Global Health Strategy Group: Antimicrobial Resistance "AMR and One Health" Wednesday 26th January 2022

DRAFT MEETING SUMMARY/MINUTES

Opening and welcome remarks: Christiane Dolecek, Associate Professor, Centre for Tropical Medicine and Global Health, University of Oxford and Mahidol-Oxford Tropical Medicine Research Unit, Scientific Lead and Co-PI on the GRAM study.

Strategy Group Chairs

- **Prof Christiane Dolecek,** Associate Professor, Centre for Tropical Medicine and Global Health, University of Oxford. Also, the scientific lead, GRAM study
- **Andrew Jack,** Financial Times Global education editor and coordinator of several health projects including 'Special Report FT Health: Future of Antibiotics'
- The Chairs introduced a brief framework for the meeting, which was followed by a series of presentations
- There was a news session in which the findings of the new global burden of AMR and progress on the FT AMR Accountability Tracker were disseminated to those present
- Invitation to 'AMR in the Community' Workshop in March

Speakers

- **Prof Bernd-Alois Tenhagen** (Head of Unit Epidemiology, Zoonoses and Antimicrobial Resistance, Federal Institute for Risk Assessment): AMR at the interface of animals and food. Followed by: In conversation with **Prof Hoa Ngo Thi** (Head of Zoonosis Group, OUCRU, Vietnam)
- **Dr Friederike Maechler** (Charité – Universitätsmedizin Berlin), and **Dr Tochi Okwor** (AMR-IPC lead, Nigeria CDC): Context-driven Infection Control Interventions
- **Prof Craig Maclean** (Dept. of Zoology, University of Oxford): Bacterial-fungal co-infections and their role in the evolution of antimicrobial resistance
- **Prof Jens Rolff** (Freie Universität Berlin, Evolutionary Biology): GlobalResist – Forecasting antibiotic resistance evolution – a new approach to address a major issue in global health
- **Dr Benn Sartorius** (Senior geospatial infectious disease modeler and global health epidemiologist): New global estimate on burden of AMR – GRAM project: University of Oxford and IHME and Global AMR Collaborators
- **Andrew Jack** (Financial Times, Co-chair AMR group): Antibiotic accountability
- **Dr Manica Balasegaram** (ED GARDP): SECURE; Exploring new models of antibiotic drug pricing and access
- **Dr Mohammed Bella Jalloh & Dr Humayra Bashir:** Invitation to AMR in the Community Workshop

Presentations

AMR at the interface of animals and food

About the Federal Institute of Risk Assessment, Germany: Epidemiology, Zoonoses and AMR Group

An independent Institute under the Ministry of Agriculture and food that provides risk assessment on consumer health issues. It separates risk assessment from risk management. The group: Epidemiology, Zoonoses and Antimicrobial Resistance is housed in the Department of Biological Safety and reports AMR data to the public, to the government, and to the European level.

- **Risk Assessment: Difference between risk and hazard**: Hazard is the potential danger a bacterium poses. However, there is need to assess the potential for exposure. Therefore, Risk is the combination of what happens when a person is exposed and how common exposure is
- **The Codex Alimentarius (Microbiological Risk Assessment)** identifies four points for risk assessment:
    - Hazard Identification
    - Exposure assessment
    - Hazard Characterisation which together leads to
    - Risk Characterisation (see figure 1 below)

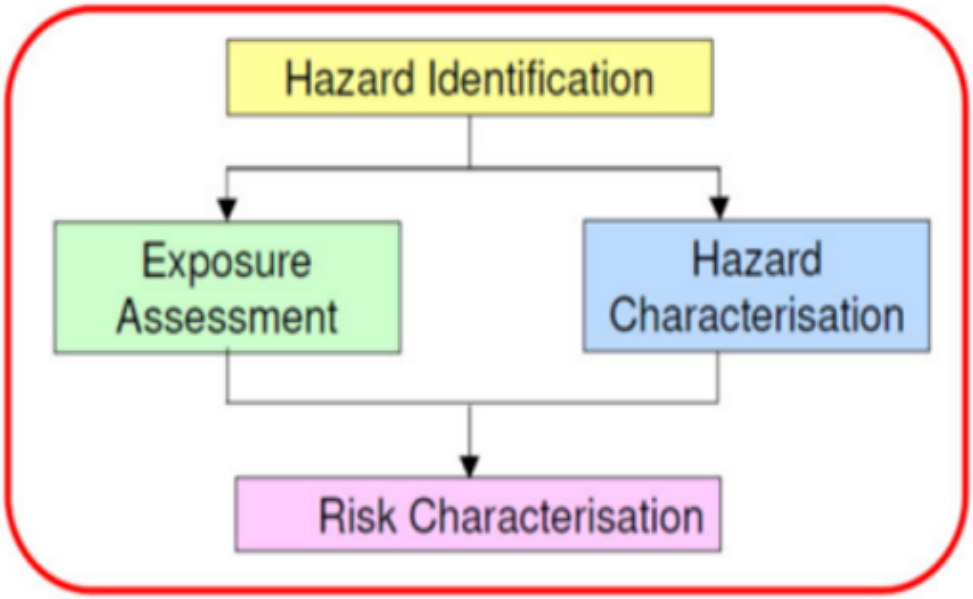


Figure 1: Microbiological risk assessment

Table 1 illustrates how exposure and hazard interact to help identify what could be dangerous (purple areas):

Additional risk		Exposure assessment		
		Negligible	Moderate	High
Hazard characterisation	Negligible			
	Mild			
	Moderate			
	Severe			

Table 1: Example – qualitative assessment

- **AMR as a One Health Topic**: An antimicrobial resistance in animals and also in humans leads to a common resistance problem. One of the main interests of the work carried out by Federal Institute is the exchange and overlap between resistance in humans and animals (see Figure 2)

