Antimicrobial use and resistance in livestock production in a One Health context

Edinburgh AMR Forum

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Till Bachman (Centre for Inflammation Research) – Introduction to AMR Ecosystem in Edinburgh and DOSA project

Shailesh Shrestha (SRUC) – Economic assessment of alternative anti-microbial use options on livestock farms

Deborah Hoyle (Roslin Institute) – Impact of the ZnO ban on post-weaning diarrhoea and AMR on commercial pig farms in the UK

Nuno Silva (Moredun Research Institute) – Livestock: Understanding the Antimicrobial Resistance and Use of Novel Antimicrobial Alternatives

Edinburgh AMR Forum and DOSA project

From Multiple Disciplines to Transdisciplinary Ecosystems for AMR

Till T. Bachmann
Infection Medicine, Edinburgh Medical School: Biomedical Sciences, University of Edinburgh
Center for Inflammation Research, Institute for Regeneration and Repair

THE UNIVERSITY of EDINBURGH Global Academy of Agriculture and Food Systems

Scottish Government Riaghaltas na h-Alba gov.scot

OECD Co-operative Research Programme

Antimicrobial use and resistance in livestock production in a One Health context
Edinburgh, 22 - 24 April 2023

Edinburgh AMR Forum

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Introduction & Contact Details

Till T. Bachmann, PhD FRSB

- Professor of Molecular Diagnostics and Infection
- AMR Strategy Lead Edinburgh Infectious Diseases
- Deputy Head of Infection Medicine
- Co-Director of Fleming Fund Fellowships Host Institution programme University of Edinburgh

- Chair of JPIAMR Scientific Advisory Board
- Longitude Prize Judge/Advisory Panel Member
- Member of the Expert Group for the WHO Global AMR Research Agenda
- Member of the Expert Group for the Quadripartite One Health Priority Research Agenda on AMR

- Infection Medicine, University of Edinburgh
  Medical School: Biomedical Sciences, University of Edinburgh
- Centre for Inflammation Research, Institute for Regeneration and Repair, University of Edinburgh
- Zhejiang University - University of Edinburgh Institute, China

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LinkedIn: linkedin.com/in/tillbachmann

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Global One Health AMR Initiatives

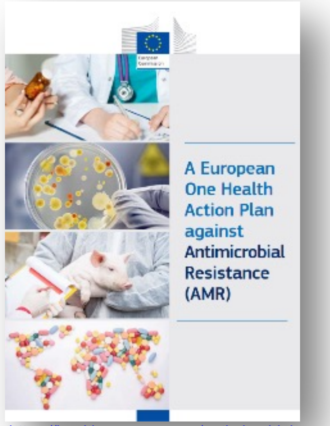
https://www.who.int/publications/i/item/9789240045408

GLOBAL LEADERS GROUP ON ANTIMICROBIAL RESISTANCE

Report of the Sixth Meeting of the Global Leaders Group on Antimicrobial Resistance

February 7 and 8, 2023

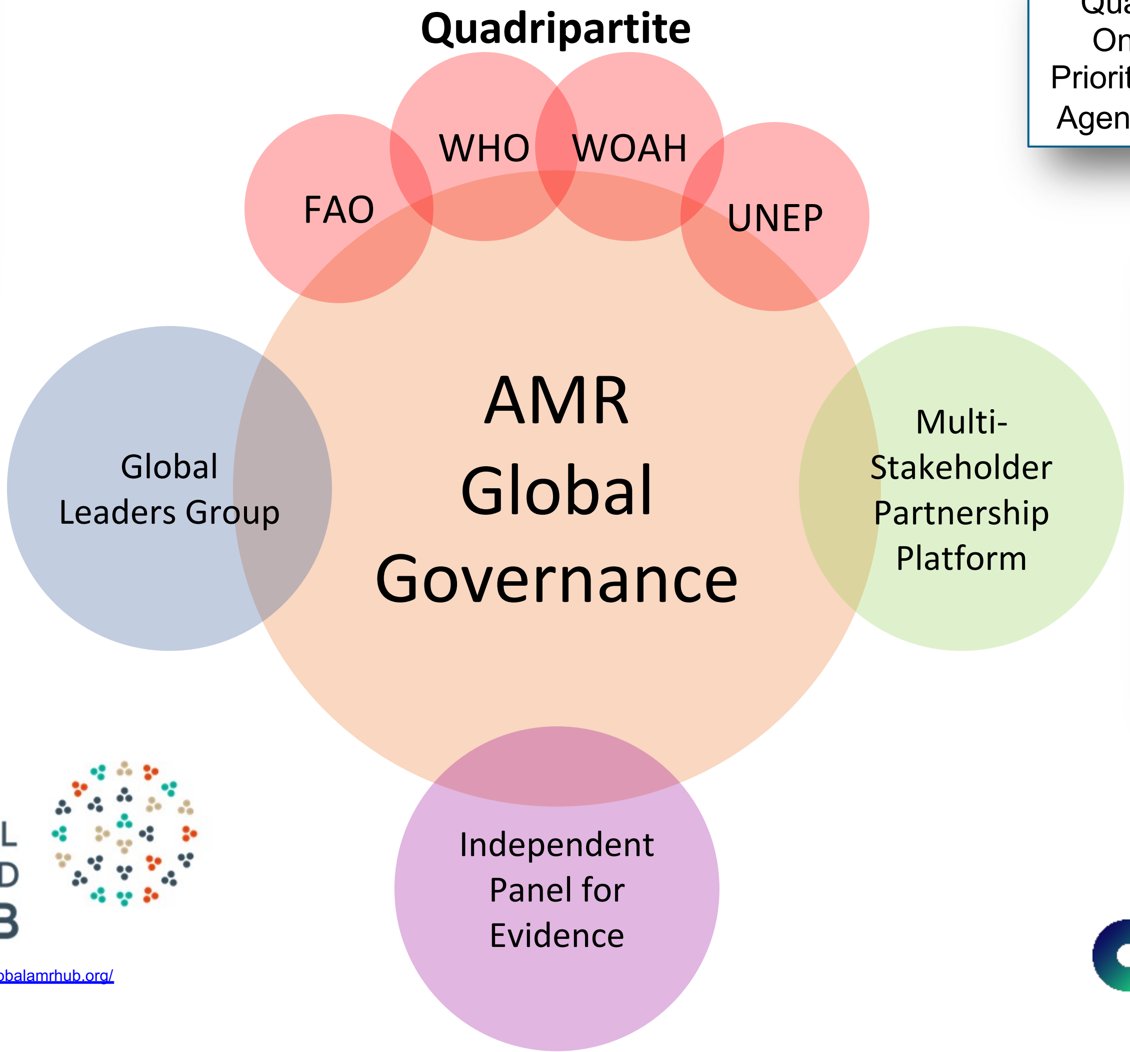
https://www.amrleaders.org/



https://health.ec.europa.eu/antimicrobial-resistance/eu-action-antimicrobial-resistance_en

GLOBAL AMR R&D HUB

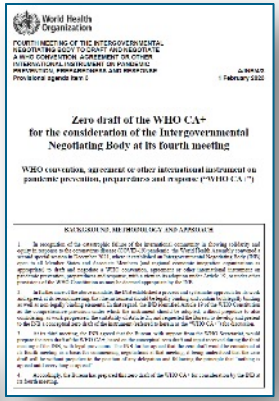
https://globalamrhub.org/



https://www.who.int/publications/m/item/public-discussion-draft-terms-of-reference-independent-panel-on-evidence-amr

Quadripartite One Health Priority Research Agenda on AMR

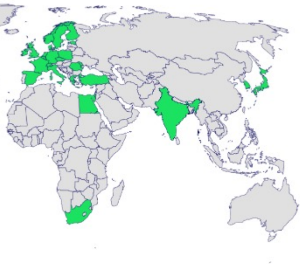
soon



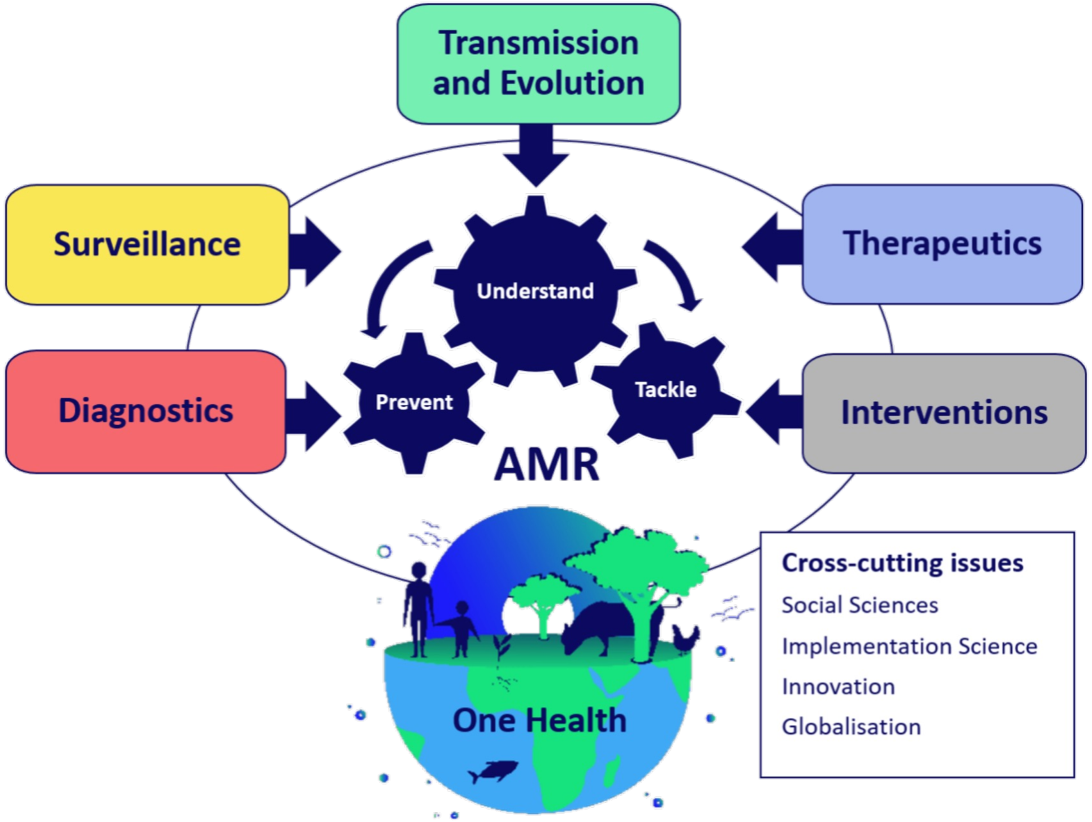
https://apps.who.int/gb/inb/e/e_inb-4.html

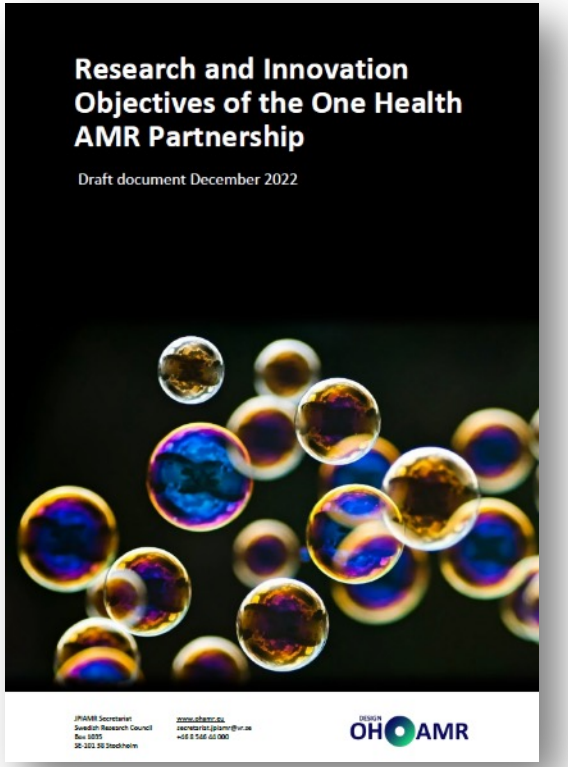
https://www.fao.org/antimicrobial-resistance/quadripartite/the-platform/en/

jpiamr



OH AMR Partnership 2025-2032




Research and Innovation Objectives of the One Health AMR Partnership

Draft document December 2022

OH AMR

2022-2023

Intervention logic: objectives, actions, impact
Research and Innovation Objectives; Roadmap of Joint Actions
Portfolio of Funding Instruments
Synergies with other Partnerships and AMR initiatives

2024

The Strategic Research and Innovation Agenda
The workplan 2025/26

2025

Launch of the OH AMR partnership and first call

www.jpiamr.eu/one-health-amr
www.ohamr.eu

DESIGN OH AMR

Edinburgh Antimicrobial Resistance Forum

Led by Edinburgh Infectious Diseases AMR Strategy Lead, Professor Till Bachmann

Network of over 200 researchers from all career stages focusing on AMR in Edinburgh

- Developing collaborative interactions
- Communicating with internal and external audiences
- Increasing industry awareness of Edinburgh's strengths in AMR research, and supporting researcher engagement with external partners

Edinburgh AMR Forum

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EDINBURGH INNOVATIONS

Summary of Activities 2021/2022

- **Core Team**: Till Bachmann, Hilary Snaith, Marissa Millar
- Set-up of AMR Forum **Working Group**, TOR, AMR strategy, regular meetings
- Set-up of AMR Forum Fortnightly **Seminar Series** (Zoom, stable audience ~30), from Oct 2022 co-sharing of some events with Microbiology Forum
- **World Antimicrobial Awareness Week** (WAAW) 2021 AMR Forum Twitter Campaign, WAAW 2022 AMR Forum Showcase event
- AMR Forum **Poster Day** 20 April 2022
- Set-up of AMR Forum **Communications Group** (Katie Atkins chair, initial discussions)
- **BBSRC Impact Accelerator Award Project** to enhance industry relations → IP Pragmatics Report → 'translational slide deck' to EI → e.g. BIO-EUROPE SPRING March 2022
- Very strong **funding and policy stakeholder** links (e.g. JPIAMR, Wellcome, UKRI, LifeArc, Gifford Baillie, Quadripartite (WHO, WOAH, FAO, UNEP), Global AMR R&D Hub), involvement with **AMR and One Health** strategy updates of global stakeholders

Edinburgh
AMR Forum

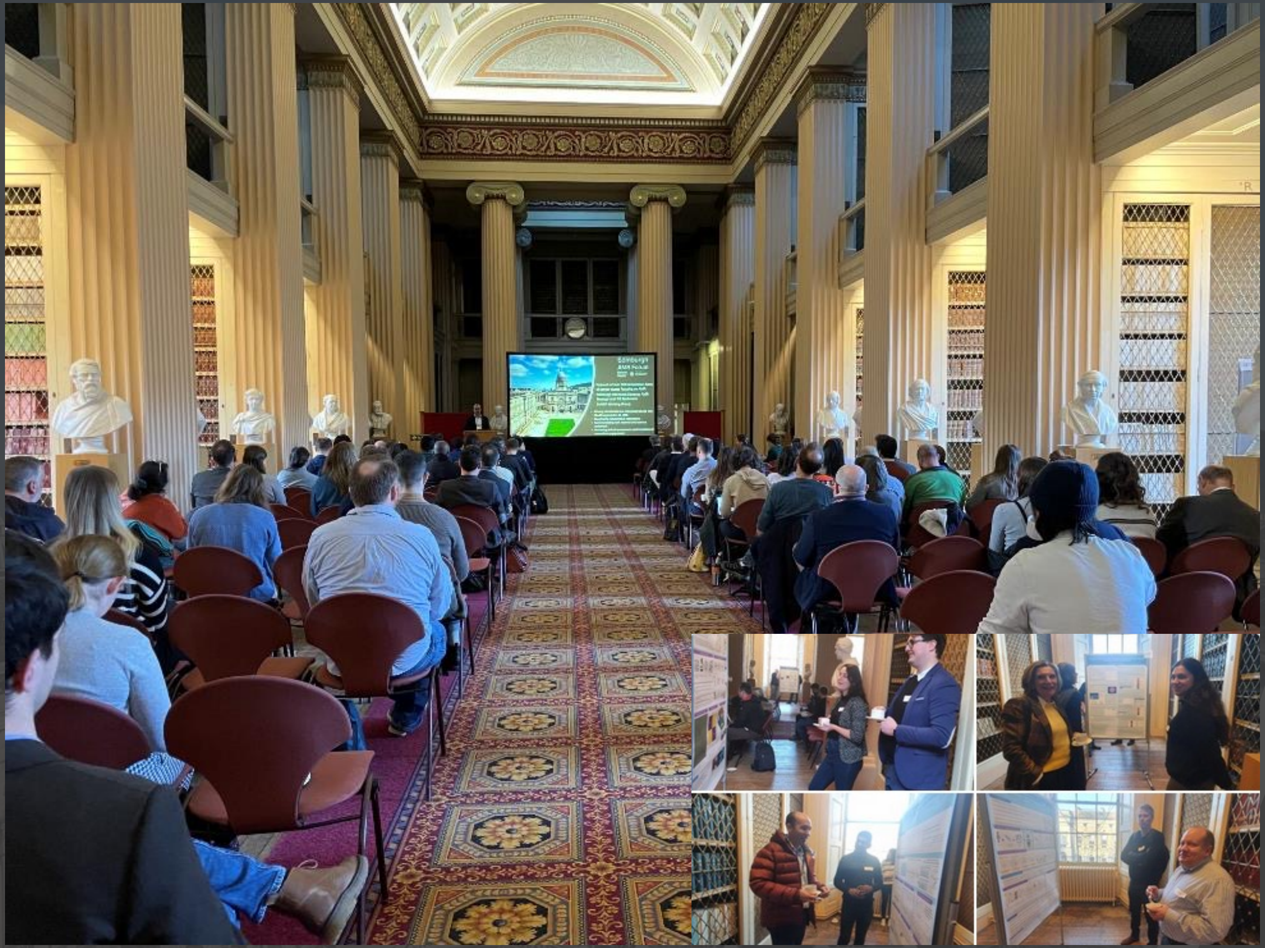
Analysis of market opportunities for industry-academia partnering in antimicrobial resistance in diagnostics

Publication numbers in particular areas of AMR research, for each selected University

