File prepared as part of work to support access to antibiotics/stewardship project for GARDP/WHO

1. Agencies that Provide Data for a possible data-sharing portal

We need a core data management mechanism as part of the bigger SECURE mechanism. Our approach visualises SECURE as an intermediary between buyers (governments, hospitals possibly, etc.) and sellers (companies) of antibiotics. Others (not the SECURE intermediary), manage the stocks and flows of products. A core part of SECURE will be an informational system that acts as a virtual inventory/supply informational system based on novel applications of AI/digital tools. The AI builds a knowledge base that predicts needs and flows, learns about how the system is performing, etc. and has the ability to self-correct and redirect flows. Many new digital and AI tools are being created (to track products, to deal with SF products, to monitor for resistance, etc.) and SECURE would piggy-back on some of those new tools, not develop a whole new system from scratch. It could nevertheless be a trailblazer in the use of such tools. Other global mechanisms do not face the stewardship challenges of abx, with stewardship an important part of the purpose of this information system, the information system sending guidance to the procurement process.

If we better know where the global system is, we can move towards fewer stock outs and more stable flows through global systems (mismatch is a supply and incentives issue but also a data management/market intelligence issue). Current country-level procurement systems have three flows: information; products; financial. They are separate but also linked. Currently, a seller needs to see/know of the financial flow matching their product flow, and this raises risks. Our task is to redesign this flow ecosystem to separate /make more independent / buffer from each other these different flows, using the SECURE mechanism as support tool (as a simple example, the SECURE mechanism's information system 'knows' where stocks are and where flows will be and also has insurance-tools built in, so it can ensure/insure supply even if currently the financial flow is not in place but will be shortly, i.e. SECURE smooths flows by a combination of data management tools, funding mechanism, its own guarantees, etc.).

Furthermore, if an abx seller sells direct to countries, a volume guarantee or a subscription fee at the country level might create perverse incentives at the local level (at the margin, the product is free). If a seller has a guaranteed volume from SECURE, they can be assured of payment for a set quantity and they do not engage in country level activity and SECURE handles the local incentives. SECURE takes some of the local mismatch of information, funding, and products and matches these up inside its informational management system (the match is not real, but virtual and guaranteed even if the timings are not synchronous on the ground) but even if there are guaranteed volumes or subscription fees and in theory uncontrolled volumes, this separation reduces perverse incentives.

Stock outs are related to funding risk. SECURE takes that away but might need insurance to do that task.

Further, a lot of our colleagues in global health (and there are many new schemes) are working to improve market intelligence. There is value in articulating the value of what they are doing by showing its value creation inside SECURE.

In our thinking on pooling forecasts, the transparency of demand at country/regional/pool level can be explicit. And we notice again the role of insurance/guarantee here to shield suppliers from forecasts being less than perfect. Insurance/guarantee issues are clearer in the case of rotating stockpiles (regional/country) which are irregular.

Table 1: Major international surveillance networks

Host	Acronym	Name	Description
European Centre for Disease Prevention and Control (ECDC)	EARS-Net	European Antimicrobial Resistance Surveillance Network	Europe-wide network of national surveillance systems of AMR for seven bacterial pathogens causing invasive infections in humans.
World Health Organization (WHO)	CAESAR	Central Asian and Eastern European Surveillance of Antimicrobial Resistance	Network of national AMR surveillance systems including all countries of the WHO European Region that are not part of EARS-Net.
European Centre for Disease Prevention and Control (ECDC)	ESAC-Net	European Surveillance of Antibiotic Consumption Network	Europe-wide network of national surveillance systems, providing European reference data on antimicrobial consumption, both in the community and in the hospital sector.
European Centre for Disease Prevention and Control (ECDC)	HAI-Net	European Healthcare Associated Infections Network	Europe-wide network, coordinating point prevalence survey of HAI and antimicrobial use in acute care hospitals, surveillance of surgical site infections, surveillance of HAI in intensive care units and the repeated prevalence surveys of HAI and antimicrobial use in long-term care facilities.
European Centre for Disease Prevention and Control (ECDC)	FWD-NET	European Food- and Waterborne Diseases and Zoonoses	Surveillance on 21 human diseases acquired through consumption of food or water, or through contact with animals. Parasitic and viral agents are included. AMR data are collected for *Salmonella*, *Campylobacter*, and *E. coli*.
European Medicine Agency (EMA)	ESVAC	European Surveillance of Veterinary Antimicrobial Consumption	Europe-wide network (30 countries) which collects standardised data on the sales of antimicrobial drugs in animals in EU/EEA.
European Food Safety Authority (EFSA)		Network on Antimicrobial Resistance Data Reporting	European network (31 countries) collecting harmonised data on antimicrobial resistance in zoonotic and indicator bacteria from food-producing animals and food in EU/EEA.
World Health Organization (WHO)	GLASS	Global Antimicrobial Resistance Surveillance System	Surveillance of human priority bacterial pathogens considered the greatest threat globally (58 countries included); includes information from other surveillance systems, such as foodborne AMR, monitoring of antimicrobial use and surveillance of HCAI. *Candida* surveillance is starting in 2020 and data will be collected retrospectively from 2019.

Host	Acronym	Name	Description
WHO AGISAR	Tricycle	One Health Surveillance	Monitoring of ESBL-*E. coli* in humans, the food-chain and the environment.
Asia Pacific Foundation for Infectious Diseases	ANSORP	Asian Network for Surveillance of Resistant Pathogens	International research group for antimicrobial researchers in the Asian region - consists of over 230 investigators and 123 centres in 14 countries in Asia and the Middle East.
MSD	SMART	Study for Monitoring Antimicrobial Resistance Trends	Monitoring the in vitro susceptibility of clinical bacterial isolates to antimicrobials in intra-abdominal infections worldwide
GSK	SOAR	Survey of antibiotic resistance	Collection of antibiotic surveillance data on the susceptibility of pathogens that cause community-acquired infections in countries where resistance data can be scarce.
Pfizer	ATLAS	Antimicrobial Testing Leadership And Surveillance	Interactive website that provides global AMR surveillance data from 60 countries. Integrates three surveillance programs (TEST: Tigecycline Evaluation and Surveillance Trial, AWARE: Assessing Worldwide Antimicrobial Resistance Evaluation, and INFORM: International Network for Optimal Resistance Monitoring). Generated global bacterial susceptibility data versus a panel of antibiotics from 760 sites in 73 countries.
Wellcome Trust, UK	SEDRIC	Surveillance and Epidemiology of Drug-resistant Infections Consortium	Network of 12 international experts to share expertise and act to tackle the gaps in AMR surveillance and epidemiology, develop guidelines and tools to encourage data sharing, translate scientific evidence into policy.
COMBACTE-Magnet	EPI-Net	Surveillance platform of antimicrobial resistance including human and animal data	Network of surveillance systems, experts and stakeholders collecting resistance data on the WHO priority pathogens for R&D of new antibiotics.
Global Action Fund for Fungal Infections	GAFFI	Surveillance of antifungal use and fungal disease	GAFFI presents burden of disease maps for fungal diseases, fungal allergies and use of antifungals.

2. Further Sources and Academic/Research Institutions

- Centre for Tropical Medicine and Global Health. See link
- Oxford/IHME - GRAM Project. See link

- IDDO. See link
- Robert Koch Institute. See link
- AMR Centre at the LSHTM. See link
- European Center for Disease Control and Prevention (ECDC). See link
- Food and Agricultural Organization of the United Nations (FAO). See link
- FAO/OIE/WHO Tripartite Organisations. See link
- Global Antibiotic Research & Development Partnership (GARDP). See link
- World Organisation for Animal Health (OIE). See link
- Global AMR R&D HUB See link

3. Oxford-based and other Research Institutions

There is a hive of activity in and around Oxford, with researchers looking to collaborate to strengthen the rich data and research that is available. This presents an opportunity for SECURE to plug in an access Work Package.

3.1 GRAM (Global Research on Antimicrobial Resistance) Project/Oxford Research Group Anti-Microbial Consumption and Resistance Burden Estimation (MICROBE)

GRAM is a flagship project supported by the UK Department of Health/Fleming Fund, the Wellcome Trust, and the Bill and Melinda Gates foundation in the first phase.

- Partnership between the Institute for Health Metrics and Evaluation (IHME) at the University of Washington and Centre for Tropical Medicine and Global Health at the University of Oxford
- Oxford Research Group Anti-Microbial Consumption and Resistance Burden Estimation (MICROBE) is investigating and quantifying levels and trends of antimicrobial resistance and antimicrobial consumption across the globe and over time to help inform policy and interventions.
- First comprehensive examination of AMR in 23 bacterial pathogens, and 88 drug bug combinations in all 204 countries. To be extended to time series estimation for 1990-2019 in the first instance and with extensions to 2023/2024 in second phase.
- Systematic search for published and unpublished datasets identified spanning more than 470 million cases or isolates (7585 study-location years) in phase 1 with further expansion in phase 2.
- Country level AMR burden in 2019 papers by WHO region in the pipeline as well as prevalence of resistance for priority bacteria-antibiotics for 2000-2019.
- Early 2023 will see release of first country-year level series of estimates for AMR associated/attributable burden.

• GRAM Phase 2 commenced in October 2022 with funding support from DHSC/Fleming Fund and the Wellcome Trust (from May 2023).
• Primary work packages focused on AMR burden function (integration into the GBD), additional work packages on QoM-SF-AMR, one-health, capacity development, establishment of global AMR hub/data repository. Willingness to add access intelligence to this.
• Strong in-house collaborators have been forged for phase 2 with IDDO/WWARN and FORESFA and OTN, e.g. ABACUS and ACORN

GRAM Project Data:
Source Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis, The Lancet, 2022.

Data inputs by source type

Source type	Number of study-GBD location-years	Sample size	Sample size units	Estimation step								
				1. Sepsis	2. Infectious syndrome	3. Case fatality rate	4. Pathogen distribution	5. Antibiotic use	6. Fraction of resistance	7. Resistance profiles	8. Relative risk of death	9. Relative length of stay
Multiple cause of death (MCoD)	2980	120,871,372	Deaths									
Hospital discharge	391	192,533,415	Discharges									
Microbial or laboratory data with outcome	1102	3,060,802	Isolates									
Microbial or laboratory data without outcome	2302	145,067,113	Isolates									
Literature studies	607	701,356	Cases or isolates									
Single drug resistance profiles	158	8,648,390	Isolates									
Pharmaceutical sales	1536	1,536	Study-country-years									
Antibiotic use among children under 5 years old who reported illness	203	151,455	Households surveyed									
Mortality surveillance (Minimally invasive tissue sampling [MITS] from Child Health and Mortality Prevention Surveillance [CHAMPS])	7	870	Deaths									
Linkage (mortality only)	38	264,010	Deaths									
Grand Total	9,324	471,300,319										

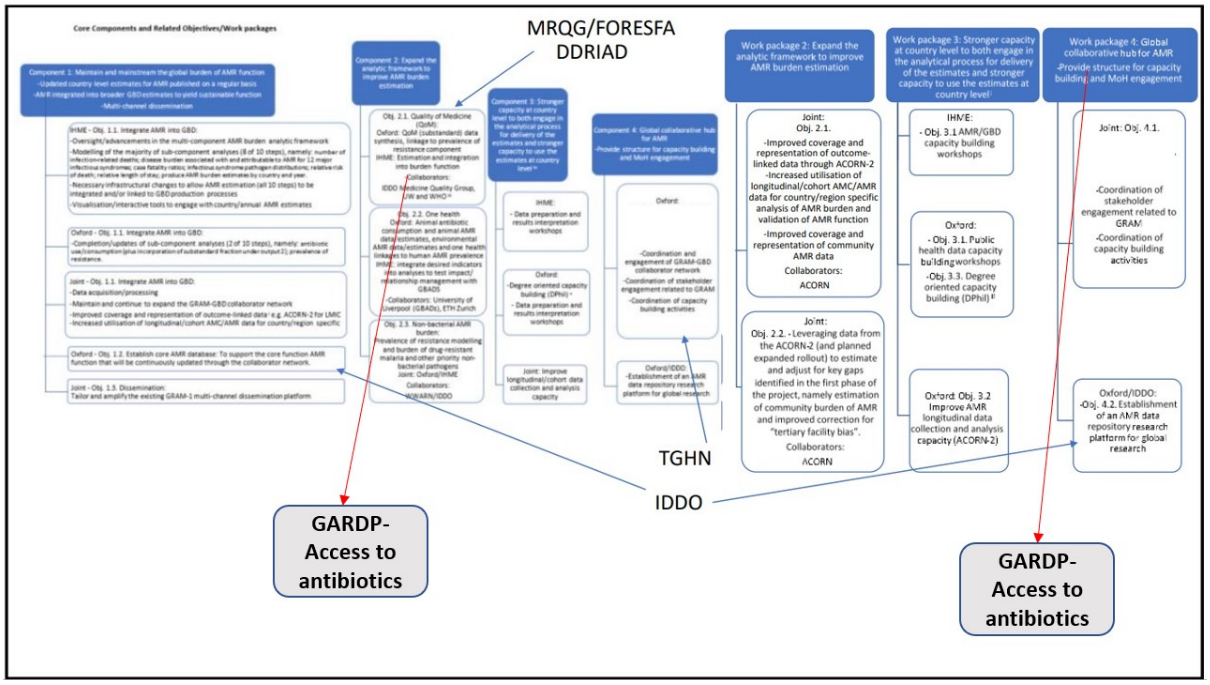
Data Input by Region & Data Gaps:

