COMRU.

AMR surveillance in LMICs: The pressing need for quality laboratory data

Paul Turner

Cambodia Oxford Medical Research Unit, Angkor Hospital for Children

Antimicrobial Resistance

For the purposes of this talk:

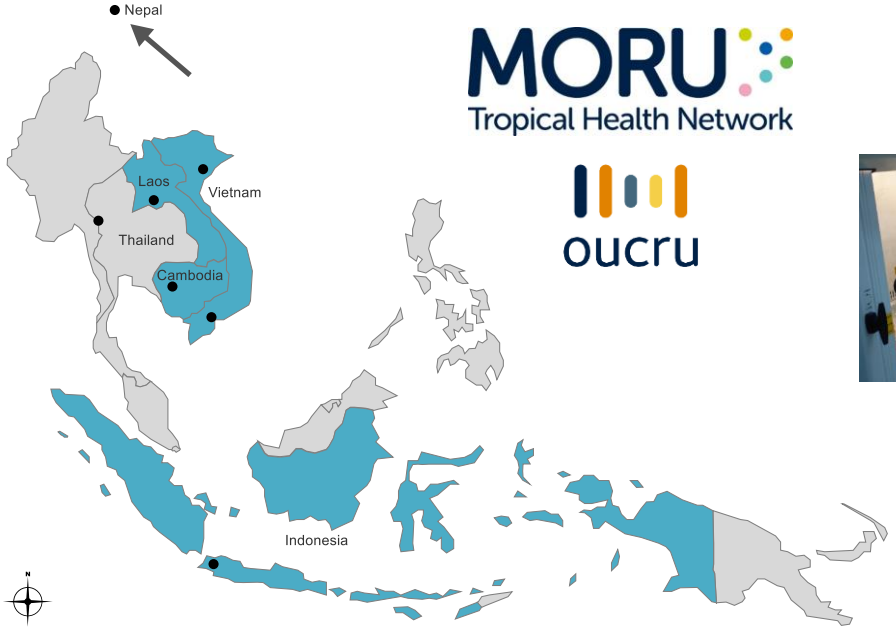
AMR = non-susceptibility of rapidly growing clinically-relevant bacteria to antimicrobial agents

(i.e. the organisms that WHO GLASS are interested in, not TB etc.)

Why do AMR surveillance?

- To estimate burden of disease
- To characterise trends in space and time
- To serve as benchmark to measure the impact of interventions
- To provide local evidence for empiric treatment guidelines and clinical decision making

Why are we involved: Clinical microbiology in SE Asia



MORU Tropical Health Network

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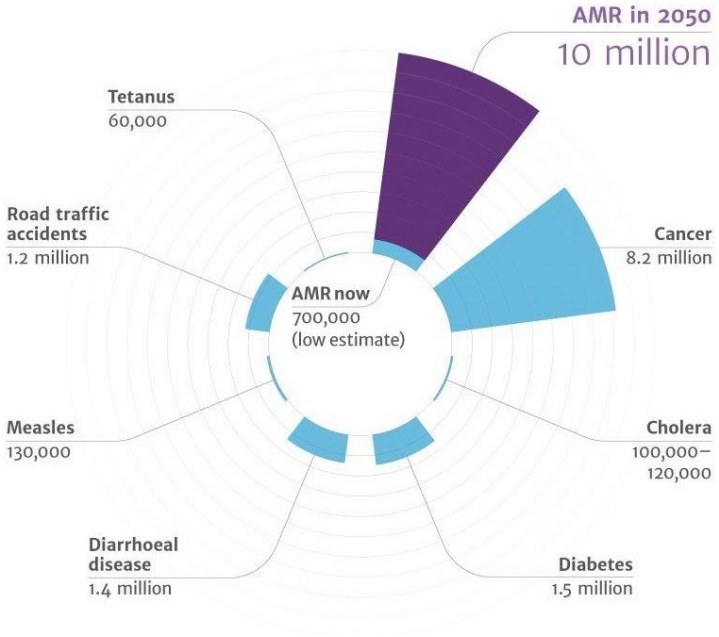
The AMR problem…



O'Neill report (2016)

PLOS | MEDICINE

ESSAY

Will 10 Million People Die a Year due to Antimicrobial Resistance by 2050?

