Impact of microbial diagnostics on the curbing of AMR in a *personal* UK perspective

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University of Edinburgh

AMR Insights
Virtual AMR Innovation Mission UK 2021
10 - 12 May 2021

Unmet Need in Clinical Microbiology

Pathogen

Susceptibility/ Resistance

Rapid Diagnostics

- Therapy Decision
- Patient Management
- Surveillance
- Narrow Spectrum Antibiotics

"I call on the governments of the richest countries to mandate now that by 2020, all antibiotic prescriptions will need to be informed by up-to-date surveillance information and a rapid diagnostic test wherever one exists."

AMR Review May 19, 2016 – Tackling Drug-Resistant Infections Globally: final report and recommendations

"… be able to report on the percentage of prescriptions supported by a diagnostic test or decision support tool by 2024."

For Dx: UK AMR Diagnostics Collaborative

There has been very little progress on the review's central and most expensive recommendations for transforming research and development incentives for antibiotics, vaccines and diagnostics.

Review of Progress on Antimicrobial Resistance: Background and Analysis, Charles Clift, Centre on Global Health Security | October 2019, Chatham House

Rapid, affordable, and effective point-of-care diagnostics are urgently needed in both community and hospital settings to distinguish between viral and bacterial infections, identify pathogens, and test for AMR and susceptibility to antibiotics. However, there is insufficient development of new products due to market failures and various barriers to uptake.

Wellcome (2020). "The Global Response to AMR: Momentum, success, and critical gaps"

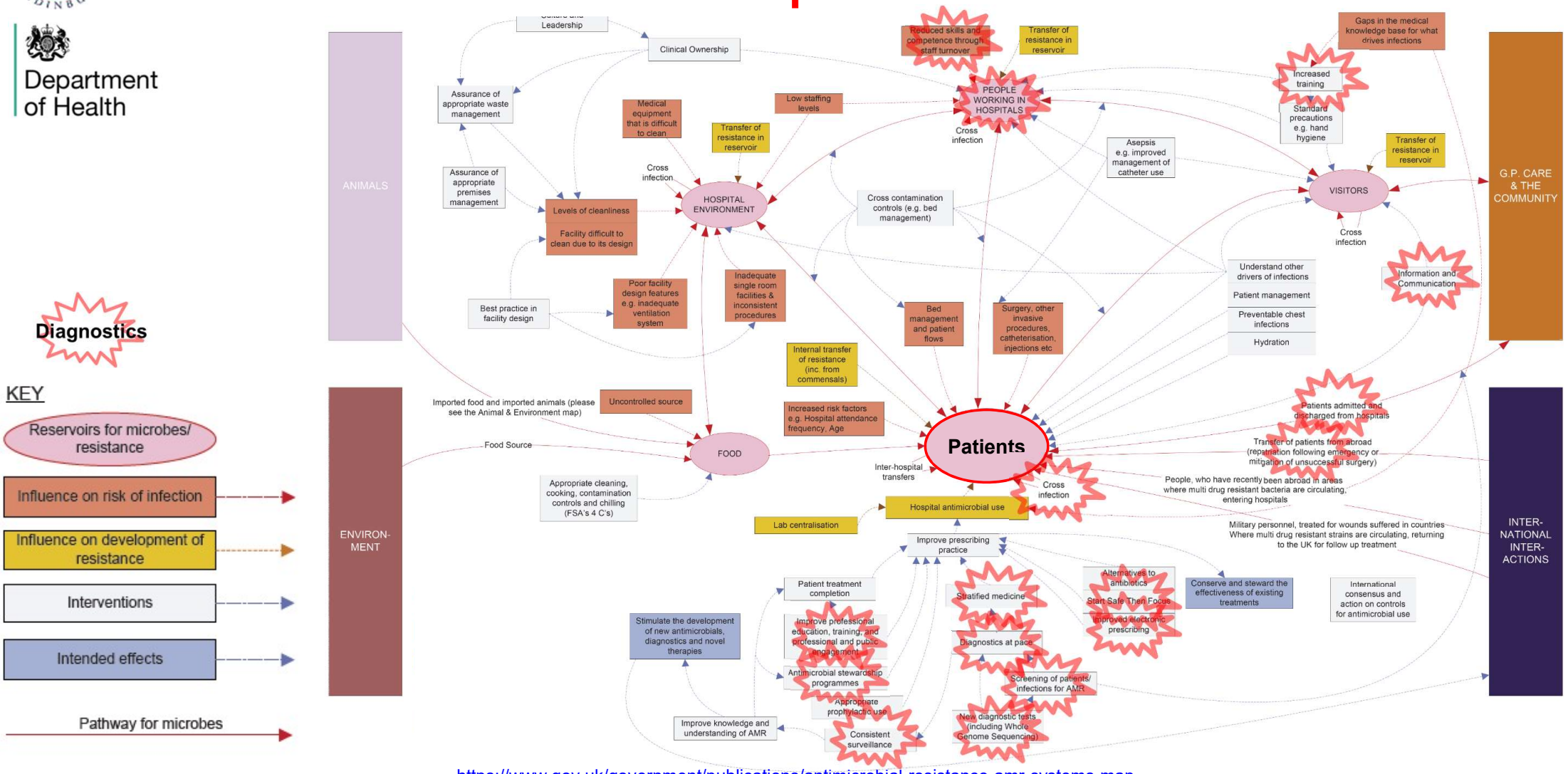
“Impact of microbial diagnostics on the curbing of AMR”

What is the framework?

Development of AMR	**Impact of AMR**	**Spread of AMR**
Inappropriate use of antibiotic increases development of AMR	**Chosen antibiotic does not work and outcome falls behind desired expectations**	**Organism of interest is exposed to AMR**
Change Of Behaviour	**New Interventions**	**New Interventions**

AMR Systems Map – Influences on the development of AMR

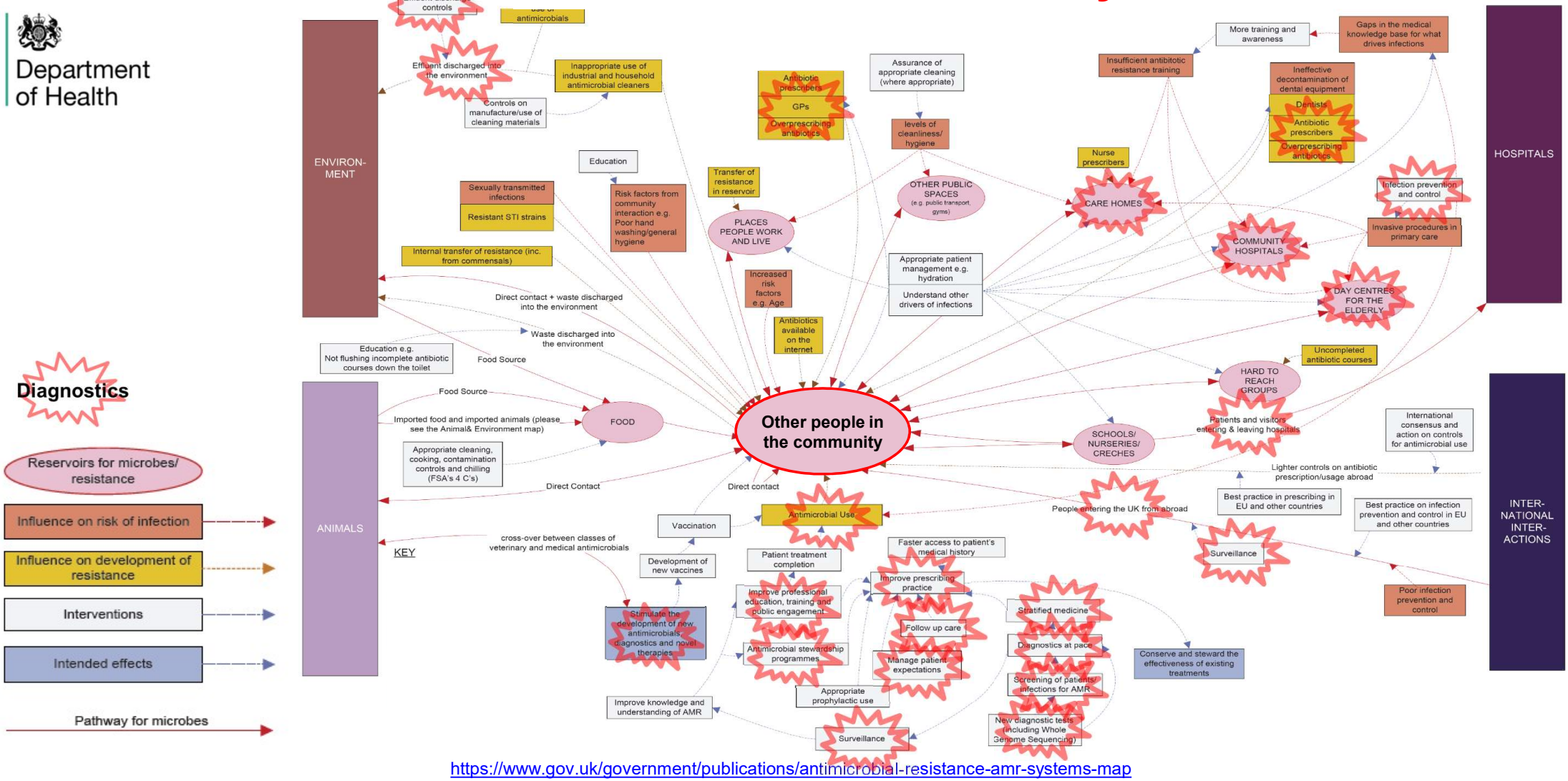
Hospital



https://www.gov.uk/government/publications/antimicrobial-resistance-amr-systems-map