Institution	Organisms		Infection type		Innate immunity/host response expertise	Evolutionary biology expertise of pathogens	Molecular/genomic expertise of pathogens	Average across fields	Total number of staff[41]	Average papers per staff[42]
	Gram +ve	Gram-ve	Nosocomial	Community-acquired						
Edinburgh	1998	2102	26095	7960	501	722	19049	8347	10865	0.76822
Cambridge	1606	1679	26211	5972	222	406	21157	8179	13720	0.596137
Sheffield	958	980	14469	4682	114	261	10453	4560	8774	0.519669
Glasgow	804	865	11762	3769	240	215	9131	3827	7870	0.486223
Imperial	1789	1817	18961	4757	277	305	14695	6086	12993	0.468395
Dundee	399	422	4182	1376	103	71	3853	1487	3362	0.442169
UCL	1645	1440	23216	7265	148	351	17766	7404	17324	0.427409
Warwick	691	725	9714	3244	95	123	7085	3097	7492	0.413336
Leeds	857	812	13106	4130	84	104	9860	4136	10487	0.394407
Oxford	1359	1481	17326	5001	189	452	13556	5623	14517	0.387369
Birmingham	1044	1043	12200	3814	169	108	9207	3941	10287	0.383077
Liverpool	857	952	9207	2876	100	206	6813	3002	8011	0.374681
Southampton	494	537	9328	2734	36	69	6430	2804	7915	0.354264
MIT	1219	1263	18532	3331	113	138	13504	5443	17065	0.318949
Institut Pasteur	548	520	1970	560	121	140	2417	897	3075	0.291568
Newcastle	517	553	6010	584	68	70	4664	1781	7956	0.223838
Manchester	561	560	9480	2613	63	70	7472	2974	13381	0.222266
U.California	4538	4669	75134	12495	506	973	837	14165	135742	0.104349

Institution	General AMR diagnostics research	Rapid testing	Automated systems, software & data analytics	Surveillance & epidemiology	Average across fields	Total number of staff[43]	Average papers per staff[44]
Edinburgh	**28384**	**3903**	**24912**	**13394**	**17648**	**10865**	**1.624321**
Cambridge	31471	4097	25434	12032	18259	13720	1.330794
Sheffield	17466	2099	15079	7193	10459	8774	1.192073
Glasgow	14099	1597	11714	6237	8412	7870	1.068837
Imperial	23413	2592	18674	8631	13328	12993	1.025745
UCL	27498	3318	23150	12974	16735	17324	0.966001
Warwick	11973	1561	10563	4752	7212	7492	0.96266
Dundee	5318	541	4318	2411	3147	3362	0.93605
Leeds	15531	2177	13441	6114	9316	10487	0.888314
Birmingham	14780	1755	12331	6404	8818	10287	0.85715
Oxford	21657	2479	16613	8976	12431	14517	0.856324
Southampton	11715	1276	9569	4020	6645	7915	0.839545
Liverpool	11250	1120	9151	4742	6566	8011	0.819592
MIT	23492	2943	18803	5625	12716	17065	0.745136
Newcastle	7414	841	5868	3292	4354	7956	0.547229
Manchester	12425	1223	9268	4375	6823	13381	0.509883
Institut Pasteur	2500	300	1818	1325	1486	3075	0.483171
U.California	99871	9141	63465	27886	50091	135742	0.369014

- UoE has the **highest number of papers** per staff (on average) in both general aspects of **AMR** and **AMR diagnostics**.
- UoE **ranks at the top** on most research areas, both in fundamental AMR research and in AMR diagnostics, showing a remarkable depth and width of expertise in AMR.
- The focus should be on further **profile building**, internal and external **messaging**, and on making potential **collaborators aware** of Edinburgh's expertise.



>130 Participants

students, researchers, funders, policy, industry, general public

"Very well organised, really enjoyed it
very, insightful, informative day with expert speakers
really enjoyed the academic and routes to translation sessions
great to hear from a broad range of people and different points of view"

Edinburgh
AMR Forum

Edinburgh
Infectious
Diseases

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21 November 2022

Playfair Library Old College

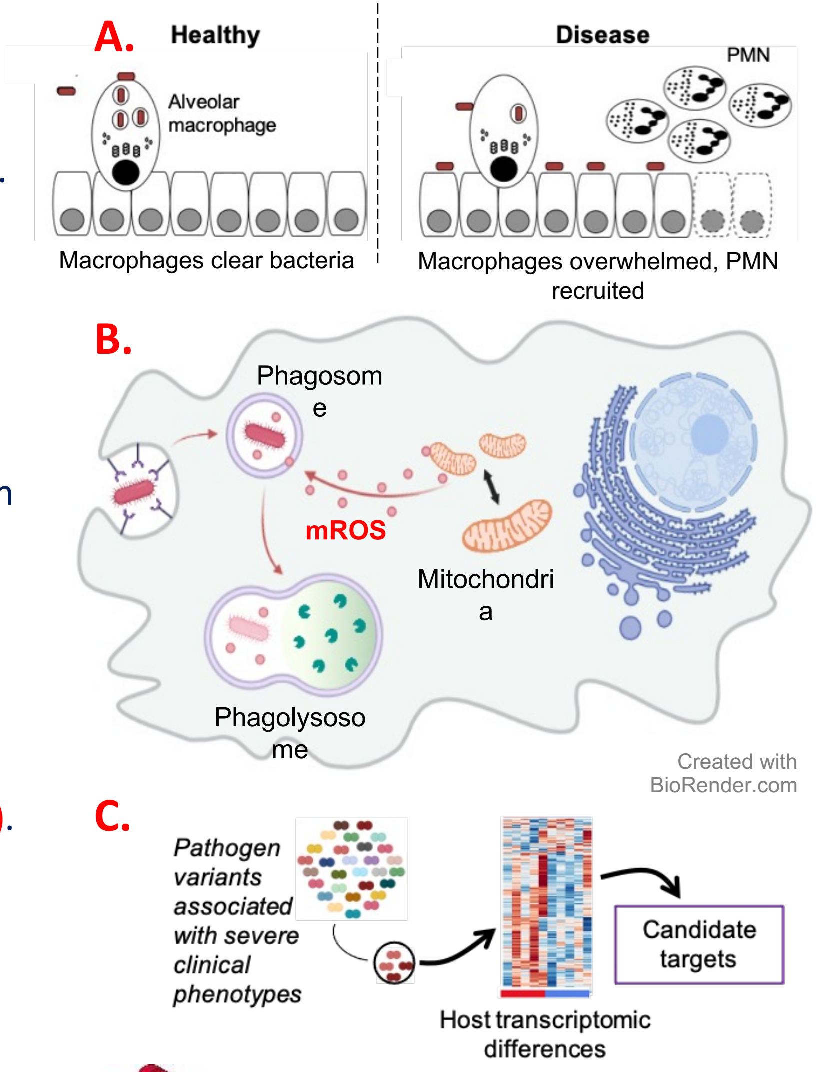
University of Edinburgh

Edinburgh AMR Forum Showcase

Innate immune microbicidal mechanisms against pathogens

PI: Prof. David Dockrell / SHIELD consortium

- **Background**:
  - Optimising innate immune responses provides a basis for host-directed therapies to combat AMR.
  - Recalibrating ineffective immune responses in disease **(A)** represents a therapeutic strategy.
- **Research synopsis**:
  - Host responses against bacteria or viral/bacterial co-infection identify key features of a successful innate immune response.
  - Rate-limiting microbicidal responses were identified in macrophages and other phagocytes.
  - *In vitro* and informatics screens identified candidate host targets - we assess these *in vivo*, through studies with susceptible patient groups, and therapeutically.
- **Key findings**:
  - Pathogens and disease states limit canonical phagolysosomal responses - mitochondrial adaption is a key strategy to enhance pathogen clearance **(B)**.
  - Apoptosis associated killing is a default mechanism to prevent intracellular pathogen survival.
  - Comparisons of immune-adaptive pathogen variants identifies novel microbicidal mechanisms **(C)**.
- **Opportunities for industrial collaboration**:
  - SHIELD consortium investigating re-purposing of drugs for validated targets.
  - Hits from host-directed screens identifying novel therapeutic targets.



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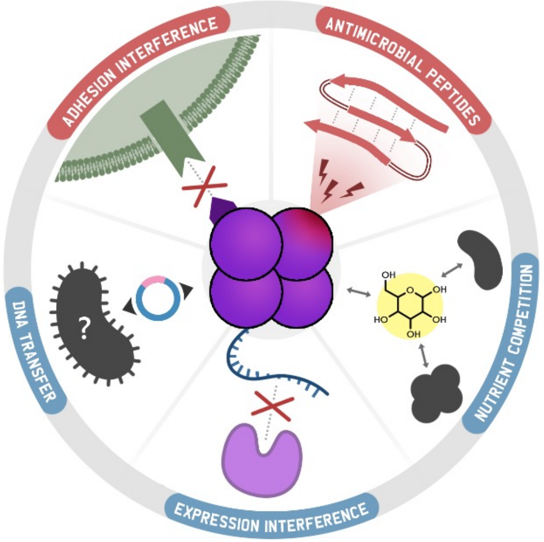
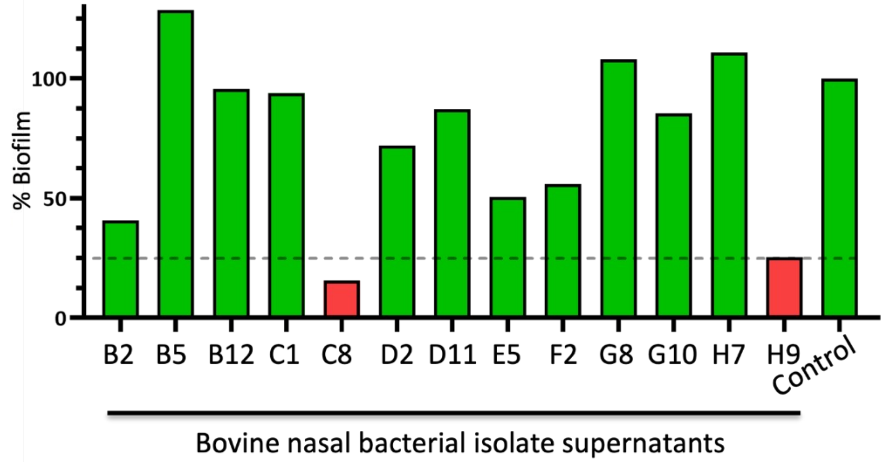
EDINBURGH INNOVATIONS

Identification of novel anti-microbials, therapeutic targets, clinical metagenomic diagnostics



PI/ Group Name: Prof Ross Fitzgerald, Laboratory for Bacterial Evolution and Pathogenesis

- Background: Director of Edinburgh Infectious Diseases & Professor of Molecular Bacteriology
- Research synopsis: Evolution of host-adaption, pathogenicity and AMR in bacterial pathogens including *Staphylococcus aureus* and *Legionella pneumophila*
- Key findings: Metagenomics of clinical samples can be used to rapidly identify pathogens and antibiotic sensitivity; Microbiome analysis has revealed novel anti-bacterial and anti-biofilm agents; Comparative genomics has revealed mechanisms of niche adaptation representing novel therapeutic targets; Comparative genomics and reverse vaccinology can be used to identify vaccine candidates;
- Opportunities for industrial collaboration: Identification of novel anti-microbials, vaccines and rapid sequence-based diagnostics



a) Different targets for anti-bacterial and anti-biofilm agents
b) Identification of novel anti-Staphylococcus aureus biofil
agents produced by bacteria in the bovine nasopharynx

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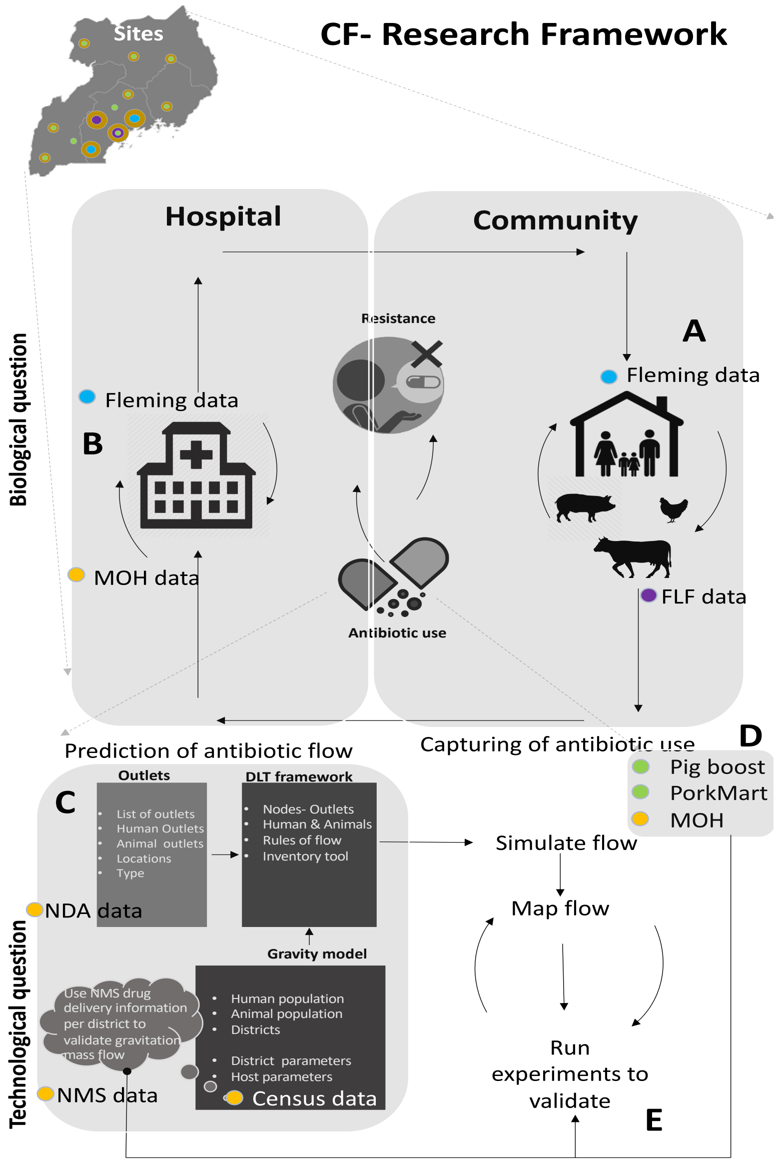
EDINBURGH INNOVATIONS

Digital one-health

PI: Adrian Muwonge, Roslin Institute

- **Background**: I am a Chancellor's Fellow based at Roslin Institute, focusing on health digital. I work in collaboration with the EERA-group, Blockchain Technology Laboratory and Edinburgh Infectious Diseases
- **Research synopsis**: My research aims to develop and apply a methodology that estimates community-generated antibiotic resistance and the antibiotic usage that drives it. This supports data-driven policy decision-making on antibiotic usage and predicts the impact of livestock-targeted interventions on human health.
- To develop such methodologies, especially in developing countries with agricultural-based economies, we must define the AMR occupational risk, i.e. how resistance is generated and spread within farming communities. Our work goes a step further to ask how we can exploit technology to estimate antibiotic resistance and usage in farming systems sustainably.
- **Key findings**: Work in progress
- **Opportunities for industrial collaboration**: I am keen on industrial collaborations



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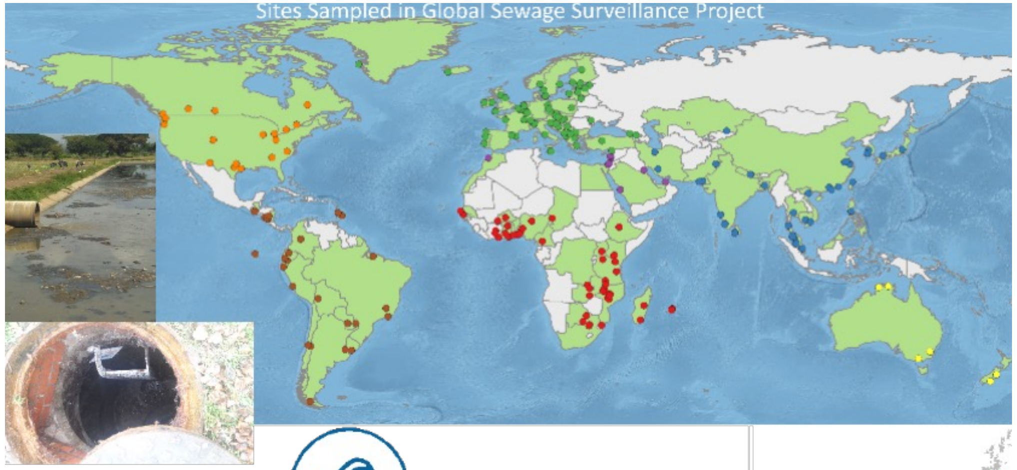
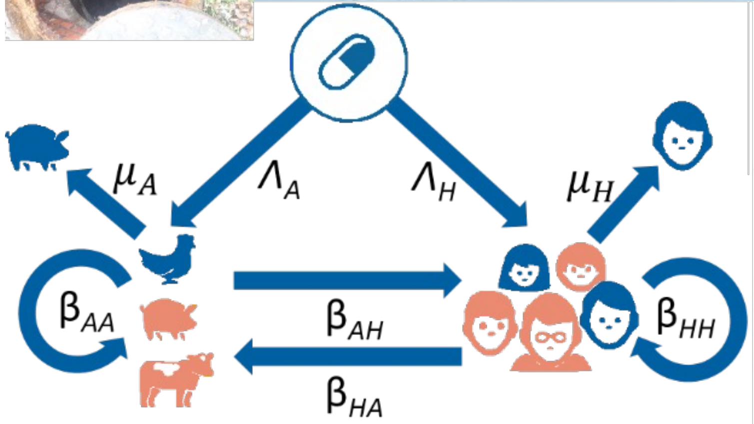
EDINBURGH INNOVATIONS

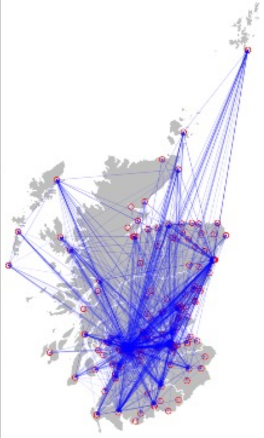
Epidemiology of Antimicrobial Resistance

Epidemiology Research Group (Prof Mark Woolhouse, Dr. Bram van Bunnik, Dr. Bryan Wee)

- **Background**: Infectious disease epidemiology, antimicrobial resistance (AMR), zoonoses, metagenomics, whole genome sequencing.
- **Research synopsis**: We use a variety of quantitative and data-intensive methods to understand the dynamics of AMR at the human and animal interface.
- **Key findings**:
    - AMR gene abundance strongly correlates with socio-economic, health and environmental factors – improving sanitation and health could potentially limit the global burden of AMR.
    - The detection of bacterial and AMR transmission requires a structured sampling framework coupled with high resolution genotyping.
    - Mathematical modelling can be used to understand the impact of One Health interventions on human health.
- **Opportunities for industrial collaboration**:
    - Analysis of AMR surveillance data (metagenomic, resistant isolates).
    - Epidemiological analysis of resistant infections / outbreaks.