Marlieke E. A. de Kraker[1]*, Andrew J. Stewardson[2], Stephan Harbarth[1]

1 Infection Control Program, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland,
2 Infectious Diseases Department, Austin Health, Heidelberg, Australia

- Current global estimates of the burden of AMR are not very informative; we need detailed, reliable data to be able to improve AMR control measures, preferably based on comprehensive, population-based surveillance data from low-, middle-, and high-income countries.

PLoS Med (2016)

…is hard to define

Improving the estimation of the global burden of antimicrobial resistant infections

Direk Limmathurotsakul, Susanna Dunachie, Keiji Fukuda, Nicholas A Feasey, Iruka N Okeke, Alison H Holmes, Catrin E Moore, Christiane Dolecek, H Rogier van Doorn, Nandini Shetty, Alan D Lopez, Sharon J Peacock, Surveillance and Epidemiology of Drug Resistant Infections Consortium (SEDRIC)

***Panel*: Key actions to improve the estimation of the global burden of AMR infections**

Strengthen health systems

- Increase country capability and capacity to:
  - Reliably detect the global priority list of AMR bacteria reported by WHO
  - Document clinical outcomes and link to laboratory data

Lancet Inf Dis (2019)

WHO Global AMR Surveillance System

GLASS is a platform for global data sharing on AMR worldwide

Specimen-based denominator

- Desire to have case-based surveillance
- Trying to avoid just isolate-based data

Enrolment unit

- Country

Thailand

Population 69,626 (2019)

Select Country: Thailand

Data Overview

Number of tested patients

Specimen t..	Community origin	Hospital origin	Unknown origin
BLOOD	27524	6199	110
GENITAL	3578	202	1
STOOL	1529	530	N.R.
URINE	16894	5502	25

N.R. : Not Reported

Number of infected patients

Specimen type	Pathogen name	Community origin	Hospital origin	Unknown origin
BLOOD	Acinetobacter spp.	156	220	1
	E. coli	996	134	1
	K. pneumoniae	354	124	2
	S. aureus	308	117	1
	S. pneumoniae	105	4	
	Salmonella spp.	84	21	1
GENITAL	N. gonorrhoeae	170		
STOOL	Salmonella spp.	375		
	Shigella spp.	18		
URINE	E. coli	2,563	754	5
	K. pneumoniae	645	334	

Brazil

Population 211,050 (2019)

Select Country: Brazil

Data Overview

Number of tested patients

Specimen t..	Community origin	Hospital origin	Unknown origin
BLOOD	27	1055	N.R.
URINE	1051	9148	N.R.

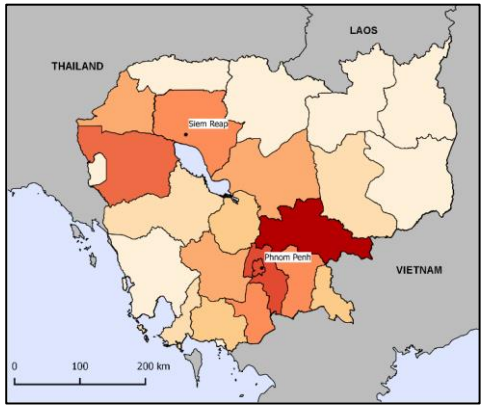
N.R. : Not Reported

Number of infected patients

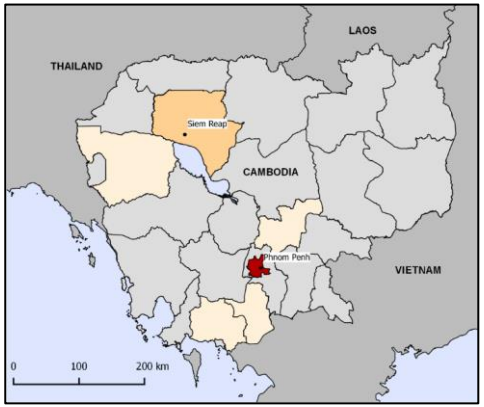
Specimen type	Pathogen name	Community origin	Hospital origin	Unknown origin
BLOOD	Acinetobacter spp.	3	29	
	E. coli	12	100	
	K. pneumoniae		90	
	S. aureus		90	
URINE	E. coli	446	2,254	
	K. pneumoniae	14	385	

LMICs – often not so many (good) microbiology laboratories

Population by province



Laboratory coverage by province



Challenges of Maintaining Good Clinical Laboratory Practices in Low-Resource Settings