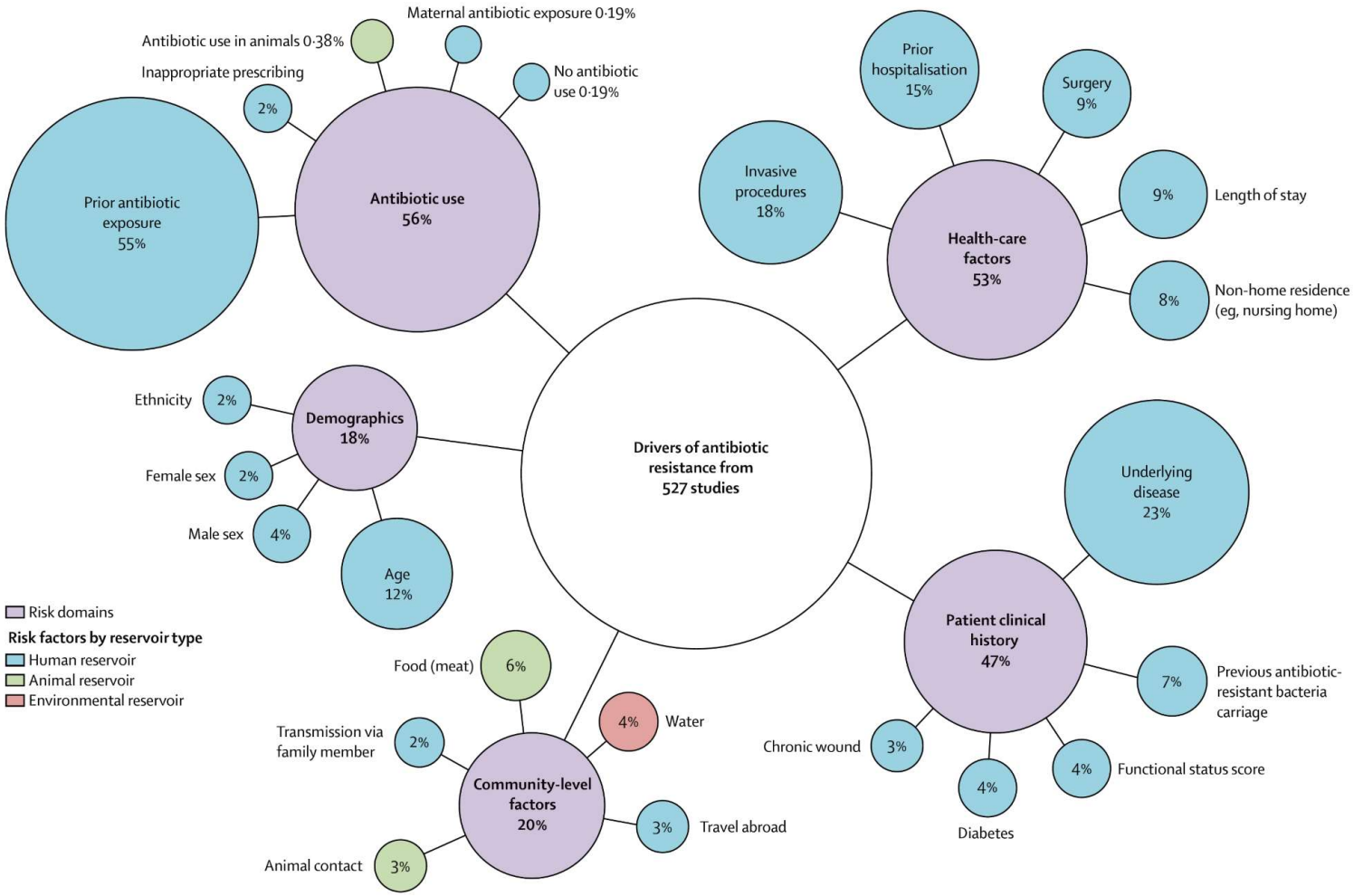
AMR Systems Map – Influences on the development of AMR

GP Care and the Community



https://www.gov.uk/government/publications/antimicrobial-resistance-amr-systems-map

Creating Evidence for **Drivers of AMR**



Gaps for studies on:

- Causal relationship between reservoirs and risk factor domains
- Low level factors associated with AMR in hospital setting
- Heterogeneous community level risk factors

Quantifying drivers of antibiotic resistance in humans: a systematic review. Chatterjee A, Modarai M, Naylor NR, Boyd SE, Atun R, Barlow J, Holmes AH, Johnson A, Robotham JV. Lancet Infect Dis. 2018 Dec;18(12):e368-e378.

Some **Molecular Diagnostic Systems** in Use or With Potential for Infectious Disease Diagnostics


www.drw-ltd.com


www.biocartis.com


www.cepheid.com


www.nanosphere.com


www.molecular.roche.com


www.check-points.com


www.curetis.com


www.alere-i.com


www.alere.com


www.biomerieux-diagnostics.com

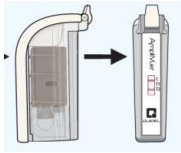

www.luminexcorp.com


www.qiastat-dx.com


www.bosch-vivalytic.com


www.blink-dx.com


www.twistdx.co.uk


www.quidel.com


www.optigene.com


www.meridianbioscience.com


www.mybinxhealth.com


www.genefluidics.com


www.daktaridx.com


www.genmarkdx.com


www.mobidiag.com


nanoporetech.com


www.dnae.co.uk


www.rheonix.com


www.corisbio.com


www.genepoc-diagnostics.com


spindiag.de


www.chipcare.ca


www.quantumdx.com


www.cubedlabs.com


www.genedriveplc.com


www.ivd-plattform.de


www.bigteclabs.com


gbscience.com

WHO AMR Diagnostics **Landscape & Gap Analysis**

Table 1. Gaps in syndromic testing at Level I and Level II healthcare facilities*

Purpose Syndromes	Fever without a known source	Sepsis	Sore throat, cough, URTI	TB[1]	Pneumonia, LRTI	Diarrhea	Visible skin/soft tissue infection	Wounds (traumatic and chronic)	Urethral and vaginal discharge	UTI
Level I										
Bacteria vs other	A	NA	A	A	A	A	NA	NA	NA	A[3]
Bacterial ID (culture, RDT, ..)	NA	NA	A, B	NA	A, B	NA	NA	NA	A, B	NA
Antibiotic Susceptibility	NA	NA	NA	NA	NA	NA	NA	NA	A, B	NA
Resistance Testing	NA	NA	NA	NA	NA	NA	NA	NA	A, B	NA
Level II										
Bacteria vs other	A	NA	A	A	A	A	A	A	NA	A[3]
Bacterial ID	B, C	B, C	A, B, C	A, B, C	A, B, C	B[2], C	A, B, C	A, B, C	A, B	A, B, C
Antibiotic Susceptibility	B, C	B, C	C	A, B, C	B, C	B[2], C	B, C	B, C	B, C	A, B, C
Resistance Testing	B, C	B, C	C	A, B, C	B, C	B[2], C	B, C	B, C	B, C	C

If test desired	Available	Not fully available or ideal	Not available

A Reduce unnecessary antibiotic prescriptions, **B** Guidance for appropriate treatment of drug-resistant infections, **C** Surveillance

*Based on informal consensus of participants attending the Technical Consultation on In Vitro Diagnostics for AMR.

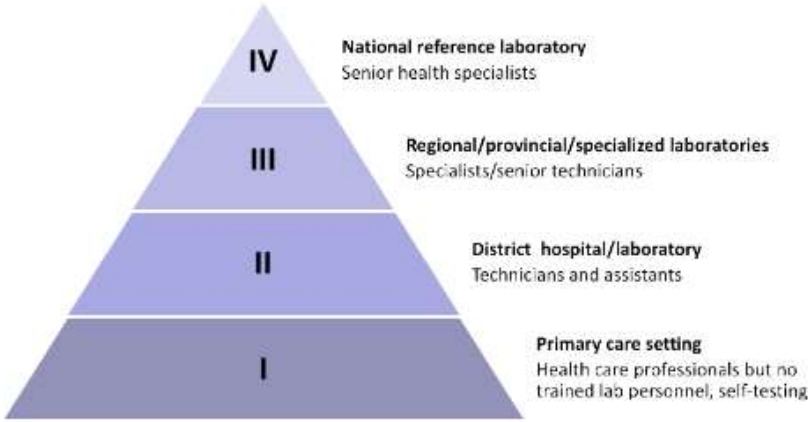
Notes:

[1] MTB, the cause of human tuberculosis, was not subjected to review for inclusion in this prioritization exercise as it is already a globally established priority. And although priority TPPs to stimulate product development have been developed, more innovative new TB diagnostics are urgently needed. The section on TB was provided by the WHO Global TB Programme.