Development and evaluation of a complex ePrescribing-based Antimicrobial Stewardship (ePAMS+) intervention for hospitals

PI/ Group Name: Professor Aziz Sheikh, Usher Institute

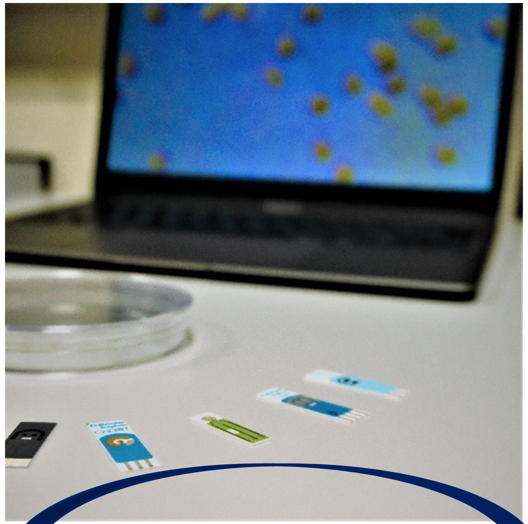
- **Background**: Despite national guidance, antibiotic prescribing rates are still increasing in hospitals. The reasons are multifactorial, including limited real-time access to information that may influence decisions to initiate antibiotics, concerns about missing potentially serious infection (e.g. sepsis), and lack of continuity of care, which limits the opportunity for an informed review of progress and results in a reluctance to delay initiation of and/or change/discontinue an antibiotic that has already been commenced. These challenges are compounded by the substantial time pressures that clinicians face.
- **Research synopsis**: A multidisciplinary collaboration to develop and evaluate a multifaceted intervention (ePAMS+) that incorporates technical, behavioural and organisational components to safely reduce inappropriate antibiotic use in adult medical in-patients.
- **Key findings**: 1) Attention to socio-organisational contexts and workflows is crucial when designing technology-based antimicrobial stewardship interventions; 2) Interventions that help reduce prescriber/reviewer uncertainty and improve multidisciplinary collaboration surrounding antimicrobial prescribing and review are most likely to be effective; 3) Larger well-designed randomised studies are needed to investigate the impact of interventions on AMS; 4) There is a need for outcome measures to be standardised and for more quantity measures to be included by researchers to measure the number or cost of antibiotics being used; and 5) We have developed an ePAMS+ intervention and are preparing to run a feasibility trial.

Contact: Rona.Sharp@ed.ac.uk (ePAMS+ Research Manager)

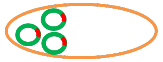
Rapid Diagnostics

PI/Group Name: Prof. Till Bachmann/Infection Medicine

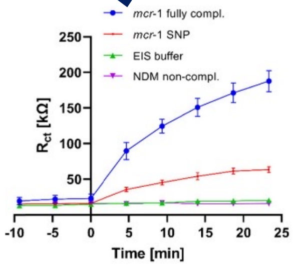
- Diagnostics are priority tools against AMR. By detecting pathogens, antibiotic resistance, antibiotic susceptibility and/or host response to infection, diagnostics enable appropriate therapy decisions, patient management, narrow spectrum drug development and surveillance.
- We study user needs for diagnostics, develop target product profiles, and do research on rapid, low complexity, cost effective diagnostics which can be used at the point of need in a One Health and Global Health context using e.g. electrochemical biosensors, artificial intelligence, microfluidics, wearable sensors and paper diagnostics. Key disease areas are urinary tract infections, sepsis, liver health.
- Key findings: Point-of-Care-Test platform for PCR free and label free detection of pathogens (e.g. *E.coli*, *P. aeruginosa*), AMR (e.g. MRSA, NDM, *mcr-1*), microRNAs, biomarkers (e.g. TREM-1, MMP9), exosomes.
- Opportunities for industrial collaboration: Target Product Profile development. Assay development for new targets/diseases. Feasibility/Design for manufacture studies. Performance analysis.
- Nat Rev Microbiol 2019, Anal Chem 2021, JAC Antimicrob Resist 2021



Electrodes for Portable AMR Tests



Bacterial pathogens with resistance gene containing plasmid



Rapid & selective detection of resistance genes without PCR amplification

Fleming Fund Fellowship scheme

Fleming Fund is £265 million UK government investment into improving laboratory capacity for diagnosis and surveillance of AMR in low and middle income countries

Edinburgh Host Institution Phase I (2019 - 21)
Ross Fitzgerald, Adrian Muwonge

- Total grant income to UoE £1.4 M
- Major support through Edinburgh Infectious Diseases
- 19 Fellowships in Uganda (2 cohorts), Malawi, Kenya
- Bespoke training and Collaborative research project

Renewal for phase II (2023 - 2025)
Till Bachmann, Adrian Muwonge, Stella Mazeri

- ~ 45 Fellowships (Uganda, Malawi, Kenya)
- Potential for mentorship networks
- Potential for linkages with other host institutions

The Fleming Fund

Edinburgh Infectious Diseases

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UKRI Transdisciplinary funding to tackle antimicrobial resistance

Edinburgh AMR Forum

- **Phase one (£3 million):** transdisciplinary **networks** to connect and expand the UK AMR communities with researchers from a broad range of disciplines with the knowledge and skills to transform our understanding of AMR and deliver innovative and effective solutions by developing and applying a diverse range of methods.
- **Phase two (£7 million):** transdisciplinary **research grants** to facilitate evidence-based decision making through timely, high impact, and independent research on AMR that meets the needs of policymakers, practitioners, industry, civil and broader society.
- AHRC, BBSRC, ESRC, EPSRC, MRC, NERC

Phase one (£3 million) – Scope

Edinburgh AMR Forum

- Transdisciplinary networks to connect and expand the **UK AMR communities** with researchers from a broad range of disciplines (**across all UKRI council remits**).
- The networks will have the knowledge and skills to
  - transform our **understanding** of AMR and
  - deliver innovative and effective **solutions** by
  - applying and developing a diverse range of **methods**.
- We expect networks to work effectively across **all disciplines**.
- Networks must be **open** to new members throughout the lifetime of the networks (100s of members)
  - Academics, business, policymakers, public, private, third sectors, end users of research, such as farmers and clinicians, representatives of civil society and people with lived experience

Timeline

31 March 2023
Phase one: opening date for expressions of interest

26 April 2023
Phase one: closing date for expressions of interest and community meeting registration

17 May 2023
Phase one: community meeting in Birmingham (in-person only)

22 May 2023
Phase one: community meeting (virtual)

25 May 2023
Phase one: community meeting in Edinburgh (in-person only)

June 2023 (to be confirmed)
Phase one: opening date

July 2023 (to be confirmed)
Phase one: closing date

April 2024 (to be confirmed)
Phase two: predicted launch

Edinburgh
MR Forum

One Health AMR Transc

Human

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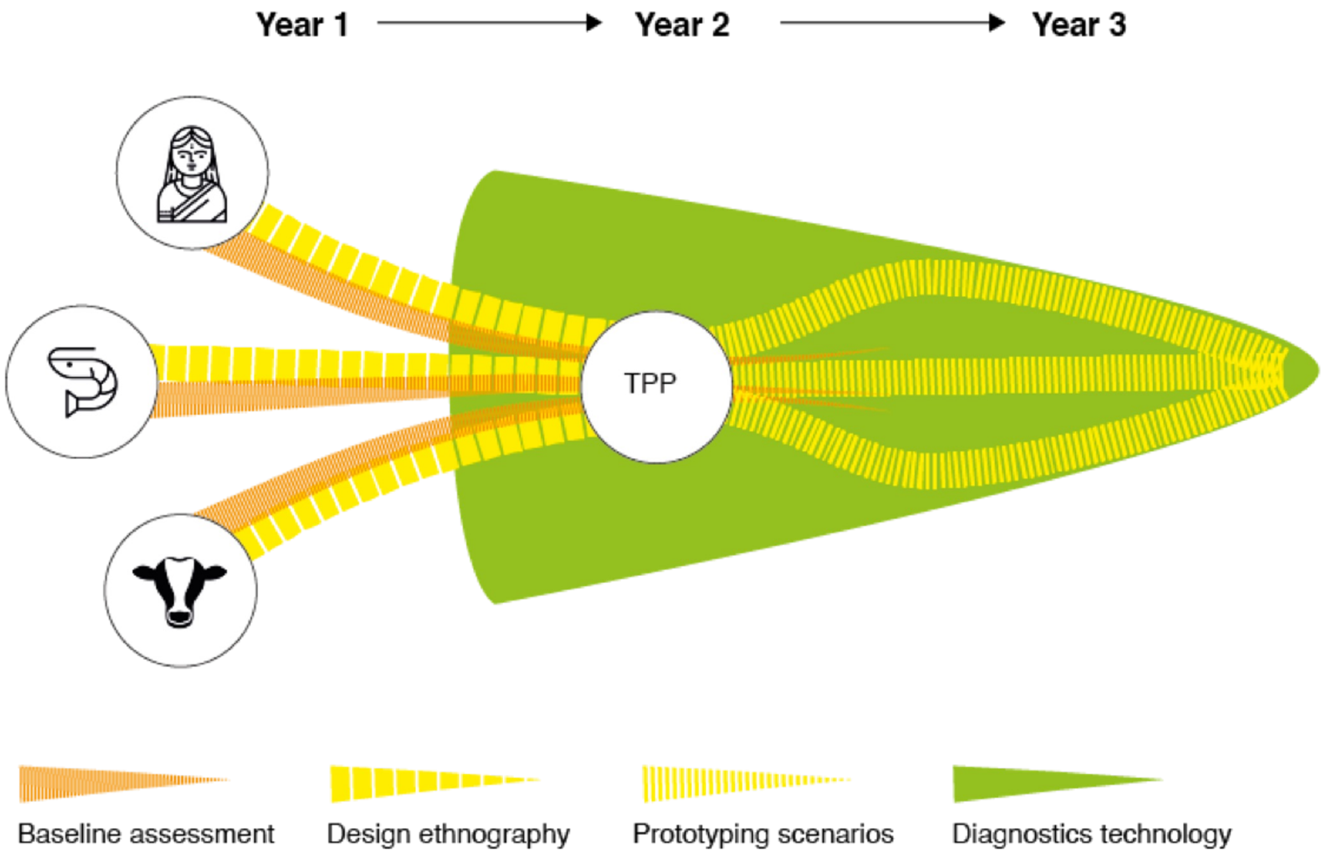
), one of
infectious
EAMRFs
spects of
MRF has
ng a wide multidisciplinary area of
lth, Global Health, diagnostics, host
eillance, genomics, epidemiology,
veterinary medicine, mathematical
, law). Edinburgh has long standing
. through DOSA, SHIELD, the MRF
d as Fleming Fund Host Institution,
osed network. It is increasingly clear
nnot be solved through one country,
e sector. Integrated One Health
g intersectorial and interdisciplinary
thinking.

Diagnostics for One Health and User Driven Solutions for AMR

2018 - 22, £3m+, UK-India, University of Edinburgh, IIT Delhi + 8 Partners

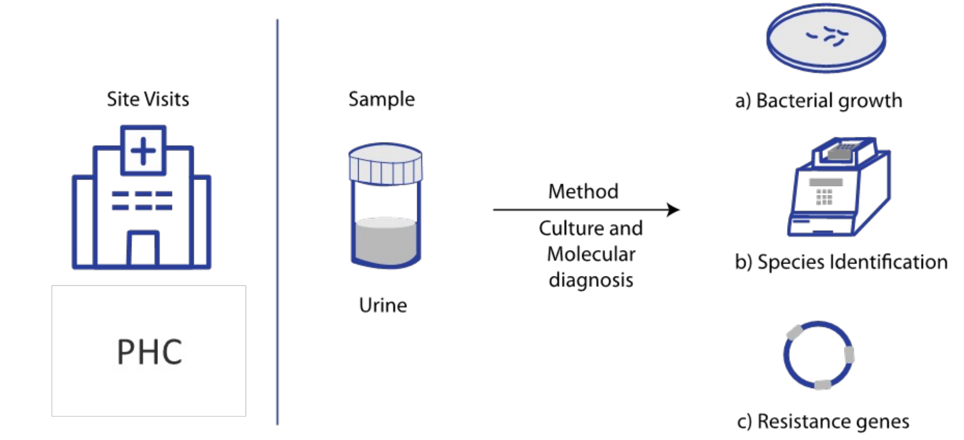
- **User mapping** studies in **Human**, **Dairy** and **Aquaculture** environment settings
- **AMR baseline** assessment in Human, Dairy and Aquaculture environment settings
- Develop rapid/POC **diagnostic** assays/ prototypes for UTI, Mastitis, AMR pathogens and antibiotic residues
- Refinement, performance benchmarking, validation and impact assessment of prototype(s) in **community settings**
- TPP - **Target Product Profile**

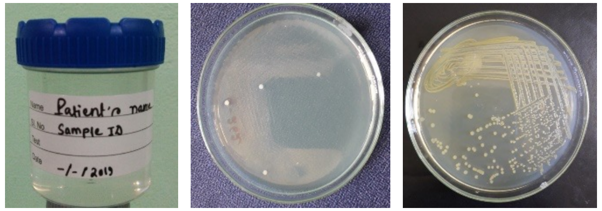


DOSA is funded by UK Research and Innovation / Economic Social Science Research Council, Newton Fund, and the Government of India's Department of Biotechnology

dosa-diagnostics.org

AMR Baseline Analysis for UTI in Community Care in Assam

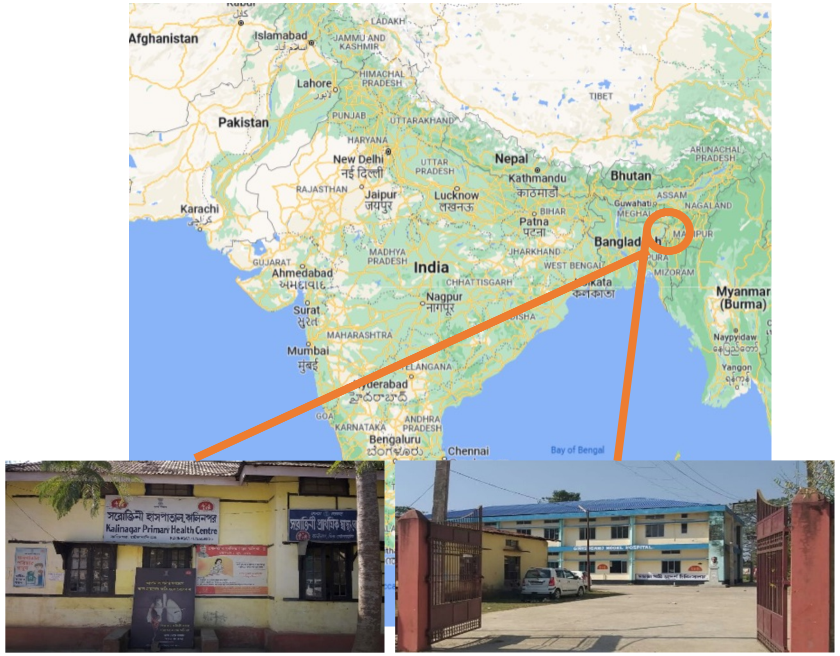




Pathogens & AMR Genes from Urine samples

E. coli, S. aureus, K. pneumoniae, K. oxytoca, S. saprophyticus

CTX-M, SHV-148, PER-1, TEM, CTX-M-15 +SHV-148, TEM +SHV-148, OXA-10, OXA-2, NDM-1, NDM-1+OXA-23, *mecA*



Antibiotic Susceptibilities

PHCs & Isolates ID	ST-types	ESBL, AmpC & Carbapenemase genes	Phylotype	Susceptibility pattern															Replicon type
				TGC	CST	SXT	IPM	ERT	MEM	NIT	CRO	CIP	AMC	TZP	FEP	AMK	GEN	NAL	
B (Ec-182)	ST3268	CTX-M-15 + CMY-42	B1																Inc P
B (Ec-146)	ST304	CTX-M-15	A																Inc P
B (Ec-10)	ST3268	SHV-148	B1																Inc F
A (Ec-144)	ST3430	PER-1	A																Inc P
B (Ec-189)	ST4671	CTX-M-15	A																Inc F
A (Ec-155)	ST361	PER-1	B1																Inc F
B (Ec-89)	ST4671	CTX-M-15	B1																Inc P
A (Ec-252)	Unknown	CTX-M-15 + DHA-1	B1																Inc P
B (Ec-3)	ST219	SHV-148 + CMY-42	A																Inc P
A (Ec-200)	Unknown	NDM-1	B1																Inc FrepB
A (Ec-237)	ST3430	CTX-M-15 + DHA-1	B1																Inc P
A (Ec-154)	ST304	TEM	A																Inc F
B (Ec-125)	ST3268	TEM + SHV-148	B1																Inc P
B (Ec-5)	Unknown	SHV-148	B1																Inc P
B (Ec-12)	ST3492	NDM-1 + CMY-42	A																IncFrepB
B (Ec-272)	ST10	CMY-42	B1																-
A (Ec-284)	ST361	-	A																-
A (Ec-167)	ST167	-	B1																-
B (Ec-56)	ST304	-	B2																-
A (Ec-76)	ST167	-	B1																-
A (Ec-106)	ST361	-	A																-
B (Ec-132)	Unknown	-	A																-
B (Ec-139)	ST4671	-	A																-
B (Ec-36)	ST167	-	B1																-
A (Ec-218)	Unknown	-	B1																-
A (Ec-244)	ST10	-	A																-
A (Ec-268)	ST167	-	B1																-