	Component 1: sepsis and infectious syndrome models*	Fraction of countries represented in component 1	Component 2: case-fatality ratio	Fraction of countries represented in component 2	Component 3: pathogen distribution	Fraction of countries represented in component 3	Component 4: fraction of resistance†	Fraction of countries represented in component 4	Component 5: relative risk	Fraction of countries represented in component 5
Andean Latin America	0	0/3	1784	2/3	12 010	2/3	538 644	3/3	4338	2/3
Australasia	320 909	1/2	94 818	1/2	6 294 677	2/2	4 653 832	2/2	5211	2/2
Caribbean	0	0/19	2858	5/19	6225	5/19	68 078	10/19	529	1/19
Central Asia	0	0/9	43 852	2/9	2785	1/9	304 341	9/9	6065	1/9
Central Europe	0	0/13	371 112	10/13	627 844	11/13	3 148 864	13/13	397 885	10/13
Central Latin America	8 130 066	2/9	3 932 601	9/9	11 641 626	8/9	829 686	9/9	20 210	5/9
Central sub-Saharan Africa	0	0/6	0	0/6	770	2/6	40 243	6/6	0	0/6
East Asia	1 189 309	1/3	385 443	2/3	257 522	2/3	2 501 536	3/3	185 980	2/3
Eastern Europe	0	0/7	118 754	4/7	64 212	5/7	968 565	7/7	102 904	4/7
Eastern sub-Saharan Africa	292	3/15	6388	4/15	68 791	9/15	474 280	14/15	3436	2/15
High-income Asia Pacific	0	0/4	135 907	3/4	99 042	3/4	18 909 332	4/4	7577	3/4
High-income North America	84 520 574	2/3	7 184 424	3/3	7 255 147	2/3	32 205 001	3/3	14 071 025	2/3
North Africa and Middle East	0	0/21	209 479	13/21	53 833	16/21	531 120	21/21	90 079	10/21
Oceania	0	0/18	0	0/18	20	1/18	4297	12/18	0	0/18
South Asia	54	1/5	77 811	4/5	51 810	4/5	1 413 840	5/5	97 131	4/5
Southeast Asia	0	0/13	195 087	9/13	91 259	8/13	3 128 014	12/13	172 947	8/13
Southern Latin America	0	0/3	200 665	3/3	73 512	2/3	740 385	3/3	5000	1/3
Southern sub-Saharan Africa	4 696 789	1/6	80 717	2/6	4 699 304	2/6	910 509	6/6	1051	1/6
Tropical Latin America	17 224 511	1/2	3 988 611	1/2	20 956 932	2/2	286 450	2/2	6443	1/2
Western Europe	10 599 906	2/24	94 506 554	20/24	105 183 184	21/24	18 909 732	21/24	932 016	21/24
Western sub-Saharan Africa	83	2/19	26 985	9/19	21 896	10/19	369 482	18/19	14 880	2/19

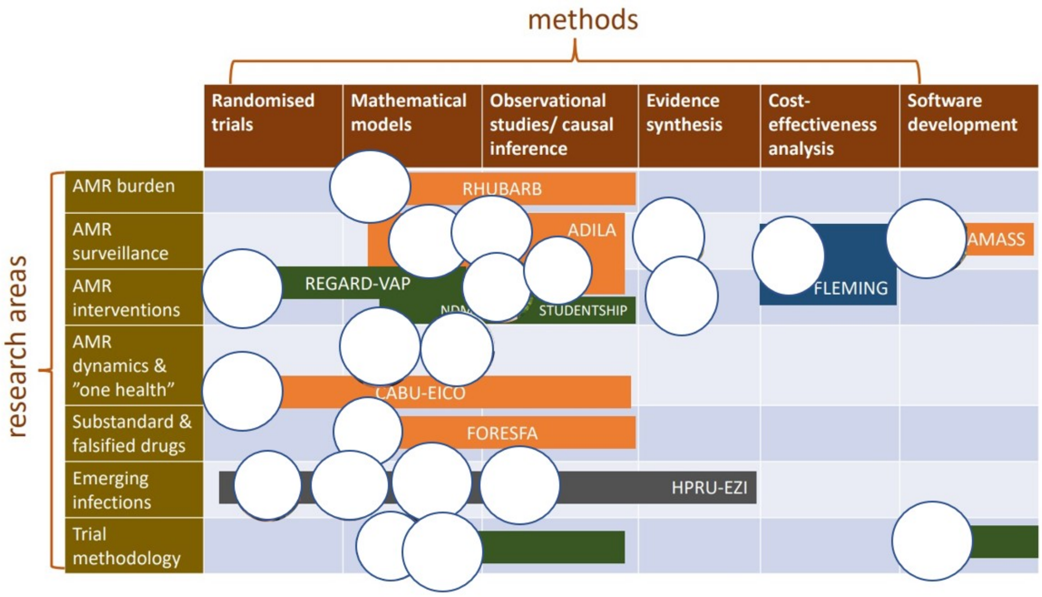
Total sample size and fraction of countries covered for each modelling component by GBD region. The units for sample size are deaths for sepsis and infectious syndrome models; cases for case-fatality ratios; cases, deaths, or isolates for pathogen distribution; pathogen-drug tests for fraction of resistance; and pathogen-drug tests for relative risk. Sample sizes reflect model-specific selection criteria, resulting in lower totals for the sepsis, infectious syndrome, case-fatality ratio, and pathogen distribution models in this table than those in figure 1. Totals for fraction of resistance and relative risk are higher in this table than in figure 1 because of the difference in units for certain source types, such as microbial data (isolates in figure 1, pathogen-drug tests here). Several data sources inform multiple components; therefore, data points should not be summed across a row as that will lead to duplication. More information on the data types used and the components that they inform is presented in the appendix (pp 8–15). GBD=Global Burden of Diseases, Injuries, and Risk Factors Study. *The data points listed in the sepsis and infectious syndrome models include only sources used to determine the fraction of sepsis in non-communicable diseases; maternal, neonatal, and nutritional diseases; and injuries, as well as the distribution of infectious syndromes; final estimates of the number of deaths in each infectious syndrome were generated by multiplying the fractions of sepsis and infection syndromes on GBD 2019 death estimates; GBD 2019 death estimates include 7417 sources with 28 106 location-years of data for under-5 mortality and 7355 sources with over 7322 location-years of data. †For sources in the fraction of resistance modelling component, de-duplication across antibiotic resistance tests was not possible, leading to potential double counting, as seen in the high-income Asia Pacific region.

Table 1: **Data included in each modelling component by region and the fraction of countries represented in each region**

3.2 Examples of possible fits of GARDP access to antibiotics:

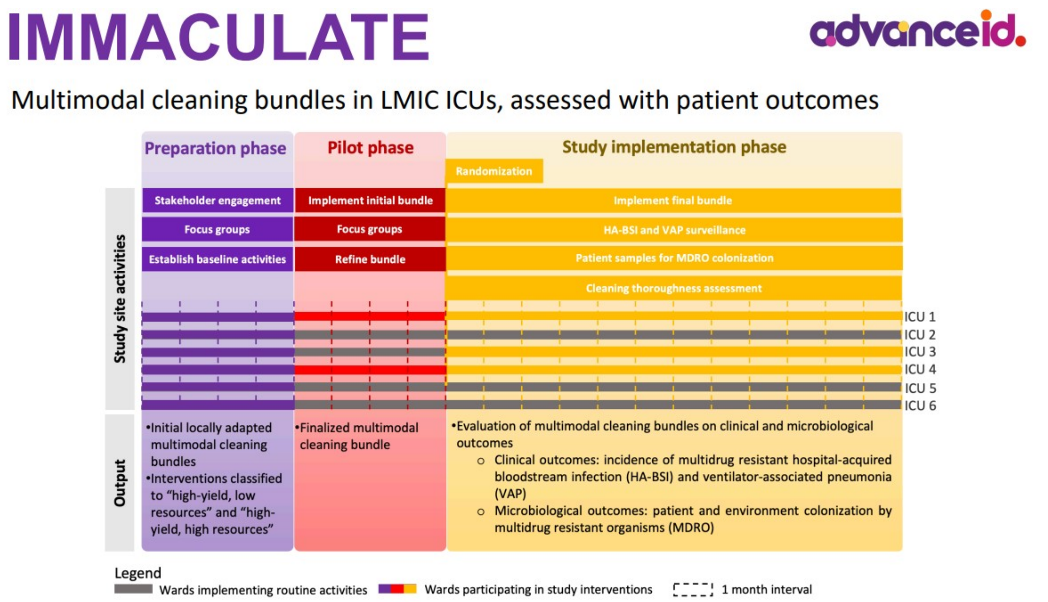


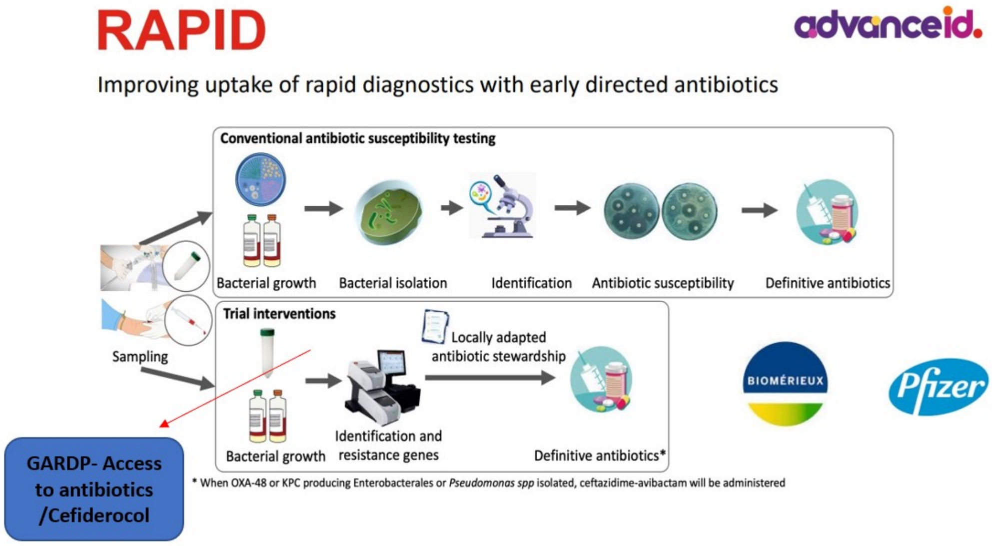
3.3 Drug-Resistant Infections and Disease Dynamics (DRIaDD)



3.4 Advance-ID

A network of more than 30 hospitals across Asia collaborating in the conduct of clinical research in infectious diseases. Their vision is 'to be the "go-to" for evaluation of new antimicrobials, diagnostics or prevention strategies relevant to antimicrobial resistance and other infectious diseases. Some of their clinical trials are:





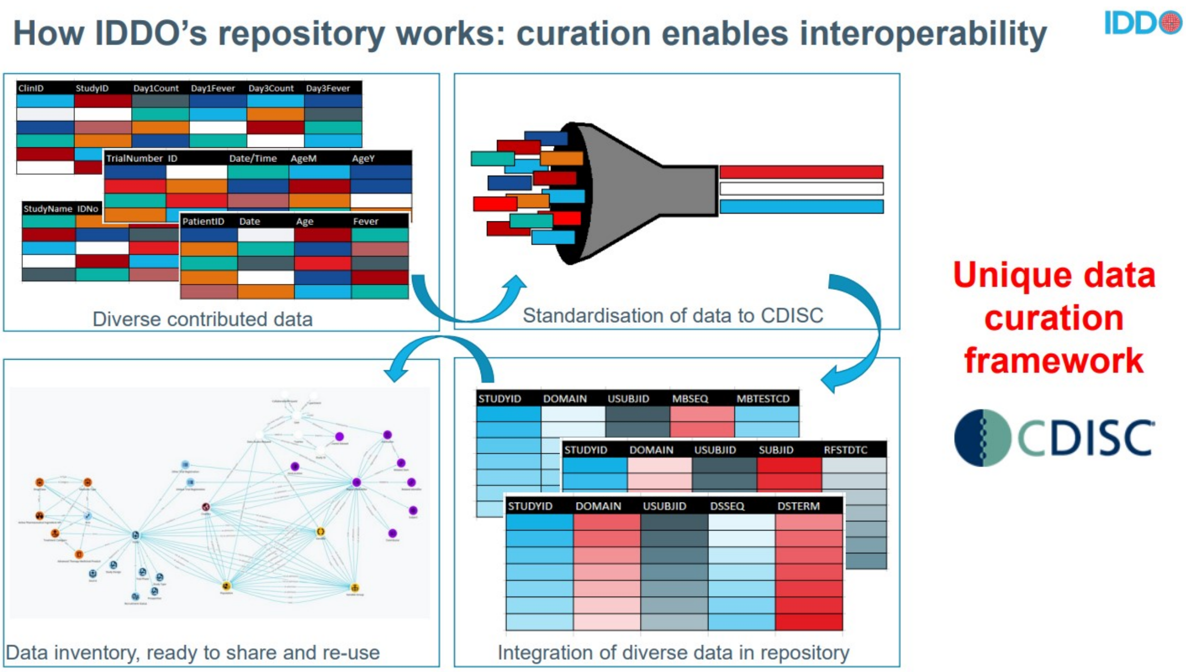
3.5 Medicine Quality Research Group

The research areas of the group include:

- Research on epidemiology, detection, forensics and public health impact of SF medical products.
- Above – plus modelling of SF-AMR interactions, and analysis of prioritization of SF in AMR NAP; workshop, with GRAM; plus ABACUS project; plus ecology of compartments where AMR is arising and lag between antibiotic use and AMR.
- Ghana, Tanzania, India, Nigeria, USA, Italy, Lao, Thailand/ modellers, WHO-ISF, other groups working on SF and AMR, pharmacologists, medicine regulators, social scientists, policy makers.
- Evaluation of screening devices for API quantitation, better links with those working on medicine quality in livestock (WOAH, FAO…) 5. In future chemometricians, microbiologists, pharmacopeial scientists.