[2] In case it is needed in special populations.

[3] Infection marker.

https://www.who.int/medicines/access/antimicrobial_resistance/en/



WHO AMR Diagnostics **Target Product Profile**

for a Multiplex Platform for Identification and Resistance Testing/AST of Prioritized Bacterial Pathogens

	Characteristic	Minimal requirement	Optional requirement
	Scope of the platform		
1	**Intended use**	For purposes of patient management and antibiotic stewardship,[1] ID of (i) multiple WHO prioritized bacterial pathogens[2] associated with clinical syndromes such as bloodstream infections, respiratory infections, urinary tract infections (UTIs) and gastrointestinal infections (GIs), and (ii) either genetic determinants of antibiotic susceptibility/resistance or phenotypic antimicrobial susceptibility[3] with respect to select antibiotics for the pathogens identified.	For purposes of patient management and antibiotic stewardship, ID of (i) multiple prioritized bacterial pathogens associated with clinical syndromes such as bloodstream infections, respiratory infections, UTIs and GIs, and (ii) either genetic determinants of antibiotic susceptibility/ resistance or phenotypic antimicrobial susceptibility with respect to the full range of antibiotics for the pathogens identified.
36	**Sample preparation**	Minimal sample processing; no more than three steps (requiring operator intervention); no more than one precision step (e.g. volumetric pipetting); centrifugation or other off-cartridge sample processing steps acceptable.	
3	**Target use setting**	Level 2[6] healthcare facility (district hospital or above) defined as having a functioning laboratory with trained personnel, water, electricity with intermittent surges and/or outages, limited climate control, dust and medical staff on-site; The target use setting does not include mobile testing facilities.	
40	**Time to result – ID and genotypic resistance testing**	≤ 90 minutes	≤ 60 minutes
49	**List price of assay cartridge**	≤ US$ 15 at volume production.	≤ US$ 10 at volume production.

https://www.who.int/medicines/access/antimicrobial_resistance/tpps-abr-diagnostics/en/

WHO **Essential Diagnostics List** 2020

https://www.who.int/publications/m/item/the-who-edl-brochure

II.a General IVDs for use in clinical laboratories *continued*

Discipline	Diagnostic test	Test purpose	Assay format	Specimen type
Clinical microbiology	Staining procedures	For the presumptive identification of pathogens and for determination of microbial morphology	Microscopic examination of slides which may use different types of microscopes and stains	Disease-appropriate specimens (e.g. sputum, venous whole blood, urine, stool, body fluids, cerebrospinal fluid or cultures)
	Culture	Initial step in detection and identification of bacterial and fungal species for selection of appropriate antimicrobial regimens	Culture on growth media plates or broth in an incubator followed by recovery of isolates and species identification (traditional manual techniques or automated equipment)	Disease-appropriate specimens (e.g. urine, stool, sputum, body fluids, e.g. cerebrospinal fluid, etc.)
	Blood culture	To detect bacterial and fungal bloodstream infections (sepsis)	Blood culture bottle in an incubator followed by recovery of isolates (traditional manual techniques or automated equipment)	Venous whole blood
	Genus and species identification of bacteria and fungi	To identify the genus or species of bacteria or fungi from microbial isolates	A range of biochemical tests that may be performed manually or on automated equipment	Microbial isolates

II.a General IVDs for use in clinical laboratories *continued*

Discipline	Diagnostic test	Test purpose	Assay format	Specimen type
Clinical microbiology *continued*	Antimicrobial susceptibility testing	Final step in selection of appropriate antibiotics after species identification and interpretation by EUCAST[21] and CLSI guidelines[22] Note: WHO regards the development of antimicrobial resistance (AMR) a high-priority global health issue. See WHO Global Antimicrobial Resistance Surveillance System (GLASS): https://www.who.int/activities/facilitating-global-surveillance-of-antimicrobial-resistance	Antimicrobial susceptibility testing of isolates may be done manually (by disc diffusion, gradient tests and broth microdilution), or by automated platforms	Microbial isolates

check the EDL and provide feedback for AMR to EDLSecretariat@who.int

The selection and use of essential in vitro diagnostics: report of the third meeting of the WHO Strategic Advisory Group of Experts on In Vitro Diagnostics, 2020 (including the third WHO model list of essential in vitro diagnostics). Geneva: World Health Organization; 2021 (WHO Technical Report Series, No. 1031). Licence: CC BY-NC-SA 3.0 IGO. https://www.who.int/publications/i/item/9789240019102

Longitude Prize

Launched in **2014**

£8 million Prize

Funded by **Nesta & Innovate UK**

1 winner, first past the post

Prize deadline **September 2022**

nesta Challenges

The Longitude Prize is a £10 million prize fund with an £8 million payout that will reward a competitor that can develop a point-of-care diagnostic test that will conserve antibiotics for future generations.

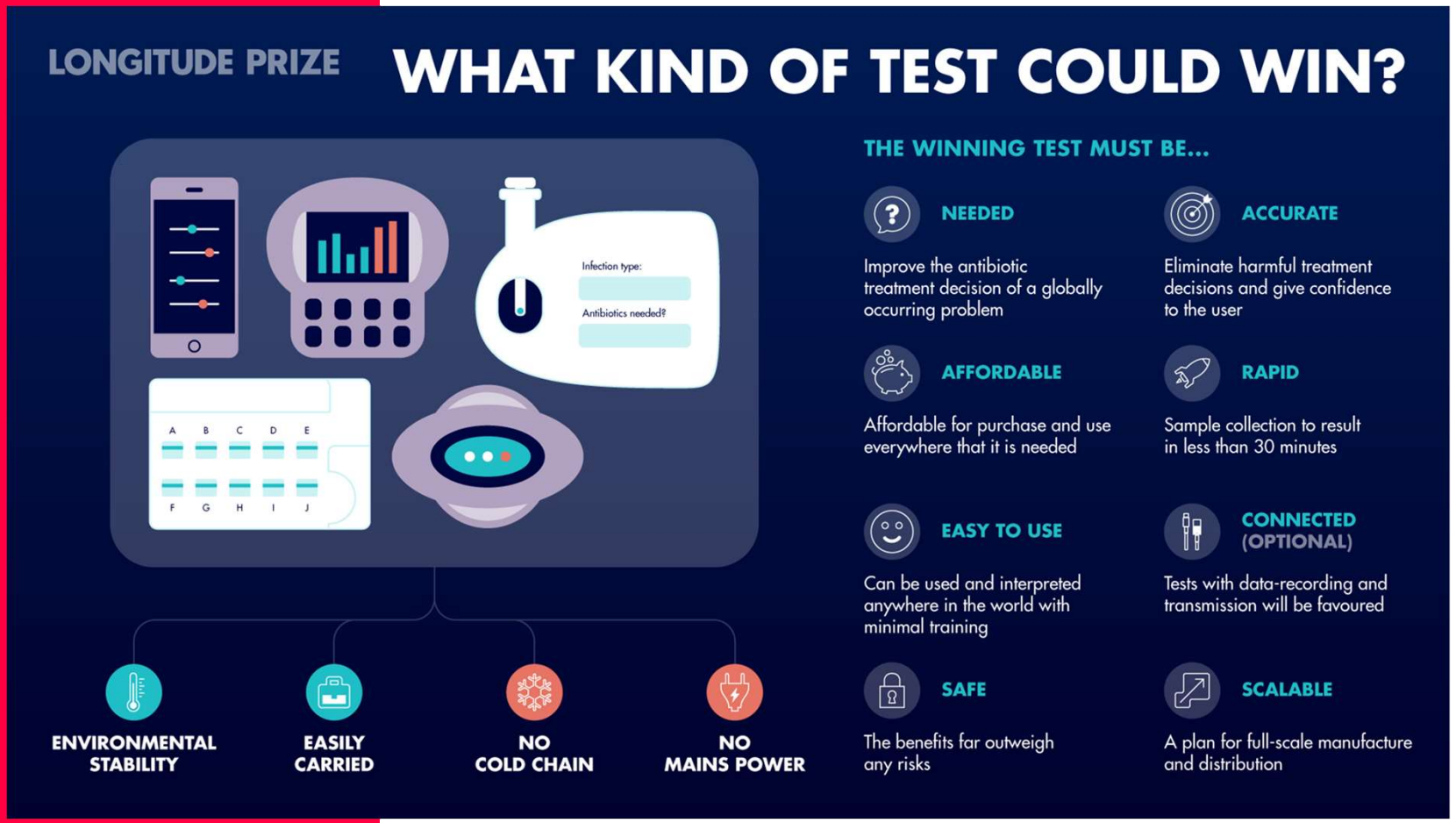
*The test must be **accurate**, **rapid**, **affordable** and **easy to use** anywhere in the world.*