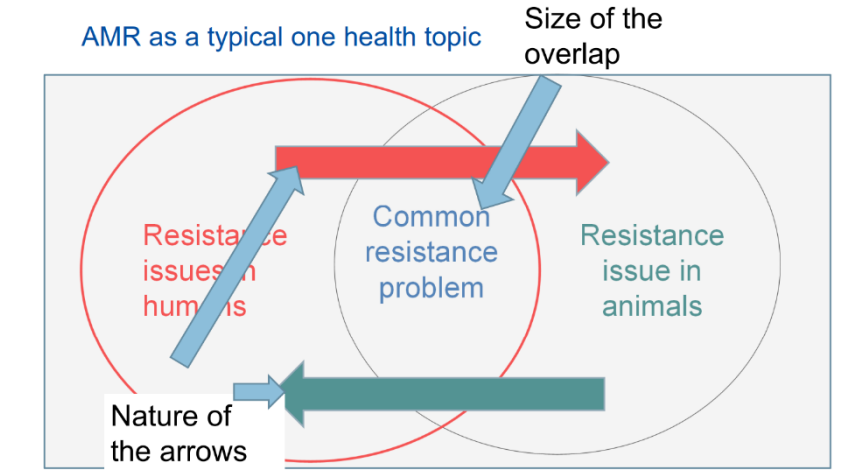


Figure 2: AMR as a One Health topic

- **Monitoring AMR through Burden sharing on a National Level, Case Study from Germany**: National monitoring system. BfR's 'Farm to Fork' monitoring i.e., farms, fruit/food harvest, retail sampling. Wildlife monitoring is also carried out, which links to the environmental aspect. A summary of how this is carried out is presented in Table 2

Isolates from humans	Robert Koch-Institute (RKI)
Animal pathogens	Federal Office for Consumer Protection & Food Safety (BVL)
Zoonotic bacteria	BfR
Commensal bacteria	

Table 2: Burden sharing to monitor AMR

- **Human to Animal Transmission of Resistance:** This is the main work of the group. More specifically, transmission via the food chain. Other pathways include by professional contact, hobbies, between animals, and from environmental emissions
- Output of work:
  - 14 standard panels of antimicrobials harmonized (in terms of bacteria, antimicrobials to test, and cut-offs to use) across Europe
  - method development
  - Advice to policy makers on i.e., effectiveness of policies/interventions, arrears needing more concentration/monitoring
  - quantification of bacteria
  - data modelling
  - collaboration with other institutes
  - designing monitoring plans
  - Improvement & standardization of methods
- Antimicrobial minimalization concept in Germany led to a 60% reduction in antimicrobial use. This was led by local veterinary authorities. However, a rise in use was subsequently seen due to lax sanctions. Those running well organized and integrated systems of production, e.g., poultry production, are more aware of the lack of sanctions, which lead to a reversion to heavier use of antimicrobials in such settings
- https://www.frontiersin.org/articles/10.3389/fvets.2020.627821/full
- Method development:
  - https://www.frontiersin.org/articles/10.3389/fmicb.2020.01678/full
  - https://pubmed.ncbi.nlm.nih.gov/34065518/
  - https://www.efsa.europa.eu/en/efsajournal/pub/5709
- Quantification and Modelling:
  - https://pubmed.ncbi.nlm.nih.gov/31328433/
  - https://pubmed.ncbi.nlm.nih.gov/30553180/

AMR at the interface of animals and humans - Vietnam

- Using social science to explore the human-animal interface of AMR
- Need for multisectoral, multidisciplinary research, including social scientists to unpack the interaction between humans and animals in relation to AMR

Examples from Vietnam:

1. VIBRE (2012): Antimicrobial drug resistance: the human-animal interface in Vietnam (AMC) - chicken farmers and farmers
2. SCENERI (2015**)**: Scientist - Community Engagement to reduce Risk of zoonotic Infection, Vietnam (OUCRU) - pig and chicken farms - AMU
3. ZELS-MPP (2016): Myanmar Pig Partnership: An integrated management-based approach for surveillance and control of zoonoses in emerging livestock systems (Uni. Of Cambridge) - Pig farms - (with participation of 2 commercial farms)
4. HECTOR (2018): The impact of Host restriction of Escherichia coli on Transmission dynamics and spread of antimicrobial Resistance (AMC) - pig-chicken - healthy human isolates

- **Antimicrobial Usage in Vietnam:** local data shows high AMU for both prophylaxis and treatment. Initiatives and National Action Plans exist, however there is need for more review of such plans and their implementation. There is also a list of Antibiotics not to be used in Animal feeds (which, concomitantly, suggests others that can be used)
- Other Challenges faced include lack of implementation and uptake of policies (such as the antibiotic stewardship in all hospitals and on the veterinary side), lack of multidisciplinary involvement and lack of supporting mechanisms for farmers
- **Possible solution**: local research which is shared between farmers, vets, policy makers

CoDe-ICI (Context-driven control interventions)

- This project is based on many activities already under way across a variety of partners.
- 2-year baseline analysis of infection control infrastructure and development of intervention trials tailored for the local LMIC setting in a network of African and Asian hospitals.
- The aim is to develop targeted tailored intervention trials suitable for local resource-constrained settings in a network of African and Asian hospitals
- **Objectives:**
    - To prioritise infection control interventions based on their likelihood of having significant impact on AMR in LMIC settings
    - To develop a network of hospitals (with necessary resources and infrastructure) in LMIC settings to participate in high-quality infection control intervention trials
    - To determine appropriate study designs for different intervention studies by evaluating previous study designs (Alpha trials) as well as trying new study designs (Adaptive platform trials)

    - To develop campaign strategies transferable to the LMIC settings involved, and
    - To develop a number of costed proposals for intervention studies in LMIC settings for which we will seek further funding
    - All the above in a contextualized manner
- Various IPC interventions exist. These interventions have been rigorously investigated for effectiveness; the catch though is that almost all these trials have been in high-income settings. This calls into question how transferrable they will be to, and how effective they will be in, low-resource settings
- Factors like Human Development Indices have been shown to affect rates of Surgical Site Infections (Bhangu et al., LID 2018). See figure 3 below