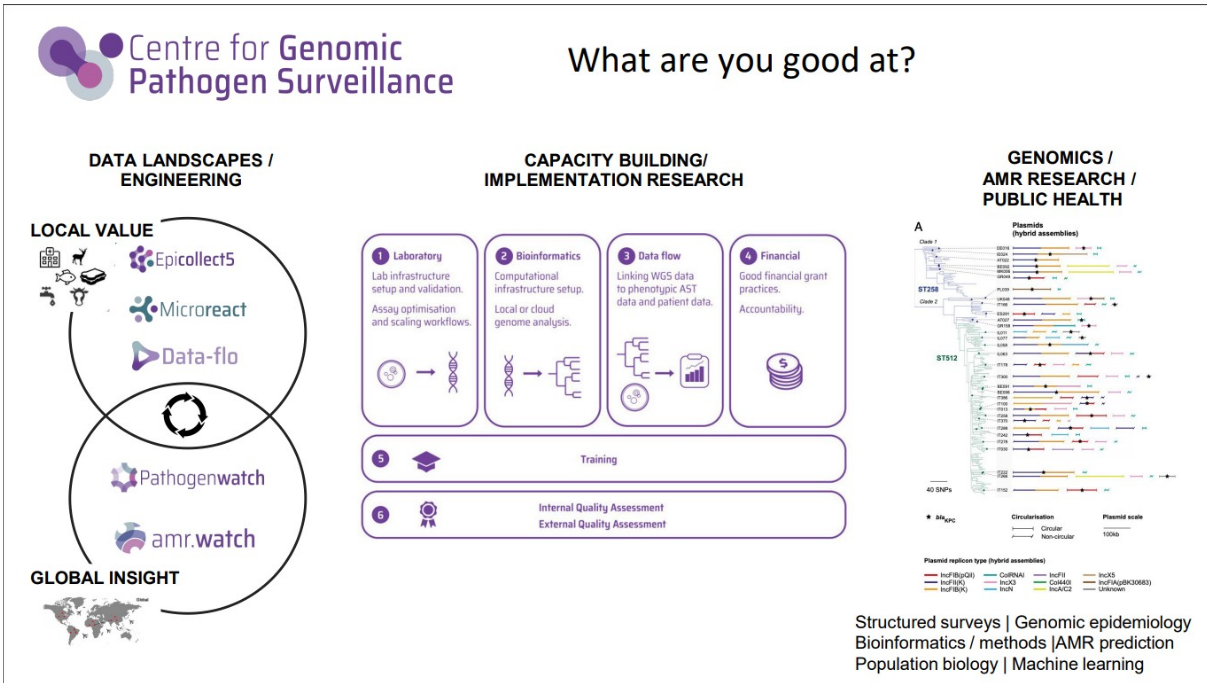
3.6 IDDO

The Infectious Disease Data Observatory aims to be FAIR, equitable and sustainable data platform for infectious diseases. Its mission is to 'accelerate the effective treatment and control of infectious diseases by strengthening research and the generation of evidence for policy through equitable data use'.



3.7. Centre for Genomic Pathogen Surveillance

The centre provides universal surveillance strategies and builds capacity in sequencing, informatics, financial management, data collection and analysis in collaboration with CDC, ECDC, FAO, NIH, NIHR and WHO.



4. Using AI to support a novel new antibiotic procurement mechanism

Lately, AI has garnered much interest and debate. It has far-reaching applications, especially in healthcare. With this in mind, The ITU/WHO set up a focus group on Artificial intelligence for health, with over 20 topic groups in areas such as radiology, dermatology, cardiology, and AI-based symptom checkers and so forth. However, its application in infectious diseases /antimicrobial resistance has been mainly limited to diagnostics, resistance modelling, new drug research and development (Topol, E.J. High-performance medicine: the convergence of human and artificial intelligence. *Nat Med* 25, 44–56 (2019). https://doi.org/10.1038/s41591-018-0300-7). With the proposal being made for new topics/subtopics like AI-based early warning scores for patient safety, there is a strong case to be made for a subtopic/topic or indeed a focus group on its own on the role of AI in supporting an antibiotic procurement mechanism. The 'silent pandemic' of AMR, as well as the double burden of lack of access and misuse of antibiotics, makes this even more justified. The focus group/sub-topic could explore the applications of AI in boosting local, regional, and perhaps even a global antibiotic procurement model/mechanism (See :https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(21)00463-0/fulltext, and two replies: https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(22)00091-2/fulltext and https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(22)00170-X/fulltext

Some of this might be addressed by AI and digital health tools, e.g:

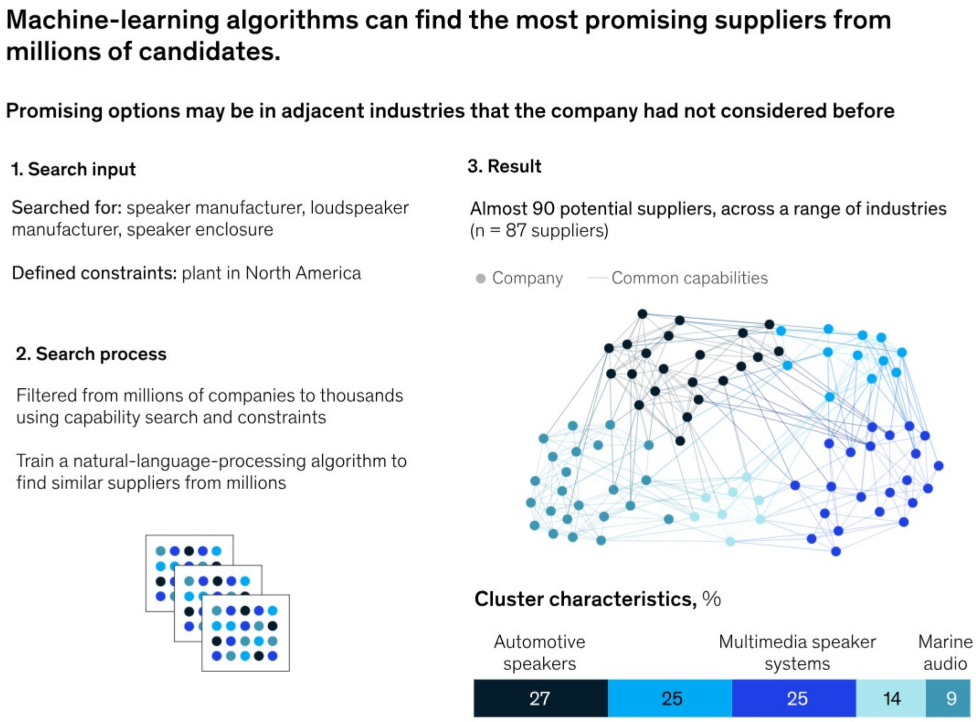
- continuous monitoring,
- filling in data gaps in of antibiotic consumption in LMICs,
- The linking of nationwide antimicrobial resistance data from the private and public sector (reflected in the work the GRAMP project is doing)
- Tracking appropriate and inappropriate use
- be flexible and based on regularly updated surveillance that can help ensure products included in the model meet regional and changing public health needs and predict coming needs based on evolution of resistance and use of currently available antibiotics.
- Consolidate the market, as far as regional epidemiology allows.
- Tracking pricing transparency, quality standards, etc.
- Tracking provisions tied to financial market incentives.

4.1. Other ways AI could help:

1. Demand Forecasting: AI algorithms can analyze historical data on antibiotic usage, patient demographics, disease patterns, and other relevant factors to forecast future demand for antibiotics. This information can help procurement agencies plan their purchasing requirements more accurately, ensuring an adequate supply of antibiotics. See https://www.forbes.com/sites/forbestechcouncil/2023/02/06/5-ways-ai-can-benefit-demand-forecasting-and-inventory-planning/?sh

2. Inventory Management: AI has already been employed for inventory management (hypersonix, https://addepto.com/blog/ai-in-inventory-management/). It could optimize inventory management by analyzing real-time data on stock levels, expiration dates, and consumption patterns. It could automatically generate purchase orders or trigger alerts when stock levels are low, helping to prevent stockouts.

3. Supplier Selection: AI can assist in evaluating potential suppliers based on factors such as product quality, price, delivery capabilities, and reliability. By analyzing large amounts of data, AI algorithms can help procurement agencies make informed decisions about selecting the most suitable suppliers for antibiotics.



Source : https://www.mckinsey.com/capabilities/operations/our-insights/with-artificial-intelligence-find-new-suppliers-in-days-not-months

4. Market Analysis: AI can monitor and analyse the antibiotic market, tracking factors such as pricing trends, availability, and regulatory changes.

5. Quality Assurance: by analyzing data from various sources, clinical trials, and adverse event reports. By using machine learning algorithms, AI can identify patterns that indicate potential issues with the quality or safety of antibiotics, helping procurement agencies ensure they are procuring reliable and effective products. Work from Oxford The Medicines quality group fits in here, and relevant the data is already available.

5. AMR Stewardship/Surveillance

Irrational antimicrobial use (AMU) in food animals has been associated with the emergence and spread of AMR. Monitoring AMU in humans and animals is a key strategic objective in the global fight against AMR. As a result, the WHO/OIE/FAO tripartite collaborations and other major partners, like the UK Fleming Fund, are already bolstering resources and capacities of a number of developing nations to monitor AMU. To support surveillance, the WHO launched its therapeutic chemical/defined daily dose (ATC/DDD) system, which aggregated data from 65 nations. Similarly, in the animal health sector, the OIE established a framework for the collection of national-level animal AMU data based on the amount of active ingredient used in milligrammes per adjusted animal biomass.

Figure 1: WHO/OIE/FAO tripartite collaboration on harmonization of antimicrobial use metrics.[1]

Efforts are being made by the tripartite collaboration on the Global Database for the Tripartite Antimicrobial Resistance (AMR) Country Self-assessment Survey (TrACSS). However, as a source of reliable and objective information about these initiatives, it contains some methodological caveats. For instance, while questions about AMR knowledge and surveillance are well-represented in the survey, the alignment with objectives for infection prevention and control, optimal medicine use, and long-term investment in novel diagnostic instruments are all far more difficult to ascertain.[2]

With respect to stewardship, while there is evidence of antimicrobial stewardship programmes (ASPs) being implemented in Gulf Cooperation Council (GCC) member states, benchmarking and mapping to international standards and frameworks has been minimal.[3] Due to specific demographic and environmental factors the Gulf Cooperation Council (GCC) region may be particularly susceptible to the threat of

[1] Global Challenges, Volume: 5, Issue: 10, First published: 10 June 2021, DOI: (10.1002/gch2.202100017)

[2] Munkholm, L., Rubin, O. The global governance of antimicrobial resistance: a cross-country study of alignment between the global action plan and national action plans. Global Health 16, 109 (2020). https://doi.org/10.1186/s12992-020-00639-3.

[3] Hashad, Perumal et al. (2020): Mapping hospital antimicrobial stewardship programmes in the Gulf Cooperation Council states against international standards: a systematic review. Journal of Hospital Infection Volume 106, Issue 3, pp. 404-418

AMR, with the marine and aquatic environment potentially playing a specific role in AMR development and propagation.

There is a pressing need for combining disparate data sources for risk assessment purposes; currently there is little systematic data gathered that answers even the most fundamental questions regarding the AMR risk associated with marine and aquatic environments.

5.1 Other Useful Data AMR Surveillance Sources

- The Global AMR R&D Hub's Dynamic Dashboard continuously collects and presents information on AMR R&D investments, products in the pipeline and push and pull incentives across three galleries. It provides an evidence base to help set priorities and maximize the impact and efficiency of resources and efforts invested into AMR R&D.