A Health Program Evaluation Framework Case Study From East Africa

Helen L. Zhang,[1] Michael W. Omondi, MSc,[2] Augustine M. Musyoka, MSc,[3,4] Isaac A. Afwamba,[3] Remigi P. Swai,[3] Francis P. Karia, MPH/MBA,[3,4] Charles Muiruri, MPH,[2] Elizabeth A. Reddy, MD,[5] John A. Crump, MD,[1-4,6] and Matthew P. Rubach, MD[1]

Service provision hampered by:

- Delays in biomedical engineer support
- Delays and extra costs in commodity procurement
- Low testing throughput
- High personnel turnover

Am J Clin Pathol (2016)

Direk Limmathurotsakul
MORU

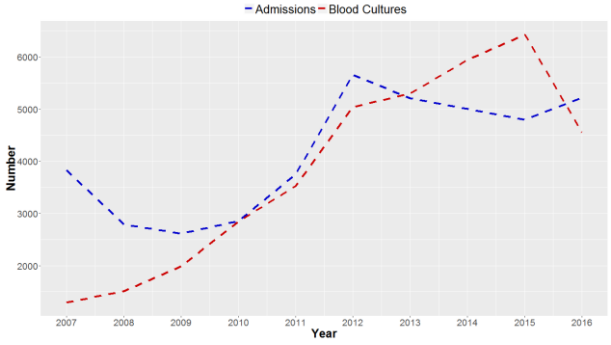
LMICs – often not so many (busy) microbiology laboratories

Am. J. Trop. Med. Hyg., 97(4), 2017, pp. 1257–1261
doi:10.4269/ajtmh.17-0193

Capacity and Utilization of Blood Culture in Two Referral Hospitals in Indonesia and Thailand

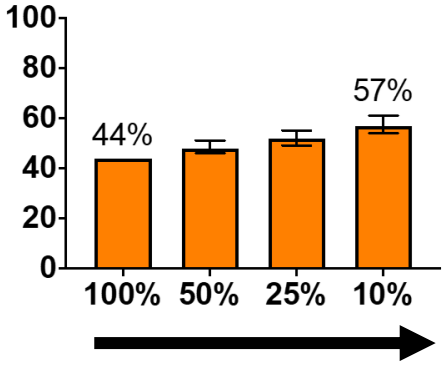
Nittaya Teerawattanasook,[1] Patricia M. Tauran,[2] Prapit Teparrukkul,[1] Vanaporn Wuthiekanun,[3] David A. B. Dance,[4,5,6] Mansyur Arif,[2] and Direk Limmathurotsakul[3,5,7*]

Angkor Hospital for Children



Proportions of 3GCREC among patients with blood culture positive for *E. coli* (%)

Total



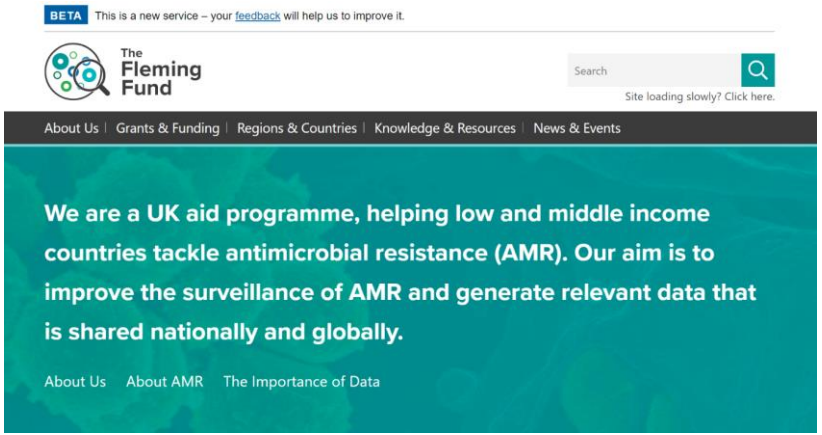
Emerg Inf Dis (2018)

