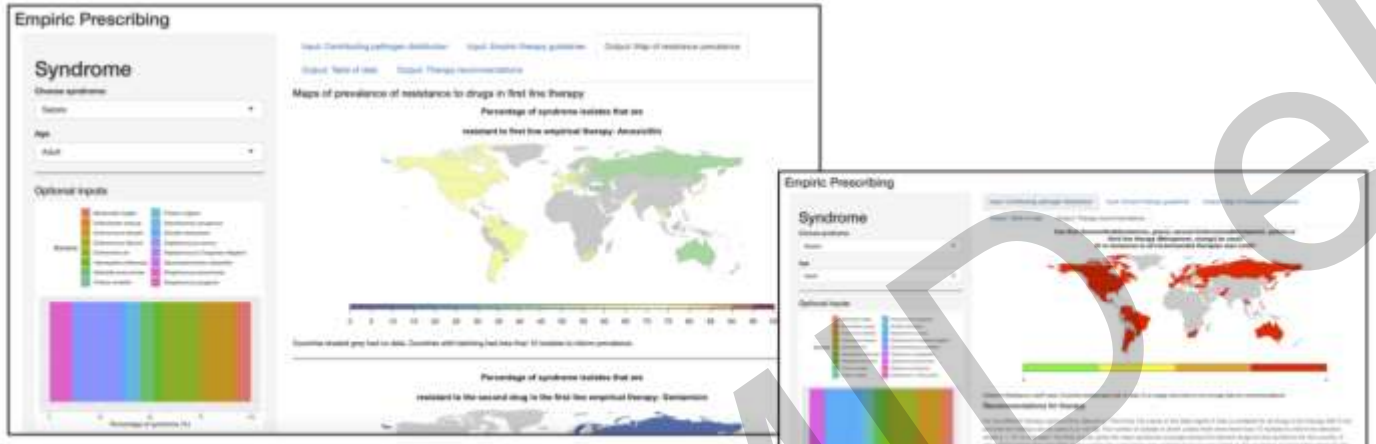
The user can specify a set of inputs which will dynamically affect the outputs:

- The "Syndrome" of interest
- The patient "Age" group
- 'Contributing pathogen distribution' (aetiology)
- The "Resistance cut-off (%)" is the resistance rate above which to recommend a switch from first to second-line antibiotic therapy.
- The "Data to include" refers to the AMR surveillance datasets used to calculate the underlying antibiotic resistance rates.

Therapy recommendations currently set

https://gwenknight.shinyapps.io/empiric_prescribing/

Objective 3: the AR.IA interactive web App



Prevalence of resistance to first line therapy

Therapy recommendations

Underlying data

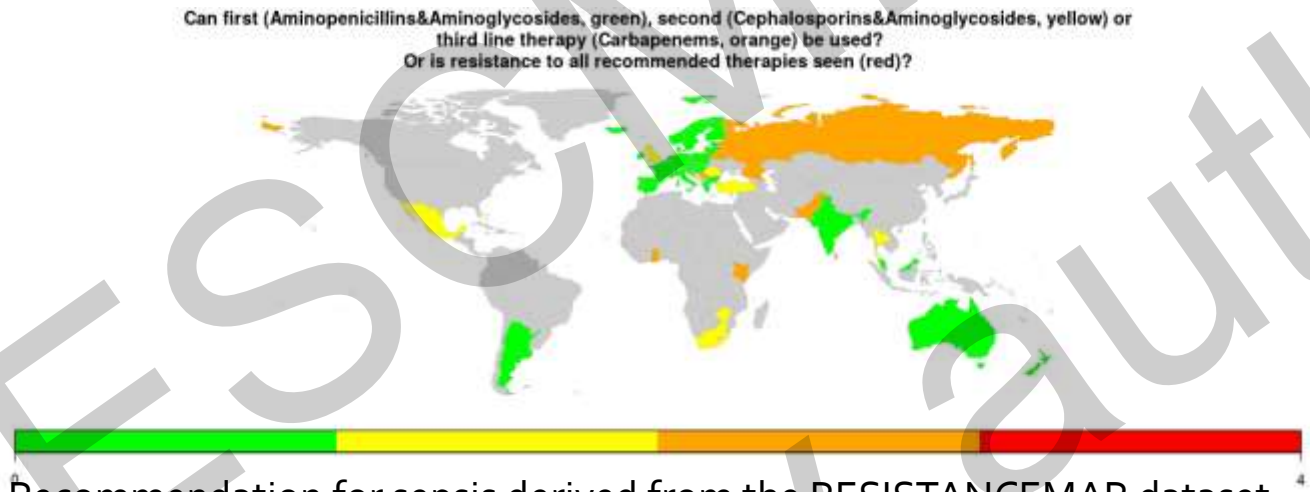
https://gwenknight.shinyapps.io/empiric_prescribing/