Figure 2: Global AMR R&D Hub Dashboard (globalamrhub.org)

- The Centre for Disease Dynamics, Economics and Policy (CDDEP) Resistance Map https://resistancemap.cddep.org/AnimalUse.php

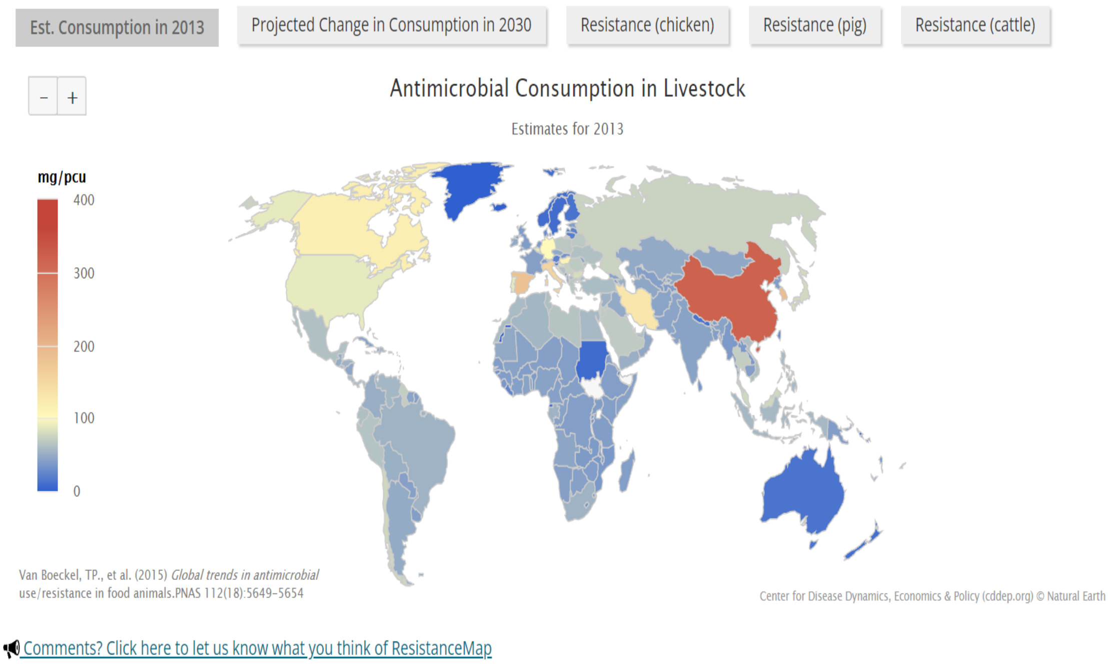


Figure 3: CDDEP Resistance Map

- WHO indicators well reflect data gaps and useful information directly and indirectly relevant for AMR: https://www.who.int/data/gho/data/indicators

- Potentially useful systematic reviews:
  - "Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis" (https://www.sciencedirect.com/science/article/pii/S0140673610614584?via%3Dihub)
  - The resistancebank.org - The open access repository for surveys and maps of antimicrobial resistance in animals https://www.resistancebank.org/

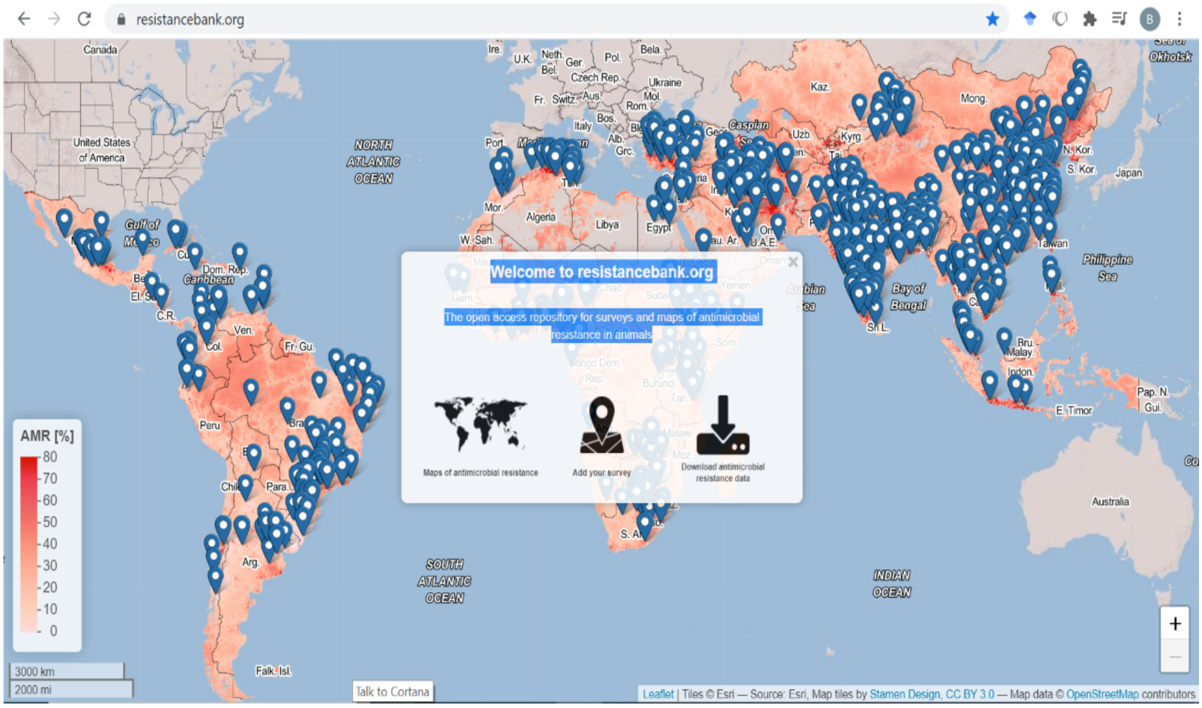


Figure 4: resistancebank.org dashboard

6. Antibiotic Sales and Consumption

- European Medicines Agency, European Surveillance of Veterinary Antimicrobial Consumption, 2015. 'Sales of veterinary antimicrobial agents in 26 EU/EEA countries in 2013'. (EMA/387934/2015)
  - See link: https://www.ema.europa.eu/en/documents/report/fifth-esvac-report-sales-veterinary-antimicrobial-agents-26-european-union/european-economic-area-countries-2013_en.pdf
  - Human consumption of antibiotics in OECD countries between 2005 and 2014
    - https://www.oecd.org/health/health-systems/AMR-Policy-Insights-November2016.pdf

6.1. Antibiotic Prescriptions in Different Countries

The following reports provide information about antibiotic prescriptions and usage in a number of countries:

- Antibiotic Use and Resistance in Bangladesh: Situation Analysis and Recommendations https://cddep.org/publications/bangladesh-situation-analysis-amr/

- Situation Analysis Report on Antimicrobial Resistance in Pakistan: Findings and Recommendations for Antibiotic Use and Resistance https://cddep.org/publications/garp-pakistan-situation-analysis/

- Om, C., Daily, F., Vlieghe, E. et al. Pervasive antibiotic misuse in the Cambodian community: antibiotic-seeking behaviour with unrestricted access. Antimicrob Resist Infect Control 6, 30 (2017). https://doi.org/10.1186/s13756-017-0187-y

- FAO and Denmark Ministry of Environment and Food – Danish Veterinary and Food Administration. 2019. Tackling antimicrobial use and resistance in pig production: lessons learned from Denmark. Rome. 52 pp. Licence: CC BY-NC-SA 3.0 IGO.

- Frumence, Mboera, Katale et al. (2021): Policy actors and human and animal health practitioners' perceptions of antimicrobial use and resistance in Tanzania: A qualitative study. Journal of Antimicrobial Resistance, Volume 25, pp.40-47

- Al-Yamani, F. Khamis, I. Al-Zakwani, H. Al-Noomani, J. Al-Noomani, S. Al-Abri Patterns of antimicrobial prescribing in a tertiary care hospital in Oman Oman Med. J., 31 (1) (2016), pp. 35-39

- A.A. Butt, C.S. Navasero, B. Thomas, S.A. Marri, H.A. Katheeri, A.A. Thani, A.A. Khal, T. Khan, A.B. Abou-Samra Antibiotic prescription patterns for upper respiratory tract infections in the outpatient Qatari population in the private sector Int. J. Infect. Dis., 55 (2017)

6.2 Measured Amount of Substandard and Falsified Medicines

Falsified and substandard (SF) medicines are a global problem that contribute to antimicrobial resistance and cause economic problems. Numerous drug sampling studies conducted in accordance with MEDQUARG criteria generate data on the prevalence of SF medicines in certain regions. A systematic review by McManus & Naughton (2020)[4] found that the prevalence of SF medicines appears to be high at 25%.

- More on medicines quality and SF by IDDO's Medicine Quality Research Group: https://www.iddo.org/research-themes/medicine-quality

7. Review of Coverage of National Action Plans and Literature on Benchmarking

- [UNGA] United Nations General Assembly. (2019). Follow-up to the political declaration of the high-level meeting of the General Assembly on antimicrobial resistance. General Assembly Seventy-third session. 07777(May), 25. https://undocs.org/en/A/73/869

[4] McManus, D., & Naughton, B. D. (2020). A systematic review of substandard, falsified, unlicensed and unregistered medicine sampling studies: a focus on context, prevalence, and quality. *BMJ Global Health*, *5*(8), e002393. https://doi.org/10.1136/BMJGH-2020-002393.

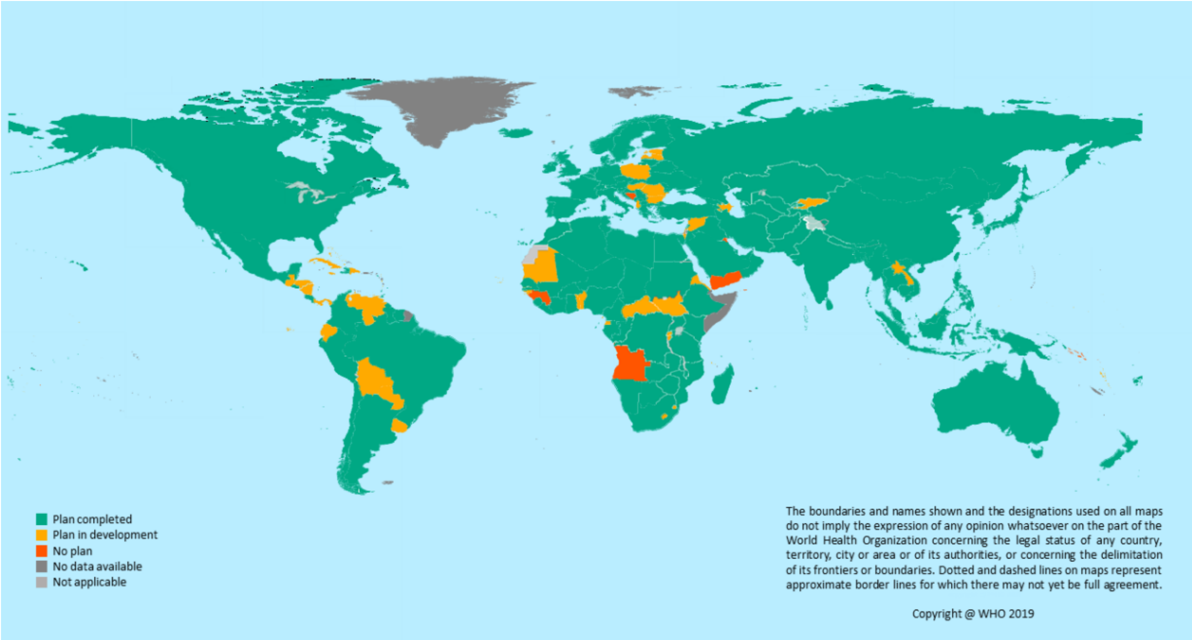


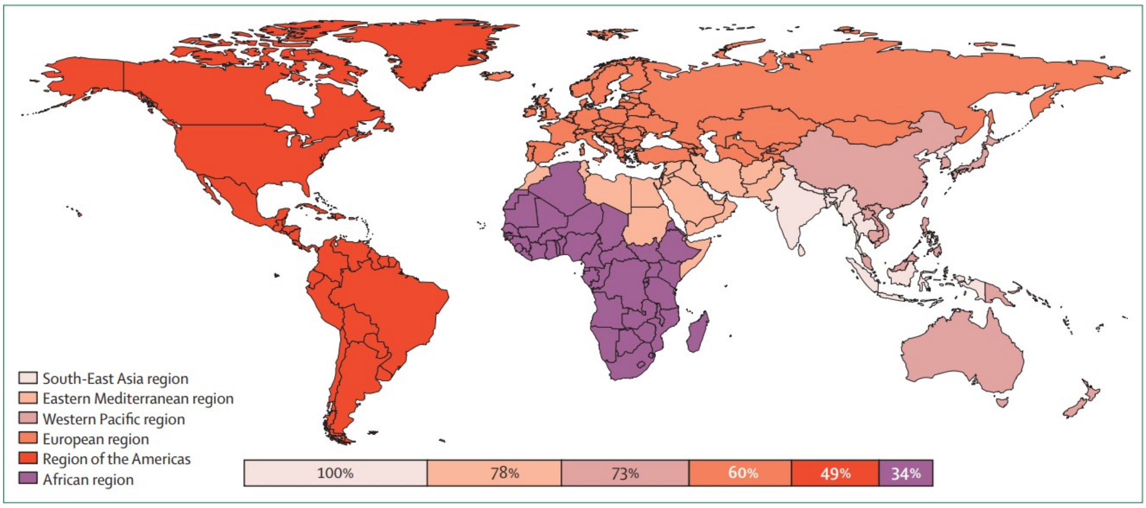
Figure 10: Progress made in the development of national action plans. ***Source*****: Reporting by WHO regional offices and on the basis of the 2018/19 country self-assessment survey on antimicrobial resistance of the Tripartite Organizations.**

- Orubu, Sutradhar et al. (2020): Benchmarking national action plans on antimicrobial resistance in eight selected LMICs: Focus on the veterinary sector strategies. Journal of Global Health 2020 Dec; 10(2) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7568929/

- Uses the WHO Global Action Plan and the WHO Manual for designing NAPs to evaluate policy content for Afghanistan, Bangladesh, Ethiopia, Ghana, Nepal, Nigeria, Pakistan, and Uganda.
    - "Operational and monitoring and evaluation (M&E) plans were assessed as: Specific, Measurable, Assignable, and Time-bound (or SMAT). Financing, targets and legislation for antimicrobial use reduction, and medicine quality assurance mechanisms were assessed using a constructed framework."
    - "All NAPs were concordant with GAP. However, gaps exist in relation to M&E, diminishing the countries' capacity to be accountable and implement corrective action if necessary.
    - Most lacked financing plans and targets for antimicrobial use reduction.
    - The antimicrobial quality assurances strategies are limited in most of the NAPs assessed.
    - A mechanism by which countries can benchmark their NAP would allow identification of specific limitations and areas of best practice."
    - NAPs were assessed as compliant with GAP if they make policy provisions for at least 80% of the recommended actions for the veterinary sector for strategic objectives 1-4 in the GAP.