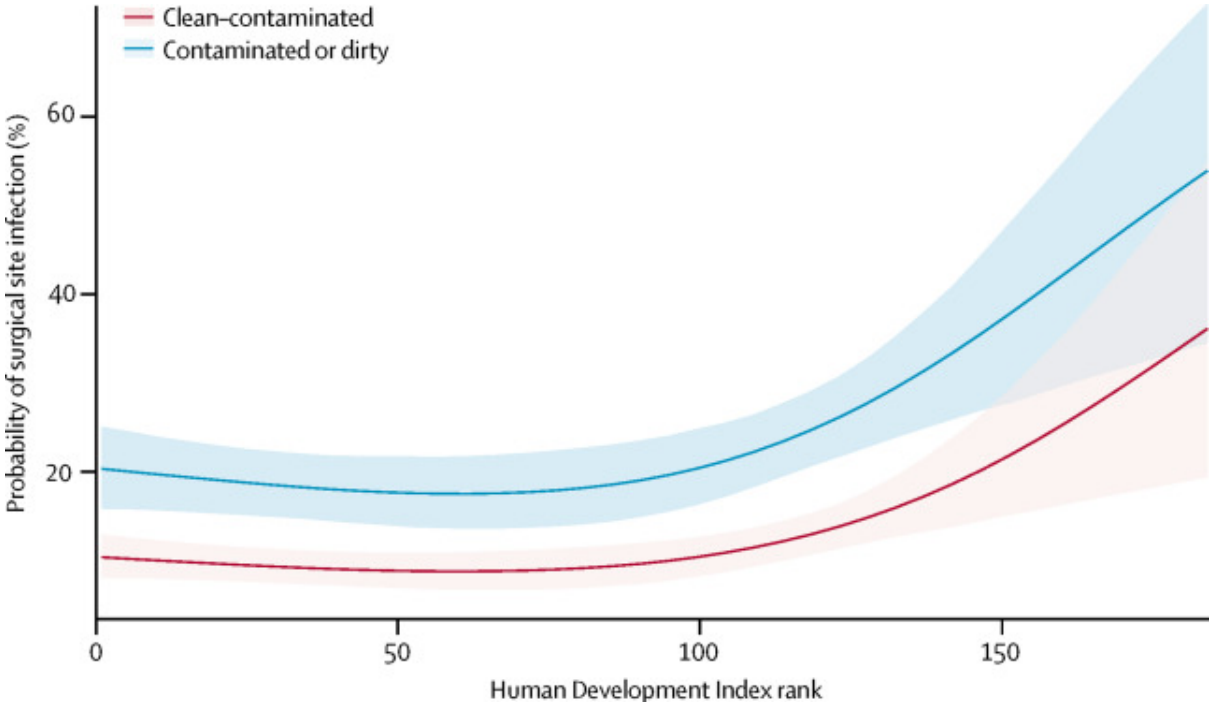


Figure 3: Human development index and probability of surgical site infection

- Challenges include a paucity of data sources to set up studies (Markwart et al., Intensive Care Med 2020). To address challenges, the team is trying to collaborate with other networks such as ACORN, NeoIPC and The ORANGE Network.
- The Task at hand (Collaborative effort, leveraging on known networks and drawing on a wide range of expertise):
    - Literature review with a focus on bloodstream hospital-acquired infections
    - Local situation reports
    - Available data, e.g., from the WHO's Infection Prevention and Control Assessment Framework (IPCAF) surveys
    - Guidelines for prevention of bloodstream/surgical site infection
    - Cleaning protocols, hand hygiene compliance
    - Screening and isolation of multidrug-resistant bacteria
    - Qualitative interviews with stakeholders

- Focus groups with stakeholders
- Multicriteria decision analysis for formal decision making related to healthcare public polices
- Population-based surveys

Figure 4: Project framework

Building a network of infection prevention and control (IPC) model hospitals: The Orange Network

- Nigeria's IPC Program is dubbed 'Turn Nigeria Orange'
- Aims in its first phase were:
  - Key process indicator - hand hygiene compliance monitoring audit
  - Outcome indicator - surgical site infection
- Strong links with other relevant programs in the country, for example with the AMR Program
- These programs are all in line with the WHO's core components for IPC programmes
- Presently a network of 33 tertiary health facilities across the 6 geopolitical zones of Nigeria (figure 5)
- To be part of the Orange Network, institutions have to meet certain criteria including developing an infection prevention and control (IPC) action plan
- Aim is to implement the 8 WHO core components of IPC within the Nigerian context (https://www.who.int/teams/integrated-health-services/infection-prevention-control/core-components) in a phased manner

- Accomplishments so far:
    - Appointment of focal persons, establishment of IPC teams and committees with TORs
    - Baseline assessments
    - IPC rounds
    - Regular meeting of the IPC committees
    - Workplans addressing facility-specific gaps and priorities

- Next steps for this IPC program are to pilot surgical site infection surveillance, expand the network to cover all public health facilities, develop IPC standards and audit to monitor the implementation of the programmes