54 competitors across 12 countries (majority: UK, EU, US and India)

Types of tests competing:

- urinary tract infections tests
- bloodstream infection and sepsis tests
- respiratory treat infections tests

Longitude Prize Criteria



nesta Challenges

Teams advancing

- Advanced technology – pathogen detection and antibiotic susceptibility and resistance tests
- Analytical performance data collected
- Attracted significant investment of funding
- Collaborative arrangements with marketing and manufacturing partner
- Clinical validation studies ongoing or planned *(Covid-19 causing delays)*

nesta Challenges

UK-India DOSA - Project
Diagnostics for One Health and User Driven Solutions for AMR

10 Partner Institutions (4 UK, 6 India)
13 PIs/Co-PIs
2018 – 2021
£3m UKRI/ESRC/Newton + DBT
https://dosa-diagnostics.org @DosaDx

University of Edinburgh
Till Bachmann, Dominic Moran, Alice Street

University of Bradford
Stephen Rimmer

University of the Arts London
Alison Prendiville

University of Southampton
Xunli Zhang

ICAR-NDRI
Naresh Kumar, Raghu Vishweswaraiah

IIT Delhi
Ravikrishnan Elangovan

Assam University
Amitabha Bhattacharjee

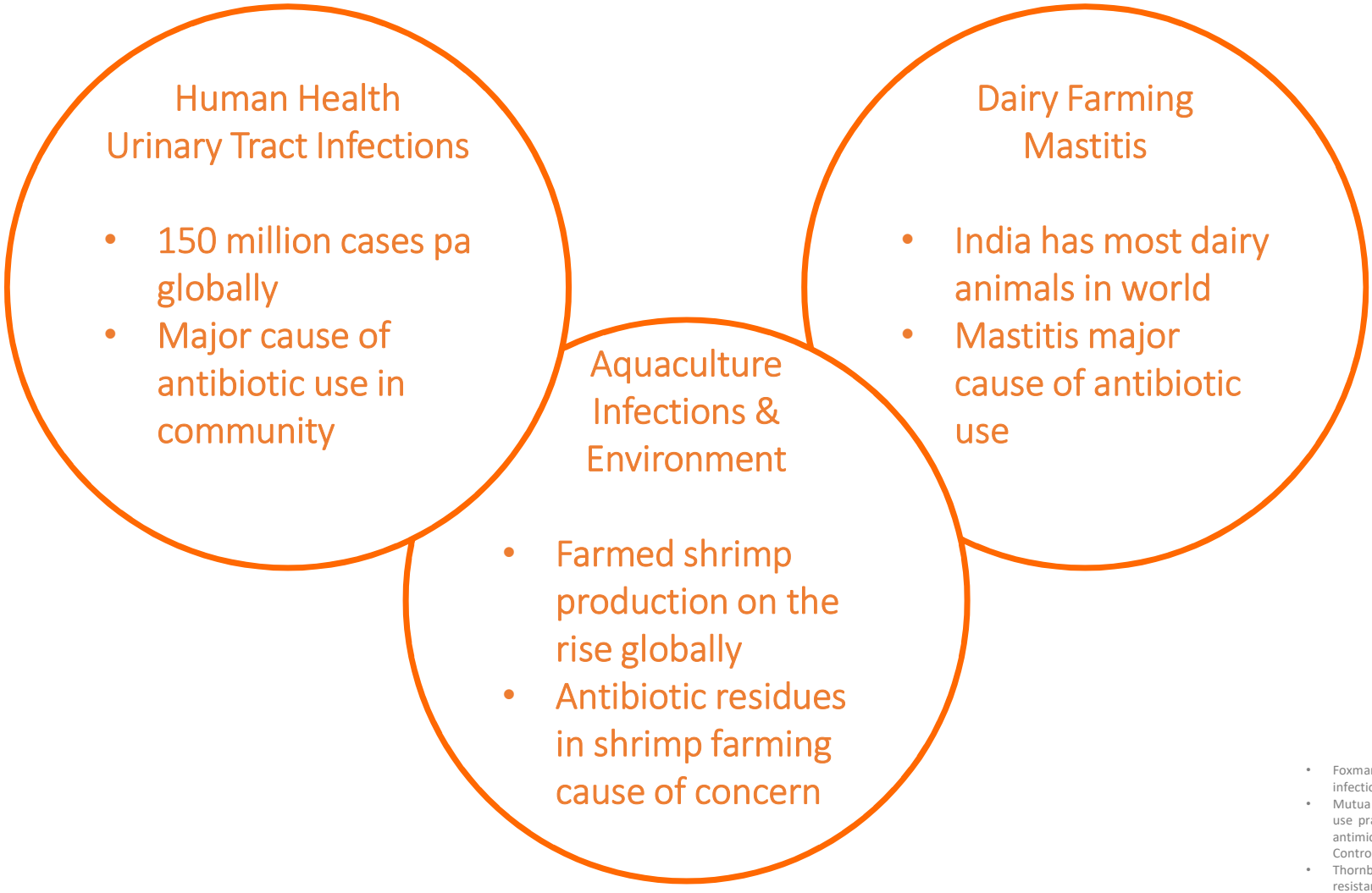
Silchar Medical College and Hospital
Debadatta Dhar

C-CAMP Bangalore
Taslimarif Saiyed

ICAR-CIFT Cochin
Sivaraman Gopalan Krishnan

DOSA is funded by UK Research and Innovation / Economic Social Science Research Council, Newton Fund, and the Government of India's Department of Biotechnology

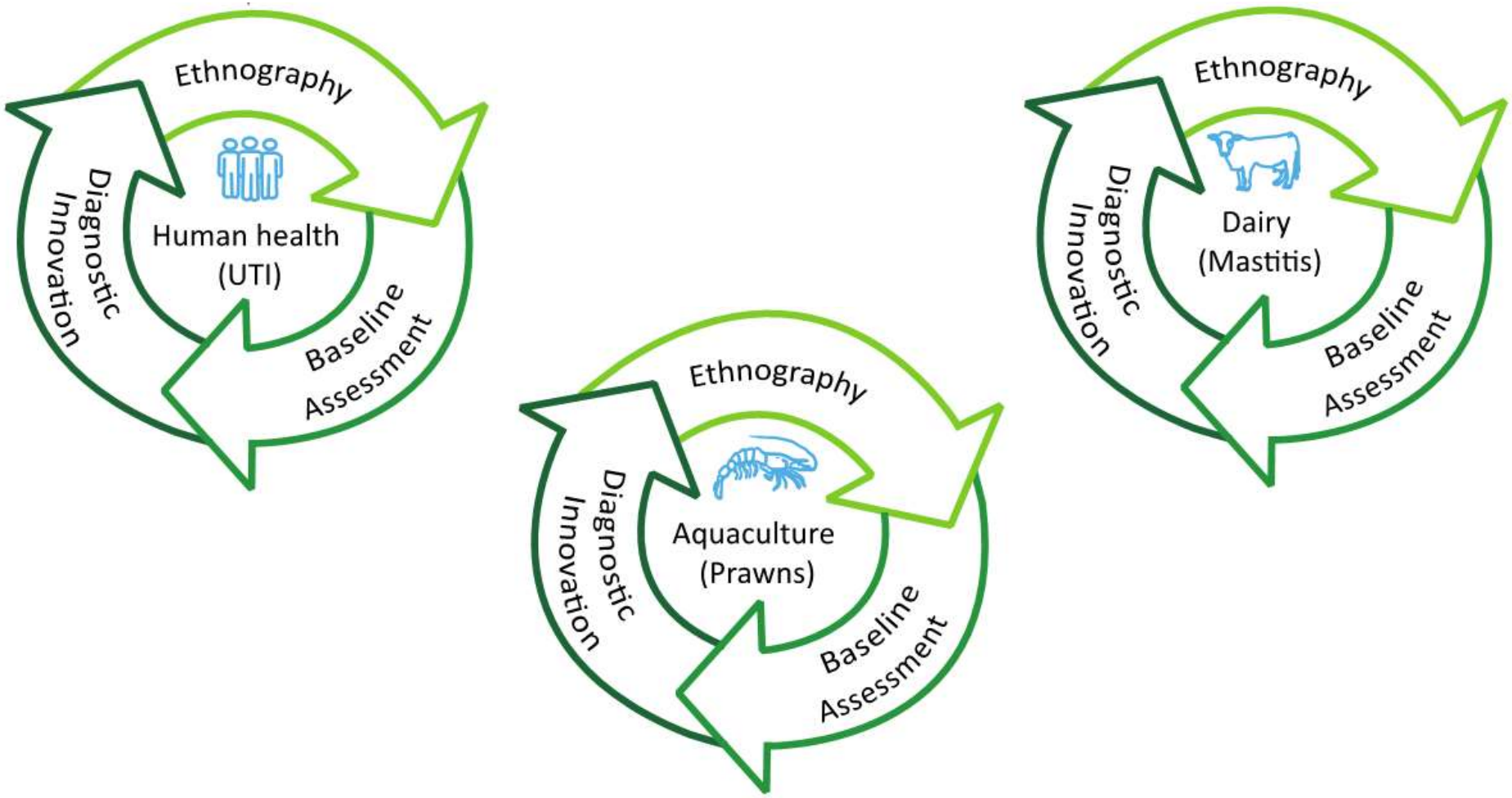
DOSA Objectives in the One Health Context



DOSA is funded by UK Research and Innovation / Economic Social Science Research Council, Newton Fund, and the Government of India's Department of Biotechnology

- Foxman B. The epidemiology of urinary tract infection. Nat Rev Urol. 2010 Dec;7(12):653-60.
- Mutua F et al. A review of animal health and drug use practices in India, and their possible link to antimicrobial resistance. Antimicrob Resist Infect Control. 2020 Jul 8;9(1):103.
- Thornber K et al. Evaluating antimicrobial resistance in the global shrimp industry. Rev Aquac. 2020 May;12(2):966-986.