- As the WHO Manual for developing NAPs elaborates, NAPs should include:
  - A strategic plan.
  - An operational plan including a financing component.
  - A monitoring and evaluation (M&E) plan. See link

- In March 2019, 67% of the 194 UN member states had a NAP. See link
- Charani et all have published an article that analysis existing national action plans for AMR that delves into the gaps and opportunities to optimize antibiotic use in humans. See Link



7.1 Cross-country comparison/benchmarking

- Targets for antimicrobial use reduction in veterinary sector according to the recommendation of the WHO
  - World Health Organization. WHO guidelines on use of medically important antimicrobials in food-producing animals. Geneva: WHO; 2017

- Medicine quality assurance: adopted medicine supply chain "framework" by Silva et al., 2019

- Used discrete variable to operationalise: yes=1 and no=0 as answers to questions whether the specific recommended actions of the WHO are met.
  - For the category of improving awareness and understanding of AMR, one of the questions is whether the government increases national public awareness of AMR through communication. This is quite a loose measure, and all countries score "yes". Whilst the appeal of a discrete variable is its relative easiness to handle, it also distorts the final product. It does not allow for a more nuanced

perspective: how much does each country spend? There is almost always room for improvement, and a discrete variable does not capture that. The same goes for the question "Is AMR in professional curricula?" Is it covered in a day, a month, or is there a focus throughout the entire year? Or take the question "vaccination". Answering it with "yes" or "no" is to simplify the problem too much.

  - However, the difficulty of a continuous variable would be to define it, and to gather data. It might take too much effort, or even be unfeasible. Therefore, the discrete approach is the second-best alternative. That is, unless one could maybe define some continuous variables for at least some of the benchmarking criteria.

- The individual discrete variables that make up the benchmarking tool are:
  - **Improve awareness and understanding of AMR:**
    - Increase national public awareness of AMR through communication.
    - AMR in professional curricula
    - Antimicrobial use and AMR in schools' curricula
    - AMR in National Risk Register
    - One-Health coalitions to address AMR
  - **Surveillance and research:**
    - Establish National Reference Centre for data collection and analysis.
    - Establish National Reference laboratory (Surveillance).
    - Strengthen surveillance by implementation of guidelines.
    - Share information regionally and globally.
    - Develop capacities to detect and report emerging resistance.
    - Monitor antimicrobial consumption.
    - Research to support new treatments.
  - **Infection Prevention and Control (IPC):**
    - Urgent action to implement hygiene and IPC
    - Hygiene and IPC in curriculum
    - Strengthen IPC policies and SOPs in HCF; M&E.
    - Antimicrobial sensitivity data
    - Animal health practices compliance with OIE and FAO/WHO codex
    - Vaccination
  - **Optimised use of antimicrobials:**
    - Distribution, prescribing, and dispensing on license
    - License only quality-assured antimicrobials
    - EML and STGs; regulation of promotion
    - Diagnosis to guide rational prescription
    - Antimicrobial Stewardship at national and local levels

        - Encourage appropriate antimicrobial use.
        - Governance of supply chain for antimicrobial agents
        - Eliminate non-therapeutic uses of antimicrobials in animals.

- **Categories for the operational plan:**
    - **Target for antimicrobial use reduction:**
        - Is there a quantitative target?
        - Any planned intervention(s) to reduce non-therapeutic antibiotic uses?
        - Any actions planned to reduce the use of reserve or Critically Important Antimicrobials (CIA)?
        - Any planned intervention to ban the use of antibiotic-containing feeds?
    - **Legislation restricting uses of antimicrobials for growth promotion or disease prevention in livestock?**
    - **Antimicrobial quality assurance strategies**
        - Is there a programme/intervention assuring the quality of antimicrobials?
        - Is there a separate veterinary medicines regulatory agency for the quality control of antimicrobials used in animals?
    - **Operational plan: is it**
        - Specific
        - Measurable
        - Assignable
        - Time-bound
    - **Monitoring and Evaluation (M&E) plan:**
        - Is there a separate M&E plan? Is it:
        - Specific
        - Measurable
        - Assignable
        - Time-bound?

- **Financing:**
    - Is each proposed activity costed?
    - Is the source(s) of funding indicated?

- **Medicine quality assurance:**
    - Is there a National Medicines regulatory Agency (NMRA)?
    - Does the NMRA oversee quality of antimicrobials?
    - Is there any mention of Good Manufacturing Practices for manufacturers?
    - Are importers/wholesalers/suppliers required to comply with quality checks?

- Any mention of Good Pharmacy Practice, or antimicrobials as Prescription Only Medicines?
- Procurement/sourcing – Quality-assured antimicrobials or good procurement practices including quality?
- Any mention of proper storage conditions for antimicrobials?
- Any mention of post-marketing surveillance for quality?

Monitoring, evaluation and review of national health strategies. A country-led platform for information and accountability. Geneva: International Health Partnership, WHO; 2011
https://apps.who.int/iris/bitstream/handle/10665/85877/9789241502276_eng.pdf?sequence=1&isAllowed=y

7.2. Codex: Code of Practice to Minimize and Contain Antimicrobial Resistance

(CAC/RCP 61- 2005):

- NAPs can also be benchmarked according to whether they satisfy the conditions that this paper outlines.
- "It is the responsibility of regulatory authorities to develop up-to-date guidelines on data requirements for evaluation of veterinary antimicrobial drug applications."
- "Other elements of the national strategy should include good animal husbandry practices, vaccination policies and development of animal health care at the farm level, all of which should contribute to reduce the prevalence of animal disease requiring antimicrobial treatment."
- "The relevant authorities should make sure that all the antimicrobial agents used in food- producing animals are prescribed by a veterinarian or other suitably trained person authorized in accordance with national legislation or used under conditions stipulated in the national legislation. (See OIE Guidelines for Antimicrobial Resistance: Responsible and Prudent Use of Antimicrobial Agents in Veterinary Medicine (Terrestrial Animal Health Code, Appendix 3.9.3)."
- "Preclinical data should be generated to establish an appropriate dosage regimen necessary to ensure the efficacy of the veterinary antimicrobial drug and limit the selection of microbial resistant microorganisms. Such preclinical trials should, where applicable, include pharmacokinetic and pharmacodynamic studies to guide the development of the most appropriate dosage regimen."
- An acceptable daily intake (ADI) and a maximum residue limit (MRL) for appropriate food stuffs (i.e., meat, milk, eggs, fish and honey) should be established for each antimicrobial agent.

- A list of MRLs for various residues of veterinary drugs in foods can be found in: Maximum Residue Limits (MRLs) and risk management recommendations (RMRS) for residues of veterinary drugs in foods CX/MRL 2-2018 (CODEX ALIMENTaRIUS International Food Standards, Food and Agriculture Organisation of the United Nations and WHO). See link
- It is necessary to establish a summary of product characteristics for each veterinary antimicrobial drug for food-producing animals, which includes information on:
    - Pharmacological properties
    - Target animal species
    - Indications
    - Target microorganisms
    - Dosage and administration route
    - Withdrawal periods
    - Incompatibilities
    - Shelf-life
    - Operator safety
    - Particular precautions before use
    - Instructions for the return or proper disposal of un-used or out-of-date products
    - Class and active ingredient of the veterinary antimicrobial drug
- Requirements for surveillance:
    - Sufficient data on the amounts of veterinary antimicrobial drugs used by veterinarians and other authorised users in food-producing animals. This data could be provided by:
        - Production data from manufacturers
        - Importers and exporters
        - If possible, data on intended and actual uses from manufacturers, wholesale and retail distributors including feed mills, and veterinary prescription records.
        - Surveys of veterinarians, farmers and producers of food-producing animals.
- For further details on how to standardise and design AMR surveillance and monitoring programmes, see: "Chapter 6.8. Harmonisation of national antimicrobial resistance surveillance and monitoring programmes" OIE. See link
    - This document serves as a potential blueprint for the development of national antimicrobial resistance surveillance and monitoring programmes, as well as for the harmonisation of existing national antimicrobial resistance surveillance and monitoring programmes in food-producing animals and animal products intended for human consumption.

    - Surveillance and monitoring of antimicrobial resistance is necessary to: 1) assess and determine the trends and sources of antimicrobial resistance in bacteria; 2) detect the emergence of new antimicrobial resistance mechanisms; 3) provide the data necessary for conducting risk analyses as relevant to animal and human health; 4) provide a basis for policy recommendations for animal and human health; 5) provide information for evaluating antimicrobial prescribing practices and for prudent use recommendations; 6) assess and determine effects of actions to combat antimicrobial resistance.
- Requirements for training of medical and veterinary staff as well as farmers and producers of food animals:
    - Information on disease prevention and management strategies to reduce the need to use veterinary antimicrobial drugs;
    - Relevant pharmacokinetic and pharmacodynamic information to enable the veterinarian to use veterinary antimicrobial drugs prudently;
    - The ability of veterinary antimicrobial drugs to select for resistant microorganisms in food-producing animals that may contribute to animal or human health problems; and
    - The need to observe responsible use recommendations and using veterinary antimicrobial drugs in animal husbandry in agreement with the provisions of the marketing authorisations and veterinary advice.
- Responsibilities of wholesale and retail distributors:
    - Distributors should encourage compliance with the national guidelines on the responsible use of veterinary antimicrobial drugs and should keep detailed records of all antimicrobials supplied according to the national regulations including:
        - Date of supply
        - Name of prescribing veterinarian
        - Name of user
        - Name of medicinal product
        - Batch number
        - Quantity supplied
    - These are also conditions that can be formulated as one of the indicators (i.e., do NAPs require such a procedure, or do countries already gather and provide such data - yes/no)
- For requirements on animal feeding, see: Codex: Code of Practice on Good Animal Feeding (CAC/RCP 54-2004). See link

7. Review of NAPs according to benchmarking criteria

List of NAPs:

- **Library of AMR national action plans:** https://www.who.int/teams/surveillance-prevention-control-AMR/national-action-plan-monitoring-evaluation/library-of-national-action-plans
- Chua, A. Q., Verma, M., Hsu, L. Y., & Legido-Quigley, H. (2021). **An analysis of national action plans on antimicrobial resistance in Southeast Asia using a governance framework approach**. *The Lancet Regional Health – Western Pacific*, *7*, 100084. https://doi.org/10.1016/J.LANWPC.2020.100084
- Reviews of countries of ASEAN, including Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, the Philippines, Singapore, Thailand, and Vietnam.
  - Categories:
    - **Policy design:** Table 3 includes more details.
    - **Strategic vision:** "All countries, except Singapore, have conducted situational analyses to assess AMR burden locally and to inform strategies to mitigate AMR. Apart from Brunei, Singapore, and Vietnam, all countries discussed objectives which were specific, measurable, and timebound."
    - **Accountability and coordination:** "The need for a ministry or intersectoral committee for coordination and implementation was mentioned in all NAPs, albeit at various degrees … Accountability, although common across all NAPs through nomination of a responsible party, was rarely discussed in detail and implications of unmet objectives were absent."
    - **Participation:** "only five NAPs stated periodic meetings and engagement activities."
    - **Transparency:** "six countries accounted for transparency by establishing platforms for data sharing, including DATA on AMU (Antimicrobial use) surveillance".
    - **Equity:** "All countries, except Brunei and Malaysia, accounted for equity, either directly by ensuring accessibility and affordability of quality antimicrobials or indirectly by maintaining uninterrupted supply chains. Singapore only mentioned about access to vaccines."
    - **Implementation tools:** Table 4 and 5 provide more details.
    - **Surveillance:** "AMU appropriateness was not as frequently stated. In addition, AMR surveillance was mainly focused on human and animal health, and less so on the environment, as only three countries highlighted environmental AMR surveillance. One of the lessons learned is that even when focusing exclusively on animal health, not enough strategic thinking about global data management plans is done. Given satellite data or GIS, there may be ways to explore global environmental data that could be linked to AMR-related data (see AMR and the environment above). Five NAPs had existing surveillance systems in public hospitals and were to be extended to private hospitals and community healthcare facilities."

- **Optimising antimicrobial usage:** "Antimicrobial stewardship programmes (ASPs), defined as coordinated interventions to improve appropriate AMU by promoting optimal drug regimen selection, was mentioned by all countries except Vietnam. Most countries discussed ASP in both human and animal health, except Cambodia and Malaysia which focused on human health only … Incentives or penalties to reduce inappropriate AMU in general (Brunei), in human health (Singapore and the Philippines), and in animal health (Malaysia), were mentioned, but no detailed plans were presented. Rapid diagnostic tools to support ASP initiatives was briefly mentioned by Singapore and rarely discussed by others." Medicines regulations were discussed but received no dedicated budget to support legislation monitoring and enforcement.
- **Infection prevention and control:** "For human health, IPC strategies included setting up dedicated committees in hospitals, developing policies on hand hygiene, and management of patients with multidrug-resistant organisms. Only Singapore mentioned ongoing regular testing of drinking water. For animal health, good agricultural practices and biosecurity improvements were recommended to prevent diseases. Environmental IPC was described by Cambodia, Indonesia, Lao, Myanmar, and Singapore. Examples included waste management systems in hospitals and farms for safe disposal of unused or expired antimicrobials and effluent treatments."
- **Education:** All NAPs featured awareness campaigns and educational programmes.
- **Research and innovation:** "Innovation was featured in all NAPs as R&D of novel therapeutics and diagnostics, and vaccines briefly, except for Cambodia, Thailand, and Vietnam. Indonesia also included a component on innovative financing. Singapore provided specific R&D examples including on-site test kits for detection of animal bacterial pathogens for diagnosis and treatment."
- **International collaboration:** "Eight countries reported data to international databases including the WHO global AMR surveillance system."
- **Monitoring and evaluation:** More information in Table 6.
- **Effectiveness:** "Eight NAPs with integrated M&E plans listed evaluation indices for each intervention."
- **Feedback mechanisms:** Missing in Laos, Malaysia, and Vietnam.
- **Reporting:** Data reporting was mentioned by all, but the frequency of the reports was sporadic and the reporting authority unclear.
- **Sustainability:** More information in Table 7
- **Funding and resource allocation:** "Four NAPs mentioned the need for regular resource assessment to assist management of budget allocation

and priorities. Other commonly discussed resources included human resources of manpower and skills, as well as facilities and infrastructure for effective implementation."