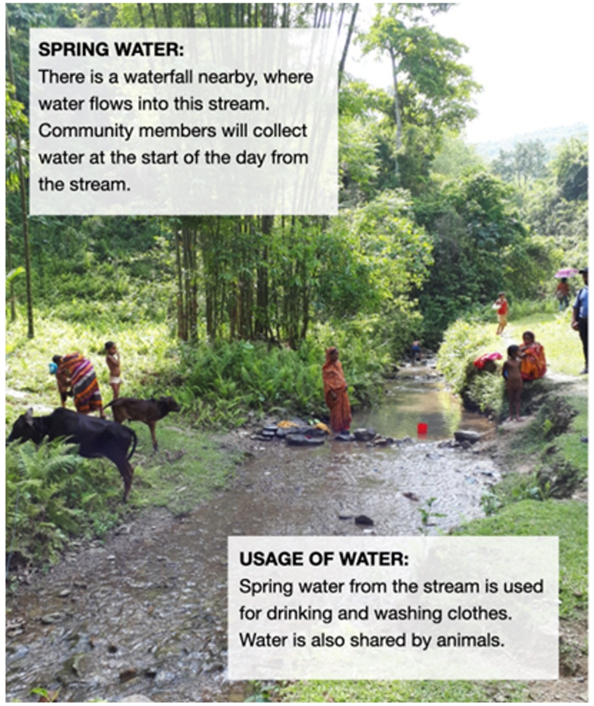
Environmental Sampling

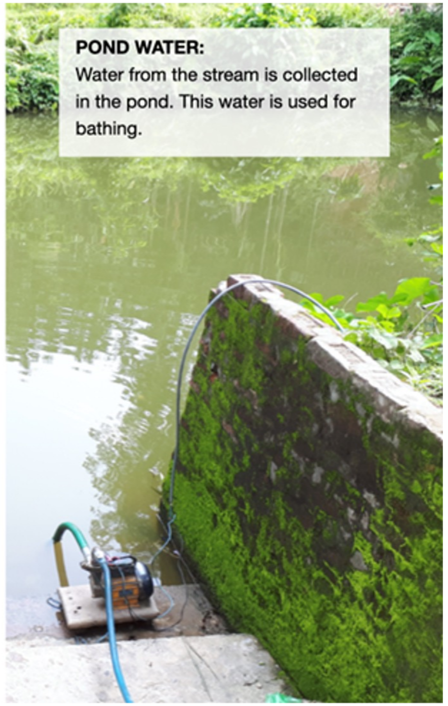
Paul D, Anto N, Bhardwaj M, Prendiville A, Elangovan R, Bachmann TT, Chanda DD, Bhattacharjee A. Antimicrobial resistance in patients with suspected urinary tract infections in primary care in Assam, India. JAC Antimicrob Resist. 2021 Dec 14;3(4):dlab164

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

Human Setting Field work in Assam

Date	Participant	Number	Data collection method
May 2019	ASHAs	57	Focus group
May 2019	Community members	92 (female) 2 (male)	Focus group
March, May, August 2019	Doctors	8	Semi-structured interviews
August 2019	PHC patients	96	Drug bag
February 2020	ASHAS/ Nurses	46	Co-design
April – May 2021	ASHAs	18	Walk through / co-design





Key observations:

- There is limited awareness on AMR
- Over the counter prescription was common
- Knowledge of antibiotics is limited
- Low awareness of Urinary Tract Infections (UTI)
- Not comfortable to seek medical care until must
- PHC are burdened with large number of patients
- Average number of patients per day >150
- No sufficient diagnostics facility at PHC

Paul D, Anto N, Bhardwaj M, Prendiville A, Elangovan R, Bachmann TT, Chanda DD, Bhattacharjee A. Antimicrobial resistance in patients with suspected urinary tract infections in primary care in Assam, India. JAC Antimicrob Resist. 2021 Dec 14;3(4):dlab164

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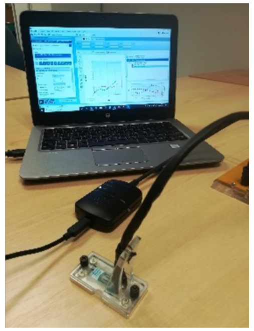
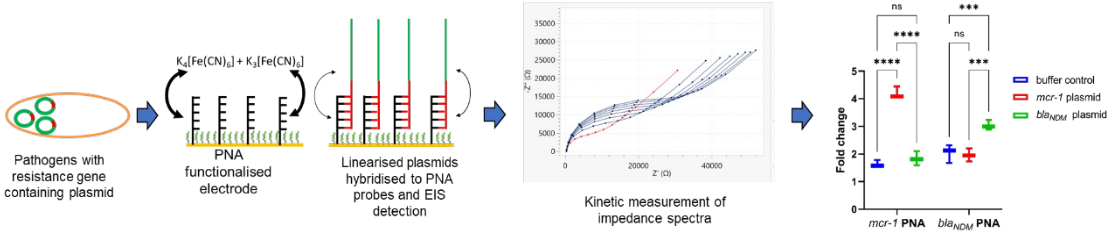
DOSA

Technology Portfolio available in DOSA

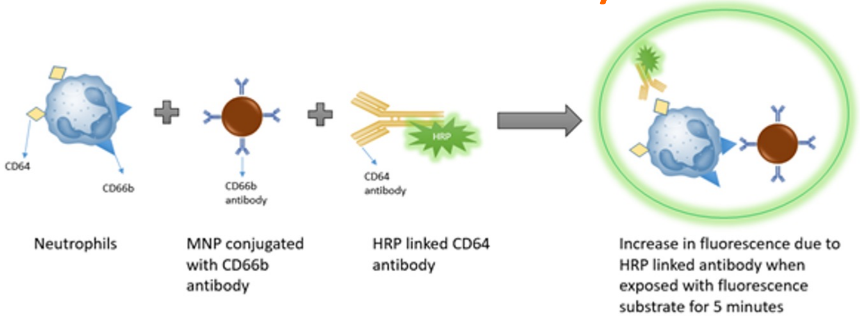
AMR gene Point of Care Test

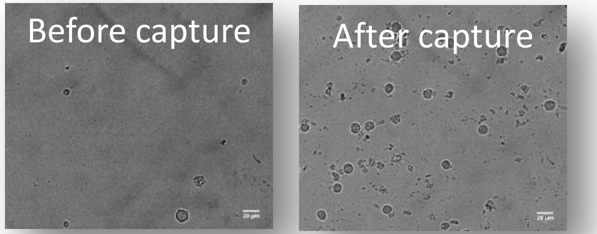
- Direct electrochemical detection of AMR genes from bacteria from urine. Current focus on carbapenem resistance
- No PCR needed
- Suitable for use at PHC level





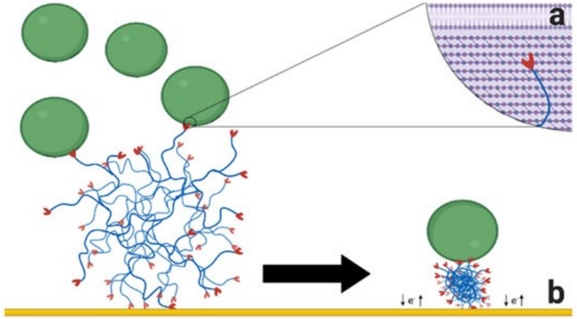
POC- nCD64 assay

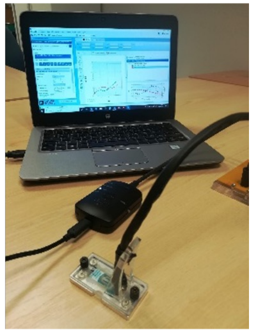




- CD64 expression in Neutrophils are strongly correlated with onset of infection
- Could be used identify bacterial infection at PHC level
- Simple proof of concept is done with Milk Neutrophils

Whole Bacteria Detection at Point of Care





Automation & Integration

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.
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.

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

User Requirements + Co-design + Target Product Profile

Co-Design with ASHAs at Primary Healthcare Centres in Assam

Real Life Walk Throughs in Assam

Workshops in Edinburgh

- **Testing in community**
- **Provide meaningful information**
- **Easy to understand, operate, and dispose**
- **Low cost**
- **Environmental stability**

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 UTI Diagnostic Solution

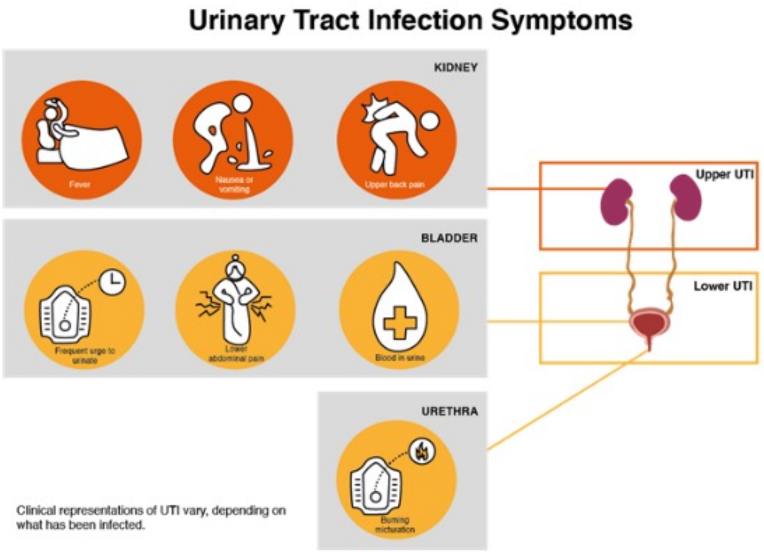
Guidance

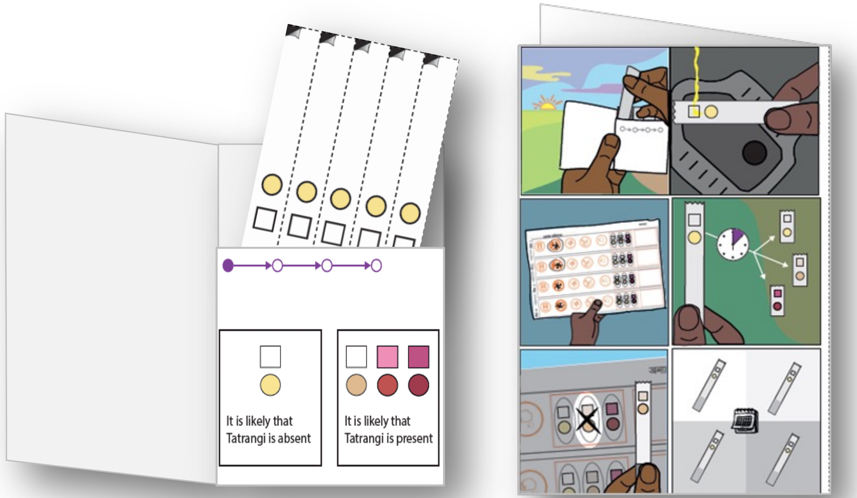
+

Diagnostic

+

Data capture





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dosa-diagnostics.org

DOSA

Why can't we just use commercial urine dip sticks??

Too many parameters to be easily understood by non trained person

Storage requirements too demanding

Too **expensive**

Not biodegradable

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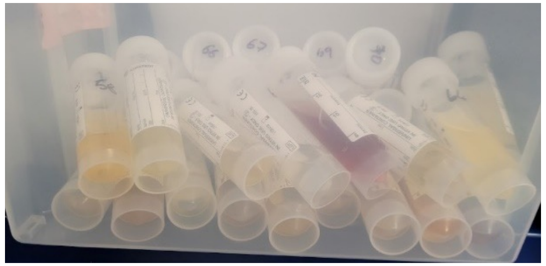
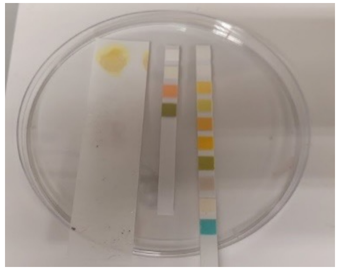
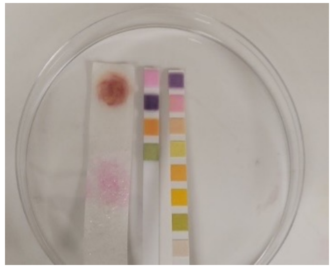
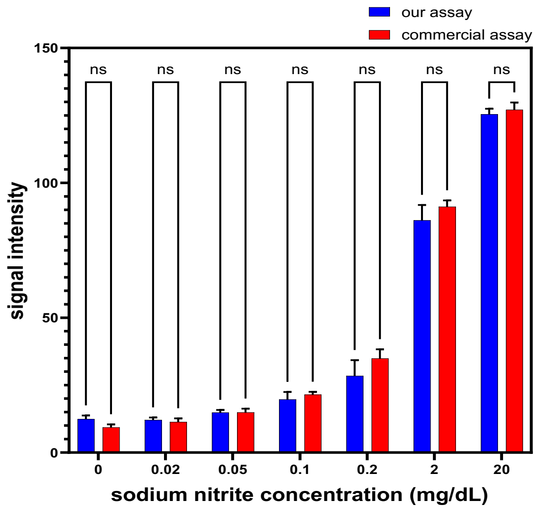
DOSA

DOSA UTI Test Strip Validation

- 100 Urine patient samples at **Edinburgh Medical School** tested with
    1. DOSA UTI paper strips
    2. Roche Combur Test UX strips
    3. SureScreen Urinanalysis reagent test strips
    4. Microbiological ID data (culture positive/negative; CFU/mL)





Signal quantification and comparison to commercial tests (SureScreen)

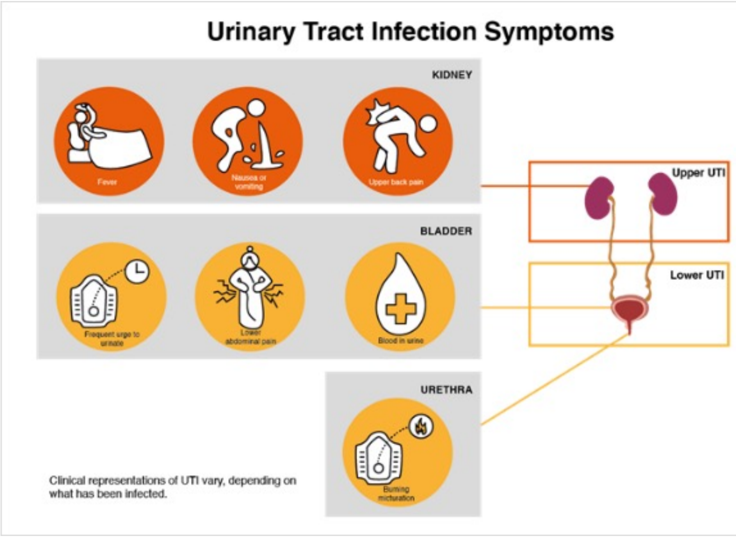
- 100 Urine patient samples tested at **Silchar Medical College** with
    1. DOSA UTI paper strips
    2. Roche Combur Test UX strips
    3. SureScreen Urinanalysis reagent test strips
    4. Siemens Multistix 10 SG Urine Test Strips
    5. Microbiological ID data (culture positive/negative; CFU/mL)

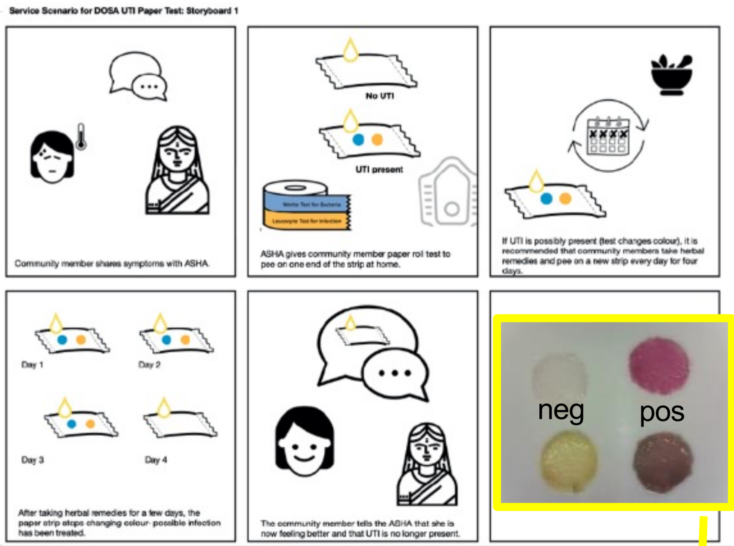

DOSA is funded by UK Research and Innovation / Economic Social Science Research Council, Newton Fund, and the Government of India's Department of Biotechnology

From Healthcare Need to Implementation of Diagnostics

Patients with Urinary Tract Infections in the community do rarely seek medical care.