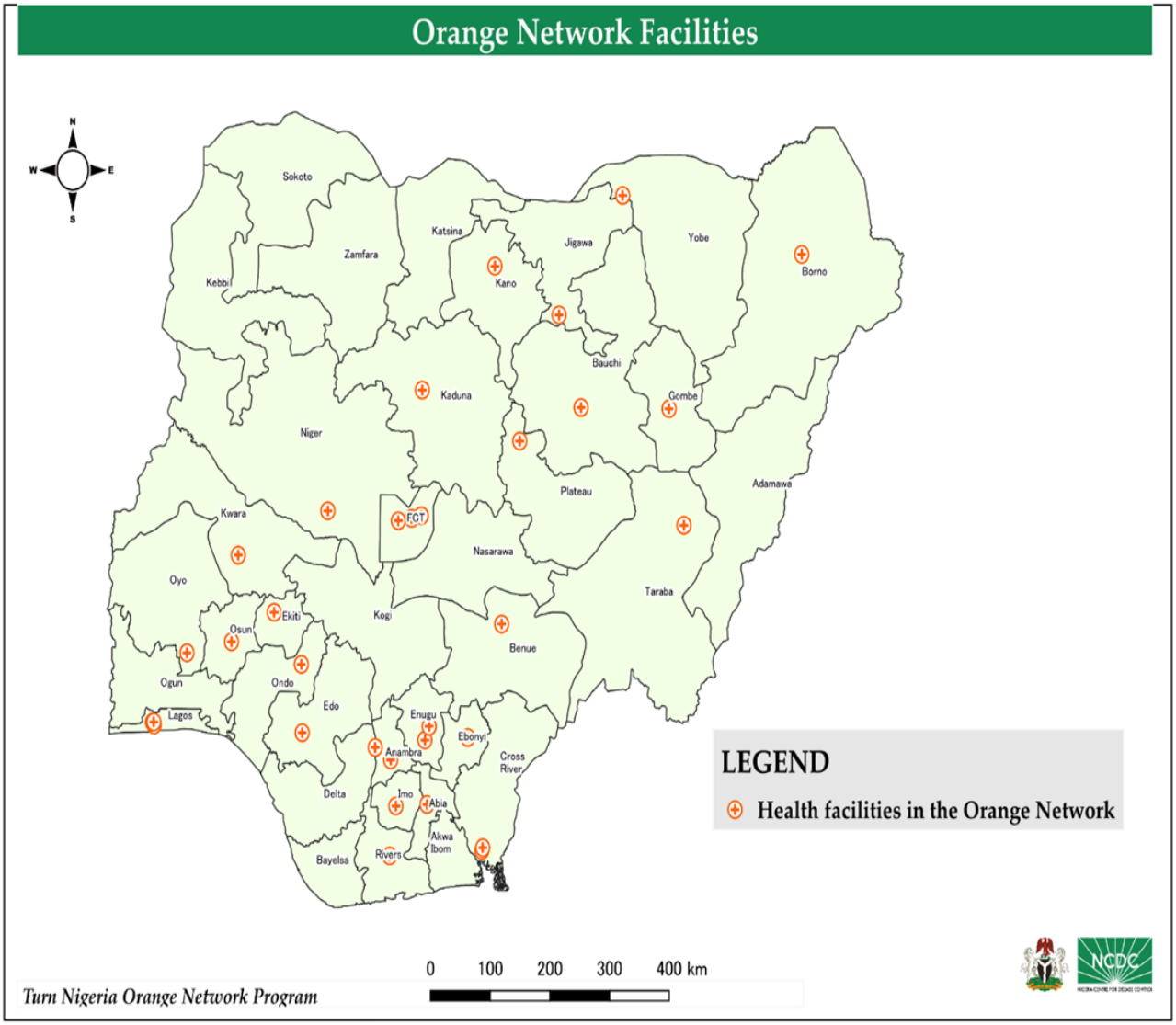


Figure 5: Orange network sites across Nigeria

Bacterial-fungal co-infections and antimicrobial resistance

- **The Problem:** Thinking has been of a single-pathogen model of infection and antimicrobial resistance. Yet, there is growing recognition of the role of polymicrobial infection in AMR
- **The Question:** How do the interactions between bacteria and fungi within the microbiome modulate the evolution of resistance?
- **The Focus:** Bacterial-fungal co-infections, specifically *Pseudomonas aeruginosa* & *Candida albicans* co-infections. Pseudomonas aeruginosa is an opportunistic bacterium which leads to lung infections in the immunocompromised. This pathogen is emerging as a global health threat due to its antibacterial resistance. Conversely, Candida albicans is an opportunistic fungus with antifungal tolerance. In individuals with Cystic fibrosis (who are immunocompromised), co-infection with pseudomonas aeruginosa and candida albicans is common, with devastating consequences, making this a very important clinical interaction
- The Project seeks to understand:
    - How bacterial-fungal interactions impact antimicrobial tolerance
    - The short-term response to antibiotics
    - Effectiveness of antimicrobials
    - How this impacts long-term evolutionary response
- Complementary expertise - Oxford population biology, Charité systems biology

The Pilot (see Figure 6):

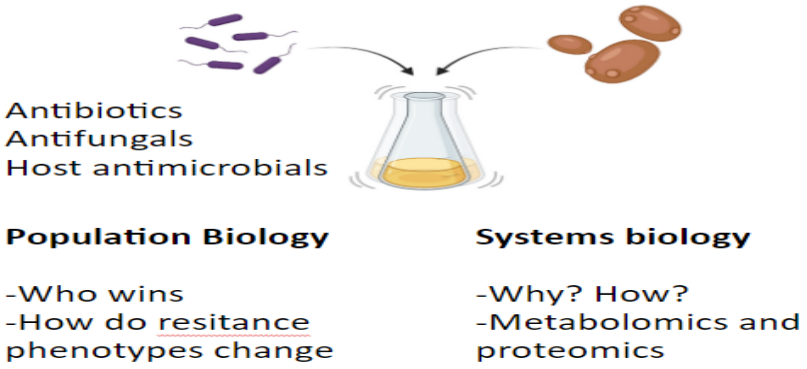


Figure 6: Bacterial-fungal co-infections and AMR

- **Long-term Vision:** Establish a collaborative partnership to tackle AMR using the combination of population biology and systems biology approaches in order to improve the use of existing antimicrobials and identify novel interventions

GlobalResist – Forecasting antibiotic resistance evolution – a new approach to address a major issue in global health

- Composed of an interdisciplinary team
- **The Problem**: Complexity of forecasting resistance, we mostly continue to use pesticides/antibiotics as if resistance is a temporary issue
- **Current Solution**: drug development, prudent use (human, animal husbandry), better and more rapid diagnostics
- **Solution proposed here:** Forecasting resistance that would be proactive, sustainable, and that could decrease the burden of newly-emerging resistance

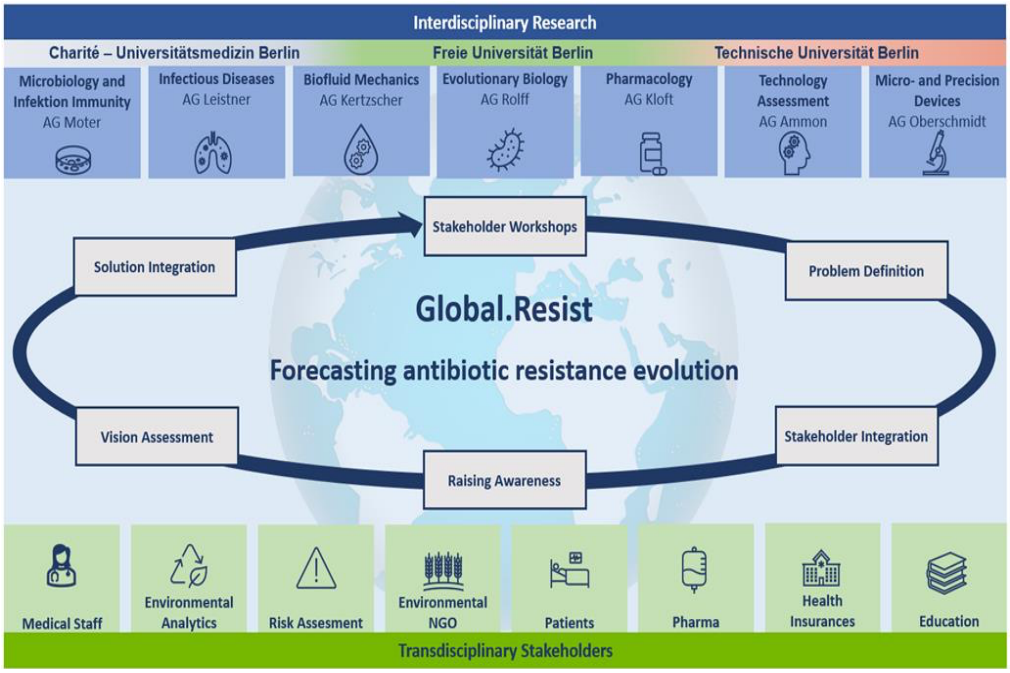


Figure 7: Global.Resist Framework

- This builds on work that is already present:
  - https://journals.plos.org/plosgenetics/article?id=10.1371/journal.pgen.100972
  - https://www.nature.com/articles/s41467-021-22757-1
  - https://pubmed.ncbi.nlm.nih.gov/31929521/
- Nevertheless, these methods are not practical for day-to-day work in hospital or farm settings
- **Goal:** to develop an experimental tool that is easy to use to estimate the risk of resistance. For instance, when hospitals develop antibiotic stewardship plans, they could test the probability of resistance evolution for their recommendation before it is applied. Of course, a big question for a 'global health project' is how scalable and affordable in a LMIC?
- **Prototype Device: Emulship**
- **The Idea**: For any antibiotic of interest or any bacterial species of interest, one could adapt this technology, and by doing so, generate experimental empirical data to estimate and inform resistance evolution for antibiotic stewardship plans for testing the

sustainability in relation to drug resistance for new drugs and also possibly contribute to individualised treatment and persistent infections