- **Expansion plans:** "Five NAPs mentioned incremental scaling of implementation plans and operations with future sustainability through continuous improvement."

  One Health engagement: "While all NAPs were designed using a One Health approach, clarity of achievable goals and future plans more frequently involved human and animal health sectors as compared to the environmental sector."

Kenya[5] launched its Laboratory based surveillance strategy, established a National data repository, fully enrolled into the WHO Global Antimicrobial Resistance Surveillance System, piloted the strategy in two sites but was not able to submit data to the global platform as anticipated due to gaps in data quality, inconsistent supply of laboratory commodities, inadequate resources, poor diagnostic stewardship and technical capacity to detect and report AMR.

- Birgand, G., Castro-Sánchez, E., Hansen, S., Gastmeier, P., Lucet, J.-C., Ferlie, E., Holmes, A., & Ahmad, R. (2018). Comparison of governance approaches for the control of antimicrobial resistance: Analysis of three European countries. *Antimicrobial Resistance & Infection Control 2018 7:1*, *7*(1), 1–12. https://doi.org/10.1186/S13756-018-0321-5
  - Analyses governance approaches within healthcare systems within England, France and Germany.
  - Most high-income countries are characterised by top-down hierarchical AMR IPC governance systems.
  - There is now a tendency towards 'network governance' approaches, in which the central government takes a less directive and more shaping role. Other actors are more involved.
    - Example: European Union's Innovative Medicines Initiative (IMI) launched 'NewDrugs4BadBugs' in 2014, a collaborative campaign that engages academics, biotech organisations, and industry researchers together to work on AMR.
- Munkholm, L., & Rubin, O. (2020). The global governance of antimicrobial resistance: a cross-country study of alignment between the global action plan and national action plans. *Globalization and Health 2020 16:1*, *16*(1), 1–11. https://doi.org/10.1186/S12992-020-00639-3

- [5] Wesangula, E. N., Githii, S., & Ndegwa, L. (2020). Implementing the national action plan on antimicrobial resistance in Kenya: Global expectations, national realities. *International Journal of Infectious Diseases*, *101*(S1), 41. https://doi.org/10.1016/J.IJID.2020.09.140

- "The article investigates the global governance of AMR. Concretely, two proxies are devised to measure vertical and horizontal alignment between the GAP and existing NAPs: (i) a syntactic indicator measuring the degree of verbatim overlap between the GAP and the NAPs; and (ii) a content indicator measuring the extent to which the objectives and corresponding actions outlined in the GAP are addressed in the NAPs. Vertical alignment is measured by the extent to which each NAP overlaps with the GAP. Horizontal alignment is explored by measuring the degree to which NAPs overlap with other NAPs across regions and income groups. In addition, NAP implementation is explored using the Global Database for Antimicrobial Resistance Country Self-Assessment."

- European Public Health Alliance. Translating political commitments into action. The development and implementation of National Action Plans on antimicrobial resistance in Europe 2018.
- Analysis of AMR Plans in the Western Pacific and South-East Asia Regions: Snell, B. (2019). Analysis of AMR Plans in the Western Pacific and South-East Asia Regions TWN Third World Network. *TWN Series on ANTIMICROBIAL RESISTANCE*. www.twn.my
- Access to Medicine Foundation (2020). *Antimicrobial Resistance Benchmark 2020 – METHODOLOGY REPORT 2019*: link

  - More here: Journal of Global Antimicrobial Resistance

  - This detailed list of priority topics could serve as inspiration on other areas that one could look for data for: https://www.jpiamr.eu/about-jpiamr/sria/

Priority topic	Research and innovation objectives
Therapeutics	
Discovery of new antimicrobials and therapeutic alternatives, and the improvement of current antimicrobials and treatment regimens	• Find new antimicrobials and targets • Develop new chemical entities and scaffolds • Improve pharmacokinetics and pharmacodynamics of antimicrobials, including neglected antimicrobials • Use personalised medicine and artificial intelligence to improve therapies • Develop alternatives for antimicrobials • Develop treatment protocols based on combination therapy using new and existing antimicrobials • Develop policy measures and economic stimuli to minimise barriers for the development, availability and introduction of new therapies and alternatives • Assess how regulation modifies and influences production and use of antimicrobials
Diagnostics	
Development and improvement of diagnostics to improve the use of antimicrobials and alternatives to antimicrobials	• Improve the efficacy of new and existing diagnostic tools to more effectively distinguish between infections, and/or detect antimicrobial susceptibility • Create support for the implementation of innovative technologies and linkage to data platforms promoting the use of narrow-spectrum antimicrobials • Improve the use of rapid diagnostics in appropriate One Health settings • Improve understanding and explore ways to overcome behavioural and socio-economic barriers limiting the adoption and use of rapid diagnostics
Surveillance	
Optimisation of surveillance systems to understand the drivers and burden of antimicrobial resistance in a One Health perspective	• Improve and standardise AMR surveillance systems, from sampling to data analysis including sampling frame, tools, methodology and reporting • Strengthen the use of surveillance data to identify human and non-human reservoirs of AMR • Optimise the use of surveillance data to estimate burden and to assess the impact of interventions • Develop novel techniques to supplement and promote the exchange of surveillance data • Improve and standardise the surveillance of antimicrobial use • Centralising registration of treatment and patient outcome

Priority topic	Research and innovation objectives
Transmission	
Understanding and preventing the transmission of antimicrobial resistance	• Unravel the complex dynamics of selection and transmission of antimicrobial resistance • Identify factors responsible for the persistence and spread of resistant organisms and resistance elements • Determine the impact on AMR of different systems of healthcare, animal production, global trade and environmental pollution and contamination
Environment	
The role of the environment in the persistence, selection and spread of antimicrobial resistance	• Determine and model the contribution of contamination sources, environmental reservoirs and exposure routes on the emergence and spread of AMR • Evaluate the relationship between AMR and the environment, climate change, and pollution • Assess the potential impact of industrial systems on AMR in the environment • Develop innovative technological, policy, social, economic and regulatory approaches to mitigate AMR in the environment
Interventions	
Investigation and improvement of infection prevention and control measures in One Health settings	• Develop innovative interventions aimed to detect, prevent and control the spread of AMR in a One Health perspective • Investigate the effectiveness of AMR prevention and control strategies to increase uptake and acceptance in One Health settings • Assess the effectiveness and cost-effectiveness of specific AMR prevention and control practices, considering different geographic and socio-economic settings • Optimise implementation strategies, including drivers for and barriers to behavioural change, to reduce AMR • Understand the prescription behaviours contributing to the responsible and prudent use of antimicrobials • Assess educational and training programmes to enhance antimicrobial awareness and stewardship

The current existing international and national surveillance systems do not meet all the needs and expectations of policymakers, public health workers and researchers. There is a large heterogeneity across countries in the levels of surveillance systems with respect to:

- quality and nature of data collections
- data source and sampling frame

- state-of-the-art microbiological diagnostics and the ability for early detection
- quality of antimicrobial susceptibility testing
- availability and quality of national reporting systems