Home Testing & Patient Education + Empowerment





Community Trials
Performance
Utility
Adoption
Impact

Regulatory

Reimbursement

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

Dairy Setting - System Mapping and Assessment of User Requirements

India is the largest producer of milk in the world with highest number of animals. (127 million tons 2018)

Antibiotics use is more prevalent in organised sector than individual cattle owners

- **Farmers are keen to adopt new technology**
- **Animal healthcare is mostly done on farm, unless condition is extreme**
- **Drive to quickly cure animal due to economical pressure**

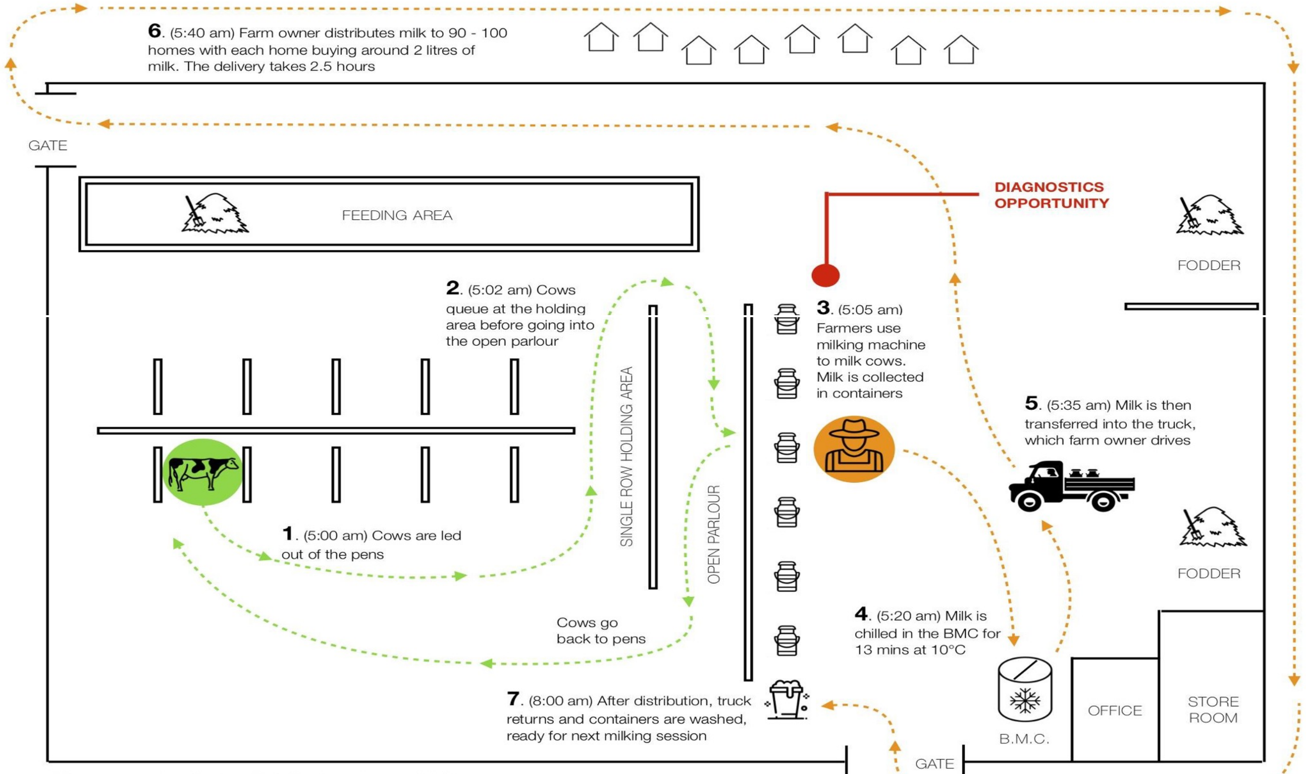
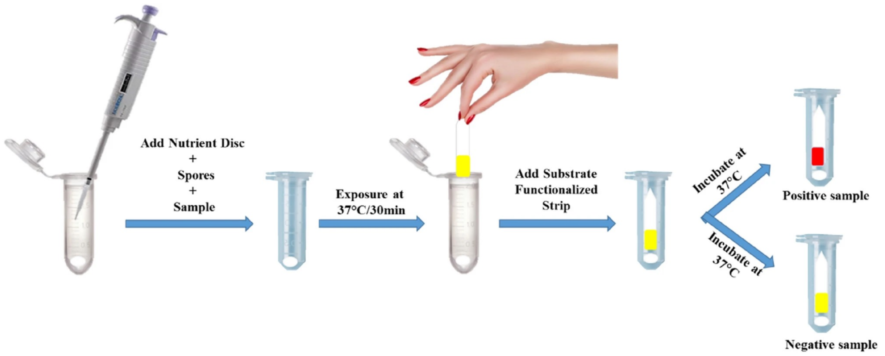


Diagram of private distributer farm of 50 cows



Goel P, Vishweswaraiah RH, Kumar N. Spore-based innovative paper-strip biosensor for the rapid detection of ß-lactam group in milk. Sci Rep. 2022 Dec 19;12(1):21965

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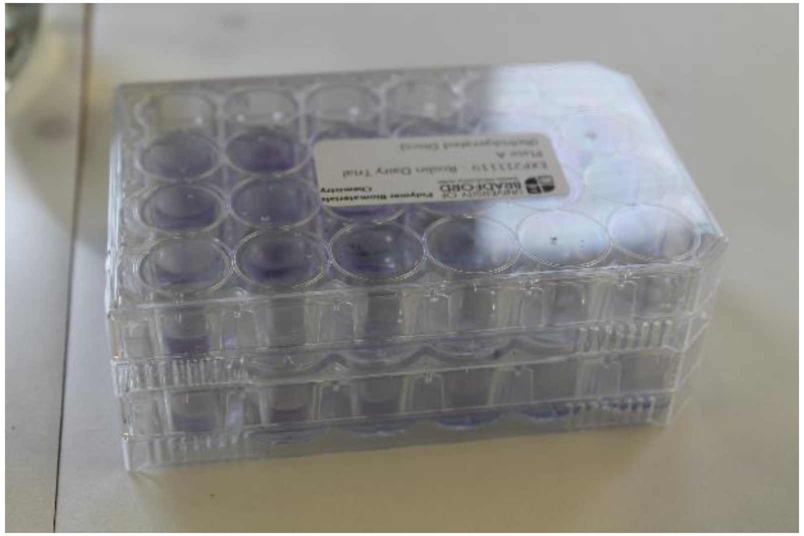
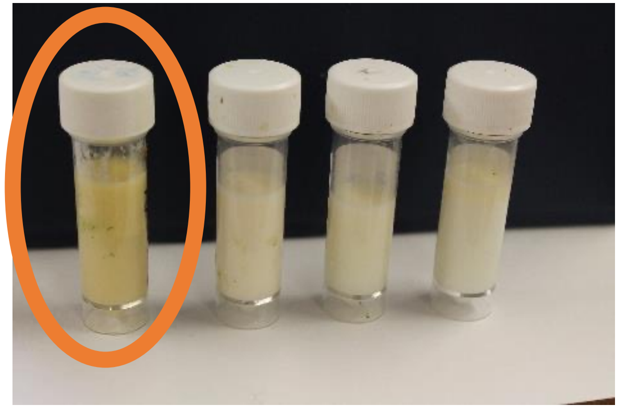
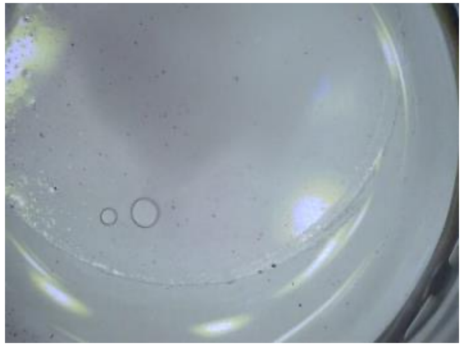
DOSA

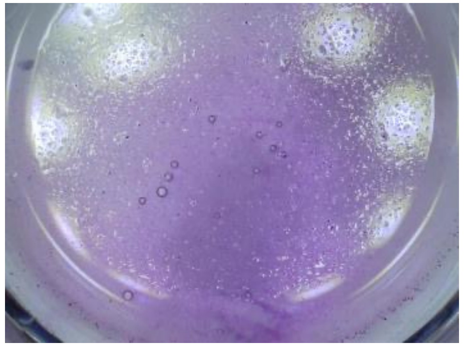
On-site Trial for Mastitis Detection

(Langhill Farm, University of Edinburgh)









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MAKING KNOWLEDGE WORK

Steve Rimmer, Edward Dyson

Many thanks to Prof Alastair Macrae, University of Edinburgh for providing access and benchmark testing

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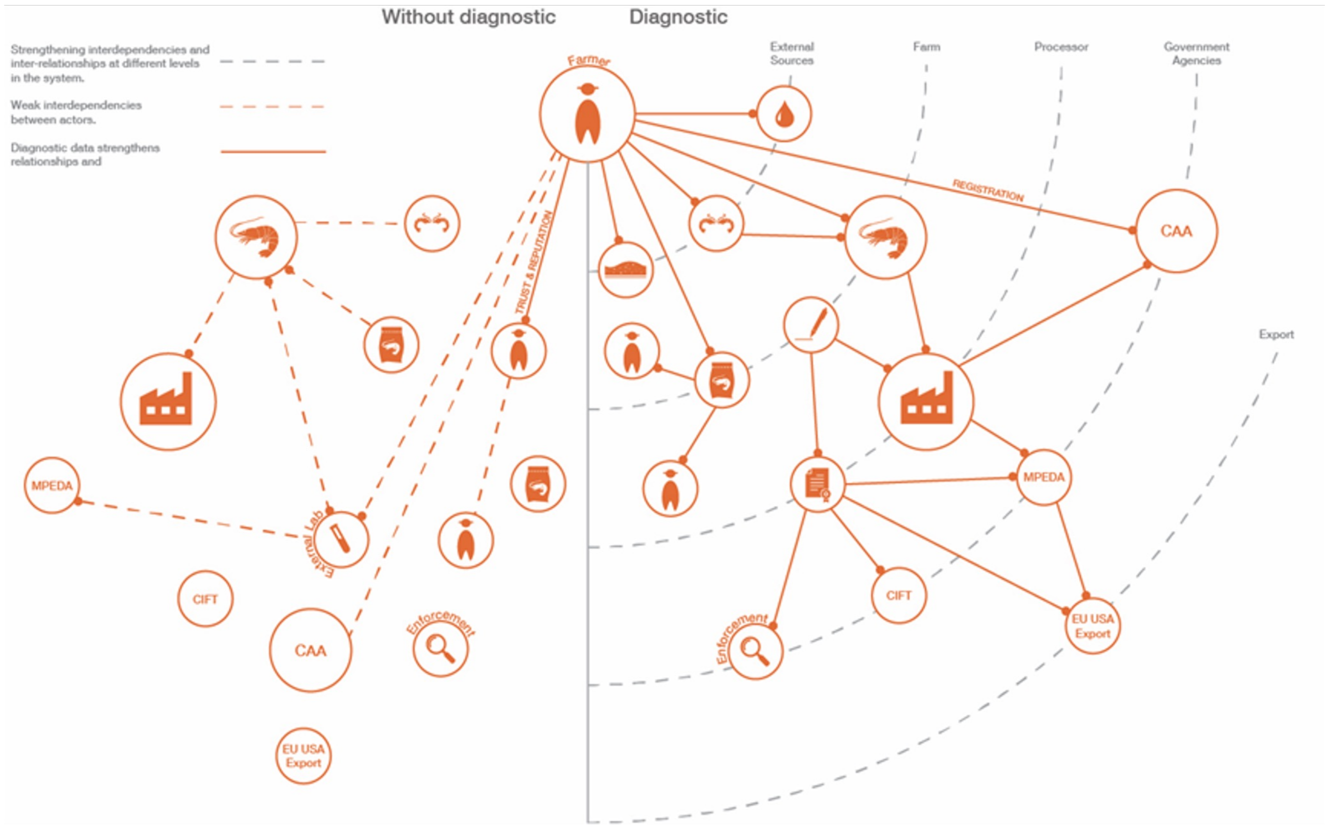
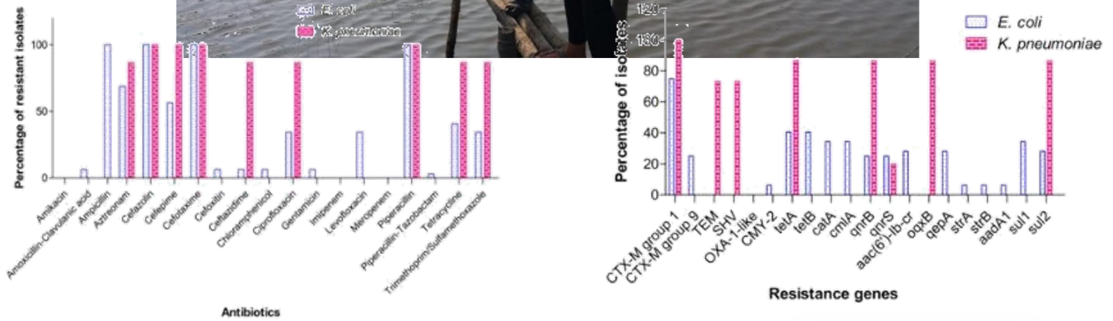
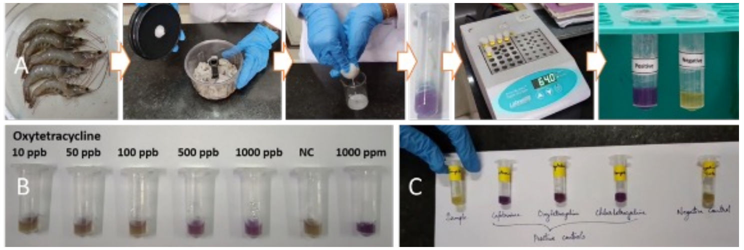
Aquaculture - Systems Approach to Diagnostic Interventions







Key observations:

- Very smart farmers, quick to adopt latest technology
- There is no tool to assess antibiotic residues or AMR rapidly
- Economic pressure is very high!
- Need structural support system

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Thanks *for your attention and to all the DOSA and JPIAMR partners and* **Teams**.

Edinburgh AMR Forum

Edinburgh Infectious Diseases | Proudly supported by THE UNIVERSITY of EDINBURGH

THE UNIVERSITY of EDINBURGH

UNIVERSITY OF Southampton

ual: university of the arts london

UNIVERSITY OF BRADFORD MAKING KNOWLEDGE WORK

World Organisation for Animal Health Founded as OIE

C-CAMP

The Fleming Fund

Global Impact Accelerator Funded by:

THE UNIVERSITY of EDINBURGH

Scottish Funding Council

GCRF

DOSA Funded by:

Newton-Bhabha Fund

DEPARTMENT OF BIOTECHNOLOGY

UKRI Economic and Social Research Council

jpiamr

Economic assessment of alternative anti-microbial use options at a farm level

Shailesh Shrestha

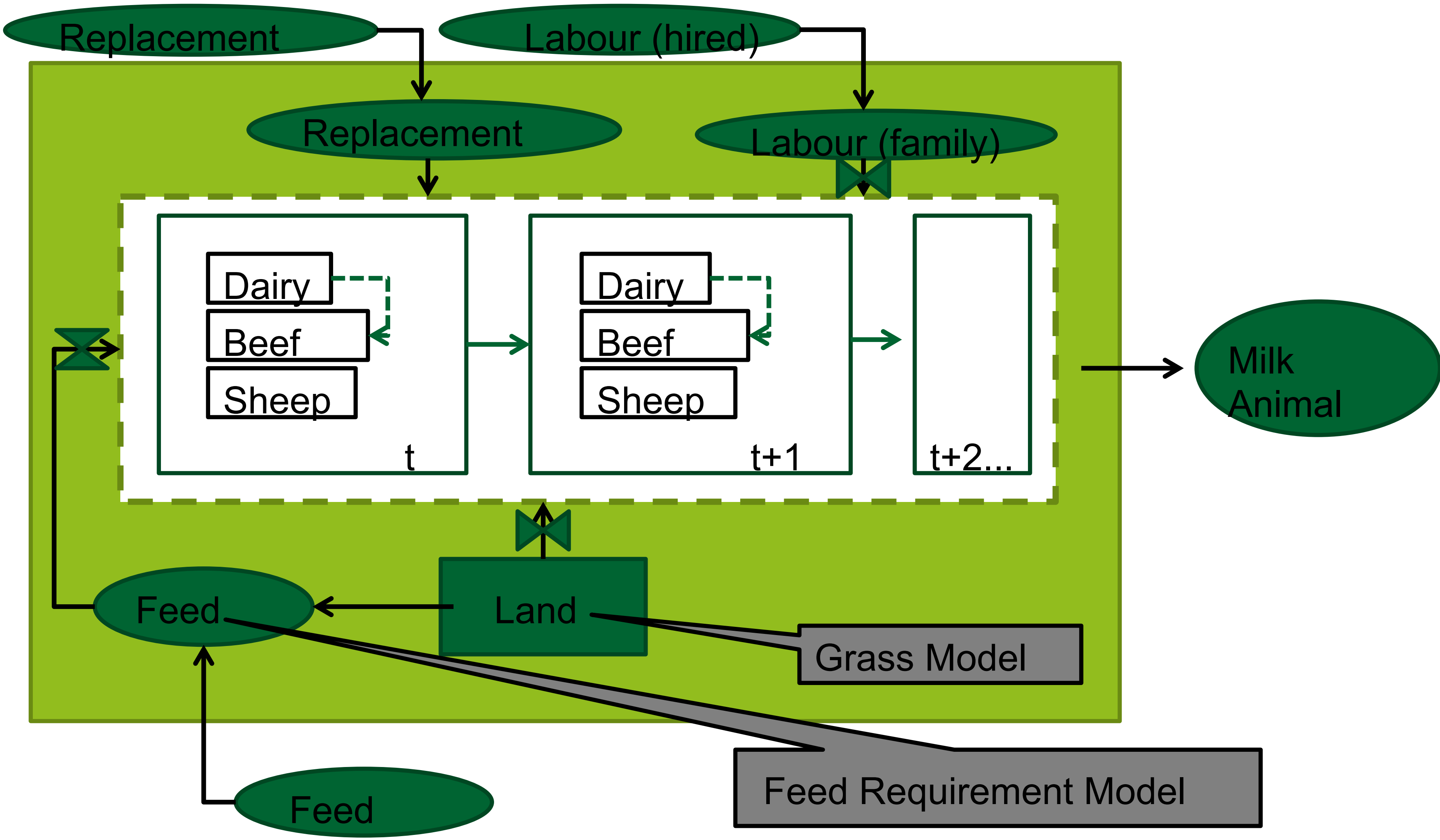
Department for Rural Economy, Environment and Society, SRUC, Edinburgh

Leading the way in Agriculture and Rural Research, Education and Consulting

Farm economy

- Farm level models
- Production based
- Farming system analysis
  - Physical interactions between activities
  - Translated to economic flows
- Optimising production economic models,
  - Maximises farm net profit/production
  - Constraint over farm resources and management practices

ScotFarm


Replacement
Labour (hired)
Replacement
Labour (family)
Dairy
Beef
Sheep
t
Dairy
Beef
Sheep
t+1
t+2...
Milk
Animal
Feed
Land
Grass Model
Feed Requirement Model
Feed

Optimising farm resource and practices

- Changes – farm plans, innovation, technology etc
- Scenarios
- Counterfactual impact assessment
  - Baseline vs Alternatives
- Feasibility of alternative options
- Identifying the best option