- Also, idea is to use it in different ways
- **Outcomes**: To add to the arsenal of methods for tackling AMR, to guide a more sustainable use of antibiotics, as resistance is delayed, incentivize the investment in drug development, reduce the spread of AMR genes and organisms into the environment and allow the treatment of persistent infections more efficiently

News Session

New global estimate on burden of AMR – GRAM project

- This paper was published in The Lancet and looks to estimate the global burden of bacterial AMR in 2019
- This is the first comprehensive examination of AMR across a wide range of bacterial pathogens and antibiotic combinations across the globe
- Incorporates the largest systematically correlated body of published and unpublished data sets, spanning in excess of 470 million cases of isolates covering a wide range of geographies and years

Main Findings:

- 4.95 million deaths associated with bacterial AMR
  - Third leading underlying cause of death among GBD level 3 causes, behind only ischemic heart disease and stroke
- 1.27 mullion deaths attributable to bacterial AMR
  - 12th leading underlying cause of death among BGD level3 causes, ahead of HIV, TB and Malaria

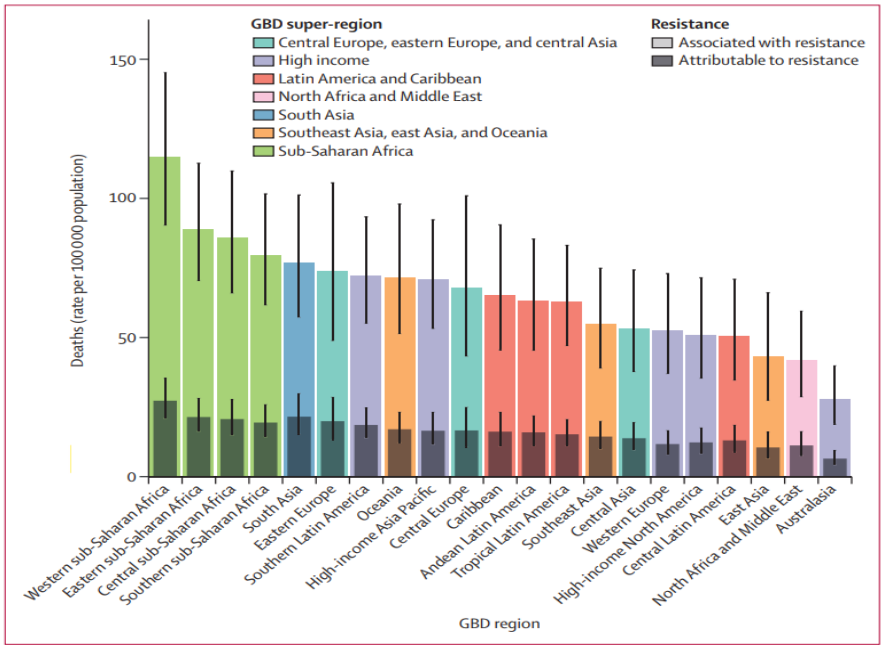


Figure 8: All-age rate of deaths attributable to and associated with bacterial antimicrobial resistance by GBD region, 2019

- Lower respiratory infections accounted for more than 1.5 million deaths associated with resistance in 2019
- Six leading pathogens for deaths associated with resistance (in order): E. coli, Staph aureus, Klebsiella pneumoniae, Strep pneumoniae, Actinobacter baumannii and Pseudomonas aeruginosa
- Top 6 pathogens responsible for 929,000 (660,000-1,270,000) deaths attributable to AMR and 3.57 (2.62-4.78) million deaths associated with AMR in 2019

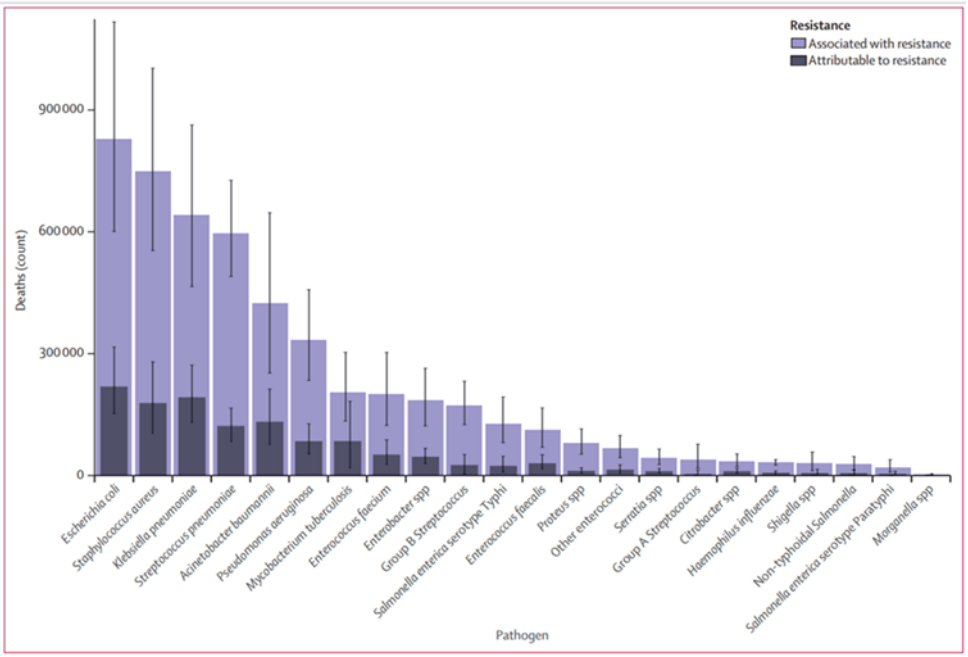


Figure 9: Global deaths (counts) attributable to and associated with bacterial antimicrobial resistance by pathogen, 2019