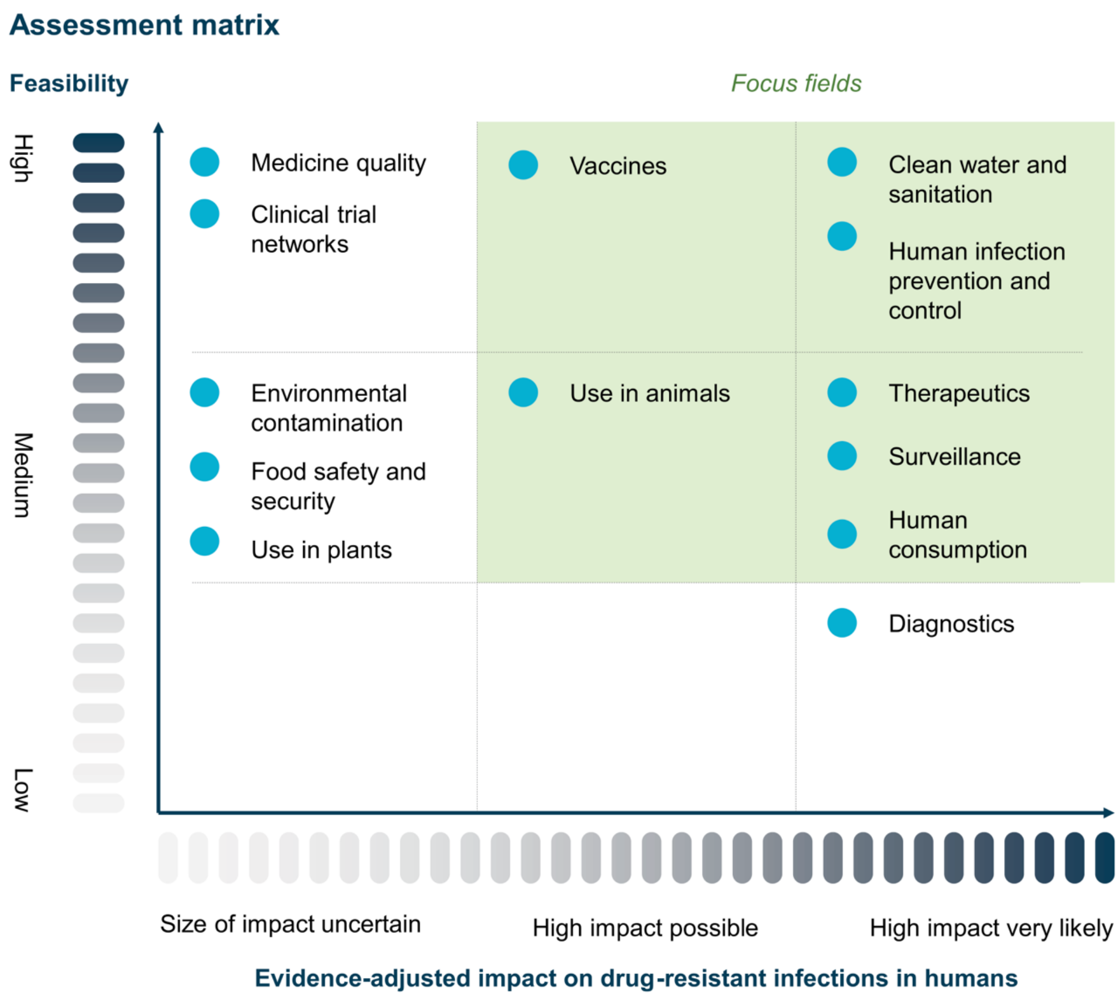
Summary of priority gaps per theme

Themes		Priority gaps moving forward	
Reduce need & unintentional exposure	Human infection prevention and control	**Gathering data on IPC**	There is often insufficient data gathering around the adherence to IPC standards
		Implementation at the point of care	In-country public health experts voiced concern about guidelines at the national level that may not translate into clinical practice (e.g. in Pakistan) ▪ Additional experts criticise translating effective HIC IPC interventions to LMIC
		Strengthening community IPC interventions	Currently, IPC interventions are focused on healthcare workers and facilities, while surveillance experts point to an underappreciation of community health settings for AMR in general
		Strengthening the AMR-specific IPC response	AMR-sensitive IPC interventions may be the most effective way for the AMR community to benefit from existing attention to IPC and its global infrastructure
	Clean water and sanitation	**Funding for AMR-sensitive WASH interventions**	On AMR-sensitive WASH interventions ▪ WaterAid estimated in June 2019 that "at current rates of progress, everyone in [the] least developed countries won't have safely managed water until 2131 – more than 100 years behind schedule"
		Improved coordination and effective mainstreaming of AMR in the WASH agenda	Experts in the WASH community expressed frustration that while lip service is frequently paid to the effectiveness of AMR-sensitive interventions and their impact on promoting WASH, this is not followed up with implementation support or funding
	Food safety and security	**LMIC action**	There is a lack of regulation enforcement with respect to the use of antimicrobials in food-producing environments (agriculture, aquaculture, and horticulture)
		Data generation on food security	At present, there is no systematic data, or estimates of the scale of risks posed to food security by AMR, and accordingly an adequate risk scoping is needed
		Reductions in overall use levels in food-producing industries	The overall excessive level of antimicrobial use in crops, livestock, and aquaculture production remains a primary driver of resistance
	Environmental contamination	**Evidence on human health impact**	Conclusive evidence of the impact of environmental AMR on human health remains elusive creating impediments to policymaker buy-in
		Awareness of the environment as a reservoir of de novo resistance development	There is the additional challenge of investigating both the roles of *very high concentrations* of antimicrobials (e.g. pharma effluence) in *a few places* as well as *much lower concentrations* of antimicrobials (e.g. excreted antibiotics) *in many places*
		Awareness and implementation among private-sector actors	There is a general lack of awareness on the impact of various pollution sources (e.g. farms, hospitals, WWTP, and esp. Indian and Chinese Gx and API pharma manufacturers)
		Engagement of the broader environmental community	Multiple experts and policymakers express frustration with attempts to engage the UN Environment Programme in the global response to AMR
Optimize use of medicines	Human consumption of antimicrobials	**Low awareness and ease of procurement**	A lack of AMR awareness (including in HIC) is compounded by the fact that procurement is frequently possible without a prescription (due to or without the involvement of trained healthcare professionals) ▪ Additional, and better enforcement of existing, regulations on over-the-counter antimicrobial sales is needed
		Limited access to effective therapeutics	Global access to antibiotics is hampered by a lack of affordability, supply chain issues, and a complex regulatory environment ▪ Other issues include weak health systems and the reluctance of drug companies to register products in LIC where they do not see a market
		Behavioural changes supported by evidence	Experts also highlighted the need for behavioural changes at all levels of the antimicrobial stewardship landscape, across payors, physicians, and patients
	Use in animals	**Evidence base**	Although transmission pathways linking animal and human AMR have been clearly demonstrated, there are still gaps in the quantification of transmission rates and the impact of AMR-specific interventions ▪ Evidence on whether an 'x-point' reduction in antibiotic use in animals leads to anywhere near a similar magnitude reduction in human drug-resistant infections is absent
		Regulatory interventions	Regulatory interventions, or threats thereof, have proven the most effective intervention in HIC, often quickly followed by voluntary industry action ▪ Consumer expectations, as well as investor demands, can be complementary levers to encourage compliance with antimicrobial use best practices
		Increased attention to aquaculture	The use of antibiotics in aquaculture is mostly unregulated in countries that account for the vast majority of use
	Use in plants	**Data on scale of use and evidence on resistance development**	Systematic data on use, stakeholder mapping of supplies and purchasers, and estimates of the resistance burden is needed ▪ Additionally, data on resistance development and transmission, and the resulting impact on human health, are currently limited to mostly individual pathogens (such as *C. auris*)
		Awareness	There is limited to no awareness in the AMR and plant health communities, both at the international and domestic levels

Shift in actions depending on time frame

Key: Advocate | Lead the field | Support implementation | Generate evidence

Themes and enablers	2020-30		2030-2050	
Human infection prevention & control	Advocate	**Boldly combat risks**	Advocate	**Maintain systemic response & prevention**
Clean water & sanitation	Advocate		Advocate	
Human consumption of antimicrobials	Lead the field / Generate evidence		Support implementation	
Use of antimicrobials in animals	Generate evidence / Advocate		Lead the field or Support implementation	
Surveillance (incl. laboratory capacity)	Lead the field		Support implementation	
Therapeutics (development & access)	Lead the field		Support implementation	
Food safety & security	Generate evidence	**Learn and build**	Lead the field or Support implementation	
Environmental contamination	Generate evidence		Lead the field or Support implementation	
Use of antimicrobials in plants	Generate evidence		Lead the field or Support implementation	
Discovery & translational research	Support implementation		Support implementation	
Diagnostics (development & access)	Support implementation		Lead the field	
Vaccines (development & access)	Support implementation / Generate evidence		Lead the field or Support implementation	
Medicine quality	Generate evidence / Advocate		Advocate	
Clinical trial networks	Support implementation		Advocate	



8. Data on AMR in the Environment

The Global Coalition on Aging's 2021 AMR preparedness index report reaffirms the caveats with data on AMR and the environment. The report examines how national governments manage antimicrobials through their life-cycle: manufacture, procurement, use in a variety of sectors (including non-human applications), and disposal.

The major limitations are a lack of data in a number of countries, the self-reported nature of the limited accessible data, and the fact that in certain countries environmental data were not tied to antimicrobials. Mezzelani and colleagues,[6] for example, discovered evidence of human pharmaceuticals in sea mussels. The ubiquitous presence of pharmaceuticals in coastal mussels provides insight into the possible ecotoxicological risk posed by these substances in marine animals. Despite the fact that these compounds were not explicitly antimicrobials, the study establishes

[6] Mezzelani, M., Fattorini, D., Gorbi, S., Nigro, M., & Regoli, F. (2020). Human pharmaceuticals in marine mussels: Evidence of sneaky environmental hazard along Italian coasts. *Marine Environmental Research*, *162*, 105137. https://doi.org/10.1016/J.MARENVRES.2020.105137

a relationship between pharmaceuticals and the environment. Moreover, the study demonstrates that seasonality had a negligible effect on bioaccumulation.

With regards to ***self-reported data***, concerns about data heterogeneity and lack of comparability between countries arise due to the varied methods used to curate the data. To address the limitations of self-reporting data, a new hospital network-based surveillance system[7] for antimicrobial resistance has been proposed as a more robust alternative to self-reporting. In many LMICs, however, major or tertiary hospitals are utilised as proxies for reporting and monitoring AMR, which is usually not generalisable.

In November 2018, the FAO launched a scoping exercise to get a good sense of the risks of antimicrobial resistance in aquaculture and the availability of data in that area, drawing on a broad range of international expertise.[8]

- A risk profiling exercise was done on two bacterial agents important to both animal and human health, namely: Streptococcus spp. and Vibrio parahaemolyticus. These bacterial agents affect tilapia and shrimp, respectively, top aquaculture species that contribute significantly to global food and nutrition security.
- The risk profiling exercise for the two bacterial pathogens revealed that in both cases the AMR risks posed by these pathogens were likely to be low, and thus the conducting of a full risk assessment was not recommended.
- The Expert Group agreed to develop a project proposal to contribute to a multisectoral project "Towards reducing aquaculture-based AMR through a cross-sectoral approach".
- See link to Expert group report: https://doi.org/10.4060/ca7442en

Furthermore, the FAO developed a framework for evaluating country antimicrobial resistance legislation, including legislation targeted at preventing food and environmental contamination.[9]

9. Sewage or Wastewater Data

In terms of data for **antimicrobial resistance in sewage or wastewater**, some adjustment or accounting of markers in rural sewage/wastewater can be seen in this paper:

[7] Donker, T., Smieszek, T., Henderson, K. L., Walker, T. M., Hope, R., Johnson, A. P., Woodford, N., Crook, D. W., Peto, T. E. A., Walker, A. S., & Robotham, J. V. (2019). Using hospital network-based surveillance for antimicrobial resistance as a more robust alternative to self-reporting. *PLOS ONE*, *14*(7), e0219994. https://doi.org/10.1371/JOURNAL.PONE.0219994.

[8] Source: https://undocs.org/pdf?symbol=en/A/73/869 Point of contact Melba.Reantaso@fao.org, http://www.fao.org/fishery/nems/41098/ar.

[9] See the FAOLEX database, available at www.fao.org/faolex/en/ See the FAO action plan on AMR here: https://www.fao.org/3/i5996e/i5996e.pdf and also see https://www.fao.org/antimicrobial-resistance/key-sectors/surveillance-and-monitoring/en/ and https://www.fao.org/antimicrobial-resistance/resources/reference-centres/en/

- Hendriksen, R.S., Munk, P., Njage, P. *et al.* Global monitoring of antimicrobial resistance based on metagenomics analyses of urban sewage. *Nat Commun* **10,** 1124 (2019). https://doi.org/10.1038/s41467-019-08853-3

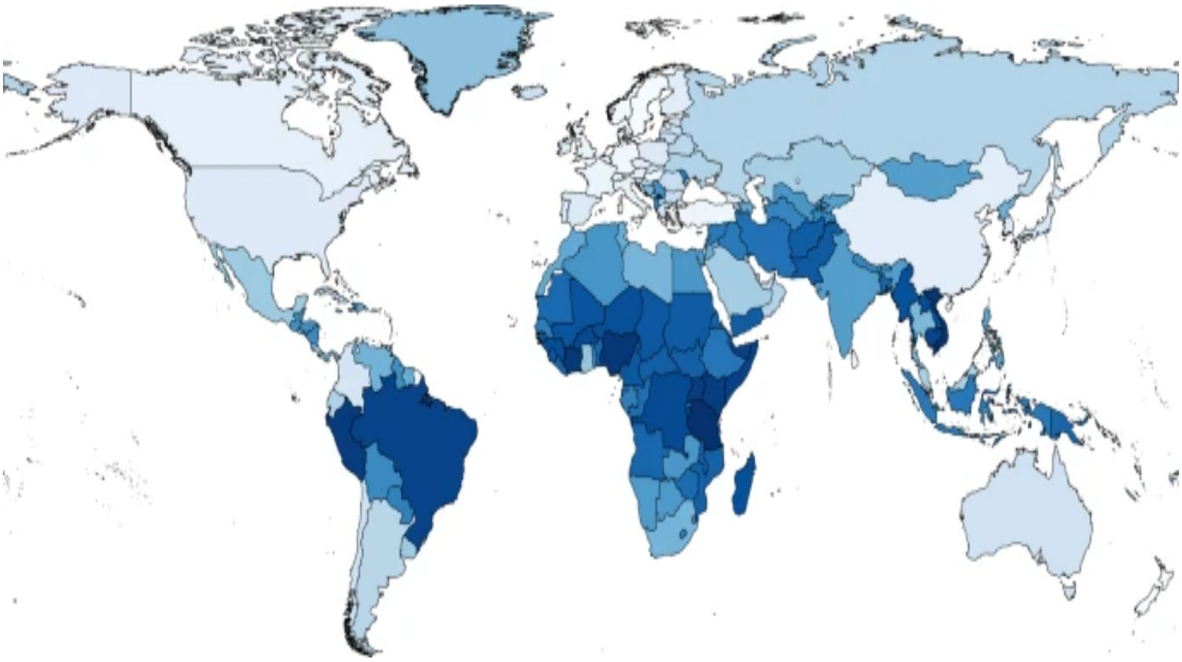


Figure 6: Global predictions of antimicrobial resistance (AMR) abundance in all countries and territories in the world. Map coloured according to predicted abundance of AMR from light blue (low AMR abundance) to dark blue (high AMR abundance). Source: (Hendriksen et al., 2019)

In the above paper the following may also be interesting with regards to the discussion of which fresh water or other indicators to leverage:

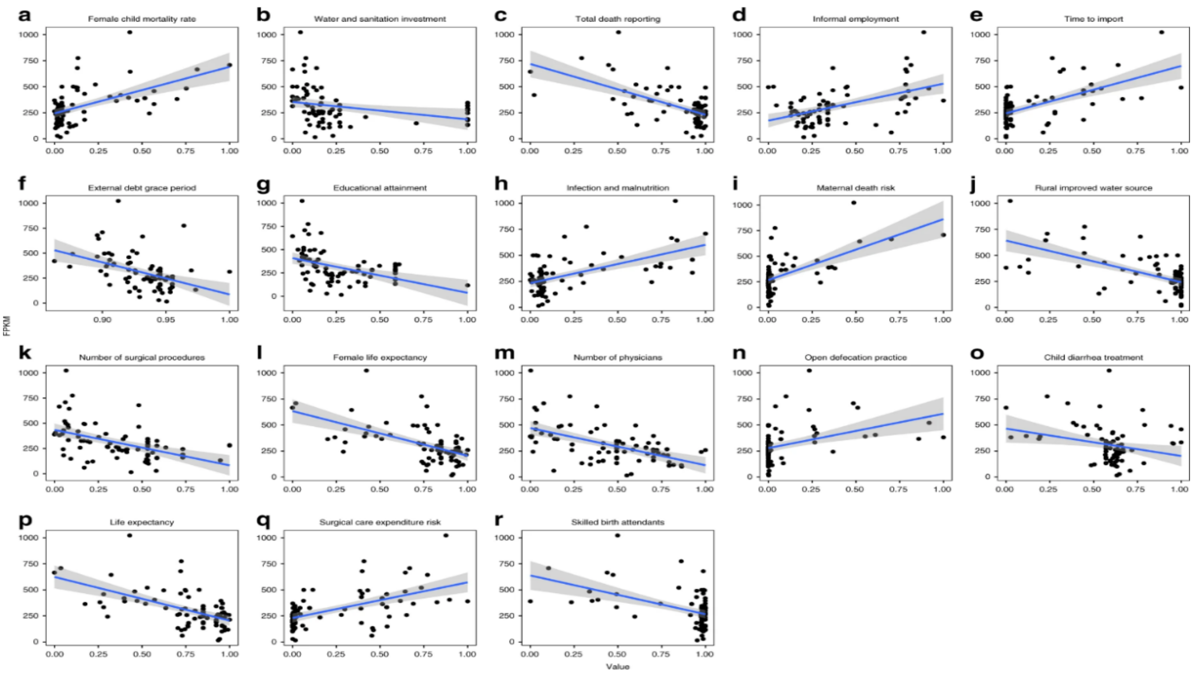


Figure 7: World Bank variables significantly associated with the observed antimicrobial resistance abundances. Source: (Hendriksen et al., 2019) See link

10. Using Global Information Systems for Mapping AMR

While antimicrobial resistance (AMR) is a global threat, there are no local AMR databases.

AMR data can be visualised in accordance with geographical regions using Geographical Information Systems (GIS) mapping technology. Several studies have examined this, and while they are isolated or case studies, they may serve as a good starting point for using GIS to fill in the data gaps associated with AMR in the environment. Moreover, integration of a GIS approach and expert knowledge of AMR can be an effective tool for gaining insights into the spatial dimension of AMR and guiding sampling campaigns and intervention points.