Outputs

- A **map of resistance rates** to first line empiric therapy for the selected syndrome.
  Grey = no isolates from syndrome-relevant sources, syndrome-contributing species and susceptibility data to calculate resistance rates.
- A **table of resistance rates** and sample sizes for the bacterial species that contribute to the syndrome, broken down by country.
- A **map and a table of recommendations** on the use of first, second or third-line empiric antibiotic therapy by country, based on the calculated resistance rates and chosen resistance cut-off.

Objective 4: country-level recommendations

Recommendation for sepsis derived from the ATLAS dataset



Recommendation for sepsis derived from the RESISTANCEMAP dataset

https://gwenknight.shinyapps.io/empiric_prescribing/

(1) 44 countries had recommendations for sepsis, whilst only 14 had recommendations for bacterial meningitis.

(2) Most of these countries were in Europe, the Americas and Asia. Only data for South Africa and Morocco existed in Africa.

This reflects the underlying ATLAS isolate selection.

(3) We found the ATLAS dataset to be biased towards higher levels of resistance (MRSA).

(4) Data (syndrome coverage) varied dramatically by country and syndrome to inform recommendations

Objective 5: strengths, limitations and future work

- Strengths
    - Interdisciplinary and iterative framework to inform antibiotic empirical guidelines globally
    - Independent sources of data integrated to add clinical value to AMR surveillance datasets
    - Included data on cost of drug to help inform decision making
    - User friendly nature of our output through AR.IA app
    - Input data that can be changed by the user. Improved as more datasets become available.

- Limitations / future work
    - Include more syndromes
    - Syndrome aetiology – poorly known, more data needed
    - Granularity: only national level guidelines possible. Institutional (e.g. hospital level) guidelines need local surveillance data.
    - Disclaimer: not to used to inform clinical decision making (patient characteristics)
    - Issues with empiric prescribing. New diagnostics would remove the need for empiric therapy

Conclusions

Q: Can the ATLAS dataset be used to inform on the appropriateness of empiric antibiotic therapies to treat common infection syndromes?

A: Yes, mostly for sepsis, pneumonia and cellulitis/skin abscess. Not enough isolates to calculate a recommendation for most other syndromes/countries.

Independent sources of data could be integrated to add clinical value to the ATLAS dataset to inform policy on antibiotic prescribing → "evidence-based prescribing"

Information on bacterial aetiologies crucial to inform empiric prescribing

Improve AMR surveillance sampling (prevalence surveys)

To inform institutional (e.g. hospital level) guidelines with local surveillance data.

The AR:IA team

From right to left:

- Gwen Knight (lead, modeller, developed shiny app)
- Quentin Leclerc (microbiologist, modeller, data comparisons)
- Nichola Naylor (economist, cost inclusions/drug availability)
- Alex Aiken (clinician, therapy guidelines)
- Francesc Coll (presenter, bioinformatician, therapy info.)

Fields of expertise represented: mathematical modeller, economist, microbiologist, bioinformatician, clinician

Project available on:
https://www.synapse.org/#!Synapse:syn18201040/wiki/588781

Objective 5: strengths, limitations and future work

- Limitations of our method and future work
  - All potential syndromes not included. Gastrointestinal tract infections to be included.
  - Not all available clinical sources used: source with at least 1,000 isolates in the ATLAS dataset.
  - In-depth systematic reviews on syndrome aetiology and account for host population and setting.
  - Time trends in suitability of empiric therapies as the ATLAS data from 2017 onwards.
  - Only considered resistance at the national level. Local level as the data becomes available.
  - We did not include all potential empiric therapies. Allow the user to input them.
  - Our recommendations cannot inform institutional (e.g. hospital level) guidelines for antibiotic empirical therapy as local surveillance data needed.
  - Disclaimer: not to used to inform clinical decision making.