- **Regional differences in AMR burden were glaring**
    - Five regions had all-age death rates associated with bacterial AMR at over 75 per 100,000: four were in sub-Saharan Africa and south Asia
    - Sub-Saharan Africa faces the highest burden, with 255,00 deaths due to AMR in 2019 and a particularly high number of deaths from kleb. pneumo and Strep. Pneumo (figure 10)
- **Key limitations** included lack of assessment of data from AMR in the environment and animal/livestock sources as determinants or predictors of human AMR; less influential predictors for many bacterial-antimicrobial combinations; sampling (tertiary bias) bias as hospital data could've been skewed more towards urban population and/or more severe disease; data scarcity especially in sub-Saharan Africa
- **Next steps**: Incorporate a novel One Health modelling framework; further work on community acquired infections; more outreach regarding data sources; expand on collaborative efforts
- **Limited community data on AMR (hence the importance of the 16 March workshop)**

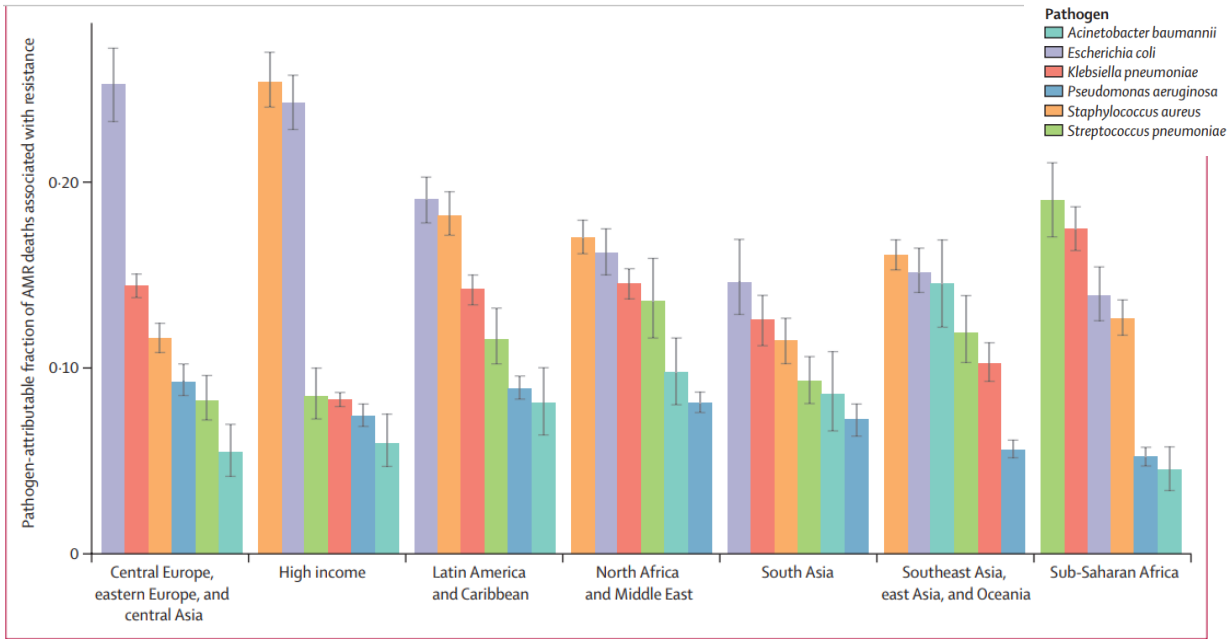


Figure 10: Pathogen-attributable fraction of deaths attributable to bacterial AMR for the six leading pathogens by GBD subregion, 2019

Update on FT Antibiotic Accountability Tracker

- Developers of the tracker are interested in providing a public outlet particularly to inform decision makers, policymakers, corporates and others who might bring pressure for necessary policy reform
- Going forward:
    - the capacity to update these existing data sets regularly and even automatically, so we can keep this sort of dashboard live of individual studies,
    - looking at ways to combine these and other datasets

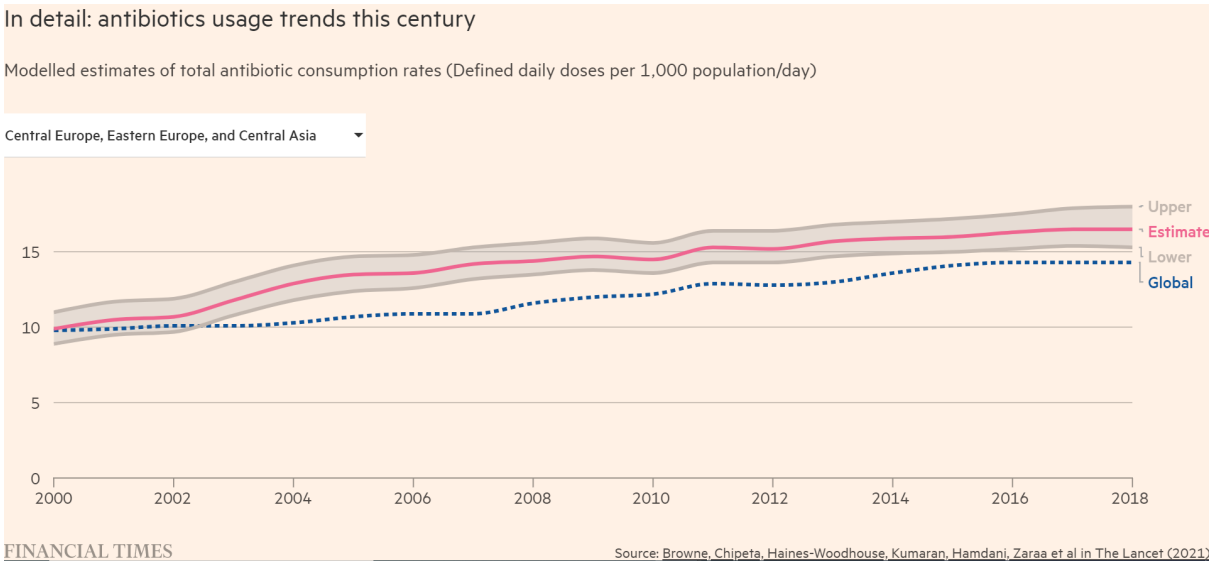


Figure 11: [Financial Times -Antibiotic usage trends in this century]

SECURE: Exploring new models of antibiotic drug pricing and access:

About GARDP:

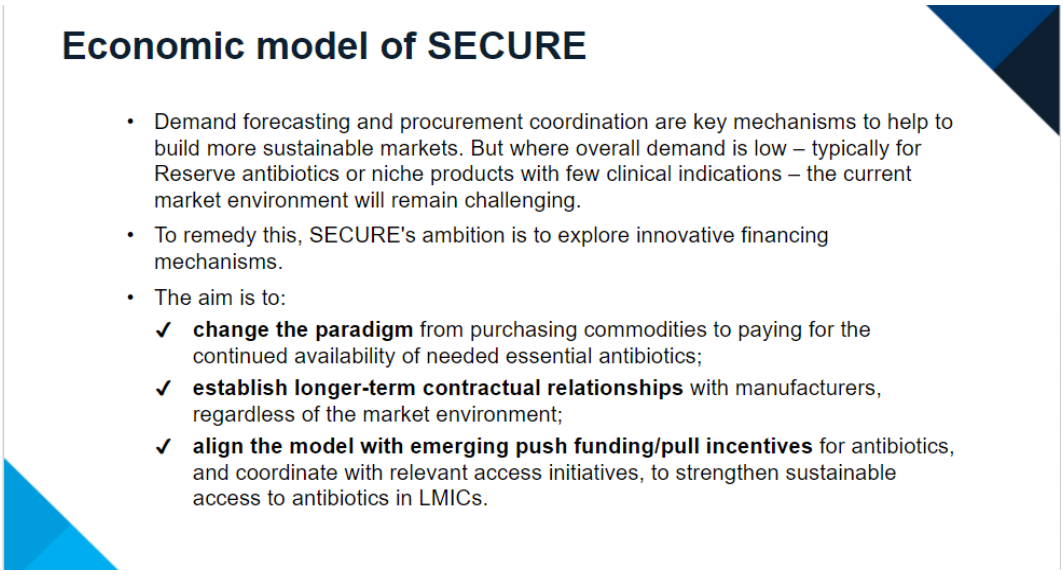
Figure 12: Mission, focus & approach of GARDP

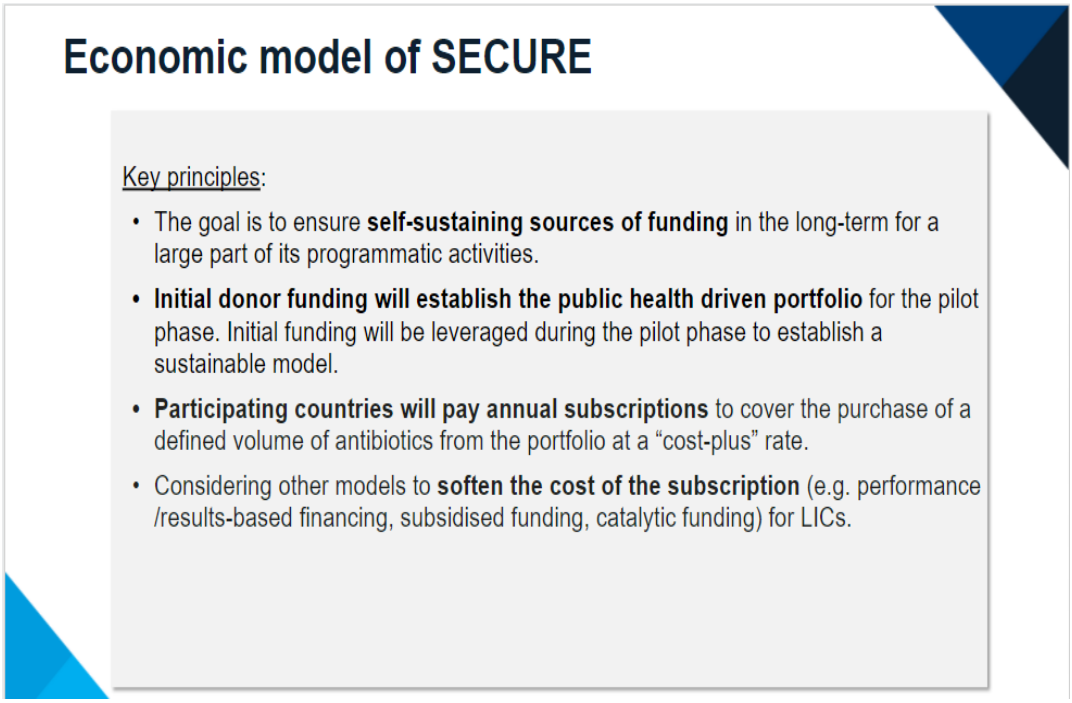
- GARDP is currently working on a project with the WHO called SECURE
- **Question:** how are repurposed drugs, new molecular entities going to be deployed
- Without appropriate access and ways to use antibiotics appropriately, we are going to fall short on some of the objectives we want to achieve in terms of AMR
- Current work has 2 components
    - Individual drug company development projects
    - How to look at a framework to support organisations and the private sector to introduce new antibiotic treatments more globally
- *The SECURE Project*: An 'Antibiotic Facility' similar to work done in areas such as TB
- SECURE's focus is on how to effectively introduce new antibiotics and secondly how to address the challenges of supply-chain interruptions and shortages of certain antibiotics

- **Objectives:**

    - To provide countries with sustainable access to new antibiotics to address drug-resistant infections, existing antibiotics that are not widely available or that suffer from frequent supply-chain interruptions and/or shortages
    - To establish a quality assured portfolio driven by public health and clinical needs and
    - To be open to all interested countries and other eligible entities

- **Economic model of SECURE:**





- **Key questions SECURE aims to answer:**
    - will any reimbursement mechanism established under SECURE be focused and more on paying for the functioning of SECURE and to ensure sustainable production and supply?
    - Would SECURE itself seek to be a 'pull incentive' to compensable patent holders for the development of new antibiotics?
    - Should a potential subscription payment model be:

        - Set up to compensate on the basis of cost-effectiveness?
        - based on a country's capacity to pay, disease burden and population size?
        - under a stewardship plan that can be monitored over time?
        - Based on agreed multi-annual payment separated from volume usage
    - Pre-pilot phase:
        - list and define potential model mechanisms
        - review- stakeholder consultation over viability of models
        - test and run- to select the most appropriate model

AMR in the Community Workshop

- Wednesday 16th March
- Concept note available here
- Aims to bring a multidisciplinary group of people particularly from the global south
- Will open further discussion on the model underlying GARDP's SECURE initiative

Discussions (including ZOOM chats) centred around the following themes

Collaboration

- Integrating Therapeutic drug development into IPC trials
- Possible collaboration between CoDe-ICI and GARDP
- Oxford-Charité collaboration in research (population biology and systems biology)