- Alhifany AA, Alqurashi AF et al. (2020). Employment of Mapping Technology in Antimicrobial Resistance Reporting in Saudi Arabia. *Geospatial Health*, *15*(1), 174–180. https://doi.org/10.4081/GH.2020.868
- Hashim AM, Elkelish A, Alhaithloul HA, El-Hadidy SM, Farouk H. Environmental monitoring and prediction of land use and land cover spatio-temporal changes: a case study from El-Omayed Biosphere Reserve, Egypt. Environ Sci Pollut Res Int. 2020 Dec;27(34):42881-42897. doi: 10.1007/s11356-020-10208-1. Epub 2020 Jul 28. PMID: 32725554.
- Galvin S, Bergin N, Hennessy R, Hanahoe B, Murphy AW, Cormican M, Vellinga A. Exploratory Spatial Mapping of the Occurrence of Antimicrobial Resistance in E. coli in the Community. Antibiotics (Basel). 2013 Jul 1;2(3):328-38. doi: 10.3390/antibiotics2030328. PMID: 27029306; PMCID: PMC4790267.

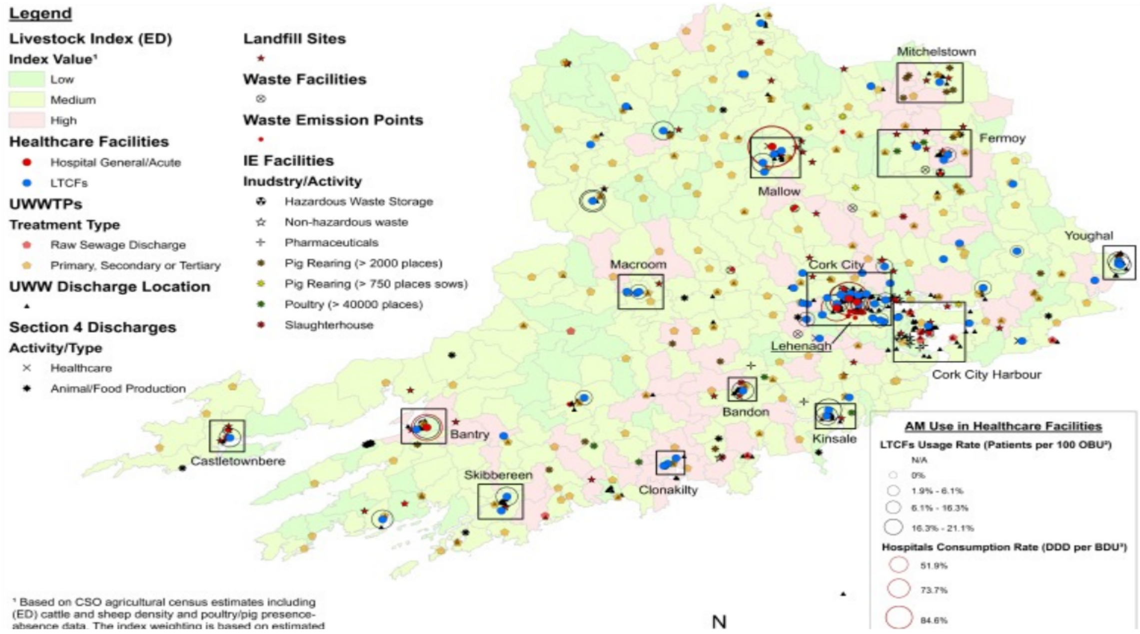


Figure 8: Composite map of potential antimicrobial resistant organisms (ARO) sources (unclassified) and healthcare facilities (including antimicrobial (AM) use) in County Cork, County Galway, and Fingal County.

Notes: Livestock index estimates are included as a base map layer. Clusters of ARO sources in urban areas are delineated. LTCFs = long-term care facilities. ED = electoral district. CSO = Central Statistics Office. Source: Chique et al. (2019).[10]

10.1. Further Resources on AMR in the environment

- M, A., C, H.-J., M, Y., AF, H., D, L., & JE, D. (2014). The occurrence of emerging trace organic chemicals in wastewater effluents in Saudi Arabia. *The Science of the Total Environment*, *478*, 152–162.
- https://doi.org/10.1016/J.SCITOTENV.2014.01.093
- Le Quesne, W. J. F., Baker-Austin, C., Verner-Jeffreys, D. W., Al-Sarawi, H. A., Balkhy, H. H., & Lyons, B. P. (2018). Antimicrobial resistance in the Gulf Cooperation Council region: A proposed framework to assess threats, impacts and mitigation measures associated with AMR in the marine and aquatic environment. *Environment International*, *121*, 1003–1010. https://doi.org/10.1016/J.ENVINT.2018.06.030
- Brower CH, Mandal S et al. (2017). The Prevalence of Extended-Spectrum Beta-Lactamase-Producing Multidrug-Resistant Escherichia Coli in Poultry Chickens and Variation According to Farming Practices in Punjab, India. *Environmental Health Perspectives*, *125*(7). https://doi.org/10.1289/EHP292

[10] Chique C, Cullinan J, Hooban B, Morris D. Mapping and Analysing Potential Sources and Transmission Routes of Antimicrobial Resistant Organisms in the Environment using Geographic Information Systems-An Exploratory Study. Antibiotics (Basel). 2019 Feb 27;8(1):16. doi: 10.3390/antibiotics8010016. PMID: 30818774; PMCID: PMC6466594.

- Amador PP, Fernandes RM et al. (2015). Antibiotic resistance in wastewater: occurrence and fate of Enterobacteriaceae producers of class A and class C β-lactamases. *Journal of Environmental Science and Health. Part A, Toxic/Hazardous Substances & Environmental Engineering*, *50*(1), 26–39. https://doi.org/10.1080/10934529.2015.964602
- Korzeniewska, E., & Harnisz, M. (2013). Extended-spectrum beta-lactamase (ESBL)-positive Enterobacteriaceae in municipal sewage and their emission to the environment. *Journal of Environmental Management*, *128*, 904–911. https://doi.org/10.1016/J.JENVMAN.2013.06.051

11. Vaccination Status

Vaccines can both directly and indirectly help prevent the emergence and spread of AMR. A vaccine against a specific bacterial pathogen decreases both the prevalence of the resistant bacterium and antibiotic use. Thus, tracking immunisation status against specific bacteria may be an important indicator of progress against AMR.

- Influenza: https://www.destatis.de/EN/Themes/Countries-Regions/International-Statistics/Data-Topic/Population-Labour-Social-Issues/Health/Influenza-2.html
- TB
    - https://journals.plos.org/plosmedicine/article/figures?id=10.1371/journal.pmed.1001012
    - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3062527/
    - https://www.gov.uk/government/publications/tuberculosis-tb-by-country-rates-per-100000-people

- Our World in Data has a lot of information on vaccine coverage. Some of these data sets can also be used for the category of education on AMR and vaccine safety.
    - https://ourworldindata.org/vaccination
    - Confidence in the effectiveness of vaccines vs perception of importance
    - Deaths caused by vaccine-preventable diseases
    - Deaths caused by vaccine-preventable diseases
    - Number of one-year-olds who did not receive the vaccine against tuberculosis (BCG)

12. Sanitation Standards

The World Health Organization (WHO)/United Nations International Children's Fund (UNICEF) Joint Monitoring Programme (JMP) includes global data on Water Supply, Sanitation and Hygiene (WASH)[11]. The portal provides data interactives with estimates for WASH for over 200 countries, areas, and territories across three

[11] Source: Water Supply, Sanitation and Hygiene (WASH) Data. World Health Organization, United Nations International Children's Fund Joint Monitoring Programme for Water Supply, Sanitation and Hygiene 2020. https://washdata.org/data.

sectors: households, schools, and health care facilities.[12] For each interactive, users can engage with global maps and view country or regional data, trends, and a breakdown of specific outcomes for drinking water, sanitation, and hygiene services.

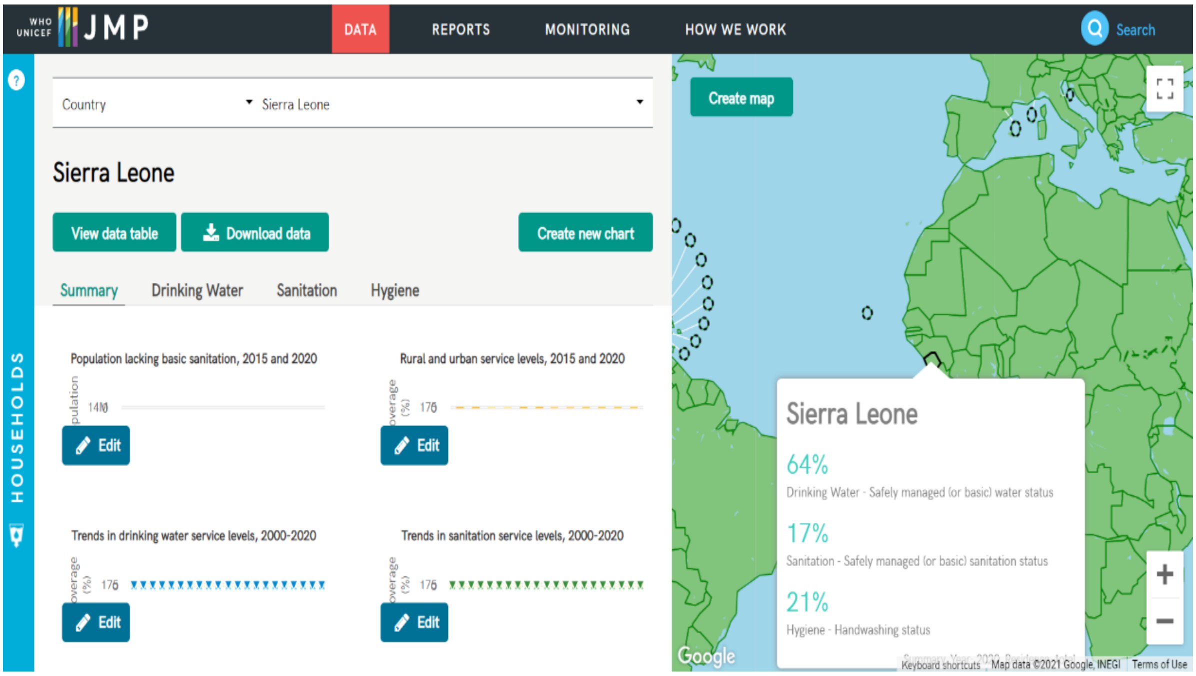


Figure 9: Joint Monitoring Programme Dashboard

Additional sources:

- One WASH – Consolidated Water Supply, Sanitation, and Hygiene Account Project (One WASH – CWA): https://projects.worldbank.org/en/projects-operations/project-detail/P167794
- https://www.worldbank.org/en/topic/sanitation#3
- https://ourworldindata.org/sanitation

13. Investment in AMR Research & Development

- **Global AMR R&D Hub, "Investments in AMR R&D,"** https://dashboard.globalamrhub.org/reports/investments/overview

- **Africa CDC Regional Investment Financing Project**
  - The aim of the project is to "to strengthen continental and regional infectious disease detection and response systems". It has five components:
    - Governance, Advocacy, and Operational Frameworks. The goal is to develop standardized guidelines and foster cooperation and coordination between the Africa CDC Secretariat and the NHPIs

[12] https://repository.gheli.harvard.edu/repository/12576/

across the continent, with a focus on data sharing on disease surveillance and outbreaks.
    - Public Health Assets. The aim is "to support the establishment of a small number of fit-for-purpose laboratories, transnational surveillance networks, emergency-response mechanisms, and other health assets designed to manage disease risks on a regional or continental scale."
    - Human Resources Development
    - Project Management: implementing ACDCP
    - Contingent Emergency Response Component. Goal is to enable Ethiopia and Zambia to request and access rapid World Bank support for mitigation, response, and recovery. See more: link

Regional Disease Surveillance Systems Enhancement (REDISEE)

- The goals are "to strengthen national and regional cross-sectoral capacity for collaborative disease surveillance and epidemic preparedness in West Africa" and "in the event of an eligible crisis or emergency, to provide immediate and effective response to said eligible crisis or emergency".
- The project:
    - Strengthens surveillance and information systems and laboratory capacity;
    - Supports national and regional efforts to enhance infectious disease outbreak preparedness and response capacity.
- This project furthermore serves as a data-source for further programming. The project is a loan agreement between the World Bank and Republic of Sierra Leone, Republic of Senegal, Republic of Guinea, ECOWAS.
- Currently at the implementation phase and no readily available data is being shared or published. See more: link

Fleming country grants:

These funds were established to assist national governments and other agencies in achieving the following objectives:

- Strengthen One Health governance structure for AMR, antimicrobial use (AMU) and antimicrobial consumption (AMC) surveillance.
- Strengthen AMR and AMU/AMC surveillance system in the human health sector.
- Strengthen AMR and AMU/AMC surveillance system in the animal health sector.

- https://www.flemingfund.org/grants/kenya-country-grant/
- https://www.flemingfund.org/grants/eswatini-country-grant/
- https://www.flemingfund.org/grants/tanzania-country-grant/
- India https://amr.cgiar.org/projects/antibiotic-use-and-antibiotic-resistance-poultry-value-chains-india-fssai-led-ilri

- https://amr.cgiar.org/projects/fleming-fund-fellows-zambia-bangladesh