Integrated Approach to One Health Diagnostic Solutions for AMR



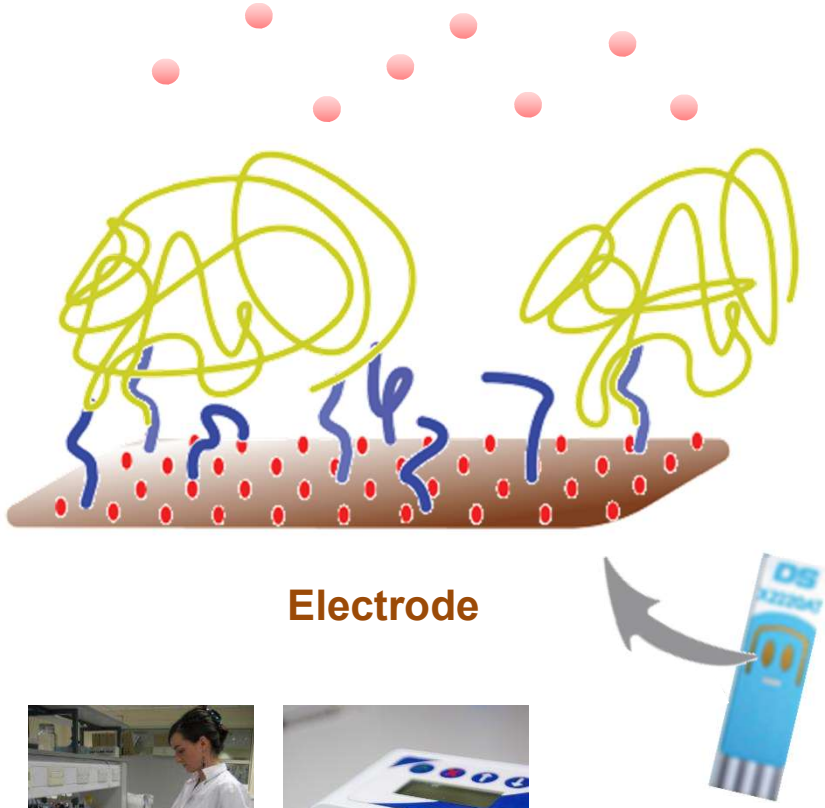
DOSA is funded by UK Research and Innovation / Economic Social Science Research Council, Newton Fund, and the Government of India's Department of Biotechnology

Electrochemical Biosensors for Amplification Free Detection

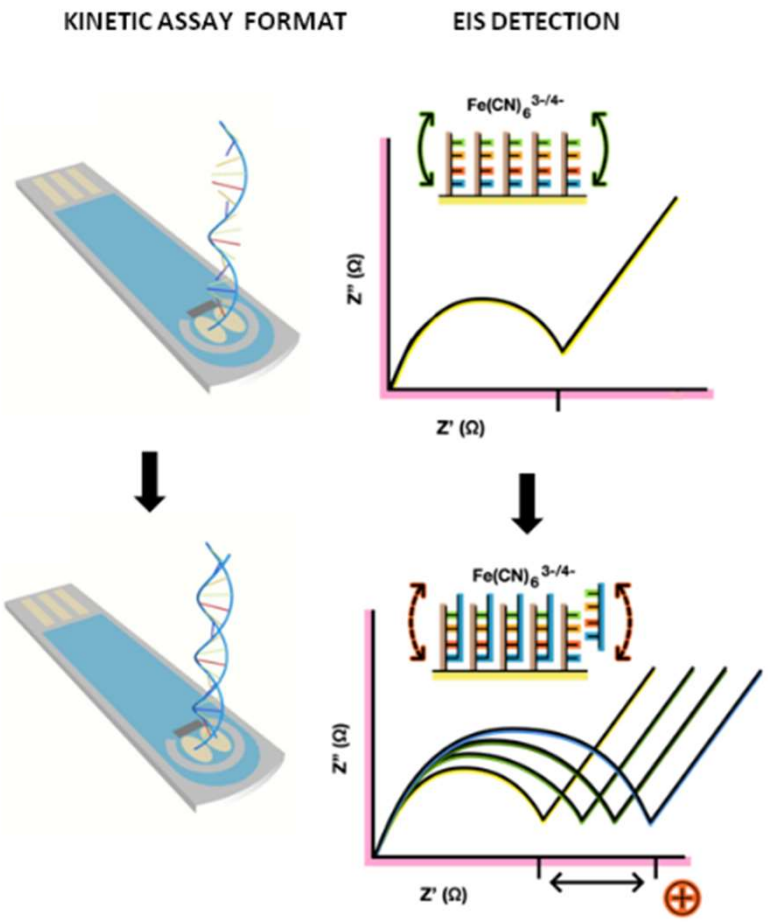
- EIS - **Electrochemical Impedance Spectroscopy**
- *How easily can an electroactive substance reach electrode surface?*

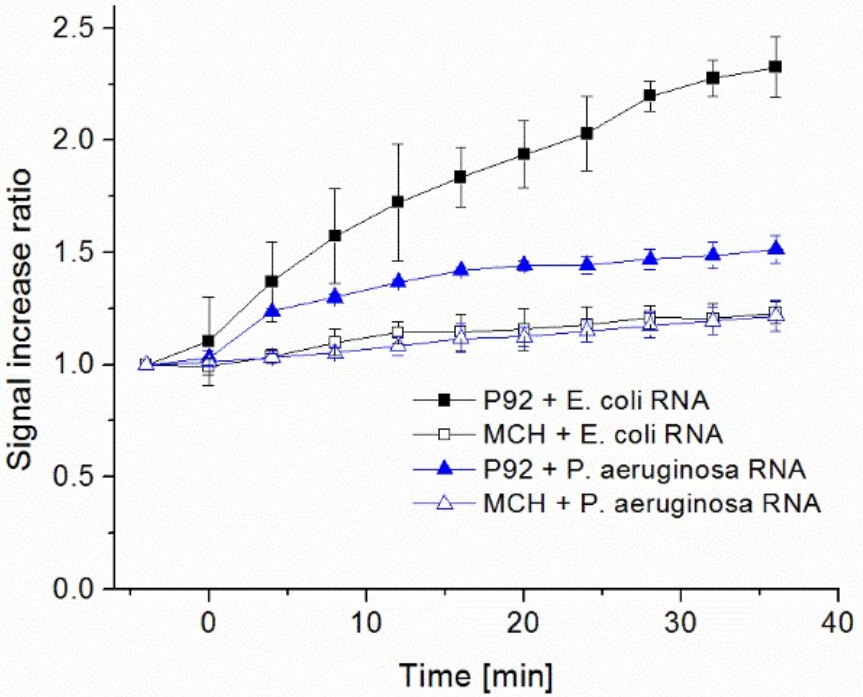
- **Label free & Amplification free**
- Small AC potential at different frequencies → current response → impedance

- Functionalisation of electrode introduces specificity
- **Platform technology**



Bacterial ID through label- and amplification-free detection of bacterial **ribosomal RNA**