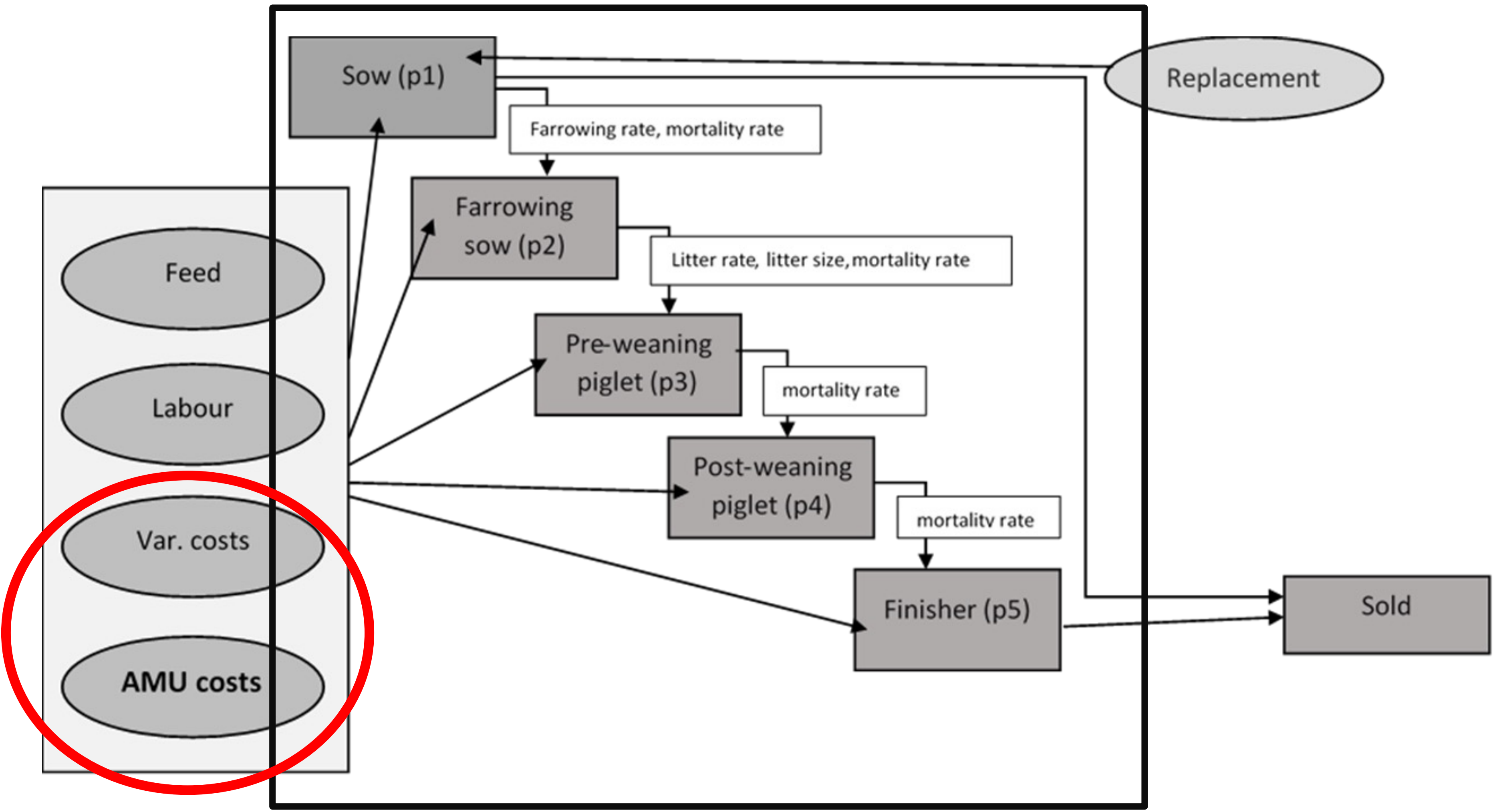
Alternative anti-microbial use

- Considered as management options
- Changes in farm plans, production and economy
- Requirements
  - implementation costs
  - additional changes - costs
  - production change
  - effectiveness

Example – AMR on UK pig farms

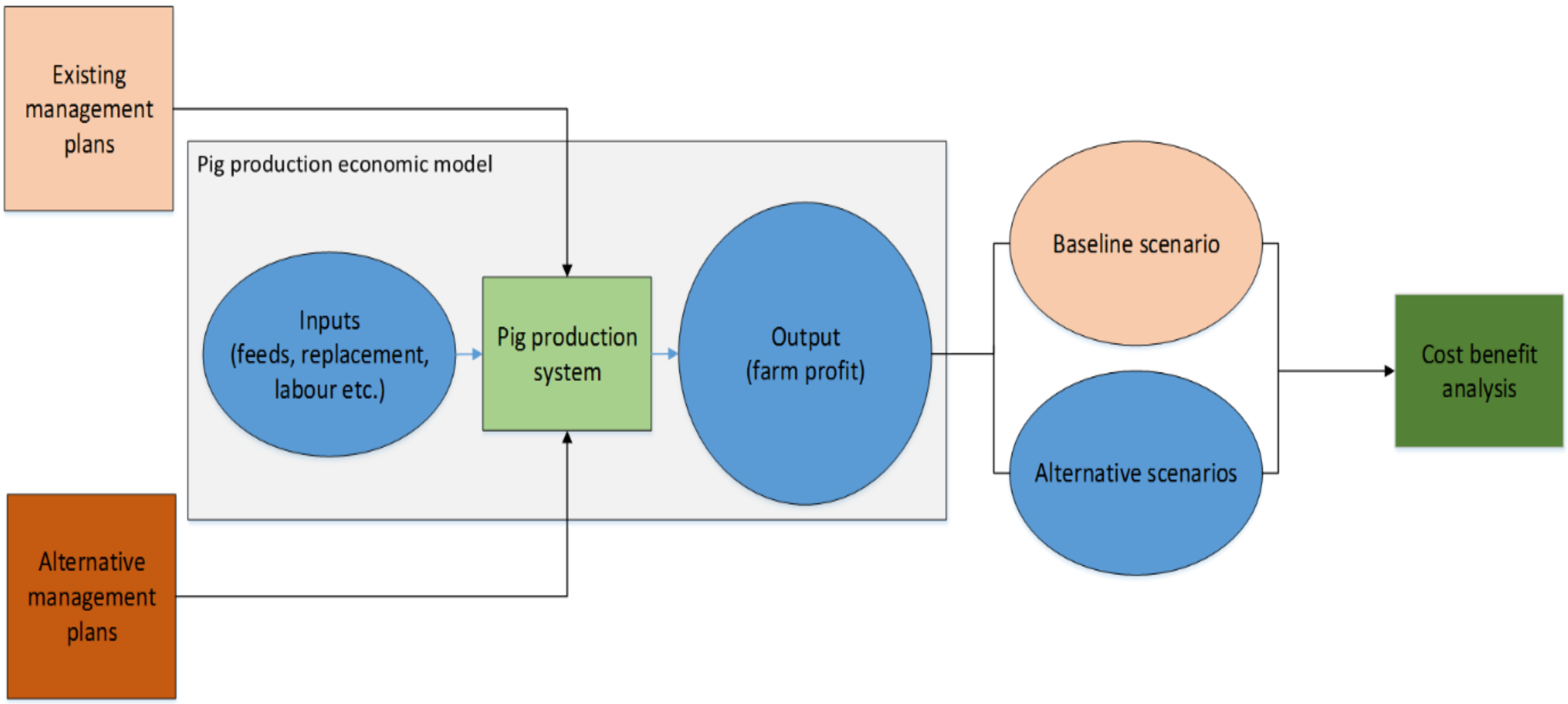
- VMD funded project 2019 - 2022
  - Data collection and analysis,
  - alternative management options to reduce AMUs
  - Identifying optimal AMUs,
- Economic assessment of alternative options
  - Pig Production Economic Model (PPEM)

PPEM



Sow (p1)
Replacement
Farrowing rate, mortality rate
Farrowing sow (p2)
Litter rate, litter size, mortality rate
Pre-weaning piglet (p3)
mortality rate
Post-weaning piglet (p4)
mortality rate
Finisher (p5)
Sold
Feed
Labour
Var. costs
AMU costs

Work flow

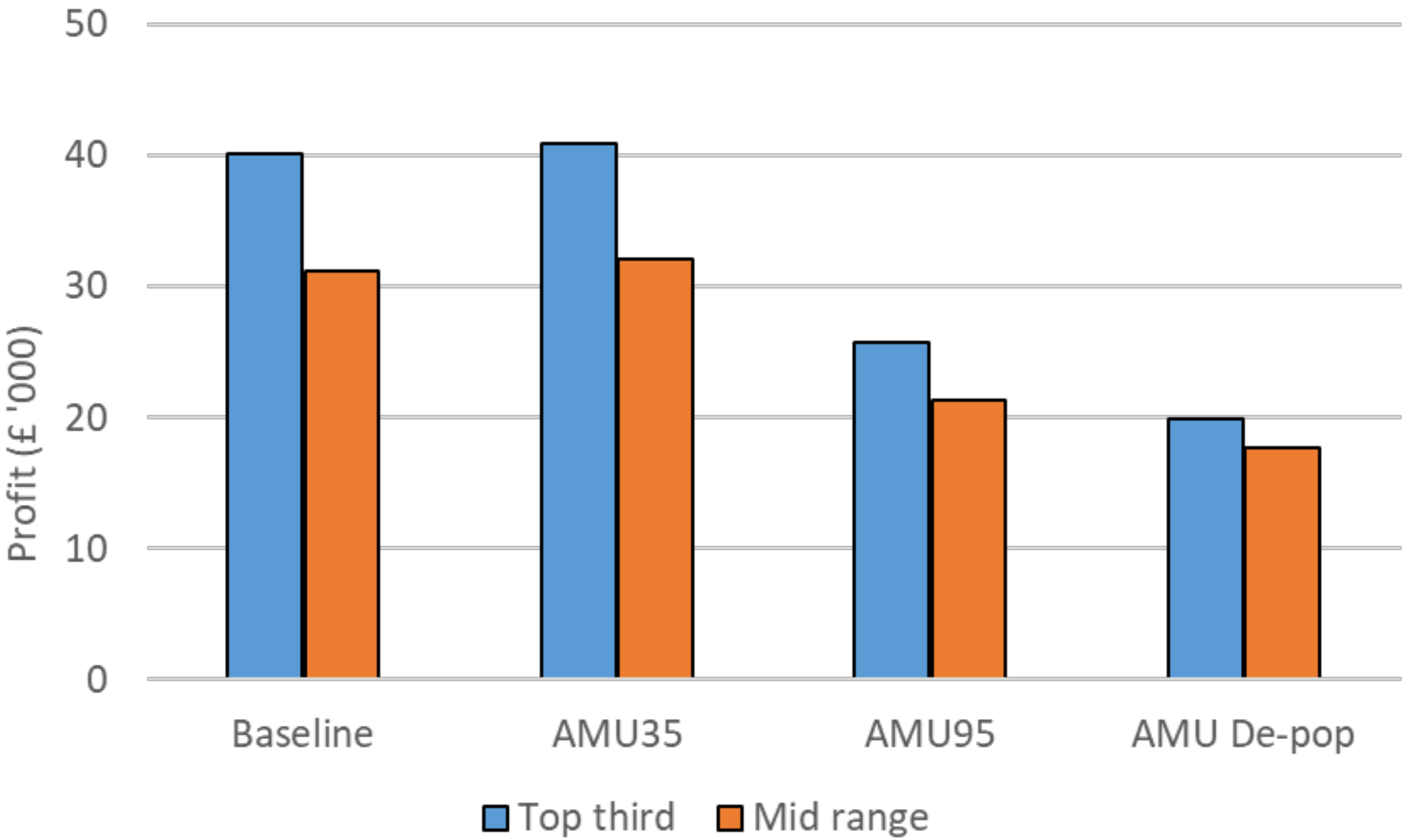


Existing management plans
Pig production economic model
Inputs (feeds, replacement, labour etc.)
Pig production system
Output (farm profit)
Baseline scenario
Alternative scenarios
Cost benefit analysis
Alternative management plans

Scenarios

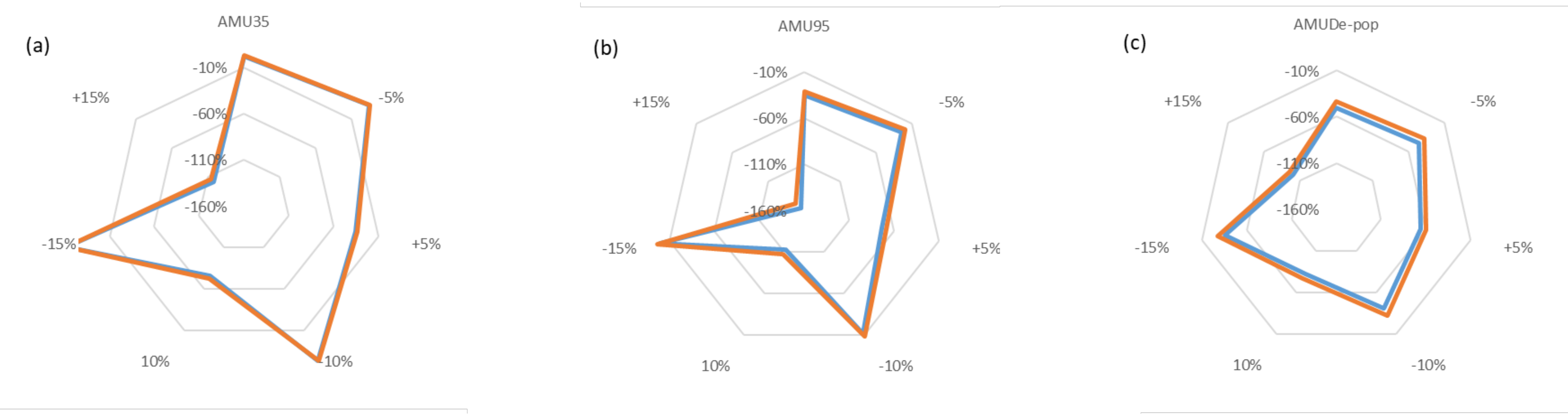
- **Baseline**: existing management conditions on an average pig farm, a comparison point
- Alternative management scenarios
  - **AMU35**: 35% AMU; 10% production and 10% farm variable costs
  - **AMU95**: 95% AMU; 10% production and 100% farm variable costs
  - **AMU De-pop**: 'all in and all out'; 95% AMU; 10% production and 50% farm variable costs

Results



50
40
30
20
10
0
Profit (£ '000)
Baseline
AMU35
AMU95
AMU De-pop
Top third
Mid range

Sensitivity analysis



Sensitivity analysis of changing feed price (±5%, ±10 and ±15%) on farm profit under; (a) AMU35, (b) AMU95 and (c) AMU De-pop scenarios [— Top third farm, — Mid-range farm]

Summary

SRUC

- Production and economy at farm level
- Implementing alternative options
- Comparing feasibility
- Identifying the most feasible and effective option

Impact of the ZnO ban on post-weaning diarrhoea and AMR on commercial pig farms in the UK

Deborah Hoyle

Roslin Institute & R(D)SVS, University of Edinburgh

Management of post-weaning diarrhoea and the implications for AMR in response to the upcoming ban on zinc oxide supplementation in pigs

Predict, Prevent and Treat
Endemic Livestock Disease

- Consortium project with industry partnership
- Workshop series – endemic livestock disease
- ZnO issue raised by feed company & producers
- Priming 12 month project, seeking onward funding

Deborah Hoyle	Roslin Institute
Mark Stevens	Roslin Institute
Ilias Kyriazakis	Queen's University, Belfast
Muna Anjum	APHA
Sam Beechener	SRUC
Abel Ekiri	University of Surrey
Roberto la Ragione	University of Surrey
Nick Wheelhouse	Edinburgh Napier University
Sophie Prentice	Innovation Lab by abagri

ROSLIN
Animal & Plant Health Agency
SRUC
Edinburgh Napier UNIVERSITY
UNIVERSITY OF SURREY
Innovation Lab by abagri
UKRI Biotechnology and Biological Sciences Research Council

Post Weaning Diarrhoea (PWD)

Primary Pathogen

- Enterotoxigenic *Escherichia coli* (ETEC)
- Toxins – heat labile (LT); heat stable (STa, STb), enteroaggregative EAST1
- Non-invasive, secretory diarrhoea
- Predominantly F4/F18 strains

Secondary Factors

- Co-infection – e.g. rotavirus, coccidian, clostridia
- Dietary
- Weaning age, mixing stress & stocking density

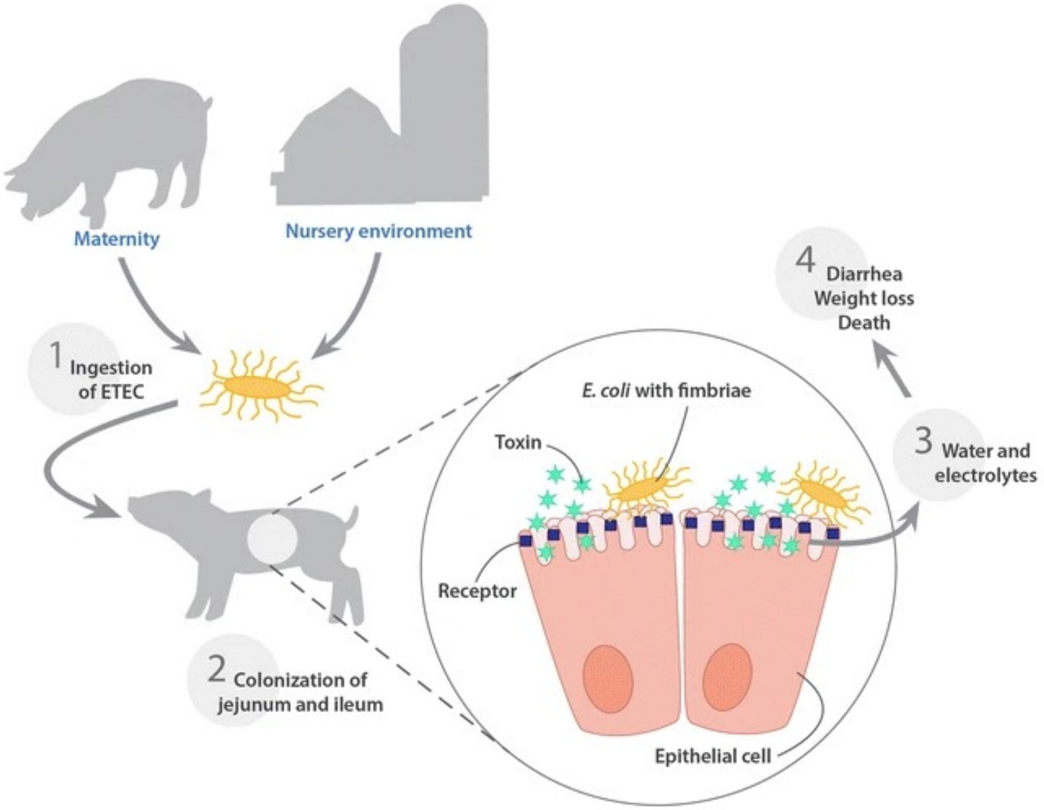


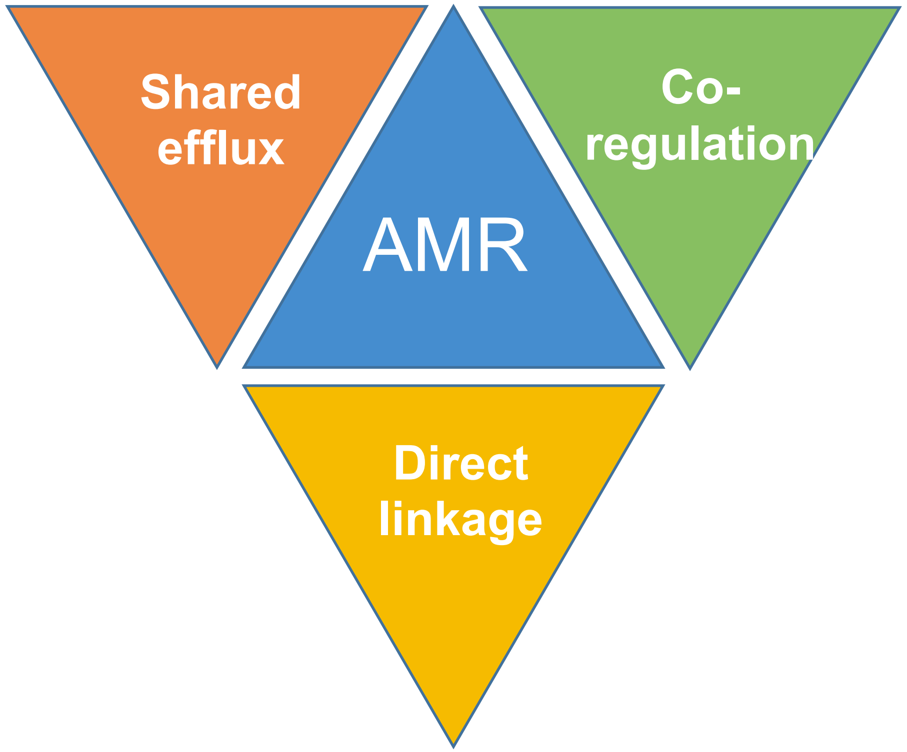
Image from: Rhouma M, Fairbrother JM, Beaudry F, Letellier A. Post weaning diarrhea in pigs: risk factors and non-colistin-based control strategies. Acta Vet Scand. 2017 doi: 10.1186/s13028-017-0299-7

PWD peaks at 7-14 days post-weaning

- Immediate: weight loss, morbidity, mortality
- Later : growth & disease resilience

PWD impacts Production & Welfare

Zinc oxide: actions & AMR



Why is ZnO used for PWD?