LMIC microbiology / AMR surveillance capacity building

Clinical bacteriology in low-resource settings: today's solutions

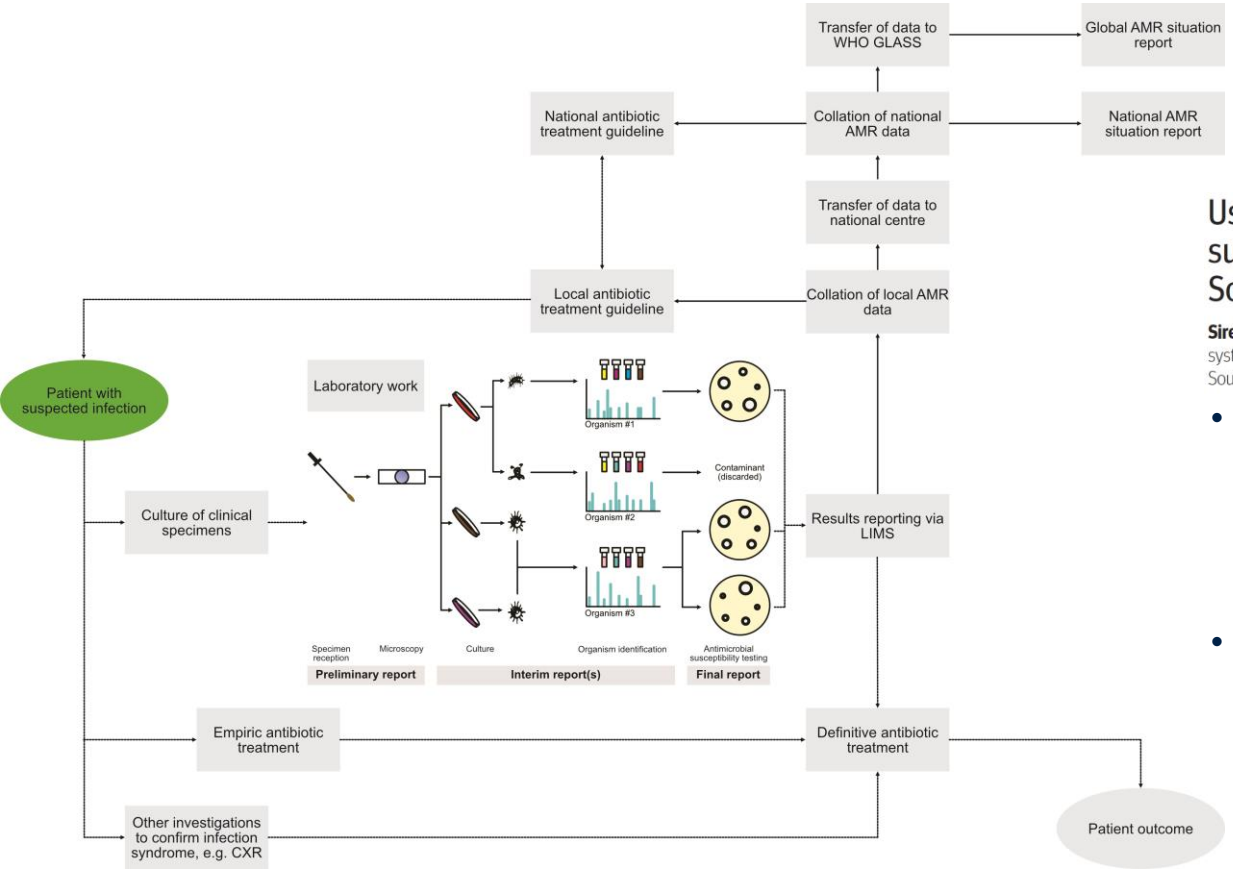
Sien Ombelet, Jean-Baptiste Ronat*, Timothy Walsh, Cedric P Yansouni, Janneke Cox, Erika Vlieghe, Delphine Martiny, Makeda Semret, Olivier Vandenberg, Jan Jacobs, on behalf of the Bacteriology in Low Resource Settings working group†*

- Availability of equipment and consumables adapted for use in low-resource settings
- Rationalised bacterial identification and antimicrobial susceptibility testing
- Communication between the laboratory and clinicians
- Prioritisation of clinically relevant specimens
- Provision of accessible and affordable training and reference materials
- Onsite validation and field adoption



Lancet Inf Dis (2016)

AMR surveillance information flow



Lancet Inf Dis (in press)

Using information technology to improve surveillance of antimicrobial resistance in South East Asia

Sirenda Vong and colleagues argue that investing in information technology surveillance systems to detect trends is an essential first step in tackling antimicrobial resistance in South East Asian countries

- Lack of IT infrastructure is often cited as a barrier to comprehensive AMR surveillance and antibiotic usage stewardship programmes in LMICs
- Few open access software options that might support an IT infrastructure for AMR surveillance are available

BMJ (2017)

How do labs store and share data?