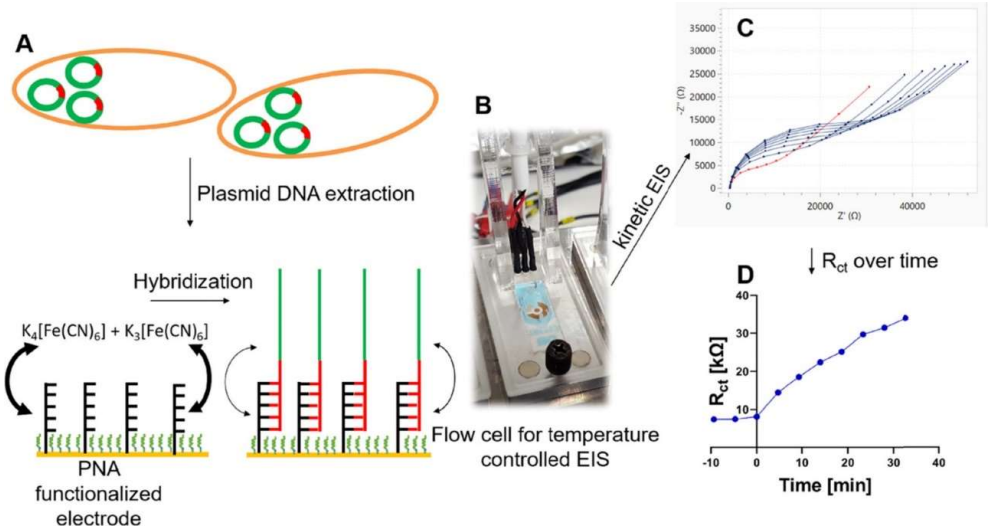


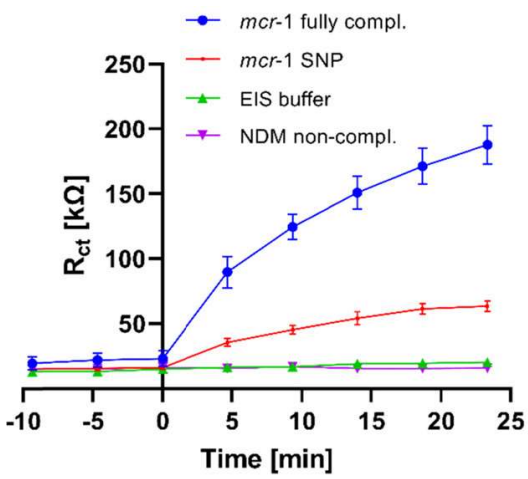
Signal increase ratios obtained at screen-printed electrodes functionalised with *E. coli* specific PNA probe P92 and MCH only (negative control) following exposure to 750 pM *E. coli* and *P. aeruginosa* rRNA. EIS measurements were continuously repeated in the presence of the target solution without any washing steps.

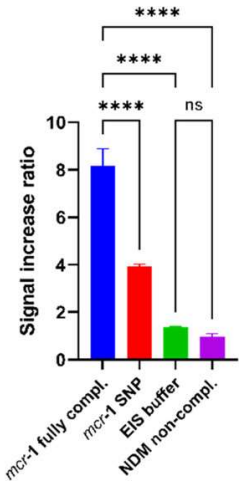
Henihan G, Schulze H, Corrigan D, Giraud G, Terry JG, Hardie A, Campbell CJ, Walton AJ, Crain J, Pethig R, Templeton KE, Mount AR, Bachmann TT 2016. Label- and amplification-free electrochemical detection of bacterial ribosomal RNA. Biosensors & Bioelectronics 81, 487-494.

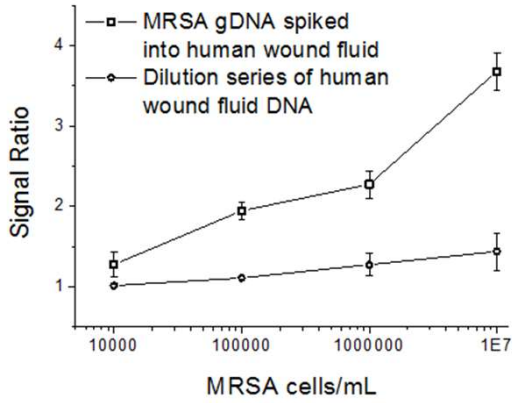
Towards **AMR POCT**

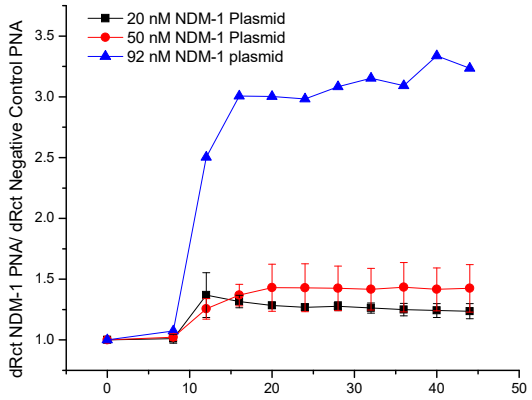
Colistin (mcr-1), **Carbapenem** (NDM-1) and **Methicillin** (mecA) **resistance** detection





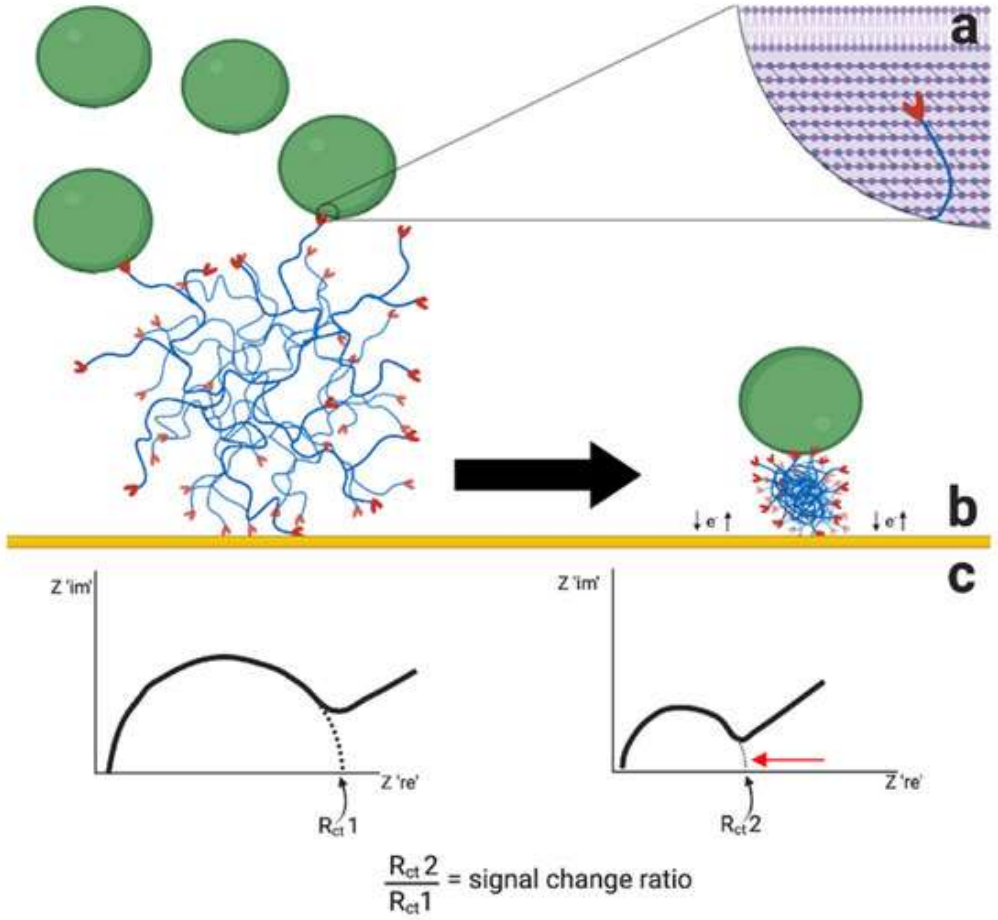


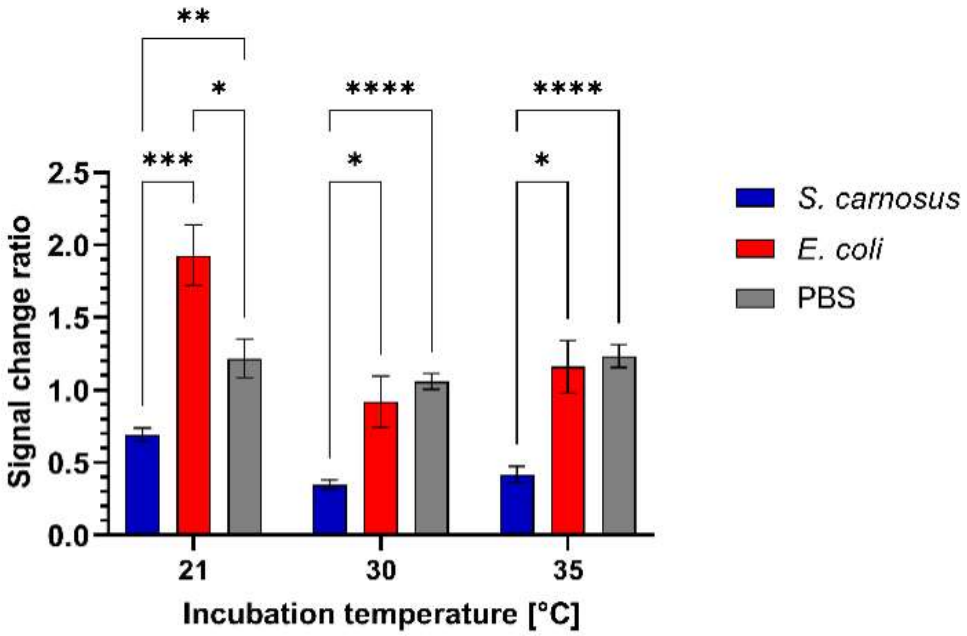




- ***Schulze H, Arnott A, Libori A, Obaje EA, Bachmann TT. Temperature-Enhanced mcr-1 Colistin Resistance Gene Detection with Electrochemical Impedance Spectroscopy Biosensors. Anal Chem. 2021 Apr 20;93(15):6025-6033.***
- *Huang JM, Henihan G, Macdonald D, Michalowski A, Templeton K, Gibb AP, Schulze H, Bachmann TT (2015) Rapid Electrochemical Detection of New Delhi Metallo-beta-lactamase Genes To Enable Point-of-Care Testing of Carbapenem-Resistant Enterobacteriaceae. Anal. Chem. 87 (15), 7738-7745.*
- *Development of a PCR-free electrochemical point of care test for clinical detection of methicillin resistant Staphylococcus aureus (MRSA). Corrigan DK, Schulze H, Henihan G, Hardie A, Ciani I, Giraud G, Terry JG, Walton AJ, Pethig R, Ghazal P, Crain J, Campbell CJ, Templeton KE, Mount AR, Bachmann TT. Analyst. 2013 Oct 15;138(22):6997-700*