- Alternative to growth promoters post 2006 ban
- Pharmacological at **2500ppm**, up to 14 days:
  - Reduces PWD incidence
  - Increases weight gain
  - Increases later resilience
- Cheap – cost-effective, easy to deliver

Mechanisms of action?

- Antibacterial action within gut
- Alters intestinal structure
- Modulates immune response

Evidence for AMR – *in vivo* feed trials

- High ZnO diet increases nasal isolation of MRSA (Slifierz *et al* 2015; Amachawadi *et al* 2015)
- Increase in faecal isolation multiply resistant *E. coli* (Bednorz *et al* 2013; Ciesinski *et al* 2018; Johanns *et al* 2019)

EU Regulatory Withdrawal of ZnO – June 2022

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

16 March 2017, EMA stated that "benefits of (therapeutic) zinc oxide for the prevention of diarrhoea in pigs do not outweigh the risks to the environment"

1. Impact on antimicrobial resistance
2. Environmental pollution
   - Zn in slurry – heavy metal - toxicity to sediment organisms and aquatic species

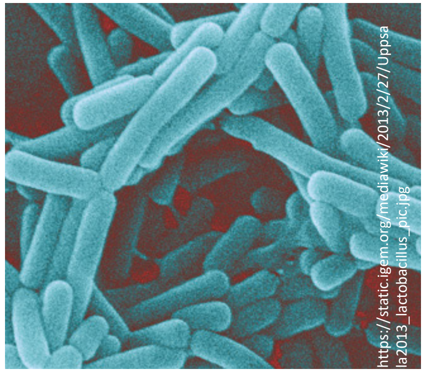
EU ban June 30th 2022 – maximum permitted **150 ppm**

UK Veterinary Medicines Directorate – supplement import prohibited 06/2022, ban June 2024

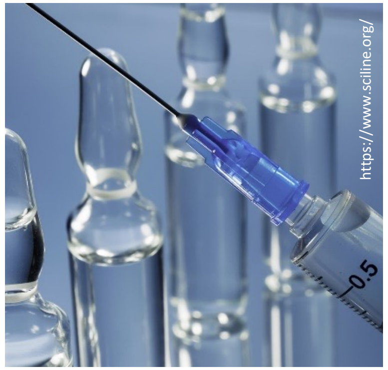
Implications for pig industry

- Increased weaning morbidity & mortality
- Initial increase in therapeutic AMU
- Economic & practical challenges
- Need for alternative prophylactics -
  - Feed enhancers
  - Bacteriophage
  - Husbandry
  - Vaccines


https://pixnio.com/fauna-animals/pigs/little-pigs#


https://static.igem.org/mediawiki/2013/2/27/Uppsala2013_lactobacillus_pic.jpg


https://upload.wikimedia.org/wikipedia/commons/



https://www.sciline.org/

Project Objectives

1. Biological measures of pathogens & AMR in the field

Q: Does removal of ZnO in commercial herds reduce AMR genes and increase pathogen prevalence in piglets?

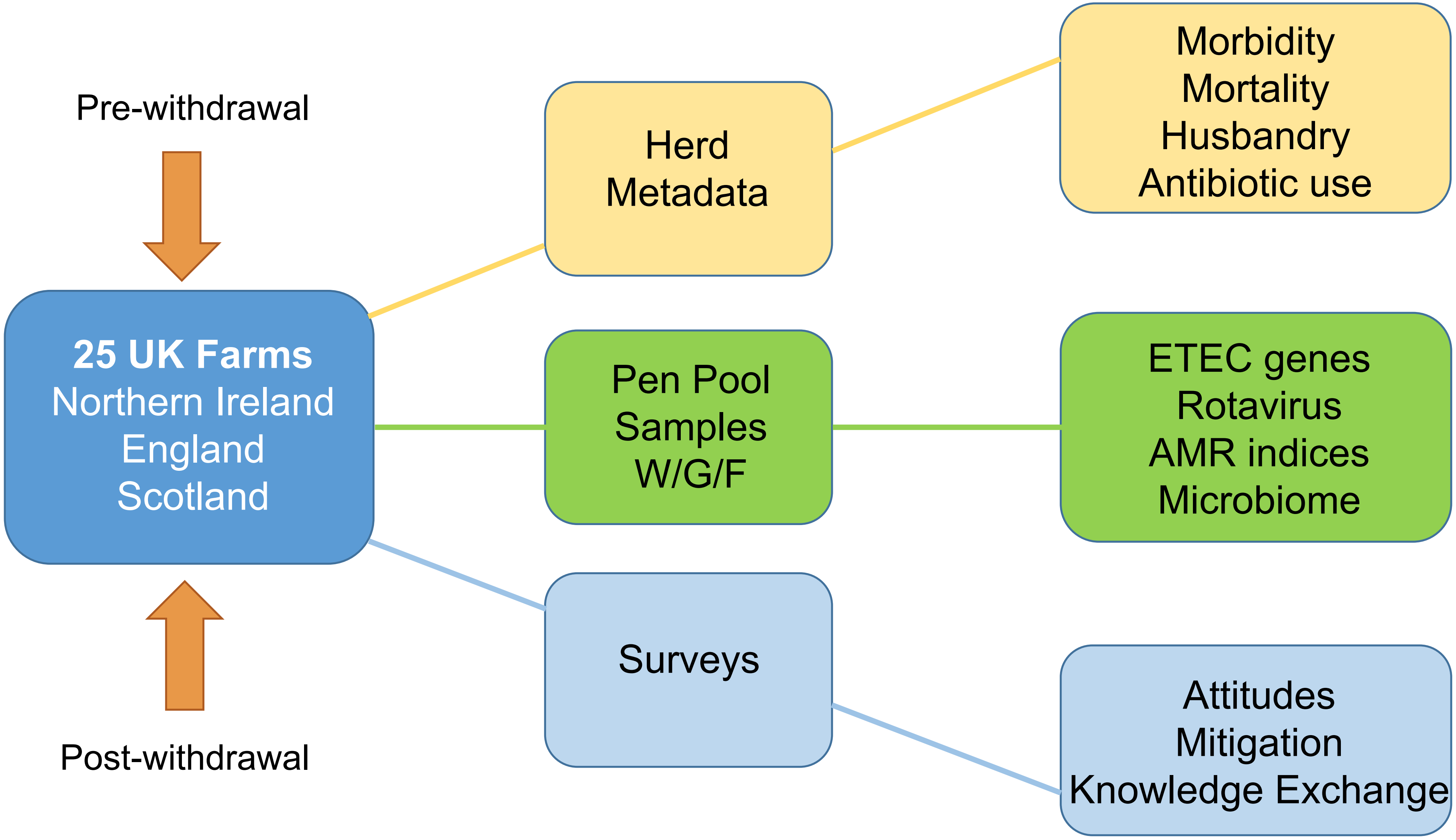
- Longitudinal survey on 25 commercial UK herds pre- and post-ZnO withdrawal
- Biobank samples as baseline for future research
- Molecular analyses for key pathogens, AMR & microbiome

2. Evidence base for intervention

Q: Can we identify on farm barriers and challenges to management of PWD disease & control?

- Longitudinal metadata analysis on study farms
- Develop and pilot on-farm epidemiological survey for industry roll-out
- Social attitudes survey & knowledge exchange “best-practice”

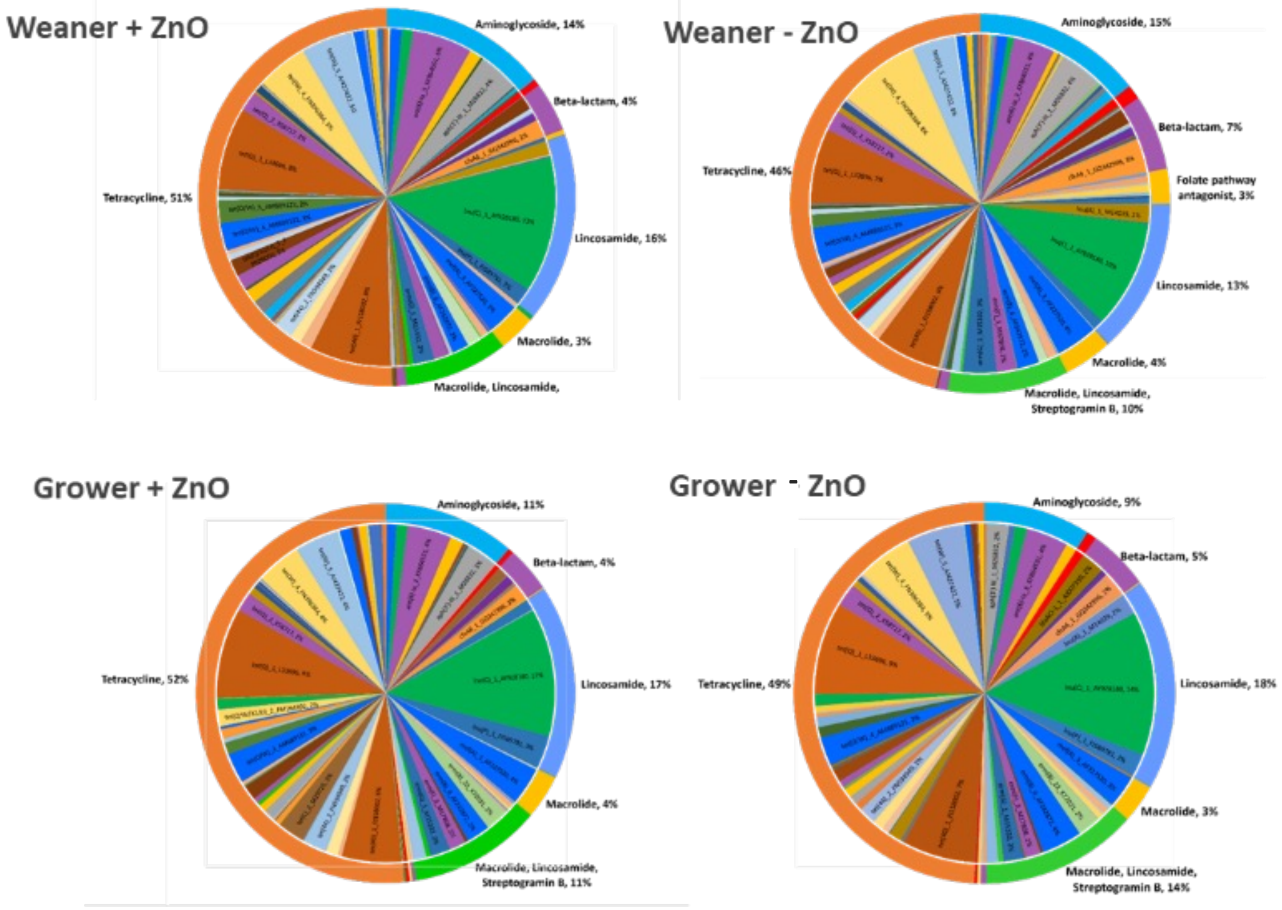
Study Design: repeated cross-sectional



Project Progress

- Sampled **25 herds** pre-withdrawal; 3 herds early post-withdrawal
- Collected **> 900 pen pool** samples from Weaner, Grower, Finishers
- Two herds: **trial +/- ZnO groups** (indoor reared & outdoor reared)
- Social survey started Feb 2023 (mitigation & attitudes)
- Wider industry epidemiological survey undergoing pilot review
- Knowledge exchange via producer groups underway

Oxford Nanopore sequencing – AMR genes in trial pigs



Future plans

Obtain funding to continue commercial herd follow-up in 12 months post-withdrawal

- Determine the consequence of ZnO removal in-field on disease, key pathogens and antimicrobial usage
- Identify microbiome communities & metabolites that may be exploited to enhance post-weaning resilience
- Compare carriage and diversity of AMR genes, mobile elements and association with metal resistance genes, before & after the ban
- Translational knowledge exchange with producers, clinicians & other stakeholders

Thank you to the project team & contributors

Special thanks to all participating farmers for their time and enabling sample collection.

Roslin

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Garth Pig Practice
RAFT Solutions Ltd
AFBI/CAFRE

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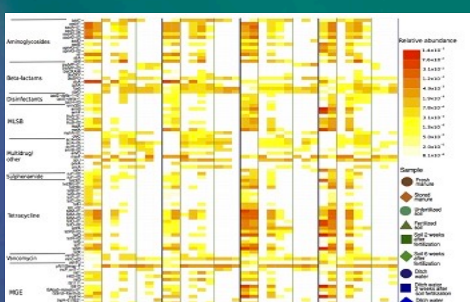
THE UNIVERSITY *of* EDINBURGH
The Royal (Dick) School of Veterinary Studies

ROSLIN

Livestock: Understanding the Antimicrobial Resistance and Use of Novel Antimicrobial Alternatives

Moredun

www.moredun.org.uk





Nuno Silva

Edinburgh 22nd May

Overview of AMR Projects at Moredun (MRI)

- Understanding the dynamics of antimicrobial resistance (AMR) at **Livestock Farms** through the **One Health** approach

  - Soil
  - Water streams
  - Livestock
  - Wildlife
  - Human (Farmers)

- Novel alternatives with **eubiotic**/ **antimicrobial** capacities in farmed animals

  - Natural products
  - Genetically engineered platform(s)

Understanding the dynamics of antimicrobial resistance (AMR) at Livestock Farms through the One Health approach

- Understanding the dynamics of antimicrobial resistance genes (ARGs) flux in the soil, water, animals and humans in different fertilisation practices for grasslands (RESAS. 2022-2027)

  - Hypothesis: Pasture soils treated with **organic fertilisers** are at higher risk of exposure to antimicrobial drug residue and AMR genes (ARGs), and this may result in a higher prevalence and diversity of ARGs and resistant bacteria in soil and in the gut flora of animals that graze on it.

  - The putative selection and spread of AMR bacteria and ARGs into soils may limit the use of organic fertilizers in grasslands. → Bio-Waste Circular Economy???

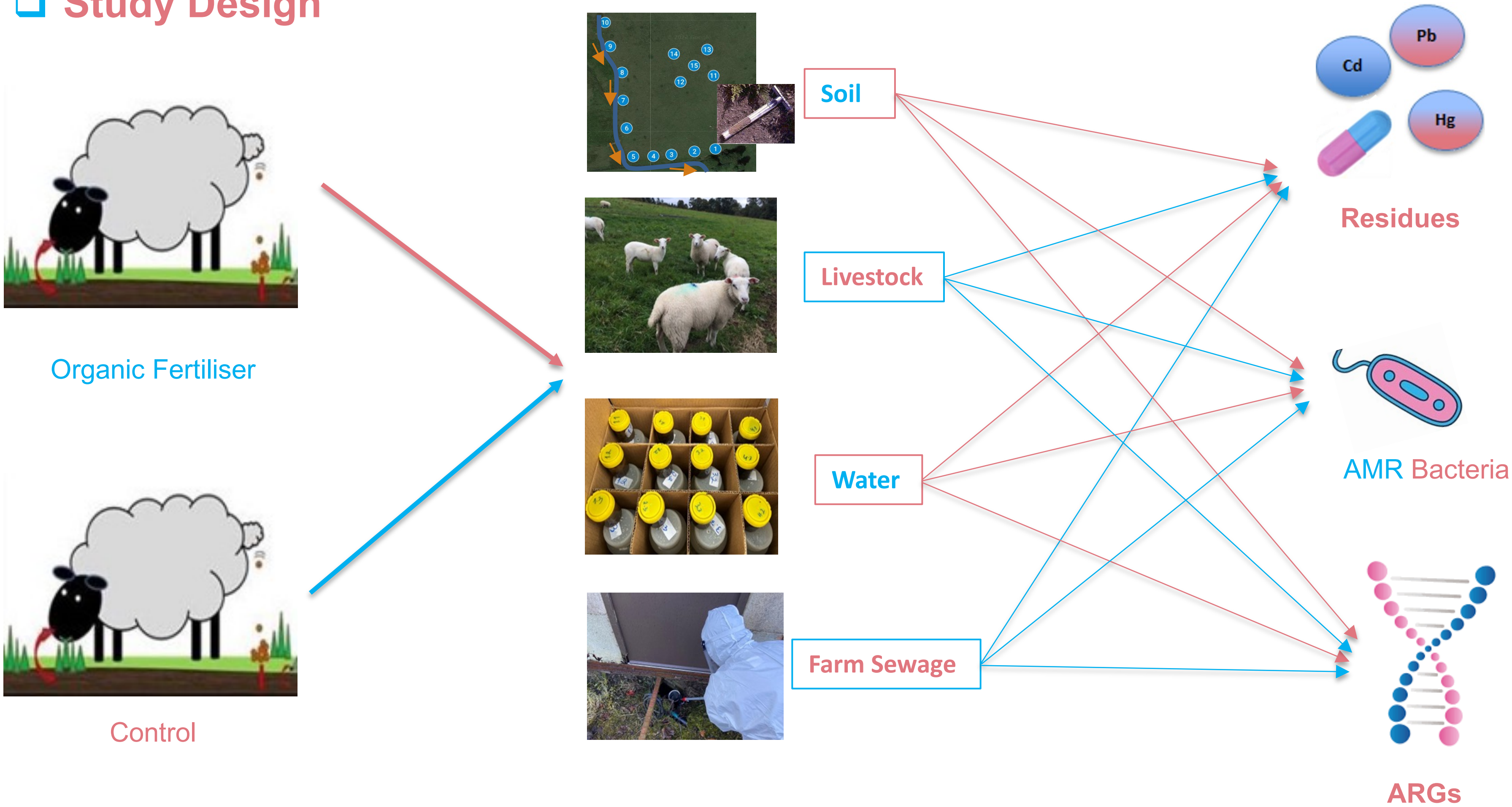
  - Fertilisation practices comparison:
    - **Manure**
    - **Slurry**
    - **Sludge pellets** (WWTP)
    - **Control** (no fertiliser / inorganic)

↓

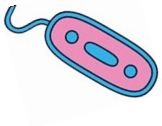
AMR- Low Risk?