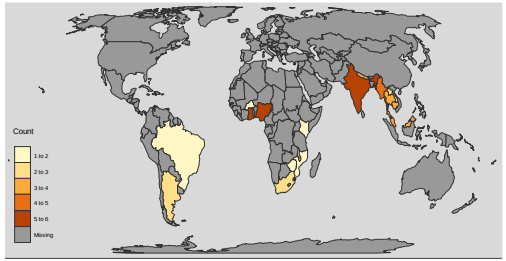
An online survey to collect information on laboratory data management

- 5th March and 29th April 2019

The intention was to capture one response per laboratory from 50 – 100 diagnostic microbiology laboratories in LMICs

Sampling was purposive

- Organisations and colleagues known to be working in, or associated with, such laboratories

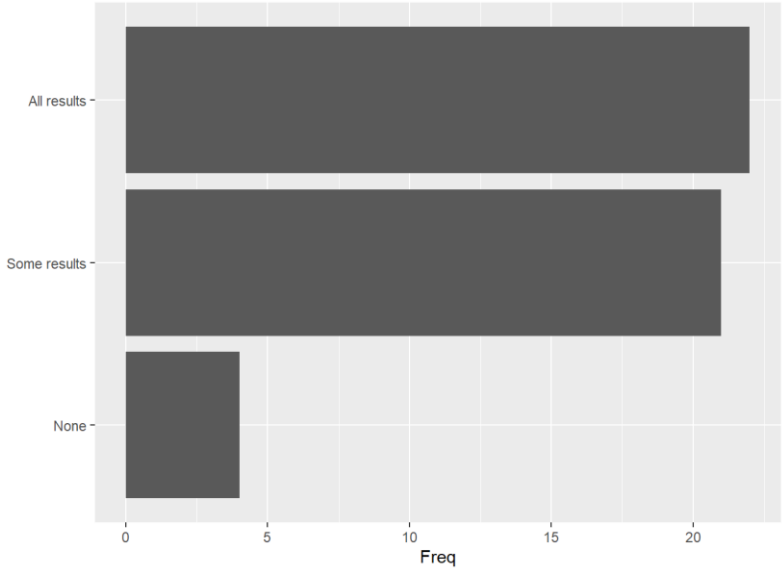


SEDRIC
The Surveillance and Epidemiology of Drug-resistant Infections Consortium

Liz Ashley
LOMWRU

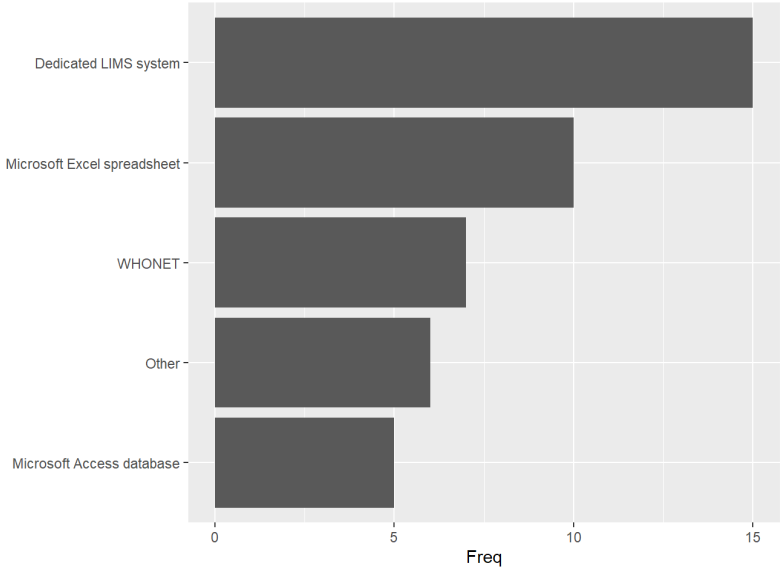
Storage of laboratory test result data

Does your laboratory routinely store test results electronically?