Bacteria Detection for POCT - **Functional Polymer** Sensors

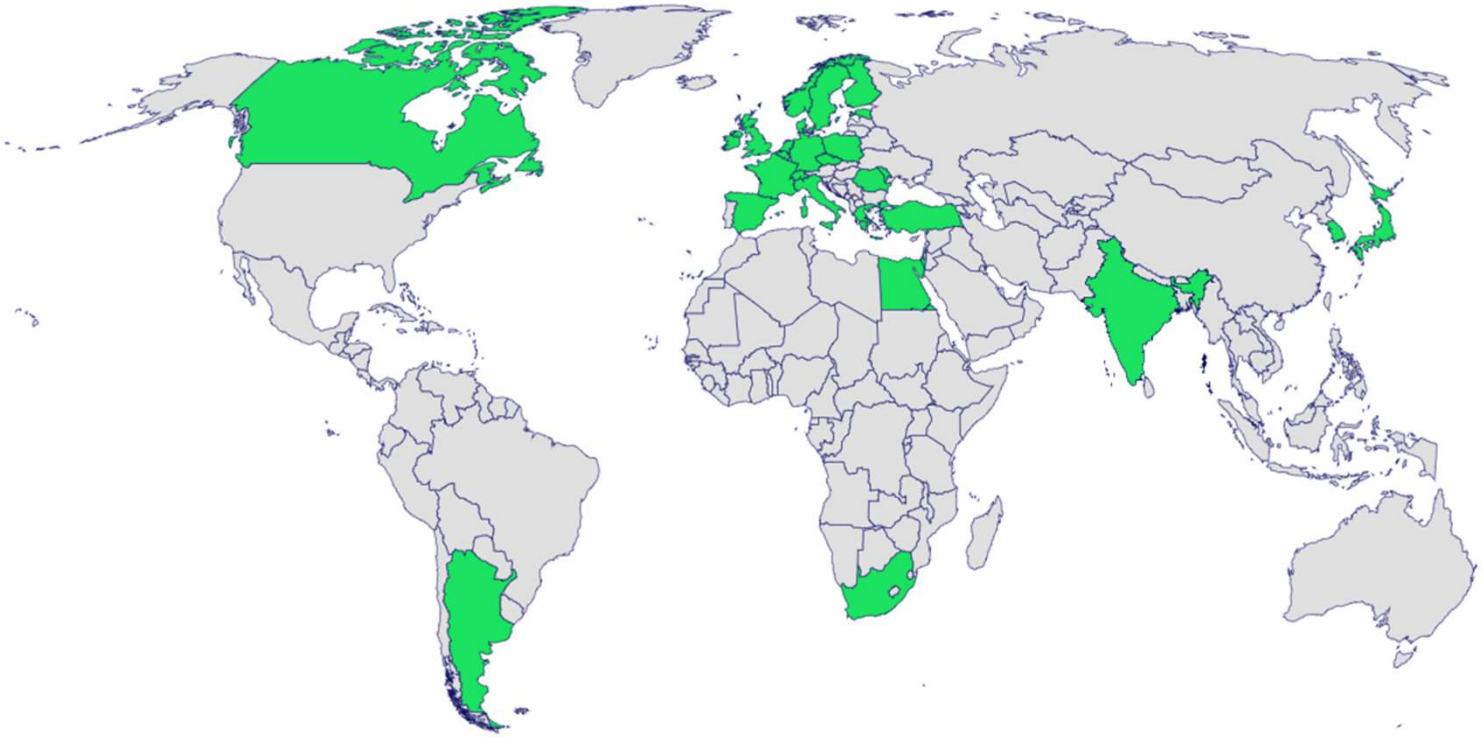




Schulze H, Wilson H, Cara I, Carter S, Dyson EN, Elangovan R, Rimmer S, Bachmann TT. Label-Free Electrochemical Sensor for Rapid Bacterial Pathogen Detection Using Vancomycin-Modified Highly Branched Polymers. Sensors. 2021; 21(5):1872.

Uniting 28 countries to address AMR

JPIAMR: A global organisation



- International collaborative platform
- Aligns national research funding
- Coordinates AMR research and funding on a global scale
- Supports One Health perspective

The European Commission (DG Research) is a full non-voting member

www.jpiamr.eu twitter.com/JPIAMR facebook.com/JPIAMR

jpiamr

JPIAMR: A global One Health AMR Research Funder

Therapeutics

Discovery of new antimicrobials and therapeutic alternatives, and the improvement of current antimicrobials and treatment regimens

Diagnostics

Development and improvement of diagnostics to improve the use of antimicrobials and alternatives to antimicrobials

Surveillance

Optimisation of surveillance systems to understand the drivers and burden of antimicrobial resistance in a One Health perspective

Transmission

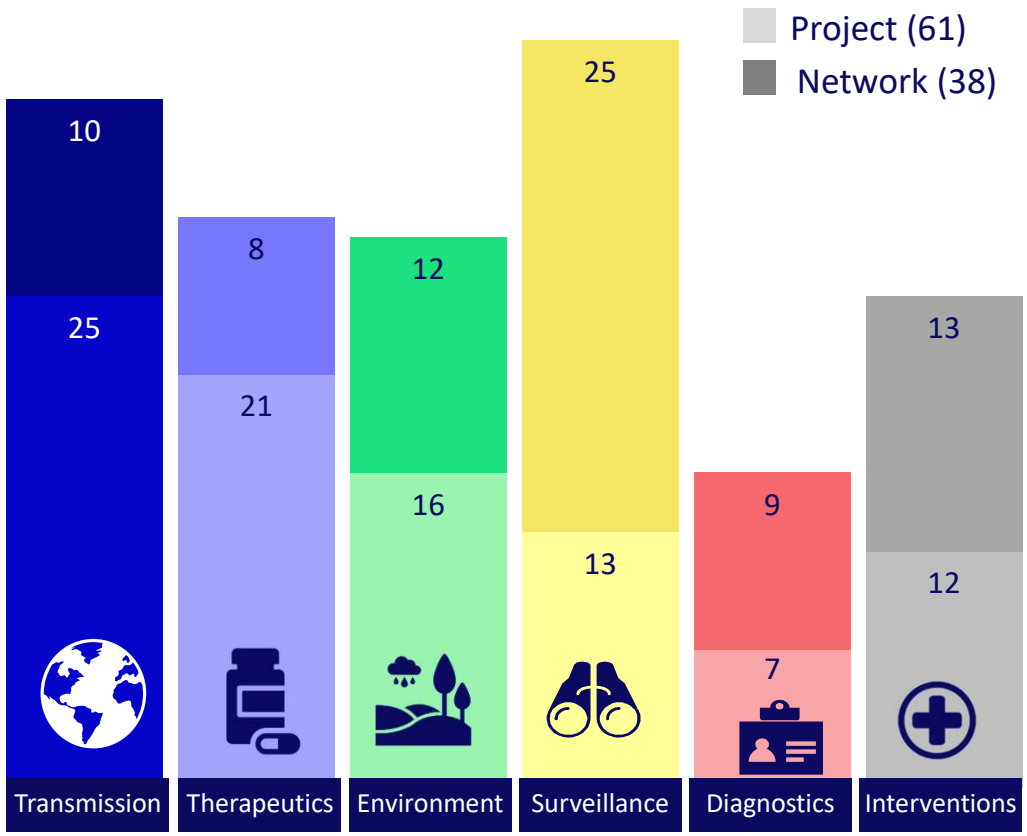
Understanding and preventing the transmission of antimicrobial resistance

Environment

The role of the environment in the persistence, selection and spread of antimicrobial resistance

Interventions

Investigation and improvement of infection prevention and control measures in One Health settings