Understanding the dynamics of antimicrobial resistance (AMR) at Livestock Farms through the One Health approach

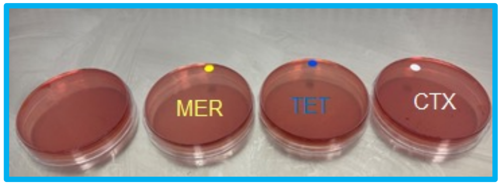
❑ Study Design

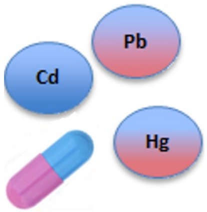


Understanding the dynamics of antimicrobial resistance (AMR) at Livestock Farms through the One Health approach



- Cultures – *E. coli*

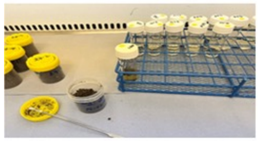




- **Antimicrobials** and **Heavy metal** residues

  ABs (TET and CFs); HM (Pb, Zn, Hg, Ni, Cd, and Cu)

- **Resistome**: **Antimicrobial Resistance Genes (ARGs)**. Presence and Relative Abundance

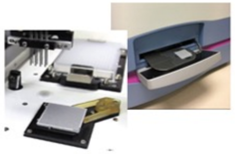


Sample

Cell Disruption

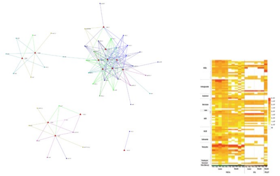
DNA Extraction

DNA Quantification



SmartChip Real-Time PCR System

SmartChip Real-Time PCR System (WaferGen-TaKaRa Bio)- **384** pre-validated **ARG** and **Mobile Genetic Elements** (MGEs) assays



- **AMR risk modelling**

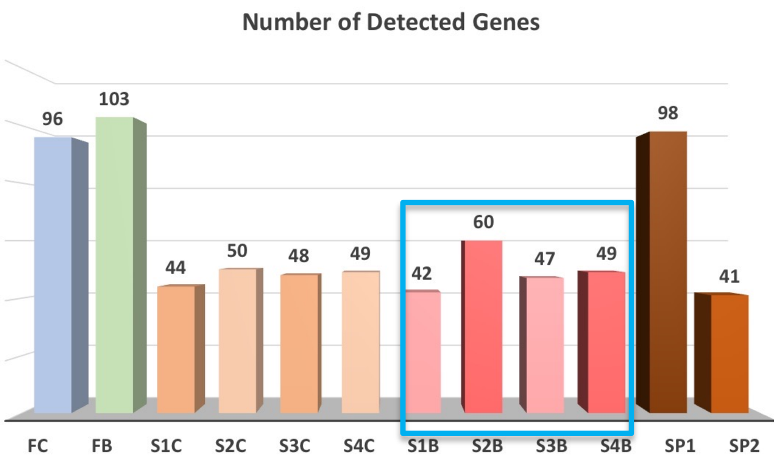
  - Risk assessment approach based on the standard *source-pathway-receptor* principle to model the transmission of AMR genes (ARGs) and/or *E. coli* from source via the environment and the food chain (pathways) to the receptor

  - Model aims to help assess the impact of different farm management approaches (e.g., organic vs. inorganic) on AMR transmission

BioSS

Understanding the dynamics of antimicrobial resistance (AMR) at Livestock Farms through the One Health approach

❑ Pilot study (2019)- Sludge Pellets



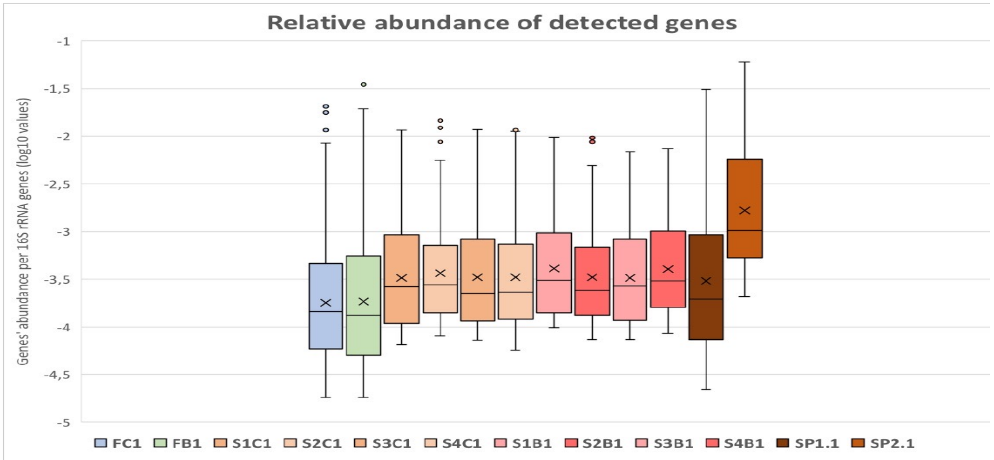


Fig.1- Distribution of positive ARG and MGE assays across different samples and Relative abundance. FC- Faecal Control; FB- Faecal sludge pellets; S1C-S4C- Soil Control; S1B- Soil sludge pellets (pre-application- Spring); S2B- Soil sludge pellets (post-application-Spring); S3B- Soil sludge pellets (pre-application-Autumn); S4B- Soil sludge pellets (post application-Autumn); SP1-SP2- Sludge pellets (Spring-Autumn).

- **A total of 125 ARGs and MGEs qPCR were positive in one or more samples.**

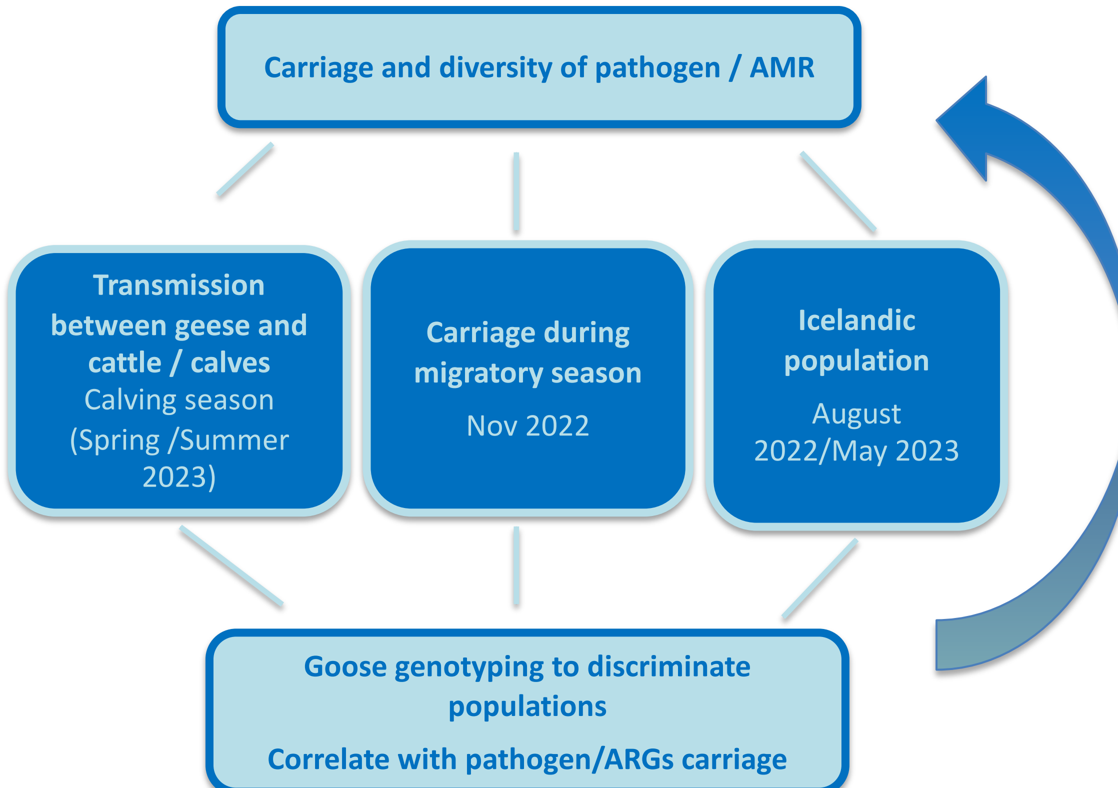
- **No significant difference between sludge pellets-treated pasture and non-treated pasture samples.**

Understanding the dynamics of antimicrobial resistance (AMR) at Livestock Farms through the One Health approach

- Microbial and AMR risks associated with expanded greylag geese in livestock and environment on the **Orkney Isles** (RESAS. 2022-2027).

- Risks associated with spread of Foodborne Pathogens and AMR in livestock and environment.

Analysis of **Resistome** and the presumed flow of ARGs between greylag geese, cattle and the wider environment



Understanding the dynamics of antimicrobial resistance (AMR) at Livestock Farms through the One Health approach

❑ Pilot study (2021)- Orkney Islands

- Evaluate the role of migratory birds (wild geese) as reservoirs and vectors of dissemination of antimicrobial resistance bacteria and resistant genes (ARGs) within livestock in the Orkney Islands.

- 2 Farms participate in the study.

- Resistance to tetracycline (78-100%) and 3rd cephalosporin (30-42%) was detected in both geese and cattle.

- ESBL-producing *E. coli* was detected on Farm 1 but only in cattle samples.

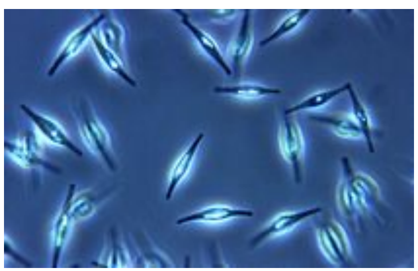
- blaCTX gene was identify in all the ESBL-producing *E. coli* (12%).

- The use of 3rd to 4th generation cephalosporins in Orkney farming is very limited or even non-existent.

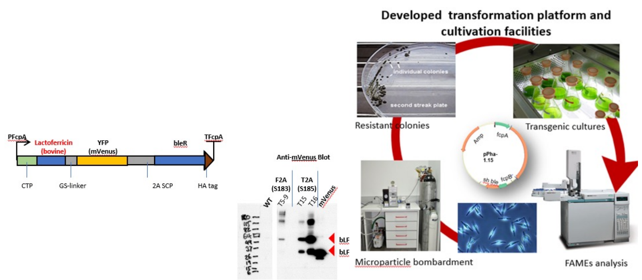
Novel alternatives with eubiotic/ antimicrobial capacities in farmed animals

Multifunctionalized Microalgae (MM) - A novel and flexible platform technology for maximising feed/energy conversion ratios and treating severe infections in livestock (I-UK; UK China collaboration to tackle antimicrobial resistance. 2019-2022).

- The project aims to investigate the capability of antimicrobial and anti-inflammatory compounds to maximise feed/energy conversion and treat severe infections in livestock. The compounds were produced using a unique, low-cost, Microalgae expression system.



Phaeodactylum tricornutum



- Engineered Microalgae strain that express **two** separate antimicrobial agents with different modes of action. → **Farmed animals**

Consortium Partners - UK

Moredun Research Institute
ROTHAMSTED RESEARCH
PML Plymouth Marine Laboratory
UNIVERSITY OF EXETER

- Amalga Technologies Ltd

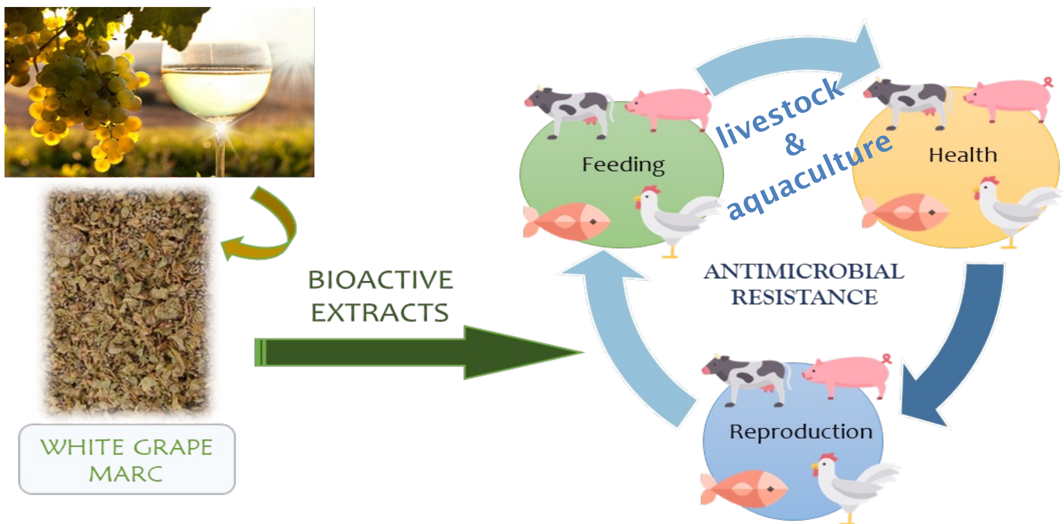
Consortium Partners - China

- Institute of Animal Science, of Chinese Academy of Agricultural Sciences
- AustAsia (AA)

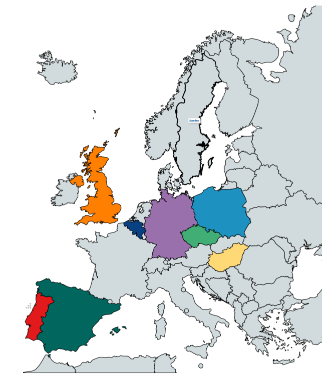
Novel alternatives with eubiotic/ antimicrobial capacities in farmed animals

❑ The power of grape extracts: antimicrobial and antioxidant properties to prevent the use of antibiotics in farmed animals (NeoGiANT) (EU H2020. 2021-2026)

- NeoGiANT will develop novel natural antimicrobial products for the control and prevention of the most relevant diseases in animal production based on natural extracts derived from agri-food byproducts as raw materials.



Applications



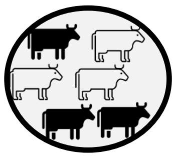
- Enhanced **feed** & **feed additive** for animal feeding
- **Natural products** for the **treatment of important diseases** in animal production (mastitis, exudative epidermitis, poultry enteric diseases, and farm fish diseases)
- **Sperm preservation**

NeoGiANT

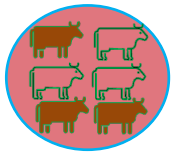
Horizon 2020
European Union Funding
for Research & Innovation

Novel alternatives with eubiotic/ antimicrobial capacities in farmed animals

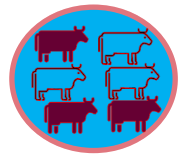
- **Calf-feeding trial – Polyphenols (PF) content**



Control group



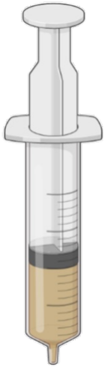
Low dose group
1000 ppm (PF) /kg feed



High dose group
2776 ppm (PF)/kg feed

- Four weeks length trial
- Growth performance
- Microbiome analysis
- *E. coli* O157 challenge study

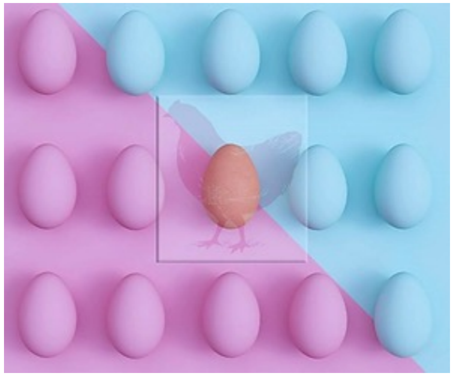
- Antimicrobial performance of optimized intramammary syringe formulations on "In vivo" models of mastitis in cattle



- Syringe prototype - PF formulation (Carbopol 974® dispersion)
- *Streptococcus uberis and Staphylococcus aureus* infection models

NeoGiANT
Horizon 2020
European Union Funding
for Research & Innovation

Thanks…



Which came first?

Antibiotic or Resistance…

NeoGiANT

Horizon 2020 European Union Funding for Research & Innovation

RIF Field Station

Moredun Research Institute

INTER ⇄ ACT

The University of Sydney

The James Hutton Institute

BioSS

Rothamsted Research

PML Plymouth Marine Laboratory

University of Exeter

University of Glasgow

SRUC

resistomap Mapping Antibiotic Resistance

Hannah Dairy Research Foundation

中华人民共和国科学技术部

Department of Health

Innovate UK

Rowett Institute of Nutrition and Health University of Aberdeen

SEFARI Leading ideas for better lives

The Scottish Government

RESAS Rural & Environmental Science and Analytical Services