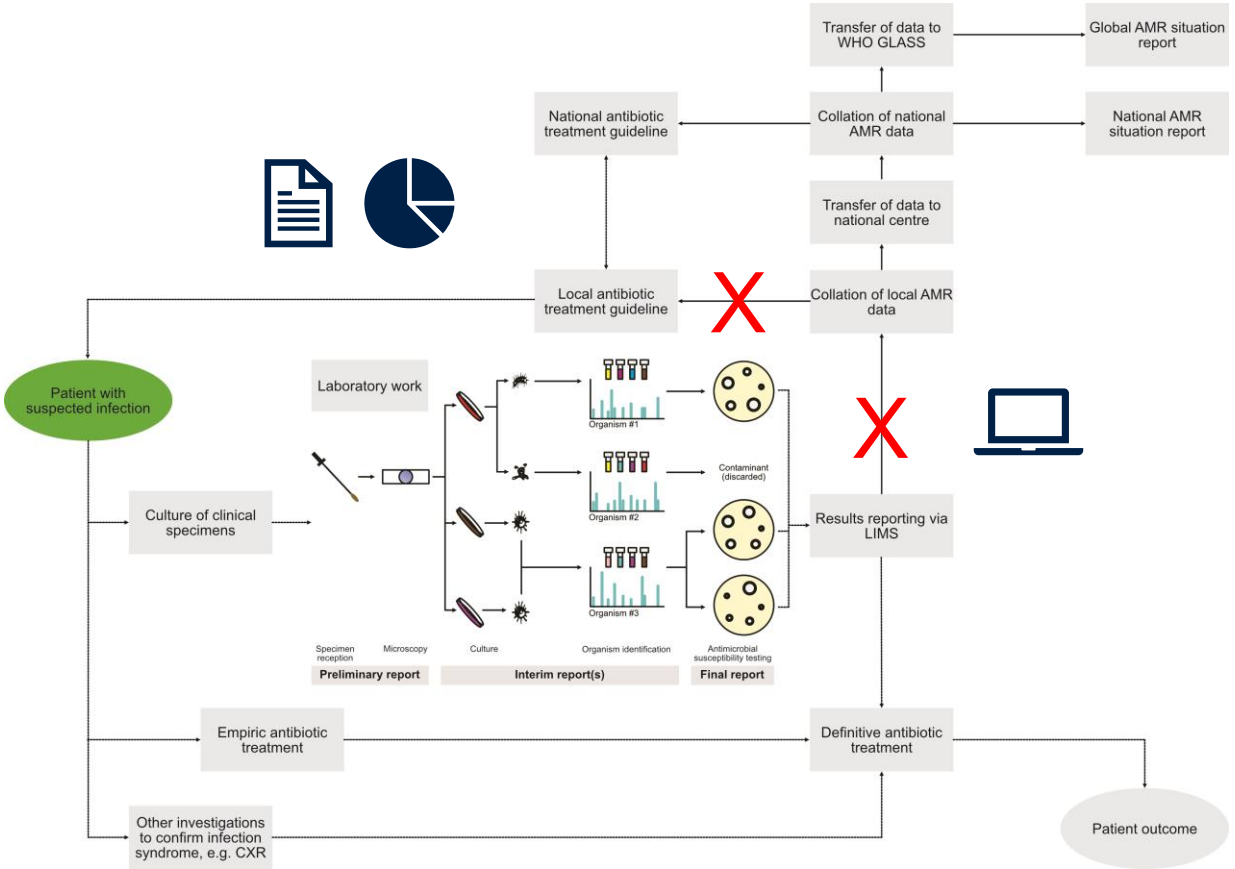
<1/2 recorded all results electronically

Primary system used for storage of laboratory data



Only 1/3 had a dedicated lab information management system

AMR surveillance information flow



Lancet Inf Dis (in press)

We need a better LIMS – fit for LMICs

- Needs to include microbiology-specific functionality
  - Multiple results are generated per specimen
  - Tests are added dynamically based on initial microscopic and culture findings
  - Result reporting is complex
  - Bacterial nomenclature changes over time
  - Periodic generation of antibiograms
- Intuitive to use but with excellent support
- Deployable in a range of settings / IT infrastructures
  - Single machine
  - Local server
  - Cloud
- Should not cost US$25,000 (or more) + annual maintenance costs
  - Must be free AND open source
  - Developers need to have funding for on-going development