On Fish, Imports & AMR

- As Europe shifts to importing more food, there are concerns of importing antimicrobial resistance from fish. This led to testing being carried out with subsequent patterns of resistance not seen in countries importing this fish. Similarly, in LMICs, because fish is often imported from long distances, there is a potential to transport resistant strains over long distances
- An ongoing area of research is whether resistance found in fish comes from heavy metals from chemicals, i.e. the environmental aspect of antimicrobial resistance
- We need to consider the dumping of antimicrobials in Africa and SEA by international companies and find ways to hold these companies to account

Choice of Antimicrobials to use

- Choosing the right antimicrobial in clinical setting or in animal husbandry
- Guidelines and recommendations are in place, though more often antimicrobial choice is an empirical decision

- In animal husbandry specifically, you make use of the data available, and the product license and limits for particular species
- In places like Vietnam, Myanmar, vets are not easily accessible nor diagnostic facilities. Thus; choice for antimicrobial used is done based on the experiences of farmers, discussion with peers, advice from drug sellers
- Additionally, cost of antibiotics, which tends to be cheap in places mentioned above impacts choice and usage
- Other factors are regulations that are applicable more to commercial farms and not subsistence farmers

Inadequate data

- A recurrent theme regarding AMR and the environment, is the need for much higher quality data from many regions of the world
- Lack of data on how to use and deploy new drugs

Learnings from COVID-19 to make SECURE platform better

- mRNA tech transfer hubs, COVAX yet to take off fully
- support and collaboration as well as the issues of intellectual property

RESOURCES SHARED BY COLLEAGUES

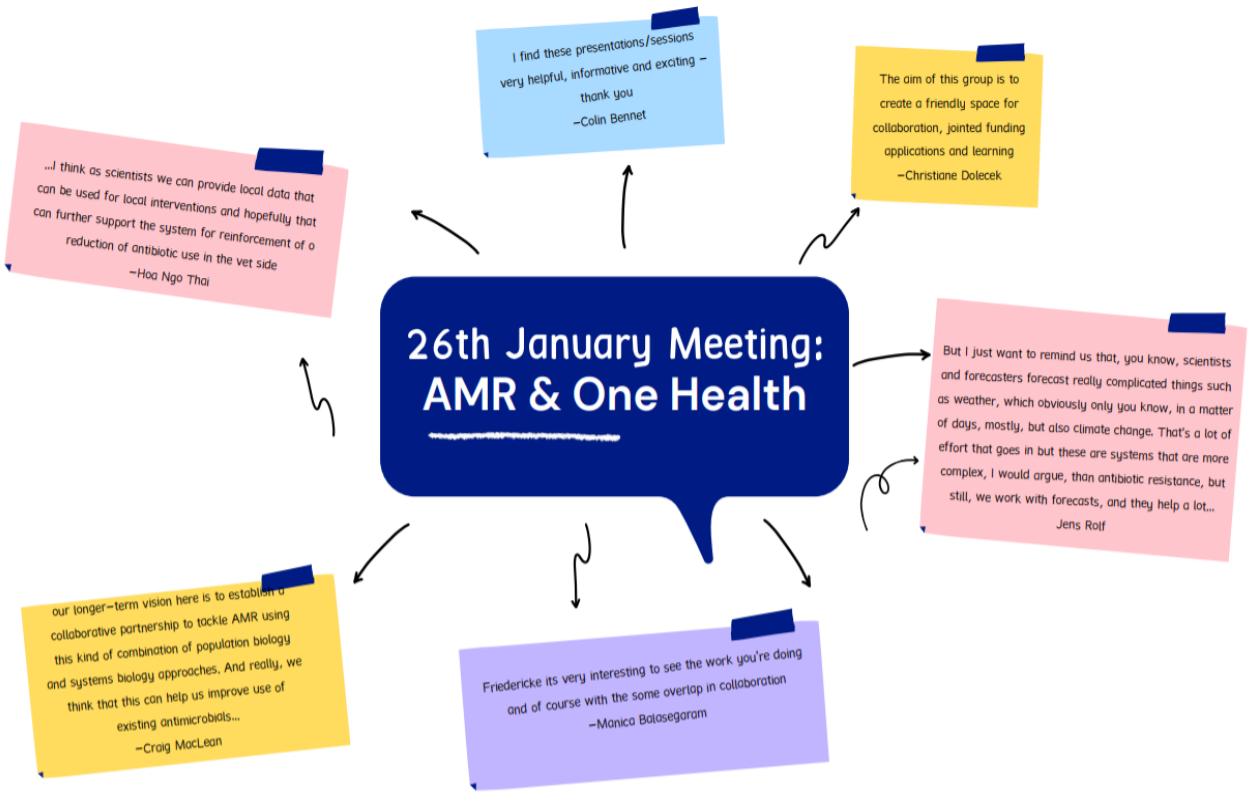
- REVERSE project: a stepped-wedge trial testing different IPC/ABS (bundles). This is a stepped-wedge trial testing different IPC/ABS (bundles) in high-prevalence settings in the EU. There is also qualitative work and discrete choice experiments in some LMIC to identify barriers and facilitators of implementation of interventions that are shown to be most effective/affordable in the trial:
  https://cordis.europa.eu/project/id/965265

- On Fish and AMR, research by Jennifer Cole and Team:
  https://www.sciencedirect.com/science/article/pii/S095671352100236X

- Part-time lectureship in Global Health advertised by RHUL on:
  https://jobs.royalholloway.ac.uk/vacancy.aspx?ref=0122-017

- Work by Financial Times Team:

  - https://www.ft.com/content/accf1951-48db-40f8-910f-16f66ff5531d
  - https://www.ft.com/content/11e4788e-82e9-4e23-bfe5-093c1ed70659 ,


26th January Meeting: AMR & One Health
I find these presentations/sessions very helpful, informative and exciting – thank you
–Colin Bennet
The aim of this group is to create a friendly space for collaboration, jointed funding applications and learning
–Christiane Dolecek
...I think as scientists we can provide local data that can be used for local interventions and hopefully that can further support the system for reinforcement of o reduction of antibiotic use in the vet side
–Hoa Ngo Thai
But I just want to remind us that, you know, scientists and forecasters forecast really complicated things such as weather, which obviously only you know, in a matter of days, mostly, but also climate change. That's a lot of effort that goes in but these are systems that are more complex, I would argue, than antibiotic resistance, but still, we work with forecasts, and they help a lot...
Jens Rolf
our longer-term vision here is to establish a collaborative partnership to tackle AMR using this kind of combination of population biology and systems biology approaches. And really, we think that this can help us improve use of existing antimicrobials...
–Craig MacLean
Friedericke its very interesting to see the work you're doing and of course with the some overlap in collaboration
–Manica Balasegaram