Projects and networks in different research priority areas

www.jpiamr.eu twitter.com/JPIAMR facebook.com/JPIAMR

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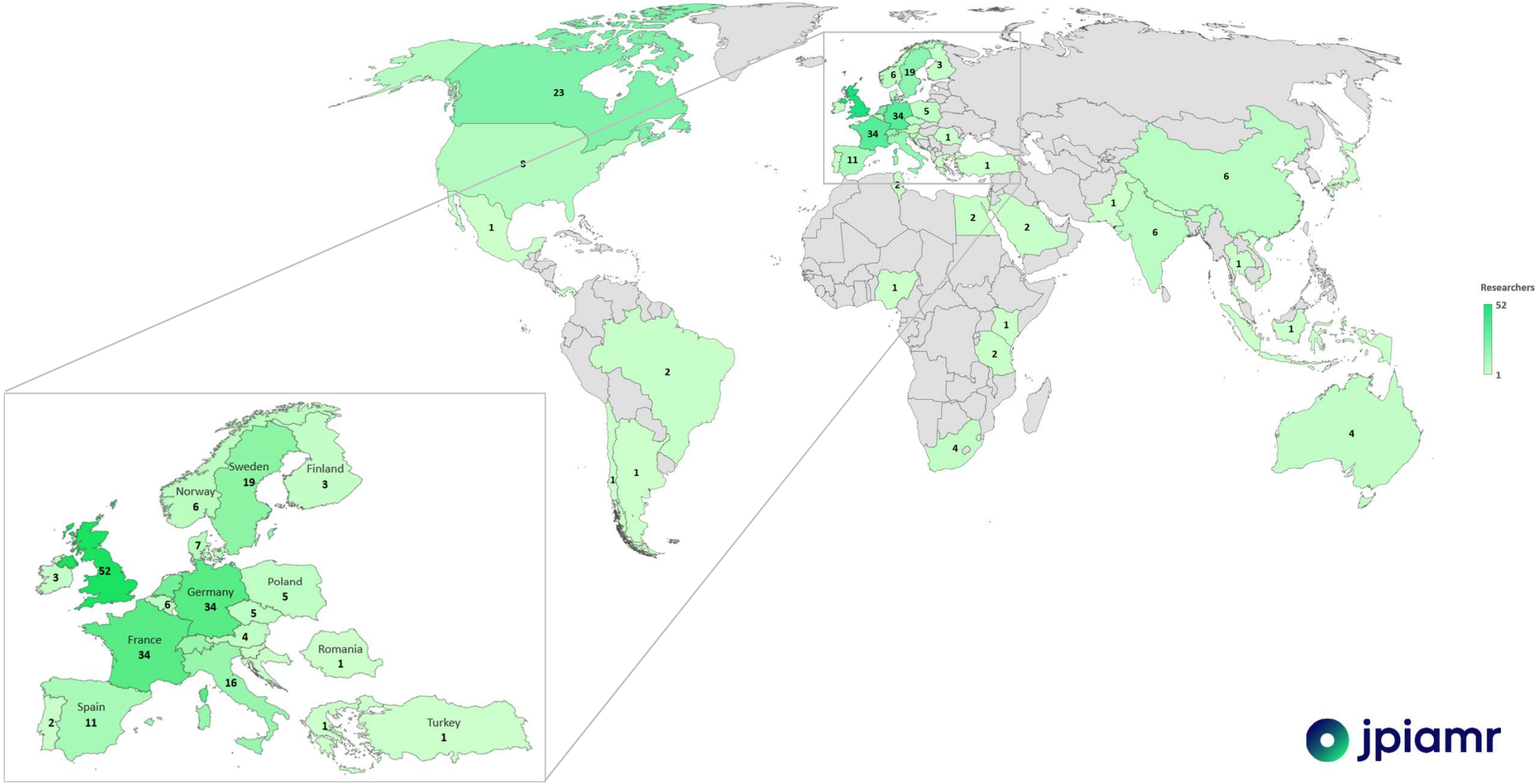
JPIAMR supported researchers worldwide on Diagnostics

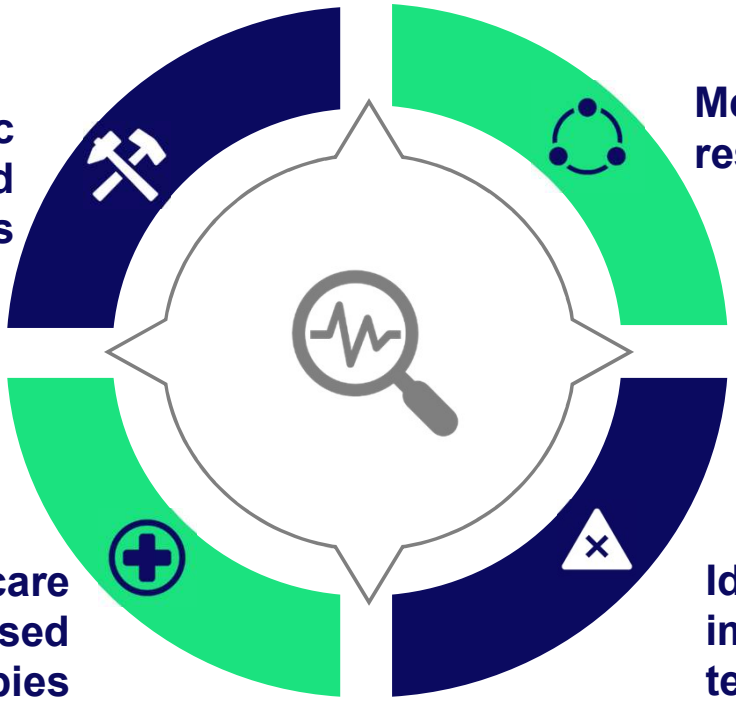


Overview of the JPIAMR diagnostics projects and networks

5.3 M€

7 projects
9 networks

324 researchers



New or improved diagnostic tools, technologies and methods

Methods to detect AMR in multiple reservoirs

Rapid diagnostics and point-of-care techniques to improve personalised therapies

Identify barriers of development and implementation of rapid diagnostic tests

JPIAMR Diagnostics Networks and Outcomes

Seq4AMR

Identify gaps and solutions to current and future NGS / AMR diagnostics

AMR Dx Global

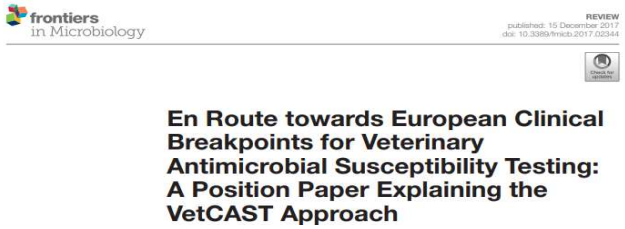
Strategic Action Plan on Teaching & Training for AMR Diagnostics

VetCAST

Define clinical breakpoints for antimicrobial drugs used in veterinary medicine in Europe to harmonise the results of AST

AMR-RDT

Identify barriers of development and implementation of RDT



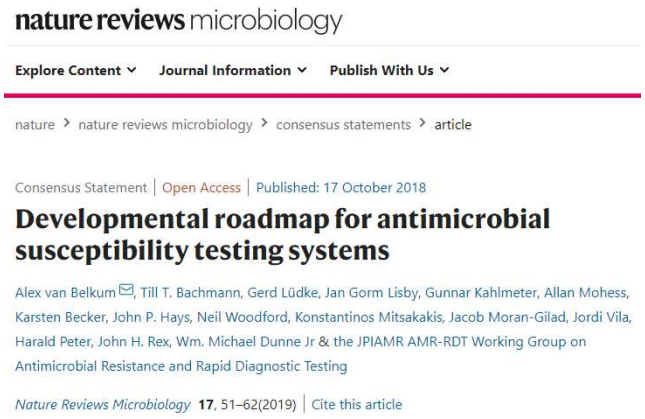
frontiers in Microbiology

REVIEW

published: 15 December 2017

doi: 10.3389/fmicb.2017.02344

En Route towards European Clinical Breakpoints for Veterinary Antimicrobial Susceptibility Testing: A Position Paper Explaining the VetCAST Approach



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Consensus Statement | Open Access | Published: 17 October 2018

Developmental roadmap for antimicrobial susceptibility testing systems

Alex van Belkum, Till T. Bachmann, Gerd Lüdke, Jan Gorm Lisby, Gunnar Kahlmeter, Allan Mohess, Karsten Becker, John P. Hays, Neil Woodford, Konstantinos Mitsakakis, Jacob Moran-Gilad, Jordi Vila, Harald Peter, John H. Rex, Wm. Michael Dunne Jr & the JPIAMR AMR-RDT Working Group on Antimicrobial Resistance and Rapid Diagnostic Testing

Nature Reviews Microbiology **17**, 51–62(2019) | Cite this article

Many Thanks for Your Attention

"Without diagnostics, medicine is blind"

Alain Mérieux, President, Fondation Mérieux

Contact Details

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- Deputy Head of Infection Medicine
- Director University of Edinburgh Postgraduate programmes Zhejiang University – University of Edinburgh Institute
- Director Clinical Microbiology and Infectious Diseases Programme University of Edinburgh
- AMR Strategy Lead Edinburgh Infectious Diseases
- Vice Chair of JPIAMR Scientific Advisory Board
- Longitude Prize Advisory Panel Member

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