Nick Feasey
MLW

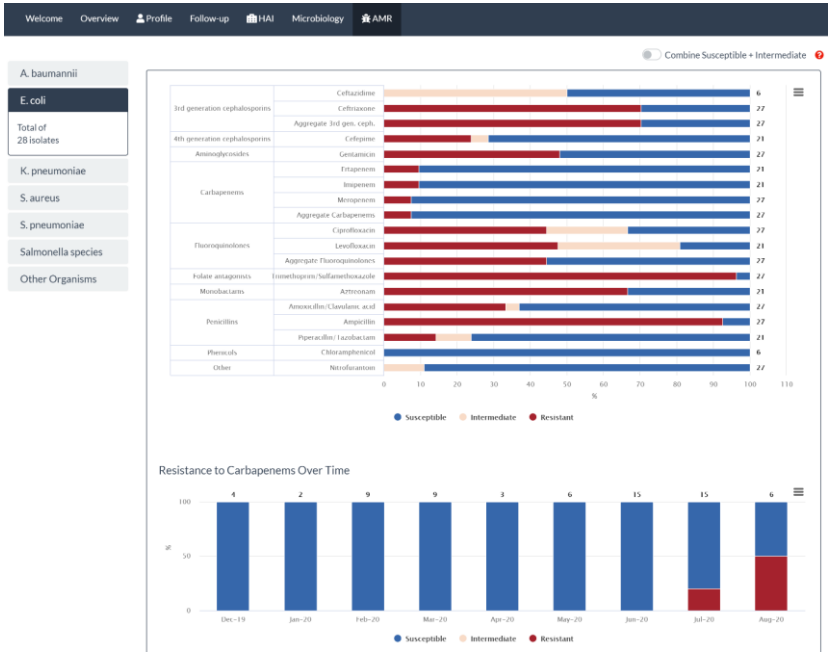
Susie Dunachie
Oxford

SEDRIC
The Surveillance and Epidemiology of Drug-resistant Infections Consortium

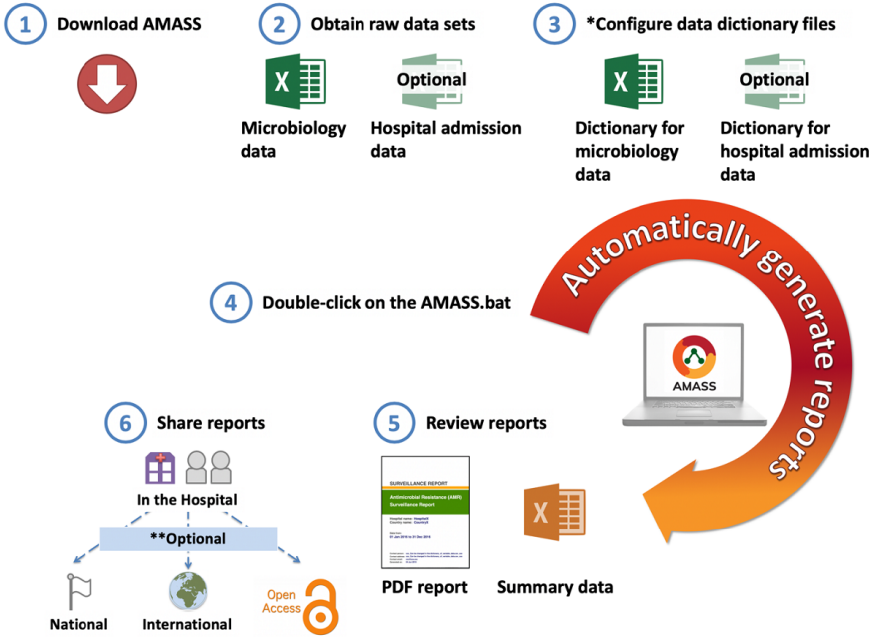
Cherry Lim
MORU

Analytics – make it simple

Dashboards - ACORN



Automated reports - AMASS



Published data quality…

Table 7 Percentage sensitivity patterns of most prevalent pathogens to selected antimicrobials

	Region	Africa		South-East Asia			
Organism	Antimicrobial	Adejuyigbe *et al* (20)	Muhe *et al* (27)	Mathur *et al* (37)	Panigrahi *et al* (39)	Darmstadt *et al* (35)	Tallur *et al* (41)
Escherichia coli	Amoxycillin (AMX)	60.0	–	–	–	–	–
	Ampicillin (AMP)	40.0	100.0	–	–	100.0	29.0
	Cefotaxime (CTX)	–	–	–	–	–	100.0
	Ceftazidime (CAZ)	–	100.0	–	–	100.0	–
	Ceftriaxone (CRO)	–	–	–	–	100.0	100.0
	Ciprofloxacin (CIP)	–	–	–	–	100.0	–
	Gentamicin (GEN)	80.0	100.0	–	–	100.0	71.0
	Imipenem (IMP)					100.0	–
Staphylococcus aureus	Amoxycillin (AMX)	73.0	–	–	–	–	–
							21.0
							–
							–
							–
							–
	Gentamicin (GEN)	85.8	–	–	–	90.0	29.0
	Imipenem (IMP)	–	–	–	–	90.0	–
Klebsiella species*	Amoxycillin (AMX)	0.0	–	–	–	–	–
	Ampicillin (AMP)	–	–	10.0	–	0.0	25.5
	Cefotaxime (CTX)	–	–	–	–	–	76.5
	Ceftazidime (CAZ)	–	–	–	22.0	33.3	–
	Ceftriaxone (CRO)	–	–	71.4	–	33.3	81.0
	Ciprofloxacin (CIP)	–	–	64.8	11.0	66.7	–
	Gentamicin (GEN)	100.0	–	42.8	–	66.7	59.5
	Imipenem (IMP)	–		100.0	–	100.0	–

*Averages were taken when more than one variant's sensitivity patterns were reported.

…there are issues to be aware of

J Glob Health. 2011;1(2):154-70

Klebsiella pneumoniae

Klebsiella species*	Amoxycillin (AMX)	0.0	–	–	–
	Ampicillin (AMP)	–	–	10.0	–
	Cefotaxime (CTX)	–	–	–	–
	Ceftazidime (CAZ)	–	–	–	22.0
	Ceftriaxone (CRO)	–	–	71.4	–
	Ciprofloxacin (CIP)	–	–	64.8	11.0
	Gentamicin (GEN)	100.0	–	42.8	–
	Imipenem (IMP)	–		100.0	–

Results look good?

"For interpretation of AST results, CLSI guideline (version X) was followed"

Nothing to worry about then…

Keep reading the CLSI doc until page 218…

Is this an isolated issue or part of a larger quality management problem?

Appendix B. Intrinsic Resistance

B1. *Enterobacteriaceae*

Organism \ Antimicrobial Agent	Ampicillin
Citrobacter freundii	R
Citrobacter koseri, ***Citrobacter amalonaticus* group**[a]	R
Enterobacter cloacae complex[b]	R
Escherichia coli	There is
Escherichia hermannii	R
Hafnia alvei	R
Klebsiella (formerly *Enterobacter*) *aerogenes*	R
Klebsiella pneumoniae, ***Klebsiella oxytoca, Klebsiella variicola***	R

Staphylococcus aureus

Staphylococcus aureus	Amoxycillin (AMX)	73.0	–	–	–	–	–
	Ampicillin (AMP)	–	–	–	–	0.0	21.0
	Cefotaxime (CTX)	–	–	–	–	–	–
	Ceftazidime (CAZ)	–	–	–	–	66.7	–
	Ceftriaxone (CRO)	–	–	–	–	90.0	–
	Ciprofloxacin (CIP)	–	–	–	–	80.0	–
	Gentamicin (GEN)	85.8	–	–	–	90.0	29.0
	Imipenem (IMP)	–	–	–	–	90.0	–

How much MRSA: no cefoxitin / oxacillin results?

- Could just guess from the imipenem or ceftriaxone data?
- But how were these results generated?

Ceftazidime for *S. aureus:* might be ok 2/3 of the time…really?

Are these isolated issues or part of a larger quality management problem?

MICRO

Microbiology Investigation Criteria for Reporting Objectively:
A framework for the reporting and interpretation of clinical microbiology data

BMC Medicine. 2019;17(1): 70

Tackling antimicrobial resistance (AMR) is a Global Health priority

Poor quality data hampers efforts to understand the burden of AMR

Use the MICRO framework to enhance the quality and scientific reporting of clinical microbiology data:

- Increase data utility and comparability
- Improve AMR surveillance
- Facilitate meta-analyses
- Inform policy and interventions from local to global levels

UNIVERSITY OF OXFORD

To sum up…

- Laboratory-based AMR surveillance in LMICs is hampered by many things

- Local data management is a major road block to progress
  - Urgently need better LIMS and IT infrastructure to support this
  - User friendly analysis tools would unlock local data use

- Perhaps more focus on the local situation might improve uptake and usefulness of global surveillance
  - If we don’t get the site level data sorted, then the global data will be wrong anyway

COMRU.

Thank you.

Cambodia Oxford Medical Research Unit

Angkor Hospital for Children | Siem Reap | Cambodia